Sudden Cardiac Death (SCD) in the young (2y-50y) in Newfoundland & Labrador: 2009-2013

By

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ABSTRACT

Sudden cardiac death (SCD) in young people is a catastrophic event, in which many productive life-years are lost and often has a genetic etiology. Several recurrent mutations (due to founder effect) in multiple genes which cause SCD, have been identified in Newfoundland and Labrador population. In this project, all cases (2y-50y) reported to the Medical Examiner office between the years (2009-2013) inclusive were ascertained, and classified into SCDs and non-SCDs by the research team based on several pre-specified contributing factors. A total of 174 out of 545 Medical Examiner cases fulfilled the SCD criteria. The overall reported incidence of SCD was 11 per 100,000 person-years, the incidence increased with age and the majority of cases observed in men. By comparing our result with the reported incidence worldwide, a higher incidence was detected. Further studies in SCD project will investigate the genetic and non-genetic implications of SCD in Newfoundland and Labrador.

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Rahaf Alkhateb

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ABBREVIATIONS

A	
AEDs	Automated External Defibrillators
AICD	Automated Implantable Cardioverter-Defibrillator
ARVC	Arrhythmogenic Right Ventricular Cardiomyopathy
B	
BBS1	Bardet-Biedl syndrome I
BrS	Brugada syndrome
BMI	Body Mass Index
C	
CAD	Coronary Artery Disease
CCRB	Centre for Clinical Research and Biostatistics
CHD	Congenital Heart Disease
CI	Confidence Interval
CIHR	Canadian Institution Health Research
CPVT	Catecholaminergic Polymorphic Ventricular Tachycardia
CRF	Chronic Renal Failure
D	
DCM	Dilated Cardiomyopathy
DNA	Deoxyribonucleic Acid
DKA	Diabetic ketoacidosis
DM	Diabetes Mellitus
E	
ECG	Electrocardiography
ERP	Early Repolarization Pattern
ESRD	End Stage Renal Disease
G	
GI	Gastrointestinal

H	
HCM	Hypertrophic Cardiomyopathy
HREA	Health Research Ethics Authority
HRS/EHRA	International Heart Rhythm Society USA/European Heart Rhythm Association
HSC	Health Science Center
HTN	Hypertension
I	
ICH	Intracerebral Haemorrhage
ICD	International Classification of Diseases
IDDM	Insulin Dependent Diabetes Mellitus
IHD	Ischemic Heart Disease
K	
KCNQ1	Potassium voltage-gated Channel subfamily Q member 1
L	
LQTS	Long QT Syndrome
LVH	Left Ventricular Hypertrophy
M	
ME	Medical Examiner
MVA	Motor Vehicle Accident
N	
NL	Newfoundland and Labrador
O	
ON	Ontario
P	
PE	Pulmonary Embolism
PKP2	Plakophilin 2
PMHx	Past Medical History
R	
RYR2	Ryanodine Receptor 2

S

SCD	Sudden Cardiac Death
SCN5A	Sodium voltage-gated Channel Alpha subunit 5
SD	Sudden Death
SIDS	Sudden Infant Death Syndrome
SQTS	Short QT Syndrome
SUD	Sudden Unexplained Death
SUDEP	Sudden Unexpected Death in Epilepsy

T

TMEM43	Transmembrane Protein 43

V

VF	Ventricular Fibrillation
VT	Ventricular Tachycardia

W

WHO	World Health Organization

RESEARCH OUTPUT AND AWARDS

Abstracts

A. Oral presentations

Rahaf Alkhateb, Simon Avis, Fiona Curtis, Terry-Lynn Young, Sean Connors, Kathleen Hodgkinson. *Sudden unexplained Death (SUD) in young people (2y-50y) in Newfoundland & Labrador*. Presented an oral presentation at PriFor 2016, the eighth annual Primary Healthcare Partnership Forum, June 29-30, Sheraton Hotel, St. John's, Newfoundland, Canada.

Rahaf Alkhateb, Simon Avis, Fiona Curtis, Terry-Lynn Young, Sean Connors, Kathleen Hodgkinson. *Sudden Cardiac Death (SCD) in young people (2y-50y) in Newfoundland & Labrador*. Presented an oral presentation at PriFor 2015, the seventh annual Primary Healthcare Partnership Forum, June 29-30, Sheraton Hotel, St. John's, Newfoundland, Canada.

B. Poster presentations

Rahaf Alkhateb, Gina Hamilton, Simon Avis, Barry Gallagher, Fiona Curtis, Terry-Lynn Young, Sean Connors, Kathleen Hodgkinson. *Sudden Cardiac Death (SCD) in young people (2y-50y) in Newfoundland & Labrador: 2009-2013*. Presented a poster at Cardiff International Cardiovascular Conference 2015, November 17-18, The City Hall, Cathays Park, Cardiff, UK.

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CONTRIBUTIONS AND CREDITS

Rahaf Alkhateb: (Memorial University of Newfoundland). I reviewed and assimilated the Medical Examiner files for all forensic deaths aged 2-50 years from the NL population for the period 2009-2013. The ME registry database contains information from all deaths referred to the ME office. I collected all the relevant clinical information from the forensic pathology cases categorized by the medical examiner as “natural”, “accident”, or “undetermined”. I led the research team meetings, and I determined the classification of cases into SCD and non SCD groups. In addition, I recorded all available demographics, internal, external, microscopic examination findings, BMI, and body organ weights in an SPSS dataset. I created a dataset with 545 cases for which there are 70 variables per individual, and I handled, processed and analysed the dataset I created by using SPSS and interpreted the study results. I did the literature review needs, and accented all the results from other studies to compare them with our cohort.

Dr. Simon Avis: (Memorial University of Newfoundland) the Chief Medical Examiner and co-supervisor. Dr. Avis provided all the forensic autopsy files; contributed to the research team meetings to review the classification of the forensic death cases into SCD and non SCD groups.

Fiona Curtis: (Memorial University of Newfoundland) genetic counsellor; contributed to the research team meetings and helped interpret any genetic findings in the Medical Examiner files.

Dr. Kathleen Hodgkinson: (Memorial University of Newfoundland) designed, supervised, and led the study; contributed to the research team meetings in order to

classify the forensic death cases into SCD and non SCD groups; and supervised the interpretation of the study results.

Chapter 1: Introduction and Literature search

1.1 Introduction

Sudden death (SD) in young people is a critical public health matter, and the loss of young lives is a devastating event for families and communities. SD in young people has received special attention over the past decades, because of the relative importance of the etiologies of SD in young people, which may increase the importance of screening programs [1]. The incidence of SD among the general population in Netherlands was estimated to be 1 in 1000 individuals, which equates to 18.5% of all deaths [2]. In young people the vast majority of SD events is caused by cardiac diseases which contain often has a hereditary component [3].

The term "sudden death" from natural causes has been used in medicine for nearly 450 years, and it generally denotes death which is nonviolent, non-traumatic, unexpected, and instantaneous or occurs within a few minutes of an abrupt change in previous clinical condition [4]. Based on the underlying cause of death, SD can be divided into sudden cardiac death (SCD), defined as SD from cardiac causes [5], and SD due to noncardiac causes, such as intracranial hemorrhage (ICH), pulmonary embolism (PE), or asthma [6,7]. Deaths in the absence of pathological causes despite autopsy is generally called sudden unexplained death (SUD) [8].

SCD is considered to be one of the most important causes of death in modern industrialized countries [5]. Most of SCD cases occur in previously healthy individuals without identifiable cardiovascular risk factors, thus the societal and psychological impacts of SCD in the young are significant in families and societies [3,9]. From an

epidemiological point of view, SCD at a young age is a major dilemma as many productive life-years are lost, and it accounts for millions of deaths worldwide [2,10,11].

Even though, prediction and prevention of SCD is an essential and active area of investigation, the true burden of this problem among young people isn't established and the epidemiology on those <50 years isn't fully understood. Disparities exist in the incidence of SCD based on the genetic and demographic characteristics of the studied populations. Several studies have highlighted the evidence for a clear genetic role in SCD [12,13].

SCD is not the same as actual death, in which the brain also dies. SCD is potentially reversible, if it is reversed quickly the brain will not die[14]. Because SCD is a reversible and preventable event and many victims who suffer SCD are considered to be at low risk of dying suddenly or usually they don't have any known heart disease, it is very important to investigate the scope and nature of this matter [15]. Identifying the mechanism of SCD will not only help to explain the cause of death, but it will enable screening methods and treatments to high risk populations which may save future lives [16]. Moreover, estimating the incidence of SCD among the general population would provide insights on supporting the application of automated external defibrillators (AEDs) in schools and public areas. For every minute that passes between the time a person collapses and defibrillation is administered, survival decreases by 10% [17] .

Debate over the use of cardiovascular screening to prevent SCD in young individuals has passionate supporters on both sides. However, this debate will continue unresolved until additional and convincing evidence is provided that either supports or rebuts the value of screening for SCD in young people [18].

Our knowledge on SCD in young people (<50 years old) in Newfoundland and Labrador (NL) is limited, even though several recurrent mutations due to founder effects [e.g. ryanodine receptor 2 gene (*RYR2*), [19] plakophilin 2 gene (*PKP2*) [20] and transmembrane protein 43 gene (*TMEM43*) [21]], which cause SCD, have been identified in this population. Investigating the burden of SCD in a founder population using a centralized database could provide insights on the role of genetic and non-genetic implications of SCD.

The aim of this study is to understand early SCD in NL. The main objectives are; a) to create a database with all cases of forensic death from ages 2-50 years in NL during the period 2009 to 2013, b) to determine the incidence of SCD and SUD (arrhythmic death), c) to classify the SCD cases based on age group, sex and underlying cardiac pathology status in which autopsy was performed, and d) to compare the incidence of SCD and SUD in NL with other studies worldwide.

1.2 Definition of SCD

Defining the problem is the first step in the process of confronting any community wide disease condition [22]. Historically, SCD has been used to refer to an unexpected death from cardiac causes within short period of time, and it was ascribed to supernatural causes. Even when medical science advanced to an era when autopsies became available, many SCD cases remained unexplained (SUD) [5,23] . The term SUD is usually used when no diagnosis can be made based on autopsy findings or toxicology screening [24]. However, SUD might also refer to cases in which the cause of death remains uncertain (i.e.

undetermined). SCD does not include the deaths that occur in the setting of terminal illness (i.e. malignancy or end stage of chronic diseases) [25,26].

To date, there is no standardized and universal definition for SCD, and numerous definitions have been used across the medical communities [27]. Uncertainty surrounding the definition of "sudden cardiac death" starts with the complex nature of this event and the limited accessibility to the information surrounding the death, such as time of onset, whether the death was expected or witnessed, and the pathological cause of death [27,28]. The definition of SCD that has been widely used based on the circumstances and the details provided by the first responders to the death event (i.e. medical examiner, physician, emergency medical provider, or police officer), medical records, and available autopsy data is considered to be: the natural death due to cardiac causes that results from an unexpected or abrupt loss of consciousness within one hour of collapse when the event is witnessed [29-31]. However, defining un-witnessed cases is difficult and various definitions have been used by the scientific community. Hinkle et al (1982) [31] defined un-witnessed SCD cases based on the position or the apparent activity of the victim at the time of death. While in an Ontario (ON) study performed by Pilmer et al (2013) [29], un-witnessed SCD cases were defined as unexpected death in the absence of recognized or suspected medical condition that may cause death (i.e. end stage renal disease (ESRD), terminal stages of cancers, or terminal illnesses). Other studies defined un-witnessed SCD cases by the time when the victim was last seen alive and healthy with a cut-off point of 24 hours in some studies [25,32-35], and 12 hours in others [36,37].

Based on the world health organization (WHO) criteria, the most acceptable definition for SCD is: the unexpected termination of life from cardiac causes that occurs

either within one hour of symptom onset when the event is witnessed, or within 24 hours of having been observed alive and free of symptoms when the event is un-witnessed [25]. Even with a well-defined definition of SCD, the burden of SCD may vary based on the sex and the age of the victim.

1.3 Demographics of SCD population

1.3.1 The influence of sex on the incidence of SCD

It has been reported in the Framingham study that SCD is more common in males than in females [38], and a female to male ratio of 1:3 has been identified in two retrospective post mortem based studies that were implemented on young people (<40 years old) in Canada and Ireland [29,39]. However; the sex distribution of SCD in the general population is significantly different based on age group, and this difference decreases in parallel with age [22]. In an ON study [29] performed in 2013, it was reported that the majority (76%) of SCD cases among young people (2-40 years old) were men. Also another large well designed retrospective post mortem based study completed in Denmark (2014) [9] reported a similar sex proportion (male: 75%) among their population (1-49 years old). However, in a retrospective death certificate based study that was completed in the United States over 10 years (1989-1998) among residents aged ≥ 35 years [11], it was demonstrated that there was no difference between men and women. Chugh et al (2004) [25] ,who completed a study on a population from Oregon with a median age 69 years, reported a low sex difference among SCD population even by using both prospective and retrospective death certificate methods. This would confirm that the difference in the sex

distribution that diminished with age isn't related to study design, but it would reflect the high overall burden of ischemic heart diseases (IHD) in men at young age, which is three to four times higher than females [30,40]. And that would be possibly explained by the protective effects of sex steroids hormones in young women [40]. In addition, there are a number of differences between male and female in cardiac electrophysiology, for example women have been noted to have longer corrected (QTc) intervals [41]. The reason for the electrophysiology differences could be explained also by the sex hormones. In some cardiac genetic disorders such as an autosomal-dominant homogeneous form of ARVC (*TMEM43* 1073C→T, S358L) [21], there is a sex influence. In ARVC men present in more sever and advanced diseases in comparing to women (86% vs. 42%). Sex differences therefore may point to a genetic background of SCD in young people.

Although the risk factors and underlying causes of SCD in females are generally assumed to be similar to those in males [34], the pathophysiology of SCD is much less certain in women and its etiology is undetermined [42]. Thus the sex differences are poorly understood and it may point to the fact that SCD is possibly more heterogeneous in women compared with men.

1.3.2 The influence of age on the incidence of SCD

In general there are two peaks in the age-related prevalence of SCD, the first peak occurs during infancy which refers to the sudden infant death syndrome (SIDS). SIDS is defined by the sudden, unexpected death of an infant younger than 1 year of age, even though the vast majority of SIDS cases occur around six months of age [43], it could happen

in children up to 2 years [44] . And the second peak is in the geriatric age group, between ages 75 and 85 years [22,30].

The incidence of SCD significantly increases with age, regardless of sex or ethnicity [32]. In the US, it has been reported that the annual incidence of SCD in 50 year-old individuals is about 100 per 100,000 populations compared to 800 per 100,000 populations among 75 years-old people [45]. Even though the incidence of SCD increases with age, the proportion of deaths that are sudden and unexpected is larger in young people where the impact of SCD on socioeconomic and families is greater [34,46]. SCD in young people is a catastrophic and devastating event. It is estimated in a well-designed study on a defined population in US, that SCD is responsible for 19% of SD in children between the age 1 and 13 years, and 30% in young people between the age 14 and 21 years [47]. The spectrum and causes of SCD in young people are diverse and some of these deaths occur due to hereditary conditions [48]. Therefore, more information about SCD in young people may help to assist in improving awareness about this lethal condition. Thus an accurate estimation of the incidence of SCD is an essential step toward understanding the magnitude of this problem, which may improve our ability to predict and prevent this event.

1.4 Incidence of SCD

Based on the WHO reports, cardiovascular disease is the top cause of death worldwide and it is responsible for about 86% of all deaths globally [49]. However, SCD is estimated to be the most common and the first presentation of cardiovascular diseases,

and it accounts for half of the mortality cases caused from cardiovascular diseases in developed countries [30]. The annual incidence rate of SCD varies among nations and age groups. In two prospective population based studies, the annual incidence of SCD was 53 per 100,000 persons in the United States among a population with a median age 69 years old [25], and 90 to 100 per 100,000 persons in Netherlands in people aged 20 to 75 years [2].

