SCOPE & NATURE OF YOUNG SUDDEN CARDIAC DEATH IN NEWFOUNDLAND & LABRADOR

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Abstract

Introduction: Sudden cardiac death (SCD) in young people (ages 2-40) is a tragedy for families and communities alike. It has multiple causes, one of which is an underlying genetic arrhythmogenic cardiomyopathy. A study from Ontario (ON) using a 2008 cohort assessed the incidence of SCD in persons aged 2-40 years to be 2.64/100,000 person-years. We hypothesized that Newfoundland & Labrador (NL) may have a higher incidence of early SCD in ages 2-40 due to possible underlying genetic causes given the historical genetic isolation of the population and the founder mutations already identified (ex. *PKP2, RYR2, TMEM43*).

Methods: We ascertained cases of sudden death from the comprehensive Medical Examiners' provincial database for the years 2008 and 1997; 2008 as a direct comparison to ON, and 1997 as it represented a time when the implantable cardioverter-defibrillator was not available in NL. Each case of sudden death was individually analyzed to determine likelihood of SCD.

Results: There were 119 cases in 2008 and 157 cases in 1997. The incidence of SCD for ages 2-40 in 2008 was 7.32/100,000 persons. This was significantly higher than the incidence in Ontario. The incidence of SCD was not significantly higher in 1997 than 2008. Coronary artery disease was a major cause of death in all cohorts, similar to Ontario (non-significant difference).

Conclusion: In general, there was a trend of more arrhythmogenic deaths in the young and more structural cardiac deaths as age increased. This reflects the cause of SCD in the young is often genetic in nature, while older deaths are often due to

coronary artery disease, a disease heavily influenced by environment. To conclude, SCD in NL occurs at a higher incidence than ON, further research is needed on the topic.

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ADLs : Activities of daily living

ARVC/D : Arrhythmogenic right ventricular cardiomyopathy/ dysplasia

BrS : Brugada syndrome

CAD : Coronary artery disease

CPVT : Catecholaminergic polymorphic ventricular tachycardia

DCM : Dilated cardiomyopathy

DNA : Deoxyribonucleic acid

HCM : Hypertrophic cardiomyopathy

ICD : Implantable cardioverter-defibrillator

LQTS : Long QT syndrome

NL : Newfoundland and Labrador

OCME : Office of the Chief Medical Examiner

ON : Ontario

RV : Right ventricle

SADS : Sudden arrhythmic death syndrome

SCD : Sudden cardiac death

SES : Socioeconomic status

SQTS : Short QT syndrome

SUD : Sudden unexpected death

TMEM43 : Transmembrane protein 43

1. Introduction

Sudden death is a devastating event for families and communities alike. Worldwide, the estimated burden of sudden cardiac death (SCD) is 4-5 million cases per year (Chugh et al., 2008). Sudden unexpected death (SUD) is defined as the sudden death of an individual who appears healthy and dies suddenly within a few minutes to several hours due to pre-existing disease or functional disorder. SUD is further defined by the anatomical cause of death after investigation i.e. which system is responsible for the death: is it the cardiovascular system, the respiratory system, the central nervous system etc. The cardiovascular system is implicated when an autopsy finds evidence of cardiac injury, thus SUD becomes SCD. The cardiovascular system is also implicated when absolutely no anatomical cause is found on autopsy, as then a cardiac arrhythmia was assumed to have occurred. In the latter, diagnosing SCD is much more difficult as all other causes of death must be excluded – which is to say all means of investigation must be exhausted Overall, SCD is a difficult diagnosis to make, as it is easy to miss given there may not be any physical findings on autopsy of arrhythmias.

SCD is typically observed in the older population; however, a portion of cases do occur in the young, without any prior symptoms (Kauferstein, Kiehne, Neumann, Pitschner, & Bratzke, 2009). In the older population the cause of SCD is often related to coronary artery disease (CAD). CAD is heart disease caused by a buildup of plaque in the coronary arteries that may eventually lead to blockages. When dealing with the young, many other etiologies are present, including structural, metabolic, and

genetic mutations that increase arrhythmogenic predisposition (Noseworthy & Newton-Cheh, 2008).

Newfoundland & Labrador (NL) is a founder population, with a high incidence of some genetic diseases (Rahman et al., 2003). This is the result of the founder effect: a loss of genetic variation that occurs when a new population is established by a very small number of individuals from a larger population. It has been estimated that 90% of the current NL population has arisen from 20,000 to 30,000 original European settlers of predominantly English and Irish decent (Parfrey, Davidson, & Green, 2002). Mating segregation, combined with low immigration, and geographical isolation of communities resulted in the genetic isolation of the population (Young et al., 1999). When a limited number of individuals bring a disease mutation into a small population, the population grows through natural expansion and (in the absence of significant in-migration) a high proportion of people will carry the chromosome on which a disease mutation is found (Rahman et al., 2003). Opposite to a founder, or inbred, population is an outbred population. This involves normal genetic variation, as mating more often occurs with those who have no familial relations. Ontario (ON) is an example of this type of population as it geographically central, non-isolated, with normal immigration rates.

A founder effect has been observed in NL for many genetic disorders One such disease is arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D), a known cause of SCD, resulting from one genetic subtype of which is caused by a

mutation in the transmembrane protein 43 (*TMEM43*) gene. This mutation (c.1073 C>T.pS358L), discovered by our laboratory (Merner et al., 2008), changes the amino acid serine to the amino acid leucine at position 358. This mutation is fully penetrant; it will show clinical signs of the disease over the lifespan in everyone who carries the gene mutation. The exact incidence of the mutation in NL is unknown, but likely >1/1000 persons (K. Hodgkinson, personal communication, September 25th, 2014). We also know that there are other founder mutations (*RYR2* (p.R176L) and *PCP2* (p.Q378X)) causing other types of cardiomyopathies and channelopathies that are responsible for young SCD in several large cohorts in NL (Hodgkinson et al., 2013; Lauson et al., 2014). Given the known mutations, we hypothesize that NL has a higher incidence of early SCD than elsewhere in Canada.

Incidence and prevalence are both measures of the extent of disease in a population. Incidence is the rate of new cases of the disease among the population. Prevalence includes both new cases and those who have contracted the disease in the past and are still surviving. With respect to SCD, we are more interested in measuring the incidence, as prevalence is not applicable because SCD is not a curable disease, no one can survive it.

Accurate incidence data has not been easy to collect, as there is no general population SCD genetic screening available in NL. Genetic screening involves testing an individual's deoxyribonucleic acid (DNA) for multiple known gene mutations. In comparison, clinical screening involves using diagnostic tests (such as

electrocardiogram, or echocardiogram) to look for phenotypic changes. Clinical screening is not very effective for SCD, as we have not found any precise markers yet. Genetic screening, however, can be quite helpful in preventing SCD depending on the gene mutation we are dealing with.

Many ethical issues arise when debating whether there should be genetic screening available, for example as part of newborn screening. Factors to consider include cost implications for the health care system, potential clinical, financial, and emotional consequences with false-positive screening results for the patients, and as well, the current lack of evidence-based guidelines to deal with management of asymptomatic patients who screen positive (Kaltman et al., 2011). As such, health care professionals are not prepared to fully deal with general population genetic screening. Unfortunately, young SCD is one of those cases where clinical screening compared to genetic screening is not effective, as SCD can present with no prior symptoms acting as a warning. This makes it important to identify which individuals are at greatest risk of preventable early SCD in order to offer prophylactic medications or devices, such as the implantable cardioverter-defibrillator (ICD) (Kauferstein et al., 2009).

1.1 Literature Search

A comprehensive literature search of numerous relevant medical databases (Pubmed and meSH, EMBASE, CINAHL, Google Scholar, and Scopus) was performed to fully understand the scope of young SCD. This was accomplished using various

combinations of the key words: “sudden cardiac death” “sudden unexpected death” “young”, “genetics”, “epidemiology”, “arrhythmogenic right ventricular cardiomyopathy”, “arrhythmogenic”, “arrhythmia”, ”cardiomyopathy”, “channelopathy”, and “non-genetic”. Reference lists of relevant papers were also surveyed to identify additional literature on topics of interest.

1.2 Describing Sudden Cardiac Death

Once SCD is diagnosed, there are more questions to answer. SCD is defined as the unexpected natural death from a cardiac cause within a short time period, generally ≤ 1 hour from the onset of symptoms, in a person without any prior potentially fatal condition (Zipes & Wellens, 1998). Physiologically, SCD often occurs when an electrically stable heart is transformed into an unstable one, causing a fatal arrhythmia. The exact cause of this transformation is richly diverse, as SCD is the final common end point of multiple disease processes; it results from a complex interplay of structural, metabolic, and genetic determinants (Noseworthy & Newton-Cheh, 2008).

SCD is a heterogeneous condition; CAD accounts for about 80% of SCDs, and the remaining 20% is attributed to cardiomyopathies and genetic diseases (Chugh et al., 2008). To complicate the matter, other medical conditions, such as diabetes (Jouven, 2005), as well as more dynamic associations, such as low socioeconomic status (SES), are also associated with SCD (Chugh et al., 2008) (Figure 1.1). The age range for SCD is wide as it occurs in individuals of all ages, from ages 2 and beyond. As age

varies, etiology of the disease may vary as well; CAD is more prevalent in the older population, and genetic conditions can exert their effects at any age – young and old. All in all, it is clear that overall incidence of SCD increases with age (Deo & Albert, 2012).

With regard to gender, SCD has a much higher incidence in men than women (Deo & Albert, 2012; Zipes & Wellens, 1998). Analysis of the Framingham Heart Study cohort showed that at age 40 the lifetime risk of SCD for men is 1 in 8, while women are three times less likely (1 in 24) (Lloyd-Jones, Berry, Ning, Cai, & Goldberger, 2009). While this reflects sex differences in the incidence of CAD, a higher incidence in men has been observed in other genetic causes of SCD as well. Australian researchers studied SCD in a cohort with age less than 35 years and found that 63% of subjects were male when CAD was excluded (Doolan, Langlois, & Semsarian, 2004). In hypertrophic cardiomyopathy (HCM) both sexes are affected by the condition, though it is more likely to be detected earlier in men (Christiaans et al., 2011; Jacoby, Depasquale, & McKenna, 2013). In a study that evaluated the largest population of patients with Brugada syndrome (BrS) thus far, they reported that men had a 5.5-fold higher risk of sudden death than did women (Brugada, Brugada, & Brugada, 2003).

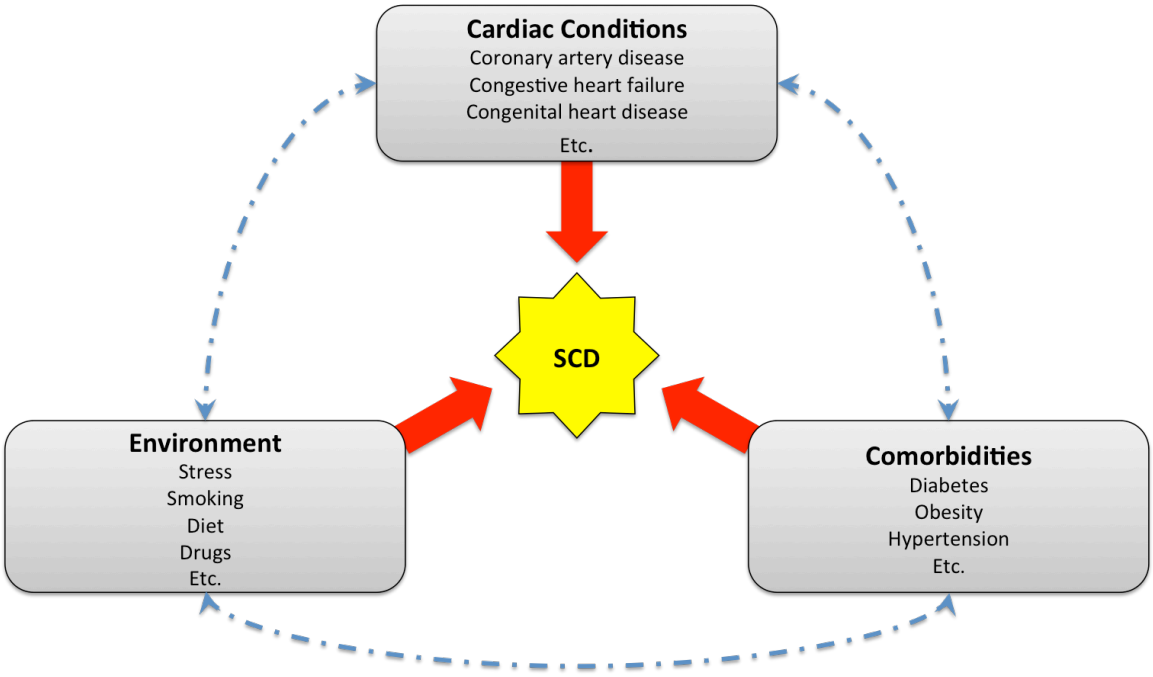

Figure 1.1: The Determinants of SCD.

While cardiac conditions, environment, and comorbidities, contribute their own influence (red arrows), these factors also are affected by one another (blue dashed arrows). Adapted from Chugh et al., 2008.

