The Family Study: Assessment of the Incidence, Etiology, Circumstances and Familial Risk for Sudden Cardiac Death and Aborted Sudden Cardiac Death in Young Individuals

by

Katherine Sarah Allan

A thesis submitted in conformity with the requirements for the degree of Doctor of Philosophy
Institute of Medical Science
University of Toronto

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Abstract

**Background:** Recent reviews have highlighted our lack of information on the incidence etiology and circumstances of sudden death (SD) in the young, particularly the distribution of underlying disorders, preventable triggers, and identifiable familial predisposition to fatal arrhythmias.

**Methods:** This study had 3 parts: (1) the development and (2) implementation of a novel, comprehensive methodology to capture all SDs and aborted SDs (both cardiac and non-cardiac) in a defined geographic area, (3) followed by a feasibility study with a case control design. We utilized a prospectively collected, population-based registry of all out-of-hospital cardiac arrests (OHCAs) in the Greater Toronto Area, to identify patients from 2009-2012. The retrospective study included cases that were OHCAs ages 2-45, treated or untreated, died or survived and we reviewed all available data for each case and adjudicated an etiology. In the feasibility study, included cases were presumed cardiac, treated OHCAs ages 18-65. Two relatives per patient were
interviewed regarding symptoms prior to the arrest, cardiac history, and family history of sudden cardiac death (SCD). Two sets of control patients were administered the same questionnaire as cases.

**Results:** We identified 656 SCDs ages 2-45 over a 4 year period, with an overall annual incidence rate of 3.97 per 100,000 persons. We report a high autopsy rate, with a shift towards ischemic heart disease as the predominant underlying etiology in adults ages 35-45, from structural heart disease and sudden unexplained deaths in children. Adults experienced their SCDs more frequently at home and at rest than did children, and most reported new symptoms in the day preceding their event. Our feasibility studies demonstrated that it is viable to obtain a reliable family history of SCD and major cardiac risk factors from both cases and controls using a self-developed survey.

**Conclusions:** By using a validated comprehensive population based registry of consecutive cases to identify all eligible patients, in combination with a novel classification methodology, large sample size, and multiple sources of data, we were able to better describe the nature and scope of the problem of sudden cardiac death within a young, urban Canadian population.
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This thesis could not have been accomplished without the input from a great number of people, whose contribution in varying ways deserves special mention.

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ARVC: Arrhythmogenic Right Ventricular Cardiomyopathy
BrS: Brugada Syndrome
CAD: Coronary Artery Disease
CHD: Coronary Heart Disease
CM: Cardiomyopathy
CPVT: Catecholaminergic Polymorphic Ventricular Tachycardia
DCM: Dilated Cardiomyopathy
DM: Diabetes Mellitus
ECG: Electrocardiogram
EMS: Emergency Medical Services
Epistry-CA: Epistry Cardiac Arrest Database
FDR: First Degree Relative
HCL: High cholesterol
HCM: Hypertrophic Cardiomyopathy
HD: Heart Disease
HTN: Hypertension
ISCH: Ischemic
LQTS: Long QT Syndrome
MI: Myocardial Infarction
NSCD: Non Sudden Cardiac Death
OHCA: Out-of-Hospital Cardiac Arrest
ROC: Resuscitation Outcomes Consortium
SADS: Sudden Arrhythmic Syndrome
SCA: Sudden Cardiac Arrest
SCD: Sudden Cardiac Death
SD: Sudden Death
SDR: Second Degree Relative
SUD: Sudden Unexplained Death
SUDEP: Sudden Unexplained Death in Epilepsy
SMH: St. Michael’s Hospital
TDR: Third Degree Relative
VASC: Vascular
VF: Ventricular Fibrillation
Chapter 1: Introduction

1.0 Background: What is the nature of the scientific problem?

Sudden death (SD) and its related synonyms are usually defined as natural events resulting in cardio-respiratory collapse within one hour of the onset of symptoms, which occur suddenly and unexpectedly (Gajewski et al. 2010). Depending on the underlying etiology, it can be divided into sudden cardiac death (SCD) e.g. death due to cardiac cause or SD due to a non-cardiac cause, such as pulmonary embolism or metabolic imbalances. Sudden deaths which have normal autopsy (e.g. disease free) and negative toxicology are termed sudden unexplained deaths (SUDs) and are presumed to be due to primary arrhythmic syndromes.

Whereas SCD in the older population is primarily due to underlying coronary artery disease (CAD), in the young (e.g. age <40), the causes of SCD are diverse and are often heritable (Semsarian et al. 2012). Depending on the definition used, how cases are ascertained and what information is obtained to determine the underlying cause of death, the exact distribution of SCD etiologies differs substantially between studies (Fishbein 2010, Kaltman et al. 2011, Maron et al. 2014). Furthermore, estimates of the incidence of young SCD vary widely from 0.7 to 13.0 per 100,000 persons/year (Berger et al. 2004, Driscoll et al. 1985, Eckart et al. 2011, Margey et al. 2011, Maron et al. 1980, Meyer et al. 2012, Pilmer et al. 2013, Risgaard et al. 2014, Shen et al. 1995, Winkel et al. 2011).

This makes comparisons of SCD rates between studies challenging, and serves to highlight the lack of clarity with regards to the true incidence and causes of SCD in the young (Kong et al. 2011).
1.1 Understanding the Methodology:

Sudden cardiac death incidence rates are calculations based on the ratio between the numbers of individuals who die suddenly within a defined geographical area (numerator) over the total population within the same region over a specified time period (denominator). If either the numerator or denominator is not well defined then the final estimated incidence rate will be highly variable (Harmon et al. 2014).

Several factors affect the identification of cases (e.g. numerator), including how SCD is defined, methods of data collection, lack of mandatory reporting requirements, inclusion of all SCD and aborted SCD events (e.g. resuscitated and survive to hospital discharge) versus only those resulting in death (e.g. SCD only) and the population examined.

The key to accurately interpreting any SCD incidence rate and the specific distribution of causes is to understand: (1) the methods used to identify cases, (2) the definition and criteria used to include or exclude SCD cases; and (3) how the cause of death is determined and classified.

1.2 Methods for Case Identification:

1.2.1 Internet and Media Searches:

Although many studies rely on the use of the media, internet or catastrophic insurance reports to identify cases (Choi et al. 2013, Maron et al. 2009), this results in an underestimation of true SCD incidence. Maron et al. developed a methodology to estimate the absolute number of sudden deaths in US competitive athletes, by creating a large registry over a 27-year period using systematic identification and tracking strategies (Maron et al. 2014, Maron et al. 2003, Maron et al. 2009). Their methods included targeted searches of archival informational databases, news media accounts, internet searches, pathology branch archives and reports submitted to the registry and
the Minneapolis Heart Institute Foundation Web site (US National Registry of Sudden Death in Athletes, http://www.suddendeathathletes.org). Using this methodology they found a total of 1866 athletes who suffered a SD event from 1980 to 2006 in 38 different sports (Maron et al. 2009). Sudden deaths were predominantly due to cardiovascular disease (56%), but also included non-cardiac causes such as trauma (22%) and heat stroke (2%). The absolute number of SDs in the cohort was somewhat higher than previous published estimates but still relatively low, with a rate of 100 per year and likely an underestimate of the true incidence. The use of public domain reporting frequently results in cases being missed, as evidenced by a retrospective cohort study from Denmark that found that only 20% of athlete SDs identified using death certificates were located through an extensive search of the media (Holst et al. 2010).

*Mandatory reporting systems or large prospective databases of all SCDs and aborted SCDs will produce the most reliable results of incidence calculations by identifying the entire numerator (e.g. all SCD and aborted SCD cases).*

**1.2.2 Death Certificates and International Classification of Diseases Codes:**

The most commonly used method to ascertain SD cases involves utilizing death certificates and international classification of diseases-10 (ICD-10) codes, despite their tendency to be prone to inconsistent or erroneous classification(Kaltman et al. 2011). Papadakis et al. used ICD-10 codes to identify SCD in the young (age ≤35) in the UK (Papadakis et al. 2009). By searching the office of national statistics (ONS) database for cardiac causes of death, they found an annual SCD incidence rate of 1.8 per 100,000 persons. A major limitation of this study was that the cause of death was ascertained only from the ONS database and that the authors did not individually examine the death certificates or autopsy reports to confirm the cause of death. This is an important
limitation, as studies have shown that there are significant discrepancies between the cause of death found at autopsy and what is documented on the death certificate (Iribarren et al. 1998, Tavora et al. 2008).

One of the main reasons for the lack of agreement between death certificates and actual cause of death on autopsy, is that deaths are often inappropriately labeled as cardiac. Tavora et al. studied a series of consecutive autopsies in cases considered to be sudden and out-of-hospital to determine the accuracy of death certificates as compared to cause of death determined by autopsy (Tavora et al. 2008). The overall discrepancy rate was 52% and was lowest in patients with known symptomatic heart disease (33% had an inaccurate cause of death listed on the death certificate) and highest in patients without a previous medical history (60% had an inaccurate cause of death listed on the death certificate). In the majority of cases (78%), the incorrect diagnosis was coronary disease listed on the death certificate when autopsy demonstrated a different cause of death.

To further illustrate this point, in a comprehensive 6 year mortality review of 4,244 OHCAs in 30- to 74-year olds, 911 (21.5%) were judged not to have SCD because they had actually been admitted to hospital or the cause of death was deemed noncardiovascular (Iribarren et al. 1998). Among the remaining cases, only 254 (5.9%) were diagnosed as SCD using a rigorous physician-based review procedure that used clinical records, autopsy reports, and an informant (next-of-kin) interview. When using only death certificate information to define SCD, compared with the physician diagnosis, sensitivity (proportion of positives that are correctly identified) was only 24%, whereas specificity (proportion of true negatives that are correctly identified) was 85%. Adding additional International Classification of Disease (ICD) codes for ischemia improved the sensitivity to 87%, whereas specificity dropped to 66%. Despite this improved sensitivity, only 27%
of the overall cases labeled SCD by death certificates agreed with the physician diagnosis.

A better approach used by Danish investigators has been to systematically investigate all SCDs by using death certificates and then linking them with autopsy data and data collected from national registries (Risgaard et al. 2014, Winkel et al. 2011, Winkel 2012). This group has extensively studied SCD rates in young individuals ages 1 to 49, reporting an overall incidence of 8.6 per 100,000 people in both autopsied and non-autopsied cases (Risgaard et al. 2014). Major strengths of their methods include linking multiple sources of information to assign the cause of death, which will improve the accuracy of their SCD incidence rates. Although more comprehensive methods than the use of death certificates alone to ascertain cases, their autopsy rates were low (62%) resulting in the inclusion of non-relevant (e.g. non-cardiac) cases, i.e. case ascertainment bias.

Relying on death certificates alone to ascertain SCD cases results in substantial misclassification errors and supports the use of validation mechanisms such as multiple data sources and physician based adjudication in order to accurately describe and estimate the true annual incidence of SCD and aborted SCD in the young.

1.2.3 Autopsy Based Registries:

Another method is to use only autopsied cases of SCD to determine incidence rates. Doolan et al sought to determine the frequency and potential causes of SCD in a young Australian population by reviewing all autopsies performed at the Department of Forensic Medicine at Westmead Hospital, Sydney from 1994-2002 (Doolan et al. 2004). They found 193 sudden, natural and presumed cardiac deaths out of 2986 autopsies ages <35, with the rest comprising non-natural or non-cardiac deaths. Using a similar methodology, a recent Canadian study found a SCD rate of 2.6/100,000 person-years in
those ages 2-40 and that the incidence rate increased in age from 0.7/100,000 (2-18 years) to 2.4/100,000 (19-29 years) to 5.3/100,000 (30-40 years) person-years (Pilmer et al. 2013).

Using only autopsied cases will improve the specificity of identifying cardiac cases, however, not all SCD cases are autopsied. Additionally, some patients with cardiac arrest survive after resuscitation, and a comprehensive accounting of cardiac arrest cases should include persons with cardiac arrest who survive to hospital discharge.

*Using autopsied cases, although more accurate at identifying those due to cardiac causes than death certificates alone, still lacks sensitivity, as not all patients are autopsied.*

**1.2.4 Out-of-Hospital Cardiac Arrest Data:**

A fourth method of addressing this problem is to use the incidence of out-of-hospital cardiac arrest (OHCA) that is primary cardiac as a surrogate for SCD rates, i.e. using cases that are identified as OHCAs of “no obvious cause” from a review of first responder records (Maron et al. 1996, Meyer et al. 2012, Cobb et al. 1992, Cobb et al. 2002, Myerburg et al. 2002). Donohoe et al. studied the frequency and characteristics of OHCA patients ages <35 attended by the London Ambulance Service (Donohoe et al. 2010). The most commonly etiology identified was presumed cardiac at 44.9% (e.g. no obvious cause – presumed cardiac), with 30% due to trauma and the rest due to non-cardiac causes (25.1%). More recently, Bray et al. in Perth Australia found an even higher percentage of presumed cardiac cases among their OHCA population of all ages at 76% (Bray et al. 2014).

Using OHCAs as a surrogate for SCD however results in overestimation of the incidence of SCDs. A recent study comparing SCD incidence for all ages generated from the
Oregon Sudden Unexpected Death Study (Oregon SUDS) to primary OHCA rates generated from the ROC-Epistry Cardiac Arrest study, found a lower incidence (60 per 100,000 in Oregon vs. 71 per 100,000 in ROC Epistry-CA). This is most likely due to the prospective multisource surveillance methods used and the thorough adjudication for causes of death employed by the Oregon SUDs group (Stecker et al. 2014, Nichol et al. 2008). Using only data available at the time of the arrest or after hospital admission may lead to misclassification in cases of vascular causes, metabolic causes, unapparent overdose, or other underlying illness that may only be evident after further medical history is obtained and autopsy and toxicology are performed.

*Without robust methods for discerning the underlying etiology for each event, there is the high likelihood of including cases which are not primarily cardiac (e.g. pulmonary embolism or drug overdose not readily apparent), leading to an overestimation of true SCDs and aborted SCD rates (Stecker et al. 2014, Etheridge et al. 2014).*

1.2.5 Multisource Surveillance and Data Collection Methods:

The Oregon SUDS group is one of a select few to use prospectively collected multisource methods to assess SCD rates in a large U.S. community (Chugh et al. 2004, Chugh et al. 2009, Chugh et al. 2009). Patients who suffer a sudden unexpected death are identified from several sources: the emergency medical response system, the county medical examiner’s office, and 16 area hospitals. Using all available medical records, a comprehensive evaluation is then performed for each case which includes analyzing the circumstances, medical records, and autopsy data. All abstracted information is assembled in a database, after which an adjudication process is employed to determine which cases meet their criteria for SCD.
Over a one year period, this group found the overall annual incidence of SCD in all residents to be 53 per 100,000, ranging from 4 per 100,000 in those ages 15-24 to 17 per 100,000 in those ages 35-44 (Chugh et al. 2004). While Chugh et al. used multiple source surveillance methods to ascertain their cases and confirmed cause of death using a comprehensive data collection system, autopsies were only performed in 12% of all cases. Given this, their SCD rate is likely an overestimate of the true annual incidence rate as a result of over inclusion of non-cardiac cases.

More recently, Meyer et al., determined the incidence, causes, and outcomes of cardiovascular-related OHCA in individuals <35 years over a 30-year period in King County, Washington (Meyer et al. 2012). Using EMS records to identify suspected SCD cases, they found that SCD is more common than expected in this population, with an average incidence of 2.28/100 000 person-years and increased with age, with the highest incidence in the 25- to 35-year group at 4.40/100 000 person-years. This study captured cases using EMS-reported records and then linked them to all available information, including EMS incident reports, autopsy reports, death certificates and hospital reports. A critical limitation to their inception cohort was the inclusion of only OHCA cases that were treated by EMS, which introduces a potentially large patient selection bias by excluding cases who are found dead. Thus, their calculated rates likely underestimate the true annual SCD incidence rates in their young population.

Perhaps the best source of SCD incidence rates comes from the US Military, due to its mandatory reporting of deaths and use of standard autopsy protocols (up to 97% of cases autopsied) (Eckart et al. 2004, Eckart et al. 2011, Eckart et al. 2006). Eckart et al. reported on 126 sudden, non-traumatic deaths ages 18 to 35 that occurred during training, of which 34.9% were attributed as sudden unexplained deaths (SUDs), 36% to
structural heart disease and 16% to coronary artery disease (Eckart et al. 2004). Survivors were not included and their incidence calculations were only based on a 6 week period (e.g. recruits were not followed over time). These incidence rates may be more generalizable to athletes rather than the general SCD population, given that basic entry military training strongly emphasizes a high degree of physical fitness and exertion (Eckart et al. 2004).

To better understand the epidemiology and to improve risk stratification and prevention of SCD among young individuals, there needs to be focused efforts on using methodologies which prospectively and accurately capture all SCD and aborted SCD cases that occur in the general population. Large OHCA registries such as the one used in this study (e.g. Epistry-CA) that capture all OHCAs where EMS personnel are activated (e.g. 911 calls) in combination with comprehensive data collection methods may overcome many of these challenges described above (Bardai et al. 2011, Nichol et al. 2008).

1.3 Definitions for Sudden Cardiac Death:
The second major barrier for determining the true magnitude of SCD incidence and its causes is the lack of consensus on its definition (Kong et al. 2011). The terms “OHCA”, “sudden death” and “sudden cardiac death” are often used interchangeably, despite having very different definitions (Kong et al. 2011). Some studies include time constraints in their definitions for SD or aborted SD (Chugh et al. 2004, Escobedo et al. 1996, Zheng et al. 2001), such as occurring within 1-6 hours of the onset of acute symptoms (Virmani et al. 2001), while others (the World Health Organization) define SD as death occurring within 24 hours following the onset of symptoms (Furberg et al. 1977).
Using a time-based system to classify deaths is problematic for several reasons. Firstly, it can result in different incidence rates, depending on the time definition for what constitutes “sudden”. Kuller et al. (Kuller et al. 1967, Kuller 1980) demonstrated that when the length of time between the onset of the terminal event and death increased, non-cardiac causes of SD such as cerebrovascular death and cirrhosis of the liver predominated. When the definition of SD was restricted to events less than 2 hours after the onset of symptoms, 12% of deaths were “sudden” and 88% of those were due to cardiac causes. When defined as within 24 hours of symptom onset, 32% of deaths were defined as “sudden” with the proportion of those defined as cardiac dropping to 75%.

Secondly, the time-frame from symptom onset to the SD event usually cannot be ascertained for unwitnessed events or from data sources such as death certificates, leading to misclassification bias. Some in-hospital deaths may occur hours to days after the initial collapse as a late result of the cardiac arrest event.

Additional confusion arises with the variability in the inclusion/exclusion criteria used by studies for SCD cases; some define SCD as death attributable to ischemic or coronary heart disease (Escobedo et al. 1996, Gillum 1989) while others broaden their criteria to include all cardiovascular or cardiac etiologies (Chugh et al. 2004, Cobb et al. 2002, Zheng et al. 2001).

*It is evident from the literature that there is no universal, standardized definition for SCD or aborted SCD that is used across all studies (Kong et al. 2011). There needs to be focused efforts on creating standard definitions for both SCD and aborted SCD to facilitate more reliable assessments of their incidence rates, which will enhance strategies for risk stratification and prevention.*
1.4 Accurately Determining and Classifying Cause of Death:

Methodologies that accurately identify the underlying causes of SCD and aborted SCD events in the young allows clinical screening programs to target the etiologies posing the greatest risk. This is an important first step, as without detailed history and autopsy data, there is the strong possibility of misclassifying cases which are not primarily cardiac or heritable (e.g. pulmonary embolism or drug overdose not readily apparent), thus leading to an overestimation of the true incidence of sudden cardiac deaths (Stecker et al. 2014, Etheridge et al. 2014).

Goraya et al. evaluated the validity of death certificate diagnosed out-of-hospital coronary heart disease and SCD in Olmsted County, Minnesota between 1981-1994 (Goraya et al. 2000). After comparing death certificate diagnosis to all available information, they found that death certificates had high sensitivity (91%) and positive predictive value (96%) when identifying out-of-hospital deaths due to coronary heart disease. However, this was not the case for out-of-hospital sudden cardiac deaths. When SCD was defined as an out-of-hospital death occurring within 24 hours of the onset of symptoms, the positive predictive value of death certificate identifying SCD was 77% and the sensitivity was 89%. Furthermore, when SCD was defined as an out-of-hospital death occurring within 1 hour of the onset of symptoms, the positive predictive value dropped to 52%.

More recently, Winkel at al. found similar results to Goraya when validating the Danish Cause of Death Registry (Winkel et al. 2011). Using autopsy reports as the gold standard to establish cause of death, they compared their results for autopsy identified SCD cases (e.g. cases where cardiac cause of death is established at autopsy) to those identified by the ICD-10 criteria denoting cardiovascular or ill-defined causes. They found that the Cause of Death Registry correctly categorized 82% of their explained SCD cases using
ICD-10 codes. In total, use of the cardiovascular or ill-defined causes ICD-10 criteria identified 716 deaths, while the authors ascertained 625 cases after reviewing death certificates. Of their 625 cases identified by the authors, only 50% of the deaths were attributed to SCD after autopsy. Thus, the positive predictive value using the author`s methodology was only 50%.

*It is important to accurately identify and classify deaths that are due to cardiac causes versus those that aren`t, for 2 main reasons: (1) cardiac causes are often heritable and thus up to 50% of first-degree relatives could be affected; and (2) to treat and prevent SCD at both a population (e.g. designing and evaluating EMS systems and AED deployment) and individual level (e.g. optimizing use of drug therapy and implantable cardioverter-defibrillators) (Stecker et al. 2014), the specific causes and their distribution need to be identified. Thus, it is essential to develop methods involving comprehensive data collection in order to accurately determine the specific cause of death.*

**1.5 What will it take to address this problem?**

Many consider SCD and aborted SCD, particularly in the young, to be an important public health issue. The ability to reliably estimate the incidence of SCD and aborted SCD in Canada and worldwide is important, as it informs our efforts to prevent it, to improve risk stratification techniques, and to direct future research that may save lives (Harmon et al. 2014). After reviewing the literature, there are 3 main actionable steps toward addressing the outlined knowledge and data gaps, as described above: (1) develop a methodology which uses multiple source methods and comprehensive data collection processes to ensure complete case ascertainment; (2) establish pragmatic, uniform definitions for SCD and aborted SCD that should not be used interchangeably; (3) accurately determine the underlying etiologies (both cardiac and non-cardiac) of all cases.
1.5.1 Methodology to Accurately Ascertain Cases:

Mandatory reporting systems for SCD and aborted SCD would provide the most reliable estimation of incidence rates, however, currently few such systems exist (Harmon et al. 2014). Large prospective out-of-hospital cardiac arrest (OHCA) registries such as the one used in this study (e.g. Epistry-CA) that capture all OHCAs where EMS personnel are activated (e.g. 911 calls) may overcome many of the challenges described above (Bardai et al. 2011, Nichol et al. 2008).

In recognition of the importance of accurately defining the incidence of young SCD, the working group of the National Heart, Lung and Blood Institute has recommended the development of a prospective, population based young SCD registry (Kaltman et al. 2011). We are fortunate to have access to such a database, the Toronto Regional RescuNet cardiac arrest database. Rescu Epistry is compliant with the Resuscitation Outcomes Consortium (ROC) Epistry-Cardiac Arrest database and is based on the Strategies for Post Arrest Care methodologies described elsewhere (Lin et al. 2011, Morrison et al. 2008).

Toronto Regional RescuNet is located at St. Michael's Hospital and is affiliated with the University of Toronto and partners with both urban and rural regions across Southern Ontario, a population of over 8.8 million residents. It is comprised of 8 land EMS agencies, the provincial air ambulance service and 32 participating destination hospitals. Patients who experience an OHCA within the catchment area of the Toronto Regional RescuNet are entered into a secure web based local database. Trained data guardians collect and input epidemiologic data from participating EMS agencies and destination hospitals.
Multiple methods are used to ensure complete data capture, such as regular hand sorting through paper EMS charts and electronic queries of EMS records by a variety of data fields (Morrison et al. 2008). In addition, there are site-specific ongoing quality assurance plans which include: initial training and continuing education of EMS providers in data collection, random record checks by both the sites and the Data Coordinating Center to confirm accuracy of data entry, and data checks in both the web-based data entry forms and the batch upload process (Morrison et al. 2008). As a further quality assurance check, the Data Coordinating Center conducts annual site visits to review a portion of entered records, data capture processes, and site-specific mechanisms (Morrison et al. 2008).

*By using an existing, validated comprehensive population based registry of consecutive cases to identify patients, including all young SCD and aborted SCD individuals, we will be able to accurately describe and estimate the incidence of SCD and aborted SCD in the young that occur within a defined geographic study area.*

**1.5.2 Standardized Definitions:**

As previously stated, using a time-frame from symptom onset to SCD is problematic (see above section 1.3). The most important question in understanding and defining SCD does not involve the timing of the moment of death, but instead should focus on “what disease, disorder or event caused the sudden death?”

As such, there is an urgent need to develop pragmatic, uniform definitions for SCD and aborted SCD, which are based on all of the clinical information available and can also be agreed upon and adopted by the major stakeholders in the medical/scientific community. These should be two distinct definitions that should not be used interchangeably, which will facilitate a more reliable assessment of the incidence of this phenomenon.
In addition to our novel methodology, we have developed detailed definitions for all of the applicable terms in our study that are based on the information available and avoid the use of time to define an event as “sudden”. Our definitions use an adjudication process to determine the underlying etiology, which will facilitate a more reliable assessment of the incidence and causes of this phenomenon and enhance strategies for risk stratification and prevention of SCD.

1.5.3 Accurate Understanding and Classification of Etiologies:

Depending on the underlying etiology, sudden death can be divided into SCD (e.g. death due to a cardiac cause, such as ischemic heart disease) and sudden death due to non-cardiac causes, such as intracranial hemorrhage. This subdivision is clinically relevant because cardiac causes are inherited in a significant proportion of young patients whereas non-cardiac causes usually are not (van der Werf et al. 2010). When SCD in the young is the result of inherited cardiac disease, it is important to optimize the cardiac and genetic assessment in first-degree relatives (HRUK position statement 2008, Ingles et al. 2007), mainly because of the autosomal inheritance pattern of most inherited cardiac diseases (e.g. first-degree relatives have a 50% chance of being affected (van der Werf et al. 2010)). Knowledge of the underlying etiology could be used to screen at-risk family members, with the ultimate aim of diagnosing disease early and therefore initiating appropriate therapeutic and preventative strategies (Semsarian et al. 2012). Moreover depending on the underlying etiology, treatment strategies differ substantially; for example someone with premature coronary artery disease would have very different treatment compared to an individual with familial long QT syndrome.

Our methodology utilizes a comprehensive evaluation of each case by reviewing all available medical records to determine the circumstances and specific cause of death.
We use the following sources of data for this evaluation: ambulance call/fire reports, emergency department reports, in-hospital medical notes and discharge summaries, consultations, clinical tests, and medical certificates of death. Where applicable and available, we review the coroner’s investigative statements, police reports, toxicology and autopsy reports. The coroner’s report includes demographic information about the deceased and details of the death investigation such as circumstances, manner of death, and medical cause of death with contributory factors. A narrative summary contains other important details such as medical history obtained from medical records, interviews with bystanders and family members/friends.

*As our methodology involves adjudicating each patient’s cause of death by consensus decision as being of as cardiac etiology or other, with specific cardiac and non-cardiac etiology classifications, this will enable as accurate an estimation as possible of the incidence, circumstances, and causes of sudden death and aborted sudden death in the young.*

**1.6 Causes of Sudden Death in the Young:**

Accurate identification of the underlying causes of young SD and aborted SD cases allows clinical screening programs to target the etiologies posing the greatest risk, such as those that are heritable or those that are known to confer high risk for SCD.

The cardiac causes of SD in the young can broadly be categorized into both structural and arrhythmogenic, heritable and acquired. An overview of the differing structural, arrhythmogenic or acquired causes of SD in the young (both cardiac and non-cardiac) will be discussed, in particular their current knowledge gaps and how our novel methodology and classification system can help address them.
1.6.1 Structural Causes of Sudden Cardiac Death:

Structural causes of SCD include inherited cardiomyopathies such as hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy (DCM) or arrhythmogenic right ventricular cardiomyopathy (ARVC); other non-heritable structural causes include myocarditis, sarcoidosis, valvular heart disease, CAD (although there is a heritable component, particularly with premature CAD), and congenital disorders of the heart.

1.6.1.1 Cardiomyopathies (CMs):

According to the SCD literature, cardiomyopathies (CMs) have been shown to account for ~15-20% of all SCDs (Corrado et al. 2003, Doolan et al. 2004, Papadakis et al. 2009, Puranik et al. 2005, Quigley et al. 2005, Wisten et al. 2002) in younger individuals. One of the widely cited classification systems was put forth by the American Heart Association, who defines cardiomyopathies as: “a heterogeneous group of diseases of the myocardium associated with mechanical and/or electrical dysfunction that usually (but not invariably) exhibit inappropriate ventricular hypertrophy or dilatation and are due to a variety of causes that frequently are genetic” (Maron et al. 2006). There are several types of inherited and acquired cardiomyopathies that will briefly be discussed: (1) heritable CMs such as hypertrophic cardiomyopathy (HCM) and arrhythmogenic right ventricular cardiomyopathy (ARVC); (2) acquired CMs such as cocaine induced. More detailed definitions and descriptions of all heritable and non-heritable causes of SCD and aborted SCD in the young can be found in Appendix 1A.
1.6.1.2 Hypertrophic Cardiomyopathy (HCM):

Hypertrophic cardiomyopathy is a structural heart disease characterized by hypertrophied, non-dilated left ventricle in the absence of another systemic or cardiac disease (e.g. hypertension) that is capable of producing significant wall thickening (Maron et al. 2006). On a microscopic level, histology shows myocyte disarray and fibrosis (Basso et al. 2001). The cause of death in HCM is usually secondary to ventricular tachyarrhythmias or mechanical obstruction of the left ventricular outflow tract (Basso et al. 2001).

Hypertrophic cardiomyopathy has an estimated prevalence of 1:500, follows an autosomal-dominant inheritance pattern and is one of the most commonly identified inherited cardiac disorders (Frenneaux 2004, Maron 2000, Maron et al. 2003, McKenna et al. 2002, Maron et al. 1995). Along with other inherited CMs, HCM shows marked phenotypic variability, even within families (Ackerman et al. 2011). Its penetrance (e.g. the proportion of mutation-positive subjects who have clinically detectable disease) increases with age but remains incomplete (Ackerman et al. 2011). Although the risk of SCD is low in patients with no clinical risk factors, the increased risk in those with one or more risk factors (positive family history of HCM, previous aborted SCD event, left ventricular wall thickness ≥ 30 mm, syncope and non-sustained ventricular tachycardia on Holter monitoring) (Maron 2002, Maron et al. 2003) justifies consideration of an implantable cardiac defibrillator (ICD) (Maron et al. 2007). Although the absolute risk of SCD may be lower in HCM than other heritable cardiac conditions, its high prevalence makes HCM one of the most frequently identified causes of SCD (Ackerman et al. 2011).

According to the literature, there is a belief that in patients with HCM, SCD is associated with exercise and in some cases, is related to high-level, high profile competitive sports
This association between exercise and SCD in patients with HCM has led to the recommendation that HCM patients should avoid competitive sports (Maron et al. 2004, Maron et al. 2003, Maron et al. 2003, Semsarian 2007), despite the fact that there remain many unknowns with regards to athletic SCDs.

The precise frequency with which SCDs and aborted SCDs due to HCM occur during exercise is unclear and whether or not these events are more common in athletes than the general population is also not certain (Link et al. 2012).

1.6.1.3 Arrhythmogenic Right Ventricular Cardiomyopathy/Dysplasia (ARVC/D):

ARVC is a progressive disorder of the right ventricle (rarely left ventricle) in which the myocardium is replaced by fatty and/or fibrous tissue (Zeigler et al. 2010). The fatty or fibrous replacement tissue is thought to disrupt the normal electrical conduction of the heart muscle, leading to high risk of arrhythmias and SCD (Ferrero-Miliani et al. 2010), particularly in younger (age <35) individuals (Tabib et al. 2003, Basso et al. 1999). The disease can involve one or both ventricles, but is most often recognized in its classic subtype with right-sided dominance, arrhythmogenic right ventricular cardiomyopathy (ARVC) (Sen-Chowdhry et al. 2007, Sen-Chowdhry et al. 2008). In the early, “concealed” phase of the disease, the heart morphology and ventricular function appear normal, however there is a tendency for ventricular arrhythmias (Ackerman et al. 2011). As the disease progresses, myocyte loss, inflammation, and fibroadiposis become more evident (Ackerman et al. 2011). Morphological abnormalities may resemble dilated cardiomyopathy, but the clinical presentation typically is with arrhythmia rather than heart failure manifestations, which happen in the later stages of the disease (Ackerman et al. 2011, Sen-Chowdhry et al. 2007). ARVC has an estimated prevalence of around 1:5000 and in the majority of cases is dominantly inherited (Ferrero-Miliani et al. 2010).
Data from young SCD cases in the Veneto region of Italy have shown a different distribution of etiologies in Italy compared to Canadian (Pilmer et al. 2013, Pilmer et al. 2014) and US results (Eckart et al. 2004, Cross et al. 2011). The most common cause of SCD in athletes from the Veneto region has been attributed to ARVC (Corrado et al. 1990, Corrado et al. 2003, Corrado et al. 2006), while in the US it is mostly due to HCM (Maron et al. 2014) or anomalies of the coronary arteries (Eckart et al. 2004, Eckart et al. 2011).