The incidence of SCD in young people has been reported in several retrospective post mortem based studies, however; there is a wide range in the incidence depending on the age group, genetic structure and autopsy rate. In an autopsy study of a population averaged ~2.5 million inhabitants in Sweden (age group 15 to 35 years old), the annual incidence of SCD was 1 per 100,000 persons [50]. A comparable autopsy study that was implemented on the same age group (15-35 years old) in Ireland the annual incidence rate of SCD was 2.85 per 100,000 persons [39]. In Denmark, a nationwide retrospective study that used multiple sources of information (death certificated, hospital discharge records, and autopsy reports), the incidence of SCD in people aged 1-49 years old was 8.6 per 100,000 persons, however; this incidence rate declined to 4.2 per 100,000 persons when only autopsied cases were considered in the incidence calculations [9]. On the other hand, a post mortem study that used coroner's reports from ON showed that the incidence of SCD in young people (2-40 years old) was 2.6 per 100,000 persons-years [29]. In a large prospective study of a population averaged ~ 2.4 million residents from Veneto region, Italy, the incidence of SCD among athletes and non-athletes people aged <35 years (excluding SIDS cases) was 0.8 per 100,000 persons [51].

These variations in the reported incidence of SCD in young people could be explained by the disparities in the definition of SCD and the methods of data collection

and ascertainment. However, by looking at the studies that used the same definition of SCD and employed a similar ascertainment methods, the differences in the incidence of SCD could be explained by the genetic structure of the population and the allele frequency of genes associated with ion channelopathy and cardiomyopathy [52]. Thus the international diversity of SCD incidence may be ascribed to different genetic backgrounds and the prevalence of recurrent mutations. The concept of recurrent (due to founder effect) gene mutations was used to explain the high proportion of SCD related to long QT syndrome gene mutations in some geographic areas [52], such as South Africa [53]. More complete picture of the contribution of the genetics in the etiology of SCD can be noted by comparing the incidences of SUD#. For instance, in the Irish population, which is considered to be relatively genetically homogenous, the incidence of SUD# was reported to be 0.74 per 100,000 person-years in the age group (15-35) years old [39], while in Sweden (considered a more diverse genetically population) the reported incidence of SUD# for the same age group (15-35) years old was 0.22 per 100,000 person-years [50]. Whereas, Behr et al. (2007) [37] reported the incidence of SUD# in UK at 0.16 per 100,000 person-years among the population aged 4-64 year old. However, in the same study (Behr et al) a prevalence of 18% of positive family history of SUD# or premature death was reported in the victims' families, and positive cardiology test for arrhythmia and other cardiomyopathies was confirmed among 25% of first degree relatives of the victims [37]. Thus the incidence of SCD/SUD varying between the populations could be explained by the genetic structure, therefore different genetic causes may influence the varied of SCD incidence.

#SUD = SCD with negative autopsy (likely arrhythmia)

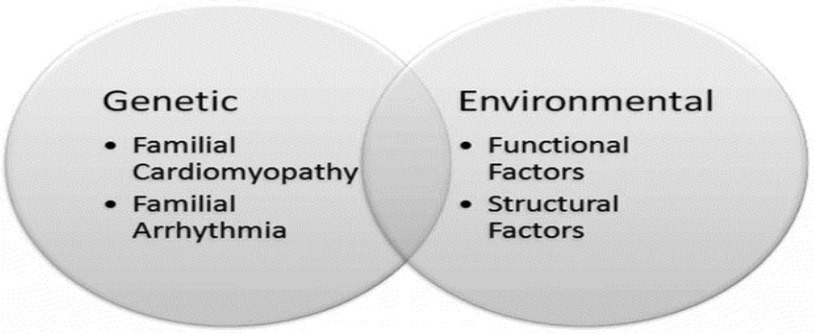
Notably, SCD is a complex outcome, thus detecting the underlying causes of SCD could help in identifying individuals at high risk and may direct the health care system toward establishing suitable screening and treatment programs.

1.5 Etiology of SCD

SCD is usually caused by electrical activity disorder in the heart (cardiac arrhythmias). Ventricular fibrillation (VF), which is an abnormal and irregular heart rhythm that causes disrupts the synchrony between the heartbeat and the pulse beat [54], is usually the cause of SCD in about 80-85% of the cases [55,56] . While in the remaining 15-20% a bradyarrhythmia, which is regular very slow heart beats [57], is recorded [58]. Evidence is accumulating that the occurrence of these arrhythmias is multifactorial and is usually the result of the interaction between structural pathological changes in the heart and genetic factors (**Figure 1.1**). The underlying causes of SCD are usually concealed and discovered with surprise only at autopsy examination including macroscopic and microscopic investigations [59]. Autopsies are usually conducted to investigate all sudden or unexpected deaths, where a physician does not know the cause of death, and deaths caused by injuries or drugs [60]. In Canada, two different death investigation systems have developed: the Coroner's system and the Medical Examiner's system, in NL the Medical Examiner's system is used. Although there are some differences between these two systems, the eventual goal of each is still the same, which is investigating the unexpected and unexplained deaths [61].

Autopsy typically addresses structural abnormalities in the heart in the majority of SCD cases in young people; however, in around 30% of SCDs in young persons, no structural abnormalities have been found [50,62]. The identification of the cause of SCD in young people is a critical step because of the genetic etiology nature among this group. Genetic etiology is mainly important in the evaluation of SCD cases where no cause of death is identified at autopsy (SUD or arrhythmic cases) [63]. The genetic testing or molecular autopsy is usually used where no cause of death is identified after autopsy. In molecular autopsy a blood sample is usually used to extract deoxyribonucleic acid (DNA), followed by DNA analysis of selected candidate genes responsible for the main primary arrhythmogenic diseases [64]. Most molecular autopsy studies performed to date are based on the current international Heart Rhythm Society USA/European Heart Rhythm Association (HRS/EHRA) guidelines [65]. The molecular autopsy usually focused on direct DNA sequencing of the protein coding exons of four genes, i.e. the three major congenital long QT syndrome (LQTS) genes: potassium voltage-gated channel subfamily Q member 1 (*KCNQ1*), sodium voltage-gated channel alpha subunit 5 (*SCN5A*), and potassium channel, voltage-gated, subfamily h member 2 (*KCNH2*), and the CPVT gene (*RYR2*) [63,66,67] .

Figure 1.1: Etiology of SCD



SCD is elicited by the interaction between environmental and genetic factors. The equilibrium prevents SCD, while alteration cause SCD. This figure is adapted by permission from Macmillan Publishers Ltd: Genetics in Medicine; Campuzano O, Beltrán-Alvarez P, Iglesias A, Scornik F, Pérez G, Brugada R. Genetics and cardiac channelopathies. *Genet. Med.* 2010;12(5):260-267. The copyright permission is shown in **Appendix A**.

1.5.1 Positive autopsy findings in SCD population

One of the most common clinical findings in SCD cases is coronary artery disease (CAD), which may induce electric instability and lethal ventricular arrhythmias [22]. It has been estimated that CAD is the cause of death in around 24% [62] to 35% [9] of SCD in people aged <35 years old and <50 years old, respectively. CAD is usually diagnosed by the presence of narrowing >70% of the luminal area in one or more major coronary arteries [68]. However; 30% to 50% narrowing in the coronary artery could induce lethal arrhythmia when it is associated with a transit coronary artery spasm [69]. Sometimes it is difficult to confirm CAD cases in vitro, or that in cases of >70% occlusion, the causes of SCD wasn't related to the CAD but an unrecognized arrhythmia may occur. Even though, the association between CAD and SCD is well established, the precise mechanism that explains the SD in some patients while others with the same cardiovascular lesions don't suffer SD, is not well understood. Several studies have emphasized the genetic

contribution on SCD among patients with CAD [70-72]. For example, Westaway et al (2011) [73] detected significant associations between DNA variants located in multiple genes and the risk of SCD in people with CAD. In addition, premature CAD may be implicated by genetic influences through different risk factors such as hypercholesterolemia, hypertension, and diabetes [74-76]. Thus the interaction between genetic factors and CAD may play an important role in increasing the risk of SCD in young people [77].

Other common structural heart disease that is associated with SCD in young people include cardiomyopathies, which are (in most cases) inherited disorders. Examples may include: hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy (DCM) and ARVC. These cardiomyopathies are characterized by visible macroscopic and microscopic cardiac structural abnormalities as shown in **Table 1.1**.

Table 1.1: Characteristics of cardiomyopathies with a known association with SCD

Cardiomyopathy	Macroscopic findings	Microscopic findings	Diagnosis	Treatment
HCM	Thickening of the heart walls which my block flow out of the ventricles [78]	myocyte hypertrophy and disarray [79]	Echocardiography, electrocardiogram (ECG), and genetic test in familial cases [78]	Antiarrhythmic treatment, surgery, and automated implantable cardioverter-defibrillator (AICD) [78]
DCM	stretching and thinning (dilating) the ventricles, which cause failure in pumping blood to the body [80]	The findings range from minimal variation in myocyte size to typical features of myofiber loss, interstitial fibrosis, and variation in myofiber size [81]	Echocardiography, ECG, and genetic test in familial cases[80]	Antiarrhythmic treatment and AICD [80]
ARVC	Thinning of the right ventricle, with fibrofatty change. And scars in the subepicardial region in left ventricles [82]	fatty or fibrofatty replacement of the myocardium which may appear randomly "moth-eaten," with destruction of the normal myocytes [82]	The diagnosis is challenging it needs several structural, histological, ECG, arrhythmic and familial features [83]	Antiarrhythmic treatment or AICD [82]

HCM and ARVC account for around 7% [9,29] and 5% [29] of SCD in young persons from diverse ethnical populations, respectively. While the prevalence of HCM and ARVC among more genetically homogeneous populations were 15% [39] and 13% [84], respectively. These variations in the prevalence could be explained by the allele frequency of genetic mutations of these cardiomyopathies among populations. However, DCM is not a very common cause of SCD and it was reported in less than 3 % of SCD in young people [9,39].

Less common structural cardiac abnormalities that are also responsible for SCD may include congenital heart diseases (CHD), endocarditis, and valvular heart disease.

1.5.2 Negative autopsy findings in SCD population

As mentioned above, not all SCD events have an obvious cause of death that can be detected by autopsy. A review of five population-based studies on SCD in young people indicated that around 30% of SCD in young people are autopsy negative [85], and these cases are generally called SUD. The mechanism of SUD is usually ventricular arrhythmia that may lead to cardiac arrest leaving no trace to be found on a comprehensive autopsy. Many SUD cases are assumed to be caused by inherited cardiac channelopathies, such as LQTS, catecholaminergic polymorphic ventricular tachycardia (CPVT), BrS, or short QT Syndrome (SQTS). Notably, several pathogenic mutations have been detected in several genes related to cardiac channelopathies such as *SCN5A*, and *KCNQ1* [86,87]. In a review of several population-based investigations of SD in young people, they illustrated that SUD accounts for a significant number of SD events in young people, and the molecular autopsy should be considered as a standard of care for post mortem examination of SUD [85]. Identifying the cause of SUD could save lives in the future by offering screening programs to the first degree relatives, who are at high risk of SUD [63,88,89].

Detecting the cause of SCD is important for screening and prevention plans among high risk populations. The etiology and the incidence of SCD may vary based on age group as well as the genetic structure of the population, however; the primary source of the data and methods of ascertainment need to be carefully considered. Thus detecting

the incidence of SCD accurately and estimating the underlying pathology cause of SCD correctly would need a well ascertained source of data, and several contributing factors need to be considered.

1.6 Data and primary sources used to identify the epidemiology of SCD

The published incidence of SCD in young people ranges widely from 1 (among general population in Sweden) [50] to 13 (among military recruits in US) [90] deaths per 100,000 population per annum. The disparities in the incidence of SCD may reflect the variations in data sources for case ascertainment, study design, the studied population, or methods used for extrapolation of rates.

An accurate estimation of SCD incidence requires a population based prospective study design [22], and that was confirmed in a large US study that compared the prospective approach to retrospective method [25]. Studies that used a retrospective death certificate based methodology usually overestimated the actual incidence of SCD by three folds compared to prospective studies [25], because death certificates usually list the primary cause of death regardless of the associated comorbidities that may contribute to the death. However, retrospective post mortem based studies may provide an accurate estimation of SCD incidence, due to the fact that autopsy is able to reveal the cause of death in around 80% of the cases [3]. Furthermore, some studies estimated the incidence of SCD in specific populations such as military recruits [90] or athletes [84] which can't extrapolate to general population. Usually there is a pre-enrolment screening for military recruits and athletes, and that may change the cause of SCD compared with the general population, by

excluding those with cardiac risk factors. Thus population based studies would provide better insights about the burden of SCD in the general population.

Regardless of the variance in the methodology of post mortem SCD studies, several potential factors, which may contribute to the death, should be taken into consideration, such as drugs, alcohol, diabetes mellitus (DM), epilepsy, and morbid obesity.

First, there are extensive data that link some drugs to increase risk of SCD. These drugs usually induce malignant arrhythmias in patients via different mechanisms. For example, typical antipsychotic and antidepressant drugs were reported to block repolarization potassium current and prolong the QT interval, which may induce ventricular arrhythmias and SCD [91-93]. Cocaine has also a sympathomimetic effect that results in an increase in heart rate, myocardial oxygen demand, temperature, and blood pressure, and consequently might lead to MI or coronary artery spasm and SCD [94-96]. The degree to which the risk of any drug has varies among people, and it usually depends on several factors, such as the genetic predisposition, medical history of LQTS or BrS, the combination of the drugs, and blood drug level [93]. SCD cases with a positive blood test for drugs that may induce arrhythmia have been evaluated carefully by several investigators [9,29,50].

Second, the relationship between alcohol and VT as well as SCD is definite; albeit complex [97]. Several epidemiological, animal and human intervention studies suggest a protective effect of light to moderate alcohol consumption [98], whereas heavy consumption can lead to cardiomyopathy, heart failure, strokes, arrhythmias, and SCD [99,100]. 'Holiday heart' due to supraventricular arrhythmias (mostly atrial fibrillation) and SCD due to VT

and ventricular fibrillation (VF) are well-recognized consequences of heavy alcohol consumption [101]. The underlying pathophysiology of alcohol-induced arrhythmias includes electrolyte abnormalities, QT interval prolongation, rebound and adrenergic hypersensitivity, decreased heart rate variability and atrial effective refractory period [102]. Most post-mortem epidemiological studies use a cut off point for blood alcohol level at the time of death, and a blood alcohol level >22 mmol/l was used as an indicator of a level that may contribute to the death by one of the studies [39].

Third, several studies have investigated and confirmed the independent role of DM in enhancing SCD. A significant association has been reported between diabetic autonomic dysfunction and prolongation of the QTc interval, which may cause SCD [103-106]. In addition, DM usually accelerates atherosclerosis with enhanced thrombogenicity [107], and sometimes causes a distinct form of cardiac dysfunction called "diabetic cardiomyopathy" [107,108]. Thus SCD cases with a long term history of DM and end organ damage have been assessed independently [50].

Fourth, sudden unexpected death in epilepsy (SUDEP) is usually referred to as SCD in epileptic people who are otherwise healthy, and the death isn't attributed to a trauma, status epilepticus, drowning, or toxins [109,110]. A recent community-based study that was conducted on a population of a contiguous region (urban and rural communities, ~2.4 million inhabitants) of Netherlands [111] reported that people with epilepsy had two to three times increased risk of VT /VF and SCD, regardless of any other cardiac risk factors. In addition, early repolarisation pattern (ERP) and severe QTc prolongation appears to be more frequent in people with refractory epilepsy [112]. So, this group of patients deserve special attention while defining SCD cases [39].