Other studies corroborate that men with BrS present with a greater risk clinical profile than women and have a worse prognosis (Benito et al., 2008). In ARVC/D, multiple studies have identified it to be a male-predominant disease (Cox et al., 2011; Merner et al., 2008), however there are also reports of equal numbers between the sexes (Dalal, 2005).

Given the wide variety of causes of SCD, there is no specific symptom set for the condition. Having said that, symptoms that are typical of any heart disease have been associated with SCD, such as syncope, dyspnea, and heart palpitations. Tragically, it is not unusual for the very first symptom of conditions causing SCD to be death itself. It is for this reason that SCD takes such a heavy toll on families and communities.

Fortunately, not all individuals at risk of SCD are asymptomatic. By tracing family health history and genetic testing a preventative therapy can be put in place. Treatments for conditions that increase the risk of SCD are similar. The therapeutic course will depend on symptoms - previous cardiac arrest or arrhythmia. Standard therapeutic options include anti-arrhythmic drugs, an ICD, cardiac pacing, or catheter ablation. For heart failure, the ICD is primary standard of care (along with anti-heart failure medications) when the patient has high-risk indicators, such as left ventricular dysfunction or reduced left ventricular ejection fraction, or heart failure symptoms (Marine & Russo, 2014a, 2014b). Evidence has shown that the ICD is the better option for treatment of heart failure when compared with anti-arrhythmic

drugs. Anti-arrhythmics are not often prescribed on their own, but more often as adjunctive therapy with the ICD. Catheter ablation is also an option for when the ICD is not indicated. Cardiomyopathies (HCM, ARVC/D and dilated cardiomyopathy (DCM)) have similar treatments, with the ICD being the gold standard for high-risk patients (Elliott & McKenna, 2014; McKenna, 2014). The difference here is that prophylactic treatment can be started in asymptomatic patients when identified as high risk due to family history (McKenna, 2014). The ICD efficacy was examined in 11 families with the *TMEM43* mutation in NL and the five-year mortality rate after ICD in males was zero compared with 28% in control subjects ($p < 0.009$)(Hodgkinson et al., 2005). For channelopathies, BrS, long QT syndrome (LQTS) and catecholaminergic polymorphic ventricular tachycardia (CPVT)), the ICD is the superior treatment though may not be the first line. Commonly, Beta-blockers are the mainstay of therapy unless there are frequent associated symptoms (Buxton, 2014; Wylie & Garlitski, 2014; Zimetbaum, Seslar, Berul, & Josephson, 2014).

Many young SCD's still occur despite the effectiveness of the ICD and drug therapy, as identifying candidates clinically for therapy can be difficult. Furthermore, genetic screening programs for SCD-causing conditions are not yet effectively used (Kaltman et al., 2011) . Research has not brought us to the level of proficient preventative medicine just yet, and thus, SCD is an unyielding burden.

1.3 Genetic Etiology

While CAD accounts for the majority of SCDs, the rest can likely be attributed to genetic causes, which includes nonischemic myopathic processes, such as cardiomyopathies, and primary defects of cardiac electrophysiology, such as LQTS (Noseworthy & Newton-Cheh, 2008). Many of these conditions show mendelian inheritance, also called monogenic, patterns. Mendelian inheritance is a description of the way traits are passed down from one generation to another – and sometimes skips generations- as a result of a mutation in one single gene (Miko, 2008). There are multiple possible patterns of inheritance that can be located on an autosome or on a sex chromosome, and the disease phenotype is described as being dominant or recessive (Chial, 2008). In cardiac genetics, many diseases display an autosomal dominant or autosomal recessive pattern (Table 1.1). Autosomal dominant diseases occur in individuals who have a single mutant copy of the disease-associated gene, and can be inherited from an affected mother or father. Thus, this mutation will be passed down to all future generations. Autosomal recessive diseases occur in individuals with two mutant alleles of the disease-associated gene. These individuals must inherit one mutant allele from each of their parents. Autosomal recessive single-gene diseases often show a pattern which the disease 'skips' one or more generations (Chial, 2008).

Observations of SCD incidence in families show a clear role for genetics. For example, in an Israeli case-control study of SCD patients, a family history of SCD was

Table 1.1: Examples of a genetic basis for structural and arrhythmogenic cardiac diseases.

Adapted from Tester & Ackerman (2009) and Jeffries & Towbin (2010).

*: These frequencies may be underestimating true numbers. This table of gene mutations can cause SCD, and thereby remove subjects from the patient count. "Frequency in patients" refers to alive patients, possible ascertainment bias here.

Cardiac Disease	Gene	Locus	Protein	Mode of Inheritance	Frequency in Patients
Hypertrophic Cardiomyopathy	TNNT2	1q32	cardiac troponin T	Autosomal dominant	3-5%
	MYBPC3	11p11.2	cardiac myosin-binding protein C	Autosomal dominant	25-25%
	MYH7	14q11.2-q12	β-myosin heavy chain	Autosomal dominant	25-25%
Arrhythmogenic Right Ventricular Cardiomyopathy/ Dysplasia	TMEM43	3p25	transmembrane protein 43	Autosomal dominant	rare*
	DSP	6p24	desmoplakin	Autosomal dominant	10-20%
	DSG2	18q12.1-q12.2	desmoglein 2	?Autosomal dominant	10-15%
Dilated Cardiomyopathy	DMD	Xp21.2	dystrophin	X-linked	?
	DES	2q35	desmin	Autosomal dominant	?
	TNNI1	1q12	cardiac troponin I	Autosomal dominant	?
Long QT Syndrome	KCNQ1	11p15.5	Kv7.1	Autosomal dominant, or recessive	30-35%
	SCN5A	3p21-p24	NaV1.5	Autosomal dominant	5-10%
	ANKB	4q25-q27	ankyrin B	Autosomal dominant	rare*
Catecholaminergic Polymorphic Ventricular Tachycardia	CASQ2	1p13.3	calsequestrin 2	Autosomal recessive	rare*
	RYR2	1q42.1-q43	ryanodine receptor 2	Autosomal dominant	50-60%
Brugada Syndrome	SCN5A	3p21-p24	NaV1.5	Autosomal dominant	20-30%
	GPD1L	3p22.3	glycerol-3-phosphate dehydrogenase 1-like	Autosomal dominant	rare*
	CACNA1C	2p13.3	l-type calcium channel	Autosomal dominant	?

associated with a 46% increased risk of SCD compared with matched controls (relative risk=1.5)(Friedlander et al., 1998). In the Paris Prospective Study I, a parental history of SCD increased the risk of fatal arrhythmia in the offspring by 80%; in subjects with both parents affected, risk of individuals with an established SCD syndrome, a family history can potentiate risk of SCD. For example, in HCM, a family history of SCD is associated with a 5-fold increase for risk of SCD (Elliott et al., 2000). This is likely due to the underlying pathogenicity of the mutation, each mutation with different clinical picture- which can even occur with mutations in the same gene (allelic heterogeneity) hence the importance of studies examining mutation variations.

The current known genetic conditions are broken into two groups, structural and arrhythmogenic. Structural diseases, which are more easily detected via autopsy, include HCM, DCM, and ARVC/D- although, these can present early in its course with no obvious structural anomalies. The arrhythmogenic diseases, often referred to as channelopathies, tend to be missed at autopsy because they cause no structural changes to the heart. This category includes BrS, CPVT, LQTS, and short QT syndrome (SQTS) (Figure 1.2).

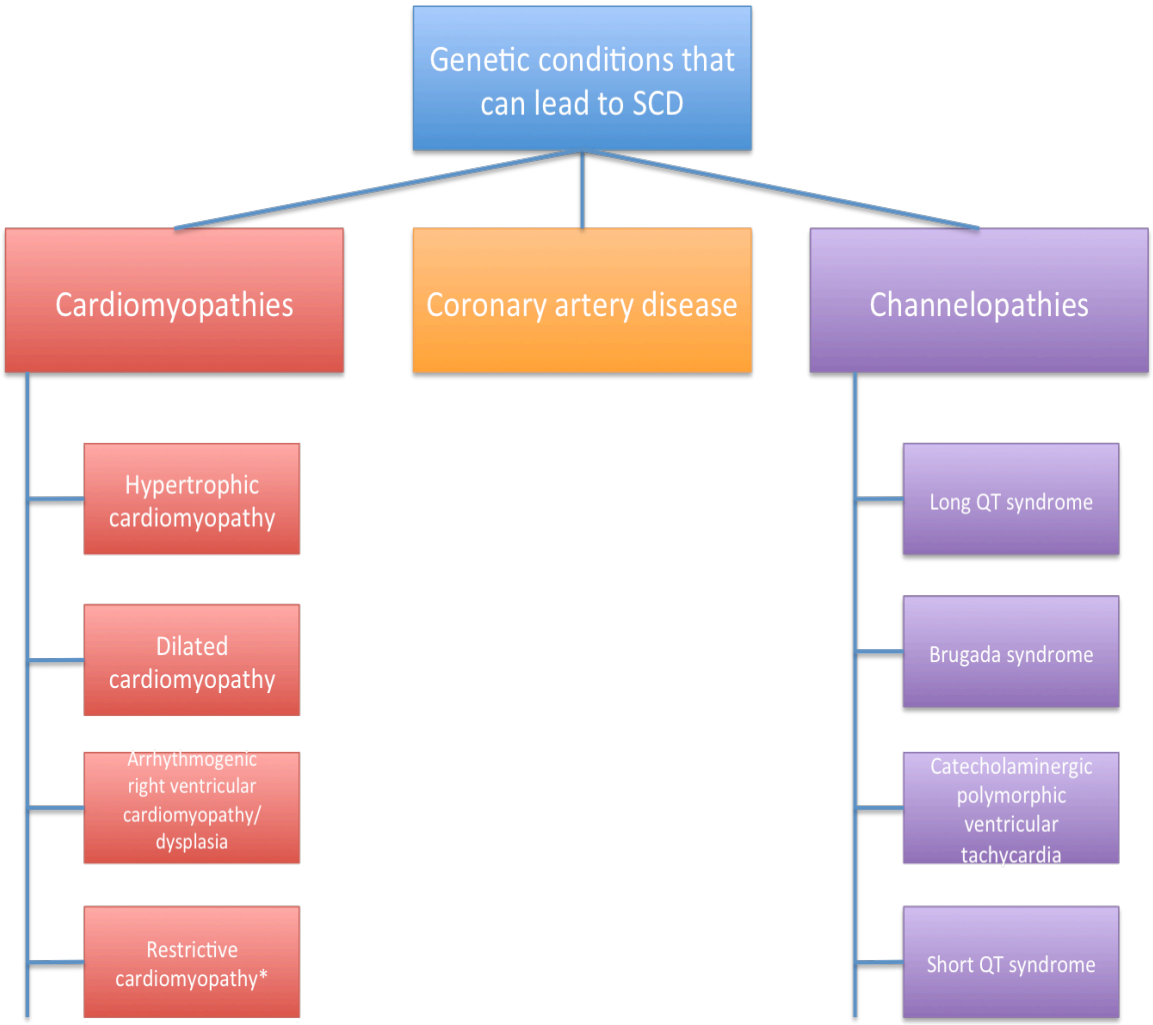

Figure 1.2: Categories of heart diseases where genes have been found to be involved, divided into cardiomyopathies, CAD, and channelopathies.

*Rare – not discussed in dissertation

1.3.1 Structural Diseases

Structural abnormalities of the heart are a significant result of genetic heart disorders (Ingles & Semsarian, 2007). The structural abnormalities that result are not identical across diseases, but typically compromise the structure of the right or left ventricle, possibly through fat deposition, hypertrophy, or dilatation. These abnormalities can go undetected throughout an individual's life, and may only be diagnosed after SCD and a meticulous autopsy. Defining the exact burden of SCD due to these cardiomyopathies is a challenging task. Overall, the contribution to SCD caused by cardiomyopathies differs with disease; ARVC/D is ranked the highest, followed by HCM, and then DCM (Sen-Chowdhry & McKenna, 2012).

DCM is the most common cardiomyopathy worldwide, characterized by dilatation and impaired contraction of the left or both ventricles (Jefferies & Towbin, 2010). The natural history of DCM is for patients to present with heart failure or an arrhythmia; heart failure or an arrhythmic event can lead to SCD (Sen-Chowdhry & McKenna, 2012).

HCM is a commonly inherited cardiomyopathy, defined by the presence of left ventricular hypertrophy in the absence of abnormal loading conditions, such as hypertension (Jacoby et al., 2013). The myocardial hypertrophy can cause numerous outcomes that may lead to SCD, for example, obstruction of the left ventricular outflow tract, atrial fibrillation, and ventricular arrhythmias (Elliott & McKenna, 2004).

Arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D) is a heritable cardiomyopathy whereby patients demonstrate a fibrofatty replacement of the myocardium of the right ventricle (RV) (Thiene, Nava, Corrado, Rossi, & Pennelli, 1988). The loss of healthy myocardium increases risk of arrhythmia, which may cause SCD. All of these cardiomyopathies involve a genetic component, meaning they are often caused by a genetic mutation. As seen in Table 1.1 (and Appendix A), there are multiple genetic mutations per condition, all affecting a different protein that alters the function of the heart. For example, ARVC can be caused by a mutation in TMEM43, desmoplakin, desmoglein 2 etc., all of which have different frequencies in different populations.