The reasons for these variations between regions is not fully understood, but could be attributed to differences in population genetics and myocardial substrate (Cross et al. 2011), or, alternatively, could be a result of differing case ascertainment strategies.

1.6.1.4 Coronary Artery Disease (CAD):

Coronary artery disease (CAD) is the primary cause of coronary heart disease (CHD) and can affect younger individuals (e.g. age <45); with CAD, atherosclerosis of the coronary arteries can lead to plaque disruption, thrombosis and/or spasm of the coronary arteries, which may result in chest pain (angina), myocardial infarction (MI) and SCD (Ferrero-Miliani et al. 2010).

At autopsy (and in this thesis), the main criteria used to diagnose CAD as the cause of death is stenosis (narrowing) of at least one or more coronary arteries due to an atherosclerotic plaque (≥70%), and/or thrombosis, with or without evidence of a healing MI (Basso et al. 2008, Damani et al. 2007) (see Appendix 2N). Previous studies of SCD in younger individuals (age <35) have observed that CAD accounts for up to 25% of all deaths (Corrado et al. 2003, Doolan et al. 2004, Papadakis et al. 2009, Puranik et al.)
Due to the limitations in SCD case ascertainment methodologies described previously, it is unknown what proportion of SCD and aborted SCD events in the young are in fact attributable to CAD vs. other causes.

1.6.1.5 Structural Acquired - Cocaine Induced Cardiomyopathy:

Cocaine causes SCD through several different mechanisms including myocardial infarction and stroke, but most commonly through cardiac arrhythmia (Karch 2009). Cocaine is strongly linked to myocardial ischemia and infarction by increasing the myocardial oxygen demand, coronary artery vasoconstriction and coronary thrombosis (Darke et al. 2006). Cocaine is also directly toxic to the myocardium and chronic use causes fibrosis due to myocardial remodeling (Karch 2009). Cocaine use has also been associated with left ventricular concentric hypertrophy (enlargement of the myocardium of the ventricle), by directly activating the gene producing calmodulin kinase II (Karch 2009). This results in pathologic concentric cardiac remodeling with enlargement of the ventricle, identical to what is seen in untreated hypertensive patients (Karch 2009).

Concentric hypertrophy predisposes individuals to an increased risk of SCD via cocaine-induced myocardial ischemia and/or arrhythmia (Benzaquen et al. 2001, Darke et al. 2005, Karch 2002, Om et al. 1993). Furthermore, regardless of what causes the remodeling in the heart (e.g. CAD or cocaine), the presence of fibrosis and cardiomegaly (enlarged heart) leads to electrical instability, predisposing individuals to an arrhythmic death (Karch 2009).
It is essential to determine which SCD and aborted SCD events are cocaine induced vs. heritable in order to direct the appropriate clinical care in survivors and first-degree family members of SCD victims. The prevalence of cocaine induced cardiomyopathies in our young population of SCD and aborted SCD individuals is currently unknown.

1.6.1.6 Structural Causes Summary:

In summary, because of the discordant and incomplete information available about the structural causes of SCD in younger individuals (both heritable and acquired), there is controversy with regards to the exact proportion of younger individuals who are at risk for SCD and whether it can be prevented by screening (Fishbein 2010). However, to perform screening, the exact phenotype in the affected or deceased SCD individual must first be determined.

Using our novel methodology to identify all structural causes of SCD in younger individuals will help provide some clarity with respect to the issues described above. Furthermore, this thesis will present data on the incidence of SCD occurring during exercise, in particular with respect to HCM, to help clarify some of the controversy surrounding the role of exercise in SCD.

1.6.2 Primary Arrhythmic Syndromes:

Arrhythmogenic causes of SCD and aborted SCD in the young include long QT syndrome (LQTS), catecholaminergic polymorphic ventricular tachycardia (CPVT), Brugada syndrome (BrS) and short QT syndrome (Cerrone et al. 2011). Collectively, these primary arrhythmogenic disorders of the heart have been defined as “ion channelopathies”, predominantly involving mutations in the K⁺, Na⁺ and Ca²⁺ channels expressed in the heart (Cerrone et al. 2011). The following arrhythmic syndromes will
briefly be discussed: long QT syndrome (LQTS) and sudden unexplained deaths (SUDs), in particular their current knowledge gaps and how our novel methodology and classification system can help address them.

1.6.2.1 Long QT Syndrome (LQTS):

Long QT Syndrome (LQTS) can be congenital or acquired; congenital LQTS is an inherited, arrhythmogenic cardiac conduction disorder, while acquired long QT syndrome occurs because of QT prolonging drugs or in rare cases because of a heart block or an MI (Roden et al. 2005). Of note, the distinction between congenital and acquired LQTS is somewhat unclear, as some genetic variants of LQTS may only express the phenotype in the presence of QT-prolonging drugs, indicating that these LQTS mutations may actually only confer a risk of acquired LQTS (Chugh et al. 2000, Roden et al. 2005).

Congenital LQTS is characterized by the distinctive ECG feature of QT prolongation and T wave abnormalities, causing ventricular tachycardia, syncope, “seizures,” and SCD in young individuals with structurally normal hearts (Ackerman et al. 2008).

The prevalence of LQTS is estimated to be 1 in 2,500 people (Schwartz et al. 2009), and phenotypic expression is quite heterogeneous, ranging from a lifelong asymptomatic state to SCD during infancy (Ackerman et al. 2011). LQTS is more likely to express itself before puberty in males and after puberty in females (Priori et al. 2003, Goldenberg et al. 2008, Hobbs et al. 2006). Certain LQTS types (1,2 and 3) are linked to variable triggers; SCD in LQTS1 is more commonly triggered by exertional activities such as swimming, and during emotional and physical stress (Shephard et al. 2009), while LQTS2 is triggered by sudden loud noises such as an alarm clock. In patients with LQTS3, SCD frequently occurs at rest or during sleep (Shephard et al. 2009).
Given the high prevalence and easily treatable nature of the disease, LQTS meets common criteria for the design of a universal screening program; however, there remains considerable debate and controversy surrounding the benefits of implementing LQTS screening (Tristani-Firouzi 2015).

**Accurate estimates of the true incidence of LQTS in the Canadian general population could be used by clinicians for risk stratification at an individual level, and ultimately for cost/benefit estimates of a potential screening process at the population level.**

### 1.6.2.2 Sudden Unexplained Death (SUD):

Although autopsy studies indicate that an estimated 60% to 75% of SCDs in young individuals are due to potentially inherited structural and arrhythmogenic cardiac diseases (Basso et al. 2001, Drory et al. 1991), many of these cases remain unexplained. In a large proportion of young SCD individuals, their hearts are found to be structurally normal in up to 43% of cases (Corrado et al. 2001, Eckart et al. 2011, Winkel et al. 2011, Winkel et al. 2014, Wisten et al. 2002) and in up to 23% of athletes (Maron et al. 2009, De Noronha et al. 2009) In the context of a negative toxicology and morphologically normal heart, the terms “sudden arrhythmic death syndrome” (SADS) or “sudden unexplained death syndrome” (SUDS) are used (Behr et al. 2007). Furthermore, deaths are classified as unexplained when an autopsy is not conducted or when patients undergo a detailed post-mortem which fails to provide a definitive cause of death, or the medical history does not provide a clear answer (Basso et al. 2001, Bowker et al. 2003).

A substantial proportion of SADS cases are caused by potentially heritable cardiac disease such as primary arrhythmic syndromes (e.g. long QT, Brugada Syndrome) and, less frequently, cardiomyopathy (Giudici et al. 2014). Yet for some cases, a causal
relationship between the clinical circumstances and the arrhythmia cannot be identified, despite extensive clinical investigation; these cases are termed “idiopathic VF” (Joint Steering Committees of the Unexplained Cardiac Arrest Registry of Europe and of the Idiopathic Ventricular Fibrillation Registry of the United States 1997).

These sudden unexplained deaths pose a serious predicament because the potential heritability of the underlying diseases means that surviving relatives may be at increased risk of SCD (Tan et al. 2005).

1.6.2.3 Acquired (Drug Induced) Arrhythmias:

Sudden cardiac death and/or ventricular arrhythmias induced by prescription drugs have become such a major public health concern over the past 20 years, that it has resulted in the removal of more drugs from the market than any other adverse drug effect (Leonard et al. 2011). The University of Arizona’s Center for Education and Research on Therapeutics (CERT) lists more than 90 currently available, potentially arrhythmogenic drugs based on evidence or suspicion that each drug prolongs the QT interval and/or causes torsade de pointes (2015).

The exact incidence of drug induced TdP in the general population is largely unknown, as most of our knowledge of the incidence, risk factors, and drug interaction of proarrhythmic drugs are derived from epidemiological studies, anecdotal case reports, clinical studies during drug development, and post-marketing surveillance (Yap et al. 2003). This has led to the creation of guidelines (Haverkamp et al. 2000, Anderson et al. 2002) aimed at predicting whether a new drug carries SCD risk.

Current predictors of SCD risk are imperfect, both for individual patients and for populations of patients who are exposed to a given drug (Roden 2004). Although it is
possible to predict that a given drug may carry some arrhythmogenic risk, this risk cannot be accurately assessed or quantified (Roden 2004).

1.6.2.4 Mechanisms Leading to Arrhythmias:

Voltage-dependent ion channels (e.g. Na⁺/K⁺) give rise to the shape and duration of the cellular action potential and the ECG (Rampe et al. 2013). A variety of different K⁺ channel subtypes are present in the heart, with the 2 most important being subtypes of the delayed rectifier current, IKr (“rapid”) and IKs (“slow”), with both participating in ventricular repolarisation (Yap et al. 2003). Blockade of either of these outward potassium currents (e.g. IKr or IKs) may prolong the action potential, however, of the two, IKr is the most susceptible to pharmacological influence (Yap et al. 2003). In the majority of cases, the blockade of IKr current by proarrhythmic drugs is at least partly responsible for their pro-arrhythmic effect, and clinically manifests as a prolonged QT interval and the emergence of other T or U wave abnormalities (Yap et al. 2003).

1.6.2.5 Psychotropic Arrhythmia Inducing Drugs:

The following arrhythmia inducing drugs will briefly be discussed in this section as they all relate to arrhythmias and SCD: antipsychotics, antidepressants and cocaine, in particular their current knowledge gaps and how our novel methodology and classification system can help address them. For more detailed information please see Appendix 1A.

1.6.2.6 Antipsychotics:

In addition to the observation that major psychiatric disorders such as depression (Alboni et al. 2008, Empana et al. 2006, Irvine et al. 1999, Luukinen et al. 2003, Whang et al. 2009) and psychosis (Bushe et al. 2010, Colton et al. 2006, Osby et al. 2000, Rasanen...
et al. 2005) are associated with an increased risk of SCD, there is growing evidence that the psychotropic drugs used to treat these disorders could also increase the risk of SCD (Kovacs et al. 2008, Ray et al. 2009, Whang et al. 2009, Ray et al. 2001). The arrhythmogenic properties of typical and atypical antipsychotic medications leading to increased risk of SCD have been noted by several studies (Hennessy et al. 2002, Straus et al. 2004). The most prominent one was published in the New England Journal of Medicine in 2009, and found that patients receiving antipsychotic monotherapy (first generation vs. second generation antipsychotics), showed a similar, dose-dependent increase in the risk of SCD, with similar adjusted incidence rate ratios (between drug present vs absent) for both typical and atypical antipsychotic drugs: 1.31 (95% CI 0.97–1.77) versus 1.59 (95% CI 1.03–2.46) for low doses, 2.01 (95% CI 1.62–2.50) versus 2.13 (95% CI 1.70–2.65) for moderate doses, and 2.42 (95% CI 1.91–3.06) versus 2.86 (95% CI 2.25–3.65) for high doses (Ray et al. 2009). These findings have been hotly disputed, in particular by the American Psychiatric Association’s Council on Research (Lieberman et al. 2012), as the studies’ relied on death certificates to evaluate SCD mortality, despite the known risk of overestimation of the true SCD incidence rate (Kaltman et al. 2011).

1.6.2.7 Antidepressants:

The use of antidepressants such as tricyclic antidepressants (TCAs), selective serotonin re-uptake inhibitors (SSRIs) and serotonin–norepinephrine reuptake inhibitors (SNRIs) have raised some concerns about their cardiotoxicity (Fanoe et al. 2014). The effect of TCAs on the QT interval have been investigated, but with mixed results; most tricyclic anti-depressants (TCAs) seem to prolong the QT interval, but there are very few reports of this causing TdP (Vieweg et al. 2004). In a large registry study from Denmark,
treatment with TCAs and SSRIs significantly increased the risk of cardiac arrest (OR 1.69 and 1.21, respectively), whereas no association was observed for SNRIs (Weeke et al. 2012). However, the average age of participants was older (67 years) and many had serious comorbidities which could have contributed or caused their SCD risk.

### 1.6.2.8 Acquired Arrhythmias - Cocaine Induced:

Cocaine affects cardiomyocytes directly via blockade of sodium and potassium channels, sequestration of calsequestrin in the sarcoplasmic reticulum and the generation of progressive oxidative stress (Stankowski et al. 2014). The blockade of sodium channels acts as a class I antiarrhythmic agent or local anesthetic (Vongpatanasin et al. 1999), while blockade of both sodium and potassium channels in the cardiomyocytes has been shown to decrease myocardial contractility, causing arrhythmia and decreasing left ventricular ejection fraction (Schwartz et al. 2010, Hale et al. 1991, Przywara et al. 1989, Wu et al. 2006).

Arrhythmias are frequently related to cocaine usage as a result of its ion-channel effects, increased sympathetic nervous system stimulation and/or myocardial ischemia (Wood et al. 2010). Several different types of arrhythmias can occur, both lethal (VT/VF) and non-lethal (sinus tach, afib) (Bauman et al. 1994), with the type dependant on both the mechanism and host level factors (Hoffman 2010). For example, arrhythmias due to sodium channel blockade may result in wide complex VT, while arrhythmias due to potassium channel blockade can result in prolongation of the QT complex, triggering VT (both monomorphic and polymorphic) (Stankowski et al. 2014). Lastly, cocaine induced ischemia or infarction can also trigger arrhythmias in the form of VT or VF (Hoffman 2010).
1.6.2.9 Summary for Heritable and Acquired Arrhythmias:

In summary, the causes of arrhythmic SCD in younger individuals are diverse, ranging from the inherited channelopathies such as LQTS to acquired arrhythmias induced by both prescription and recreational drugs. Therefore, it is vitally important to determine not only the underlying etiology but also the underlying genetic component and how this could impact on the clinical and genetic evaluation of surviving family members who are at risk of the same disease (Semsarian et al. 2012). The identification of an underlying genetic component, which predisposes individuals to the risk of SCD, could then be used to screen at-risk family members, with the ultimate aim of diagnosing disease early and therefore initiating appropriate therapeutic and preventative strategies (Semsarian et al. 2012).

Furthermore, there is some controversy as to the exact incidence of both acquired and inherited arrhythmic causes of SCD in younger individuals, due to differing study methodologies, varying age ranges and included patient populations.

By using a validated comprehensive population-based registry of consecutive cases to identify patients, our novel classification algorithm, large sample size, and inclusive data collection methods, we will be able to better characterize the nature and scope of this problem within a young, urban Canadian population.

Lastly, to our knowledge, few SCD studies (Risgaard et al. 2014, Winkel et al. 2011) have discussed or compared the toxicological profiles of young SCD and aborted SCD individuals and how prescription and recreational drugs may have contributed to these deaths. Most SCD studies tend to exclude individuals who have a positive toxicology or a toxicology level considered above therapeutic values. This is an important limitation,
especially with individuals prescribed or taking arrhythmogenic drugs, which can act as independent triggers for underlying heart disease. *This thesis could help provide clarity as to the role that QT-prolonging drugs might play in individuals with underlying heart disease and concomitant cardiac risk factors, with the eventual goal of helping to enhance or inform guidelines for their safe administration.*

1.7 Non-Cardiac Causes of Sudden Death in the Young:

Sudden death is not synonymous with cardiac arrest. Although cardiac arrest (cessation of cardiac mechanical activity (McNally et al. 2011)) eventually occurs in all sudden deaths, it is often assumed that most, if not all sudden deaths without obvious cause in the young are caused by a primary cardiac disorder. This assumption has not been carefully tested.

Additionally, in young individuals, the proportion of SDs that is cardiac in nature may be much lower than expected; Bardai et al, using a detailed review of 233 cases of pediatric OHCA, found only 90 (38.6%) OHCAs were the result of cardiac causes (Bardai et al. 2011). Similarly, a 4-year study of all OHCAs in London, UK in individuals ages < 35 found only 44.9% of cases were due to an underlying presumed cardiac condition (Donohoe et al. 2010). Most importantly, no autopsy records were used to confirm etiology so the actual number of cardiac deaths are likely much lower than reported.

Non-cardiac causes of sudden death (potentially mislabeled as “sudden cardiac”) are numerous and can include overdose, respiratory arrest, trauma, underlying chronic medical conditions as well as sudden unexplained death in epilepsy (SUDEP). Furthermore, mental illnesses such as depression and psychosis have also been associated with increased risk of cardiovascular disease and/or SD.
The only non-cardiac causes or contributors to death in young individuals to be described in detail in this thesis will be SUDEP, depression and psychosis, primarily because the mechanisms by which these individuals die may be due to cardiac conditions.

For detailed definitions of the non-cardiac causes of death and aborted non-cardiac deaths used in this thesis, see Appendix 2N.

1.7.1 Sudden Unexpected Death in Epilepsy (SUDEP):

Individuals with epilepsy are at substantially higher risk of dying suddenly (24-40 times higher) when compared to the general population (Ficker et al. 1998, Ficker 2000). Sudden unexpected death in epilepsy (SUDEP) has been defined as the sudden, unexpected, witnessed or unwitnessed, non-traumatic, and non-drowning death of a subject affected by epilepsy, with or without evidence of a seizure in which autopsy does not reveal an anatomical or toxicological cause of death (Nashef 1997, Nashef et al. 1997, Nashef et al. 2012). A probable SUDEP case is when clinical criteria are met with no competing cause of death and there is no autopsy performed (Annegers 1997).

The incidence of SUDEP varies depending on the cohort studied, but among the general population has been estimated at 0.35/1000 patient-years (Nashef et al. 1995, Tomson et al. 2005, Annegers et al. 1998, Sperling et al. 1999, Walczak et al. 2001, Lhatoo et al. 2001). Among the general population with epilepsy, SUDEP is estimated to account for 7-17% of all deaths and up to 50% of deaths in patients with refractory epilepsy (Ficker 2000, Pedley et al. 2002). Thus the risk of death among patients with epilepsy is not trivial.

The main risk factors for SUDEP include poor seizure control, high seizure frequency, onset of epilepsy at a young age and long duration of epilepsy (Tomson et al. 2008,
Surges et al. 2012). The exact mechanism by which epilepsy patients die suddenly is not well understood, however there are several postulated theories, each or all of which could cause unexpected death.

Respiratory changes induced by seizures can be lethal and may involve pulmonary dysfunction and suppression of brainstem respiratory and arousal centers (Richerson et al. 2011). Cardiac events are also thought to contribute to cases of SUDEP (Tomson et al. 2005, Tomson et al. 2008, Schuele 2009, Glasscock et al. 2010, Espinosa et al. 2009, Dasheiff 1991). Seizure-induced arrhythmias have been observed to occur in both animals and humans (Schuele 2009, Devinsky 2004).

Recent studies suggest that there may be ion channel abnormalities (particularly sodium channels) expressed in both the brain and heart that may lead independently, to seizures and “primary” ventricular arrhythmias not associated with a seizure.

_A better understanding of the incidence and risk factors for SUDEP is needed in order to prioritize clinical treatment and prevention research and to help advise epilepsy patients and their families more accurately of their risk for SUDEP (Thurman et al. 2014)._  

**1.7.2 Depression and Sudden Death:**

The link between depression and coronary heart disease related mortality is widely recognized but still controversial, mainly because of the difficulties in defining the prognostic role of depression in patients with heart disease (Empana et al. 2006, Turagam et al. 2012, Whang et al. 2009). Even fewer studies have examined a direct link between SD/OHCA and depression (Alboni et al. 2008, Empana et al. 2006, Whang et al. 2009, Irvine et al. 1999, Luukinen et al. 2003). Empama et al., used data from a large population based case–control study of risk factors for OHCA patients ages 40-79,
conducted among enrollees of a health maintenance organization in Washington State (Empana et al. 2006). Clinical depression was defined as physician diagnosis of depression or the use of antidepressant treatment within the year before the event. Compared with non-depressed subjects, the adjusted relative risk (RR) of cardiac arrest was increased in less severely depressed subjects (RR 1.30, 95% CI 1.04–1.63) and further increased in severely depressed ones (RR 1.77, 95% CI 1.28–2.45), suggesting a dose effect, whereby the risk of OHCA increased with increasing severity of clinical depression. Additionally, they found a similar association in patients with and without prior heart disease. However, it is not clear if this is a causal association, as it is possible that depression and the subsequent cardiovascular events are caused by undiagnosed subclinical manifestations of cardiovascular disease (Alboni et al. 2008, Wolff et al. 2005).

Whang et al. studied depressive symptoms and a proxy variable for clinical depression (severe symptoms and/or antidepressant medication use) and their relationship to cardiac events in the Nurses' Health Study (Whang et al. 2009). In this cohort of women without baseline coronary heart disease, they found that depressive symptoms were significantly associated with fatal coronary heart disease (Hazard Ratio 1.49) even after controlling for cardiac risk factors. Furthermore, they found that a measure of clinical depression, including antidepressant use, was specifically associated with SCD (Hazard Ratio 3.34).

These results suggest that depressive symptoms increase the risk of cardiovascular mortality and, in particular, of sudden death (Alboni et al. 2008). Yet in the cardiovascular world of SD literature, this topic has received little attention; studies with larger population samples such as ours, including differing age groups and genders, are needed, as it is
still not known what severity and duration of depression increases the risk of sudden death (Alboni et al. 2008).

1.7.3 Psychosis and Sudden Death:

Individuals with schizophrenia are known to have poor physical health (de et al. 2011) and there is a large body of evidence which has observed their shortened life expectancy compared to the general population (Osby et al. 2000, Rasanen et al. 2005, Colton et al. 2006, Bushe et al. 2010). The main reasons for their sudden and unexpected deaths include suicide, accidents and cardiovascular disorders (Colton et al. 2006, Bushe et al. 2010, Ruschena et al. 1998, Appleby et al. 2000, Loas et al. 2008, Manu et al. 2011), in addition to the use of psychotropic medications (Hennessy et al. 2002, Straus et al. 2004, Ray et al. 2009, Honkola et al. 2012, Kovacs et al. 2008).

Autopsy findings in patients with schizophrenia who die suddenly have rarely been reported in the past 20 years (Ifteni et al. 2014). Studies from the US (Chute et al. 1999), Australia (Sweeting et al. 2013) and Romania (Ifteni et al. 2014) all observed that the majority of natural deaths in schizophrenics were caused by atherosclerotic heart disease, however in both the Romanian and Australian studies, a small proportion of SDs (~11%) remained unexplained (e.g. SUDS). The significance of these findings remains unclear, as of these studies were limited by selection bias and incomplete clinical data.

A large scale study such as ours could help to understand the distribution of SDs and aborted SDs that are attributable to psychosis and could lead to larger scale studies as to how these deaths could potentially be prevented or predicted.
1.8 Triggers, Warning Signs and Familial Inheritance:

Uncertainty over the best approach to preventing SCD and aborted SCD in the young is largely due to a lack of data regarding its true incidence and etiology, but can also be attributed to the dearth of knowledge surrounding avoidable triggers, potential warning symptoms and identifiable familial predisposition. A discussion of these issues, in particular their current knowledge gaps and how this thesis can help address them will be provided below.

1.8.1 Triggers:

It is a long held belief that for an SCD event to occur, it is necessary to have both a substrate (e.g. CAD or myocardial scar) and a trigger (external factor believed to cause acute cardiovascular instability) (Chugh et al. 2008). This trigger can vary and depends on the underlying inherited cardiac disease (Dewar 2015). Observational studies have indicated that environmental triggers may precipitate ventricular arrhythmias and ultimately SCD (Shephard et al. 2009). For example, HCM, LQTS and Brugada Syndrome have been associated with potentially avoidable triggers such as physical activity, sudden loud noises and fevers. In fact, in HCM up to 70% of SCD events have been observed to occur during or immediately after vigorous exercise (Maron et al. 1996, Maron 2003, Maron 2007).

Currently, it is unknown how many young, asymptomatic Canadians there are, who have an inherited cardiac disease that given the right trigger, could result in a lethal ventricular arrhythmia (Dewar 2015).
Acquisition of detailed descriptions of the potential triggers of SCDs and aborted SCDs in the young could provide relevant information of precipitant factors associated with young SCD.

Sudden cardiac death among athletes is widely accepted to be the most common cause of death in this population (Harmon et al. 2014). Although the number of deaths during competitive sports is quite small, ~100-150 deaths during sports in the US annually (Maron et al. 2009, Maron et al. 1986, Maron 2007, Drezner et al. 2008, Thompson et al. 2007), the intense media coverage makes it appear that SCD among athletes is more common than in non-athletes (Link et al. 2012).

Rates of SCD among athletes varied substantially from 1:917,000 (Roberts et al. 2013) to 1:3000 (Harmon et al. 2011) per year. Studies which had higher methodological quality yielded consistent incidence rates in the range of 1:40,000 to 1:80,000 athletes per year (Corrado et al. 2003, Holst et al. 2010, Steinvil et al. 2011). Subgroups of patients such as males and African-American athletes and basketball players, were at much higher risk for SCD (Harmon et al. 2011). Critical weaknesses of the study which found an incidence rate of 1:40,000 athletes per year include case identification using a retrospective search of media reports, broad age range and an imprecise denominator (Steinvil et al. 2011). The Danish study which found an incidence rate of 1:82 645 athletes per year was limited by its ability to accurately identify competitive athletes from the available information on death certificates (Holst et al. 2010).

Development of a preparticipation screening program to detect cardiac conditions which predispose individuals to the risk of SCD during exercise/sport must be sensitive, specific, feasible and cost effective in order to be effective (Harmon et al. 2011). Screening must be able to identify cardiac conditions at risk for SCD.

*In order to achieve this, a thorough understanding of the exact incidence is critically important. A secondary analysis of our SCD data could help provide a clearer picture of the true incidence of SCD and aborted SCD among young athletes, which would enable a more accurate estimation of the cost/benefit of a preparticipation screening program.*

**1.8.2 Warning Symptoms:**

Because few individuals display clinical symptoms prior to their SCD or aborted SCD event or their symptoms are misdiagnosed as more benign conditions, they are often unaware they are at risk (Dewar 2015). Furthermore, attempts to identify symptoms that
are specific to young patients at risk of SCD have not been successful, as studies have most often analyzed the general population, where up to 80% of the individuals who suffer SCD have coronary heart disease (Wisten et al. 2005). Müller et al., attempted to investigate the conditions preceding OHCA events by collecting detailed information from bystanders or emergency physicians on medical history, medications, first-registered arrhythmia, and signs or symptoms present for up to 24 hours prior to the event (Müller et al. 2006). The most frequently reported symptom was angina, followed by dyspnea, nausea/vomiting, and dizziness/syncope, with no symptoms being reported at all in 25% of patients. Unfortunately no autopsy reports were used to confirm the cause of death and thus the reported symptoms may not be specific to the cardiac SCD population.

More recently, several others have attempted to characterize the prevalence of warning symptoms in children and young adults who suffered SCD and aborted SCD (Drezner et al. 2012, Winkel et al. 2014). Drezner et al. performed a retrospective cross-sectional survey of members of Parent Heart Watch, a national organization of parents and families with a child who suffered SCD in order to investigate warning symptoms and family history of cardiovascular disease (Drezner et al. 2012). Seventy-two percent of SCD individuals were reported by their parents to have at least one cardiovascular symptom before their event, with fatigue (44%) and presyncope (30%) being the two most common. These cardiovascular symptoms first occurred, on average, 30 months (range, 19 to 71 months) before the SCD and were reported to the child’s physician in 41% of cases. The main limitation of this study was the high potential for recall and reporting bias when inquiring about the presence of warning symptoms before SCD, which may result in an overestimation of the true prevalence. Additionally, the study was not designed to compare symptom differences among the reported etiologies and thus it
is possible that different causes of SCD may affect the likelihood and types of reported symptoms.

Knowledge of preceding sentinel symptoms is essential for effective and timely initiation of potential measures to prevent (e.g. implantable cardioverter-defibrillators) and treat young SCD (e.g. beta blockers, AED placement). In addition, a careful description of the triggers and circumstances of SCD and aborted SCD could help direct the clinical evaluation of surviving first-degree family members.

1.8.3 Familial Inheritance of Sudden Cardiac Death:

Family members of SCD patients may be at greater risk for cardiac events compared to the general population. Independent of modifiable and genetic risk factors, several studies have suggested that a family history of SCD increases the individual risk for sudden cardiac death (Dekker et al. 2006, Friedlander et al. 1998, Jouven et al. 1999, Kaikkonen et al. 2006). A higher prevalence of a family history of SCD has been well documented in relatives of those with inherited arrhythmic syndromes and also in those with structural diseases (Hendrix et al. 2011), (Behr et al. 2008), (van der Werf et al. 2010). However, due to incomplete penetrance, differing SCD definitions and case ascertainment strategies, the prevalence of SCD (and thus the estimate of risk) in the first-degree relative of an SCD individual is unknown.

Previous studies (Friedlander et al. 1998, Jouven et al. 1999) of older individuals have identified the presence of familial clustering of SCD as a clinical expression of CAD, but these studies were subject to various methodological limitations; for example, Friedlander et al (Friedlander et al. 1998), used a combined outcome and did not separate the SCD risk from the risk of myocardial infarction. In the Paris (Jouven et al.
1999) study, a selected subgroup of SCD patients were examined (male civil servants) and causes of death were obtained from death certificates, a method that has been shown to be imprecise for classifying deaths due to ischemic SCD (Engel et al. 1980, Folsom et al. 1987, Kircher et al. 1985, Ruidavets et al. 1990). Using these methods would likely tend to reduce the overall strength of the association between SCD and family history of SCD.

Kaikkonen et al., (Kaikkonen et al. 2006) were the first group to establish a family history of SCD as an independent risk factor for SCD in subjects with CAD. They found the incidence of SCD in the families of SCD individuals to be higher (46%) than that in the families of acute MI survivors (30%) or the families of healthy controls (18%). More recently they compared a family history of SCD in non-ischemic and ischemic heart disease individuals and found that SCD in ischemic heart disease (but not non-ischemic disease) has a strong familial pattern in cases with and without a prior MI (Hookana et al. 2012). In addition, studies of early repolarization syndrome, a newly identified potentially inherited arrhythmic factor, suggest that there is an increased risk of developing VF in the context of ischemia, providing additional evidence for a link between SCD, ischemia, susceptibility to arrhythmia, and SCD (Rosso et al. 2011, Viskin et al. 2012).

In 2012 Ranthe et al., examined the effect of a family history of premature death and cardiovascular death on the risk of early cardiovascular disease by linking all individuals in the Danish Civil Registration System to several different national databases that included family relations, inpatient visits, death certificates and medical history including prescribed medications (Ranthe et al. 2013). They observed that a family history of premature cardiovascular death was consistently and significantly associated with a risk
of early cardiovascular disease, ischemic heart disease and ventricular arrhythmia: Incidence Rate Ratios (IRRs) 1.72 (95% CI 1.68-1.77), 2.21 (95% CI: 2.11 to 2.31), and 1.94 (95% CI: 1.70 to 2.20), respectively. With two cardiovascular deaths in a family, the corresponding IRRs for ventricular arrhythmia was 6.18 (95% CI: 3.32-11.50). A major limitation for this study was the reliance on death certificates instead of autopsies and the inherent inaccuracy of these for etiology of death (Winkel et al. 2011, Roulson et al. 2005, Gjersoe et al. 1998).

*It is evident that there is a strong heritable component to the majority of the cardiac diseases which cause SCD and aborted SCD in the young. For this reason, it is important to determine not only the underlying etiology but also the underlying familial pattern to cardiac diseases and how this could impact on the clinical and genetic evaluation of surviving family members who may be at increased risk for the same disease (Semesharian et al. 2012).*

1.8.4 Triggers, Warning Symptoms and Familial Inheritance Summary:

Although it is universally accepted that the main goal of both the cardiology and sporting communities is to prevent SCD in young individuals, the data surrounding outcomes and the risks and benefits of screening, including cost-effectiveness, remain sufficiently incomplete to resolve ongoing debates related to screening and intervention strategies (Thompson et al. 2007, Pelliccia et al. 2010, Myerburg et al. 2007, Chaitman 2007, Corrado et al. 2007, Viskin 2007, Douglas 2008, Maron 2010). Additional research to address these knowledge gaps would ensure that healthcare policy and practice, including screening, is based on robust evidence (Link et al. 2012, Hlatky 2004).
This thesis will comprehensively analyze the triggers and circumstances just prior to and during a young SCD or aborted SCD event by using EMS records, coroner reports as well as bystander, patient and first-degree relative interviews, as this knowledge could add a great deal to our understanding of when and to whom young SCA events occur and may help identify persons at risk and other preventative strategies.

Young SCD may be the first “symptom” of inherited cardiac disease; thus, early identification is difficult in apparently healthy individuals (Amital et al. 2004, Drory et al. 1991). The proportion of young victims of SCD and aborted SCD who have a prior history of such symptoms is unknown. Our novel methodology and comprehensive data collection methods could be used to assess the proportion of young SCD and aborted SCD patients who have a prior history of premonitory cardiac symptoms, with the ultimate aim of helping clinicians identify those individuals and families who may be at greater risk.