Moreover, severe obesity is considered to be a serious contributing factor among the SCD population, because severe obesity (body mass index (BMI)>50 kg/m^2) is significantly associated with obstructive sleep apnea (OSA) in about 80% of cases [113]. OSA is a clinical condition that causes hypoxia during sleep, because of the recurrent episodes of complete obstruction (apnea) or partial obstruction (hypopnea) of the upper respiratory track [114]. Obesity is considered a major risk factor for OSA, as it causes magnification of soft tissue structures within and around the respiratory track, and leads to a significant narrowing of the pharyngeal airway [115,116]. In a study that enrolled 52 individuals with a mean BMI 50 kg/m^2, it was reported that OSA in morbidly obese patients is associated with increased risk of cardiac arrhythmias and SD [117]. A Long-term study of OSA patients that followed up 168 patients from Ireland showed that after an average of 7 years, SCD was very common among the studied population, especially those who are noncompliant with OSA treatment [118]. Even though, morbid obesity is usually associated with several important morbidities such as, diabetes, hypertension, coronary heart disease, and cancer, SCD is considered the most important endpoint [119]. Thus, SCD in morbid obese people need to be evaluated individually especially in NL that has the highest prevalence of obesity in Canada[120]. Based on the most recent data, obesity rate with BMI>40 kg/m^2 has been increased in province 73% from 2001 to 2011 [121].

Beside the contributing factors mentioned above, accidents as a cause of SCD need to be examined individually with special attention. It is reported that 1/1000 of motor vehicle accidents (MVA) are caused by cardiovascular events [122], however; these cases are difficult to assess because autopsies in such cases are sometimes limited to the

investigation of the injuries and to predisposing factors like alcohol or drug levels. In a recent study [123] it was reported that the prevalence of severe CAD and acute myocardial ischemia was very high among individuals who suffered an MVA, and erratic driving behaviour before the collision would suggest a possible correlation between the incident of abrupt cardiovascular changes and MVA. Thus, the circumstances surrounding accident cases needs to be evaluated carefully. Also, in cases of drowning (considered the leading cause of traumatic related death in young people) a significant number of them have a negative autopsy, and a cardiac channelopathy may be the actual cause of death [124].

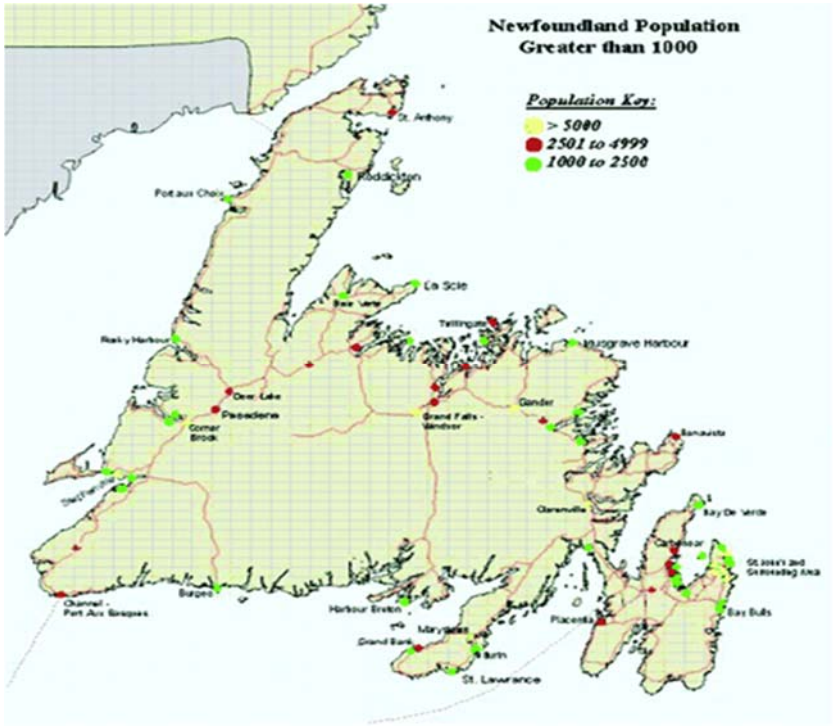
Detecting the incidence of SCD using post mortem population based studies, needs a well-designed study that considers all the factors that may contribute to the SCD. In addition, the genetic structure of the studied population needs to be taken into consideration while interpreting the results.

1.7 The role of the population genetic structure in SCD

Arrhythmias that lead to SCD usually depends on the critical interaction between environmental and genetic factors [87]. Hence, detecting the risk factors of SCD including candidate genes would be more informative if it is studied on genetically isolated populations (founder populations) [125]. Founder populations are usually established by a very small number of individuals from a larger population which leads to reduced genetic diversity among the population (founder effect) [125]. These populations tend to have many advantages and are often used in genetic research, because they are assumed to have

reduced genetic diversity, along with increased prevalence for some diseases [126] [125]. One of the most impressive examples of isolated homogenous populations is the Newfoundland and Labrador population, which started from about 20,000 settlers in 1760, the majority of the population individuals were English or Irish descent (**Figure 1.2**). Throughout the 17th–20th centuries, intermarriage among these diverse settlements was limited because of religious, linguistic, socioeconomic, and geographic barriers, and their offspring remained close to the original settlements, and that resulted in a relatively homogeneous genetically population [127-130]. Expected genetic consequence of these historical phenomena is genetic drift, which acts to randomly increase some alleles to fixation and send others to extinction. Thus, the NL population is enriched for certain genetic diseases, such as Bardet–Biedel syndrome [130] and nonpolyposis colorectal cancer [131]. Though the NL population has been especially valuable for mapping rare monogenic diseases, it could also be well suited for detecting the variants associated with the increased risk of SCD [132]. Thus, understanding the population history and the genetic structure will help detecting the genetic and non-genetic background of complex diseases including SCD.

Figure 1.2: Newfoundland population, Statistic Canada 2001



This figure is adapted by permission of Oxford University Press; Rahman P, Jones A, Curtis J, et al. The Newfoundland population: A unique resource for genetic investigation of complex diseases. *Hum Mol Genet*. 2003;12(Suppl 2):R167-R172. The copyright permission is shown in **Appendix B.**

1.8 Rational and research question

In this research project we studied the NL population, which is a Caucasian genetically isolated population with several recognized cardiac monogenic disorders [133]. In 2008, a founder mutation in the *TMEM43* gene was found to cause ARVC in NL [21]. This finding determined the etiology of one of the important causes of SCD in the province. Recently, it has been reported that the incidence of SCD in NL in adults is three times higher than the incidence in ON, when a cohort from 2008 was compared directly between the two provinces using a similar method of ascertainment [29,134]. The reasons for

these differences need to be further investigated, and any association that exists between SCD in young people and potential risk factors need to be identified.

In this research thesis we examined the following question: Does NL have a higher incidence of young SCD (2-50 years old) than worldwide records?

This research aimed to create a database with forensic death cases in people aged 2-50 years in NL population during the period 2009-2013 inclusive; identify the incidence of SCD and SUD [#]; and compare the incidence of SCD and SUD [#] in NL with worldwide records. In addition, we aimed to describe the SCD cases based on age, sex, and underlying cardiac pathology. Characterization of the SCD population will help in understanding the scope and nature of this major health problem.

This is a retrospective population-based study in NL of 545 cases aged 2–50 years, identified in the years 2009- 2013 from the Medical Examiner (ME) registry database at the Health Science Center (HSC), St. John's, NL. ME cases are those where death is unexplained and an autopsy is required to investigate the cause of death. This research therefore doesn't take into account deaths that were not assessed as ME case. The research was achieved initially by reviewing all the ME files that fulfill the inclusion and exclusion criteria. ME files were completely reviewed, and were classified into SCD and non SCD groups. SCD was defined as an event resulting in death or terminal life support that occurred either within one hour of symptom onset (witnessed) or within 24 hours of having been observed alive and symptom free (un-witnessed), in which the underlying cause is cardiac [25]. Classification was completed by the research team at the HSC, and several contributing factors were considered in the ascertainment. All the

SUD = SCD with negative autopsy (likely arrhythmia)

available data of demographics, internal, external, microscopic examination findings, BMI, and body organ weights were entered in an SPSS dataset. The statistical analysis was completed using SPSS.

Chapter 2: Materials and Methods

2.1 Ethics approval

This research study was approved by the health research ethics authority (HREA) of NL (HREA Reference#: 12.199).

2.4 Population study

The target population of this research consists of the cases of sudden death reported to the ME office at HSC in St. John's, NL. ME cases are those where the death is unexplained and an autopsy is required to detect the cause of death, therefore a death certificate is not provided by the local medical practitioner. ME autopsies in NL are done at local hospitals by accredited ME pathologists. All the results; however; are validated by Dr. Simon Avis, the Chief Medical Examiner in St. John's and the data kept in a centralized database at HSC. Cases that should be immediately notified to a medical examiner or an investigator include those that are[135]: a) result of violence, accident, or suicide; b) unexpected, when the person was in good health; c) the victim was not under the care of a physician; d) the cause of death is undetermined; or e) the death happened as the result of improper or suspected negligent treatment.

The ME files are kept in a centralized database at the ME office and usually contain several documents, the description of the documents included in ME files is shown in **Table 2.1**.

Table 2.1: The description of the documents included in ME files

Final report	This includes all the personal information related to the deceased: name, age, sex, date of birth, date of death, place of death, address, occupation, immediate cause of death, conditions that may contribute to the death but not related to the immediate cause of death, autopsy status, manner of death (natural, accident, suicide, homicide, and undetermined), and a narrative section for the circumstances of death. The cause of death is usually classified based on the international classification of diseases (ICD), injuries and causes of death as last revised by the international conference for that purpose and published by the WHO [136], **Appendix C.**
Autopsy report	"Autopsy" means the dissection of a body for the purpose of examining organs and tissues to determine the cause of death, manner of death, or the identity of the person. An autopsy report usually includes internal and external examination findings, chemical, histological, microbiological or serological tests, and other laboratory investigations, **Appendix D**.
Registration of death form	This form is a permanent legal record issued by the government of NL.
Scene report	This form includes all the personal information of the victim, the time of last seen alive, date and time of death, medical history, and circumstances surrounding the death based on interviews of family members, friends, and eye witnesses. In addition, this form provide information about the weather condition at the time of death, **Appendix E**.
Narrative and synopsis of case from police report	This report includes all the detailed information about the death circumstances and the police analysis.
Witness statement (R3 statement)	This statement includes all the witnesses' declarations about the victim and the circumstances of death.
Medical and hospital records	Whenever they are available
Reports from the children's aid society and work place safety and insurance board	Whenever they are available based on the death circumstances.

In this thesis project we included ME files of; a) people aged 2-50 years old of both sexes, we started recruiting cases from 2 years old to avoid SIDS cases which is caused by a different physiological mechanism,; b) death cases reported between the years 2009 to 2013; and c) manner of death listed as "natural", "accident", or "undetermined". I excluded cases of; a) people younger than two years or older than 50 years; and b) manner of death listed as "homicide" or "suicide".

2.5 Data collection

This study is a retrospective population-based study of all SCD cases in NL. The study data comprises all the ME files that fulfil the inclusion criteria as mentioned in **Section 2.4**. This resulted in 545 potential cases. I reviewed extensively and carefully each record, extracted all the required information directly from the ME files, and recorded all the information on an abstraction form, **Appendix F**. After that, I stored all the extracted information in SPSS dataset.

All the cases included in this study were classified into SCD or non SCD groups based on the methodology used previously by Pilmer et al (2013) [29]. In this study, SCD was defined as an event resulting in death or terminal life support that occurred either within one hour of symptom onset when the case was witnessed, or within 24 hours of having been observed alive and symptom free when the case was un-witnessed, where underlying cause of death was cardiac [25].

The classification into SCD or non SCD was created during panel meetings, which included the chief medical examiner (Dr. Simon Avis), a genetic counsellor (Fiona

Curtis), the study supervisor (Dr. Kathleen Hodgkinson) and myself. The classification process was performed in two steps: firstly we excluded 277 cases that satisfied at least one of the following criteria:

- Non cardiac etiology (gastrointestinal (GI) bleeding, PE, ICH, lethal drug level in blood, sepsis, diabetic ketoacidosis (DKA), dissection aorta, smoke inhalation, pedestrian accident, and undetermined cases in which suicide status can't be confirmed).
- Post operation cases, in which death occurred within 10 days of the operation and the death happened because of the complication of the operation.
- Witnessed death cases with symptoms > 1 hour.
- Un-witnessed death cases that were last seen alive and healthy > 24 hours, even if the circumstance of death appeared to be SCD (i.e. missing people for more than 24 hours).
- Cases that were not sudden or not unexpected, such as terminal illness, chronic renal failure (CRF) and on dialysis, and in hospital deaths.
- Out of the province origin.

Secondly; the remaining 268 files were reviewed extensively and were classified into four groups: group A, group B, group C, and group D. This classification was completed based on several contributing factors, such as:

- Blood alcohol level ≥ 24 mmol/l.
- Any blood level of cocaine.
- Morbid obesity (BMI>50 kg/m^2).

- Insulin dependent DM (IDDM) + end organ damage.
- Epilepsy.
- Hazard condition in accident cases (i.e. bad weather condition, high speed, no seatbelt, no helmet, or moose accident).
- Prescribed or non-prescribed toxic level of drugs in the blood.
- Combined medical condition that may contribute to the death (i.e. sever hypertension or pneumonia).

The definition of the SCD groups is presented in **Table 2.2**.

Table 2.2: The description of SCD groups.

SCD group	Definition	Example
Group A	Natural or undetermined manner of death cases without any contributing factor	A healthy 30 years old man, with no previous medical history, suddenly collapsed while making a cup of tea, and the toxicology reports were negative for blood alcohol and/or any other drug (prescriber or non-prescribed)
Group B	Natural or undetermined manner of death cases with only one contributing factor, or accident cases without any contributing factor explaining the accident in which the cause of death is most likely from cardiac causes	A previously healthy 25 years old man found dead at home, last seen alive 30 minutes before, where the toxicology report showed a blood alcohol level > 24 mmol/l. Another example would be, a single MVA on a safe straight road on a clear day, with no evidence of an attempt to avoid the accident, with no hazard that would explain the accident
Group C	Accident cases with only one contributing factor, which makes the cause of death possibly cardiac	A single MVA on a safe straight road in a clear day, however; the driver's blood test was positive for a trace amount of cocaine
Group D	This group includes all death cases with more than one contributing factor	A healthy 40 year old individual found dead in bed, who was last seen alive an hour before, the toxicology report confirms a blood alcohol level >24 mmol/l with a toxic level of morphine.

For the purpose of analysis in this study, groups A and B were considered as SCD group, this follows the procedure followed by pilmer 2013 [29]. Groups C and D were considered non SCD group. At the end of collecting the data, I created a dataset with 545 cases for which there are 70 variables per individual, the description of the collected variables is shown in **Appendix G**.

2.6 Data analysis

2.6.1 Classifying and calculating the incidence of SCD

The primary response variable used was the dichotomous value of likelihood of SCD (SCD - non SCD). This variable was defined based on the exclusion criteria, and the contributing factors of the study as described above (**Section 2.5)**, with a final decision made at the panel meeting assessment. There were several explanatory variables, which were collected directly from the ME files, **Appendix G**.

The SPSS statistical package was used to define SCD cases based on age group and sex. The overall, age and sex related incidence rates of SCD were calculated using the following equation

$$incidence\ rate\ per\ 100{,}000 = 100{,}000 \times \frac{n}{N}$$

Where n equals the number of SCD cases reported, and N equals the estimation of the provincial population. Statistics Canada estimation of the NL population was obtained by using CANSIM table 051-0001 [137]. The Confidence Intervals (CIs) for the incidence rates were calculated using statistical calculator provided by the Centre for Clinical Research and Biostatistics (CCRB) [138].