1.3.2 Arrhythmogenic Diseases

Arrhythmogenic heart conditions are not anatomically apparent in the heart, as they operate on a non-structural level. Given the physical subtleness of these conditions, assessing the true burden is quite difficult. To illustrate, a 2001 Italian study examining young SCD victims (≤35 years of age) found that 16 subjects (6%) died with an apparently normal heart, and the cause of SCD unexplained (Corrado, Basso, & Thiene, 2001). It is these cases of SUD, or studies that cannot explain SCD, that likely etiology may be a type of channelopathy.

BrS is an arrhythmic syndrome characterized by increased risk for sudden death resulting from episodes of polymorphic ventricular tachyarrhythmia's (Chen & Priori, 2008). CPVT is another heritable arrhythmia that typically manifests with

exertional syncope or sudden death (Priori, 2002). LQTS is a type of channelopathy that involves delayed repolarization of the myocardium, resulting in an increased risk of an arrhythmia and thus SCD (D. Tester & Ackerman, 2009). SQTS, a more recently recognized clinical syndrome, is the opposite of LQTS in that it involves a short QT interval which increases risk of SCD (D. Tester & Ackerman, 2009). Again, all of these conditions significantly involve a genetic component (Table 1.1 & Appendix A).

1.4 Non-Genetic Etiology

As previously mentioned, SCD is the result of a complex interplay of multiple factors – not all are genetic. Firstly, there are medical conditions that can cause or contribute to SCD. Diabetes mellitus is a significant risk factor for SCD, proven in multiple studies, including the Paris Prospective Study I, which found through multivariate analysis that diabetes independently conferred a significant risk for SCD (relative risk= 2.64, 95% confidence interval= 1.26–5.53) (Jouven, Desnos, Guerot, & Ducimetiere, 1999). Other comorbidities included in the equation are smoking and obesity, often due to a lack of physical activity and/or diet. These environmental factors have already been proven to have a negative impact on cardiac health by increasing risk of CAD, and thus SCD. A recent case-control study on firemen ≤ 45 years old found that of the 87 SCD victims, 63% were obese and 67% had CAD (Yang et al., 2013). Cardiomegaly was also found in 66% of victims and this was associated with five-fold increased risk of SCD (Yang et al., 2013). As

well, hypertension was associated with a 12-fold increased risk of SCD, and smoking and cardiovascular disease showed to be independent risk factors for SCD (Yang et al., 2013). Finally, another environmental factor that ties all of this together is low SES. In the ongoing Oregon Sudden Unexpected Death Study, a 2-year prospective evaluation of the potential relationship between SES and occurrence of SCD was performed (Reinier et al., 2006). This investigation included all cases of SCD in a large urban and suburban US county (population of 670,000). Incidence of SCD based on address of residence was 30% to 80% higher among residents of neighborhoods in the lowest SES quartile compared to neighborhoods in the highest SES quartile. However, the study did not correct for any additional possible confounding factors (such as smoking, obesity, diabetes etc.), and therefore it is difficult to comment on the validity of the SES-SCD relationship. While it remains unexplored to the fullest extent, it is clear there will always be multiple environmental factors at work.

There are other non-genetic causes that could act as a more direct trigger of SCD, such as alcohol consumption, physical activity, or a viral infection. Alcohol has long been known to be the culprit of cardiac arrhythmias amongst heavy drinkers, for example by causing an atrial fibrillation the heart cannot get out of on its own (Koskinen, Kupari, Leinonen, & Luomanmaki, 1987). The relationship between alcohol and arrhythmias is complicated and controversial, dependent on many factors, such as gender, age, amount of alcohol consumed, and whether or not an individual is alcohol dependent (Wannamethee, Shaper, Macfarlane, & Walker,

1995). For certain, arrhythmias due to alcohol do occur, most commonly via atrial fibrillation, but other mechanisms are possible, such as ventricular tachycardia (George & Figueredo, 2010) . Physical activity has been under suspicion by many as a trigger for SCD, as SCD is a common cause of death in athletes; however, recent studies have shown that the majority of SCD victims died while sedentary (Chugh et al., 2008; Reddy et al., 2009). These studies have looked at SCD in the general population, and have not accounted for which victims were athletes, therefore these data does not speak to the relationship of SCD and athletes, but more so to the average individual. Finally, a very serious and proven cause of SCD is a bacterial infection, such as infective endocarditis (Thuny et al., 2013).

All of these factors could possibly cause SCD, or could also interact with underlying genetic mutations to cause a disease phenotype. While non-genetic factors, such as obesity, smoking, hypertension etc., indisputably play a role in SCD, the majority of them will take effect in an older aged population, that is to say that for young SCD these factors have less impact, but as middle age nears they likely play a bigger role.

1.5 Characterized Populations Dealing with Young SCD

There are a number of studies that have examined the causes of young SCD in specific populations. Current literature suggests there is significant mortality associated with genetic cardiac disorders. A study completed in 2004 by Doolan et al. analyzed sudden deaths in Australian subjects (≤35 years of age) that occurred

from 1994-2002 (Doolan et al., 2004). In total, there were 193 deaths classified as SCD. These deaths were caused by CAD (24%), HCM (15%), congenital heart disease (7%), a group classified as 'other' which included aortic dissection and valvular heart disease (11%), and a group with no structural anomalies thus presumed arrhythmic (31%). In this very young cohort, there is likely a genetic component at play, as a third of the deaths have no structural issues at all.

A 2001 Italian study by Corrodo et al. examined 273 subjects who had suffered SCD (≤35 years of age) with apparently normal hearts (Corrado et al., 2001). The hearts of the subjects were analyzed using a detailed protocol that included both histological and macroscopic analysis. They found 72% of the victims had an underlying cardiac abnormality, such as a cardiomyopathy or CAD. The remaining 28% had a macroscopically normal heart; however, upon further histologic examination 79% of these cases revealed concealed pathologic substrates such as ARVC/D and focal myocarditis. A total of 16% showed neither macroscopic nor histologic abnormalities leaving the mechanism of SCD unexplained. There is no mention of blinding in this study for the pathologists, which is a significant potential for bias. There was a control group of 20 hearts from age- and sex-matched subjects who died suddenly of drug abuse or extra-cardiac causes. None of the control hearts exhibited significant coronary, myocardial, valve, or conduction system abnormalities. This particular study again highlights that there are possibly genetic abnormalities present, or environmental exposures that have left no trace.

Tragically, there are always cases where no evidence of SCD is present, aside from the death, which typically leads to a misdiagnosis of cause of death.

A study published in 2011 by Eckart et al. reported on the incidence and nature of sudden death in a large but select group of United States military recruits (Eckart et al., 2011). They identified 902 predominantly male subjects (mean age 38 +/- 11 years) for whom the cause of death was of potential cardiac etiology. Sudden death was attributed to a cardiac condition in 79% and was unexplained in 21%. From reviewing the literature it is clear that there is a common trend of high rates of young SCD mortality.

In Canada, only two studies have been completed looking at SCD incidence in the young. One study by Lim et al. (2010) in British Columbia found an incidence of SUD, in ages 0-35, of 3.07 per 100,000 per year, and 1.75 per 100,000 per year of SCD, demonstrating there is indeed a large burden associated with young sudden death. More recently, Pilmer et al. (2013) completed a study for the year 2008 in ON, examining the scope and nature of SCD in ages 2-40. They found that incidence of SCD increased with age, and those below age 30 are more likely to suffer from a primary arrhythmia syndrome (odds ratio= 2.97, p<. 001). These Canadian studies show that young SCD is a relevant issue here, though more research is needed to fully characterize the issue, as Canada is a genetically diverse population.

1.6 Newfoundland and Labrador (NL): A Founder Population

In 2008, Merner et al. identified a genetic mutation in patients and extended relatives from 15 unrelated families with Newfoundland ancestry- in *TMEM43* gene that causes autosomal dominant ARVC/D. This mutation (p.S358L) changes the amino acid serine to the amino acid leucine at position 358. Our team showed that the clinical consequence of harboring the *TMEM43* mutation is early SCD (50% of untreated males deceased by 40 years, 80% by 50 years)(Merner et al., 2008). Treatment for ARVC/D using the ICD is a very effective treatment method if the mutation or heart condition is known (Hodgkinson et al., 2005).

Although it is currently known that this mutation is present in the NL population, the determination of its physical effect comes from the ascertainment of families manifesting early SCD. We do not currently know the exact incidence of the p.S358L mutation in the population, and ongoing studies aim to determine the answer. We do know, however, that a multitude of genetic mutations are causing cardiac problems in the NL populations as currently the Cardiac Genetics Clinic under Eastern Health in St. John's, NL has been referred 649 families with various cardiac conditions. The condition/reason for referral with the highest number of families is SCD (K. Hodgkinson, personal communication, September 25th, 2014).

From an environmental risk factor point of view, NL is on the high end of the spectrum when it comes to risk of heart disease (Asghari et al., 2015; Filate, Johansen, Kennedy, & Tu, 2003). When it comes to obesity, a recent study showed

NL to be the 'heaviest' province in Canada, and projected this to be the trend for the future (Twells, Gregory, Reddigan, & Midodzi, 2014). While obesity itself is not life threatening, the sequelae it can cause are highly related to heart disease – hypertension, diabetes type II, CAD, and stroke (Luo et al., 2007). NL is also in the top range for the provinces in highest percentage of smokers, hypertension, lack of physical activity, and diabetes (Statistics Canada, 2014a). All of these factors contribute to the multifactorial etiology of heart conditions. On a final note, while environment undoubtedly plays a role for these health factors, there is likely a genetic component involved in these conditions as well. Environment is not solely to blame as some factors, such as hypertension and obesity, have a genetic component as well (Bell, Walley, & Froguel, 2005).

1.7 Medical Examiner Protocol and Reports

The duties of medical examiners are relevant to this project as the data is collected from a medical examiner's database. In Canada, medical examiners are mandated to investigate all deaths that are sudden, unexpected, or from non-natural causes. These investigations, completed region-by-region, answer the following 5 questions: who was deceased; how, when and where the death occurred; and by what means the death occurred. After completion of the investigation, all deaths are centralized to the Office of Chief Medical Examiner (OCME) for the province.

The medical examiner's report includes personal information and results from the medical investigation– date of death, manner of death, reported cause of death,

environment of death, as well as a narrative section that includes other relevant information such as medical history, and interviews from friends, family, or eyewitnesses. On occasion, when circumstances require it, police reports or insurance company reports are also in the report. See Appendix B for a sample Medical Examiner's report.

1.8 Study Rationale and Hypothesis

The scope and nature of SCD in NL population is unknown. One study from ON using a 2008 cohort assessed the incidence of SCD in persons aged 2-40 years old to be 2.64 per 100,000 (Pilmer et al., 2013). We have chosen this study for comparison because we are able to replicate their rigorous methodology for the exact same year (2008). As well, ON, in contrast to the founder population in NL, is a large Canadian outbred population, thus we will be able to directly compare the incidence of young SCD of a founder population (NL) to an outbred population (ON).

We hypothesize that NL may have a higher incidence of early SCD in this age category due to the known mutations causing heart diseases and unknown underlying genetic causes, given the historical genetic isolation of the population. We hope to better understand the scope and nature of SCD in NL to help inform health policy, therapy, and prevention.

1.9 Study Objectives

The objectives of this study are to:

1. Ascertain the number of SCDs in young persons (ages 2-40) from a provincial registry of medical examiner-referred sudden deaths in 2008.
2. Make a direct comparison with ON, a comparably more outbred population. The initial analysis will focus on ages 2-40 then we will add ages 41-50 to the cohort, as we know that many deaths due to *TMEM43* occur in that decade, as well as due to CAD.
3. Gather data for ages 2-50 from the year 1997 – a year before the ICD was an available treatment in NL – to observe any SCD rate differences with 2008 (a year where treatment was readily available in NL).

2. Methods

2.1 Cohorts of Interest

I collected qualitative data on the years 2008 and 1997. The year 2008 is significant because we can compare our data to an ON study that collected data from the year 2008 (Pilmer et al., 2013). For comparison with our 2008 data, we collected qualitative data from 1997 because it is a year when the ICD, an effective heart disease treatment, was not available for insertion in NL. This is in comparison to 2008, when the ICD was readily available in NL.

The age groups we were interested in are 2-40 and 2-50 years. The 2-40 age group is the range the ON study used, therefore we wanted to have an exact comparison group. We also decided to collect from ages 41-50 because we know that many SCDs occur in this age range, and we want to capture the full spectrum of young SCD.

For simplification purposes, I will refer to the NL 2008 ages 2-40 as cohort A, NL 2008 ages 2-50 as cohort B, and NL 1997 ages 2-50 as cohort C (Table 2.1).