The identification of an underlying genetic component for a cardiac disease, that predisposes individuals to SCD, could be used to screen at-risk family members, with the ultimate aim of diagnosing disease early and therefore initiating appropriate therapeutic and preventative strategies (Semsarian et al. 2012).

This thesis will assess if it is feasible to obtain a family history of SCD and major cardiac risk factors from aborted SCD patients and/or first-degree relatives of SCD individuals using a self-developed survey.

1.9 Chapter Summary:

In order to define and quantify the burden of SCD and aborted SCD in the young, there needs to be focused efforts on (1) using methodologies which prospectively and accurately capture all SD and aborted SD cases (both cardiac and non-cardiac) that
occur in the general population; (2) creating standardized, pragmatic definitions that can be used uniformly across studies; (3) integrating multiple sources of data with a rigorous adjudication process to identify and classify the underlying etiology attributed to the SD or aborted SD event.

This thesis will describe the development of a novel methodology to account for all sudden deaths (SDs) and aborted SDs (both cardiac and non-cardiac) in a defined geographic area over a 4 year period (2009-2012). This methodology will provide a pragmatic algorithm for assigning cause of death, to yield optimum sensitivity (capturing all SDs and aborted SDs) and specificity (assigning precise cause of death and thus identifying the “true” cardiac and non-cardiac causes).

By using a validated comprehensive population-based registry of consecutive cases to identify patients, we will start with a comprehensive inception cohort and systematically review abstracted data from ambulance call/fire reports, in-hospital records, police reports, coroners’ investigations, autopsies, histopathology, and any toxicology information available. Each patient event will be adjudicated by consensus decision as being of cardiac etiology or from another cause, with specific cardiac and non-cardiac etiology classifications to enable as accurate an estimation as possible of the incidence, etiologies, circumstances, and familial inheritance of sudden death and aborted sudden death in the young.

In addition to our novel methodology, we have developed practical definitions for all of the applicable terms in our study that are based on the information available and avoid the use of time to define an event as “sudden”. Our definitions use an adjudication process to determine the underlying etiology, which will facilitate a more reliable
assessment of the incidence of this phenomenon and enhance strategies for risk stratification and prevention of SD.

Using this combined framework, this thesis will attempt to answer some of the many described knowledge gaps on this important public health issue.
Chapter 2: Research Objectives

2.0 Overall Aims:

The incidence and causes of SD and aborted SD in the young are currently not known; we aim to accurately identify and describe all possible sudden deaths and aborted sudden deaths in young persons within a defined geographical area.

2.1 General Objective:

To understand the incidence, etiology, circumstances and familial pattern of sudden cardiac death (SCD) and aborted SCD in the young.

2.2 Specific Objectives:

1. To develop a comprehensive methodology that will be used to identify and evaluate the epidemiology, etiologies and circumstances of SD in the young.
2. To develop clear and pragmatic definitions for all applicable terms.
3. To accurately assess the incidence rates and distribution of etiologies, both cardiac and non-cardiac, in young SD and aborted SD individuals.
4. To determine the triggers and circumstances of SCD and aborted SCD in the young.
5. To assess the familial inheritance of SCD and aborted SCD in the young and their first-degree family members.
Chapter 3: Methods

3.1 Study Design:

This study had two parts: (1) the first was a retrospective study which used systematically collected records to identify sudden death (SD) cases of all causes including EMS reports, in-hospital information, medical records from the family physician, death certificates, coroner investigative statements, autopsy, toxicology and police reports. In total, 3271 out-of-hospital cardiac arrests (OHCAs) were reviewed. The study was approved by the St. Michael's Hospital Research Ethics Board.

(2) The second was a feasibility study that was performed using 2 pilot studies, had a case control design and was also approved by the St. Michael's Hospital Research Ethics Board.

3.2 Study Setting and Population:

The study used data from the Toronto Regional RescuNet cardiac arrest database, compliant with the Resuscitation Outcomes Consortium (ROC) Epistry-Cardiac Arrest database and manual of operations. (Lin et al. 2011, Morrison et al. 2008) Briefly, Toronto Regional RescuNet is comprised of 8 land Emergency Medical Services agencies (Toronto, York, Peel, Durham, Hamilton, Halton, Simcoe, Muskoka), the provincial air ambulance service (Ornge) and 43 participating destination hospitals. Patients who experienced an OHCA within the catchment area of the Toronto Regional RescuNet (estimated population of 8.8 million) are entered into a secure web based local database. Trained data guardians collect epidemiologic data from the participating EMS agencies and destination hospitals.
3.3 Definition of Terms:

The process of classifying out-of-hospital (OHCA) deaths is complicated, particularly in the young. For example, deaths can be categorized by cause; (i.e. underlying disease most responsible for death), by the mechanism of the terminal event (e.g. ventricular fibrillation, hemorrhage, or respiratory arrest); and by the timing of death (e.g. “unexpected” vs “gradual”). (Figure 3A)

Figure 3A: OHCA and Sudden Death Classification Algorithm:

**3.3.1 Out-of-Hospital Cardiac Arrest Events:** similar to Bardai et al\(^2\), in this study, we defined OHCA events as out-of-hospital, unexpected and abrupt loss of consciousness with loss of vital signs resulting in death, or if successfully resuscitated, survival to hospital admission and/or discharge (Bardai et al. 2011).
3.3.2 Sudden Deaths: were defined as those events that, after adjudication, were due to natural causes (both cardiac and non-cardiac) and were not due to accident, suicide, or homicide.

For simplicity of definition, we included patients who had been successfully resuscitated and survived to hospital admission and/or discharge as “aborted sudden death” (e.g. SD survivors).

Sudden deaths were further classified as being either unexpected or expected, cardiac or non-cardiac.

3.3.3 Unexpected Deaths: were deaths that occurred abruptly, witnessed or unwitnessed, in an apparently healthy individual.

3.3.4 Expected Deaths: A death that was imminently expected, such as where the underlying disease was sufficiently severe that death was not surprising or preventable, would thus be classified as “expected” even though the actual terminal event may have been “sudden”.

For example, a patient with known terminal cancer, who suffers a cardiac arrest, would be classified as “expected non-cardiac” (e.g. underlying etiology cancer) and would not be included in our unexpected cardiac SD cohort. In the cases of terminal heart disease where recovery seems impossible and the patient is at home or health care facility in palliative care, we define death as “cardiac expected”.

3.3.5 Cardiac Deaths: were those that were due to an underlying cardiac etiology such as: structural heart disease, ischemic heart disease, suspected primary arrhythmias, and congenital heart disease.
3.3.6 **Non-Cardiac Deaths:** were those that were due to an underlying non-cardiac etiology such as sudden unexpected death in epilepsy (SUDEP), sepsis or metabolic imbalances (e.g. diabetic ketoacidosis).

3.3.7 **Undetermined Deaths:** cases that lacked sufficient information to arrive at an etiology or that had 2 or more competing etiologies, either cardiac or non-cardiac were classified as **undetermined.** Potential contributory factors (such as comorbidities or toxicology), which could also have contributed to the arrest or death were noted.

3.3.8 **Sudden Unexplained Deaths (SUDs):** were defined as any sudden unexpected deaths, **unexplained** by preexisting disease and without identifiable anatomical or toxicological cause on autopsy (e.g. presumed primary arrhythmic).

3.3.9 **Premonitory Symptoms:** were those thought to be cardiac in origin (e.g. chest pain, dyspnea, palpitations and syncope) as well as any that were considered to be new onset for the patient’s current state of health. Symptoms were recorded at 4 different timeframes: within 1 hour of the onset of symptoms, from 1 hour to 24 hrs preceding the death, the week prior to the death and the months prior to the death as reported by the aborted OHCA patient, bystanders and family/friends.

3.3.10 **Physical Activity Level** at the time of the event was defined as any form of physical activity that the subject was performing immediately prior to experiencing SD. An estimated metabolic equivalent (MET) score was assigned to each type of physical activity based on the criteria described by Ainsworth et al (Ainsworth et al. 1993, Ainsworth et al. 2000). Physical activity was classified into 4 groups: Rest (MET 0.9-1.3), light to moderate activity (MET 1.4-5.9), heavy activity (MET score ≥ 6) or unknown.

3.3.11 **First and Second Degree Family Members:** First-degree family members were defined as the biological parents, siblings and children of young SD or aborted SD
patients. Second-degree family members were defined as aunts, uncles, grandparents and cousins.

3.4 Retrospective Study Case Identification:

Identified OHCAs from the Epistry-CA database were ages 2-45 years who were attended by paramedics responding to a 911 call, whether treated (e.g. receive basic or advanced cardiac life support) or untreated (e.g. are deemed to be obviously dead), and whether they died or survived. We included all cases that were designated `no obvious cause` or presumed cardiac etiology by EMS and trained data abstractors and also included cases that could have been potential SDs from a cardiac cause (e.g. drownings and motor vehicle collisions.

As per the standardized Utstein criteria (Jacobs et al. 2004, Jacobs et al. 2009, Morrison et al. 2008) for reporting cardiac arrest data, an arrest is presumed to be of cardiac etiology (e.g. “no obvious cause”) unless it is known or likely to have been caused by trauma, submersion, drug overdose, asphyxia, exsanguination or any other non-cardiac cause as best determined by rescuers. Paramedics and in-hospital coordinators can also list contributing causes for an arrest, which are thought to contribute to the event but are not the direct cause (e.g. patient was a known drug user and suspect drug poisoning but no direct evidence currently available).

We limited cases to the age range of 2-45 for the following reasons: age 2 was chosen as the lower age cutoff for our cohort to exclude any possible deaths that may have been caused by Sudden Infant Death Syndrome (SIDS), as these cases are considered to be a different entity from sudden death and to generally occur before the age of one year (Brion et al. 2012, Krous et al. 2004). We chose 45 years as the upper age cutoff, to
reduce overlap with sudden death due to atherosclerotic coronary artery disease and also to maximize our capture rate for heritable cardiac syndromes, as some types of structural heart disease such as dilated cardiomyopathy or arrhythmogenic right ventricular cardiomyopathy have varying age-dependent onset, such that an individual is more likely to show a disease phenotype with increasing age (Ackerman et al. 2011).

3.4.1 Feasibility Study Case Identification and Recruitment:

We included consecutive EMS attended, non-traumatic OHCAs in a 3-year period (2010-2012) ages 18-65 years, whether they died or survived, by reviewing abstracted data from ambulance call reports, in-hospital chart review, coroner investigative statements and autopsy reports, if available. Patients who had expected cardiac and non-cardiac deaths (e.g. severe preexisting illness) or had limited information were excluded.

In the first pilot study (2010-2011), we enrolled consecutive EMS-attended, non-traumatic out-of-hospital cardiac arrests ages 18-65 years from Toronto and Durham regions, that occurred during 2010, whether they died or survived. We further restricted the inclusion criteria to exclude patients who had a known cardiac history and focused instead on patients who were “presumably healthy” and experienced an OHCA event. Eligible SCD cases and/or their next of kin were contacted through a general letter of notification (Appendix 3A,B) about the study, which was mailed to them. Two weeks after mailing, a trained interviewer attempted to contact the individual by phone to ask if the family or aborted SCD individual would be interested and willing in participating (Appendix 3C,D)

In the second pilot study (2012-2013), we enrolled consecutive EMS attended, non-traumatic OHCAs ages 18-45 years from Toronto that occurred during 2011-2012,
whether they died or survived and included those with or without a previous cardiac history.

Deceased SCD cases were identified and enrolled using 2 complementary methods. A list of all coroner’s cases were retrospectively identified from the Epistry CA database and were referred to the Office of the Chief Coroner for follow-up and confirmation of the cause of death. For these cases, the investigating coroner contacted the family and asked if they were willing to be contacted by the study coordinator. If the family agreed, the study coordinator was provided with their contact information.

The second method by which we contacted and enrolled deceased SCD cases was by accepting direct referrals for cases in which a coroner’s investigation was conducted. For these cases, the investigating coroner contacted the family and asked if they would be willing to be contacted by the study coordinator. If the family agreed to participate, a trained interviewer followed up with the family via phone to perform the interview.

Aborted SCD cases were contacted as described above via notification letter and then by telephone.

3.4.2 Feasibility Study: Heart Disease Control Identification and Recruitment:

Controls with diagnosed heart disease (coronary artery disease or structural heart disease) were identified by reviewing the daily lists of scheduled coronary angiography procedures at SMH. Consecutive eligible participants aged 18-65 years, with no history of SCD were recruited in-hospital before or after their procedures (Appendix 3E Control Consent), as most are required to stay overnight after their procedure. Controls were administered the same questionnaire (Appendix 3F) as SCD cases.
3.4.3 Feasibility Study: Healthy Control Identification and Recruitment:

Controls free of diagnosed heart disease were recruited from the Family Practice Units at St. Michael’s Hospital. Pamphlets (Appendix 3G) and posters (Appendix 3H) that described the study and its purpose were placed in all of the Family Practice waiting rooms and interested participants were directly approached for study participation by the trained interviewers. If individuals consented to participate, interviews were subsequently performed in the waiting room. Neighbourhood controls were also recruited by asking the spouses of young SCD patients as well as friends and or neighbours who might be interested in participating. If he/she agreed to participate, trained interviewers would follow up via phone for consent and to perform the interview.

3.5 Data Collection:

3.5.1 Paramedic and Fire Reports:

Collected data from ambulance call and fire reports include: patient identifiers, past medical history, medications, narrative details about the circumstances of the event, call characteristics, prehospital interventions including the defibrillator monitor recording during the resuscitation, and outcomes.

3.5.2 In-Hospital Information:

In-hospital data coordinators abstracted data from ED reports, in-hospital medical notes and discharge summaries, consultations, clinical tests, and medical certificates of death.

3.5.3 Coroner Reports:

A coroner opens a death investigation in order to answer 5 questions: “who died, when and where he or she died, what is the cause and the manner of death?” All investigated
deaths have a file which contains a Coroner’s Report and, if applicable, an autopsy report. Other forms may include police reports, toxicology reports, and reports from other investigating bodies (e.g. Ministry of Labour Workplace Safety, etc.).

The coroner’s report includes information about the deceased as well as pertinent details of the death investigation such as circumstances, manner of death, and medical cause of death with contributory factors. It also contains a narrative summary which contains other important details such as medical history obtained from medical records, interviews with bystanders and family members/friends.

3.5.4 Conduct of Autopsies:

In Ontario, there are ~97,000 deaths per year (Statistics Canada 2014) and about 20,000 of these have a coroner investigation. Autopsies are conducted when indicated or when coroners are not otherwise able to determine the cause and manner of the death, such as in the case of homicides, suicides and any other suspicious deaths. There are approximately 6000 forensic autopsies conducted per year in Ontario through the Provincial Forensic Pathology Unit. The Provincial Forensic Pathology Unit in Toronto conducts about 2500 autopsies while the remaining forensic autopsies are performed at one of 5 regional pathology units (London, Hamilton, Kingston, Sudbury and Ottawa) with a small minority are conducted at community hospitals by a registered provincial forensic pathologist. All autopsies are conducted by a registered forensic pathologist and follow a standardized protocol in which all organs are examined both macroscopically and microscopically. In some cases only an external examination is conducted (e.g. hangings due to suicide). In circumstances where the death is suspected to be due an underlying cardiac or arrhythmic cause, the heart may also be sent to a specialized cardiovascular pathologist for further examination.
3.5.5 Toxicology:

Toxicology is performed depending on the circumstances at the scene as well as findings from the coroner investigation and the post mortem. It is usually performed to aid in the death investigation, such as in circumstances where the manner or cause of death is unclear or if the cause of death is thought to be related to drugs. If an anatomic cause of death is found at autopsy then toxicology may not be usually performed unless it is thought to play a contributing role in the death. The Centre for Forensic Science has standard protocols for toxicology testing which include a general drug screen protocol for ethanol and drugs of abuse and a comprehensive drug screen for 300 prescription and over the counter drugs. Testing is performed in a sequential manner such that if a drug is detected at a level considered to be either toxicologically significant or fatal, further testing is not performed (as the cause of death is now known).

3.5.6 Additional Data Collection - Feasibility Study:

For a subset of cases (n=12) we requested past medical history from family doctors to verify the accuracy of the self-reported medical health history.

3.5.7 Patient and Family Interviews:

Trained interviewers (n=10) conducted detailed standardized interviews with SCD survivors (Appendix 3I) and/or next of kin of SCD patients (Appendix 3J) to obtain information on patient medical history, family medical history, triggers, circumstances and premonitory symptoms. Two individuals per patient were interviewed to assess the reliability of the obtained information. Interviews were tape recorded for re-abstraction purposes, to assess and minimize intra-observer and inter-observer variability. Each interview lasted approximately 1-2 hrs. The interviews were carried out 3-12 months after
the date-of-death to provide time for families to grieve but soon enough to enable recall of events and applicable information.

3.5.8 Development of Surveys:

Quantitative data were recorded using several developed and pilot-tested data collection tools (Appendices 2K, L). An extensive literature search did not find any validated surveys that collect family history of SCD and all of the different variables that we wished to study, necessitating the creation of a new instrument. This entailed contacting the authors (Friedlander et al. 1998, Kaikkonen et al. 2006) of several previous SCD studies to receive copies of their data collections tools. We then combined elements from these SCD surveys with elements from a large scale cardiac risk factor survey (Yusuf et al. 2004) to create unified data collection tools. Content validity of these data collection tools was established by a panel of SCD and cardiology experts. Reliability of the data collection tool items was calculated based on the 2 pilot administrations.

Data was systematically collected from interviews with SCD survivors and at least one of their first-degree family members. For deceased SCD individuals, two first-degree family members (siblings, parents, or children in order of preference) or a spouse and one first-degree family member were interviewed. We interviewed a minimum of two sources for each case in order to assess the reliability of the supplied information about the medical history and family health history. In cases where one individual was a poor health historian or unable to provide sufficient detail, a 3rd first-degree relative (if available) was sought and interviewed. In addition, if the information provided by 2 first-degree relatives disagreed, we interviewed a 3rd first-degree relative in order to come to a consensus decision. As an example, if there was any disagreement on the primary outcome (e.g. family history of SD one person says yes and one person says no) or one
or more of the other family history variables, we sought out a 3rd first degree family member to corroborate the information. If the information provided from the 3rd first-degree relative disagreed with that provided by the other 2 sources as outlined above, the case was excluded from the primary analysis.

The medical history information supplied for each SCD or aborted SCD case or control individual (healthy and heart disease) were verified by requesting medical health records from his/her own family physician or by comparing to the in-hospital information abstracted by the in-hospital coordinators in the Epistry-CA database.

First-degree family members of control patients (healthy and heart disease) were not contacted to verify the self-reported family health history for feasibility issues. Thus, only the family history information collected from next-of-kin for SCD cases or directly from aborted SCD cases was used to provide an estimate of the potential bias caused by proxy respondents.

3.6 Sudden Cardiac Death Case Eligibility Review Process:

Using our prespecified inclusion criteria and study definitions described above to identify all potential sudden and unexpected deaths (both cardiac and non-cardiac), a corresponding list of 3271 OHCAs was generated from the database.

3.6.1 Stage 1 Review Process:

We first attempted to match all deceased OHCAs identified from the database to a coroner investigative report (including a death certificate) and autopsy report if available; all resuscitated OHCAs were matched to their corresponding ED reports, in-hospital reports, and discharge summaries, where available. Both types of cases were then abstracted on standardized forms (Appendix 2M, 2O); which contained all applicable
information and a “final etiologic category” for adjudication. Potential contributory factors (such as comorbidities or toxicology), which could also have contributed to the arrest or death were noted.

Using the abstracted data from ambulance call reports, in-hospital charts, death certificates, police reports, coroner investigative statements, autopsy results, and toxicology reports, the primary author (KA) identified cases that were **non-sudden deaths** (both cardiac and non-cardiac) and excluded these from the analysis (Figure 3B). Any OHCA cases that remained **unmatched** to discharge summaries and/or death certificates were also excluded from the analysis.

**Figure 3B: Stage 1 Review and classification of all potential sudden unexpected deaths from 2009-2012.**

Inclusion Criteria:
- Ages 2-45
- EMS Response
- Presumed cardiac etiology
- Motor vehicle collisions

**Legend:** **Non-Sudden, Expected Etiologies Cardiac and Non-Cardiac** included drug overdose, trauma, cancer, complex chronic care and congestive heart failure.
3.6.2 Stage 2 Review Process:

After the stage 1 review process, the remaining cases which met the study definition for *sudden unexpected deaths* were adjudicated using all available sources of information (Figure 3C). Initially, an independent assessment was made by the primary author, followed by a consensus review with 2 cardiologists. In cases with incomplete information or where the 3 reviewers could not come to an agreement, a decision was reached by consensus. Autopsy-based macroscopic and histological criteria that were used to assign cases to cardiac or non-cardiac categories as well as their specific definitions are described in detail in Appendix 3N. Cases with contributing toxicology results were jointly reviewed with a coroner, cardiac pathologist and toxicologist.

Figure 3C: Stage 2 Review and classification of all potential sudden unexpected deaths from 2009-2012.

Legend: Sudden Unexpected Cardiac Etiologies included ischemic heart disease, structural heart disease, primary arrhythmic syndromes, congenital cardiac disease and undetermined cardiac. Sudden Unexpected Non-Cardiac Etiologies included non-cardiac vascular, sudden unexplained death in epilepsy, infectious, metabolic, respiratory, anaphylaxis and undetermined non-cardiac. Undetermined Etiologies included advanced decomposition and undetermined due to lack of information. See Appendix 3N for further detail.
After the stage 1 and stage 2 review processes, all of the remaining sudden unexpected deaths were classified into 3 categories: (1) *sudden unexpected cardiac etiologies* (e.g. structural heart disease, ischemic heart disease, primary arrhythmic etc); (2) *sudden unexpected non-cardiac etiologies* (e.g. vascular, metabolic imbalances, sudden unexplained death in epilepsy, etc); (3) *undetermined* due to lack of information (e.g. from either autopsy or discharge summary to make a definitive decision regarding cause of death). Cases from categories (2) and (3) were excluded from the analysis. The remaining cases formed the cohort of *sudden unexpected cardiac deaths* and *aborted sudden unexpected cardiac deaths* (Figure 3D).

In non-autopsied cases including aborted SCDs and SCD cases that died in-hospital without a coroner investigation, the same criteria and review process as described above were used to categorize cases.
Figure 3D: Sudden Unexpected Cardiac Death Cohort ages 2-45 Years from 2009-2012.

3.7 Statistical Analysis:

3.7.1 Retrospective Study:

Descriptive statistics were used to summarize and if applicable, to assess the distribution of all variables. Continuous variables were summarized as means and standard deviations, while categorical variables were summarized as counts and percentages.

Cases were grouped into 3 age ranges: 2-17; 18-34, 35-45 years, which is reflective of the age cutoffs used in similar type studies (Pilmer et al. 2013, Vaartjes et al. 2009, Winkel et al. 2011, Wisten et al. 2002). Selected categorized data (i.e. etiology type, gender, etc.) were compared using the $\chi^2$ test (Pearson/Fisher exact where appropriate).
The age-specific annual incidence rate per 100,000 person-years was calculated for the 3 age groups: 2-17, 18-34, 35-45 years and the entire cohort (ages 2-45 years), and was based on the mean resident population of Canadians aged 2-45 years within the study geographic area, as provided by Canadian Census Data from 2011. Confidence intervals for incidence rates were calculated using Poisson distribution based on the reported cases relative to the at-risk population size for the study area between 2009-2012.

Relative risk ratios and their corresponding 95% CIs were calculated by using children (ages 2-17 years) as the referent.

All calculations and data analysis were performed with SPSS software (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp).

3.7.2 Feasibility Study:

Descriptive statistics were used to assess the distribution of all variables. Continuous variables were summarized as means and standard deviations, while categorical variables were summarized as counts and percentages. To determine differences between cases and controls, selected categorical values (e.g. medical history, family health history, etc.) were compared using the \( \chi^2 \) test (Pearson/Fisher exact where appropriate), and continuous variables (e.g. age) were compared between cases and control groups using one-way analysis of variance (ANOVA).

Logistic regression was used to assess whether there were differences between cases and controls with respect to a family history of SCD among first-degree relatives (e.g. odds ratios and their 95% CIs), both unadjusted and adjusted for age and gender.
An inter-rater reliability analysis using the Kappa statistic was performed to determine consistency among and within raters and to compare the reliability of self-reported patient information against medical records and between family members. To test the reliability of the patient self-reported information, we compared patient responses to their medical chart. We chose to test the validity of 6 medical history variables considered the most predictive of SCD risk: prior history of hypertension, diabetes mellitus, hyperlipidemia, coronary artery disease, stroke and previous myocardial infarction. We also tested the reliability of case self-reported family history (n=8 variables including family history of SCD) by comparing the information obtained from cases and/or their surrogate (e.g. spouse or first-degree relative) and a different first-degree next of kin family member. Lastly, we tested the reliability of collected information between trained interviewers (KA vs. SC or KA vs. CT) on 18 medical history variables and tested the intra-rater (KA vs. KA) agreement reliability for all groups across 18 medical history variables.
Chapter 4: Retrospective Study Results

4.0 Abstract:

Background:
Recent reviews have highlighted our lack of information on the incidence and etiology of sudden cardiac death (SCD) and aborted SCD in the young, in particular, the distribution of underlying disorders and preventable triggers.

Methods: This was a retrospective study that utilized a prospectively collected, population-based registry of all out-of-hospital cardiac arrests (OHCAs) in the Greater Toronto Area, to identify patients from 2009-2012. Included patients were those ages 2-45 years who were attended by paramedics responding to a 911 call, treated or untreated, deceased or resuscitated. We reviewed all OHCAs assigned “no obvious cause”, and ones that could potentially have been a result of sudden death, based on abstracted data from ambulance/fire call reports, in-hospital charts, police reports, coroner investigative statements, autopsy reports, and toxicology results. Each OHCA was adjudicated by consensus decision as cardiac etiology or other cause, with specific cardiac and non-cardiac etiology classifications.

Results: Of the 28,417 OHCAs and traumas of all ages and causes which occurred between 2009-2012, 3271 (11.5%) cases met our initial prespecified inclusion criteria and study definitions. Of these, only 20% (656/3271) of cases identified by EMS and Data Guardians as “presumed cardiac” etiology were in fact SD cases of cardiac etiology. We identified 656 sudden unexpected cardiac cases ages 2-45 years over a 4 year period, with an overall annual incidence rate of 3.97 per 100,000 persons. Adults ages 35-45 years had over 14 times the risk for SCD compared to children (RR 14.42, 95% CI 10.15-20.23). We report a high autopsy rate (434/529; 82%), and even higher in
coroner investigated cases (434/487; 89.1%), with a shift towards ischemic heart disease as the predominant underlying etiology (40.9%) with increasing age, from structural heart disease and sudden unexplained deaths in children. Adults experienced their SCD events more frequently at home (73.5%) and at rest (75.8%) than did children, and most reported new symptoms (65.6%) in the day preceding their event.

Conclusions: By using a validated comprehensive population based registry of consecutive cases to identify all eligible patients, in combination with a novel classification methodology, large sample size, and multiple sources of data, we were able to better describe the nature and scope of the problem of SCD within a young, urban Canadian population.

4.1 Results - Retrospective Study:

As outlined in Chapter 1, this work was divided into 5 separate objectives from 2 studies (Retrospective Study and Feasibility Study). This chapter will discuss the study results in the context of objectives 1-4.

4.2 Objective 1 - Novel Methodology - Case Eligibility Review Results:

In total there were 88,280 out-of-hospital cardiac arrests (OHCAs) and traumas of all ages and causes that were entered in the Epistry database from 2005-2015 (Figure 4A). A total of 28,417 OHCAs and traumas of all ages and causes, occurred within the study time period (2009-2012), and of these, 3271 (11.5%) cases met our initial prespecified inclusion criteria and study definitions (Chapter 3).
4.3 Stage 1 Review Process Results:

Of the total identified 3271 OHCAs, 94.4% (3088/3271) died and 2613/3088 (84%) were matched to a coroner file (including a death certificate), while 2444/3088 (79.1%) OHCAs had autopsy reports available for review.

Using the abstracted data from ambulance call reports, in-hospital charts, death certificates, police reports, coroner investigative statements, autopsy reports, and toxicology reports, the primary author (KA) identified 1984/3271 (60.7%) cases as being non-sudden deaths (both cardiac and non-cardiac) and excluded these from the analysis. A small proportion of OHCA cases (4%; 130/3271) remained unmatched to discharge summaries or death certificates and were also excluded from the analysis (Figure 4B).
Figure 4B: Results from Stage 1 Review and Classification of all Potential Sudden Unexpected Deaths from 2009-2012.

Legend: Non-Sudden, Expected Etiologies Cardiac and Non-Cardiac included drug overdose, trauma, cancer, complex chronic care and congestive heart failure.

4.4 Stage 2 Review Process Results:

After the stage 1 review process, a total of 1157/3271 (35.4%) met the study definition for sudden unexpected deaths and were further classified using all available information. Of these, the primary author classified 39.3% (419/1157) cases using all available information and the rest 738/1157 (60.7%) were adjudicated jointly by the primary author and 2 cardiologists using all available information. Of the 738 adjudicated cases, 102/738 (13.8%) cases were jointly reviewed with a coroner, cardiac pathologist and toxicologist.

After both the stage 1 and stage 2 review processes, 35.4% (410/1157) of the sudden unexpected deaths were classified as having sudden unexpected non-cardiac etiologies and were excluded (Figure 4C). A small proportion, 7.8% (91/1157) did not have sufficient information available (e.g. from either autopsy or discharge summary) to
make a definitive decision regarding cause of death and were also excluded from the analysis.

Figure 4C: Results from Stage 2 Review and Classification of all Potential Sudden Unexpected Deaths from 2009-2012.

Legend: Sudden Unexpected Cardiac Etiologies included ischemic heart disease, structural heart disease, primary arrhythmic syndromes, congenital cardiac disease and undetermined cardiac. Sudden Unexpected Non-Cardiac Etiologies included non-cardiac vascular, sudden unexplained death in epilepsy, infectious, metabolic, respiratory, anaphylaxis and undetermined non-cardiac. Undetermined Etiologies included advanced decomposition and undetermined due to lack of information. See Appendix 3N for further detail.

A total of 656/1157 (56.7%) sudden unexpected deaths were thus classified as being sudden unexpected cardiac cases and formed the study cohort. Within this cohort, 529/656 (80.6%) died and 434/529 (82%) had autopsy-explained cardiac etiology; the other 18% (95/529) did not have autopsy reports and were adjudicated as cardiac etiology using discharge summaries and all other available information. There were 127/656 (19.4%) survivors with adjudicated cardiac etiology using all available information (Figure 4D)
Figure 4D: Breakdown of Sudden Unexpected Cardiac Deaths ages 2-45 years from 2009-2012.

656 Sudden Unexpected Cardiac Deaths
- 375 Explained after autopsy or discharge summary review
- 99 Unexplained after autopsy (e.g. primary arrhythmic)
- 95 No autopsy performed
- 87 Undetermined cardiac etiologies

127 (19.4%) Aborted Cardiac Unexpected Deaths
434 (82.0%) Autopsied Sudden Unexpected Cardiac Deaths
95 (18.0%) Non-Autopsied Cardiac Unexpected Deaths

4.5 Comparison of EMS and Rescu Data Guardian Classification of OHCA Cases with Adjudicated Etiologies

Of the total 3271 OHCAs identified, 63% (2062/3271) were designated as “no obvious cause” or presumed cardiac by data guardians using the Utstein criteria (Figure 4E), 34.1% (1117/3271) were designated as “obvious cause” and 2.8% (92/3271) were not classified as either.
Stage 1: Review and abstraction of ambulance call reports, in-hospital data, coroner investigative statements, autopsy reports, toxicology, police reports.

Stage 2: Adjudication by 3 reviewers

3271 OHCAs ages 2-45 with EMS

2062 (63%) OHCAs with Site Classification = No Obvious Cause

626 (19.1%) Cardiac Unexpected Categories
- Structural Heart Disease
- Ischemic Heart Disease
- Suspected Primary Arrhythmic
- Other Cardiac
- Undetermined Cardiac

397 (12.1%) Non-Cardiac Unexpected Categories
- SUDEP
- Infectious
- Metabolic
- Respiratory
- Anaphylaxis
- Undetermined Non-Cardiac

882 (27.0%) Expected Cardiac and Non-Cardiac Categories
- Congestive Heart Failure
- Drug Overdose
- Trauma
- Cancer
- Complex Chronic Care

157 (4.8%) Undetermined Lack of Info Advanced Decomp

After adjudication (stages 1 and 2) by the primary author and 2 cardiologists and using abstracted data from ambulance call reports, in-hospital charts, police reports, coroner investigative statements, autopsy results, and toxicology reports, only 20% (656/3271) of the primary cardiac OHCAs were classified as having an unexpected, cardiac etiology, while 12.5% (410/3271) were classified as having an unexpected non-cardiac etiology. The majority of OHCAs (60.7%; 1984/3271) were classified as expected cardiac and non-cardiac etiologies, with 6.7% (221/3271) classified as undetermined due to lack of...
Figure 4F: Review and classification of OHCAs from 2009-2012 according to Data Guardian’s Site Classification – Compiled Consort

Stage 1: Review and abstraction of ambulance call reports, in-hospital data, coroner investigative statements, autopsy reports, toxicology, police reports.