2.6.2 Comparing the incidence of SCD with worldwide studies

To compare the incidence rates resulted from our study with other worldwide studies for the same age group, I used SPSS to calculate Pearson Chi-square statistic ($\chi 2$) or Fishers Exact test (when required) and identify the significance (*p-value*)*. The calculation was performed based on the number of SCD cases reported in our study and comparable studies per capita. The results of our study was compared with other four studies which used a similar definition for SCD and conducted a close case ascertainment methods as described in **Tables 2.3** and **2.4**.

Table 2.3: Description of the worldwide studies that we compared our results to their results.

Country of study	Years of study	Definition of SCD	Source of information
Sweden [50]	1992-1999	1 hr if witnessed - 24 hrs if unwitnessed	Forensic autopsy database
Denmark [9]	2007-2009	1 hr if witnessed - 24 hrs if unwitnessed	Death certificates, hospital discharge records and autopsy reports
Ireland [39]	2005-2007	1 hr if witnessed - 24 hrs if unwitnessed	Death certificates and post mortem examination reports
Canada ON [29]	2008	1 hr if witnessed – or unexpected if unwitnessed	Coroner cases

*p-value: the threshold significance level was set as <0.05[139]

Table 2.4: The case selection methods used in the comparable worldwide studies

Country of study	Inclusion criteria	Autopsy rate in SCD population	Exclusion criteria
Sweden [50]	Natural death cases, both sexes, age group 15-35 years	Most of the SCD cases were autopsied	Excluded all unnatural cases, non-sudden ,extra cardiac causes of death, previous medical history (DM, epilepsy, alcohol or substance abuse), high risk behaviour or on medication (potentially arrythmogeneic), blood alcohol level > 22 mmol/l
Denmark [9]	All death cases that are sudden and unexpected, both sexes, age group 1-49 years	56 % of the cases were autopsied	Excluded all non-sudden, extra cardiac causes of death, cases with incomplete files, cases with competing causes (no details were provided)
Ireland [39]	All death cases that are sudden and unexpected, both sexes, age group 15-35 years	All SCD cases were autopsied	Excluded all non-sudden cases, non-autopsied SCD, extra cardiac causes of death, electrocution, drowning, poisoning, drug overdose, presence of cocaine in blood, epilepsy, blood alcohol level >22 mmol/l
Canada ON [29]	All natural–cardiac, natural–other, accidental, or undetermined death cases, both sexes, age group 2-40 years	Most of cases were autopsied	Excluded all non-sudden, extra cardiac causes of death, SCD cases with > 1 contributing factor (i.e. toxicology, alcohol, or hazardous conditions)

2.6.2.1 Comparison of SCD incidence in this study with Ontario (ON) study

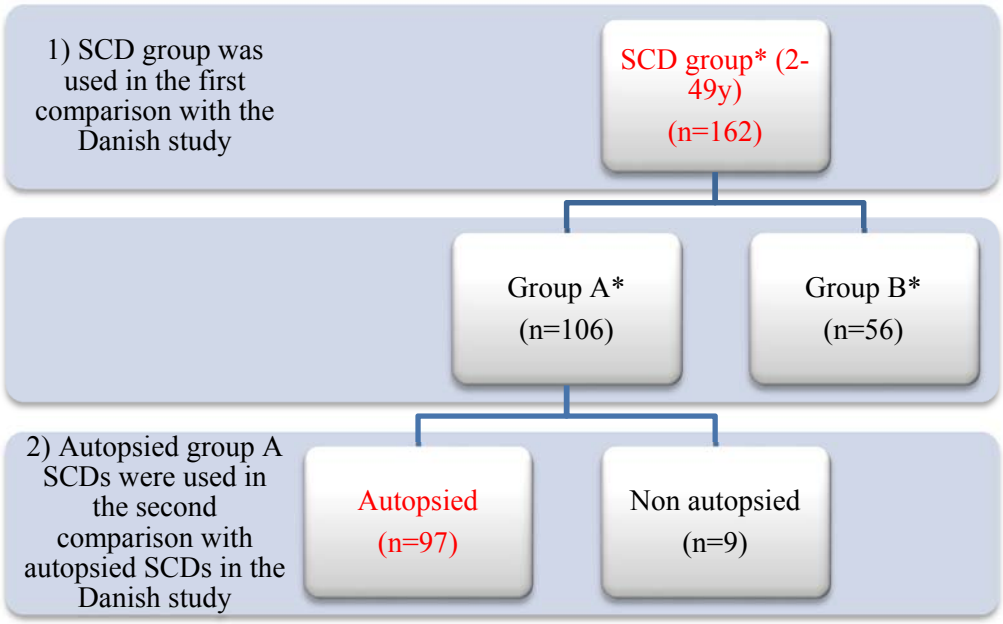
The incidence of SCD in the age groups: 2-18, 19-29, 30-40 and 2-40 years old were compared with ON study by Pilmer et al (2013) [29] for the same age groups. This is a direct comparison between the two provinces as both had a single tertiary location for the collection and maintenance of all forensic deaths, and the methodology to determine the likelihood or not of a death being supposed SCD was the same in both Provinces.

2.6.2.2 Comparison of SCD incidence in this study with Denmark study

The incidence of SCD in our population for the age group (2-49) years old was compared with the Danish study[9], which reported the incidence of SCD in young people (1-49) years old. In this comparison I calculated the incidence of SCD for the comparable age group using the equation mentioned in **Section 2.6.1**, and compared it with incidence of SCD reported in Denmark study using Pearson Chi-square statistic ($\chi 2$). Additional analysis was implemented to compare the incidence of SCD using group A* cases in which autopsy was completed in our study, with the incidence of SCD in the Danish study using only autopsied SCD cases. I performed the later analysis to get the populations in both studies comparable to each other and to increase the confidence of our results, **Figure 2.1**.

*Group A: natural or undetermined death with NO contributing factor.

Figure 2.1: Flow chart for the comparison of SCD with the Danish study



*SCD group: group A: natural or undetermined death with NO contributing factor; group B: natural or undetermined death with one contributing factor OR accidental deaths without any factor explaining the accident.

2.6.2.3 Comparison of SCD incidence in this study with studies from Sweden and Ireland

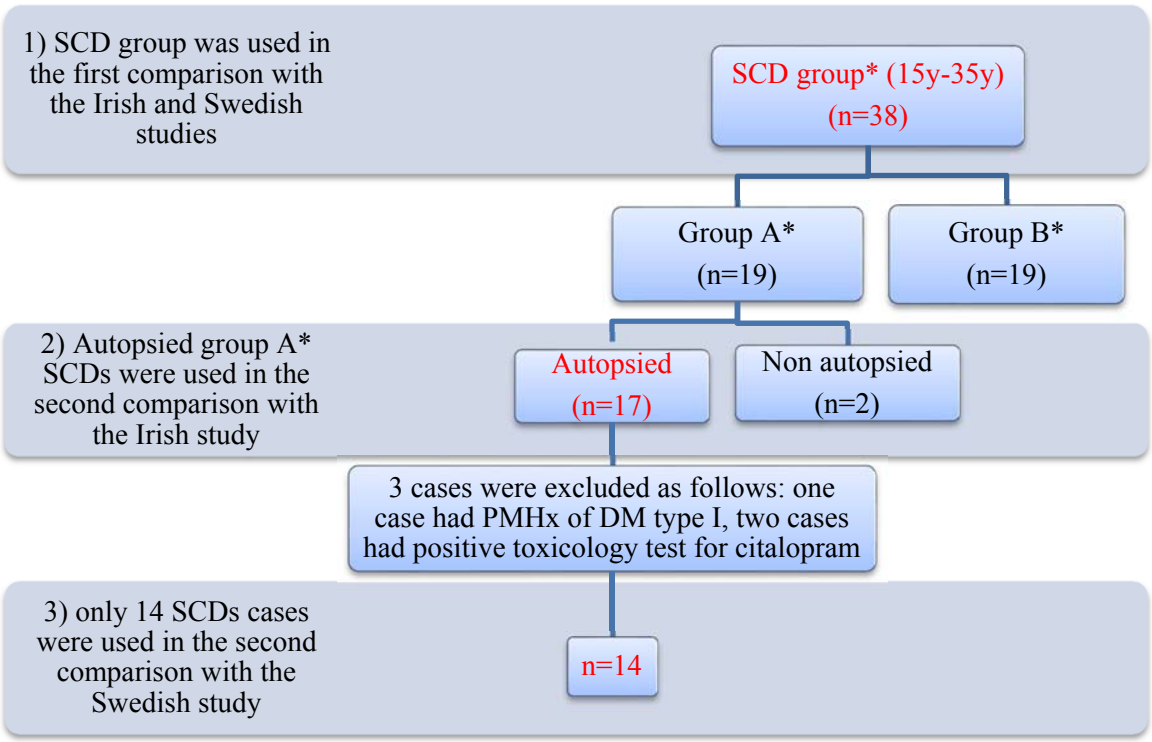
The incidence rate of SCD in the age group 15-35 years old was compared with the incidence rates reported in the Irish and Swedish studies [39,50] for the same age group. This comparison was completed in two stages: (1) The incidence of SCD reported in our study was compared with the incidence of SCD reported in the Irish and Swedish studies for the same age group [39,50]. (2) The analysis was rechecked to include only group A* autopsied SCDs from our data with the same criteria of SCD from Irish and Swedish

* Group A: natural or undetermined death with NO contributing factor.

studies [39,50]. However, by comparing the incidence of group A* autopsied SCD between our study and the Swedish study, three cases were excluded as follows: one case had a past medical history (PMHx) of DM type I (without end organ damage); and two cases had a positive blood test within therapeutic level for citalopram, which may induce cardiac arrhythmia [140]. I excluded these three cases and used only 14 cases, because as mentioned in **Table 2.4** such cases were excluded in Swedish study [50], accordingly we have tried to get further accurate comparison and get a very close ascertainment for SCD cases, **Figure 2.2**.

* Group A: natural or undetermined death with NO contributing factor.

Figure 2.2: Flow chart for the comparison of SCD with the Irish and Swedish studies



* SCD group: group A: natural or undetermined death with NO contributing factor; group B: natural or undetermined death with one contributing factor OR accidental deaths without any factor explaining the accident.

2.6.3 Underlying pathology of SCD

Descriptive statistics were used to obtain the number and percentage of medical causes of death in autopsied SCD cases. The mean of the coronary artery narrowing in autopsied cases, in which the cause of death was CAD, was also obtained, a bar chart that shows the mean and mode of CAD severity among the population was drawn as well.

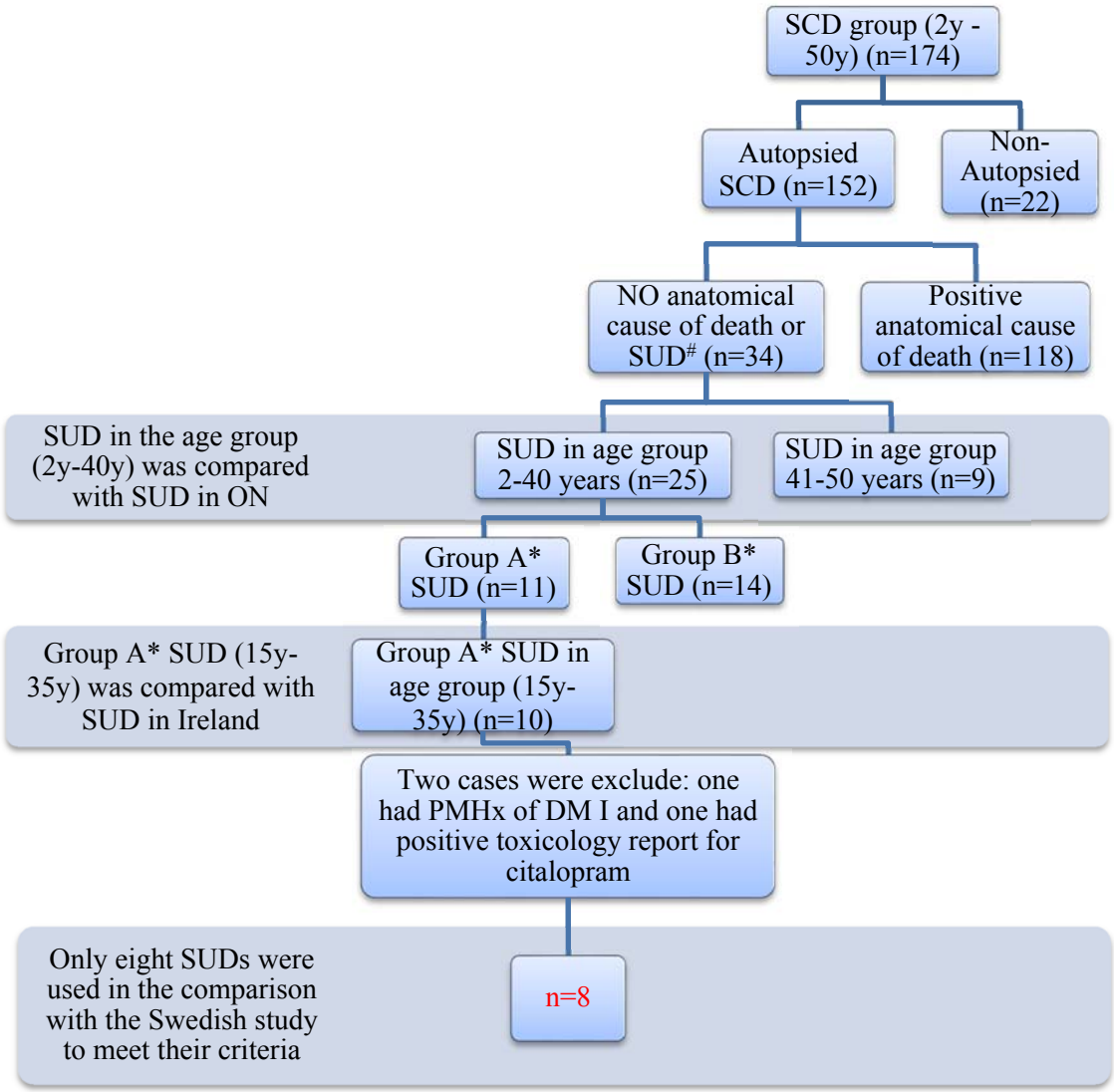
2.6.4 Incidence of SUD

SUD was defined as SCD where the autopsy finding was negative which leave malignant arrhythmias is as the most likely explanation. The incidence of SUD was calculated using the same methods mentioned in **section 2.6.1**. The incidence of SUD was also compared with the studies conducted in ON[29] , Denmark [9], Ireland [39] and Sweden [50] using Pearson Chi-square statistic ($\chi 2$) or Fishers Exact Test (when applied)**.**

The incidence of SUD in the age group 2-40 years old was compared with the incidence of SUD reported in ON study [29]. Moreover, the incidence of SUD in group A* among the age group 15-35 years old was compared with the incidence of SUD in Ireland [39] for the same age group. And the incidence of SUD among the age group (15-35) years was also compared with Swedish study [50]; however, in this comparison with the Swedish study I excluded two cases from the SUDs reported in our study to meet the Swedish study criteria. The excluded cases were as follow: one case with PMHx of DM type I without end organ damage, and the second one had a positive blood test for citalopram. As mention in **Table 2.4,** such cases were excluded in the Swedish study. Thus, I used only (n=8) SUD cases to increase the accuracy of our comparison. **Figure 2.3**.

*Group A: natural or undetermined death with NO contributing factor.

Figure 2.3: Flow chart for the comparison of SUD with the ON, Irish and Swedish studies



SUD = SCD with negative autopsy (likely arrhythmia)
* SCD group: group A: natural or undetermined death with NO contributing factor; group B: natural or undetermined death with one contributing factor OR accidental deaths without any factor explaining the accident.