2.2 Data Collection

This epidemiologic study incorporated a retrospective cohort design, with an emphasis on replicating the ON study's methods as closely as possible to allow us to directly compare with their results. Qualitative data was collected on 276 cases. Cases of potential relevance were identified from the database of the OCME of NL (Figure 2.1). All files contained a medical examiner's report, and an autopsy

Table 2.1: Labeling of the cohorts

Cohort group	Labeled Cohort
NL 2008, age 2-40	A
NL 2008, age 2-50	B
NL 1997, age 2-50	C

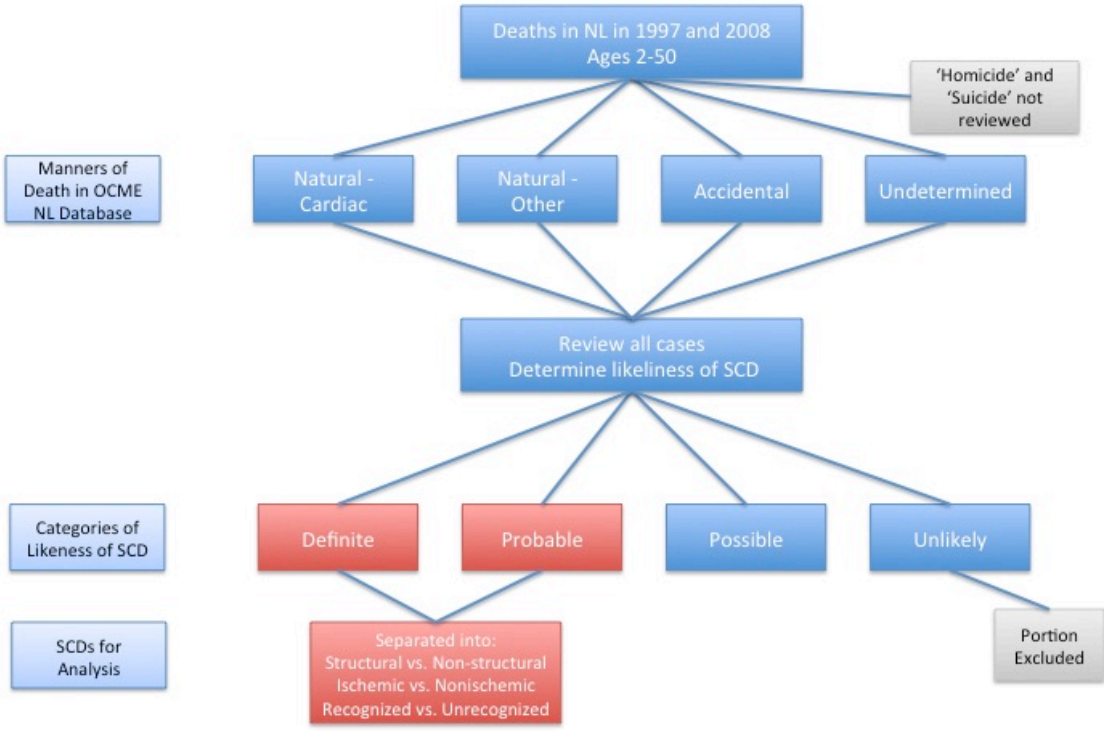

Figure: 2.1: Process of categorizing deaths and assigning to category of SCD.

See Tables 2.1 & 2 for definitions of manners of death and categories of likeliness of SCD, respectively. Red boxes indicate the cases we assigned as SCD and thus analyzed.

report if conducted. Additional information, such as police reports or reports for insurance companies were available depending on the circumstances of the death. See Appendices B and C for a sample Medical examiner's report and the full chart audit form.

SUD was defined as an event resulting in death or terminal life support within 1 hour of collapse, or an unwitnessed, but unexpected death in the absence of a known or suspected condition that may predispose to terminal illness (Eckart et al., 2011). Deaths were further defined as cardiac in origin if there was autopsy-confirmed heart disease with circumstances consistent with a potential cardiac cause of death. SCD was also declared when the autopsy showed no identifiable cause of death, and it was therefore presumed a cardiac arrhythmia took place. SUD below the age of 2 years was considered a separate entity and was not included. A portion of cases did not have an autopsy completed, and SUD was then classified at the discretion of the Chief Medical Examiner.

Cases of potential relevance were reviewed by myself after satisfying 3 inclusion criteria: (1) date of death in 2008 (same year as ON) or 1997, (2) age at death between 2-40 or 41-50, and (3) manner of death (a universal pathologist classification method) listed as "natural-cardiac", "natural-other", "accidental" or "undetermined" (Table 2.2). This yielded 70 cases for 2008 ages 2-40 and 49 cases for 2008 ages 41-50 to review. For 1997, this yielded 90 cases ages 2-40 and 67 cases ages 41-50 to review. Considering the small yield of number of subjects, every case was reviewed in detail. Cases that were not sudden, not unexpected, or not of

Table 2.2: Manners of death used by forensic pathologists.

Manner	Definition
Natural - Cardiac	Death due to natural disease processes in cardiac nature
Natural- Other	Death due to natural disease processes of unknown system
Accidental	Death due to injury where there is no evidence of intent to harm
Undetermined	Inadequate information regarding circumstances of death to determine manner

possible cardiac etiology were excluded after review. For example, cases were excluded when cause of death was clearly non-cardiac, such as sepsis or pneumonia, and as well cases involving passengers and pedestrians of motor vehicle accidents, and house fires.

Data was collected on all 276 cases, which were considered possible SCDs. These data included demographic information, such as date of birth, sex, and death information including date, location, cause, and manner of death. Autopsy findings, especially related to cardiac conditions, were noted, as was any known history of cardiac or other disease. Cardiac pathology discovered on autopsy was listed separately from any known preexisting cardiac conditions. Since the files did not contain copies of the individual's medical charts, previous medical conditions were noted at the discretion of the investigating medical examiner and abstracted by a single investigator.

Additional data collected included premonitory symptoms, nature of physical activity and intensity at the time of death, medication or substance use, cardiac risk factors, and narrative details about the circumstances of death from the available evidence. Premonitory symptoms, symptoms within 24 hours prior to death and also prior to the 24 hours, included potential cardiac symptoms, such as chest pain, shortness of breath, and syncope. Physical activity level at the time of death was determined from the medical examiner's narrative and was classified as during sleep, at rest, during light to moderate activities of daily living (ADLs), during moderate to vigorous exercise or unknown. Subjects were classified as dying at rest

if the event was described as such by an eyewitness or if the decedent was found in a position suggesting rest. Light to moderate ADLs included activities such as housework and other nonphysically strenuous activities such as driving. Moderate to vigorous exercise included any sporting or fitness activities such as swimming and running, as well as any strenuous physical work or chores such as shoveling snow. Further investigations such as requests for additional medical records or personal interviews were not obtained because of the retrospective nature of the study.

2.3 Likeliness of SCD

After I collected all data, each case was reviewed by myself and an expert panel: an experienced expert in genetic cardiac arrhythmias (K.H.), an experienced cardiac genetic counselor (F.C.), and an experienced expert in cardiac pathology and the provincial death investigation system (S.A., Chief Medical Examiner, Province of NL). The expert panel and I, using the same system as ON, categorized each subject into likeliness of SCD. All 276 subjects were assigned to a category of likelihood of SCD by reviewing all data collected, incorporating information from across the file, including medical cause of death, underlying pathology, description of the environment and circumstances, and contributing factors and comorbidities (Table 2.3). The first category, 'sudden death', comprised those who died of sudden death with no additional factors contributing to death (ex. alcohol, toxicology, hazardous conditions) (labeled 'definite'- Table 2.3). This group also included those who had only one contributing factor, other than cardiac disease

Table 2.3: Likeliness of SCD categories.

Categories	Criteria
Sudden Death	
Definite	SCD with no additional factors
Probable	SCD with 1 potential contributing factor
	Examples: 24 year old male died during nap after exercising, 28 year old male found in bed with high alcohol level (not fatal level)
Possible	Accidents with 1 contributing factor
	Example: 27 year old male died in motor vehicle accident in icy weather
Unlikely	Greater than 1 contributing factor
	Example: 49 year old male, canoe overturned, no life jacket, alcohol involved

or primary arrhythmia that was not of sufficient gravity to have caused death (labeled 'probable'- Table 2.3). For example, an individual with positive toxicology (non-lethal) with no other anatomical cause other than a possibly enlarged heart was a presumed arrhythmia. The next category, 'possible sudden death', was for 'accidental' cases whereby there was only one contributing factor, aside from the accident. In essence, this category hoped to capture accidents that may have been caused by an arrhythmia. To note, accidents with zero contributing factors were placed in the 'probable' group. An example of this would be a car accident with no logical contributing factors (high speed, bad weather, alcohol, etc.).

Finally, the last category was 'unlikely', which comprised any deaths that had more than one contributing factor. At this point, we moved a portion of the 'unlikely' s to an exclusion group if they were not sudden, not unexpected, or not of possible cardiac etiology. This was in an effort to keep methodology similar to the ON study.

The 'sudden death' category was further broken down into whether the SCD was caused due to an underlying structural heart issue or no anatomical cause. The structural cases were further categorized into ischemic and non-ischemic. Also noted was whether the structural cases were recognized or unrecognized by the subject prior to death (Figure 2.1).

2.4 Statistical Analysis

I performed all statistical analysis using SPSS version 20. Descriptive statistics were completed, and the Chi-square test was used with the addition of

Fisher's exact test if the sample size was small. A p-value of <.05 was considered significant.

3. Results

3.1 Incidences

In the 2008 2-40 cohort (A), 17 deaths were adjudicated as SCD from an estimated population of 232,210 people (Statistics Canada, 2014b). The number of cases in comparison with the ON cohort is n=17 for NL vs. n=174 for ON, shown in Figure 3.1 (Pilmer et al., 2013). Based on the estimated population, the incidence in NL of cohort A is 7.32/100,000 persons. When the cohort was expanded in 2008 to those aged 50 years old (B), 44 deaths out of a population of 316,244 were adjudged to be SCD (Figure 3.2), giving an incidence of 13.9/100,000 persons. In 1997, 66 deaths out of a population of 406,173 in age's 2-50 cohort (C) were found to be SCD (Figure 3.2), giving an incidence of 16.23/100,000 persons. The incidences for each cohort, and the ON cohort, based on age and the gender breakdown is shown in Table 3.1 and 3.2. See Appendix D for primary data.

Comparing the NL cohort A to the ON data, NL has a significantly higher incidence of SCD than ON ($p<.0001$) (Table 3.1). When comparing age groups between the cohorts, NL becomes significantly higher for age groups 19-29 and 30-40 ($p=.028$ & $p=.008$, respectively) (Table 3.1). There is also a clear trend here that SCD increases with age. There is a gender difference in the NL data, as the cohort is 65% male. While this may present some issues for the study, ON has the same gender bias and the chi-square comparing NL to ON gives a non-significant difference (Table 3.1). Comparing the 2008 NL (B) data to 1997 NL (C), there is a general trend of more SCDs in 1997 but it is a non-significant difference (Table 3.2).

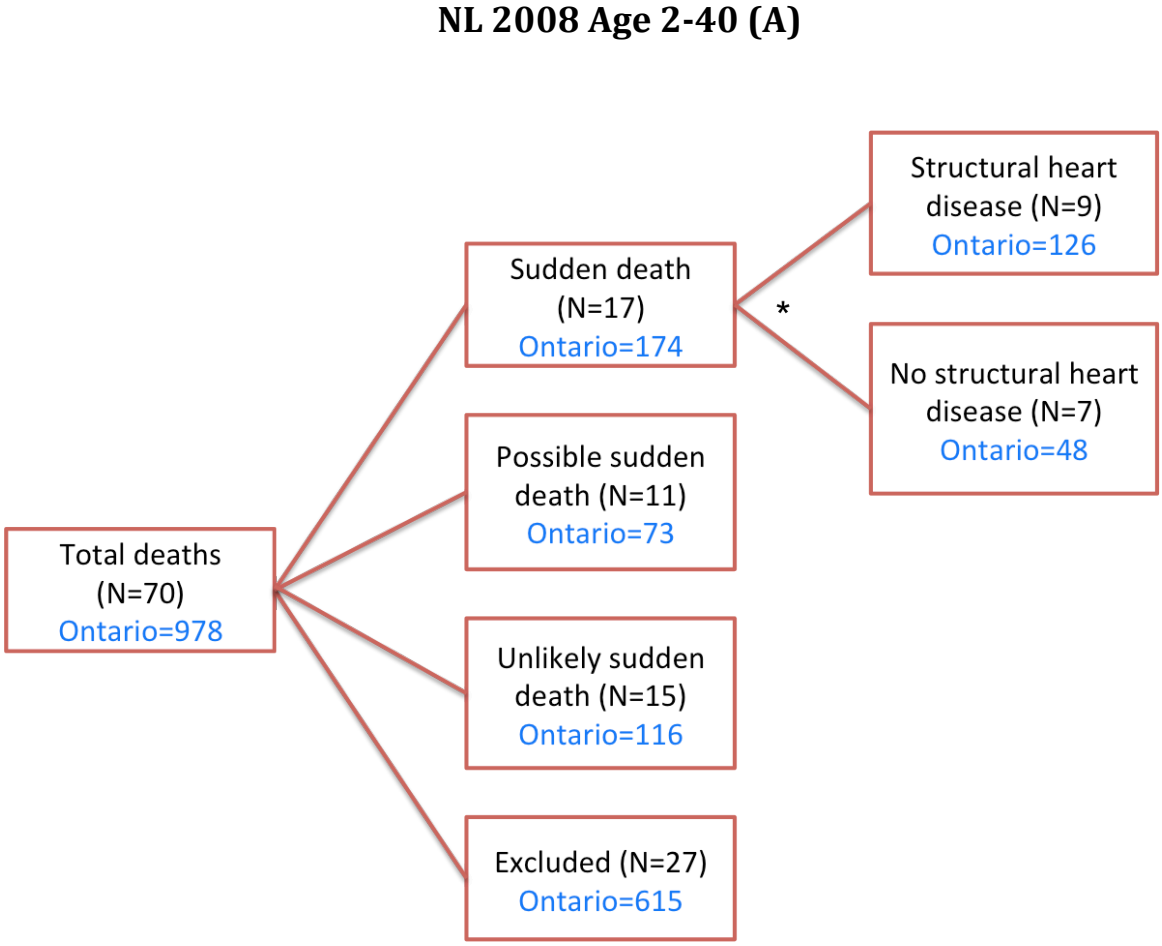

Figure 3.1: Review of all potential SCD cases in NL in 2008 age's 2-40 (A) in comparison to ON (2008, age's 2-40) (Pilmer et al., 2013).