Stage 2: Adjudication by 3 reviewers

3271
OHCAs ages 2-45 with EMS response

1117 (34.1%)
OHCAs with Site Classification = Obvious Cause

2062 (63.0%)
OHCAs with Site Classification = No Obvious Cause

92 (2.8%)
OHCAs with Site Classification = Blank

656 (20.0%)
Cardiac Unexpected Categories
Structural Heart Disease
Ischemic Heart Disease
Suspected Primary Arrhythmic
Other Cardiac
Undetermined Cardiac

411 (12.6%)
Non-Cardiac Unexpected Categories
SUDEP
Infectious
Metabolic
Respiratory
Anaphylaxis
Undetermined Non-Cardiac

1984 (60.7%)
Expected Cardiac and Non-Cardiac Categories
Congestive Heart Failure
Drug Overdose
Trauma
Cancer
Complex Chronic Care

220 (6.7%)
Undetermined
Lack of info
Advanced Decomp

Cardiac
Non-Cardiac
Expected
Unknown
information (either no match to a coroner record or insufficient autopsy information to identify the exact etiology) (Figure 4F).

### 4.6 Incidence and Event Characteristics for Sudden Unexpected Cardiac Cases:

The highest possible SCD incidence rate for autopsied, non-autopsied and aborted SCDs was 3.97 (95% CI, 3.82-4.12) per 100,000 persons in those ages 2-45 years. Adults ages 35-45 years had over 14 times the risk for SCD compared to children (RR 14.42; 95% CI 10.15-20.23). Males had higher SCD incidence rates than females (Appendix 4B). Age-related distribution of incidence rates are presented in Table 4A.

**Table 4A: Incidence of SCD and Aborted SCD in the Cardiac Cohort Ages 2-45 from 2009-2012**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Ages 2-17</th>
<th>Ages 18-34</th>
<th>Ages 35-45</th>
<th>Ages 2-45</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population at Risk from 2009-2012</td>
<td>5,434,520</td>
<td>6,465,080</td>
<td>4,614,680</td>
<td>16,514,280</td>
</tr>
<tr>
<td>Total Unexpected Cardiac Events*</td>
<td>35</td>
<td>195</td>
<td>426</td>
<td>656</td>
</tr>
<tr>
<td>Incidence Rate per 100,000 persons annually (95% CI)</td>
<td>0.64 (0.37-0.91)</td>
<td>3.02 (2.78-3.26)</td>
<td>9.23 (8.94-9.52)</td>
<td>3.97 (3.82-4.12)</td>
</tr>
<tr>
<td>Relative Risk (95% CI)</td>
<td>1.0</td>
<td>4.72 (3.27-6.71)</td>
<td>14.42 (10.15-20.23)</td>
<td>N/A</td>
</tr>
<tr>
<td>Total Unexpected Cardiac Deaths**</td>
<td>21</td>
<td>150</td>
<td>358</td>
<td>529</td>
</tr>
<tr>
<td>Incidence Rate per 100,000 persons annually (95% CI)</td>
<td>0.39 (0.12-0.65)</td>
<td>2.32 (2.08-2.56)</td>
<td>7.76 (7.47-8.05)</td>
<td>3.20 (3.05-3.35)</td>
</tr>
<tr>
<td>Relative Risk (95% CI)</td>
<td>1.0</td>
<td>5.95 (3.80-9.48)</td>
<td>19.89 (12.93-31.17)</td>
<td>N/A</td>
</tr>
<tr>
<td>Total Unexpected Aborted Cardiac Deaths***</td>
<td>14</td>
<td>45</td>
<td>68</td>
<td>127</td>
</tr>
<tr>
<td>Incidence Rate per 100,000 persons annually (95% CI)</td>
<td>0.26 (-0.008-0.52)</td>
<td>0.70 (0.45-0.94)</td>
<td>1.47 (1.18-1.76)</td>
<td>0.77 (0.62-0.85)</td>
</tr>
<tr>
<td>Relative Risk (95% CI)</td>
<td>1.0</td>
<td>2.69 (1.48-4.92)</td>
<td>5.65 (3.22-10.17)</td>
<td>N/A</td>
</tr>
</tbody>
</table>

*includes both sudden cardiac deaths and aborted cardiac deaths
**includes only sudden cardiac deaths (e.g. die from the event)
***includes only aborted cardiac deaths (e.g. resuscitated from the event)
Table 4B shows subject and event characteristics. The mean age of cardiac cases was 35.7 ± 8.8 years (Figure 4F) and most were males (76.4%; 501/656). Almost 60% were unwitnessed and over one-third received bystander CPR, with significantly more children receiving bystander CPR than adults. (57.1% vs. 33.7%, p=0.005). The initial rhythm was shockable in 47.6% of the cases, while over half were found in a non-shockable rhythm (PEA or asystole).

Most patients died at the scene or in the ED, with significantly fewer adults being admitted to hospital than children (24.6% vs. 57.1%, p<0.0001). Overall survival was 19.4%, with significantly more children surviving than younger adults (ages 18-34 years) (40.0% vs. 23.1%, p<0.0001). Most events occurred at home, with few occurring in a public place.
# Table 4B: Baseline Characteristics of SCD and Aborted SCD in the Cardiac Cohort Ages 2-45 from 2009-2012¹

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Ages 2-17</th>
<th>Ages 18-34</th>
<th>Ages 35-45</th>
<th>P value†</th>
<th>Ages 2-45</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male Gender (%)</td>
<td>26/35 (74.3)</td>
<td>142/195 (72.8)</td>
<td>333/426 (78.2)</td>
<td>0.33</td>
<td>501/656 (76.4)</td>
</tr>
<tr>
<td>Age ± SD</td>
<td>12.6 ± 4.8</td>
<td>28.1 ± 4.9</td>
<td>41.1 ± 2.8</td>
<td>N/A</td>
<td>35.7 ± 8.8</td>
</tr>
<tr>
<td>Treated By EMS (%)</td>
<td>33/35 (94.3)</td>
<td>141/195 (72.3)</td>
<td>309/426 (72.5)</td>
<td>0.02</td>
<td>483/656 (73.6)</td>
</tr>
<tr>
<td>Bystander CPR (%)</td>
<td>20/35 (57.1)</td>
<td>73/195 (37.4)</td>
<td>136/426 (31.9)</td>
<td>0.007</td>
<td>229/656 (34.9)</td>
</tr>
<tr>
<td>Bystander Witnessed (%)</td>
<td>23/35 (65.7)</td>
<td>71/171 (41.5)</td>
<td>151/380 (39.7)</td>
<td>0.05</td>
<td>245/586 (41.8)</td>
</tr>
<tr>
<td>EMS Witnessed (%)</td>
<td>0</td>
<td>18/194 (9.3)</td>
<td>37/422 (8.8)</td>
<td>0.21</td>
<td>55/651 (8.4)</td>
</tr>
<tr>
<td>Initial Rhythm</td>
<td></td>
<td></td>
<td></td>
<td>0.92</td>
<td></td>
</tr>
<tr>
<td>VF/VT (%)</td>
<td>17/31 (54.8)</td>
<td>61/134 (45.5)</td>
<td>144/301 (47.8)</td>
<td>0.64</td>
<td>222/466 (47.6)</td>
</tr>
<tr>
<td>PEA/Asystole (%)</td>
<td>11/31 (35.5)</td>
<td>59/134 (44.0)</td>
<td>121/301 (40.2)</td>
<td>0.61</td>
<td>191/466 (41.0)</td>
</tr>
<tr>
<td>Not shockable/AED no shock (%)</td>
<td>3/31 (9.7)</td>
<td>12/134 (9.0)</td>
<td>33/301 (11.0)</td>
<td>0.81</td>
<td>48/466 (10.3)</td>
</tr>
<tr>
<td>Missing (%)</td>
<td>0/31</td>
<td>2/134 (1.5)</td>
<td>3/301 (1.0)</td>
<td>N/A</td>
<td>5/466 (1.1)</td>
</tr>
<tr>
<td>Shocks Given (%)</td>
<td>22/35 (62.9)</td>
<td>81/195 (41.5)</td>
<td>179/426 (42.0)</td>
<td>0.05</td>
<td>282/656 (43.0)</td>
</tr>
<tr>
<td>Location of Arrest</td>
<td></td>
<td></td>
<td></td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td>Public (%)</td>
<td>13/35 (37.1)</td>
<td>34/195 (17.4)</td>
<td>94/426 (22.1)</td>
<td>0.03</td>
<td>141/656 (21.5)</td>
</tr>
<tr>
<td>Private (%)</td>
<td>22/35 (62.9)</td>
<td>145/195 (74.4)</td>
<td>315/426 (73.9)</td>
<td>0.34</td>
<td>482/656 (73.5)</td>
</tr>
<tr>
<td>Other (%)</td>
<td>0</td>
<td>16/195 (8.2)</td>
<td>17/426 (4.0)</td>
<td>N/A</td>
<td>33/656 (5.0)</td>
</tr>
<tr>
<td>Prehospital ROSC (%)</td>
<td>16/34 (47.0)</td>
<td>53/190 (27.9)</td>
<td>99/413 (24.0)</td>
<td>&lt;0.0001</td>
<td>168/637 (26.4)</td>
</tr>
<tr>
<td>Admitted</td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Died at Scene (%)</td>
<td>2/35 (5.7)</td>
<td>70/195 (35.9)</td>
<td>185/426 (43.3)</td>
<td>&lt;0.0001</td>
<td>257/656 (39.2)</td>
</tr>
<tr>
<td>Died ED (%)</td>
<td>13/35 (37.1)</td>
<td>70/195 (35.9)</td>
<td>143/426 (33.6)</td>
<td>0.34</td>
<td>226/656 (34.5)</td>
</tr>
<tr>
<td>Admitted (%)</td>
<td>20/35 (57.1)</td>
<td>55/195 (28.2)</td>
<td>98/426 (23.0)</td>
<td>0.0002</td>
<td>173/656 (26.4)</td>
</tr>
<tr>
<td>Survived to Hospital Discharge (%)</td>
<td>14/35 (40.0)</td>
<td>45/195 (23.1)</td>
<td>68/426 (16.0)</td>
<td>0.0003</td>
<td>127/656 (19.4)</td>
</tr>
</tbody>
</table>

¹Denominators change due to missing data.
†Pearson χ²/Fisher’s Exact Test comparison across 3 age categories.
Figure 4G: Age Distribution Cardiac Unexpected Deaths 2009-2012

4.7 Comparison of EMS and Rescu Data Guardian Classification of Sudden Unexpected Cardiac Cases:

When comparing how EMS and Rescu Data Guardian classified the cases (n=656) adjudicated by our 2 stage review process as sudden unexpected cardiac (Table 4C), both EMS and Data Guardians classified these cases as presumed cardiac cause (e.g. no obvious cause) in the vast majority of cases (85.8% vs. 95.4%).
Table 4C: EMS and Data Guardian Utstein Designation of Cardiac Cases 2009-2012 Ages 2-45 Years

<table>
<thead>
<tr>
<th>EMS Designation</th>
<th>Ages 2-17 (n=35)</th>
<th>Ages 18-34 (n=195)</th>
<th>Ages 35-45 (n=426)</th>
<th>Ages 2-45 (n=656)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Obvious Cause (%)</td>
<td>28 (80)</td>
<td>163 (83.6)</td>
<td>372 (87.3)</td>
<td>563 (85.8)</td>
</tr>
<tr>
<td>Obvious Cause (%)</td>
<td>5 (14.3)</td>
<td>5 (2.6)</td>
<td>3 (0.7)</td>
<td>13 (2)</td>
</tr>
<tr>
<td>Not Determined (%)</td>
<td>2 (5.7)</td>
<td>27 (13.8)</td>
<td>51 (12)</td>
<td>80 (12.2)</td>
</tr>
<tr>
<td>Data Guardian Designation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No Obvious Cause (%)</td>
<td>30 (85.7)</td>
<td>184 (94.4)</td>
<td>412 (96.7)</td>
<td>626 (95.4)</td>
</tr>
<tr>
<td>Obvious Cause (%)</td>
<td>5 (14.3)</td>
<td>5 (2.6)</td>
<td>4 (0.9)</td>
<td>14 (2.1)</td>
</tr>
<tr>
<td>Not Determined (%)</td>
<td>0</td>
<td>6 (3.1)</td>
<td>10 (2.3)</td>
<td>16 (2.4)</td>
</tr>
</tbody>
</table>

4.8 Detailed Causes of OHCAs:

The specific etiology for each OHCA case for the entire cohort ages 2-45 years was determined after review of all available information as described in Chapter 3 of this thesis (e.g. Stages 1 and 2 Review Process).

4.8.1 Etiologies of Sudden Unexpected Cardiac Cases:

In the overall SCD and aborted SCD study population (n=656), the most common causes of death were ischemic heart disease (40.9%; 268/656) and structural heart disease (28.4%; 186/656) (Table 4D). Children and younger adults died more frequently from structural heart disease and sudden unexplained death (SUD) (e.g. presumed primary arrhythmias). Surprisingly, almost 20% of younger adults (aged 18-34 years) died from premature ischemic heart disease (19.5%; 38/195).
Table 4D: Cardiac Etiologies by Age Category 2009-2012

<table>
<thead>
<tr>
<th>Etiology Type</th>
<th>Ages 2-17 (n=35)</th>
<th>Ages 18-34 (n=195)</th>
<th>Ages 35-45 (n=426)</th>
<th>P Value†</th>
<th>Ages 2-45 (n=656)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Structural Heart Disease (%)</td>
<td>14 (40.0)</td>
<td>63 (32.3)</td>
<td>109 (25.6)</td>
<td>0.07</td>
<td>186 (28.4)</td>
</tr>
<tr>
<td>Ischemic Heart Disease (%)</td>
<td>0</td>
<td>38 (19.5)</td>
<td>230 (54.0)</td>
<td>&lt;0.0001</td>
<td>268 (40.9)</td>
</tr>
<tr>
<td>Sudden Unexplained Deaths (%)</td>
<td>13 (37.1)</td>
<td>57 (29.2)</td>
<td>29 (6.8)</td>
<td>&lt;0.000</td>
<td>99 (15.1)</td>
</tr>
<tr>
<td>Other* (%)</td>
<td>2 (5.7)</td>
<td>9 (4.6)</td>
<td>5 (1.2)</td>
<td>0.02</td>
<td>16 (2.4)</td>
</tr>
<tr>
<td>Undetermined-Cardiac** (%)</td>
<td>6 (17.1)</td>
<td>28 (14.4)</td>
<td>53 (12.4)</td>
<td>0.63</td>
<td>87 (13.3)</td>
</tr>
</tbody>
</table>

*Other includes congenital HD, anomalous coronary arteries, endocarditis, tamponade and commotio cordis.
**Undetermined-Cardiac includes patients with competing cardiac etiologies or those without autopsy in whom the etiology was considered to be cardiac.
†Pearson χ²/Fisher’s Exact Test comparison across 3 age categories.

The specific types of structural heart disease were determined from autopsy for each age category and the overall study population (Table 4E). Heritable cardiomyopathies were the predominant underlying etiology across all age groups and there was a significant association across age categories (p<0.0001). Children had the highest percentage of HCM (as a proportion of structural causes) compared to adults (28.6% vs. 2.9%, p<0.0001). In adults, acquired cardiomyopathies due to hypertension or myocarditis accounted for almost 40% (69/186) of the SCD and aborted SCD events.

The most common non-ischemic structural causes of death in this study (as a proportion of all structural causes) were nonspecific cardiomyopathies at 25.8% (48/186), hypertensive cardiomyopathies at 26.9% (50/186) and dilated cardiomyopathies at 11.3% (21/186). Fibrotic cardiomyopathies, defined as interstitial, diffuse or patchy myocardial fibrosis without left ventricular hypertrophy, or other structural abnormalities, accounted for just over 6% of SCD events.
Table 4E: Types of Cardiac Structural Heart Disease in Cardiac Cases by Age Category 2009-2012

<table>
<thead>
<tr>
<th>Type of Structural HD</th>
<th>Ages 2-17 (n=14)</th>
<th>Ages 18-34 (n=63)</th>
<th>Ages 35-45 (n=109)</th>
<th>P Value (^*)</th>
<th>Ages 2-45 (n=186)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARVC (%)</td>
<td>3 (21.4)</td>
<td>6 (9.5)</td>
<td>5 (4.6)</td>
<td>0.06</td>
<td>14 (7.5)</td>
</tr>
<tr>
<td>Cardiomyopathy Non Specific (%)</td>
<td>3 (21.4)</td>
<td>21 (33.3)</td>
<td>24 (22.6)</td>
<td>0.24</td>
<td>48 (25.8)</td>
</tr>
<tr>
<td>Duchene Muscular Dystrophy Cardiomyopathy (%)</td>
<td>0</td>
<td>1 (1.6)</td>
<td>1 (0.92)</td>
<td>0.85</td>
<td>2 (1.1)</td>
</tr>
<tr>
<td>Fibrotic Cardiomyopathy (%)</td>
<td>1 (7.1)</td>
<td>3 (4.8)</td>
<td>8 (7.3)</td>
<td>0.80</td>
<td>12 (6.5)</td>
</tr>
<tr>
<td>Dilated Cardiomyopathy (%)</td>
<td>2 (14.3)</td>
<td>5 (7.9)</td>
<td>15 (13.8)</td>
<td>0.56</td>
<td>22 (11.8)</td>
</tr>
<tr>
<td>Hypertrophic Cardiomyopathy</td>
<td>4 (28.6)</td>
<td>1 (1.6)</td>
<td>4 (3.7)</td>
<td>0.001</td>
<td>9 (4.8)</td>
</tr>
<tr>
<td>Hypertensive Cardiomyopathy</td>
<td>0</td>
<td>9 (14.3)</td>
<td>41 (38.0)</td>
<td>0.0002</td>
<td>50 (26.9)</td>
</tr>
<tr>
<td>Myocarditis</td>
<td>1 (7.1)</td>
<td>12 (19.0)</td>
<td>6 (5.5)</td>
<td>0.02</td>
<td>19 (10.2)</td>
</tr>
<tr>
<td>Sarcoidosis</td>
<td>0</td>
<td>1 (1.6)</td>
<td>3 (2.8)</td>
<td>0.74</td>
<td>4 (2.2)</td>
</tr>
<tr>
<td>Valvular Cardiomyopathy</td>
<td>0</td>
<td>4 (6.3)</td>
<td>2 (1.8)</td>
<td>0.21</td>
<td>6 (3.2)</td>
</tr>
</tbody>
</table>

\(^*\)Pearson \(\chi^2\)/Fisher’s Exact test between 3 age groups, where appropriate.

4.8.2 Etiologies of Sudden Unexpected Non-Cardiac Cases:

In the overall non-cardiac study population (n=410), the predominant etiology was vascular non-cardiac (28.0%; 115/410), followed by metabolic imbalances (19.0%; 78/410), sudden unexplained death in epilepsy (SUDEP) at 17.1% (70/410) and infectious conditions (17.8%; 73/410). A small percentage of non-cardiac cases had other non-cardiac etiologies such as anaphylaxis or asthma (9.3% (38/410) or could not be determined due to competing non-cardiac causes or lack of autopsy (8.8%; 36/410). See Appendix 4A for further detail.
4.8.3 Expected Cardiac and Non-Cardiac Cases:

Of the 3271 OHCAs, 1984 (60.6%) had expected cardiac and non-cardiac etiologies. The majority were traumatic OHCAs (1032/3271; 31.5%), followed by drug overdoses (767/3271; 23.4%), cancer/DNR (111/3271; 3.4%), complex chronic care (71/3271; 2.2%) and congestive heart failure (3/3271; 0.1%) (Figure 4F).

4.8.4 Undetermined Cases:

Of the 3271 OHCAs, 221 (6.7%) had an undetermined etiology due to lack of information, lack of autopsy (172/221; 77.8%) or advanced decomposition (49/221; 22.2%).

4.8.5 Autopsy and Toxicology Results for Sudden Unexpected Cardiac Cases:

Among the unexpected cardiac cohort, there were 127/656 (19.3%) survivors. Of the 529 SCD deaths, 487 (92.0%) were coroner cases and 434/487 (89.1%) had an autopsy performed (Table 4F). A small percentage died in-hospital without a coroner investigation or autopsy performed (42/529; 8.0%).

Toxicology was performed in 60% of autopsied cardiac cases and almost 30% had one or more CNS active drugs (defined as antipsychotics, antidepressants or opioids) or alcohol detected. Drugs or alcohol were detected at a therapeutic or non-toxic level in 30.6% (80/261) of cardiac cases and at a significant level in 11.5% (30/261) of cardiac cases that underwent toxicology testing.
### Table 4F: Toxicology and Autopsy Results of Cardiac Cases Ages 2-45 from 2009-2012

<table>
<thead>
<tr>
<th>Variable</th>
<th>Ages 2-17 (n=35)</th>
<th>Ages 18-34 (n=195)</th>
<th>Ages 35-45 (n=426)</th>
<th>Ages 2-45 (n=656)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Unexpected Cardiac Deaths (%)</td>
<td>21/35 (60.0)</td>
<td>150/195 (76.9)</td>
<td>358/426 (84.0)</td>
<td>529/656 (80.6)</td>
</tr>
<tr>
<td>Coroner Cases (%)</td>
<td>21/21 (100)</td>
<td>145/150 (96.7)</td>
<td>321/358 (89.7)</td>
<td>487/529 (92.0)</td>
</tr>
<tr>
<td>Autopsy Rate* (%)</td>
<td>20/21 (95.2)</td>
<td>137/145 (94.5)</td>
<td>277/321 (86.3)</td>
<td>434/487 (89.1)</td>
</tr>
<tr>
<td>Toxicology</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive** (%)</td>
<td>1/20 (5.0)</td>
<td>43/137 (31.4)</td>
<td>83/277 (30.0)</td>
<td>127/434 (29.3)</td>
</tr>
<tr>
<td>Negative*** (%)</td>
<td>12/20 (60.0)</td>
<td>60/137 (43.8)</td>
<td>60/277 (21.7)</td>
<td>132/434 (30.4)</td>
</tr>
<tr>
<td>Not Done (%)</td>
<td>7/20 (35.0)</td>
<td>33/137 (24.1)</td>
<td>133/277 (48.0)</td>
<td>173/434 (39.9)</td>
</tr>
<tr>
<td>Toxicology Level</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Toxic Level¹ (%)</td>
<td>1/20 (5.0)</td>
<td>30/137 (21.9)</td>
<td>49/277 (17.7)</td>
<td>80/434 (18.4)</td>
</tr>
<tr>
<td>Significant Level² (%)</td>
<td>0</td>
<td>7/137 (5.1)</td>
<td>23/277 (8.3)</td>
<td>30/434 (6.9)</td>
</tr>
<tr>
<td>Toxic Level³ (%)</td>
<td>0</td>
<td>6/137 (4.4)</td>
<td>11/277 (4.0)</td>
<td>17/434 (3.9)</td>
</tr>
</tbody>
</table>

*Autopsy rate is for coroner cases only.

**Positive tox screen means one or more drugs were detected.

***Negative tox screen means no drugs were detected.

¹Indicates a drug detected at a low level such as therapeutic (according to toxicology drug standards) and would be considered non-contributory to cause of death.

²Indicates a drug detected at a significant level (according to toxicology drug standards) and would be considered to have contributed to the cause of death.

³Indicates a drug detected at a toxic level (according to toxicology drug standards) and would be considered to have contributed to the cause of death.

The most commonly detected drugs at all levels were CNS active, such as recreational depressants (alcohol or opioid), antipsychotics and antidepressants. Cocaine and other prescription drugs constituted the rest.

### Table 4G: Drug Toxicology of Autopsied Cardiac Cases Ages 2-45 from 2009-2012

<table>
<thead>
<tr>
<th>Type of Drug Detected</th>
<th>Non-Toxic (n=77)</th>
<th>Significant (n=28)</th>
<th>Toxic (n=17)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antipsychotics (%)</td>
<td>7 (9.1)</td>
<td>0</td>
<td>2 (11.7)</td>
</tr>
<tr>
<td>Antidepressants (%)</td>
<td>5 (6.5)</td>
<td>0</td>
<td>1 (5.9)</td>
</tr>
<tr>
<td>Recreational Depressants* (%)</td>
<td>39 (50.6)</td>
<td>15 (53.6)</td>
<td>8 (58.8)</td>
</tr>
<tr>
<td>Cocaine (%)</td>
<td>6 (7.8)</td>
<td>8 (28.5)</td>
<td>2 (11.7)</td>
</tr>
<tr>
<td>Other prescription drugs** (%)</td>
<td>20 (26)</td>
<td>5 (17.9)</td>
<td>4 (23.5)</td>
</tr>
</tbody>
</table>

*Either alcohol or opioids (e.g. methadone, oxycodone, codeine) used for recreational purposes.

**Defined as another prescribed drug e.g. anticonvulsant, benzodiazepine, etc. detected on toxicology.

In the SUDs or presumed arrhythmic cases, toxicology was performed in over 70% (71/99) of cases and of these, over a quarter (26/99) had a positive toxicology detected.
at autopsy (Table 4H). The main types of drugs detected were CNS active such antipsychotics, antidepressants, recreational depressants and other prescription medications. In contrast to the main cohort, no cocaine was detected at any level.

Table 4H: Drug Toxicology of Autopsied SUD Cases Ages 2-45 from 2009-2012

<table>
<thead>
<tr>
<th>Type of Drug Detected</th>
<th>Detected Drug Level – SUD Cases (n=26)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Non-Toxic (n=16)</td>
</tr>
<tr>
<td>Antipsychotics (%)</td>
<td>4 (25)</td>
</tr>
<tr>
<td>Antidepressants (%)</td>
<td>4 (25)</td>
</tr>
<tr>
<td>Recreational Depressants* (%)</td>
<td>5 (31.2)</td>
</tr>
<tr>
<td>Cocaine (%)</td>
<td>0</td>
</tr>
<tr>
<td>Other prescription drugs** (%)</td>
<td>3 (18.7)</td>
</tr>
</tbody>
</table>

*Either alcohol or opioids (e.g. methadone, oxycodone, codeine) used for recreational purposes. **Defined as another prescribed drug e.g. anticonvulsant, benzodiazepine, etc. detected on toxicology.

4.9 Sensitivity Analysis:

We used different assumptions and data sources to report upper and lower boundaries of SCD incidence rates.

Using deceased, primary OHCA cases (e.g. only ambulance call reports) to identify potential SCD cases (n=1911) the annual SCD incidence rate was 11.57 (95% CI, 11.06-12.10) per 100,000 persons.

Using deceased, primary OHCA cases in which a coroner investigation had been performed (e.g. ambulance call reports and coroner reports) to identify potential SCD cases (n=1711), the annual SCD incidence rate decreased to 10.36 (95% CI, 9.88-10.86) per 100 000 persons.

Using deceased, primary OHCA cases in which a coroner investigation and an autopsy was performed (e.g. ambulance call reports, coroner reports and autopsy reports) to identify potential SCD cases (n=1562), the annual SCD incidence rate decreased to 9.46 (95% CI, 9.00–9.94) per 100 000 persons (Table 4I).
Using deceased, primary OHCA cases which were adjudicated by our 3 reviewers as having a cardiac etiology (n=529), and the annual SCD incidence rate decreased dramatically to 3.20 (95% CI, 2.94-3.22) per 100,000 persons. At the last stage when we included adjudicated OHCA cases of cardiac etiology, non-survivors, with a coroner investigative statement, autopsy and toxicology, the annual SCD incidence rate decreased further to 1.59 (95% CI, 1.41-1.79) per 100,000 persons.

Table 4I: Sensitivity Analysis of Annual SCD Incidence Rates

<table>
<thead>
<tr>
<th>OHCA Cases (no adjudication)</th>
<th>SCD Incidence Rate per 100,000 persons annually</th>
</tr>
</thead>
<tbody>
<tr>
<td>OHCA “no obvious cause” presumed cardiac, non-survivors (n=1911)</td>
<td>11.57 (95% CI, 11.06-12.10)</td>
</tr>
<tr>
<td>OHCA “no obvious cause” presumed cardiac, non-survivors, with only a coroner investigation (n=1711)</td>
<td>10.36 (9.88-10.86)</td>
</tr>
<tr>
<td>OHCA “no obvious cause” presumed cardiac, non-survivors, with a coroner investigation and an autopsy (n=1562)</td>
<td>9.46 (9.00-9.94)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Sudden Unexpected Cardiac Cases (with Adjudication)</th>
<th>SCD Incidence Rate per 100,000 persons annually</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCD cases of cardiac etiology, non survivors (n=529)</td>
<td>3.20 (2.94-3.49)</td>
</tr>
<tr>
<td>SCD cases of cardiac etiology, non survivors with only a coroner investigation (n=487)</td>
<td>2.95 (2.70-3.22)</td>
</tr>
<tr>
<td>SCD cases of cardiac etiology, non survivors with a coroner investigation and an autopsy (n=434)</td>
<td>2.63 (2.39-2.89)</td>
</tr>
<tr>
<td>SCD cases of cardiac etiology, non survivors with a coroner investigation, autopsy and toxicology (n=216)</td>
<td>1.59 (1.41-1.79)</td>
</tr>
</tbody>
</table>

4.10 Subject Characteristics for Sudden Unexpected Cardiac Cases:

Baseline medical history for the cardiac cohort (n=656) was collected from all available information including ambulance/fire call reports, in-hospital charts, police reports, coroner investigative statements, and autopsy reports. Cases were divided into 3 age groups and by gender to compare characteristics.

4.10.1 Medical History for Sudden Unexpected Cardiac Cases:

In the overall cohort, only 11.9% (78/656) reportedly had no past medical history (e.g. “apparently healthy”), 81.7% (536/656) had a reported medical history of some kind and
in 42 (6.4%) nothing was recorded (Table 4J). Rates of cardiac risk factors such as hypertension, hyperlipidemia, diabetes, prior MI and smoking increased with age.

A small percentage of cases were diagnosed with an arrhythmia prior to the event (6.5%; 39/602) and/or had an implanted cardioverter defibrillator (2.5% 15/604). More children (9.4%; 3/32) and young adults (8.8%; 15/170) had a history of a diagnosed seizure disorder compared to older adults (4.0%; 16/400).
Table 4J: Medical History of All Cardiac Cases Ages 2-45 from 2009-2012¹

<table>
<thead>
<tr>
<th>Variable</th>
<th>Ages 2-17 (n=35)</th>
<th>Ages 18-34 (n=195)</th>
<th>Ages 35-45 (n=426)</th>
<th>Ages 2-45 (n=656)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No past medical history (e.g. healthy) (%)</td>
<td>11/35 (31.4)</td>
<td>26/195 (13.3)</td>
<td>41/426 (9.6)</td>
<td>78/656 (11.9)</td>
</tr>
<tr>
<td>Past Medical Hx (%)</td>
<td>21/35 (60.0)</td>
<td>151/195 (77.4)</td>
<td>364/426 (85.4)</td>
<td>536/656 (81.7)</td>
</tr>
<tr>
<td>Family Hx (%)</td>
<td>6/35 (17.1)</td>
<td>19/195 (9.7)</td>
<td>57/426 (13.4)</td>
<td>82/656 (12.5)</td>
</tr>
<tr>
<td>HTN (%)</td>
<td>0</td>
<td>16/172 (9.3)</td>
<td>111/400 (27.8)</td>
<td>127/604 (21.0)</td>
</tr>
<tr>
<td>Lipid (%)</td>
<td>0</td>
<td>4/172 (2.3)</td>
<td>47/400 (11.8)</td>
<td>51/604 (8.4)</td>
</tr>
<tr>
<td>Diabetes Mellitus (%)</td>
<td>0</td>
<td>13/172 (7.6)</td>
<td>70/399 (17.5)</td>
<td>83/603 (13.8)</td>
</tr>
<tr>
<td>Obesity (%)</td>
<td>1/32 (3.1)</td>
<td>30/172 (17.4)</td>
<td>72/400 (18.0)</td>
<td>103/604 (17.1)</td>
</tr>
<tr>
<td>Prior MI (%)</td>
<td>0</td>
<td>5/172 (2.9)</td>
<td>35/400 (8.8)</td>
<td>40/604 (6.6)</td>
</tr>
<tr>
<td>Arrhythmia (%)</td>
<td>1/32 (3.1)</td>
<td>14/172 (8.1)</td>
<td>24/398 (6.0)</td>
<td>39/602 (6.5)</td>
</tr>
<tr>
<td>ICD/Pacemaker (%)</td>
<td>1/32 (3.1)</td>
<td>7/172 (4.1)</td>
<td>7/400 (1.8)</td>
<td>15/604 (2.5)</td>
</tr>
<tr>
<td>Smoking (%)</td>
<td>1/32 (3.1)</td>
<td>25/169 (14.8)</td>
<td>114/400 (28.5)</td>
<td>140/601 (23.3)</td>
</tr>
<tr>
<td>Seizure Disorder (%)</td>
<td>3/32 (9.4)</td>
<td>15/170 (8.8)</td>
<td>16/400 (4.0)</td>
<td>34/602 (5.6)</td>
</tr>
<tr>
<td>Mental Health</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mood Disorder (%)</td>
<td>0</td>
<td>20/170 (11.8)</td>
<td>51/400 (12.8)</td>
<td>71/602 (11.8)</td>
</tr>
<tr>
<td>Psychosis (%)</td>
<td>0</td>
<td>11/170 (6.5)</td>
<td>23/400 (5.8)</td>
<td>34/602 (5.6)</td>
</tr>
<tr>
<td>Other Psych (%)</td>
<td>0</td>
<td>7/170 (4.1)</td>
<td>18/400 (4.5)</td>
<td>25/602 (4.2)</td>
</tr>
<tr>
<td>Illicit Drug Use (%)</td>
<td>2/32 (6.3)</td>
<td>25/169 (14.8)</td>
<td>51/400 (12.8)</td>
<td>78/601 (13.0)</td>
</tr>
<tr>
<td>Etoh Abuse (%)</td>
<td>0</td>
<td>11/169 (6.5)</td>
<td>59/398 (14.8)</td>
<td>70/599 (11.7)</td>
</tr>
<tr>
<td>Medications***</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac (%)</td>
<td>4/32 (12.5)</td>
<td>24/140 (17.1)</td>
<td>133/332 (40.1)</td>
<td>161/504 (31.9)</td>
</tr>
<tr>
<td>Diabetic (%)</td>
<td>0</td>
<td>8/140 (5.7)</td>
<td>42/332 (12.7)</td>
<td>50/504 (9.9)</td>
</tr>
<tr>
<td>Antibiotic (%)</td>
<td>0</td>
<td>13/140 (9.3)</td>
<td>14/331 (4.2)</td>
<td>27/503 (5.4)</td>
</tr>
<tr>
<td>Antipsychotic (%)</td>
<td>0</td>
<td>15/195 (7.7)</td>
<td>26/426 (6.1)</td>
<td>41/656 (6.3)</td>
</tr>
<tr>
<td>Antidepressant (%)</td>
<td>0</td>
<td>17/195 (8.7)</td>
<td>44/426 (10.3)</td>
<td>61/656 (9.3)</td>
</tr>
<tr>
<td>Anticonvulsant (%)</td>
<td>2/32 (6.3)</td>
<td>13/140 (9.3)</td>
<td>25/332 (7.5)</td>
<td>40/504 (7.9)</td>
</tr>
<tr>
<td>Opioid (%)</td>
<td>0</td>
<td>17/140 (12.1)</td>
<td>50/331 (15.1)</td>
<td>67/503 (13.3)</td>
</tr>
</tbody>
</table>

¹Denominators are different due to missing data.
*Includes one of depression, anxiety, bipolar, schizoaffective disorder or manic depressive.
**Includes one of OCD, borderline personality disorder or suicide attempt.
***Medications are assessed per drug not per patient. E.g. patients could have been taking multiple medications and thus categories are not additive.
4.10.2 Mental Health History for Sudden Unexpected Cardiac Cases:

In adults, rates of depression were ~12% (71/602), while rates of psychosis were 5.6% (34/602). Rates of drug abuse (13.0%; 78/601) and ethanol abuse (11.7%; 70/599) were similar across the cohort and age categories.