The incidence of group A* SUD for the population (2-49 years) was compared with the incidence of SUD in Denmark [9]. In this analysis I used 12 out of 15 group A* SUDs described in our study and 30% (n = 41) of SUDs reported in Danish study [9], because of the positive toxicology test in those cases. So that we compared the SUD incidence rates between our study and Danish one after excluding the cases with a positive toxicology test, even though the illegal drugs were found in trace amount and the prescribed drugs were detected in therapeutic level. These incidence rates could represent the actual SUD incidence in both countries among people <50 years old, **Figure 2.4**.

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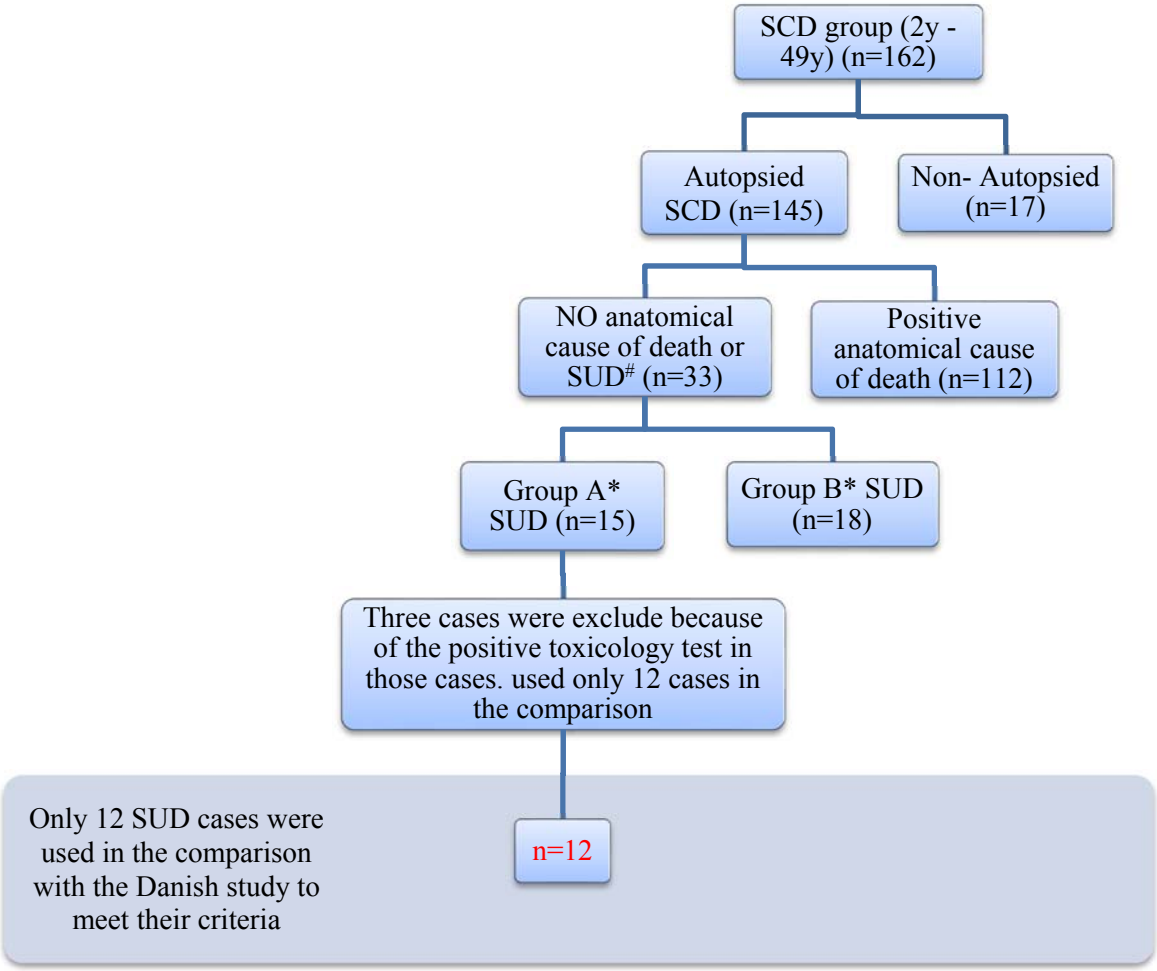
* SCD group: Group A: natural or undetermined death with NO contributing factor; group B: natural or undetermined death with one contributing factor OR accidental deaths without any factor explaining the accident.

Figure 2.4: Flow chart for the comparison of SUD with the Danish study.



SUD = SCD with negative autopsy (likely arrhythmia)
* Group A: natural or undetermined death with NO contributing factor; group B: natural or undetermined death with one contribut*ing factor OR accidental deaths* without any factor explaining the accident.
@ Only 40% of the cases were used in the comparison because of the positive toxicology test in the rest (60%) of the cases

Chapter 3: Results

3.1 Ascertainment of SCD cases

In this study, we collected deaths reported to the ME office during the period 2009 to 2013 with a manner of death listed as (natural, accident and undetermined). The population of this project included all the individuals in the NL province aged 2-50 years old.

During the studied period (2009-2013) inclusive, there were a total of 545 ME cases, in which 277 cases were excluded in the study based on the exclusion criteria explained in **Section 2.5**. The rest of the files (n=268 cases) were reviewed extensively and were classified into two categories (SCD and non-SCD) based on the contributing factors explained in **Section 2.5**, **Figure 3.1**.

As a result, a total of 174 deaths (64.9% of the eligible cases) were considered as SCD. This approximates to three SCDs per month in the (2-50 years) age group, over a five year period. The majority (77%, n=134) of the 174 SCD cases were males, this sex difference was statistically significant (*p*-value <0.0001), **Table 3.1**.

Figure 3.1: Flow chart of case selection process for ME cases

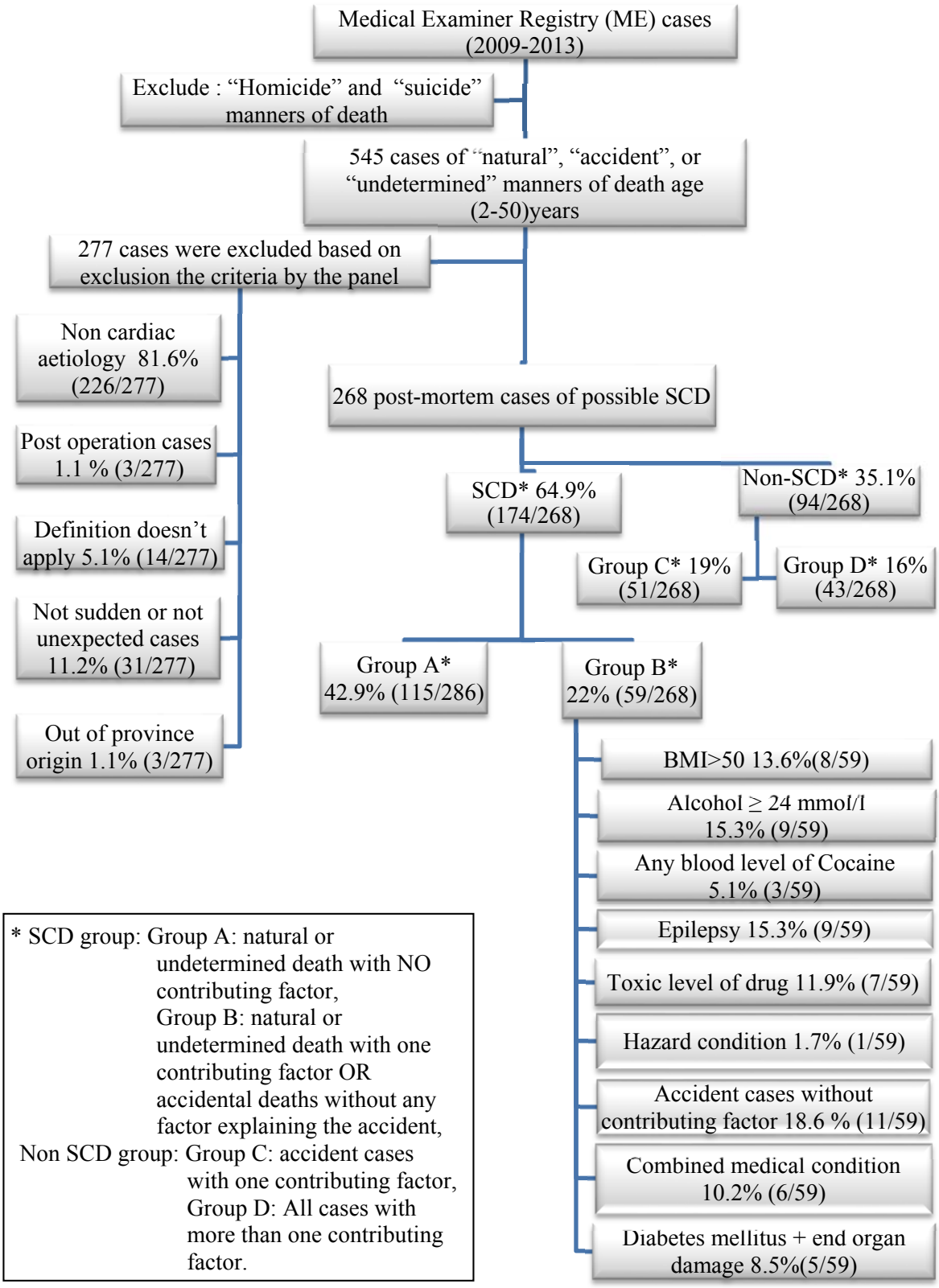


Table 3.1: Sex distribution of SCD group*

	2009	2010	2011	2012	2013	Total
Total Number	36	37	33	41	27	174
Male	30 (83.3%)	28 (75.7%)	25 (75.8%)	31 (75.6%)	20 (74.1%)	134 (77%)
Female	6 (16.7%)	9 (24.3%)	8 (24.2%)	10 (24.4%)	7 (25.9%)	40 (23%)

* SCD Group: group A: natural or undetermined death with NO contributing factor; group B: natural or undetermined death with one contributing factor OR accidental deaths without any factor explaining the accident.

3.2 Incidence rate of SCD

During the period 2009-2013 inclusive, the average incidence of SCD in the overall population (2-50 years old) was about 11 per 100,000 person-years (95% C.I: 9.47-12.75). This equated to a male incidence 3.2 times higher than females (16.3 vs 5.06 per 100,000 person-years). Also, the incidence of SCD was identified to increase with age, **Table 3.2**.

Table 3.2: Incidence rate of SCD group* by age group

Age group	Incidence rate per 100,000 person-years	95% C.I
2-18 years old	1.53	0.73-3.21
19-29 years old	4.6	2.82-7.52
30-40 years old	10.64	7.79-14.59
41-50 years old	27.12	22.55-32.66

* SCD Group: group A: natural or undetermined death with NO contributing factor; group B: natural or undetermined death with one contributing factor OR accidental deaths without any factor explaining the accident.

The number of SCD cases, population number and the incidence of SCD for each age group, year and sex is shown in **Appendices H, I, and J** respectively.

The incidence rate of SCD was compared with four other studies [9,29,39,50] using the same comparable age group as mentioned in **Sections 2.6.2**, **2.6.2.1**, **2.6.2.2**, and **2.6.2.3**. The incidence of SCD in NL was observed to be significantly higher than the incidence reported in ON [29], Denmark [9], Sweden [50] and Ireland [39] ; however, no significant difference was reported between our results and ON study [29] in the age group (2-18 years) as shown in **Table 3.3**.

Table 3.3: Comparing the incidence of SCD* with other studies

Age group	Incidence of SCD in our study per 100,000 person-years	Incidence of SCD in other studies per 100,000 person-years	P-value[$]
2-18	1.53	ON: 0.7	**0.082
19-29	4.6	ON: 2.4	***≤ 0.027
30-40	10.64	ON: 5.3	***≤ 0.0001
2-40	5.3	ON: 2.6	***≤ 0.0001
2-49	10.5	Denmark: 8.6	***≤ 0.017
15-35	5.78	Sweden: 1	***≤ 0.0001
15-35	5.78	Ireland: 2.85	***≤ 0.0001

* SCD Group: group A: natural or undetermined death with NO contributing factor; group B: natural or undetermined death with one contributing factor OR accidental deaths without any factor explaining the accident.
$ P-value: the threshold significance level was set as <0.05[139]
: Fisher Exact Test, *: Pearson Chi-Square, detailed SPSS analysis shown in **Appendix K**.

The incidence of SCD was also compared with the Danish [9], Swedish [50] and Irish [39] studies using the strict ascertainment methods mentioned in **Sections 2.6.2.2** and **2.6.2.3**. The incidence rates of SCD in our study were significantly higher than the incidence rates stated in the Sweden [50] and Denmark [9] studies, however; there was no significant difference between our study and the Irish study [39], **Table 3.4**.

Table 3.4: Comparing the incidence of SCD using the strict ascertainment methods with other studies

Age group	Incidence of SCD in our study per 100,000 person-years	Incidence of SCD in other studies per 100,000 person-years	P-value[$]
2-49	6.3[a]	Denmark: 4.2	[b] ≤ 0.0001
15-35	2.13[a, c]	Sweden: 1	[b] ≤ 0.01
15-35	2.58[a]	Ireland: 2.8	[b] 0.7

$ P-value: the threshold significance level was set as <0.05[139]
a: Using only autopsied group A SCDs (group A: natural or undetermined death with NO contributing factor), **b**: Pearson Chi-Square, **c**: After excluding three cases: one case had PMHx of DM type I, two cases had positive toxicology test for citalopram, detailed SPSS analysis shown in **Appendix L**

3.3 Causes of SCD in the SCD group

The pathological causes of SCD were confirmed in 87.4% (n=152) of the SCD group* cases by autopsy reports, while in the rest of non-autopsied cases (n=22) the cause of death was reported based on the confirmed PMHx (three cases of CAD, three cases of CHD, and one case of valvular hear disease) or based on the circumstance of death (sudden and unexpected with positive cardiac risk factors).

In the SCD autopsied cases, the most common finding was CAD (57.9%), and the second most common (21.7%) cause was morphologically normal heart with suspected arrhythmia, **Table 3.5**.

* SCD Group: group A: natural or undetermined death with NO contributing factor; group B: natural or undetermined death with one contributing factor OR accidental deaths without any factor explaining the accident.

Table 3.5: Causes of death in autopsied cases in SCD group*

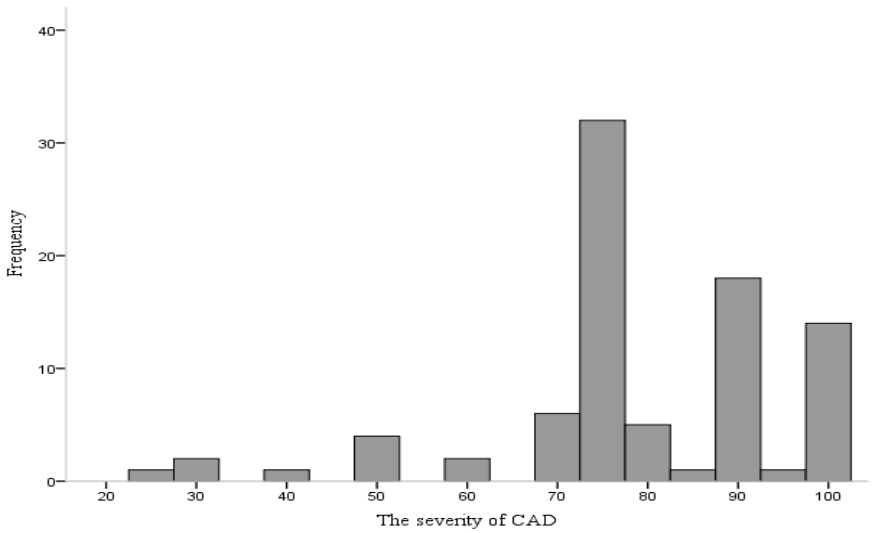
Cause of death	Number of cases (Total=152)	Percent (%)
Coronary artery disease	88	57.9
No anatomical cause	34	22.4
Others**	20	13.2
Cardiomyopathy	7	4.6
Congenital heart disease	3	2.0

* SCD Group: group A: natural or undetermined death with NO contributing factor; group B: natural or undetermined death with one contributing factor OR accidental deaths without any factor explaining the accident.
**others: includes endocarditis and valvular hear disease

About five percent of SCD in NL is attributed to cardiomyopathy these cases were as follow: five cases were reported as ARVC with positive pathological findings (fatty infiltration of the myocardium, inflammatory infiltration, and fibrofatty replacement), however the genetic testing for TMEM 43 founder mutation was confirmed in two cases only. The other two cardiomyopathy cases were stated as hypertrophy cardiomyopathy (HCM) with positive pathological finding for left ventricular hypertrophy (LVH > 2 cm), and no genetic testing were performed on those cases.