*: Cases with no autopsy could not be segregated any further (n=1)

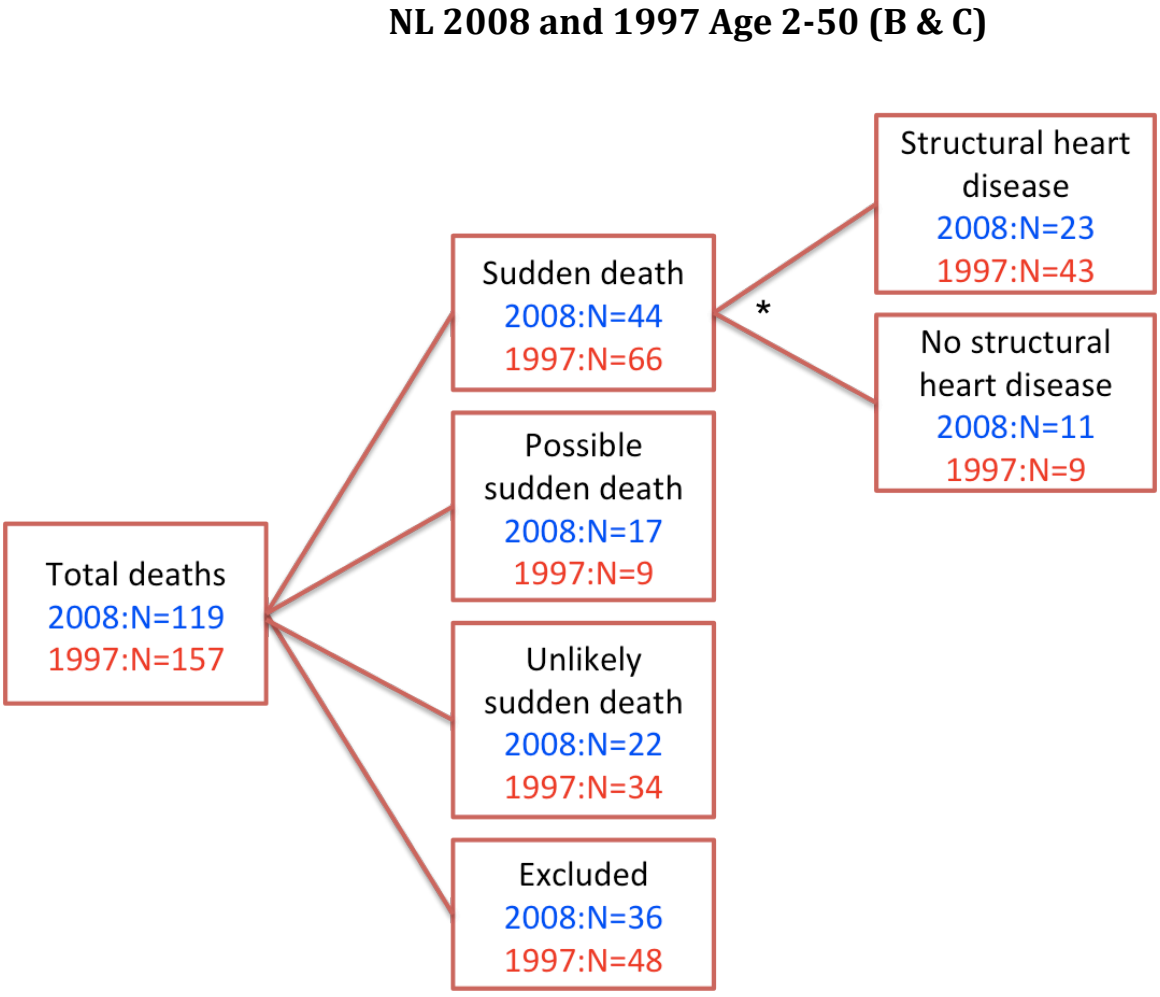

Figure 3.2: Review of all potential SCD cases in NL 2008 in ages 2-50 cohort **(**B**)**, in comparison to NL 1997 age's 2-50 cohort (C).

*: Cases with no autopsy could not be segregated any further (n=10 for 2008, n=14 for 1997)

Table 3.1: Comparisons of incidence and gender for NL 2008 age's 2-40 (A) and ON 2008 ages 2-40 (Pilmer et al., 2013).

* = Significant difference, p<. 05

†= Fishers exact test used, expected cell count <5

See Appendix D for primary data

	NL 2008 2-40 (A)	ON 2008 2-40	Chi-square value, significance (p-value)
Incidences			
Overall	7.32/100,000	2.64/100,000	X^2= 17.625, p<.0001*
Ages 2-18	2.15/100,000	0.7/100,000	X^2= 2.418, p= .158†
Ages 19-29	7.52/100,000	2.4/100,000	X^2= 6.488 p= .028*†
Ages 30-40	13.74/100,000	5.3/100,000	X^2= 8.929 p=.008*†
Gender			
Male (%)	65%	76%	X^2= 1.024, p=.379†

Table 3.2: Comparisons of incidence and gender for NL 2008 age's 2-50 (B) and NL 1997 age's 2-50 (C).

†= Fishers exact test used, expected cell count <5

See Appendix D for primary data

	NL 2008 2-50 (B)	NL 1997 2-50 (C)	Chi-square value, significance (p-value)
Incidences			
Overall	13.9/100,000	16.23/100,000	X^2= .626, p=. 429
Ages 2-18	2.15/100,000	2.32/100,000	X^2= .007, p=1.00 †
Ages 19-29	7.52/100,000	7.70/100,000	X^2= .002, p=. 969
Ages 30-40	13.74/100,000	18.1/100,000	X^2= .486, p=. 486
Ages 41-50	32.1/100,000	43.7/100,000	X^2= 1.496, p=. 221
Gender			
Male (%)	80%	76%	X^2= .216, p=. 642

Gender-wise, we see the same trend here, a male-bias present, but again there is a non-significant difference between the two cohorts (Table 3.2).

3.2 Cause of Death

After excluding the cases without autopsy for analysis, in cohort A there are 9 cases with structural heart problems, and 7 without any identifiable cause. In the older age cohorts, B and C, there are more 'structural' deaths than 'no anatomical cause' deaths (B= 23 'structural', 11 'no anatomical cause', C= 43 'structural', 9 'no anatomical cause' (Figures 3.3 & 3.4). This sharp increase in 'structural' deaths is likely observed due to the added age group (41-50's), as both cohorts possess large structural numbers in these groups (2008= 14, 1997= 24). When comparing the ratio of 'structural' to 'no anatomical cause' between cohort A and ON, there is a non-significant difference (p=. 172). As well, comparing cohort B with cohort C gives a non-significant result (p=. 106). Overall, it is clear there are more structural heart issues in the older population, and more unexplainable deaths appear to be in younger age.

Upon further investigation of the subjects with structural cardiac issues, there were a small number of subjects that recognized a heart issue before death. In cohort A 11.1% had a recognized issue. In cohort B, 4.3% had a recognized issue. In cohort C, 30.2% had a recognized issue.

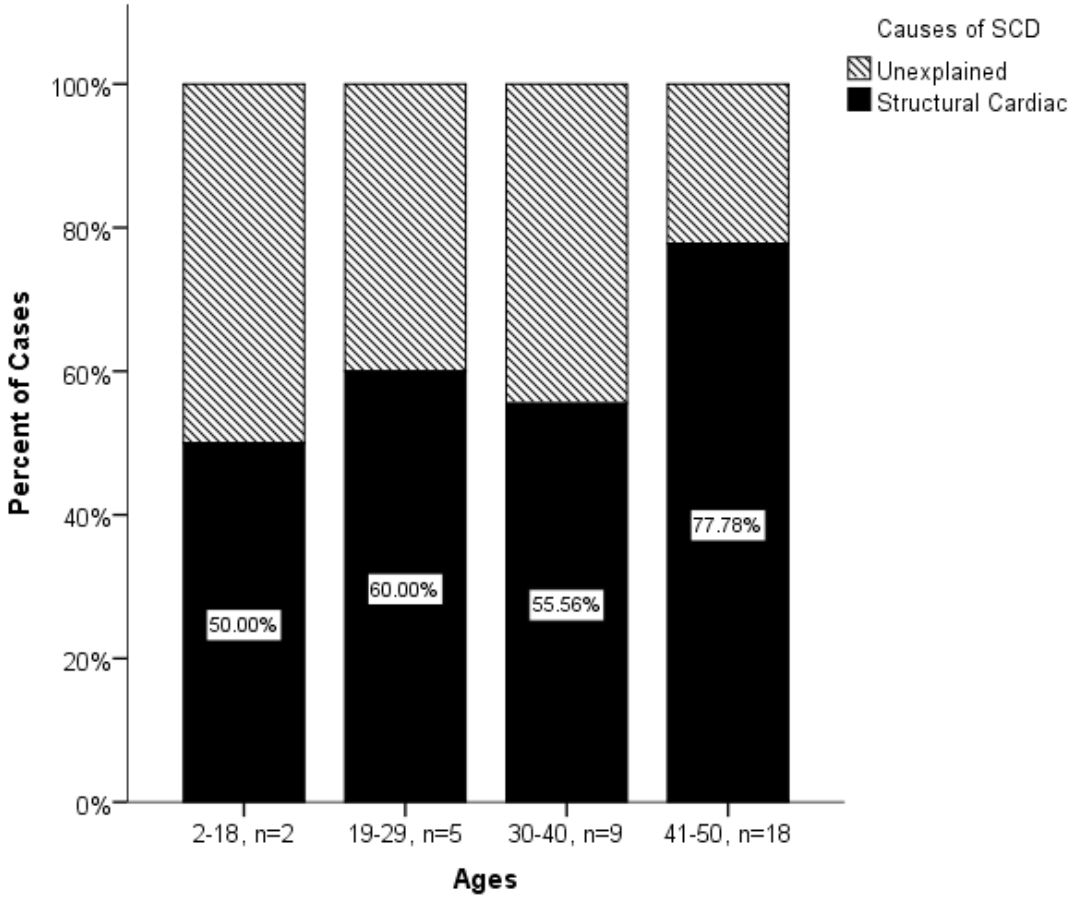

Figure 3.3: Causes of SCD by age in NL 2008 cohort (B).

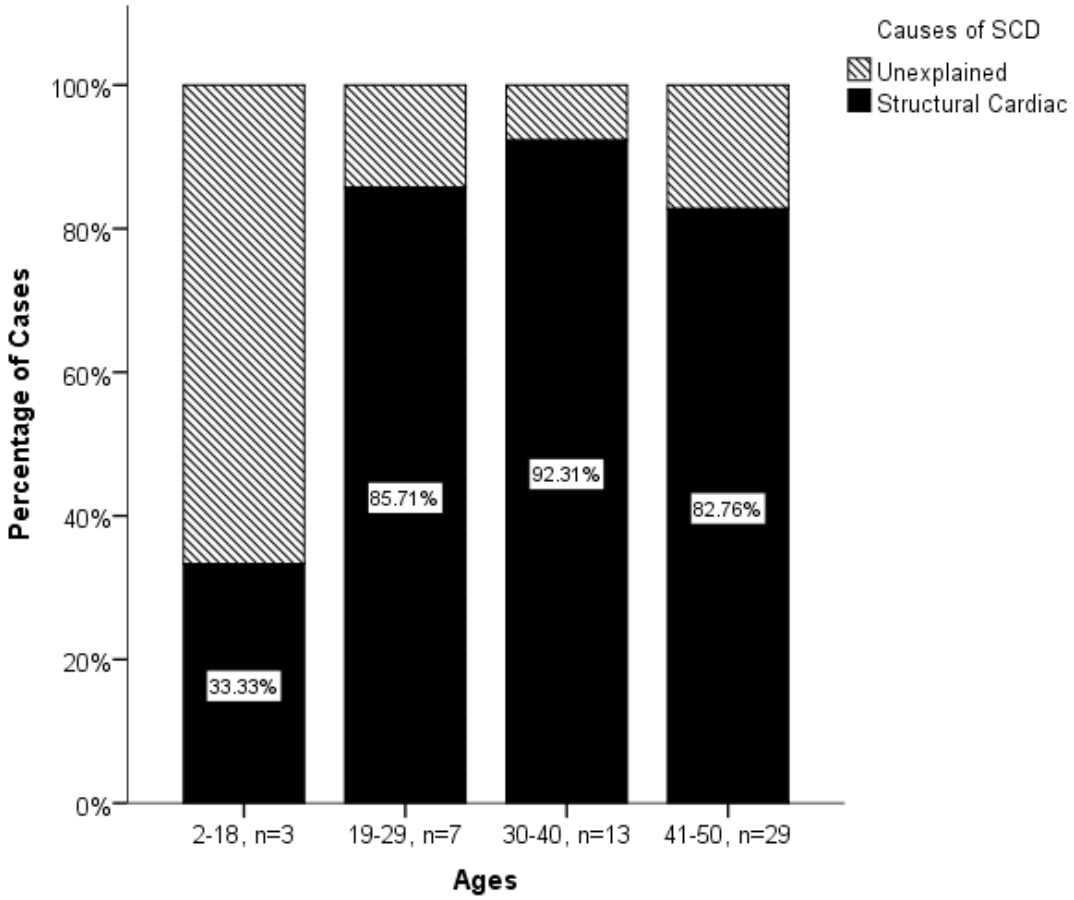

Figure 3.4: Causes of SCD by age in NL 1997 cohort (C).