4.10.3 Prescribed Medication History for Sudden Unexpected Cardiac Cases:

Over a third of SCD and aborted SCD cases were prescribed cardiac medications. Less than 10% of subjects had prescribed diabetic medications or antibiotics. Rates of prescribed psychotropic medications such as antidepressants (9.3%; 61/656) and antipsychotics (6.3%; 41/656) were similar to their diagnosis rates across age categories. Prescribed rates of opioids ranged from 12.1% (17/140) in younger adults to 15.1% (50/331) in older adults. Of the 99 SUD cases, over a third were prescribed one or more psychotropic medications such as antidepressants, antipsychotics or opioids.

4.11 Circumstances and Activity Levels for Sudden Unexpected Cardiac Cases:

Adults were more likely to arrest in a private residence than children (73.5% vs 57.1% respectively, p=0.03), with location being significantly associated with age (p=0.04). There was a tendency of fewer adults than children suffering an arrest in public non-recreational (21.7% vs. 31.4% respectively p=0.06) and recreational settings (4.7% vs 11.4% respectively p=0.06) (Table 4K), with location being significantly associated with age categories (p<0.0001).

Significantly more adults died at rest than children (75.8% vs. 45.7%, respectively p<0.0001), with children more likely to arrest during moderate to vigorous levels of exercise than adults (42.9% vs. 10.8% respectively p<0.0001); Rates of SCD and aborted SCD post-exercise were similar across all age groups and the entire cohort.
Table 4K: Circumstances and Activity Level of Cardiac Cases Ages 2-45 from 2009-2012¹

<table>
<thead>
<tr>
<th>Variable</th>
<th>Ages 2-17 (n=35)</th>
<th>Ages 18-34 (n=195)</th>
<th>Ages 35-45 (n=426)</th>
<th>P Value†</th>
<th>Ages 2-45 (n=656)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Environment</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Private Residence (%)</td>
<td>20/35 (57.1)</td>
<td>144/195 (73.8)</td>
<td>313/426 (73.5)</td>
<td>0.10</td>
<td>477/656 (72.7)</td>
</tr>
<tr>
<td>Public Non Recreational* (%)</td>
<td>11/35 (31.4)</td>
<td>37/195 (19.4)</td>
<td>98/426 (23.0)</td>
<td>0.21</td>
<td>146/656 (22.3)</td>
</tr>
<tr>
<td>Public Recreational** (%)</td>
<td>4/35 (11.4)</td>
<td>14/195 (7.2)</td>
<td>15/426 (3.5)</td>
<td>0.03¹,²</td>
<td>33/656 (5.0)</td>
</tr>
<tr>
<td>Circumstances</td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Rest (%)</td>
<td>16/35 (45.7)</td>
<td>145/195 (74.4)</td>
<td>326/436 (76.5)</td>
<td>0.09</td>
<td>487/656 (74.2)</td>
</tr>
<tr>
<td>During Exercise (%)</td>
<td>15/35 (42.9)</td>
<td>36/195 (18.5)</td>
<td>63/426 (14.8)</td>
<td>&lt;0.0001</td>
<td>114/656 (17.4)</td>
</tr>
<tr>
<td>1-60 Mins Post Exercise (%)</td>
<td>4/35 (11.4)</td>
<td>14/195 (7.2)</td>
<td>34/426 (8.0)</td>
<td>0.69</td>
<td>52/656 (7.9)</td>
</tr>
<tr>
<td>Unknown (%)</td>
<td>0</td>
<td>0</td>
<td>3/426 (0.7)</td>
<td>N/A</td>
<td>3/656 (0.5)</td>
</tr>
<tr>
<td>In Bed (%)</td>
<td>5/35 (14.3)</td>
<td>62/195 (31.8)</td>
<td>117/426 (27.5)</td>
<td>0.09</td>
<td>184/656 (28.0)</td>
</tr>
<tr>
<td>Exercise Level</td>
<td></td>
<td></td>
<td></td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td>Light (%)</td>
<td>4/35 (11.4)</td>
<td>20/195 (10.3)</td>
<td>60/426 (14.1)</td>
<td>0.4</td>
<td>84/656 (12.8)</td>
</tr>
<tr>
<td>Moderate (%)</td>
<td>15/35 (42.9)</td>
<td>30/195 (15.4)</td>
<td>37/426 (8.7)</td>
<td>&lt;0.0001</td>
<td>82/656 (12.5)</td>
</tr>
</tbody>
</table>

¹Denominators are different due to missing data.
*Defined as one of: office, roadway, school, mall, etc.
**Defined as a recreational facility such as a gym, athletic centre, park or community centre.
†Pearson χ²/Fisher’s Exact Test across 3 age categories.

4.11.1 Premonitory Symptoms of Sudden Unexpected Cardiac Cases:

Almost 60% (373/656) of SCD and aborted SCD individuals reported experiencing a new symptom prior to their SCD and aborted SCD event (Table 4L). New symptoms were reported more frequently in the 24 hours preceding the event (65.6%; 319/486) than in the week prior (22.6%; 110/486). Adults reported new onset symptoms more frequently than did children (57.5% vs. 45.7%), both in the 1-24 hours (65.9% vs. 59.3%) or week (23.5% vs. 7.4%) preceding their SCD or aborted SCD event.
Table 4L: Symptoms Prior to SCD Event in Cardiac Cases Ages 2-45 from 2009-2012¹

<table>
<thead>
<tr>
<th>Variable</th>
<th>Ages 2-17 (n=35)</th>
<th>Ages 18-34 (n=195)</th>
<th>Ages 35-45 (n=426)</th>
<th>P Value†</th>
<th>Ages 2-45 (n=656)</th>
</tr>
</thead>
<tbody>
<tr>
<td>New Symptoms (%)</td>
<td>16/35 (45.7)</td>
<td>110/195 (56.4)</td>
<td>247/426 (58.0)</td>
<td>0.38</td>
<td>373/656 (56.9)</td>
</tr>
<tr>
<td>Symptoms 1-24 hrs (%)</td>
<td>16/27 (59.3)</td>
<td>95/142 (66.9)</td>
<td>208/317 (65.6)</td>
<td>0.75</td>
<td>319/486 (65.6)</td>
</tr>
<tr>
<td>Seizure &lt; 24 hrs (%)</td>
<td>6/27 (22.2)</td>
<td>33/143 (23.1)</td>
<td>34/317 (10.7)</td>
<td>&lt;0.0001</td>
<td>73/487 (15.0)</td>
</tr>
<tr>
<td>Symptoms Past Week (%)</td>
<td>2/27 (7.4)</td>
<td>28/143 (19.6)</td>
<td>80/316 (25.3)</td>
<td>0.06</td>
<td>110/486 (22.6)</td>
</tr>
<tr>
<td>Saw MD 30 days prior (%)</td>
<td>3/35 (8.6)</td>
<td>31/193 (16.1)</td>
<td>64/422 (15.2)</td>
<td>0.69</td>
<td>98/650 (15.1)</td>
</tr>
</tbody>
</table>

¹Denominators are different due to missing data.
†Pearson χ²/Fisher’s Exact Test across 3 age categories.
Chapter 5: Feasibility Study Results

5.0 Abstract

**Background:** Family members of sudden cardiac death (SCD) patients may be at greater risk for cardiac events compared to the general population; independent of modifiable and genetic risk factors, several studies have suggested that a family history of SCD increases the individual’s risk for SCD.

**Objectives:** To assess the feasibility of collecting family history of SCD in first and second-degree family members of affected individuals as compared to control groups. As a secondary objective, the incidence of prior symptoms and SD triggers were studied.

**Methods:** This feasibility study had a case control design and utilized a prospectively collected, population-based registry of all out-of-hospital cardiac arrests (OHCAs) in the Greater Toronto Area, to identify cases from 2010-2012. Cases were defined as OHCA patients aged 18-65 years who arrested from a cardiac cause (died or survived) and had an EMS response. Two relatives per patient were interviewed regarding symptoms prior to the arrest, cardiac history, and family history of SCD, defined as unexpected out-of-hospital death in a first-degree relative. Two sets of control patients, one with heart disease (HD) and one healthy with no HD or SCD, were administered the same questionnaire as cases, asking detailed questions about their family and personal medical history.

**Results:** Complete family and medical histories were obtained for 74 SCD and aborted SCD individuals, 50 HD control patients and 53 healthy controls [mean ages: 49.6 ± 11.7 (case), 53.7 ± 9.6 (HD), 36.4 ± 12.3 (healthy); % male: 88.9 (case), 76.0 (HD), 56.6 (healthy)]. In the cases, the underlying etiologies were ischemic heart disease (45/74; 60.8%), non-ischemic structural heart disease (6/74; 8.1%), sudden unexplained death
Rates of a family history of SCD among first-degree relatives were no different between cases and HD controls (20/71; 28.2% vs. 14/50; 28.0%, p=0.984), but significantly differed between cases and healthy controls (20/71; 28.2% vs. 3/52; 5.8%, p=0.002). After adjusting for age and sex, the odds ratio of having a positive family history of SCD in cases was 2.2 (95% CI 0.5-9.2; p=0.3) as compared to healthy controls and was 1.2 (95% CI 0.5-2.9; p=0.6) in cases as compared to HD controls. Medical and family history reported by aborted SCD patients and first-degree family members had a high level of agreement when compared to both medical records (Ƙ=066-1.0 for 5/6 variables) and between relatives (Ƙ = 0.6-0.8 for 6/8 variables). More than half of SCD or aborted SCD patients experienced one or more warning symptoms in the 60 minutes preceding their event (41/72; 56.9%). The majority of cases died during rest (70.8%) while a minority experienced their event either during or immediately following exercise (29.2%).

**Conclusions:** Our pilot studies demonstrated that it is feasible to obtain a reliable family history of SCD and major cardiac risk factors from aborted SCD patients and/or first-degree relatives of SCD individuals using a novel, survey. Furthermore, we observed that differences in SCD prevalence exist between family members of SCD patients in comparison to first and second-degree relatives of control patients. A high proportion of SCD patients experienced symptoms in the hour preceding their arrest, with most arresting during rest.
5.1 Results - Feasibility Study:

As outlined in Chapter 1, this work was divided into 5 separate objectives from 2 studies (Retrospective Study and Feasibility). This chapter will discuss the study results from the feasibility study in the context of objective 5 (Familial inheritance of SCD).

5.2 Case Recruitment Pilot #1 (2010-2011):

The first pilot study took place from January 1, 2010 to December 31, 2011 (Figure 5A). A total of 375 OHCAs from Toronto and Durham regions that occurred in 2010 were identified from Epistry-CA using the pre-specified inclusion criteria of: ages 18-65 years, EMS treated, no obvious cause etiology and no known cardiac history. This number was reduced to 269/375 (72%) of eligible patients after review of ambulance call and/or fire reports and in-hospital information. The 106/375 (28%) excluded OHCAs were of non-cardiac causes such as, cancer/complex chronic care, homeless/jail, or had age < 18 years or had a previous known cardiac history.

Mailing information in the Epistry-CA database was available for 202/269 (75%) of eligible patients. Notification letters were mailed to all 202 patients. Telephone information was available in the database for 129/202 (64%) of eligible patients. Of the 129 eligible patients, we successfully contacted and interviewed 55/129 (43%) cases; 21/129 (16%) refused participation in the study; 10/129 (8%) temporarily opted out of the study, and 43/129 (33%) were unreachable or never responded to repeated voicemails.

The average interview duration was 31.8 ± 27.9 minutes. The average follow-up time to complete a full case (e.g. all questionnaires and reach 2 individuals per case) was 7.2 ± 11 days (range 1-35 days) and the number of phone calls needed to complete a case was 3.8 ± 2.2 calls (range 1-9 calls). For the unreachable cases (e.g. no answer), we
called them on average 5.2 ± 2.4 times (range 2-12 calls) and spent on average 22.6 ± 8 days (range 13-41 days) attempting to follow up. In total over 562 phone calls were made to completed and unreachable cases.

**Figure 5A: Recruitment for Pilot #1 2010-2011**

- **Inclusion Criteria**
  - 18-65 years
  - EMS treated
  - “No Obvious Cause”
  - No previous cardiac hx

- **Excluded (n=106)**
  - 14 Cancer/chronic care
  - 6 Homeless/jail
  - 17 Drug overdose
  - 36 Previous cardiac history
  - 16 non-cardiac
  - 3 Out of country
  - 1 age < 18 years
  - 13 Lack of info

- **375 OHCAs from Toronto/Durham in 2010**
- **202 eligible patients with mailing information**
- **129 patients with telephone contact information**
  - 55 patients consented and interviewed
  - 21 patients who opted out
  - 10 patients who temporarily opted out
  - 43 unreachable patients
5.3 Case Recruitment Pilot #2: (2012-2013):

Due to the difficulties with recruitment in the first pilot study, in the second pilot study we restricted our inclusion criteria to ages 18-45 years for the following reasons: (1) we hypothesized that younger SCD and aborted SCD individuals would be more likely to be living with next-of-kin such as a spouse, parent or child, which would make the contact process easier (e.g. we would be more likely to reach an individual who knew/lived with the deceased); (2) younger patients would theoretically have younger first-degree relatives and thus would be more likely to have available relatives for us to contact (e.g. someone who is 65 years may not have living parents vs. a 35 year old). We also used differing and complementary recruitment strategies in an attempt to boost enrollment.

The second pilot study took place from January 1, 2012 to December 31, 2013 (Figure 5B). A total of 182 OHCAs from Toronto that occurred during 2011-2012 were identified from Epistry-CA using the pre-specified inclusion criteria of: ages 18-65 years, EMS treated and no obvious cause. This number was reduced to 64/182 (35%) of eligible patients after review of ambulance call and/or fire reports, in-hospital information and autopsy information (where available). The 118/182 (65%) excluded OHCAs were of non-cardiac causes (e.g. terminal illness, hangings, drug poisonings and traumas).

We choose to mail eligible patients from only 2011 for feasibility issues and to increase our chances of success. Of the 28 eligible patients from 2011, 24/28 (86%) had both mailing and telephone information available. Of the 24 patients, we interviewed 8 cases; 8 opted out of the study; 1 temporarily opted out of the study, and 7 were unreachable.
Coroners referred 9 families of deceased SCD individuals to us which occurred during 2012-2013 and we interviewed all 9 of them (Figure 5C).

Two heart disease controls were later identified as having experienced aborted SCD events and were then reassigned to the case arm (Figure 5C)
5.4 Subject Characteristics of Sudden Cardiac Death Cases and Control Patients:

In total from both pilot studies we collected complete information from 74 cases, 50 heart disease controls and 53 healthy controls. Of the 74 cases, 39/74 (52.7%) died and 35/74 (47.3%) survived. The underlying etiologies were predominantly structural, followed by...
sudden unexplained deaths and vascular non-cardiac. In a subset of cases, there was insufficient information to determine the exact cardiac etiology (Table 5A).

Table 5A: Etiologies of Cases

<table>
<thead>
<tr>
<th>Etiology Type</th>
<th>Ischemic Heart Disease (%)</th>
<th>Structural Non Ischemic Heart Disease (%)</th>
<th>Sudden Unexplained Death (%)</th>
<th>Vascular (%)</th>
<th>Undetermined Cardiac (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cases (n=74)</td>
<td>45/74 (60.8)</td>
<td>7/74 (9.5)</td>
<td>4/74 (5.4)</td>
<td>3/74 (4.1)</td>
<td>15/74 (20.3)</td>
</tr>
</tbody>
</table>

5.5 Medical History of Sudden Cardiac Death Cases and Control Patients:

On average, healthy controls were younger, more predominantly female, consumed less alcohol and smoked less frequently compared to the cases and the heart disease controls (Table 5B). They were also less frequently prescribed cardiac or diabetic medications and rates of cardiac risk factors were also significantly lower than in cases or heart disease controls. No differences were found between all 3 groups with respect to education level, living alone, exercise habits, and frequency of medical checkups within the prior year.

Heart disease controls were prescribed cardiac medications significantly more often than cases (46/50; 92.0% vs. 33/72; 45.8%; p<0.0001) and also had significantly higher rates of cardiac risk factors in comparison to cases (Table 5B).
Table 5B: Baseline Characteristics of Cases and Controls

<table>
<thead>
<tr>
<th>Patient Characteristic</th>
<th>Cases (n=74)</th>
<th>Heart Disease Controls (n=50)</th>
<th>Healthy Controls (n=53)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years) ± SD</td>
<td>49.6 ± 11.7</td>
<td>53.7 ± 9.6</td>
<td>36.4 ± 12.3</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>Sex Male (%)</td>
<td>64/72 (88.9)</td>
<td>38/50 (76.0)</td>
<td>30/53 (56.6)</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>Ethnicity (%)</td>
<td>Caucasian 71.4 South Asian 10.4</td>
<td>Caucasian 52.0 South Asian 20.0</td>
<td>Caucasian 37.0 South Asian 38.9</td>
<td>0.003*</td>
</tr>
<tr>
<td>Completed high school or undergrad (%)</td>
<td>High school 28/72 (38.9) Undergrad 28/72 (38.9)</td>
<td>High school 13/50 (26.0) Undergrad 26/50 (52.0)</td>
<td>High school 9/53 (17.0) Undergrad 29/53 (54.7)</td>
<td>0.20</td>
</tr>
<tr>
<td>Live Alone (%)</td>
<td>5/72 (6.9)</td>
<td>7/50 (14)</td>
<td>10/53 (18.9)</td>
<td>0.13</td>
</tr>
<tr>
<td>Consume Alcohol (%)</td>
<td>62/72 (86.1)</td>
<td>34/50 (68)</td>
<td>32/53 (60.4)</td>
<td>0.009*</td>
</tr>
<tr>
<td>Exercise ≥1 per week (%)</td>
<td>49/72 (68.1)</td>
<td>32/50 (64.0)</td>
<td>36/53 (67.9)</td>
<td>0.88</td>
</tr>
<tr>
<td>Current Smoking Status (%)</td>
<td>25/72 (34.7)</td>
<td>12/50 (24.0)</td>
<td>12/53 (22.6)</td>
<td>0.005*</td>
</tr>
<tr>
<td>Ex-Smoking Status (%)</td>
<td>26/72 (36.1)</td>
<td>16/50 (32.0)</td>
<td>8/53 (15.1)</td>
<td>0.005*</td>
</tr>
<tr>
<td>Average BMI (SD)</td>
<td>27.9 ± 5.8</td>
<td>28.6 ± 4.5</td>
<td>25.1 ± 5.6</td>
<td>0.01*</td>
</tr>
<tr>
<td>Medical Checkup within prior year (%)</td>
<td>55/72 (67.6)</td>
<td>45/50 (90.0)</td>
<td>45/53 (84.9)</td>
<td>0.13</td>
</tr>
<tr>
<td>Prescribed Cardiac Medications (%)</td>
<td>33/72 (45.8)</td>
<td>46/50 (92.0)</td>
<td>8/53 (15.1)</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>Prescribed Diabetes (%)</td>
<td>9/72 (12.5)</td>
<td>12/50 (24.0)</td>
<td>1/53 (1.9)</td>
<td>0.003*</td>
</tr>
<tr>
<td>Medications (%)</td>
<td>Cases</td>
<td>Controls</td>
<td>P-value</td>
<td></td>
</tr>
<tr>
<td>-----------------</td>
<td>-------</td>
<td>----------</td>
<td>---------</td>
<td></td>
</tr>
<tr>
<td><strong>Hypertension (%)</strong></td>
<td>25/72 (34.7)</td>
<td>26/50 (52.0)</td>
<td>4/53 (7.5)</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td><strong>Diabetes Mellitus (%)</strong></td>
<td>9/72 (12.5)</td>
<td>13/49 (26.5)</td>
<td>2/53 (3.8)</td>
<td>0.013*</td>
</tr>
<tr>
<td><strong>High Cholesterol (%)</strong></td>
<td>27/72 (37.5)</td>
<td>33/50 (67.3)</td>
<td>3/53 (5.7)</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td><strong>Coronary Artery Disease (%)</strong></td>
<td>12/72 (16.7)</td>
<td>37/50 (74.0)</td>
<td>0</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td><strong>Non-Fatal MI (%)</strong></td>
<td>6/72 (8.3)</td>
<td>15/50 (30.0)</td>
<td>0</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td><strong>Stroke (%)</strong></td>
<td>0</td>
<td>(4.0)</td>
<td>0</td>
<td>0.08</td>
</tr>
</tbody>
</table>

*Significant association across categories Pearson $\chi^2$

### 5.6 Family History of Sudden Cardiac Death Among First and Second-Degree Family Members:

No differences were found between cases and both control groups regarding a family history of hypertension, diabetes mellitus, heart disease, myocardial infarction, stroke and expected sudden cardiac death (Table 5C unadjusted).
Table 5C: Family Medical History Cases and Controls

<table>
<thead>
<tr>
<th>Family Health Characteristic</th>
<th>Cases (n=74)</th>
<th>Heart Disease Controls (n=50)</th>
<th>Healthy Controls (n=53)</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Family History of Hypertension (%)</td>
<td>43/71 (60.6)</td>
<td>28/50 (56.0)</td>
<td>29/52 (55.8)</td>
<td>0.83</td>
</tr>
<tr>
<td>Family History of Diabetes (%)</td>
<td>24/71 (33.8)</td>
<td>27/50 (54.0)</td>
<td>18/52 (34.6)</td>
<td>0.05</td>
</tr>
<tr>
<td>Family History of Heart Disease (%)</td>
<td>33/71 (46.5)</td>
<td>28/50 (56.0)</td>
<td>20/52 (38.5)</td>
<td>0.38</td>
</tr>
<tr>
<td>Family History of Myocardial Infarction (%)</td>
<td>16/71 (22.5)</td>
<td>14/50 (28.0)</td>
<td>5/52 (9.6)</td>
<td>0.08</td>
</tr>
<tr>
<td>Family History of Stroke (%)</td>
<td>11/71 (15.5)</td>
<td>5/50 (10.0)</td>
<td>4/52 (7.7)</td>
<td>0.48</td>
</tr>
<tr>
<td>Family History of Expected Sudden Death (%)</td>
<td>11/71 (15.5)</td>
<td>5/50 (10.0)</td>
<td>2/52 (3.8)</td>
<td>0.11</td>
</tr>
</tbody>
</table>

*Non-significant association across categories Pearson χ²

Unadjusted rates of a family history of SCD among first-degree relatives (FDRs) were no different between cases and heart disease controls (20/71; 28.2% vs. 14/50; 28.0%, p=0.9) but significantly differed between cases and healthy controls (20/71; 28.2% vs. 3/52; 5.8%, p=0.002) and between heart disease and healthy controls (14/50; 28.0%, vs. 3/52; 5.8%, p=0.003) (Table 5D).
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Cases (n=74)</th>
<th>Heart Disease Controls (n=50)</th>
<th>Healthy Controls (n=53)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Family History of Sudden Death Among First-Degree Relatives (%)</td>
<td>20/71 (28.2)</td>
<td>14/50 (28.0)</td>
<td>3/52 (5.8)</td>
<td>0.005**</td>
</tr>
<tr>
<td>Family History of Sudden Death Among Second-Degree and Third-Degree Relatives (%)</td>
<td>29/71 (40.8)</td>
<td>4/50 (8.0)</td>
<td>9/52 (17.3)</td>
<td>&lt;0.0001  **</td>
</tr>
<tr>
<td>Total Number of First-Degree Relatives</td>
<td>23</td>
<td>15</td>
<td>3</td>
<td>0.006**</td>
</tr>
<tr>
<td>Average Age at Death of First-Degree Relatives ± SD</td>
<td>65.8 ± 14.7</td>
<td>63.9 ± 12.3</td>
<td>68.3 ± 6.5</td>
<td>0.85</td>
</tr>
<tr>
<td>Percentage Male of First-Degree Relatives</td>
<td>17/23 (73.9)</td>
<td>10/15 (66.7)</td>
<td>3/3 (100.0)</td>
<td>0.49</td>
</tr>
<tr>
<td>Total Number of Second-Degree and Third-Degree Relatives</td>
<td>41</td>
<td>4</td>
<td>9</td>
<td>&lt;0.0001  **</td>
</tr>
<tr>
<td>Average Age at Death of SDR and TDR ± SD</td>
<td>61.0 ± 15.4</td>
<td>78.0 ± 4.2</td>
<td>68.0 ± 8.0</td>
<td>0.21</td>
</tr>
<tr>
<td>Percentage Male of Second-Degree and Third-Degree Relatives</td>
<td>33/41 80.5</td>
<td>2/4 50.0</td>
<td>5/9 55.5</td>
<td>0.11</td>
</tr>
</tbody>
</table>

*Significant association across categories Pearson χ²/Fisher’exact
**One-way analysis of variance significant association across categories.

The unadjusted odds ratios of having a positive family history of SCD in cases as compared to healthy controls was 6.41 (95% CI 1.79-22.7; p=0.002) and was 1.00 (95% CI 0.45-2.26; p=0.9) in cases as compared to HD controls. After adjusting for age and sex, the odds ratio of having a positive family history of SCD was 2.2 (95% CI 0.5- 9.2; p=0.3) in cases as compared to healthy controls and was 1.2 (95% CI 0.5-2.9; p=0.6) in cases as compared to HD controls.

The Cox and Snell R² value, a pseudo R², which is an indicator of the goodness-of-fit of the logistic regression model was only 0.155, indicating that age and sex explain only a small proportion (15.5%) of the variation within this model.
Significant differences were also found between cases and both control groups when comparing unadjusted rates of a family history of SCD among second-degree relatives (SDRs) (29/71; 40.8% cases vs. 4/50; 8.0% heart disease, p<0.0001 and 29/71; 40.8% cases vs. 9/52; 17.3% healthy, p=0.006).

The unadjusted odds ratio of having a positive family history of SCD among second-degree relatives of cases was 3.22 (95% CI 1.36-7.63; p=0.006) as compared to healthy controls and was 7.94 (95% CI 2.58-24.5; p<0.0001) in cases as compared to HD controls. After adjusting for age and sex, the odds ratio of having a positive family history of SCD in cases was 3.3 (95% CI 1.2-9.1; p=0.02) as compared to healthy controls and was 8.4 (95% CI 2.7-26.3; p<0.0001) in cases as compared to HD controls.

Among the cases with familial SCD a small proportion (2/74; 2.7%) had a family history of > 1 FDR with SCD, versus 2% (1/50) in families of heart disease controls and none in the families of healthy controls. When comparing a family history of SCD among SDRs, 8/74 (10.8%) cases had a more frequent history of familial SCD vs. none in the heart disease controls and 3/53 (5.7%) in healthy controls.

### 5.7 Symptoms, Circumstances and Triggers:

Almost 60% of SCD cases reported one or more new symptoms in the hour preceding their SCD or aborted SCD event (Table 5E). New symptoms were also reported in the 24 hours before the event by a third of patients and by over 20% of subjects in the weeks to months leading up to the SCD or aborted SCD event.

In the hour preceding the SCD or aborted SCD event, the most commonly reported new symptoms were: dyspnea (15/74; 20.3%), chest pain (14/74; 18.9%), dizziness (9/74; 12.2%), diaphoresis (8/74; 10.8%) and feeling “unwell” (9/74; 12.2%).
The majority (70%) of SCD cases experienced their event during rest while 30% experienced their event either during or immediately following exercise.

Table 5E: Circumstances and Symptoms

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>All Cases (n=72)**</th>
<th>Deceased (n=39)</th>
<th>Survivors (n=33)**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptoms &lt; 1 hour</td>
<td>41/72 (56.9%)</td>
<td>21/39 (53.8%)</td>
<td>20/33 (60.6%)</td>
</tr>
<tr>
<td>Symptoms &lt; 24 hrs</td>
<td>25/72 (34.7%)</td>
<td>15/39 (38.4%)</td>
<td>10/33 (30.3%)</td>
</tr>
<tr>
<td>Symptoms 1-7 days</td>
<td>19/72 (26.4%)</td>
<td>14/39 (35.9%)</td>
<td>5/33 (15.1%)</td>
</tr>
<tr>
<td>Symptoms past 30 days</td>
<td>15/72 (20.8%)</td>
<td>7/39 (17.9%)</td>
<td>8/33 (24.2%)</td>
</tr>
</tbody>
</table>

**Activity Level**

<table>
<thead>
<tr>
<th>Activity Level</th>
<th>All Cases (n=72)**</th>
<th>Deceased (n=39)</th>
<th>Survivors (n=33)**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rest</td>
<td>51/72 (70.8%)</td>
<td>30/39 (76.9%)</td>
<td>21/33 (63.6%)</td>
</tr>
<tr>
<td>Moderate Exertion</td>
<td>11/72 (15.3%)</td>
<td>5/39 (12.8%)</td>
<td>5/33 (15.1%)</td>
</tr>
<tr>
<td>Vigorous Exertion</td>
<td>10/72 (13.9%)</td>
<td>4/39 (10.2%)</td>
<td>7/33 (21.2%)</td>
</tr>
</tbody>
</table>

*Symptoms include any of: chest pain, dyspnea, leg/arm/stomach/back pain, headache, palpitations, nausea/vomiting, dizziness, diaphoresis, cold/hot flashes and fatigue.

**Info was missing for 2 survivors

5.8 Agreement of Self-Reported Survey Data:

When testing the agreement of patient self-reported information against their medical chart, for all groups (e.g., cases, heart disease and healthy controls) 5/6 variables (hypertension, diabetes mellitus, hyperlipidemia, coronary artery disease, stroke and previous myocardial infarction) had kappa scores ranging from 0.6 to 1.0 indicating substantial to near perfect agreement, as defined by Landis et al. (Landis et al. 1977) (Table 5F). The exception was a history of high cholesterol for cases, which only had a kappa score of 0.348 (fair agreement).
Table 5F: Agreement Scores – patient self-reported vs. medical records

<table>
<thead>
<tr>
<th>Medical History Variable*</th>
<th>Cases (n=12)</th>
<th>Heart Disease Controls (n=53)</th>
<th>Healthy Controls (n=29)</th>
</tr>
</thead>
<tbody>
<tr>
<td>History of Hypertension</td>
<td>Kappa = 0.74 (substantial)</td>
<td>Kappa = 0.96 (near perfect)</td>
<td>Kappa = 1.0 (perfect)</td>
</tr>
<tr>
<td>History of Diabetes Mellitus</td>
<td>Kappa = 1.0 (perfect)</td>
<td>Kappa = 0.95 (near perfect)</td>
<td>Kappa = 1.0 (perfect)</td>
</tr>
<tr>
<td>History of Hyperlipidemia</td>
<td>Kappa = 0.35 (fair agreement)</td>
<td>Kappa = 0.91 (near perfect)</td>
<td>Kappa = 1.0 (perfect)</td>
</tr>
<tr>
<td>History of Coronary Artery Disease</td>
<td>Kappa = 1.0 (perfect)</td>
<td>Kappa = 0.80 (near perfect)</td>
<td>Kappa = 1.0 (perfect)</td>
</tr>
<tr>
<td>History of Stroke</td>
<td>Kappa = 1.0 (perfect)</td>
<td>Kappa = 0.66 (substantial)</td>
<td>Kappa = 1.0 (perfect)</td>
</tr>
<tr>
<td>History of Previous Myocardial Infarction</td>
<td>Kappa = 1.0 (perfect)</td>
<td>Kappa = 0.84 (near perfect)</td>
<td>Kappa = 1.0 (perfect)</td>
</tr>
</tbody>
</table>

*All medical history variables were self-reported as diagnosed by a physician.