The severity of CAD was reported in 87 out of 88 CAD cases, the mean CAD narrowing was estimated to be 78.9% and the most frequent CAD narrowing (the mode) was 75%, **Figure 3.2**. In one case there was no coronary artery narrowing defined on autopsy, and the underlying pathological cause of death was reported as small vessels myocardial disease by the pathologist, and was classified in the CAD category by the chief medical examiner.

Figure 3.2: Severity of CAD in autopsied cases in the SCD group



3.4 Incidence rate of SUD

SUD cases were defined as SCD cases in which autopsy and toxicology test failed to detect the cause of death, and malignant arrhythmias was believed to be the cause of death. We reported 34 SUD cases in the SCD group* and the annual incidence was 2.1 per 100,000 persons (95% C.I: 1.5 - 3), this comprised of males (2.4 per 100,000 persons, 95% C.I: 1.5-3.7) and females (1.9 per 100,000 persons, 95% C.I: 1.2- 3.1). However, only 15 SUD cases were detected in group A* among the total population (2-50 years old). Men had the higher percentage of overall SUD (n=11, 73.3%) in comparing with women. Moreover, the annual incidence of SUD in the group A* among different age group was reported in **Table 3.6**. The highest incidence of SUD was stated in the age group 15-35 years old.

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* SCD Group: Group A: natural or undetermined death with NO contributing factor; group B: natural or undetermined death with one contributing factor OR accidental deaths without any factor explaining the accident.

Table 3.6: Incidence rate of SUD# in the group A* by age group

Age group	Incidence rate per 100,000 person-years	95% C.I
2-40 years old	0.94	0.5 - 1.7
2-50 years old	0.95	0.6 - 1.6
15-35 years old	1.5	0.8 - 2.8

SUD = SCD with negative autopsy (likely arrhythmia)
* Group A: natural or undetermined death with NO contributing factor.

The incidence of SUD was compared with the incidence of SUD in Ontario [29], Denmark [9], Ireland [39] and Sweden [50] using the methods explained in **Section 2.6.4**. The results of the comparison are shown in **Table 3.7**.

Table 3.7: Comparing the incidence of SUD# with worldwide studies

Age group	Incidence of SUD in our study per 100,000 person-years	Incidence of SUD in other studies per 100,000 person-years	P-value[$]
2-40	[a] 2.1	Ontario: 0.73	[b] ≤ 0.0001
15-35	[c] 1.5	Ireland: 0.76	[b] ≤ 0.05
15-35	[c, d] 1.2	Sweden: 0.22	[b] ≤ 0.0001
2-49	[c, e] 0.78	[f] Denmark: 0.39	[b] ≤ 0.03

#SUD = SCD with negative autopsy (likely arrhythmia)
$ P-value: the threshold significance level was set as <0.05[139]
a: Using SUD cases in the SCD group: group A: natural or undetermined death with NO contributing factor; group B: natural or undetermined death with one contributing factor OR accidental deaths without any factor explaining the accident.
b: Pearson Chi-Square, **c**: using only group A SCD cases, **d**: after excluding 2 cases from SUD group A as follows: PMHx of DM I and positive toxicology report for citalopram, **e**: after excluding 3 cases from SUD group A with positive toxicology report, **f**: after excluding 70% of the cases (n=94) with positive toxicology report, detailed SPSS analysis shown in **Appendix M**.

The incidence of SUD in NL in young (2-50) years old was identified to be statistically significant higher than any reported incidence of SUD worldwide among different age groups, taking into consideration the difference in the ascertainment methods.

Chapter 4: Discussion and Conclusion

Sudden cardiac death is considered to be the most common mode of death in developed countries [2,141]. An accurate estimation of SCD incidence, etiology, and potential risk factors could help preventing this devastating event. The purpose of this thesis was to investigate the scope and nature of SCD among young people (2-50) years old in NL.

By using the ME registry data including autopsy reports, we have conducted a retrospective population based study on SCD in NL during the period from 2009 to 2013. The method of case selection and the definition of SCD followed in this project was used previously [29]. The aim of this study was to report the incidence rates of SCD and SUD (SCD with negative autopsy (likely arrhythmia)); categorize the SCD cases based on the age group, sex and underlying cardiac pathology; as well as compare the incidence of SCD and SUD in NL with other studies.

We have identified 174 deaths as SCD group including autopsied and non-autopsied cases. The overall annual incidence rate was 11 per 100,000 person-years, however the incidence dropped to 6.38 per 100,000 person-years by using only autopsied group A (natural or undetermined death with NO contributing factor) SCD cases. Furthermore, the incidence of SUD in the whole population (2-50) years was 2.1 per 100,000 persons, and the incidence of SUD declined to 0.94 per 100,000 person years by using only group A (natural or undetermined death with NO contributing factor) SUD cases.

The risk of SCD increased with age and primarily was observed in men. The most common pathological findings in SCD cases were CAD (57.9%) and morphological normal heart or arrhythmia (21.7%). When we compared our results with the reported incidence rates in worldwide studies we found a statistically significant difference in most incidence rates of SCD and SUD (.SCD with negative autopsy (likely arrhythmia))

The reported incidence of SCD in our population (2-50) years old is considered to be higher than the incidence rates reported by others [9,29,142,143], even when only autopsied group A (natural or undetermined death with NO contributing factor) cases were used in our calculations. This result confirmed our hypothesis where our assumption was that the NL population had a high incidence of SCD. The high incidence of SCD in NL could be explained by the potential genetic risk factors, taking into consideration that NL is a founder population and several founder mutations in multiple genes, which cause SCD, have been identified previously in this population [19-21]. However, multifactorial risk factors should be considered as well, such as obesity, considering the fact that NL has the highest obesity and overweight percentages when compared to other provinces in Canada [120]. It has been reported in several epidemiological studies that obese people have approximately twice the risk of SCD, when compared with age matched control groups [144]. Obesity has been evidenced to increase the risk of atrial fibrillation, changes in QTc duration, and SCD [145,146]. It is also shown that obesity is associated with a variety of ECG abnormalities including prolonging QT interval, which increases susceptibility to ventricular arrhythmia and SCD [147]. These electrophysiological abnormalities in obese people's hearts are usually caused by the fatty infiltration / degeneration of the conducting nerve system in the heart, which may lead to lethal arrhythmias and SCD [148],

or the free fatty disposition in the myocardium that would lead to cell injury and death [149].

In addition, obesity may contribute to SCD through atherosclerosis and cardiovascular events, DM, and hypertension [150]. Despite these association between obesity and SCD, very few epidemiological studies have examined this association and further investigations need to be conducted [147]. Therefore, future studies should explore the genetic and non-genetic factors that may contribute to the SCD among NL population.

Sex may be another significant factor in SCD. In our research project, we reported that men had the greater percentage of SCD cases (n=134, 77%). This finding and the male to female ratio of 3:1 of SCD supports other studies that reported a similar ratio [29,39,50]. For example, Pilmer et al (2013) [29] reported a high incidence of SCD in males compared to females (76% vs. 24%), and Margey et al (2011) [39] stated that most SCD cases in their study occurred in men (77.5% vs. 22.5%), and in the Swedish study [50], SCD in males accounted for 73% of the total SCD cases. Therefore, these results may confirm the influence of sex hormones on the risk of SCD in young people.

Age may also have an important role in SCD, in the current study, we have identified an increased incidence of SCD with age. Interestingly, our findings were in agreement with the results reported by other investigators [29]. The incidence of SCD in our study gradually increased throughout different age groups. In particular, the incidence of SCD was detected to be 1.53 per 100,000 person-years in the age group (2 to 18 years), 4.6 per 100,000 person-years in the age group (19 to 29 years), 10.64 per 100,000 person-years in the age group (30 to 40 years), and 27.12 per 100,000 person-years in the age group (41-50 years). A similar finding reported in Pilmer et al (2013) study [29]. So our results confirmed the general agreement that SCD increases with age [29,45] .This finding

could be also explained by the confirmed association between the elevation in the risk of CAD with age [151].

The two most common underlying cardiac pathologies reported in SCD autopsied cases, which accounted for 87.4% (n=152 cases) of the total cases, were CAD (57.9%) with a mean coronary stenosis of 78.9 %, and morphologically normal heart and presumed arrhythmia (21.7%) of the SCD cases. While cardiomyopathies, CHD and other cardiac pathologies reported in the rest of the cases (20.4%), however; ARVC accounts for 3.3 % of SCDs in our population which is close to the reported incidence in the comparable Danish study[9]. CAD is known as the most common structural cardiac cause of death in populations younger than 50 years, however it accounted for only one third of the cases as reported by other studies [9,142,143,152] . The high percentage of CAD reported in our study (57.9%) could be explained by two points. First, the high prevalence of obesity [153] and the high fat, sugar and salt consumption, and the low fresh foods intake [154] in NL population may increase the risk of cardiovascular heart diseases and CAD, and consequently increase the risk of SCD. Second, the genetic structure of the NL population may increase the prevalence of the variants accounted for increasing the risk of SCD in people with CAD [73]. Even though, the percentage of morphologically normal hearts or arrhythmias reported in our study is considered to be lower than the percentage reported by other studies [9,29,39] , the incidence of SUD (SCD with negative autopsy (likely arrhythmia)) calculated in our study population was significantly higher than incidence rates reported in other studies among different age groups (**Section 3.4)**.

In this research project we performed a direct comparison by using Pearson Chi-square statistic ($\chi 2$) between our study and the studies conducted in Denmark, Ireland,

Sweden, and Canada ON. However, comparing SCD incidence rates between studies is generally difficult due to variations in case definition, method of ascertainment, post mortem rates, and the ethnic variations among the studied populations. Thus I compared the incidence of SCD and SUD (SCD with negative autopsy (likely arrhythmia)) with its measures in other studies that used a similar definition for SCD mentioned in **Section 2.5**, and used a close methodology of case ascertainment. Though, special case ascertainments were used when applicable.

Initially, by comparing the incidence rates of SCD with ON study [29], which used a similar methodology of ascertainment, statistically significant differences were reported between both studies in the age groups (19-29, 30-40, and 2-40 years old) (**Section 3.2**). No statistically difference was reported between both studies in the age group (2-18 years), which could be explained by the low incidence rate or small sample size in this age group, however this result came in agreement with the previous study [134]. In addition, a statistically significant difference (p-value < 0.05) was reported between both studies regarding to the incidence of SUD in the age group (2-40 years old) as mentioned in **Section 3.4**. These significant differences in the SCD and SUD (SCD with negative autopsy (likely arrhythmia)) incidence rates could be explained by the difference in the ethnicity structure of both populations, considering that ON population is more diverse when compared with the NL population, which is more homogenous.

Furthermore, when we compared our incidence results with the Danish study [9], statistically significant differences were reported in the incidence rates of SCD and SUD between both studies, taking into consideration the differences in the ascertainment methods (**Sections 2.6.2.2 and 2.6.4**). Since the Danish population showed high levels of

genetic homogeneity [155], these differences in the incidence rates of SCD and SUD could be due to the data sources used in the Danish study [9] or due to non-genetic risk factors.

The low autopsy rate reported in the Danish study [9] (56%) and the use of a non-centralized database could affect the accuracy of estimating the incidence of SCD in the Danish study [9]. Moreover, the Danish population has a low obesity rate among adults when compared to the NL population (19.3% [156] vs. 35.2% [120]), which may play an important role in elevating the risk of SCD in NL when compared with Denmark.

On the other hand, by comparing the incidence rate of SCD between our results and the Irish study findings [39], there was no statistical significant difference in the incidence of SCD between both studies, which may reflect the Irish influence on the genetic heritage and the lifestyle of Newfoundlanders [157]. In addition, the Irish population is considered to be one of the most obese populations in Europe (27%) [158], hence this fact may also explain the close incidence rates between our study and the Irish one [39]. However, a statistically significant difference was reported in the incidence rate of SUD (SCD with negative autopsy (likely arrhythmia)) between our study and the Irish one, which may be explained by the genetic drift phenomena in NL population [133]. Because of this drift, the NL population may have an elevated incidence of particular genetic disorders, and SUD that is caused by inherited cardiac channelopathies could be one of those genetic disorders.

Finally, when we compared our study with the Swedish study, statistically significant differences were reported in the incidence rates of SCD and SUD. These differences could be explained by the different inclusion and exclusion criteria used by both studies. In particular, in the Swedish study all the accident cases were excluded and

only natural manner of death cases were included in the downstream analysis of the study, whereas in our study, all accidents and natural manner of death cases were included in the study. Since a significant number of MVA and drowning are caused by cardiovascular events [122,124], excluding the accident cases may underestimated the incidence of SCD as shown in the results of the Swedish study. Furthermore, based on the WHO statistics, the obesity rate in Sweden is 20.5%, [156] which is lower than the obesity rate in NL (35.2%) [120]. Therefore, the difference in data source and obesity rates may explain the differences in the incidence rates of SCD and SUD (SCD with negative autopsy (likely arrhythmia)) between both studies.

Similar to other studies used retrospective post mortem data, the present study has some strengths and limitations. The strengths of the study are as follows; a) the definition of SCD employed in this study was clearly stated since it is the most acceptable definition of SCD used so far ; b) the comprehensive and systematic nature of the data collection method was applied in a well-defined population without ascertainment bias; c) the use of a centralized database that contain all forensic data and autopsy reports from throughout the province, we captured up the vast majority of SCDs occurred in NL; d) the data is sufficient to provide an accurate estimation for SCD incidence rate, since the data includes death certificates, post mortem examination reports (external and internal), and other documents that explain the incident of SCD in detail; and e) we have tried to estimate the maximum number of SCD cases by reviewing accidental cause of death cases including drowning and MVA, which may have been directly precipitated by fatal arrhythmias.

The limitations of this study are similar to those reported by other studies such as; a) the retrospective nature of the study; b) the ME data used in this project focuses on the cause of death, and obvious issues from the medical charts are not acceded. However in the future of this research, we will obtain a consent to review medical records; c) lack of autopsy examination in some cases, although; autopsy was performed in ~ 87.4 % of the cases, and this number is considered higher than the autopsy rates reported in other postmortem population based studies [9,143,159], d) the lack of molecular autopsy in some undetermined manner of death cases. In the upcoming steps of this research, we will obtain a consent from family members of the victims to conduct molecular autopsy; e) we may have underestimated the incidence of SCD, because we excluded all the cases in which the definition doesn't apply (i.e. unwitnessed cases that were last seen alive >24 hours or witnessed cases with symptoms > 1 hour) and we missed the cases of residents who suffered SCD while travelling out of province; f) ECGs were not available before death, thus we couldn't evaluate LQTS or other arrhythmogenic disorders; g) there was no expert cardiac pathologist reviewing the files; and h) even though post mortem and autopsy examination guidelines are available through the college of physicians and surgeons of NL, autopsy were usually performed in local hospitals, and variations in the quality of the examination and reports may occur, however all the reports in the province were validated by the chief medical examiner Dr. Simon Avis, which may minimize the variations among the reports throughout the province.