CAD was a major cause of death in all 3 cohorts. In subjects in the 'structural' disease category, in cohort A, 4/9 (44%) subjects had CAD. In cohort B, 16/23 subjects (70%) had CAD, and in cohort C, 34/43 (79%) subjects had CAD. Looking at the entire cohort, cause of death aside: cohort A had 6/16 (38%) subjects with evidence of CAD, cohort B had 19/34 (56%) of subjects with evidence of CAD, and cohort C had 36/52 (69%) of subjects with evidence of CAD. The ON cohort for 2008 2-40's had 49% (comparison: p= .782) of those with structural heart disease with CAD, and 36% of all SCDs (comparison: p= .918) with CAD. There does not appear to be any difference between NL and ON with respect to CAD.

While CAD played a big role in all three cohorts, the second most common cause of death was 'no anatomical cause'. The 3rd most common category was labeled 'other', which is a miscellaneous category (Figures 3.5 & 3.6).

3.3 Location, Activity Level, & Symptoms

In cohort A, 65% of subjects died in their home. For cohort B, 59% died in their homes, and for cohort C 56% died at home. The small number of cases in each cohort that did not die at home succumbed at work, school, or public places. The ON cohort found that 72% of their subjects died at home (Pilmer et al., 2013).

Examining activity level at time of death shows that the vast majority of cases in 2008 died while at rest or in sleep (cohort A= 71%, cohort B =75%). Cohort C had only 36% of subjects die while at rest or sleep, however, there were

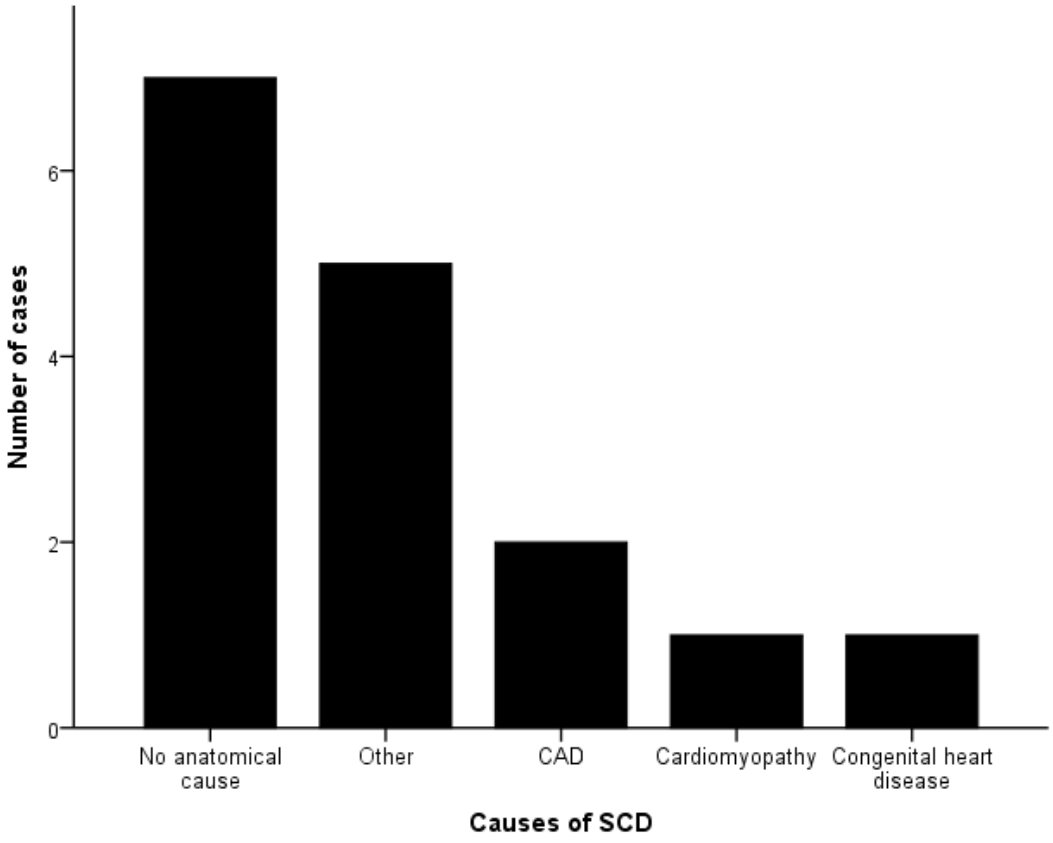

Figure 3.5: Causes of SCD in the 2008 NL 2-40 cohort (A).

'Other' category includes valvular disease, structural anomaly, myocarditis, suspicious car accident, and a drug overdose.

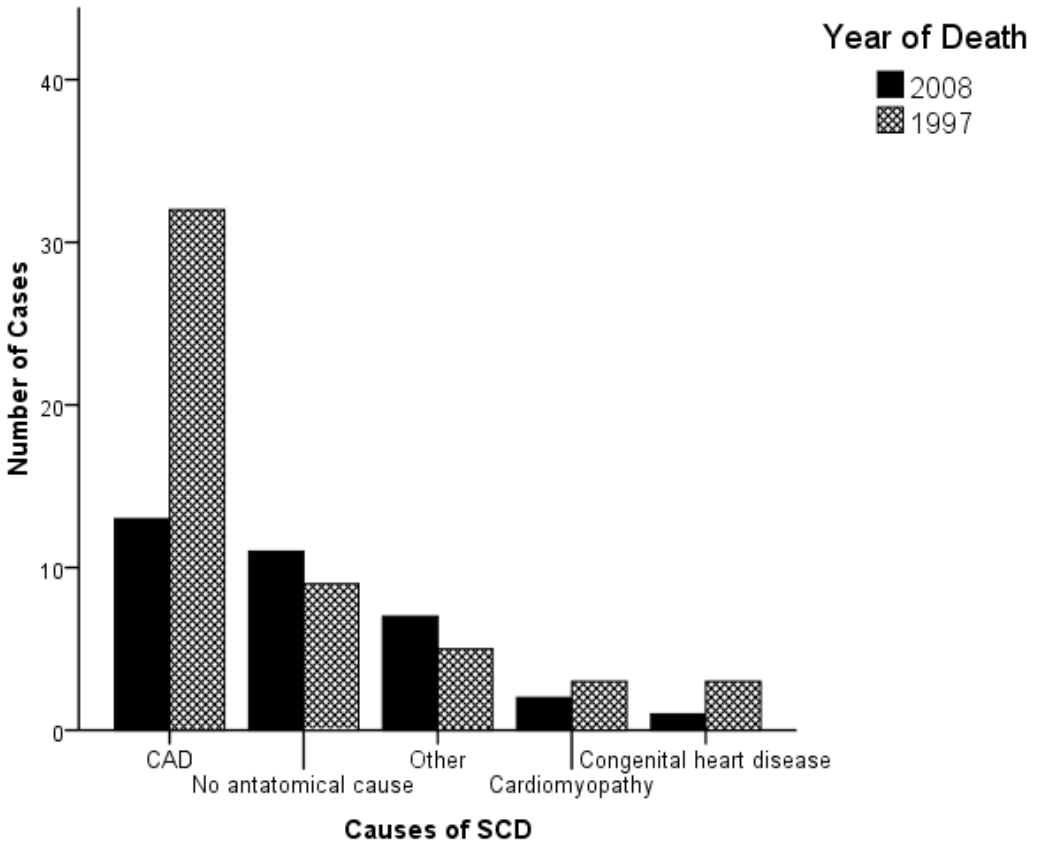

Figure 3.6: Causes of SCD in the 2008 and 1997 NL 2-50 cohort (B & C).

'Other' category includes valvular disease, structural anomalies, myocarditis, suspicious accidents, a drug overdose, a genetic condition, an AV node tumor, and a mitral valve prolapse.

16 cases with 'unknown' locations of death in this cohort due to lack of autopsy report detail. The second largest category for activity level was light-moderate activity. In cohort A, 24% died during light-moderate exercise. In cohort B, 14% of subjects died during light-moderate exercise, and in cohort C, 30% of subjects died during light-moderate exercise. The last category remaining, and also the smallest category, is moderate-vigorous activity. Cohort A, B, and C all had small numbers (5%, 11%, and 9%, respectively). The ON cohort found a similar trend: 11% of their cases died during moderate-vigorous activity (Pilmer et al., 2013). As well, ON found that 33% of their 2-18 age group died during moderate-vigorous activity; however, in our cohorts all moderate-vigorous deaths were above the age of 30. Some examples of moderate-vigorous activities in the NL cohorts are: playing racquetball, manual labor, swimming, and militia training exercise.

In general, there were very few cases in all cohorts that experienced symptoms before death. In cohort A, 3 of 17 subjects had chest pains. Two of these 3 subjects went to a physician for investigation, however both were dismissed (strained muscle in chest and bronchopneumonia). In cohort B, 8 out of 44 had chest pain, while one other person had shortness of breath and one other had presyncope. Three of the 8 individuals sought medical attention, but all were dismissed. In cohort C, 7 had chest pains, 2 had shortness of breath, and 8 had 'other' symptoms (ex. stomach sick, dizzy, heartburn). Nine of these 17 subjects sought investigation, and 6 were dismissed. Three were awaiting further cardiac investigation.

4. Discussion

The question this current study poses is whether the scope and nature of SCD in NL is of significance, and whether it is a greater health issue in NL than ON. We hypothesized that NL may have a higher incidence of early SCD in this age category due to the known mutations causing heart diseases and unknown underlying genetic causes, given the historical genetic isolation of the population. We ascertained cases of sudden death (SD) for the year 2008 and 1997 (prior to the availability of ICDs in NL) and each case was analyzed to determine likelihood of SCD. The 2008 cohort (A) was compared to a similar ON cohort. We found that there is a statistically significant increased incidence of SCD in ages 2-40 in comparison with ON in 2008. We also found that the incidence of SCD increases with age, and males are more often the victims when compared to the opposite gender. With regards to cause of death, younger individuals often show no anatomical cause on autopsy and older individuals tend to show more structural cardiac issues. Any structural conditions present were most often previously undiagnosed. The majority of deaths took place while at rest at home, and symptoms leading up to death were uncommon.

4.1 Incidence

In all cohorts we found a high incidence of SCD. Similar numbers are noted between 2008 and 1997, for all age groups. The study was created with similar methodology to Pilmer et al. (2013) for making direct comparisons with another Canadian province. They found that for ages 2-40 in the year 2008 the incidence was 2.64 per 100,000 persons. As already noted, our incidence surpasses this by almost 3 times.

Finding other comparable studies is a difficult task as methodology varies greatly throughout the literature. This variation often involves the nature of the study (retrospective or prospective), different age groups, criteria for inclusion or exclusion of the SD group, and inclusion or exclusion of non-autopsied cases. There is one other significant study in Canada (British Columbia) that assessed incidence of SCD in those aged 0-35 from 2005-2007 (Lim et al., 2010). Lim et al. (2010) examined all deaths that were placed in the 'natural' and 'undetermined' categories, and 'accidental' deaths were not included. Using similar inclusion and exclusion criteria to ours, they found the incidence of SCD was 1.75 per 100,000 persons per year (Appendix E). NL truly has a higher incidence.

Other studies with fairly comparable methodology were completed in Ireland, England, and Denmark (See comparison table in Appendix E). In Ireland, a group of researchers looked at SCD in ages 15-35 from 2005-2007 (Margey et al., 2011). The same definition of sudden death was used as our NL study. Unlike the current study, all cases with any presence of drugs that are known to cause SCD (ex. cocaine, high alcohol) were excluded. The incidence found was 2.85/ 100,000 persons per year. In England and Wales, researchers examined deaths from ages 1-34 through years 2002-2005 (Papadakis et al., 2009). Their classification system did include some 'accidental' deaths, such as drowning incidents, as they recognized these might represent misclassified cardiac deaths. Overall, they found an incidence of 1.8/ 100, 000 persons per year.