For 6/8 family history variables (e.g. family history of hypertension, diabetes, hyperlipidemia, heart disease, myocardial infarction, stroke, expected cardiac death and sudden cardiac death), kappa scores between proxy first-degree family members ranged from 0.6-0.8 indicating substantial agreement (Table 5G). One variable (family history of hyperlipidemia) had only moderate agreement (kappa=0.44) between first-degree family members. For the primary outcome, a history of SCD among first-degree family members, the kappa score was only 0.49 or moderate agreement.
**Table 5G: Agreement scores – case self-reported family medical history**

<table>
<thead>
<tr>
<th>Variable*</th>
<th>Comparison</th>
<th>Kappa Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Family History of Hypertension (n = 13)</td>
<td>Case vs. NOK or NOK vs. NOK</td>
<td>0.65 (substantial)</td>
</tr>
<tr>
<td>Family History of Diabetes Mellitus (n = 14)</td>
<td>Case vs. NOK or NOK vs. NOK</td>
<td>0.66 (substantial)</td>
</tr>
<tr>
<td>Family History of Hyperlipidemia (n = 16)</td>
<td>Case vs. NOK or NOK vs. NOK</td>
<td>0.44 (moderate)</td>
</tr>
<tr>
<td>Family History of Heart Disease (n = 16)</td>
<td>Case vs. NOK or NOK vs. NOK</td>
<td>0.85 (near perfect)</td>
</tr>
<tr>
<td>Family History of Non-Fatal Myocardial Infarction (n=16)</td>
<td>Case vs. NOK or NOK vs. NOK</td>
<td>0.81 (near perfect)</td>
</tr>
<tr>
<td>Family History of Stroke (n=16)</td>
<td>Case vs. NOK or NOK vs. NOK</td>
<td>0.67 (substantial)</td>
</tr>
<tr>
<td>Family Hx Expected Sudden Death (n=26)</td>
<td>Case vs. NOK or NOK vs. NOK</td>
<td>0.65 (substantial)</td>
</tr>
<tr>
<td>Family Hx Unexpected Sudden Death (n=26)</td>
<td>Case vs. NOK or NOK vs. NOK</td>
<td>0.49 (moderate)</td>
</tr>
</tbody>
</table>

*All medical history variables were self-reported as diagnosed by a physician.

We tested the agreement of collected information between trained interviewers (n=3) on 18 medical history variables (Table 5H). For healthy controls, kappa scores ranged from 0.78-1.0 for all 18 variables; for heart disease controls, only one variable (previously saw a cardiologist) was in the moderate agreement (kappa=0.57) range, while the rest of the variables all ranged from 0.7-1.0 in agreement. For cases, kappa scores ranged between 0.65-1.0 (substantial - perfect agreement) for all 18/18 variables.
Table 5H: Agreement Scores: inter-rater validation

<table>
<thead>
<tr>
<th>Inter-Rater Agreement for 18 Medical History Variables</th>
<th>Cases (n=10)</th>
<th>Heart Disease Controls (n=18)</th>
<th>Healthy Controls (n=18)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kappa = 1.0 for 17/18 variables (perfect agreement)</td>
<td>Kappa = 1.0 for 9/18 variables (perfect agreement)</td>
<td>Kappa = 1.0 for 17/18 variables (perfect agreement)</td>
<td></td>
</tr>
<tr>
<td>Kappa = 0.57 (moderate) for 1/18 variables</td>
<td>Kappa = 0.7-0.8 for 8/18 variables (substantial)</td>
<td>Kappa = 0.78 for 1/18 variables (substantial agreement)</td>
<td></td>
</tr>
</tbody>
</table>

Our last agreement test involved the intra-rater agreement for all groups (e.g. degree of agreement among repeated administration of the survey performed by a single interviewer) across 18 medical history variables (Table 5I). For cases and both control groups, the majority of kappa scores for the variables ranged from 0.6-1.0 (substantial to perfect agreement).

Table 5I: Agreement Scores: intra-rater validation

<table>
<thead>
<tr>
<th>Intra-rater Agreement for 18 Medical History Variables</th>
<th>Cases (n=7)</th>
<th>Heart Disease Controls (n=9)</th>
<th>Healthy Controls (n=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kappa = 1.0 for 16/17 variables (perfect agreement)</td>
<td>Kappa = 0.8-1.0 (perfect agreement) for 16/18 variables</td>
<td>Kappa = 1.0 for 17/18 variables (perfect agreement)</td>
<td></td>
</tr>
<tr>
<td>Kappa = 0.65 for 1/17 variables (substantial)</td>
<td>Kappa = 0.78 (substantial agreement) for 2/18 variables</td>
<td>Kappa = 0.46 for 1/18 variables (moderate agreement)</td>
<td></td>
</tr>
</tbody>
</table>
Chapter 6: Discussion and Conclusions

6.0 Summary of Findings:

In this study we developed and implemented a novel, comprehensive methodology to capture all sudden deaths (SDs) and aborted SDs (both cardiac and non-cardiac) in a defined geographic area over a 4 year period (2009-2012). This methodology addresses the limitations of previous studies, by utilizing a prospective registry and pragmatic algorithm to assign cause of death, yielding optimum sensitivity (capturing all SDs and aborted SDs) and specificity (assigning precise cause of death and thus identifying the “true” cardiac and non-cardiac causes). Our calculated SCD incidence rates are similar to those found in other studies, however the distribution of causes for SCD and aborted SCD events differs substantially, in particular the rates of structural heart disease such as hypertrophic cardiomyopathy and arrhythmogenic right ventricular cardiomyopathy. Comparable to other studies, most SCD and aborted SCD events occurred at home and during rest. Lastly, almost two-thirds of young SCD and aborted SCD individuals experienced one or more premonitory symptoms in the hours prior to their event.

6.1 The Importance of Using Prospective Registries:

Despite estimates that SCD is the most common cause of death in the US (Myerburg 1987), data describing the incidence of SCD and aborted SCD in the U.S. population appear to be inconsistent, making it difficult to estimate the actual burden of this problem. This may be in part due to the modest and incomplete epidemiological surveillance efforts dedicated to SCD and heart disease overall (Stecker et al. 2014).

For example, heart disease deaths are tracked nationally in the US only using death certificates as part of the CDC’s National Vital Statistics System (Stecker et al. 2014). However, death certificates have been repeatedly shown to inaccurately reflect the mode
of cardiovascular death when compared with detailed clinical review of cases (Chugh et al. 2004, Every et al. 1997, Iribarren et al. 1998). Moreover, the annual statistics on heart disease and stroke reported annually by the American Heart Association are based on the Framingham Heart Study, Atherosclerosis Risk in Communities Study, and Cardiovascular Health Study (Go et al. 2014). However, these 3 studies represent <0.5% of the US population and many of the national inferences of heart disease are derived from only 10 333 patients in 2 cohorts of Framingham Heart Study (Go et al. 2014, Stecker et al. 2014). Similarly, there are few efforts worldwide to track the burden of SCD and aborted SCD, nor is it reported as part of the Global Burden of Diseases Study (Go et al. 2014, Murray et al. 2012)

Large prospective OHCA registries such as the one used in this study (e.g. Epistry-CA) that capture all OHCAs where EMS personnel are activated (i.e. 911 calls) or mandatory reporting systems may overcome many of these challenges (Bardai et al. 2011, Nichol et al. 2008).

One of the major strengths of using this prospective registry, is that all patients who experience an OHCA within its catchment area are entered within 24 hours into a secure web based local database, along with detailed epidemiologic data from participating EMS agencies and destination hospitals. Multiple methods are used to ensure complete data capture, and there are site-specific ongoing quality assurance plans to confirm the accuracy of data entry (Morrison et al. 2008).

By using this database, we have been able to more accurately capture all possible SCD and aborted SCD cases occurring within a defined geographic area than previous studies. To our knowledge, this is one of the first studies to estimate rates of SCD and aborted SCD using a prospective surveillance system, in combination with rigorously
adjudicated cause-of-death information on younger individuals. These results allow for a comparison of premature death between those due to cardiac causes and other types and could help to guide resource allocation for preventing and treating SCD (Stecker et al. 2014)

6.2 The Importance of Accurate Case Ascertainment:

To our knowledge, this study is one of the first to estimate rates of SCD and aborted SCD in the young using a prospective surveillance system, in combination with rigorously adjudicated cause-of-death information. This is a major strength, as most of the available estimates for SCD incidence rely on retrospective death certificate-based methodology (Hendrix et al. 2010, Margey et al. 2011, Papadakis et al. 2009, Risgaard et al. 2014, Wisten et al. 2002, Wren et al. 2000, Hofer et al. 2014, Vaartjes et al. 2009). Retrospective assessment is problematic for 2 reasons: (1) death certificates often overestimate the true incidence rate and (2) there are usually major discrepancies between the cause of death found at autopsy and what is listed on the actual death certificate (Iribarren et al. 1998, Tavora et al. 2008).

The Oregon SUDs study in Multnomah County, Oregon was the first group to highlight the importance of using prospective, multiple-source surveillance methods when assessing the incidence of SCD (Chugh et al. 2004). Using their methods they found an incidence rate of 53 per 100,000 when collected prospectively versus 153 per 100,000 collected retrospectively using death certificates, demonstrating that the use of death certificates results in a significant (almost 3-fold) overestimation of SCD incidence.

We demonstrated this in our sensitivity analysis by using different assumptions and data sources to report upper and lower boundaries of SCD incidence rates (section 4.9). Using only one data source (EMS records) resulted in an SCD incidence rate 3.6 times higher
than the SCD incidence rate calculated using multiple sources of data. These results support our use of validation mechanisms such as numerous data sources and physician based adjudication in order to accurately describe and estimate the annual incidence of SCD and aborted SCD in the young.

Moreover, several studies have shown that the cause of death listed on the death certificate often disagrees with the findings at autopsy (Goraya et al. 2000, Tavora et al. 2008, Ceelen et al. 2015, Lloyd-Jones et al. 1998, Eriksson et al. 2013), resulting in inaccurate incidence rates. In a study by Ceelen et al. (2015), that measured the agreement between the cause of death established by the forensic physician (based on medical history and external exam) and autopsy results in young SD individuals in the Netherlands, they found little agreement, most of the presumed heart disease cases were confirmed by autopsy but not recognized by the forensic physician in 75% of cases. Overall, the cause of death reported by the forensic physician agreed with the autopsy results in only 17% of cases.

It is important to accurately identify and classify deaths that are due to cardiac causes versus those that aren’t, as cardiac causes are often heritable and thus up to 50% of first-degree relatives could be affected. Yet to treat and prevent SCD at both a population and individual level, the specific causes and their distribution need to be identified. Our methodology utilizes a comprehensive evaluation of each case by reviewing all available medical records to determine the circumstances and precise cause of death and thus facilitates as accurate an estimation as possible of the incidence, circumstances, and causes of sudden death and aborted sudden death in the young.

Additional difficulties stem from the lack of uniform terminology for the cause of death listed on the certificate (Fox et al. 2004). We experienced this first hand when reviewing
the coroner records from the Office of the Chief Coroner of Ontario. As an example, if the cause of death was due to a myocardial infarction, this could have been listed in numerous different ways such as: (1) acute myocardial ischemia, (2) acute atherothrombosis, (3) acute coronary artery thrombosis, (4) acute myocardial infarction, (5) acute coronary interplaque hemorrhage, (6) acute myocardial infarction and (7) ventricular arrhythmia, etc.

If we had relied upon only the medical cause of death listed on the death certificate to identify cases, we may not have (a) captured all of these events or (b) classified them in a consistent manner. Furthermore, listing so many differing causes on the death certificate means that Provincial and National Statistics Agencies will categorize SCDs into very different subsets in their databases, and thus any researcher using these databases to determine incidence rates will face certain challenges (Dewar 2015).

In addition, if SCD is listed as the primary cause of death on the death certificate, there is the potential to miss important comorbidities which may have directly contributed to the cause of death (Kong et al. 2011). As an example, a coroner report we reviewed listed SCD as the primary medical cause of death. The contributing cause of death was listed as atherosclerotic heart disease. By relying solely on the medical cause of death listed on the death certificate, we would have misclassified this case as primary arrhythmic, when in fact the underlying etiology was due to ischemic heart disease.

6.2.1 Pitfalls of Using Primary Out-Of-Hospital Cardiac Arrest Rates as Surrogates for Sudden Cardiac Death Incidence Rates:

Another method commonly utilized to identify and calculate SCD incidence rates, is to use the incidence of apparently primary OHCA as a surrogate for SCD rates; this means using cases that are identified as OHCA of “no obvious cause” from only a review of first
responder records (Cobb et al. 2002, Cobb et al. 1992, Donohoe et al. 2010, Meyer et al. 2012, Myerburg et al. 2002). However, without detailed history and autopsy data available, there is the strong possibility of including cases which are not primarily cardiac or heritable leading to an overestimation of true cardiac unexpected deaths (Etheridge et al. 2014, Stecker et al. 2014).

This was evident from our own dataset. Of the initial 3271 OHCA cases which met all of our inclusion criteria, EMS designated 57.3% (1874/3271) as having “no obvious cause” or presumed cardiac etiology. After review of in-hospital information and contributory factors, data guardians reclassified 63% (2062/3271) of these same OHCA cases as being “no obvious cause”.

Using our methodology, which links all available information, including ambulance call reports, in-hospital charts, police reports, coroner investigative statements, toxicology and autopsy reports to adjudicate cases, we found that only 20% (656/3271) of these same OHCAs had a primary cardiac etiology (e.g. no obvious cause – presumed cardiac) responsible for cause of death. The majority of cases (73.3%, 2394/3271) had non-cardiac etiologies, while a very small percentage (6.7%; 221/3271) remained undetermined due to lack of information pertaining to cause of death.

Our results are supported by observations made by the Oregon SUDS group, who compared SCD incidence rates generated from their own multiple source surveillance dataset to primary OHCA rates generated from the ROC-Epistry Cardiac Arrest study (Nichol et al. 2008, Stecker et al. 2014). They found a lower incidence rate (60 per 100,000 in Oregon vs. 71 per 100,000 in ROC Epistry-CA), most likely due to their multisource case ascertainment methods and thoroughly adjudicated causes of death.
Evidently, if we had relied upon only primary OHCA rates designated as “no obvious cause”, as a surrogate measure for SCD and aborted SCD incidence rates, this would have resulted in a substantial overestimation of the true incidence and ultimately would have contributed to the discordance that surrounds how to effectively predict or prevent this important phenomenon.

6.3 Differences in Sudden Cardiac Death Definitions:

Another major barrier for determining the true magnitude of SCD and aborted SCD rates is the lack of consensus on their definitions and appropriate designations (Kong et al. 2011). The terms “OHCA”, “sudden death” and “sudden cardiac death” are often used interchangeably, despite having very different meanings (Kong et al. 2011). Some studies include time constraints in their definitions for SCD or aborted SCD (Chugh et al. 2004, Escobedo et al. 1996, Zheng et al. 2001), such as occurring within 1-6 hours of the onset of acute symptoms (Virmani et al. 1980), while the World Health Organization defines SCD as death within 24 hours following the onset of symptoms (Furberg et al. 1977).

Further confusion is created due to the differing etiologies included or excluded from these studies; some define sudden cardiac death as death attributable to ischemic or coronary heart disease (Escobedo et al. 1996, Gillum 1989) or broaden their criteria to include all cardiovascular or cardiac etiologies (Chugh et al. 2004, Cobb et al. 2002, Zheng et al. 2001). To date, there is no universal, standardized definition for SCD or aborted SCD that is used across all studies that examine this important issue (Kong et al. 2011).

We developed practical definitions and a straightforward algorithm system to classify all SCDs and aborted SCDs, which are based on all of the information available. Our
definitions and classification system avoids the use of time to define an event as “sudden”, and instead uses an adjudication process to determine the underlying etiology in apparently healthy individuals who experience an abrupt loss of vital signs.

Patients are initially divided into 2 main categories: expected and unexpected cardiac arrests; patients who fall into the “unexpected” (e.g. sudden) category are healthy individuals who experience an abrupt witnessed or unwitnessed collapse. In contrast, those who fall into the “expected” (e.g. non-sudden) category are those individuals in which disease is so severe that death is inevitable (e.g. terminal cancer). We then further sub-classify patients into cardiac and non-cardiac etiologies, based on the underlying etiology responsible for the arrhythmic event. In essence, our method assigns a cause of death for an arrhythmic event that results from a chain of causal events.

As an example, severe coronary artery disease causes an occluded or thrombosed artery in an individual, which results in myocardial ischemia and then VF. Using our methodology, this event would be described as sudden unexpected cardiac with an ischemic etiology. By using the underlying etiology to classify and describe SCD and aborted SCD events, our method avoids the major pitfalls of time-based definitions and may facilitate a more accurate estimation of the incidence of this phenomenon thus enhancing strategies for risk stratification and prevention of SCD.

To test this hypothesis, we used different time based definitions for SCD to assess how accurately they classified cases compared to our method. When we applied the most commonly used definition for SCD (e.g. collapse within one hour of symptom onset) to the 3271 total eligible OHCA patients, this captured 641/3271 (19.5%) cases, of which only 245/641 (38.2%) had underlying cardiac etiologies. Evidently if we had used time-based definitions to capture SCD and aborted SCD cases, we would have either missed
a substantial proportion of cardiac cases or misclassified non-cardiac causes as cardiac. Thus, future efforts need to focus on establishing precise, uniform definitions of SCD and aborted SCD based on the underlying etiology that can agreed upon and adopted by the major stakeholders in the medical/scientific community.

6.4 Accurate Determination of Etiologies:

Accurate characterization of the underlying causes of young SCD and aborted SCD cases allows clinical screening programs to target the etiologies posing the greatest risk. In our study we describe all of the cardiac and non-cardiac diseases leading to SD and aborted SD in the young, stratified by both age and gender. Strengths of our study included a comprehensive evaluation of each case, performed by review of all available information to determine the circumstances and specific cause of death, supported by a high percentage of autopsy cases.

Risgaard et al. examined this issue in their nationwide study of SCD among individuals ages 1 to 49 years in Denmark, by using different assumptions to report the upper and lower boundaries of SCD incidence rates and causes of SCD in their cohort (Risgaard et al. 2014). Including only OHCA cases without an autopsy, the initial SCD rate was reported as 7.1 per 100,000 persons. When they only included OHCA cases in which just an external examination had been performed, the annual SCD incidence rate decreased to 5.2 (95% CI, 4.8–5.7) per 100 000 persons. Lastly, including autopsied cases that had both histopathology and toxicology, the SCD incidence rate decreased to just 2.4 per 100,000 persons, demonstrating the crucial importance of using all available clinical information to accurately determine incidence rates.

Moreover, current treatment for OHCA relies on an understanding of the underlying etiology responsible for the cardiac arrest event. For example, defibrillation is key for
successful resuscitation from shockable rhythms such as VF/VT (due to cardiac causes), but is not effective for other cardiac arrest rhythms such as those with pulseless electrical activity and asystole (e.g. non-cardiac causes) (Link et al. 2010). Current survival rates from OHCA are unacceptably low (Eisenberg et al. 2001, Meaney et al. 2010), and have not increased with time (Sasson et al. 2010), despite numerous iterations of guidelines (AHA 2005, Berg et al. 2010, Kleinman et al. 2015) aimed at improving resuscitation outcomes. Treatment strategies for cardiac arrest can only evolve further based on new information on the distribution of underlying causes for OHCA which are generated from clinical research, such as this study (Institute of Medicine 2015). Our comprehensive data collection methods, detailed definitions and multi-step adjudication process for determining etiologies will help further our understanding of to whom and why young individuals suffer cardiac arrest events.

**6.5 Comparison of Sudden Cardiac Death Incidence Rates:**

Depending on how cases are ascertained, the definition used and what information is employed to assess the underlying cause of death, the incidence of SCD in the young differs substantially between studies (Fishbein 2010, Kaltman et al. 2011, Maron et al. 2014). Previous SCD studies have been conducted on selected populations, and this is one of the first to include an unselected population of both SCD and aborted SCDs cases in individuals ages 2-45. Similar to others, we found that SCD incidence increased substantially with age, with adults ages 35-45 having over 14 times the risk compared to children.

In individuals aged 2 to 45 years, we found an annual incidence rate of 3.8 per 100 000 persons, whereas the incidence rate was 9.23 per 100 000 persons in those aged 35 to
45 years. These rates are higher than what has been reported in most other studies (Papadakis et al. 2009, Hofer et al. 2014, Margey et al. 2011, Meyer et al. 2012, Pilmer et al. 2013, Risgaard et al. 2014, Vaartjes et al. 2009, Winkel et al. 2011). These differences could be attributed to the younger age ranges examined in previous studies (35 versus 45 ours) but are more likely due to differences in case ascertainment strategies. Most of the studies used retrospective death certificate-based methodologies to identify their SCD cases instead of prospective surveillance or registries. This is problematic, as death certificate data have been demonstrated through several validation studies to overestimate the incidence of SCD (Every et al. 1997, Fox et al. 2004, Goraya et al. 2000, Iribarren et al. 1998). More importantly, they do not account for aborted SCD cases in their incidence calculations. To the best of our knowledge, our study is only the second to report incidence rates which include both SCD and aborted SCD cases.

The group from King County Washington was the first to determine the incidence, causes and outcomes for both SCD and aborted SCD patients, by using a retrospective cohort of OHCA patients ages 0 to 35 over a 30 year period (Meyer et al. 2012). A total of 361 EMS treated cases were identified, with an overall incidence of 2.28 per 100 000 person-years. Similar to our methods, they used all available medical records, including autopsy reports to determine the cause of death. However, there is an important limitation to their inception cohort; the lack of non-EMS treated cases introduces a large and important patient selection bias. In our study, over 26% of the sudden unexpected cardiac cases were not treated by EMS, having been deemed “obviously dead”. Their calculated rates likely underestimate the true annual SCD incidence rates in their young population and explain why their rates are lower than the ones observed in our study.
As most other studies of SCD in the young have been conducted in younger (e.g. age <35) (Doolan et al. 2004, Eckart et al. 2004, Margey et al. 2011, Meyer et al. 2012, Papadakis et al. 2009, Pilmer et al. 2014, Winkel et al. 2011, Wisten et al. 2002, Wren et al. 2000) or older populations (e.g. age >50) (Chugh et al. 2004, Byrne et al. 2008), there is a paucity of data on the incidence and etiologies of SCD under age 50. Risgaard et al. were the first to examine SCD incidence in a nationwide population of Danes ages 1-49 (Risgaard et al. 2014). Using a death certificate based methodology to identify cases, they found an annual SCD incidence rate of 2.3 per 100,000 persons in those ages 1 to 35 years, 21.7 per 100,000 persons in individuals ages 36 to 49 years and overall was 8.6 per 100,000 persons. The discrepancy between their calculated rates and ours is not surprising given the differing age cutoffs (45 in ours vs. 49 in theirs), however, more likely their incidence rates are overestimations due to the inherent limitations with their case ascertainment strategies.

It is important to fully understand the epidemiology of SCD under age 50, as numerous heritable cardiac diseases have a variable age of onset, with some not manifesting until middle age.

6.6 Causes of Sudden Death – Cardiac and Non-Cardiac:

6.6.1 Cardiac Etiologies:

In our study we found the predominant underlying etiologies for SCD events to be structural (both ischemic and non-ischemic), followed by sudden unexplained deaths (SUDS). It is also evident from our dataset as well as others that the predominant etiology changes with age, with ischemic heart disease becoming more prevalent with advancing age.
These results are comparable to those found in recent reports on SCD in young people, which reported rates of ischemic heart disease ranging from 12-36%, structural heart disease ranging from 19-36% and SUDs ranging from 20-30% (Corrado et al. 2006, Eckart et al. 2004, Eckart et al. 2011, Meyer et al. 2012, Pilmer et al. 2013, Risgaard et al. 2014, Winkel et al. 2011, Wisten et al. 2002). The likely discrepancies are due to the varying age cutoffs (age <40 or <35 vs. 45 in this study), the differing case ascertainment strategies and range of autopsy rates.

The largest comparable datasets are derived from nationwide studies of SD in Denmark; this group has reported extensively on SCD rates in young individuals under age 50 (Risgaard et al. 2014, Winkel et al. 2011). In the autopsied under 35 cohorts from both studies, they reported SUD as the highest proportion of all SCDs (between 30-48%), followed by CAD at 15%. This is very different from our study, where both structural heart disease and SUD accounted for a third of all SCDs. As this study involves a more recent population based sample that is derived from a larger and more ethnically diverse population in Ontario, this could account for the observed differences in etiologies. However, it is more likely that differences in case ascertainment strategies are responsible for the conflicting results. Although the Danes used more comprehensive methods than others who use death certificate based methodologies, because their autopsy rates were low (56-62%) they are limited by the inclusion of non-relevant (e.g. non-cardiac) cases, resulting in case ascertainment bias.

It is reassuring to note that our results are most similar to those derived from the US Military, who have mandatory reporting of deaths and use standard autopsy protocols (up to 97% of cases autopsied) (Eckart et al. 2006, Eckart et al. 2004, Eckart et al. 2011). Eckhart et. al., reported on 126 sudden, non-traumatic deaths ages 18 to 35 that
occurred during training, of which 34.9% were attributed to SUDs, 36% to structural heart disease and 16% to coronary artery disease (Eckart et al. 2004).

Interestingly, in individuals ages 18-34 years, CAD accounted for almost 20% of all SCDs and over half of SCDs in the 35-45 age group. It is well known that CAD plays a major role in older populations (Margey et al. 2011, Chugh et al. 2004, Bowker et al. 2003); however, it is surprising that premature CAD played such a large role in this unselected population aged <45 years. The high prevalence of obstructive CAD among young SCD patients highlights not only the importance of considering myocardial ischemia in all patients with ventricular arrhythmias, despite their deceptively young ages (Cross et al. 2011), but also the importance of implementing vigorous preventive health measures in much younger patients (e.g. 20’s).

The reported rates of hypertrophic cardiomyopathy (HCM) in our study are substantially lower than those reported by the US studies of SCD in athletes (Maron 2003, Maron et al. 2009) (5.4% in our cohort vs. 36%) and in the US military (Eckart et al. 2004, Eckart et al. 2011) (5.4% vs. 12.8%). Maron et al., has performed several systematic evaluations of competitive young athletes who die suddenly identified from news media outlets, registries and informal reports from high schools and colleges (Maron et al. 1996, Maron et al. 2009, Maron et al. 2013, Maron et al. 2014). In these studies he observed that the most common cardiovascular disease diagnosed at autopsy was HCM (up to 36%) and malformations of the coronary arteries (17%). However, there are several important limitations with these studies, such as incomplete case ascertainment and patient selection biases. Methods involving review of death certificates, insurance reports, public media reports, and other available electronic resources are clearly susceptible to
inconsistent or inaccurate classifications as described previously, and result in inadequate case ascertainment (Kaltman et al. 2011).

Furthermore, in order to be included in their patient cohort, they excluded anyone who had evidence of drug use on postmortem toxicology or did not have accessible autopsy information. This is problematic as in our cohort, up to 30% (129/434) of all SCD cases had a positive toxicology screen, with a majority of those (62%, 80/129) having therapeutic or non-toxic levels of drugs detected but not considered contributory to the cause of death. Although we report a very high autopsy rate (up to 89%), a small percentage of SCD cases (6.4%) died in-hospital and 20% survived (2 of which had HCM). To exclude these types of patients from their SCD cohort introduces a major patient selection bias and thus their results likely overestimate the true proportion of HCM in the general population.

The strength of our methods is reflected by the similar rate of HCM (5.4%) compared to autopsy series studies from Ontario (Pilmer et al. 2013), Italy (Corrado et al. 2003) and Denmark (Risgaard et al. 2014, Winkel 2012). Because our study started with a comprehensive inception cohort, not subject to inaccuracies in coding of causes of death, and systematically considered coroners’ investigations, autopsy, histopathology, and toxicology information, it likely better describes the nature and scope of HCM than previous studies.

Arrhythmogenic right ventricular cardiomyopathy (ARVC) accounted for 8.7% of autopsied SCD individuals ages 2-45 and for 10.7% of those under age 35. Although less frequent when compared to Veneto, Italy, it is higher than the ranges found in other autopsy studies performed in Ontario (Pilmer et al. 2013) and Denmark (Risgaard et al. 2014, Winkel 2012). Possible reasons include the larger, more ethnically diverse population in
Ontario, unlike Italy and Denmark, as well as differing case ascertainment strategies and patient inclusion criteria. As an example, Corrado et al., used a comprehensive clinicopathological prospectively collected registry to assess the annual incidence of SCD in young (age <35) athletes and non-athletes in the Veneto region of Italy (Corrado et al. 2006). Strengths of the study included using a systematic approach to case ascertainment and linking clinical information to post-mortem reports. However, the small homogenous population (~8% of the Italian population) that was studied may not be generalizable to other parts of the world and it wasn’t clear from their methods if they excluded cases without autopsy information, which would lead to a selection bias in their overall cohort.

The proportion of individuals diagnosed with hypertensive cardiomyopathy on autopsy in our cohort is higher than what has been reported elsewhere. A Finnish study observed rates of hypertensive cardiomyopathies at 15.5% (Hookana et al. 2011), while recent studies in Denmark reported rates of 5.7% and 7.7% (Risgaard et al. 2014, Winkel et al. 2011) for “hypertrophic hearts”. These discrepancies are likely due to differences in the cardiomyopathy classification system used at autopsy. A diagnosis of hypertensive cardiomyopathy is based on both macroscopic and microscopic findings in the heart in the absence of any other disease (e.g. CAD or valvular disease). In addition, the patient must have a history of hypertension or evidence of renovascular hypertensive changes at autopsy (Burke et al. 2011, Risgaard et al. 2014). If the pathologist does not take all of these factors into account when determining cause of death, this could result in misclassifications of this etiology.

Additionally, the socioeconomic and cultural backgrounds of countries could have an impact on the etiology of SCDs among younger individuals (Reinier et al. 2006). For
example, high salt consumption in the Western diet could partly explain the differences in rates of hypertensive cardiomyopathies. This assumption is supported by the high rates of diagnosed hypertension (27.8%) found in those ages 35-45 in our cohort.

The prevalence of fibrotic CM, (defined here as unexplained myocardial fibrosis without evidence of other macroscopic or histologic abnormalities (Hookana et al. 2011)), was also a more common finding at autopsy than reported by others. Chugh et al., as part of the Oregon SUDS study reported on several victims of SCD whose hearts were structurally normal except for the presence of myocardial fibrosis on histologic examination (Chugh et al. 2003). Despite descriptions of a strong association between SCD and myocardial fibrosis in otherwise healthy hearts (Chugh et al. 2000, Chugh et al. 2003, John et al. 2004), there is a distinct underreporting of this particular etiology in the literature, primarily due to the lack of histologic examination in most SCD studies. Future studies on the causes leading to myocardial fibrosis are needed to better understand the mechanisms of this disease entity.

6.6.2 Non-Cardiac Etiologies:
Most studies of SCD in young individuals exclude or do not report on non-cardiac etiologies, citing only those deaths that are due to underlying cardiac disorders (Corrado et al. 2006, Eckart et al. 2011, Meyer et al. 2012, Pilmer et al. 2013, Risgaard et al. 2014, Winkel et al. 2011, Wisten et al. 2002). This is despite the fact that the causes of SCD in this population are known to be quite diverse. In our cohort we found that only 31.8% of all deaths identified as “no obvious cause” (e.g. presumed cardiac), were in fact due to underlying cardiac etiologies and the rest were due to unexpected and expected non-cardiac causes. The predominant non-cardiac etiologies was vascular non-cardiac
(28.0%), followed by metabolic imbalances (19.0%), sudden unexplained death in epilepsy (SUDEP) at 17.1% and infectious conditions (17.8%).

A small proportion of studies have reported non-cardiac etiologies in their young SCD cohorts (Anderson et al. 1994, Bardai et al. 2011, Corrado et al. 2003, Donohoe et al. 2010, Doolan et al. 2004, Drory et al. 1991, Eckart et al. 2004, Margey et al. 2011, Vaartjes et al. 2009, Wren et al. 2000), while most tend to exclude them and focus only on cardiac causes. Of these 10 studies, 6 used death certificates or EMS records to identify and classify their cases, the limitations of which have already been discussed earlier in great detail.

The other 4 studies were autopsy based, of which 2 reported extremely small numbers of non-cardiac deaths; Corrado et al. (Corrado et al. 2003) reported on SCDs among young individuals, both athletes and non-athletes in Veneto, Italy and reported only 44/545 (8.1%) died from 3 non-cardiac etiologies while Eckart et al. (Eckart et al. 2004) reported only 18/126 (14.3%) non-cardiac SDs, the majority of which were attributed to vascular non-cardiac disorders.

Two other autopsy based studies reported more extensively on non-cardiac causes of SD among their young SD cohorts; Anderson et al. (Anderson et al. 1994) reviewed all unexpected autopsied SDs from natural causes over a 12 year period and reported only 28.2% were due to cardiovascular causes while 25.2% were attributed to alcoholism and the other 46.6% were due to non-cardiac acute and chronic causes such as epilepsy, respiratory, diabetes and obesity, etc. Doolan et al., also reviewed all autopsies that occurred between 1994-2002, reporting that non-cardiac deaths accounted for 63.3% of natural deaths versus 29.5% in those ages 35 or younger (Doolan et al. 2004). Major methodological limitations of both studies include the identification and inclusion of...
autopsied cases from single geographic centres, as only individuals who received an autopsy were included in their patient populations.

It is important to accurately determine the underlying causes of SCD in young individuals, as deaths due to cardiac causes are primarily heritable, whereas non-cardiac causes usually are not. Once identified, the underlying cause can help to guide the clinical and genetic evaluation of surviving family members who may be at increased risk for SCD (Semsarian et al. 2012).