In conclusion, this study is one of the first studies to identify and characterize SCD in young people (2-50 years) in the province of Newfoundland and Labrador. We have reported a high overall incidence rate of 11 per 100,000 persons for the years 2009-

2013. The incidence of SCD increased with age and the most common causes of SCD were CAD followed by SUD (SCD with negative autopsy (likely arrhythmia)). Because CAD and SUD are preventable, strategies need to be set to prevent such occurrence as possible.

Our future plans aim to a) include data from 17 years (1997-2013); b) obtain DNA samples from the stored forensic tissues to asses known NL mutations causing SCD and assess the molecular causes of death in those most likely to be SCD in this cohort; c) assess the level of obesity in the SCD cohort and to examine the relationship between obesity and SCD; and d) determine any temporal changes in causes of death over the 17 years of data. We are planning in the near future to detect the possible potential genetic risk factors of SCD in NL. We expect to discover unique variants that may play an important role in increasing the risk of SCD and SUD among NL population, which is a founder population, thus detecting novel variants more significant than other populations. Because of the limitation of the available data and current guidelines regarding the molecular autopsy, the selection of cases for a molecular autopsy is not a uniform in the clinical practice. Therefore the future steps of this research will have a potential impact on the Medical Examiner guidelines by considering a molecular autopsy as a standard of care in all sudden unexplained deaths.

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Appendix C: Copy of final report

Newfoundland & Labrador
Office of the Chief Medical Examiner

Form ME 3

FINAL REPORT

File Number _____

Name _____ Age _____ Sex _____ Date of Birth _____

Date of Death _____ Place of Death _____

Address _____

Occupation _____

Immediate cause of death (a) _____
DUE TO or as a consequence of

(b) _____
DUE TO or as a consequence of

Other significant conditions contributing to the death but not casually related to the immediate cause (a) (c) _____

Autopsy: Yes No Name of Pathologist _____

Manner of Death: Natural _____ Accident _____ Suicide _____ Homicide _____ Undetermined _____

Circumstances of Death:

In your opinion was this death preventable? Yes No

Public inquiry recommended Yes No

Comments:

Name and Address of attending Physician _____

Date body released _____ Funeral Home _____

I, _____ a medical examiner for the Province of Newfoundland and Labrador, appointed under the Fatalities Investigations Act, do certify that I did make all reasonable investigations to ascertain the cause and manner of death and that the facts contained herein regarding the death are true and correct to the best of my knowledge and belief.

_____ _____ _____
Medical Examiner Date Chief Medical Examiner

Appendix D: Copy of external examination report and autopsy protocol

Newfoundland & Labrador
Office of the Chief Medical Examiner

Form ME 2

EXAMINATION REPORT

Name _____ File Number _____

Age _____ Sex _____ Race _____ Place of Exam _____

Date of Death _____ Date of Examination _____

Clothing:

Valuables:

Disposition of Valuables _____
Evidence of Injury:

Evidence of Treatment:

Height ____ Weight ____ Tattoo or distinguishing marks _____

Lividity: Present ____ Absent ____ Back ____ Front ____ Left ____ Right ____

Color: Normal ____ Other _____ Fixed: Y N

Rigidity: None ____ Slight ____ Moderate ____ Full ____

Hairline: Normal ____ Receded ____ Head Hair: Color _____ Length _____

Body Hair: Male ____ Female ____ Average ____ Reduced ____ Preadolescent ____

Scalp _____ Ears _____

Eyes: Closed _____ Open _____ Color _____ Arcus _____

Conjunctiva _____

Nose _____ Mouth _____

Teeth: Natural: Upper _____ lower _____ Edentulous: upper _____ lower _____

Face _____ Neck _____

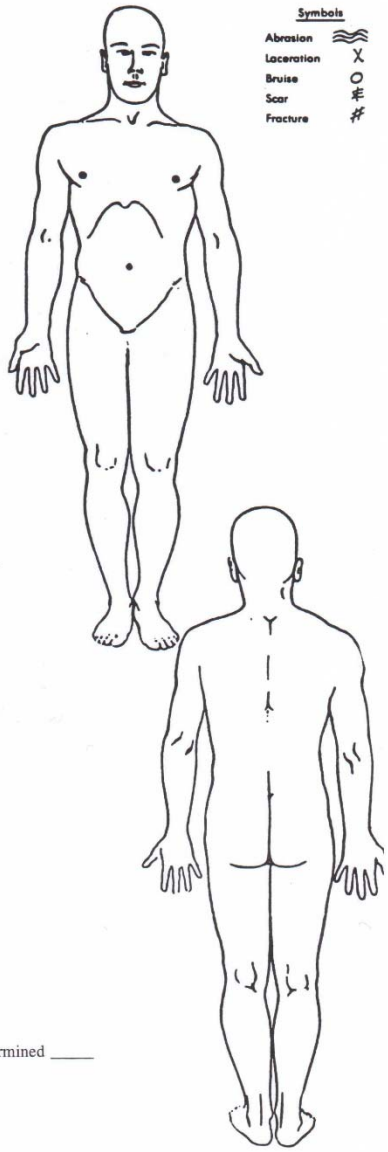
Chest _____ Abdomen _____

Back _____ Genitalia _____

Upper limbs _____ Lower limbs _____

Toxicology: Yes _____ No _____

Summary (History and relevant findings):



Cause of Death _____

Manner of Death: Natural _____ Accident _____ Suicide ____ Homicide _____ Undetermined _____

I hereby certify that I have examined the body and, in my opinion its appearance and the circumstances surrounding death indicate that the named person died on the above date and from the causes and manner stated herein.

_____ Medical Examiner

_____ Print Name

_____ Chief Medical Examiner

AUTOPSY PROTOCOL

CASE NUMBER _____ NAME OF DECEASED _____

AGE _____ SEX : _____ IDENTIFICATION _____

AUTHORITY _____ INVESTIGATOR _____

FINGERPRINTS _____ PHOTOGRAPHY _____

DATE OF DEATH _____ EXAMINATION DATE _____

PATHOLOGIST _____ ASSISTANT _____

TIME BEGAN _____ TIME FINISHED _____

AUTOPSY _____ INSPECTION _____

CLOTHING 1)
2)
3)
4)
5)
6)
7)
8)
9)

Abbreviations
CW -cut away prior to receipt
R -removal prior to receipt
D -defect (gsw, knife)
B -blood-stained
T -torn
F -soiled with feces
U -urine-stained
WM -white metal
YM -yellow metal

OTHER ITEMS WITH OR UPON BODY (NOT Rx) NO JEWELRY

EXTERNAL EXAMINATION

Development: Normal Other _____

Race: White Black Other _____

Sex: Male Female Fetus Infant Child Adolescent

Build: Slight x Average x Large/Muscular/Heavy set

Age: _____ apparent; recorded ____ years mths. weeks days

Length: _____ feet _____ ins. _____cm. crown-heel_____
crown-rump _____ chest_____ head_____

Nutritional status: Emaciated x Average x Obese Very Obese

Weight: _____ lbs. _____ kg. Unclothed Clothed

Preservation: Good Very early Early Moderate Advanced Bones

Embalmed: No Yes

Lividity: Absent Reduced Ill-defined Developed Well-Developed

Back Front Right Left Upper Lower Patchy

Color: Normal Other_____

Rigidity: None Slight Moderate Full/Well Marked/Muscular

Case # _____

Hairline: Normal Receded _____ ins. On top Back of head

Head hair: _____
amount character color length (max) ins.

Eyebrows: _____

Beard: _____ Moustache: _____

Body hair: Male Female Preadolescent Slight Average Plentiful

Scalp: _____

Ears: _____ Lobes pierced: right x ____ left x _____

Eyes: Closed Open Clear Slightly cloudy Cloudy Opaque

Irides _____ Arcus _____ Pupils _____ mm

Lens opacities _____ Other _____

Nose: _____

Mouth: _____

Teeth: Edentulous Natural Dentures: Upper Lower

Face: _____

Neck: _____

Pectoral Area/Breasts: _____

Abdomen: _____

Limbs: Equally Symmetrically Developed _____

Genitalia: Circumcised _____ Uncircumcised _____

Back/Buttocks: _____

Markings:

Scars: (diagram as required)

Tattoos: (diagram as required)

Other surface features:

Case # _____

Photos taken: Yes ____ No ____ Police ____ Personal _____

Medical Record Seen: No _____ Yes _____

Medications with body: No _____ Yes _____ See list _____

Evidence Submitted: No _____ Yes _____

Handwashings Head hair Standard Clothing Fingernail Clippings

Rape Kit Paint chips Glass Fibers Hairs

Shot Wads _____ Gunpowder Bullet(s) x _____

Evidence of Treatment
(diagram as required)

Evidence of Injury
(diagram as required)

Case # _____

Internal Examination

Brain _____ gm

Heart _____ gm

R. Lung _____ gm

L. Lung _____ gm

Liver _____ gm

Spleen _____ gm

R. Kidney _____ gm

L. Kidney _____ gm

R. Pleural _____ ml

L. Pleural _____ ml

Pericardial _____ ml

Peritoneal _____ ml

Stomach _____ ml

_____

Bladder _____ ml

_____

Gall bladder _____ ml

Body wall fat ____ in. (max)

Appendix: Present Absent

Uterus _____

Tubes _____

Ovaries _____

Special Notes:

Head

Central Nervous System

Neck

Cavities

Cardiovascular

Respiratory

Hepatobiliary

Lymphoreticular

Urinary

Genital

Gastrointestinal

Endocrine

Musculoskeletal

Miscellaneous

Appendix E: Copy of scene report

Newfoundland & Labrador
Office of the Chief Medical Examiner

Form ME 1

SCENE REPORT

File Number _____

Name _____ Age ____ Sex ____ Date of Birth _____ Race _____

Address _____ Phone _____

Occupation _____ Employer _____

Next of kin _____ Address _____ Phone _____

Relationship _____ Notified _____ By _____

Source of identification _____ Positive _____ Tentative _____ Unknown _____ Confirmed _____

Place of Death _____ Hospital: DOA ER OR PORR Inpatient Nursing home

Last seen alive _____ Time _____ By _____ Phone _____

Death occurred _____ Time _____ Witness _____ Phone _____

Found dead _____ Time _____ By _____ Phone _____

Pronounced _____ Time _____ By _____ Phone _____

Incident of trauma _____ Date _____ At work _____ Location _____

Doctor at scene _____ Name _____ Officer at scene _____ Name _____

Attending or Family Physician _____ Address _____

Pertinent Medical History:

Circumstances surrounding death:

Scene diagram

Temperature _____ Outside weather _____

_____
Signature of Officer or Medical Examiner

Appendix F: Extraction Form*

Data Collection	
Autopsy #	
Study Number	
Postal Code	
Year of Birth	
Date of death	
Sex	
Height (cm)	
Weight (kg)	
BMI	
Manner of Death	
Death Factor	
Medical Cause of Death	
Underlying pathology (pick 1 or more)	
Previously known cardiac disease	
If yes, indicate underlying pathology (pick 1 or more)	
If yes, indicate additional information of interest (testing performed, previous health records)	
Cardiac risk factors	
Other potentially contributory medical conditions	
Medications before death	

*This form was designed by **Gina Hamilton** (a master student who assented a direct comparison between cases of SCD in NL in 2008 with a comparable study in Ontario from the same year. This data doesn't overlap with this thesis)

Non-prescription or recreational drugs (not including vitamins)	
Circumstances/location of death	
Activity level at onset of fatal event	
Specify if known	
Symptoms in preceding 24 hours	
If symptoms, circumstances (same definitions as above)	
Symptoms prior to preceding 24 hours	
If symptoms, circumstances (same definitions as above)	
Were symptoms preceding death investigated?	
List/summarize medical investigations/test results:	
Reported family history of sudden death or arrhythmia	
If yes, circumstances of death	
If positive family history of sudden death, closest affected individual	
Genetic Testing?	
Additional comments from the narrative	

Appendix G: The description of the collected variables.

Study number	I gave a number for each case to define them
Study year	The year in which the file was created
Autopsy number	ME file number
Address	As listed in the final report
Year of birth	The year of birth of the subject as listed in the final report
Age at death	The age of the subject at death as listed in the final report
Date of death	The date of death of the subject as listed in the final report (dd/mm/yyyy)
Sex	1) Male 2) Female
Height	As listed in the autopsy report (cm)
Weight	As listed in the autopsy report (Kg)
BMI	Calculated based on the weight and height (Kg/m^2)
BMI categories	1) <19.9 (underweight) 2) 20-24.9 (normal) 3) 25-29.9 (overweight) 4) 30-34.9 (obese) 5) >35 (morbid obese)
Manner of death	1) Natural-cardiac 2) Accident 3) Undetermined 4) Natural-other 5) Natural-central nervous system (CNS) 6) Natural-gastrointestinal (GI) 7) Natural-genitourinary (GU) 8) Natural-musculoskeletal 9) Natural-respiratory 10) Natural-hepatobiliary systems 11) Natural-endocrine
Medical cause of death	As listed in the final report
Underlying pathology	1) CAD 2) Congenital heart disease (CHD) 3) Cardiomyopathy 4) Unknown or no anatomic cause of death, 5) Other
Previously known cardiac disease	1) Yes 2) No
If previously known cardiac disease present: indicate the underlying pathology	1) CAD 2) CHD 3) Cardiomyopathy 4) Valvular heart disease 5) Other

If previously known cardiac disease present indicate details about the cardiac history	A details about the past cardiac history were provided based on the medical charts, scene report and final reports
Cardiac risk factors	1) Smoking 2) DM 3) Hypertension (HTN) 4) Elevated blood cholesterol 5) Obesity (BMI>30)
Presence of any other potentially contributory medical conditions based on investigating coroner information	1) Yes 2) No
If any other potentially contributory medical conditions present: list all the medical conditions	Details about the medical conditions were provided based on the final report, scene report and medical charts
Presence any medications prescribed before death	1) Yes 2) No
If medications prescribed before death list all medications	Details about all medications prescribed before death as listed in the final report, medical charts and scene report
Presence any non-prescription or recreational drugs (not including vitamins) in the blood based on the toxicology reports	1) Yes 2) No
If any non-prescription or recreational drugs present: list them	Details about any non-prescription or recreational drugs were provided based on the final report, scene report and toxicology report
Circumstances and location of death	1) Home 2) Workplace 3) School 4) Other 5) Unknown
The level of activity at the time of death (if available)	This information was provided based on the narrative part in the final report or eye witnesses declaration in the police report 1) Rest 2) Sleeping 3) Light to moderate level of activity including daily life activity (housework, driving walking) 4) Moderate to vigorous level of activity (running, swimming, shovelling) 5) Other
The location of the death if available	This information was provided based on the final report and scene report
Presence of any symptoms in the preceding 24 hours before death	1) Syncope 2) Presyncope 3) Chest pain 4) Palpitation 5) Cardiac arrest

	6) Shortness of breath 7) Other
Presence of symptoms prior to the preceding 24 hours of death	1) Syncope 2) Presyncope 3) Chest pain 4) Palpitation 5) Cardiac arrest 6) Shortness of breath 7) Other
If the symptoms preceding the death present: were they investigated?	1) Yes 2) No
The investigations' results	Details were provided based on the final report, scene report, or medical report
Reported family history of SCD or arrhythmia	1) Yes 2) No
If positive family history of SCD, indicate the closest affected individual	1) Sibling 2) Child, parent 3) Second degree relative 4) Third degree relative 5) Unknown
The presence of any genetic testing	1) Yes 2) No
Is the nature of death cardiac?	1) Yes 2) No 3) Possible
Was an autopsy performed	1) Yes 2) No
SCD classification	1) Group A 2) Group B 3) Group C 4) Group D
If CAD presented what is the severity of narrowing in the coronary artery	The information was provided based on the autopsy report
If definite or probable SCD indicate if there was any anatomic cause or underlying structural disease	1) Yes 2) No
Was the disease ischemic or non-ischemic	1) Ischemic 2) Non ischemic
Was the case excluded?	1) No 2) Yes
If the case was excluded indicate the exclusion criterion used	1) Non cardiac etiology 2) Post operation cases 3) definition doesn't apply: witnessed cases with > 1 hour of symptoms, or un-witnessed case that last seen alive >24 hours 4) Not sudden or not unexpected cases 5) Out of province origin