There were two studies completed in Denmark spanning nine years (2000-2009) that used the same methodology (Risgaard, Winkel, Jabbari, Behr, et al., 2014; Winkel et al., 2011). These methods closely resemble ours, and their age group reached age 49 which we can compare to with our age 2-50 cohort. Another similarity is that they included non-autopsied cases. We do differ in the use of extra information outside the autopsy file: these studies used the Danish National Patient Registry for supplementary health information on patients. For the age group 1-35, the 2011 and 2014 studies found similar results: 2.8 per 100,000 person years and 2.3 per 100,000 persons, respectively. Interestingly, NL differs in the older age groups: Risgaard et al. (2014) found that for ages 1-49 the incidence was 8.6 per 100,000 persons and for ages 36-49 the incidence was 21.7/100,000. NL has an overall higher incidence in our 2-50 age groups, however, 8.6/100,000 is the next highest value found in the literature. The incidence for ages 36-49 is much higher than our comparable values (13.7/100,000 and 18.1/100,000 for 2008 and 1997, cohorts B & C, respectively). A possible explanation for this hike in incidence might be due to their greater percentage of non-autopsied cases (51%) compared to our 23% (2008) and 21% (1997) of non-autopsied cases. As well, it was already noted these studies had access to a much greater amount of health data on the subjects.

A consistent trend, shown in every one of these studies reviewed, is SCD increases in numbers with increasing age, and that it is certainly more common in males (Lim et al., 2010; Margey et al., 2011; Papadakis et al., 2009; Pilmer et al., 2013; Risgaard, Winkel, Jabbari, Behr, et al., 2014). The actual incidences of SCD are

not such a consistent trend; we have a higher spectrum of numbers. The most likely explanation for the spike in numbers is that NL is a founder population. We directly compared with a comparably more outbred population (ON) and found NL to have a significantly higher SCD incidence. It has been established that there are lethal SCD genes present in NL (Merner et al., 2008), and this may account for the higher incidence. Certainly we know that *TMEM43* plays a role in SCD in NL; however, we also know that there are multiple mutations present in NL as our clinic has 649 families referred total, and the category/condition with the largest number of families is SCD (K. Hodgkinson, personal communication, September 25th, 2014).

To confirm our suspicions of genetic etiology of young SCD in NL we hope to perform DNA testing of the victims in our present cohort with a panel of genetic mutations, TMEM43 included. When genetic testing is completed at time of autopsy, it is referred to as a molecular autopsy. It is a crucial step for identifying cause of young SCD, especially when there are no structural findings on autopsy. This has been done before in various studies and has shown diagnostic yield of the molecular autopsy to be up to 35% (D. J. Tester & Ackerman, 2007; D. J. Tester, Spoon, Valdivia, Makielski, & Ackerman, 2004). Other studies report different numbers (Dean et al., 2015; D. J. Tester, Medeiros-Domingo, Will, Haglund, & Ackerman, 2012), within a 0-35% range, that may be a reflection of a variety of clinical and methodological issues relating to selection bias of population studied, genetic mutations included on the panel etc. (Semsarian, Ingles, & Wilde, 2015).

The pertinent question is: what else could cause this increase? Lifestyle factors come to mind, and more specifically obesity. Obesity is linked with SCD (Tavora et al., 2012), and NL is one of the 'heaviest' provinces in Canada (Canada, 2011; Twells et al., 2014). The comorbidities associated with obesity are proven risk factors for heart disease (Luo et al., 2007; Van Gaal, Mertens, & De Block, 2006; Zalesin, Franklin, Miller, Peterson, & McCullough, 2011). Conversely, it is possible for obese persons to be living without any comorbidity at all, which begs the question: is obesity alone a causative factor for SCD? To further understand how obesity is contributing to SCD, we need to see the health records of the SCD subjects. In saying so, lifestyle factors will be looked at more in-depth in upcoming studies.

4.2 Causes of Death

From autopsy review, information on cause of death can be deducted. We found in cohort A that 9/16 (56%) had structural abnormalities noted on autopsy, while 44% could not be given a cause of death, as no anatomic abnormalities were present. This ratio between 'structural' and 'no anatomical cause' was similar to what Pilmer et al. (2013) found (non-significant difference). As previously discussed, we have found that NL has a higher incidence of SCD than ON. The results show that NL has proportionally more deaths in arrhythmic deaths *and* structural deaths; neither category alone accounts for the difference between NL and ON. With the notion that arrhythmias are often due to a genetic cause and that the majority of structural deaths come from CAD, this could possibly mean that NL has more genetic related cardiac deaths.

Similar proportions of numbers can be noted in other studies as well. In a comparable retrospective study in Australia, autopsies were reviewed between 1994-2002 in those aged 35 and less (Doolan et al., 2004). This review showed that 31% of SCDs had no established cause of death. In the Irish review conducted by Margey et al. (2011) on 14-35 year olds, they found that 26.7% of SCD victims had SADS (sudden arrhythmic death syndrome) – a synonym for no anatomical cause found on autopsy. In both of these studies, the category of 'no anatomical cause' was considered the highest in their cohorts.

Contrary to this, the English study on those ages 1-34 years found ischemic heart disease to be the highest category (33.5%) with SADS in third at 14% (Papadakis et al., 2009). In the Veneto region of Italy a study was completed whereby they analyzed 273 SCDs in the time frame of 1979-1998 (Corrado et al., 2001). The cases were analyzed in a similar manner as previously mentioned studies, however there was further microscopic and histologic analysis than in comparable studies. They initially found that 28% of their cases appeared to have no anatomical cause of death- a number similar to other reports. However, with further analysis, 79% of those cases were found to have actual physiological issues discovered with a more thorough autopsy, leaving only 6% of the 273 victims to have died with no anatomical cause of death. This is an interesting and unique finding, and speaks to the idea that we may need more rigorous and thorough autopsies on possible SCDs.

CAD was widespread in our study, being the top cause of death in the 2008 and 1997 age's 2-50 cohorts (B & C), and 3rd in 2008 2-40 cohort (A). ON showed a similar amount of CAD in their cohort (non-significant difference). In the Danish study by Risgaard et al., they, similar to us, examined an older cohort, 1-49 years old (2014). Their most common cause of death was CAD (158/439; 36%). Another study with an older age sample was completed in the United States by Eckart et al. (2011). They found that for subjects ≥35 years the leading cause of death was CAD, with an incidence of 13.69 per 100,000 person-years for those ≥35 years. Both of these studies report the same trend that our study also corroborates: in those ≤35 years old, SUD is significantly more common than CAD ($p<.001$), and in those ≥35 years old, CAD is significantly more common than SUD ($p<.001$) (Eckart et al., 2011; Risgaard, Winkel, Jabbari, Behr, et al., 2014).

It is clear from our study and previous literature that there is a portion of deaths that appear to be due to an arrhythmia, as no cause of death is found on autopsy. These deaths tended to occur in the younger ages. Genetic testing at time of autopsy would help clarify the cause of these deaths by possibly diagnosing a channelopathy. As for structural diseases, CAD is the most prevalent and most commonly reported in the literature, and tends to effect the older populations.

4.3 Circumstances of Death

The current study shows that the majority of victims of SCD died during rest or during sleep, with the smallest proportion dying during moderate to vigorous

activity. In the SCD field of research, athletic activity has long been under suspicion for causing SCD (Maron, Roberts, McAllister, Rosing, & Epstein, 1980). There is an abundance of evidence to support this theory (Harmon, Drezner, Wilson, & Sharma, 2014); however, it appears that SCD is more prevalent in the general population, and here athletic activity is not the causative agent (Risgaard, Winkel, Jabbari, Glinge, et al., 2014). The ON study found a similar result, with 11% of SCDs occurring during moderate-vigorous activity (Pilmer et al., 2013). This is further corroborated by the Irish group that found 7.7% (9/116) of subjects. SCDs occurred during athletic activity while the majority died during rest or sleep (Margey et al., 2011). Finally, the same result was seen in Denmark where only 11% (43/409) of subjects died during vigorous activity while 84% (347/409) of subjects died during rest or sleep (Winkel et al., 2010).

Ascertaining whether the victim was symptomatic or not before death can be a challenging task, as it is not always properly documented and we did not have access to medical records. We found that only a small percentage of victims in all cohorts displayed any premonitory symptoms. The literature tends to agree with this finding. Eckart et al. (2011) documented symptoms in 278 (53%) of those who died, such as chest pain, dyspnea, and syncope. While this is indeed a higher number than we found, they agreed that it is difficult to obtain any prodrome as it most often occurs immediately antecedent to death. Contrary to these findings, a recent study examined CAD victims (age 1-35 years) by comparing their symptoms with sex and age matched controls that died in accidents (Jabbari et al., 2013). They found that

62% of young persons with SCD experienced angina before death. There is a wide spectrum of causative diseases and syndromes that cause SCD, therefore it is logical that there may be a wide spectrum of symptoms as well.

4.4 Limitations

Notably, a few limitations are present regarding discrepancies between our study and the ON study. Most importantly, we endeavored to design our study based directly on the ON published manuscript (Pilmer et al., 2013), which was lacking in explicit methodology in some areas. For example, the manner in which they made exclusions was unclear, and led to us using a slightly different process. That being said, the data used for primary analysis (the 'sudden death' group) was collected exactly as ON indicated, therefore overall this is a minor limitation. It's also challenging to directly compare ourselves to ON when we have knowingly used a completely different panel of individuals to assess the likeliness of SCD. However, for NL to reach a non-significant difference compared to ON, we would have had to incorrectly assess 6 deaths, as non-significance ($p>.05$) is reached at 11 sudden deaths (we had 17). Proportionally, this is a large number to have erred and is thus unlikely.

More limitations stem from the retrospective nature of this study. Data collection was limited to what was in the files – which at times was missing information - as the primary purpose of these files is to satisfy pathology requirements, not SCD requirements. To stay true to the design and the ON study, we did not attempt to look for additional information elsewhere. For example, not

every file included toxicology info, which may contribute to SCD. However, the vast majority had toxicology in the file when the circumstances of death suggested it.

Another important limitation that became apparent with file review was the different standard of autopsy reporting between pathologists. While the Chief Medical Examiner reviews all autopsies, there are certainly differences between files depending on the pathologist who performed the autopsy. Firstly, not all subjects had autopsies, which is typically at the discretion of the pathologist, and sometimes the families. This often occurred in motor vehicle accidents, where cause of death was presumed to be the accident. In our analysis, however, the main 'sudden death' group (2-40) had only 1 subject without autopsy, thus it likely did not impact our final result. Also dependent on the pathologist is the list of major findings for an autopsy, noted on the first page. We found that some lists would be missing a SCD major finding, of for example an enlarged heart, while others might have included it - it was not consistent. This could easily influence a reader of an autopsy to miss the finding of an enlarged heart, as the 'major findings' are summarized on the first page. An example of this was a case of a 27 year old male involved in a skidoo accident, with cause of death presumed asphyxia/drowning, and incidentally had a 650g heart and fat in the right ventricle. The cardiomegaly here was not researched any further and was listed with no further investigations. For our study, we paid attention to the entirety of the autopsy and this type of incidental finding was not likely to be have been missed.

Finally, something that is missing from most autopsies is the molecular pathology. This would indicate whether the subject had any significant genetic mutations that could have caused their death. Very few of the reviewed files included this, as it is not yet part of the standard autopsy. We are hoping to review DNA from fixed blocks in a future study.

On a final note, the sample size in this study is small, however, it is as large as it can be given our population numbers. With this, it is possible we are missing some significant relationships in the data because our numbers are too small to show significance. We are currently working to collect more data from different years to hopefully better this issue.

4.5 Strengths

A significant strength of this study is that we are essentially a single-center study that captures all cases in NL. We do indeed have a centralized database, but more than that is that all cases in NL are sent directly to the Chief Medical Examiner (S.A.) to be reviewed, which limits any bias in ascertainment because we used a single assessor. Additionally, it increases the likelihood that we captured all SCD cases in NL in 2008 and 1997. Another important advantage of the study is that it was designed as closely as possible to replicate a non-founder population (ON) study, allowing us to make a direct comparison between founder and non-founder populations.

4.6 Future Research and Conclusion

This study is the very first piece of the puzzle; it provides the basic information we need to start understanding the burden SCD causes in NL. We know already there are genetic mutations in the NL population, and now we have a potential measure of this effect. To confirm that the deaths we measured are an outcome of genetics, a next step would be to investigate molecular studies; all SCD subjects in 2008 have fixed tissue blocks, we will be testing these for mutations. It would also be important to examine lifestyle and environmental factors in future studies that might be responsible for the effect we have seen. Finally, we will assess more years to confirm the numbers we have described, to make sure the incidence rates are consistent over time. It is reassuring, however, that we found a very similar incidence for the year 1997, which would indicate the numbers from 2008 are not outliers.

To conclude, NL has a significantly higher incidence of SCD in the 2008 2-40 year old cohort than the comparable ON cohort. These deaths comprise both structural and arrhythmogenic diseases, with the trend of more arrhythmogenic issues in the young and more structural disease with age. The incidence of SCD increases with age, and is more prevalent in males. The burden that the NL population endures is still not fully understood, however, this study has brought to light that SCD is a significant source of young death in the province, and will inform health policy in a way that will hopefully work to prevent many future sudden deaths.