Individuals with epilepsy are at substantially higher risk of dying suddenly (24-40 times higher) when compared to the general population (Ficker et al. 1998, Ficker 2000). Among the general population with epilepsy, SUDEP is estimated to account for 7-17% of all deaths and up to 50% of deaths in patients with refractory epilepsy (Ficker 2000, Pedley et al. 2002). In our cohort, deaths attributable to SUDEP accounted for 17% of all non-cardiac deaths across the cohort and almost a quarter of all non-cardiac deaths in children and younger adults ages 18-34. Thus the risk of SCD among patients with epilepsy is not trivial.

The exact mechanism by which epilepsy patients die suddenly is not well understood, however, cardiac arrhythmias, central or peripheral hypoventilation, and "brain shutdown" are all considered as the main candidate hypotheses (Devinsky 2004). In our study we classified SUDEP cases as being non-cardiac in etiology, despite the belief that some seizures are thought to initiate cardiac dysrhythmias and lead to SUDEP (Surges et al. 2009, Surges et al. 2009), as the degree to which they contribute remains unclear (Moghimi et al. 2013).

A better understanding of the incidence and risk factors for SUDEP is needed in order to prioritize clinical treatment and prevention research and to help advise epilepsy patients
and their families more accurately of their risk for SCD (Thurman et al. 2014). To our knowledge, our study has one of the largest and most inclusive cohorts of SUDEP patients, and thus it could provide valuable insights as to risk estimates and patient characteristics for this poorly understood phenomenon.

### 6.7 EMS Event Characteristics and EMS Record Based Categorization of SCD:

This study is the largest and only one of its kind to describe the epidemiology, distribution of causes and EMS event characteristics for young SCD and aborted SCD individuals. Previous studies describing EMS event characteristics focused only on OHCA pediatric populations (Atkins et al. 2009, Gerein et al. 2006, Herlitz et al. 2005, Lopez-Herce et al. 2004), or larger OHCA adult populations (Bray et al. 2014, Nichol et al. 2008), and used primary OHCA incidence rates as surrogate measures for SCD incidence.

In our SCD and aborted SCD cohort, the majority of patients were treated, witnessed and received bystander CPR. The proportion of SCD and aborted SCD patients with an initial shockable rhythm ranged from 45% in adults to 55% in children. Survival ranged from as high as 40% in children to only 16% in adults ages 35-45, with the overall survival in the entire cohort being around 20%. These percentages are higher than what has been observed in previous SCD studies; Chugh et al. observed that only 35% of SCD patients had an initial shockable rhythm (Chugh et al. 2004), with 8% survival, while Donohoe et al. found only 12.9% of all EMS treated patients were initially in VF/VT (Donohoe et al. 2010) and only 5.6% survived to hospital discharge.

The discrepancies between their studies and ours are likely due to differing case ascertainment strategies and data collection methods. Donohoe et al. used death certificates to identify their cohort and did not confirm cause of death using additional medical records or autopsy reports. While Chugh et al. did use multiple source
surveillance methods to ascertain their cases and confirm cause of death, autopsies were only performed in 12% of cases. This is problematic as the probability of including non-cardiac cases and thus non-shockable rhythms is high.

Using shockable rhythm as a surrogate for cardiac etiology, we tested this hypothesis by analyzing the proportion of VF/VT observed over the entire cohort labeled by EMS as “no obvious cause” - presumed cardiac to those adjudicated as SCD and aborted SCD by our reviewers. Out of the 1080 treated OHCA cases identified by EMS and data guardians as “no obvious cause”, 244/1080 (22.6%) had VF/VT, 146/1080 (13.9%) had PEA and 490/1080 (45.4%) had asystole recorded as the initial rhythm. Overall survival in the entire cohort was 138/1080 (12.8%) and was 100/244 (41.0%) in the VF/VT cohort.

Using our adjudication and review process, of the 1080 treated OHCAs identified by EMS/data guardians as “no obvious cause”, 656/1080 (60.7%) were adjudicated by us as sudden deaths due to cardiac cause, of which 222/656 (47.6%) had an initial rhythm of VF/VT, with an overall survival of 19.4% (127/656). Clearly, using the EMS/data guardian classification system of “no obvious cause” – presumed cardiac as a surrogate measure for SCD and aborted SCD incidence in young individuals will result in substantial misclassification bias and thus overestimate the true annual SCD incidence due to the high proportion of non-cardiac cases.

Furthermore, presuming that OHCA due to “no obvious cause” is a surrogate for events due to cardiac etiologies will also translate into an underestimation of the true annual incidence of primary VF/VT, and may account for why some studies have reported a dramatic decline in VF/VT as the first recorded rhythm in OHCA over the past several decades (Becker et al. 2008, Cobb et al. 2002, Weisfeldt et al. 2011).
In our study, in addition to data from EMS and hospital records, the added information from coroner investigative statements, toxicology and autopsy reports enabled a broader and more efficient exclusion of non-cardiac etiologies of SCD. For example, patients who died after a non-cardiac terminal illness (e.g. cancer) were classified as expected non-cardiac deaths and were excluded. Although the proportion of VT/VF and overall survival is higher among our cohort, the results are likely to be a more accurate assessment of the occurrence of sudden death due to cardiac etiology in the general population than what has been observed in previous studies.

This assumption is supported by the results found by Meyer et al., who examined the incidence, causes and survival trends of SCDs in young individuals ages 0 to 35 (Meyer et al. 2012) over a 30 year period. Similar to our study, they used a prospectively collected OHCA database to ascertain cases and then linked all available clinical information to determine etiologies, reporting overall rates of VF/VT ranging from 46-55% with survival as high as 40%. In their cohort, medical records were available for 314/361 (86.9%) cases and autopsy reports for 161/221 (72.8%), and are thus more likely to accurately represent the true incidence of SCD in their cohort.

6.8 Patient Characteristics of Sudden Unexpected Cardiac Cases:

In our study, the majority of SCD and aborted SCD cases had a previous medical history of some sort, which is in direct contradiction to the literature (Khayyam-Nekoueii et al. 2013). There is this belief that SCD only happens to seemingly “healthy” individuals with no prior warning; it is often quoted that for 50% of males and up to 64% of women, SCD can be the first sign of underlying coronary heart disease (Kannel et al. 1985). However, comparisons of past medical history information gathered by other SCD studies is
difficult, as only a select few provide this level of detail (Eckart et al. 2004, Link et al. 2010, Risgaard et al. 2014).

The Danish SCD registries are the only large population based SCD studies which have reported on the past medical history information for their autopsied and non-autopsied SCD cases (Risgaard et al. 2014, Winkel et al. 2011). In SCD individuals younger than age 35, up to 76% had no reported previous medical history, while in a larger, older cohort (under age 50), only 41.8% had no past medical history. Similar to ours, they defined past medical history as known heart disease, major mental/physical disabilities or chronic diseases associated with increased risk of cardiovascular disease. It is not clear if their definition included prescribed cardiac or psychiatric medications, which could explain some of the differences between their findings and ours. More likely, the discrepancies are due to differences in study methodologies, SCD definitions, patient inclusion criteria and our comprehensive data collection methods.

Our data suggests that the assumption that SCD occurs as the first manifestation of disease, cardiac or otherwise, is in fact false. In our cohort, over a third of adults were previously prescribed cardiac medications and had at least one or more cardiac risk factors for coronary heart disease. Given these findings, there should be a continued focus on heart disease prevention and awareness in the general population through appropriate therapeutic intervention and lifestyle modification.

6.8.1 Depression and Sudden Cardiac Death:

Depression has been shown to be an independent risk factor for morbidity and mortality in patients with coronary heart disease (CHD), especially following acute coronary syndrome (Frasure-Smith et al. 1995, Khayyam-Nekouei et al. 2013). It also occurs quite commonly among cardiac patients with several studies showing that the prevalence of

The rates of depression in our study (11.8% ages 2-45) are similar to those found in the few studies which have examined a direct link between SCD/OHCA and depression (Alboni et al. 2008, Empana et al. 2006, Irvine et al. 1999, Luukinen et al. 2003, Whang et al. 2009). In a OHCA cohort ages 40-79 examined by Empana et al., the overall rates of clinical depression were 13.5% in all OHCA cases and 16% in those diagnosed previously with heart disease (Empana et al. 2006), with a dose-type effect, whereby as the risk of depressive symptoms increased, so did the risk for OHCA, regardless of any underlying heart disease: (Odds Ratio 1.30 in less depressed subjects vs. OR 1.77 for severely depressed subjects). This association was also observed in 2 other studies, one in the general population (Luukinen et al. 2003) and the other in patients with acute myocardial infarction (Irvine et al. 1999). However, these studies examined significantly older populations (ages >40 or >70) and used differing definitions for defining depression, as such their results may not be as reflective as those observed in our younger population. Moreover, previous SCD/OHCA studies failed to establish a consistent threshold for the level at which depressive symptoms begin to exert cardiotoxic effects (Alboni et al. 2008). Therefore, future studies with larger population samples, including differing age groups and genders, are needed to help answer these outstanding questions with regards to what links may exist between depression and SCD and also what level and duration of depression can increase the risk of SCD (Alboni et al. 2008).

6.8.2 Psychosis and Sudden Cardiac Death:

Individuals with schizophrenia are known to have poor physical health (de et al. 2011) and there is a large body of evidence which has observed their shortened life expectancy

Autopsy findings in patients with schizophrenia who die suddenly have rarely been reported in the past 20 years (Ifteni et al. 2014). Studies from the US (Chute et al. 1999), Australia (Sweeting et al. 2013) and Romania (Ifteni et al. 2014) all observed that the majority of natural deaths in schizophrenics were caused by atherosclerotic heart disease, however in both the Romanian and Australian studies, a small proportion of SCDs (~11%) remained unexplained (e.g. SUDS or presumed arrhythmic syndromes). The significance of these findings remains unclear, as all of these studies were limited by selection biases and incomplete clinical data.

In our study, 34 SCD individuals (5.6%, 79.4% male) were identified as having a diagnosis of schizophrenia, of which two-thirds were prescribed antipsychotics. The main causes of death in the SCD cohort were ischemic heart disease (38.2%), followed by structural heart disease (26.7%) and SUDs (26.7%) In the non-cardiac cohort, an additional 3.4% individuals were also identified as having a diagnosis of schizophrenia, with metabolic disorders (e.g. diabetic ketoacidosis) identified as the main cause of death (57.1%).

Our study findings support what has been observed by others, that the main causes of death are due to coronary heart disease and highlights the importance of regular clinical follow-up for patients diagnosed with schizophrenia, including lifestyle and risk factor
modification. Furthermore, as over a quarter of deaths in this population remained unexplained and could be attributable to inherited or acquired primary arrhythmic syndromes, targeted screening of first-degree family members for schizophrenics should be strongly encouraged to prevent further SCDs.

6.8.3 Drug Related Induced Sudden Cardiac Death:

In our study, a high proportion of SCD and aborted SCD patients were prescribed one or more psychotropic medications (defined here as antidepressants, antipsychotics or opioids), which could have contributed to their event. In addition, the main psychotropic medications detected at autopsy in our cohort following toxicology testing were recreational depressants (either alcohol or opioids), followed by cocaine, antipsychotics and antidepressants.

The arrhythmogenic properties of typical and atypical antipsychotic medications leading to increased risk of SCD have been noted by several studies (Hennessy et al. 2002, Straus et al. 2004). The most notable one was published in the New England Journal of Medicine in 2009, and found that patients receiving antipsychotic monotherapy (first generation vs. second generation antipsychotics), showed a similar, dose-dependent increase in the risk of SCD, with similar adjusted incidence rate ratios for both typical and atypical antipsychotic drugs: 1.31 (95% CI 0.97–1.77) versus 1.59 (95% CI 1.03–2.46) for low doses, 2.01 (95% CI 1.62–2.50) versus 2.13 (95% CI 1.70–2.65) for moderate doses, and 2.42 (95% CI 1.91–3.06) versus 2.86 (95% CI 2.25–3.65) for high doses (Ray et al. 2009). However, these findings have been disputed, in particular by the American Psychiatric Association's Council on Research (Lieberman et al. 2012), as the study's methods relied on the use of death certificates to evaluate SCD mortality, despite it being
known that these methods result in a substantial overestimation of the true SCD incidence rate (Kaltman et al. 2011).

In our study, ~6% of the total SCD cohort were prescribed antipsychotics and over a quarter of SCD deaths which had no toxicological or anatomical cause of death (e.g. sudden unexplained deaths SUDS), had therapeutic levels of antipsychotics or antidepressants detected at autopsy. It is possible that these drugs induced a fatal arrhythmia in these patients through prolongation of the QT interval, despite being found in therapeutic concentrations. Another possibility is that the SCD patients may carry gene mutations for primary arrhythmogenic diseases such as long QT syndrome or Brugada syndrome, which may have been triggered by therapeutic concentrations of these medications. In these types of cases, clinical and genetic evaluation of first-degree family members can help determine the underlying etiology for the death in up to 61% of the cases (Hendrix et al. 2011, Hofman et al. 2010)

Our study findings highlight the importance of not only regular clinical follow-up for patients diagnosed mental illness, but prudent use of psychotropic therapies, with the ultimate goal to reduce morbidity and mortality in those with depression and psychotropic illnesses.

6.9 Circumstances of Sudden Unexpected Cardiac Cases:

Similar to other cases, the majority of SCD and aborted SCD events occurred at home, with a small proportion occurring in public locations such as work, school or athletic recreational facilities. Adults were more likely to arrest at home compared to children; over 42% of pediatric SCDs occurred in public, of which 28.6% occurred at school in the context of exercise and the rest occurred in public recreational facilities such as pools and athletic fields, also in the context of exercise/sport. This has important implications
as OHCA patients who suffer a witnessed cardiac arrest with a shockable rhythm and who receive prompt CPR and defibrillation have markedly improved survival rates (Page et al. 2000, Valenzuela et al. 2000). Thus the dissemination of public-access AEDs at schools and public recreational places, with CPR training for teachers, students and the lay public is warranted to shorten the time to defibrillation and improve outcomes after OHCA at schools (Cave et al. 2011).

6.10 Triggers of Sudden Unexpected Cardiac Cases:
It is widely believed that SCD is the leading medical cause of death in athletes, despite the fact that its exact incidence remains unclear (Harmon et al. 2014). Extensively quoted US SCD studies relied upon the use of media reports or catastrophic insurance claims as their primary method for case ascertainment, and thus potentially underestimated the exact risk of SCD in athletes (Maron et al. 1998, Maron et al. 2009). However, some of the better quality studies have observed that the incidence of SCD during exercise in the general population is in fact much lower than these initial estimates.

In contrast, to this literature, our study, observed that only 12.5% of all SCD and aborted events occurred during moderate to vigorous recreational exercise. It is reassuring to note that our estimates are comparable to the recent Danish (Risgaard et al. 2014, Winkel et al. 2011) and Ontario (Pilmer et al. 2013) population based SCD autopsy studies, which reported only 8-11% of deaths before age 50 as having occurred during sports or vigorous activity. Variability in results between SCD studies are largely due to differences in methodology, such as reliable case ascertainment, the accuracy of both the population numerators and denominators and which types cases are excluded or included. Thus, better quality studies with mandatory reporting of SCD and aborted SCD events during sport/exercise are required to obtain more accurate information in both the
general population as well as athletes (Harmon et al. 2014). Few such registries exist, thus a secondary analysis of our SCD data could help provide a clearer picture of the true incidence of SCD and aborted SCD among young athletes, with the further aim of more accurately estimating the cost/benefit of preparticipation screening.

Children were more likely to arrest during or immediately following moderate to vigorous activities. These activities included sports such as: soccer, swimming, running and basketball. The etiologies most commonly associated with SCD during exercise/sport in children were structural cardiomyopathies 42.1% and SUDS at 36.8%.

These proportions were similarly distributed in children who arrested during rest; 37.5% were attributed to SUDS, while 50% had an underlying etiology of structural cardiomyopathies. This is in contrast to a recent Ontario study which found that presumed arrhythmias were more commonly associated with SCD during sleep (Pilmer et al. 2014). It is not known why our data differs from theirs, however, differing case ascertainment strategies, SCD definitions and data sources are likely causes. Regardless, our data supports the need of more careful cardiac screening in the pediatric population combined with CPR training and AED placement in schools and recreational facilities.

6.11 Premonitory Symptoms of Sudden Unexpected Cardiac Cases:

In our study, new symptoms were reported by almost two-thirds of SCD and aborted SCD individuals in the 24 hour prior and less frequently in the weeks to months leading up to the SCD event. Additionally, adults reported new onset symptoms more frequently than did children. A history of cardiac symptoms, such as syncope or chest pain, could serve as a “red flag” for clinicians as a way of identifying those individuals who may be at higher risk of SCD. Yet the proportion of young SCD or aborted SCD individuals who
have a prior history of such symptoms is unknown; although screening of athletes or children for such symptoms is widely recommended, the frequency and nature of potential warning symptoms in SCD patients is also not clear.

A limitation of our study was the lack of a control group to assess the background frequency of cardiovascular type symptoms in the general population. In addition, our study was not powered to detect differences in symptoms that could have been attributed to differing cardiac etiologies. Thus the current predictive value of our findings to help identify those at risk for SCD and aborted SCD remains unknown.

On the other hand, the SCD Danish group recently published 2 observational studies documenting symptoms before SCD in young people (age <35) with CAD and with ARVC as compared to control groups (Jabbari et al. 2013, Sadjadieh et al. 2014). They found a total of 31 (79%) people with SCD due to CAD who experienced cardiac symptoms such as angina (n=24, 62%) and dyspnea during the 12 months before death, and this was significantly higher than in the control group (p<0.001). In the ARVC group, 50% of patients (8/16) experienced antecedent cardiac symptoms as compared to only 1 patient in the healthy control group. Of note, none of the ARVC patients were diagnosed before death. A total of 37.5% (6/16) of patients with ARVC died during strenuous physical activity and 4 of the deaths were sports-related SCDs.

In both studies though, only patients with autopsy confirmed CAD or ARVC were included, thus missing those cases without autopsy or who experienced aborted SCD; their results are likely an underestimation of the true prevalence of symptoms among young SCD patients. Future work should include larger sample sizes, both types of SCD
patients and all cardiac etiologies in order to better understand the significance of reported symptoms and aid with SCD risk stratification.

6.12 Limitations - Retrospective Study:

By using an OHCA based registry to identify all possible SCD and aborted SCD cases, we rely upon activation of the local EMS. It is possible that some OHCA cases were not captured by the EMS system and that the actual incidence of OHCA in this population could be higher. Yet in this particular age group, it is highly unlikely that EMS would not be activated, particularly if the death is unexpected. Our data supports this hypothesis, as when linking EMS records from Epistry-CA database to death certificates/coroner records, a very small percentage remained unmatched (4.1%; 130/3271). Moreover, to further verify the capture of all OHCAs in the Epistry-CA database, redundant sources of information are regularly searched, such as hand sorting through paper EMS charts, electronic querying of EMS records by a variety of data fields including dispatch call type, vital signs, diagnosis, NEMSIS (Jacobs et al. 2004) codes or a combination of all of these fields (Morrison et al. 2008).

Another limitation is that we were not able to determine the specific cardiac etiology in a small proportion of cases (87/656; 13.3%). This occurred primarily in survivors (5.6%; 38/656), due to lack of detailed information in the database regarding the exact cardiac etiology and in a small percentage of cases, where an autopsy was not performed (21/656; 3.2%) or where the autopsy could not pinpoint the precise cardiac etiology (29/656; 4.4%). Despite a comprehensive review of all available information for each case, there are inherent limitations in current autopsy protocols and coroner diagnoses which can complicate the determination of a specific disorder as the cause for the SCD event (Meyer et al. 2012). As shown in the sensitivity analysis (Chapter 4 Section 4.6.1),
incomplete data such as lack of autopsies and toxicology data bring some uncertainty into the estimates of the SCD incidence rates. However, the lack of autopsy information was counterbalanced by the high availability of coroner investigative statements (92%), which is a unique data source from which we were able to extract important information about the cause and circumstances of death. Moreover, we report an autopsy rate (89%) higher than most other parts in the world, with the exception of Eckart et al. from the US Department of Defense, who report an autopsy rate of 97% or greater (Eckart et al. 2004, Eckart et al. 2006, Eckart et al. 2011). In addition, our results support the notion that an autopsy should always be conducted in cases of young, sudden and unexpected deaths, a recommendation that has been put forth by most of the major North American and European Electrophysiology Societies (Ackerman et al. 2011) including the Canadian Heart Rhythm Society (Gollob et al. 2011).

Lastly, there is recall bias associated with the information collected by EMS providers, the coroners and family/patient interviews. As an example, prescription and over-the-counter medications may not have been completely captured, as coroners rely on information supplied by family members and bystanders at the scene and via follow up with the family physician (if available) for a full listing of all medications. However, toxicology is usually performed in all cases where there is suspicion of a contribution to cause of death.

However, such a history can only be obtained by careful interviewing of family members, even if these interviews are subject to recall biases. Coroners and EMS personnel obtain this information from family members, bystanders, and/or hospital personnel/family physicians immediately following the SCD event, thus, the event history is gathered fairly closely to the actual event. In addition, we reviewed and cross referenced all available
sources of information where available, such as EMS reports, ED reports, discharge summaries, coroner investigative reports, post-mortem and police reports, all of which provide a narrative summary describing the patient’s reported activities and symptoms prior to their SCD or aborted SCD event.

6.13 Conclusions – Retrospective Study:

1. By using an existing, validated comprehensive population based registry of consecutive cases to identify patients, in addition to our detailed definitions and inclusive data collection methods, we have developed a novel methodology to accurately describe and estimate the incidence of SCD and aborted SCD in the young that occurred within a defined geographic study area. Our unique methods combined with a multi-step adjudication process for determining etiologies will ensure that our calculated rates more accurately reflect SCD and aborted SCD rates than other studies. Importantly, our detailed information sets allow assessment of the frequency of co-morbidities that are possibly related to sudden deaths such as psychiatric illness, diabetes, and drug abuse.

2. We developed detailed definitions for all of the applicable terms in our study that are based on the information available and avoid the use of time to define an event as “sudden”. Our definitions use an adjudication process to determine the underlying etiology, which facilitates a more reliable assessment of the incidence of SCD and enhances strategies for risk stratification and prevention of SCD.

3. Using our novel methodology and comprehensive data collection processes, we identified 656 sudden unexpected cardiac cases, both SCD and aborted SCD, with an overall annual incidence rate of 3.80 per 100,000 persons. Our incidence rates are higher
than those reported by other studies, primarily due to differing case ascertainment strategies and SCD definitions used between studies.

We report a high autopsy rate in all SCD cases, and even higher in those investigated by a coroner, which facilitated an accurate description of the underlying etiologies responsible for SCD and aborted SCD events our young population.

Similar to others, we observed a relationship between increasing age and the proportion of individuals with underlying ischemic heart disease, however the overall distribution of etiologies in our SCD and aborted SCD population differed, in particular the proportion of individuals diagnoses with HCM and ARVC.

4. In our study, the majority of SCD and aborted SCD cases had a previous medical history either cardiac or psychiatric, which is in direct contradiction to the literature.

Similar to other cases, the majority of SCD and aborted SCD events occurred at home, with a small proportion occurring in public locations such as work, school or athletic recreational facilities.

New symptoms were reported by almost two-thirds of SCD and aborted SCD individuals in the 24 hour prior and less frequently in the weeks to months leading up to the SCD event.

6.14 Discussion - Feasibility Study:

6.14.1 Summary of Findings:

In the series of case control pilot studies, we demonstrated that it is feasible to obtain a family history of SCD and major cardiac risk factors from aborted SCD patients and/or first-degree relatives of SCD individuals, using self-developed surveys. Despite the complexity of patient recruitment, our results suggest that a family history of SCD
appears to cluster in certain families, perhaps signifying a genetic predisposition. Rates of major cardiac risk factors differed among the groups, with heart disease patients having higher rates of hypertension, hyperlipidemia and coronary artery disease as compared to cases and healthy controls. Most SCD and aborted SCD patients experienced their cardiac arrest event during rest, while a small proportion occurred during or immediately following exercise. A notable proportion of SCD patients experienced one or more warning symptoms in the 60 minutes preceding their arrest. As this was a feasibility study, these results should be interpreted with caution until future studies that are appropriately powered can be performed to help interpret these preliminary findings.

6.15 Factors Leading to Recruitment Issues:

In the first pilot study we only enrolled a total of 55 (27%) out of 202 eligible patients. This was due to several factors. Firstly, reliable mailing information in the OHCA database was only available for 202/269 (75%) of these eligible patients, which limited the number of individuals that we could contact. This was mainly because the contact information for OHCA patients who lived alone and died would become out-dated after his/her death. Notification letters were sent to all 202 patients but only reached a small proportion of individuals or their families, as most envelopes were returned unopened. Secondly, telephone information was available for only 129/202 (64%) patients in the OHCA database, as EMS do not routinely record this information. Thirdly, it took over 562 phone calls to attempt to reach all 129 patients and of these, we interviewed only 55 (43%) cases. This was because most patients were only available during evening or weekend hours and not during the day. When we shifted our calling hours to match, we tended to reach more individuals.
In the second pilot study we relied on the investigating coroners for help with recruitment, as coroners had accurate contact information to reach next of kin and had already developed an established relationship with the family. When coroners introduced and explained the idea of our research study, this provided credence to the idea and family members were more willing to participate. Consequently, we were able to increase our enrollment numbers (from 55/129; 43% to 17/33; 51.5%) and spend less time attempting to track down and contact eligible patients and their families.

In order to identify and recruit SCD patients, future studies will need to tightly collaborate with the Office of the Chief Coroner in order to be successful.

6.16 Feasibility of Collecting Reliable Patient and Family History:

We found that patients self-report their medical history reliably, as compared to what is recorded in their medical charts by healthcare providers. When we tested the agreement of patient self-reported information against their medical chart, for all groups and 5/6 variables, kappa scores ranged from 0.6 to 1.0, indicating substantial to near perfect agreement. The exception was a history of high cholesterol which had only fair agreement (kappa=0.35). This is not unexpected, as a previous study which assessed how accurately patients recalled the result of their most recent cholesterol test found that 45% of individuals who reported normal cholesterol levels actually had elevated levels, and 56% of individuals with elevated levels did not identify this by self-report (Newell et al. 2000).

The preferred way to collect family history information is to use the family study method (Andreasen et al. 1977), which involves directly interviewing all available first-degree relatives about any disease/illness they themselves have had. This is not applicable for
sudden death and is time-consuming, expensive and not feasible if the first-degree relatives are not readily available. An alternative technique is the family history method (Andreasen et al. 1977), which involves interviewing individuals or their relatives about any diseases or illnesses in any of the individual’s first-degree relatives. This technique is not as accurate as the family study method (Mendlewicz et al. 1975, Rimmer et al. 1969, Woodruff, Jr. et al. 1971); however it can provide very useful information about familial prevalence.

Our use of the family history technique showed that collecting family history in this manner is very reliable, as multiple family members had substantial or near perfect agreement on 7 out of 8 major cardiac risk factors among first-degree relatives.

The finding of only moderate agreement on the main outcome, a family history of SCD among first-degree relatives, is likely explained by the type of family member that we interviewed. Parents and siblings provided the most detailed and reliable family history while children were not as aware of their parent’s family health history, particularly among second and third-degree family members. We attempted to interview parents and siblings of SCD patients where available but often times had to rely on whomever was willing and able to be interviewed. If sample sizes had been larger, it would have been useful to examine the study results according to the source of information or restrict the analysis to only cases where parents or siblings were the proxy to see if the results differed by source. To our knowledge, we are the first study of this kind to use this technique for collecting family health history and to show the reliability of this method.
6.17 Family History of Sudden Cardiac Death:

Previous studies (Friedlander et al. 2002, Jouven et al. 1999) of older individuals have reported the role of a family history of SCD as an independent risk factor for SCD, but these studies lacked comprehensive autopsy evidence of the cause of the SCD event; thus, there remains some uncertainty about the familial predisposition of SCD as a manifestation of an acute coronary event (Kaikkonen et al. 2006). To determine the exact etiology for the SCD, autopsy data, including information on the circumstances of the death, provides the best opportunity for a well-informed cause-of-death diagnosis (Lahti et al. 1998). A large proportion of deaths defined as sudden by clinical criteria may be due to a variety of non-cardiac or non-arrhythmic causes (Huikuri et al. 2003). In our study, autopsy reports were available for 27/39 (69.2%) SCD individuals, comparable to those reported by others (range 75%-97%) (Eckart et al. 2004, Eckart et al. 2011, Pilmer et al. 2013, Risgaard et al. 2014, Winkel et al. 2011), and with our comprehensive data collection methods and careful review process we were able to adjudicate an exact cardiac etiology for the majority (59/74; 79.8%) of all SCD cases.

Data from prior studies indicate that the proportion of first-degree relatives with a family history of SCD ranges between 11-30% (Behr et al. 2007, Hendrix et al. 2011, van der Werf et al. 2010). None of these studies compared the proportion of first-degree relatives having a family history of SCD to any control groups. In a larger study of SCD in adults ages 18-65 years, the proportion of families of SCD patients who had a positive family history of SCD was 46% as compared to 30% and 18% in families of heart disease and healthy controls, respectively (Kaikkonen et al. 2006).

In contrast to the literature, data from our feasibility study indicates that the proportion of first-degree relatives of SCD patients who have a positive family history of SCD were no
different from first-degree relatives of heart disease and healthy controls after adjusting for age and gender. These results are likely due to our small sample size, as previous sample size calculations estimated a need for at least 250 individuals per group to detect a 10% difference between groups.

Additionally, these differences could be explained by our heterogeneous SCD cohort. Prior studies only included patients with ischemic heart disease, while we included patients with multiple, heritable cardiac etiologies. Alternatively, for a small proportion of aborted SCD cases, we did not have sufficient information to determine the exact cardiac etiology and thus may have included cases in our analyses which might not be directly heritable or that may be due to shared environmental exposures (e.g. CAD). Future studies with larger sample sizes and a matched age and sex design are needed to analyze the significance of these findings.

6.18 Familial Inheritance of SCD across Multiple Generations:

To our knowledge, our study is one of a select few which have examined a family history of SCD among multiple generations of family members as compared to control populations (Ranthe et al. 2012, Ranthe et al. 2013). Ranthe et al., examined cardiovascular disease (CVD) occurrence in a nationwide cohort and found that CVD risk was significantly increased in the SCD cohort, particularly among younger (age <35 years) members (Ranthe et al. 2013). The type of kinship also affected the risk for CVD; a family history of SCD in a first-degree relative had higher CVD risk than having SCD in a second-degree relative and the risk was more pronounced in those younger than 35 years (4-fold versus 2-fold increased risk for CVD). However, this analysis was limited by their use of outcomes gathered from a large, national patient registry of patient diagnoses; these large databases are often prone to incomplete or erroneous
classification and coding\textsuperscript{2} which could result in misclassification and overestimation of risk estimates.

A major strength of our study is the use of an existing, validated comprehensive population-based registry of consecutive OHCA cases covering a large urban area, in combination with comprehensive data collection methods, to identify and describe the etiologies and circumstances of SCD patients.

In our cohort ages 18-65 we found no differences when comparing a family history of SCD among first-degree relatives between cases and both control groups after adjusting for age and sex but did find significant differences when comparing a family history of SCD between second-degree relatives of cases and both control groups. This has important implications, as it is well known that a family history among first-degree relatives confers higher risk for disease for the affected individual, however, the effect of having a positive family history of SCD among second or third-degree relatives is less well understood and warrants further investigation.

\textbf{6.19 Lack of Major Cardiac Risk Factors among Cases:}

Several clinical factors have been associated with SCD, including CAD (Kannel et al. 1975), left ventricular dysfunction (Al-Khatib et al. 2007), acute or chronic heart failure (Al-Khatib et al. 2007), diabetes (Jouven et al. 1999), and lifestyle factors such as smoking (Kaikkonen et al. 2009, Kannel et al. 1975). Similar to others (Kaikkonen et al. 2006, Kaikkonen et al. 2009), in our study, cases reported significantly lower rates of most major cardiac risk factors when compared to heart disease and healthy controls. This is not unexpected, as SCD can often be a first manifestation of CAD without any clear, prior evidence; in almost 50\% of cases, SCD is the first sign of the coronary
disease (Kannel et al. 1985, Lloyd-Jones et al. 2010, Myerburg et al. 2009, Rea et al. 2010). Additionally, even though CAD is the most commonly associated condition with SCD, only a small percentage of patients with CAD (13-20%) will actually develop SCD (Kannel et al. 1987). Once CAD has been diagnosed and treated, the risk of SCD decreases (Mahmoud et al. 2011). Thus, the use of a family history of SCD in combination with multiple clinical risk factors may help with earlier identification and therefore direct appropriate therapeutic and preventive strategies in this particular sub-population.

6.20 Symptoms and Circumstances:

Sudden death before age 45 is often the first indication of inherited cardiac disease; accordingly, early identification is difficult in apparently healthy individuals (Amital et al. 2004, Drory et al. 1991). However, a history of cardiac symptoms (e.g. syncope, chest pain, etc.) could serve as a “red flag” for clinicians as a way of identifying those individuals who may be at higher risk of SCD. Similar to previous studies (Drezner et al. 2012, Muller et al. 2006, Winkel et al. 2014, Wisten et al. 2005), we showed that prodromal symptoms are present in almost two-thirds of patients in the hour preceding their arrest and are also present in some patients in the days to weeks leading up to the event. The most commonly reported symptoms, chest pain, dyspnea and diaphoresis, are those typically associated with ischemia, reflected by the older age and underlying etiologies of our cohort. In contrast, only 50% (12/24) of younger patients (age <45 years), experienced symptoms preceding their arrest, and their reported symptoms were more vague, such as dyspnea, presyncope and fatigue. As we did not include a control group to assess the background frequency of cardiovascular type symptoms in the general population, the
current predictive value of our findings to help identify those at risk for SCD remains unknown.