The presence of any contributing factors.	1) Yes 2) No
If contributing factors present, indicate the contributing factor	1) Blood alcohol level ≥ 24 mmol/l 2) Any blood level of cocaine 3) Morbid obesity (BMI>50) 4) Insulin dependent diabetes mellitus + end organ damage 5) Epilepsy 6) Hazard condition in accident cases (bad weather, speed, seatbelt, helmet or moose) 7) Toxic level of drugs in the blood 8) Combined medical condition
Body organs weight measured in grams from autopsy reports, if autopsy was performed	• Brain • Heart • Right ling • Left lung • Liver • Spleen • Right kidney • Left kidney • Pancreas
Likelihood of SCD	1) SCD group 2) Non SCD group

Appendix H: The number of cases in SCD group*

Age group	Year / sex	2009	2010	2011	2012	2013	Total
2-50	Male	30	28	25	31	20	134
	Female	6	9	8	10	7	40
	Total	36	37	33	41	27	174
2-18	Male	1	0	3	0	1	5
	Female	0	0	1	0	1	2
	Total	1	0	4	0	2	7
19-29	Male	1	2	1	4	2	10
	Female	1	2	1	1	1	6
	Total	2	4	2	5	3	16
30-40	Male	10	8	2	7	3	30
	Female	0	3	0	5	1	9
	Total	10	11	2	12	4	39
41-50	Male	18	18	19	20	14	89
	Female	5	4	6	4	4	23
	Total	23	22	25	24	18	112
15-35	Male	9	4	3	8	3	27
	Female	1	3	2	2	3	11
	Total	10	7	5	10	6	38
2-40	Male	12	10	6	11	6	45
	Female	1	5	2	6	3	17
	Total	13	15	8	17	9	62
2-49	Male	28	28	23	28	17	124
	Female	6	8	8	9	7	38
	Total	34	36	31	37	24	162

* SCD Group: group A: natural or undetermined death with NO contributing factor; group B: natural or undetermined death with one contributing factor OR accidental deaths without any factor explaining the accident.

Appendix I: NL population numbers

Age group	Year / sex	2009	2010	2011	2012	2013
2-50	Male	159,600	159,646	158,744	157,336	155,851
	Female	160,132	159,676	158,597	157,315	155,990
	Total	319,732	319,322	317,341	314,651	311,841
2-18	Male	47,488	46,974	46,775	46,518	46,117
	Female	45,222	44,901	44,652	44,314	44,070
	Total	92,710	91,875	91,427	90,832	90,187
19-29	Male	34,573	35,335	35,446	35,242	34,991
	Female	34,188	34,532	34,563	34,425	34,070
	Total	68,761	69,867	70,009	69,667	69,061
30-40	Male	36,132	36,058	35,714	35,240	34,924
	Female	38,026	37,925	37,600	37,262	36,893
	Total	74,158	73,983	73,314	72,502	71,817
41-50	Male	41,407	41,279	40,809	40,336	39,819
	Female	42,693	42,318	41,782	41,314	40,957
	Total	84,100	83,597	82,591	81,650	80,776
15-35	Male	65,837	66,293	66,087	65,673	65,385
	Female	65,897	65,972	65,729	65,321	64,708
	Total	131,734	132,265	131,816	130,994	130,093
2-40	Male	118,193	118,367	117,935	117,000	116,032
	Female	117,436	117,358	116,815	116,001	115,033
	Total	235,629	235,725	234,750	233,001	231,065
2-49	Male	155,379	155,291	154,380	153,061	151,485
	Female	155,777	155,319	154,178	153,048	151,539
	Total	311,156	310,610	308,558	306,109	303,024

Appendix J: Incidence of SCD* per 100,000 populations

Year / Age group		2009	2010	2011	2012	2013	Average incidence of SCD per 100,000 populations
2-50	Male	18.79	17.54	15.75	19.7	12.83	16.3
	Female	3.75	5.64	5.04	6.36	4.49	5.06
	Total	11.26	11.59	10.4	13.03	8.66	11
2-18	Male	2.11	0	4.63	0	2.17	1.78
	Female	0	0	2.24	0	2.27	0.91
	Total	1.08	0	4.37	0	2.22	1.53
19-29	Male	2.89	5.66	2.82	11.35	2.22	4.99
	Female	2.93	5.79	2.89	2.9	2.94	3.5
	Total	2.91	5.73	2.86	7.18	4.34	4.6
30-40	Male	27.68	22.19	5.6	19.86	8.59	16.78
	Female	0	7.91	0	13.42	2.71	4.81
	Total	13.48	14.87	2.73	16.55	5.57	10.64
41-50	Male	43.47	43.61	46.56	49.58	35.16	43.68
	Female	11.71	9.45	14.36	9.68	9.77	10.99
	Total	27.35	26.32	30.27	29.39	22.28	27.12
15-35	Male	13.67	6.03	4.54	12.18	4.59	8.2
	Female	1.52	4.54	3.04	3.06	4.64	3.36
	Total	7.59	5.29	3.79	7.63	4.61	5.78
2-40	Male	10.15	8.45	5.09	9.4	5.17	7.65
	Female	0.85	4.26	1.71	5.17	2.61	2.92
	Total	5.52	6.36	3.41	7.3	3.89	5.3
2-49	Male	18.02	18.03	14.9	18.3	11.2	16.11
	Female	3.85	5.15	5.2	5.9	4.62	4.93
	Total	10.92	11.6	10.05	12.1	7.92	10.5

* SCD Group: group A: natural or undetermined death with NO contributing factor; group B: natural or undetermined death with one contributing factor OR accidental deaths without any factor explaining the accident.

Appendix K: SPSS output for comparing the incidence SCD in our study with worldwide studies

a) Comparing the incidence of SCD in the SCD group with ON study for the age group 2-18 years

Number_people * Country Crosstabulation

Count

		Country		Total
		NL (2-18)	ON (2-18)	
Number_people	SCD	7	18	25
	Population	457024	2659952	3116976
Total		457031	2659970	3117001

Chi-Square Tests

	Value	df	Asymptotic Significance (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	3.554[a]	1	.059		
Continuity Correction[b]	2.568	1	.109		
Likelihood Ratio	2.939	1	.086		
Fisher's Exact Test				.082	.063
N of Valid Cases	3117001				

a. 1 cells (25.0%) have expected count less than 5. The minimum expected count is 3.67.

b. Computed only for a 2x2 table

b) Comparing the incidence of SCD in the SCD group with ON study for the age group 19-29 years

Number_people * Country Crosstabulation

Count

		Country		Total
		NL (19-29)	ON (19-29)	
Number_people	SCD	16	47	63
	Population	347349	1912810	2260159
Total		347365	1912857	2260222

Chi-Square Tests

	Value	df	Asymptotic Significance (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	4.871[a]	1	.027		
Continuity Correction[b]	4.131	1	.042		
Likelihood Ratio	4.218	1	.040		
Fisher's Exact Test				.035	.026
N of Valid Cases	2260222				

a. 0 cells (0.0%) have expected count less than 5. The minimum expected count is 9.68.

b. Computed only for a 2x2 table

c) Comparing the incidence of SCD in the SCD group with ON study for the age group 30-40 years

Number_people * Country Crosstabulation

Count

		Country		Total
		NL (30-40)	ON (30-40)	
Number_people	SCD	39	109	148
	Population	365735	1963314	2329049
Total		365774	1963423	2329197

Chi-Square Tests

	Value	df	Asymptotic Significance (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	12.676[a]	1	.000		
Continuity Correction[b]	11.884	1	.001		
Likelihood Ratio	10.938	1	.001		
Fisher's Exact Test				.001	.000
N of Valid Cases	2329197				

a. 0 cells (0.0%) have expected count less than 5. The minimum expected count is 23.24.

b. Computed only for a 2x2 table

d) Comparing the incidence of SCD in the SCD group with ON study for the age group 2-40 years

Number_people * Country Crosstabulation

Count

		Country		
		NL (2-40)	ON (2-40)	Total
Number_people	SCD	62	174	236
	Population	1170108	6536076	7706184
Total		1170170	6536250	7706420

Chi-Square Tests

	Value	df	Asymptotic Significance (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	22.525[a]	1	.000		
Continuity Correction[b]	21.673	1	.000		
Likelihood Ratio	19.228	1	.000		
Fisher's Exact Test				.000	.000
N of Valid Cases	7706420				

a. 0 cells (0.0%) have expected count less than 5. The minimum expected count is 35.84.

b. Computed only for a 2x2 table

e) Comparing the incidence of SCD in the SCD group with Denmark study for the age group 2-49 years

Number_people * Country Crosstabulation

Count

		Country		Total
		NL	Denemark	
Number_people	SCD	162	893	1055
	Population	1539295	10409107	11948402
Total		1539457	10410000	11949457

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	5.746[a]	1	.017		
Continuity Correction[b]	5.528	1	.019		
Likelihood Ratio	5.461	1	.019		
Fisher's Exact Test				.018	.009
N of Valid Cases	11949457				

a. 0 cells (0.0%) have expected count less than 5. The minimum expected count is 135.92.

b. Computed only for a 2x2 table

f) Comparing the incidence of SCD in the SCD group with Sweden study for the age group 15-35 years

Number_people * Country Crosstabulation

Count

		Country		Total
		NL	Sweden	
Number_people	SCD	38	181	219
	Population	656864	17074639	17731503
Total		656902	17074820	17731722

Chi-Square Tests

	Value	df	Asymptotic Significance (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	114.331[a]	1	.000		
Continuity Correction[b]	110.538	1	.000		
Likelihood Ratio	62.030	1	.000		
Fisher's Exact Test				.000	.000
N of Valid Cases	17731722				

a. 0 cells (0.0%) have expected count less than 5. The minimum expected count is 8.11.

b. Computed only for a 2x2 table

g) Comparing the incidence of SCD in the SCD group with Ireland study for the age group 15-35 years

Number_people * Country Crosstabulation

Count

		Country		Total
		NL	Ireland	
Number_people	SCD	38	116	154
	Population	656883	4065513	4722396
Total		656921	4065629	4722550

Chi-Square Tests

	Value	df	Asymptotic Significance (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	14.903[a]	1	.000		
Continuity Correction[b]	14.018	1	.000		
Likelihood Ratio	12.571	1	.000		
Fisher's Exact Test				.000	.000
N of Valid Cases	4722550				

a. 0 cells (0.0%) have expected count less than 5. The minimum expected count is 21.42.

b. Computed only for a 2x2 table

Appendix L: SPSS output for comparing the incidence of SCD in our study with worldwide studies using strict ascertainment methods SCD

a) Comparing the incidence of SCD with Denmark study for the age group 2-49 years

Number_people * Country Crosstabulation

Count

		Country		
		NL	Denmark	Total
Number_people	SCD	97	439	536
	Population	1539360	10409107	11948467
Total		1539457	10409546	11949003

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	12.981[a]	1	.000		
Continuity Correction[b]	12.520	1	.000		
Likelihood Ratio	11.739	1	.001		
Fisher's Exact Test				.000	.000
N of Valid Cases	11949003				

a. 0 cells (0.0%) have expected count less than 5. The minimum expected count is 69.06.

b. Computed only for a 2x2 table

b) Comparing the incidence of SCD with Ireland study for the age group 15-35 years

Number_people * Country Crosstabulation

Count

		Country		
		NL	Ireland	Total
Number_people	SCD	17	116	133
	Population	656883	4065513	4722396
Total		656900	4065629	4722529

Chi-Square Tests

	Value	df	Asymptotic Significance (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	.141[a]	1	.707		
Continuity Correction[b]	.063	1	.802		
Likelihood Ratio	.145	1	.704		
Fisher's Exact Test				.791	.401
N of Valid Cases	4722529				

a. 0 cells (0.0%) have expected count less than 5. The minimum expected count is 18.50.

b. Computed only for a 2x2 table

c) Comparing the incidence of SCD with Sweden study for the age group 15-35 years

Number_people * Country Crosstabulation

Count

		Country		Total
		NL	Sweden	
Number_people	SCD	14	181	195
	Population	656883	17074639	17731522
Total		656897	17074820	17731717

Chi-Square Tests

	Value	df	Asymptotic Significance (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	6.600[a]	1	.010		
Continuity Correction[b]	5.662	1	.017		
Likelihood Ratio	5.222	1	.022		
Fisher's Exact Test				.020	.015
N of Valid Cases	17731717				

a. 0 cells (0.0%) have expected count less than 5. The minimum expected count is 7.22.
b. Computed only for a 2x2 table

Appendix M: Comparing the incidence of SUD [SCD with negative autopsy (likely arrhythmia)] in our study with worldwide studies.

a) Comparing the incidence of SUD with ON study

Number_people * Country Crosstabulation

Count

		Country		
		NL (2-40)	ON (2-40)	Total
Number_people	SCD	25	48	73
	Population	1170108	6536076	7706184
Total		1170133	6536124	7706257

Chi-Square Tests

	Value	df	Asymptotic Significance (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	20.597[a]	1	.000		
Continuity Correction[b]	19.144	1	.000		
Likelihood Ratio	16.228	1	.000		
Fisher's Exact Test				.000	.000
N of Valid Cases	7706257				

a. 0 cells (0.0%) have expected count less than 5. The minimum expected count is 11.08.

b. Computed only for a 2x2 table

b) Comparing the incidence of SUD with Ireland study

Number_people * Country Crosstabulation

Count

		Country		
		NL	Ireland	Total
Number_people	SCD	10	31	41
	Population	656883	4065513	4722396
Total		656893	4065544	4722437

Chi-Square Tests

	Value	df	Asymptotic Significance (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	3.761[a]	1	.052		
Continuity Correction[b]	2.936	1	.087		
Likelihood Ratio	3.183	1	.074		
Fisher's Exact Test				.067	.051
N of Valid Cases	4722437				

a. 0 cells (0.0%) have expected count less than 5. The minimum expected count is 5.70.

b. Computed only for a 2x2 table

c) Comparing the incidence of SUD with Sweden study

Number_people * Country Crosstabulation

Count

		Country		Total
		NL	Sweden	
Number_people	SCD	8	38	46
	Population	656864	17074639	17731503
Total		656872	17074677	17731549

Chi-Square Tests

	Value	df	Asymptotic Significance (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	24.156[a]	1	.000		
Continuity Correction[b]	20.471	1	.000		
Likelihood Ratio	13.091	1	.000		
Fisher's Exact Test				.000	.000
N of Valid Cases	17731549				

a. 1 cells (25.0%) have expected count less than 5. The minimum expected count is 1.70.

b. Computed only for a 2x2 table

d) Comparing the incidence of SUD with Denmark study

Number_people * Country Crosstabulation

Count

		Country		
		NL	Denmark	Total
Number_people	SCD	12	41	53
	Population	1539445	10409107	11948552
Total		1539457	10409148	11948605

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	4.496[a]	1	.034		
Continuity Correction[b]	3.668	1	.055		
Likelihood Ratio	3.790	1	.052		
Fisher's Exact Test				.041	.035
N of Valid Cases	11948605				

a. 0 cells (0.0%) have expected count less than 5. The minimum expected count is 6.83.

b. Computed only for a 2x2 table