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Appendices

Appendix A – Current Known Gene Mutations Discovered with a Potential for SCD ("ClinVar," 2014; "Gene," 2014; "MalaCards Human Disease Database," 2014)

Cardiac Disease	Gene	Locus	Official full name
Hypertrophic Cardiomyopathy	ACTC1	15q14	actin, alpha, cardiac muscle 1
	CALR3	19p13.11	calreticulin 3
	CAV3	3p25	caveolin 3
	CMH21	7p12.1-q21	cardiomyopathy, familial hypertrophic, 21
	COA5	2q11.1	cytochrome c oxidase assembly factor 4
	CSRP3	11p15.1	cysteine and glycine-rich protein 3
	JPH2	20q13.12	junctophilin 2
	MT-ATP6	--	mitochondrially encoded ATP synthase 6
	MT-TG	--	mitochondrially encoded tRNA glycine
	MT-TH	--	mitochondrially encoded tRNA histidine
	MT-TI	--	mitochondrially encoded tRNA isoleucine
	MYBPC2	19q13.33	myosin binding protein C
	MYBPC3	11p11.2	cardiac myosin-binding protein C, fast type
	MYH6	14q12	myosin, heavy chain 6,cardiac muscle, alpha
	MYH7	14q11.2-q12	β-myosin heavy chain
	MYL2	12q24.11	myosin, light chain 2, regulatory, cardiac, slow
	MYLK2	20q13.31	myosin light chain kinase 2
Hypertrophic Cardiomyopathy Cont'd	MYL3	p21.3-p21.2	myosin light chain 3,alkali; ventricular, skeletal, slow
	MYO6	6q13	myosin VI
	MYOZ2	4q26-q27	myozenin 2

	NDUFV2	18p11.22	NADH dehydrogenase flavoprotein 2, 24kDa
	NEXN	1p21.1	nexilin (F actin binding protein)
	PLN	6q22.1	phospholamban
	PRKAG2	7q36.1	protein kinase, AMP-activated, gamma 2 non-catalytic subunit
	SLC25A4	4q35	solute carrier family 25 (mitochondrial carrier; adenine nucleotide translocator), member 4
	TCAP	17q12	titin-cap
	TNNC1	3p21.1	troponin C type 1 (slow)
	TNNI3	19q13.4	troponin I type 3 (cardiac)
	TNNT2	1q32	cardiac troponin T type 2
	TPM1	15q22.1	tropomyosin 1 (alpha)
	TTN	2q31	titin
	VCL	10q22.2	vinculin
Arrhythmogenic Right Ventricular Cardiomyopathy/ Dysplasia	CTNNA3	10q22.2	catenin (cadherin-associated protein), alpha 3
	DSC2	18q12.1	desmocollin 2
	DSG2	18q12.1-q12.2	desmoglein 2
	DSP	6p24	desmoplakin
	JUP	17q21	junction plakoglobin
	PKP2	12p11	plakophilin 2
	RYR2	1q43	ryanodine receptor 2 (cardiac)
Arrhythmogenic Right Ventricular Cardiomyopathy/ Dysplasia Cont'd	TGFB3	14q24	transforming growth factor, beta 3
	TMEM43	3p25.1	transmembrane protein 43

Dilated Cardiomyopathy	ABCC9	12p12.1	ATP-binding cassette, sub-family C (CFTR/MRP , member 9
	ACTC1	15q14	actin, alpha, cardiac muscle 1
	ACTN2	1q42-q43	actinin, alpha 2
	BAG3	10q25.2-q26.2	BCL2-associated athanogene 3
	CMD1B	9q13-q22	cardiomyopathy, dilated 1B (autosomal dominant)
	CMD1H	2q14-q22	cardiomyopathy, dilated 1H (autosomal dominant)
	CMD1K	6q12-q16	cardiomyopathy, dilated 1K (autosomal dominant)
	CMD1Q	7q22.3-q31.1	cardiomyopathy, dilated 1Q (autosomal dominant)
	CRYAB	11q22.3-q23.1	crystallin, alpha B
	CSRP3	11p15.1	cysteine and glycine-rich protein 3
	DES	2q35	desmin
	DMD	Xp21.2	dystrophin
	DNAJC19	3q26.33	DnaJ (Hsp40)homolog, subfamily C, member 19
	DOLK	9q34.11	dolichol kinase
	DSG2	18q12.1-q12.2	desmoglein 2
	DSP	6p24	desmoplakin
	EYA4	6q23	EYA transcriptional coactivator and phosphatase 4
	FHL2	2q12.2	four and a half LIM domains 2
	FKTN	9q31-q33	fukutin
Dilated Cardiomyopathy Cont'd	FOXD4	9p24.3	forkhead box D4
	GATAD1	7q21-q22	GATA zinc finger domain containing 1

	GJA5	1q21.1	gap junction protein, alpha 5, 40kDa
	KCNH2	7q36.1	potassium voltage-gated channel, subfamily H (eag-related), member 2
	LAMA3	18q11.2	laminin, alpha 3
	LAMA4	6q21	laminin, alpha 4
	LDB3	10q22.3-q23.2	LIM domain binding 3
	LMNA	1q22	lamin A/C
	MT-TH	--	mitochondrially encoded tRNA histidine
	MT-TY	--	mitochondrially encoded tRNA tyrosine
	MURC	9q31.1	muscle-related coiled-coil protein
	MYBPC3	11p11.2	myosin binding protein C, cardiac
	MYH6	14q12	myosin, heavy chain 6,cardiac muscle, alpha
	MYH7	14q12	myosin heavy chain 7, cardiac muscle, beta
	MYPN	10q21.3	myopalladin
	NEXN	1p21.1	nexilin (F actin binding protein)
	PDCD1	2q37.3	programmed cell death 1
	PLN	6q22.1	phospholamban
	PRDM16	1p36.23-p33	PR domain containing 16
	PSEN1	14q24.3	presenilin 1
	PSEN2	1q42.13	presenilin 2
	RAF1	3p25	Raf-1 proto-oncogene, serine/threonine kinase
Dilated Cardiomyopathy Cont'd	RBM20	10q25.2	RNA binding motif protein 20
	RYR2	1q43	ryanodine receptor 2 (cardiac)

	SCN5A	3p21	sodium channel, voltage-gated, type V, alpha subunit
	SDHA	5p15	succinate dehydrogenase complex, subunit A, flavoprotein
	SGCD	5q33-q34	sarcoglycan, delta (35kDa dystrophin-associated glycoprotein)
	TAZ	Xq28	tafazzin
	TCAP	17q12	titin-cap
	TMPO	12q22	thymopoietin
	TNNC1	3p21.1	troponin C type 1 (slow)
	TNNI1	1q12	troponin I type 1 (skeletal, slow)
	TNNI3	19q13.4	troponin I type 3 (cardiac)
	TNNT2		troponin T type 2 (cardiac)
	TPM1	15q22.1	tropomyosin 1 (alpha)
	TTN	2q31	titin
	TXNRD2	22q11.21	thioredoxin reductase 2
	VCL	10q22.2	vinculin
	ZASP	7	ZO-2 associated speckle protein
Long QT Syndrome	AKAP9	7q21-q22	A kinase (PRKA) anchor protein 9
	ALG10	12p11.1	ALG10, alpha-1,2-glucosyltransferase
	ANK2	4q25-q27	ankyrin 2, neuronal
	ANKB	4q25-q27	ankyrin B
	CACNA1C	2p13.3	l-type calcium channel
	CALM2	2p21	calmodulin 2 (phosphorylase kinase, delta)
	CAV3	3p25	caveolin 3
	KCNE1	21q22.12	potassium voltage-gated channel, Isk-related family, member 1
Long QT Syndrome Cont'd	KCNE2	21q22.12	potassium voltage-gated channel, Isk-related family,

			member 2
	KCNH2	7q36.1	potassium voltage-gated channel, subfamily H (eag-related), member 2
	KCNJ2	17q24.3	K inwardly-rectifying channel, subfamily J, member 2
	KCNJ5	11q24	potassium inwardly-rectifying channel, subfamily J, member 5
	KCNQ1	11p15.5	potassium voltage-gated channel, KQT-like subfamily, member 1
	NOS1AP	1q23.3	nitric oxide synthase 1 (neuronal) adaptor protein
	SCN4B	11q23.3	sodium channel, voltage-gated, type IV, beta subuni
	SCN5A	3p21-p24	sodium channel, voltage-gated, type V, alpha subunit
	SNTA1	20q11.2	syntrophin, alpha 1
Catecholaminergic Polymorphic Ventricular Tachycardia	ANK2	4q25-q27	ankyrin 2, neuronal
	ASPH	8q12.1	aspartate beta-hydroxylase
	CALM1	14q32.11	calmodulin 1 (phosphorylase kinase, delta)
	CALR	19p13.3-p13.2	calreticulin
	CAMP	3p21.3	cathelicidin antimicrobial peptide
Catecholaminergic Polymorphic Ventricular Tachycardia Cont'd	CASQ2	1p13.3	calsequestrin 2

	FKBP1B	2p23.3	FK506 binding protein 1B, 12.6 kDa
	KCNJ2	17q24.3	K inwardly-rectifying channel, subfamily J, member 2
	RYR1	19q13.1	ryanodine receptor 1 (skeletal)
	RYR2	1q43	ryanodine receptor 2 (cardiac)
	TRDN	6q22.21	triadin
Brugada syndrome	CACNA1C	2p13.3	calcium channel, voltage-dependent, L type, alpha 1C subunit
	CACNB2	10p12	calcium channel, voltage-dependent, beta 2 subunit
	GPD1L	3p22.3	glycerol-3-phosphate dehydrogenase 1-like
	HCN4	15q24.1	hyperpolarization activated cyclic nucleotide-gated potassium channel 4
	KCNE3	11q13.4	potassium voltage-gated channel, Isk-related family, member 3
	SCN1B	19q13.1	sodium channel, voltage-gated, type I, beta subunit
	SCN3B	11q23.3	sodium channel, voltage-gated, type III, beta subunit
	SCN5A	3p21-p24	sodium channel, voltage-gated, type V, alpha subunit
Short QT Syndrome	CACNA2D1	7q21-q22	calcium channel, voltage-dependent, alpha 2/delta subunit 1
Short QT Syndrome Cont'd	KCNH2	7q36.1	potassium voltage-gated channel, subfamily H (eag-related), member 2
	KCNJ2	17q24.3	K inwardly-rectifying

			channel, subfamily J, member 2
	KCNQ1	11p15.5	potassium voltage-gated channel, KQT-like subfamily, member 1

Appendix B – Sample Medical Examiner's report

Newfoundland & Labrador
Office of the Chief Medical Examiner

Form ME 3

FINAL REPORT

File Number [redacted]

Name [redacted] Age 28 Sex M Date of Birth [redacted]

Date of Death 97/6/30 Place of Death [redacted]

Address [redacted]

Occupation [redacted]

Immediate cause of death (a) Cardiac arrhythmia

DUE TO or as a consequence of

(b) Arrhythmogenic right ventricular dysplasia

DUE TO or as a consequence of

(c)

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

Autopsy: (Yes) No Name of pathologist [redacted]

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

Circumstances of Death: 28 yr old ♂ ε FH of ARVD, witnessed collapse.

In your opinion was this death preventable? Yes (No)

Public inquiry recommended Yes (No)

Comments:

Name and Address of attending physician

Date body released 97/7/1 Funeral Home

I, [redacted] a medical examiner for the Province of Newfoundland & 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.

[redacted] 97/8/10 [redacted]

Medical Examiner Date Chief Medical Examiner

OFFICE OF THE CHIEF MEDICAL EXAMINER

Appendix C- Chart Audit Form

Data Collection
Autopsy #
Study Number
Postal Code
Year of Birth
Date of death
Sex
Height (cm)
Weight (kg)
BMI
Manner of Death
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
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 D - Primary data used for analysis.

NL and ON population data: Stats Canada (Statistics Canada, 2014b) and Pilmer el, 2013, respectively.

	NL 2008 2-40 (A) & 2-50 (B)		NL 1997 2-50 (C)		Ontario 2008 2-40	
	Deaths (n=)	Population size	Deaths (n=)	Population size	Deaths (n=)	Population size
Overall	17 (A) 44 (B)	232,210 (A) 316,244 (B)	66	406,713	174	6,602,680
Ages 2-18	2	92,982	3	129,125	19	2,652,751
Ages 19-29	5	66,452	7	90,909	47	1,945,419
Ages 30-40	10	72,776	18	99,593	105	1,980,743
Ages 41-50	27	84,034	38	87,043		
Male (n/total deaths)	11/17 (A) 35/44 (B)		50/66		132/174	

Appendix E – Comparison of incidences across the literature

Author	Population	Year	Age Group	Incidence (person-years)	Key Differences
Current study	NL, Canada	2008	2-40 years	7.32/100,000	N/A
Current study	NL, Canada	2008	2-50 years	13.9/100,000	N/A
Current study	NL, Canada	1997	2-50 years	16.23/100,000	N/A
Pilmer et al., 2013	ON, Canada	2008	2-40 years	2.64/100,000	None
Lim et al., 2010	British Columbia, Canada	2005-2007	0-35 years	1.75/100,000	No accidentals included
Margey et al., 2011	Ireland	2005-2007	15-35 years	2.85/100,000	Cases with drug involvement excluded
Papadakis et al., 2009	England and Wales	2002-2005	1-34 years	1.8/100,000	No access to autopsy files, only used office of national statistics database
Winkel et al., 2011	Denmark	2000-2006	1-35 years	2.8/100,000	Used info outside of autopsy file
Risgaard et al., 2014	Denmark	2007-2009	1-49 years	8.6/100,000	Used info outside of autopsy file and used high number of non-autopsy cases
			36-49 years	21.7/100,000	