6.21 Limitations – Feasibility Study:

This study has several limitations. Recall bias is one of the major limitations associated with the case control design, and usually results in underreporting of past exposures in the control group or overreporting in the case group, causing overestimation of any association between exposure and outcome (Pandis 2014). To control for this recall bias, we asked detailed questions about the reported event from both cases and controls to confirm that the death was sudden and unexpected by our criteria. In addition, for cases, we used other sources of information such as ambulance call reports, medical records, coroner investigative statements, autopsy and police reports to verify the agreement of the self-reported information, including the circumstances, symptoms and family health history. The reliability of this data is reflected by the strong agreement between data sources on variables which contribute to SCD risk. Coroner investigative statements were available in 27/39 (69%) of cases, which often contain detailed medical history including symptoms as described by bystanders. We did not test the reliability of the self-reported family health history collected from either control group because of feasibility issues (mainly lack of man-power and funds). Thus our results should be interpreted with caution until future studies with larger sample sizes can be performed to confirm our findings.

In our study, the ages of the healthy controls were significantly younger and had a higher proportion of females than the cases and heart disease controls. This is an important limitation as the risk for SCD is strongly linked to both increasing age (Eckart et al. 2011, Marijon et al. 2011, Pilmer et al. 2013, Winkel et al. 2011) and male gender (Albert et al.)
Thus the lack of familial SCD in our healthy control group could be attributed to the younger ages of the first and second-degree relatives, as the younger population in the healthy control group would not have as many relatives old enough to experience the main outcome (sudden cardiac death); thus the measured event rate for this group may be an underestimation of the true SCD rate.

We attempted to control for age and sex with respect to a family history of SCD among first-degree relatives of cases and controls using logistic regression but the results were non-significant, likely due to the small sample size and lack of other cardiac risk factors which contribute to SCD risk in the model. Our small sample size precludes the use of multivariable modeling and thus future, larger studies should include additional covariates.

Last, the results of our study may not be generalizable because controls recruited from a single academic institution may not be representative of the general population (i.e. inner city urban population).

6.22 Conclusions – Feasibility Study:

Our pilot study demonstrates that it is feasible to obtain a family history of SCD and major cardiac risk factors from aborted SCD patients and/or first-degree relatives of SCD individuals using a self-developed survey. In addition, we developed a methodology to obtain self-reported information from patients that is reliable and efficient. Using this data, we showed that differences in SCD prevalence exist between both first and second-degree family members of SCD patients in comparison to first and second-degree family members of healthy control patients. Furthermore, a high proportion of SCD patients experienced symptoms in the hour preceding their arrest. These results suggest the
possible contribution that a detailed family history may make in evaluations of surviving family members with regards to early cardiovascular disease risk.

6.23 Overall Study Conclusions:

The true incidence of SCD and aborted SCD in Canada and worldwide remains unclear, with a wide range in the available estimates. In order to advance our knowledge and understanding of the epidemiology of SCD and to improve risk stratification and prevention, there needs to be focused efforts to create standardized definitions of SCD and aborted SCD and to expand research efforts both locally and nationally to accurately capture all cases of SCD and aborted SCD prospectively and more broadly across communities.

Our study utilized a comprehensive inception cohort, not subject to inaccuracies in coding of causes of death, and systematically considered ambulance call reports, in-hospital data, coroners’ investigations, autopsy, histopathology, and toxicology information. Furthermore, by using a validated comprehensive population based registry of consecutive cases to identify all eligible patients, in combination with a novel classification methodology, large sample size, and multiple sources of data, we were able to better describe the nature and scope of the problem of sudden death of possible cardiac origin within a young, urban Canadian population.

It is hoped that our novel methodology and subsequent results will help to fill in the gaps on this important public health issue. Establishing rigorous case ascertainment strategies in combination with definitional agreement for SCD and aborted SCD from both the medical community and in the literature will facilitate a more reliable evaluation and comparison of treatments, utilization, and outcomes, which will ultimately enhance our strategies for risk stratification and prevention of SCD.
Chapter 7: Future Directions

7.0 Future Directions:

7.1 Introduction:

In this study, we described the incidence, etiology, circumstances and familial pattern of SD and aborted SD (both cardiac and non-cardiac) in the young within a defined geographic area. This study increased our knowledge of why and under what circumstances young people die suddenly, however, there are unanswered questions still remaining. To help address some of these gaps, future work is recommended.

7.2 Validation of Our Methodology and Definitions:

The first 2 objectives for this study were to develop a pragmatic methodology and detailed definitions in order to accurately describe the epidemiology of SCD and aborted SCD events in a young urban population. The next step would be to validate our methodology and definitions by using an external dataset to assess its sensitivity and specificity and generalizability. Ideally the dataset should originate from a prospectively collected database such as the one used in this study. There are 2 other Canadian resuscitation Outcomes Consortium sites, Vancouver and Ottawa, which have similar databases that could serve this purpose. A future study could be to collaborate with one or both of these sites in order to validate our methods.

7.3 Distribution of Etiologies Among Young Sudden Death Individuals:

The third aim of this study was to assess the incidence rates and distribution of etiologies, both cardiac and non-cardiac, in young SD and aborted SD individuals. An interesting finding from this study was that only 20% of the entire cohort had a primary cardiac etiology attributed as the cause for their unexpected SD event. The majority of SD events were due to unexpected non-cardiac causes such as vascular bleeds or infectious illness.
and expected causes such as cancer or complex illnesses. As treatment and prevention of SD requires a thorough understanding of the underlying etiology, future work should compare the cardiac and non-cardiac cohorts, both unexpected and expected to determine if there are important differences that could be used to direct appropriate therapeutic or preventive interventions.

Additionally, it is often presumed that SD occurs in only “healthy” individuals, when in fact our data would suggest otherwise. In our study we found that a high proportion of individuals who experienced a SD or aborted SD event had some sort of past medical history, including prescribed medications and mental health disorders. This is in direct contrast to the literature (>80% our cohort vs. 39% Winkel et al. 2011) and deserves careful exploratory analysis, in particular to assess the frequency of co-morbidities such as psychiatric illness, drug abuse and cardiac disease risk factors (e.g. diabetes, hypertension, etc), which are all known to contribute to SD risk. A future study could link our SCD dataset to data from the Institute of Clinical Evaluative Science (ICES) to assess the prior healthcare consumption pattern of these individuals and to see if these events could have been either prevented or perhaps predicted.

7.4 Impact on Policy:

7.4.1 St. Michael’s Hospital:

When a SCD or aborted SCD event due to a heritable cardiac cause (e.g. ischemic heart disease) occurs in a young person, it is important that first-degree family members are referred to specialist arrhythmia clinics that have the expertise to provide appropriate clinical care (Bai et al. 2009, Behr et al. 2008, Hofman et al. 2010, Nunn et al. 2011, Priori et al. 2006, Priori et al. 2013, van der Werf et al. 2010). The ideal clinic uses a multidisciplinary approach, consisting of assessment by cardiac electrophysiologists,
cardiac nurses, clinical genetic counselors and medical geneticists (Hofman et al. 2013, Ingles et al. 2007). Clinical management strategies usually include a thorough review of the autopsy report and any genetic testing results, assessing the circumstances at the time of death, collecting a detailed family history (up to 3 generations), genetic counselling, clinical investigations and if merited, genetic testing to identify candidate genes that can be used for further cascade screening of other relatives in the family (Hofman et al. 2013, Ingles et al. 2007, Priori et al. 2013).

We established a specialist arrhythmia clinic at St. Michael`s Hospital in the late 1980`s, and as a result of this study as well as our participation in the Cardiac Arrest Survivors with Preserved Ejection Fraction (CASPER) study, we seem to have vastly improved our identification and treatment of young SCD and aborted SCD patients and their families. For study patients, we now follow the same standardized approach as outlined above, ensuring that individuals and their families receive the appropriate diagnostic and therapeutic care. However, a future study should confirm that our approach is indeed systematic for all SCD patients and their families at St. Michael`s Hospital, not just those who are enrolled in research.

The identification and treatment of SCD patients and their families by specialist clinics is reliant on the fact that both families and community based healthcare providers are aware of the need for expert clinical assessment. In this study, we demonstrated that coroners inconsistently identify and recommend that families of young SCD individuals seek clinical care. As a result, we have initiated discussion with the Office of the Chief Coroner of Ontario to help improve the processes of care for these types of patients and their families. A future study could examine how to increase awareness among coroners, by the use of educational seminars and/or newsletters, etc.
Another important issue is that referral recommendations can occur from several different sources, not just the investigating coroners. In our study we showed that many deaths occurred in Emergency Departments or Intensive Care Units from various hospitals and not all involved a coroner. Thus, a critical unanswered question remains - with whom does the responsibility lie to inform the family to seek follow up care? The ED physicians? Or Intensive Care physicians? Or the family doctor? As a first step, a future study could assess the frequency of referrals made by ED and ICU physicians in our institution, with the ultimate goal of testing different communication strategies in order to raise awareness and change practice among the different types of healthcare providers.

7.4.2 Office of the Chief Coroner of Ontario:

A critical step to reducing the incidence of SCD and aborted SCD in the young is a systematic and standardized approach to the death investigation by coroners and pathologists in order to establish the cause of death and/or diagnosis (Ferrero-Miliani et al. 2010).

First, non-cardiac causes such as cerebrovascular events, or accidental overdoses must be ruled out, as well as non-hereditary cardiac causes of SCD such as myocarditis, or anomalous coronary artery anatomy (Semsarian et al. 2012). A comprehensive toxicology screen is important, not only to exclude non-cardiac causes but also to detect drugs that could interfere with the normal heart rhythm, such as QT prolonging medications (Basso et al. 2008).

Furthermore, specimens for genetic analysis should be collected, and these should be taken from two different tissues to ensure that there is at least one source of high quality
DNA (e.g. blood and spleen/muscle tissue) (Ferrero-Miliani et al. 2010, Bennett et al. 2013, Priori et al. 2013, Semsarian et al. 2012).

Lastly, the actual death investigation itself should include the collection of relevant information such as the circumstances of death, activities immediately preceding death, the presence of drugs and prescriptions at the scene as well as both medical and family history (Basso et al. 2008, de la Grandmaison 2006, Cohle et al. 2001).

Despite the publication of several recommended guidelines that describe how pathologists and coroners should investigate SCD cases (Basso et al. 2008, Osborn et al. 2015), the investigative practices of coroners and medical examiners vary considerably across Canada (Dewar et al. 2012). In particular, collection of post-mortem genetic samples, the cause/manner of death classification and written recommendations for first-degree relatives of young SCD victims to be clinically assessed, all show considerable variation between and within provincial jurisdictions (Dewar et al. 2012).

A study by Lim et al., which reviewed all cases involving individuals ages 0-35 years, with death due to natural disease or an undetermined cause from the British Columbia Coroners Service (BCCS) database observed that there was no standardized approach used to manage cases identified as sudden unexplained deaths (SUDs) (Lim et al. 2010). As a result, the post-mortem examination could be adversely affected, as the pathologist may not have access to all of the relevant information.

Furthermore, Lim et al., found that relatives of victims were not consistently referred to medical professionals after a family member’s SUD; a recommendation for clinical follow-up was made in only 26% of autopsy-negative SUDs and 28% of SUDs in which the cause of death was due to autopsy proven heart disease.
Currently, the Ontario Office of the Chief Coroner (OCCO) is the only provincial agency with comprehensive guidelines for young SCD investigations (Dewar et al. 2012). These guidelines were created in 2008 after a collaboration between the Ottawa Heart Institute and the OCCO (University of Toronto Heart Institute 2008). In spite of these guidelines, we found that only 53% (77/143) of potentially heritable cardiac disease cases from 2009-2012 had a recommendation for clinical follow-up by either the pathologist or coroner. A future study should contact these families to determine if they did in fact receive appropriate clinical care, such as referral to an electrophysiologist and/or arrhythmia clinic.

As part of our knowledge translation strategies, we have been providing regular updates to the OCCO on these issues and as such, they are currently revising their SCD standard operating procedures for both coroners and pathologists to reflect both our suggestions and the updated guidelines (e.g. autopsy, genetic, etc.) for SCD investigations (Priori et al. 2013). The new guidelines should be released by the OCCO in the Fall of 2015. Thus, an additional future study could examine if rates of clinical follow-up increase after implementation of the new guidelines.

Moreover, it was not clear to us after reviewing the case files if the clinical follow-up recommended by coroners did in fact occur or was received by family members. A common refrain that we kept hearing after contacting the families of SCD patients, was that the coroner never told them to seek clinical assessment or that SCD was a “heritable” condition. Further investigation determined that coroners did in fact make the recommendation to families but this was accomplished verbally (phone or in person) very soon after the death occurred and so the message was simply lost during the grief process. A planned future study with the OCCO is to test several different modes of
communication (e.g. phone, letter, etc.) at different timings to determine the appropriate method to provide families this important message.

Another issue involves how these cases are labeled by coroners on the death certificate; many young SCD cases are labeled as “Undetermined” in both the cause and manner of death, leaving families without definitive answers. In the study by Lim et al. (2010), of the 35 cases determined to be due to SUD (e.g. autopsy and toxicology negative), 48.6% (17/35) were labeled as undetermined, while the rest were labeled as presumed cardiac arrhythmia (20/35; 28.6%) and sudden unexpected death (8/35; 22.9%). In our study, we found similar results, with 43.4% (285/656) of cases labeled as undetermined and the rest labeled with a variety of different terminologies such as: SUD, sudden arrhythmic syndrome (SADs), cardiac dystymia, cardiac arrhythmia, suspected cardiac arrhythmia, etc.

This is very problematic for 2 reasons: (1) the lack of standardized terminology means that the surviving relatives of SCD patients are not necessarily provided with an explanation for the cause of death and thus additional cases of SUD may not be prevented (as up to 50% of first-degree relatives are at risk); (2) listing so many differing mechanisms on the death certificate means that Provincial and National Statistics Agencies will categorize SCDs into very different subsets in their databases, and thus any researcher using these databases to determine incidence rates will face substantial challenges. A future collaborative project could be to help the OCCO develop standardized definitions that could be used by coroners when completing death certificates.
7.4.3 Legislation - AED Placement:

In our study we found that almost half of pediatric SCDs occurred in public, of which two-thirds occurred at school in the context of exercise with the rest occurring in public recreational facilities such as pools and athletic fields. This has important implications, as OHCA patients who suffer a witnessed cardiac arrest with a shockable rhythm and who receive prompt CPR and defibrillation have markedly improved survival rates (Valenzuela et al. 2000, Page et al. 2000).

Thus, the dissemination of public-access AEDs at schools and recreational facilities, with CPR training for teachers, students and the lay public is warranted to shorten the time to defibrillation and improve outcomes after OHCA at schools (Cave et al. 2011).

In support of this, in 2013 the Public Health Agency of Canada allocated nearly $10 million to install public access defibrillators in recreational/sports complexes across Canada, as well as training staff in their use, testing and maintenance (Dewar 2015).

However, organizations must apply to receive an AED from this program and only schools with high recreation and sport use are eligible (Heart and Stroke Foundation 2015). Provincial legislation mandating AED installation and training across all public buildings, including schools would help save lives. In Ontario, Bill 41, “Defibrillator Access Act” was tabled in 2010 and after passing 2 readings, was then referred to the Standing Committee on Justice Policy where it has remained for the past 5 years with no further progress:


A future project could entail partnering with the Heart and Stroke Foundation of Ontario and other support groups to provide evidentiary support and advocacy for this legislation.
7.5 Improvements to Health – Potential Screening Initiatives

Detailed knowledge of SCD is critical for targeting SCD-specific prevention and treatment at the patient level (e.g. targeted family screening) and population level (e.g. prevention screening in athletes) (Stecker et al. 2014).

7.5.1 Targeted Familial Screening:

An important element to reducing the occurrence of SCD and aborted SCD events in the young is timely clinical and genetic assessment of patients and their first-degree relatives after they experience a SCD event. Clinical investigations should include a diagnostic cascade approach starting with a detailed patient and family medical history, and non-invasive tests, such as electrocardiography (resting and signal-averaged ECG) and echocardiography (Dewar 2015). In some cases, an exercise test or pharmacologic provocation (epinephrine or procainamide challenge) is needed to unmask the disease phenotype, as exercise and other stressors are common triggers for specific syndromes (Dewar 2015, Bennett et al. 2013).

In addition, the molecular autopsy, or the retrieval of genetic material at autopsy and its subsequent analysis for genetic mutations that might cause a certain disease, offers an opportunity to make a diagnosis (Edwards 2005). This can be particularly helpful in sudden unexplained deaths (SUDS), as it was recently shown that genetic testing can play a critical role in identifying ‘silent’ diseases such as Long QT Syndrome, Brugada Syndrome and Catecholaminergic Polymorphic Ventricular Tachycardia (Tester et al. 2007, Tester et al. 2004, Brugada 2000).

Familial screening of individuals with inherited cardiac disease thus represents an obvious target for these clinical and genetic assessments, as in general, up to half of these relatives could be at increased risk (Ferrero-Miliani et al. 2010). Studies in the
Netherlands (Hendrix et al. 2011, Hofman et al. 2007), Holland (Tan et al. 2005), England (Behr et al. 2003) and Canada (Krahn et al. 2009) have shown that the diagnostic yield of workup in relatives of young SCD and aborted SCD individuals ranges from 14% to as high as 61% (Ferrero-Miliani et al. 2010).

Clearly it is possible to identify a substantial number of affected relatives of young SCD individuals, which in turn makes a strong case for recommending the screening of relatives in families experiencing young SCD (Ferrero-Miliani et al. 2010). However, even though it is highly recommended that relatives of young SCD and aborted SCD individuals should be referred for cardiogenetic screening, it does not happen routinely, nor is there a standard approach for the actual screening/assessment process.

A targeted screening program for the families of SCD victims, particularly high-risk subgroups such as young individuals with cardiac symptoms and competitive athletes, could have significant impact, as the burden of SCD in younger individuals within the study area may be fairly high. In addition, each young individual at risk could have a minimum of 2 first-degree relatives who are potentially at risk, meaning there could be substantial numbers of individuals at risk for SCD per year in the proposed study area that could potentially benefit from some form of targeted risk assessment.

In this study, we developed successful methods to both identify and contact SCD patients and their families; thus a future study could use these methods to systematically track and contact these families to offer targeted screening and appropriate therapeutic intervention.

7.5.2 Athlete Preparticipation Screening:

The exact incidence of SCD in athletes is hotly debated and largely unknown in the US and Canada (Harmon et al. 2011). There are huge variations in reported SCD rates
among athletes in the United States, ranging from 1:23 000 to 1:300 000 (Drezner 2005, Drezner 2009, Maron et al. 1998, Maron 2003, Maron 2007, Maron et al. 2009, Van Camp et al. 1995), primarily due to the reliance on the use of media reports, retrospective surveys, voluntary registries, and insurance claims data to identify potential SCD cases (e.g. the numerator). Studies that only use catastrophic insurance claims to identify cases are likely to underestimate the incidence of SCD, as insurance claims only provide information on deaths which occur during school-sponsored sporting events, and do not include cases that occur during individual activity, unofficial practices or deaths which occur outside of sport (Harmon et al. 2014).

Furthermore, other studies have used imprecise estimations or potentially biased methods for calculating the denominator (Harmon et al. 2011). For example, the US Registry for Sudden Death in Athletes (USRSDA) (Maron et al. 2006, Maron et al. 2009), which has collected information on SD in athletes since 1980 using mostly media searches and self-reports, arbitrarily set their athlete population (e.g. the denominator) at 10.7 million, with no description of how this was determined (Harmon et al. 2014).

A more accurate estimation of athlete SCD is critical, for both primary (e.g. preparticipation screening) and secondary (emergency response planning) prevention (Harmon et al. 2011).

A secondary analysis of our SCD data could help provide a clearer picture of the true incidence of SCD and aborted SCD among young athletes, as well as a more accurate estimate of the cost/benefit of preparticipation screening.
7.6 Family History of Sudden Cardiac Death Among First-Degree Relatives:

Our pilot study demonstrated that it is feasible to obtain a family history of SCD and major cardiac risk factors from aborted SCD patients and/or first-degree relatives of SCD individuals using a self-developed survey.

In contrast to the literature, data from our feasibility study indicated that the proportion of first-degree relatives of SCD patients who had a positive family history of SCD were no different from first-degree relatives of both types of control groups, even after adjusting for age and sex. Future studies should recruit larger sample sizes and carefully select more appropriate control groups in order to strengthen the study design. Larger sample sizes would allow for multivariate conditional logistic regression to estimate adjusted odds ratios and 95% confidence intervals for a family history of SCD among first-degree family members of cases and controls, and also account for factors such as smoking status, history of hypertension, diabetes, heart disease, stroke and prior myocardial infarction in addition to age and gender.

Furthermore, larger sample sizes will also allow for analysis of secondary outcomes, such as the proportion of individuals who have a family history of multiple SCDs among first-degree family members, as compared to controls, by using generalized linear mixed models (GLMM) (Diggle et al. 2002); GLMM uses a hierarchical approach to allow adjustment for risk factors in addition to both random and fixed effects. This is important, as random effects will allow adjustment for within family clustering and for other fixed effects such as: age, sex, smoking status, body mass index, etc.
7.6.1 Family History of Sudden Cardiac Death Among Second and Third-Degree Relatives:

In our cohort ages 18-65 years we found significant differences when comparing a family history of SCD among second-degree relatives between cases and both control groups. This has important implications, as it is well known that a family history among first-degree relatives confers higher risk for disease for the affected individual, however, the effect of having a positive family history of SCD among second or third-degree relatives is less well understood and warrants further investigation. A future study with larger sample sizes could examine this finding in greater detail.

7.7 Summary:

By using a validated comprehensive population based registry of consecutive cases to identify all eligible patients, in combination with a novel classification methodology, large sample size, and multiple sources of data, we were able to better describe the nature and scope of the problem of sudden cardiac death within a young, urban Canadian population. However, many questions still remain unanswered. To address these gaps and to further advance our knowledge and understanding of the epidemiology of SCD and aborted SCD among the young, there needs to be a focused efforts to create standardized methodologies and definitions and to expand both local and national research efforts to accurately capture all cases of SCD and aborted SCD prospectively and more broadly across communities.
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Dewar, L. A National Strategy for the Prevention of Sudden Death in the Young. 2015.


Heart and Stroke Foundation. AED Program Overview. 2015.


sudden cardiac arrest in children and young adults 0 to 35 years of age: a 30-year review. *Circulation* 126(11): 1363-1372.


van der Werf, C., I. M. van Langen, and A. A. Wilde. 2010. Sudden death in the young: what do we know about it and how to prevent? Circ. Arrhythm. Electrophysiol. 3(1): 96-104.


1.0 Causes of Sudden Cardiac Death (SCD) in the Young:

The causes of SCD in the young can broadly be categorized into both structural and arrhythmogenic. Heritable structural causes of SCD not discussed in the main thesis include: dilated cardiomyopathy (DCM) as well as non-heritable structural causes such as myocarditis, sarcoidosis, valvular heart disease and congenital disorders of the heart.

1.1 Dilated Cardiomyopathy (DCMs):

Dilated cardiomyopathies (DCMs) are characterized by a dilated left ventricle and impaired systolic dysfunction. If no primary cause is identified (e.g. CAD), then the term idiopathic DCM (IDCM) is used and this type of DCM is considered heritable; if 2 or more relatives are diagnosed with IDCM, then it is termed familial DCM (FDCM). It has a prevalence of 1:2500 and is the most frequent form of CM in children. In DCM there is an increase in ventricular chamber size and the ventricular wall thickness is significantly reduced, leading to heart failure and an increased risk of thrombi in the ventricle. Although this can lead to both symptomatic and asymptomatic arrhythmias, SCD is not a frequent manifestation of the disease.

Patients with a family history of idiopathic DCM follow an autosomal dominant inheritance pattern, however these cases are sporadic as most idiopathic DCM patients do not have a family history of the disease and some X-linked, recessive, and mitochondrial patterns of inheritance can also occur. The sensitivity of genetic testing is estimated at 15% to 25% depending on the number of genes tested and the phenotypic expression of the person being tested. There are a broad variety of encoded proteins implicated in the
Appendix 1A: Causes of SCD and Aborted SCD in the Young

Pathogenesis of DCM, including cytoskeletal proteins, myofilament proteins, proteins of the nuclear envelope, and ion channels\textsuperscript{64-66}. Idiopathic DCM shows age-dependent penetrance, meaning that an individual who carries a disease-causing rare variant is more likely to show a disease phenotype with increasing age; thus, a normal phenotypic assessment by echocardiogram and ECG does not exclude the possibility of later onset disease\textsuperscript{48}.

The age of onset for DCM can vary, ranging from early infancy through late adulthood and there can be variable age of onset within one family carrying the same genetic predisposition to DCM\textsuperscript{48}. Manifestations of the disease can also vary by individual, even among family members who all have the same variant, from a very mild case (e.g., minimal systolic dysfunction) to aggressive, fully developed disease\textsuperscript{48}.

Genetic testing for patients with DCM and their first-degree family members is also recommended, as is the early use of an ICD prior to the occurrence of life-threatening syncope or sudden cardiac death\textsuperscript{67}.

1.2 Acquired (Non-Heritable) Cardiomyopathies:

Cardiomyopathies can be acquired due to behavioural or medical conditions. The following acquired cardiomyopathies will briefly be discussed and the autopsy criteria we used to categorize them: hypertensive/alcoholic CM, fibrotic CM, valvular CM, myocarditis, and sarcoidosis.
Appendix 1A: Causes of SCD and Aborted SCD in the Young

1.2.1 Hypertensive and Alcoholic Cardiomyopathies:

Systemic hypertension is a common cause of ventricular hypertrophy and heart failure and often is the underlying condition in some dilated forms of cardiomyopathy\textsuperscript{87}. Patients with hypertensive left ventricle hypertrophy are predisposed to arrhythmias and SCD\textsuperscript{88}. Chronic hypertension results in a progression from a hypertrophied to a dilated ventricle mimicking dilated cardiomyopathy at the end stages; up to one third of patients with dilated cardiomyopathy have a history of hypertension\textsuperscript{89}. Furthermore, acute alcohol intoxication can cause reversible cardiac dysfunction, and chronic ingestion of large quantities of alcohol increases the risk of dilated cardiomyopathy\textsuperscript{87}.

1.2.2 Fibrotic Cardiomyopathy:

Endocardial disease refers generally to fibrous thickening of the endocardium, which can be caused by a variety of etiologies, both idiopathic and secondary (e.g. ischemia or hypertension)\textsuperscript{85}. The most common endocardial lesion is fibrosis, which causes white discoloration with thickening of the otherwise thin, translucent endocardium\textsuperscript{85}. Histologically, there may be multiple foci of subendocardial necrosis or patchy replacement fibrosis of varying ages and sizes\textsuperscript{85}. In addition, fibrosis may be interstitial, compact, patchy, or diffuse. The amount and texture of the fibrosis plays an essential role in propagation of the electrical impulse\textsuperscript{91}.

Flow-related disturbances caused by ischemia or structural heart disease can cause focal endocardial fibrosis through myocardial remodeling; remodeling involves individual myocytes, the collagen network that supports them and the ion channels that penetrate
Appendix 1A: Causes of SCD and Aborted SCD in the Young

them, with the end result being a fibrotic ventricle due to increased myocardial collagen content\textsuperscript{85, 92}. Either acute or chronic ischemia as a result of a myocardial infarction, coronary artery disease or cocaine use can all cause this myocardial fibrosis remodeling process.

A strong association between myocardial fibrosis and SCD in otherwise normal hearts has been described previously in at least 3 studies\textsuperscript{93-95}. Chugh et al., as part of the Oregon Sudden Unexpected Death study (Oregon SUDS) reported on several victims of SCD whose hearts were structurally normal except for the presence of myocardial fibrosis on histologic examination\textsuperscript{96}. John et al. characterized in detail the phenotype of SCD patients with idiopathic myocardial fibrosis, in 6 patients identified from a post-mortem, consecutive 13-year series of 270 subjects presenting with SCD\textsuperscript{95}. Ventricular interstitial remodeling was assessed quantitatively and qualitatively and compared to 6 age- and sex-matched control subjects who suffered non-cardiac death. Overall myocardial collagen volume fraction was 1.6-fold higher in the idiopathic group vs. controls. In addition, the collagen volume fraction increase was diffuse but disproportionately so in the LV inferior wall (3.4-fold increase).

1.2.3 Valvular Cardiomyopathy:

The most common valve disease causing SCD is aortic stenosis\textsuperscript{85}. In children, subvalvular or supravalvular aortic stenosis may cause SCD, whereas in adults both congenitally bicuspid and calcified trileaflet valves are the cause\textsuperscript{102-105}. These types of valvular heart disease account for approximately 2\% of SCD in adults\textsuperscript{85}. Mitral valve
Appendix 1A: Causes of SCD and Aborted SCD in the Young

prolapse is another uncommon cause of SCD. Sudden cardiac death mechanisms are ventricular arrhythmias and heart failure from severe regurgitation.

1.2.4 Myocarditis:
Myocarditis refers to myocardial inflammation that is not secondary to ischemia, and results from both direct invasion of the myocardium and postinfectious immune-mediated myocyte damage. It can be idiopathic, caused by specific infections, and result from immune disturbances or a combination of both. There is no uniformly used pathologic or clinical classification, and histopathologic criteria for diagnosis have not been rigorously established.

The incidence of myocarditis in SCD varies widely; in an autopsy series of young military SCD patients, the incidence of diffuse myocarditis was 20%, but is < 5% in children and <2% in adults in most series of sudden cardiac deaths. These wide variations are likely attributable to differing SCD definitions, case ascertainment strategies and methodologies.

1.2.5 Sarcoidosis:
Sarcoidosis is a multisystem disease of unknown etiology, which has the characteristic pathology of epithelioid granulomas in association with other inflammatory cells in various organs. In the United States, the annual incidence is between 10 and 35 per 100,000 individuals.

The possible causes of sarcoidosis include environmental, infectious and autoimmune factors. It mostly affects the lungs and lymph nodes, however, additional organs can be
Appendix 1A: Causes of SCD and Aborted SCD in the Young

affected or even be the predominant clinical feature of the disease in more than a third of patients\textsuperscript{109}. All layers of the heart can be involved by sarcoidosis and in addition, the heart weight is increased due to the presence of granulomas and scar, and cardiac remodeling due to valve disease or heart failure\textsuperscript{85}.

The clinical manifestations of cardiac sarcoidosis include conduction abnormalities, arrhythmias, heart failure and SCD. In the United States, approximately 50% of all deaths related to cardiac sarcoidosis are sudden and unexpected\textsuperscript{110-112}.

1.3 Other Structural Causes of SCD – Congenital Heart Disease and Anomalies of the Coronary Arteries:

Left ventricular noncompaction is presumed to be a congenital cardiomyopathy which is characterized by a spongy left ventricular myocardium\textsuperscript{85}. Structurally, it is characterized by an increase in the trabeculated, noncompacted myocardium at the endocardium compared to the compacted outer myocardium\textsuperscript{85}. The incidence of left ventricular noncompaction among patients with established cardiomyopathy ranges from 9.5% in children\textsuperscript{113} to 3\%\textsuperscript{114} and 16% in adults\textsuperscript{115}. The natural history of the disease includes progressive systolic dysfunction and heart failure, thromboemboli, arrhythmias, and SCD\textsuperscript{85}.

Congenital abnormalities of the heart (multiple chambers or valves) and aortic arch are relatively common, with an overall incidence estimated at 1\%\textsuperscript{85}. Atrial septal defect (ASCD) accounts for about one third of the cases of congenital heart disease detected in adults, and results in shunting of blood from one atrium to the other\textsuperscript{116} Over the years, the increased volume of blood flowing through the chambers of the right side of the heart
Appendix 1A: Causes of SCD and Aborted SCD in the Young

usually causes right ventricular dilatation and failure\textsuperscript{117, 118}. Patients with large shunts often die of right ventricular failure or arrhythmia in their 30s or 40s\textsuperscript{117-120}.

Ventricular septal defect (VSCD) is the most common congenital cardiac abnormality in infants and children\textsuperscript{116}. Up to 40\% of these defects close spontaneously by the time the affected child reaches 2 years old and 90\% of defects that eventually close do so by the time the child reaches age 10\textsuperscript{121, 122}. Despite its benign clinical course, serious arrhythmias can occur in 16-31\% of patients\textsuperscript{123}.

Tetralogy of fallot (TOF) is characterized by a large ventricular septal defect, an aorta that overrides the left and right ventricles, obstruction of the right ventricular outflow tract, and right ventricular hypertrophy\textsuperscript{124}. Surgical repair is performed to relieve symptoms and to improve survival. Patients who have their TOF repaired are thereafter usually asymptomatic, but their survival is somewhat poorer than that of an age-matched control population because of an increased risk of SCD\textsuperscript{124}.

Coronary artery anomalies (CAAs) are a diverse group of congenital disorders whose manifestations and pathophysiological mechanisms are highly variable\textsuperscript{125}. Whereas some CAAs may cause occasional ischemia, others (e.g., anomalous origination of the left coronary artery from the pulmonary artery) cause chronic ischemia, while still others only predispose the patient to minor complications such as clotting, spasm, or atherosclerotic plaque\textsuperscript{125}. In a continuous series of 162 patients with sudden unexpected death, the incidence of CAA-related sudden death was found to be 0.6\% (1 of 162 cases)\textsuperscript{126}. 

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Appendix 1A: Causes of SCD and Aborted SCD in the Young

1.4 Primary Arrhythmic Syndromes:

The following channelopathies not discussed in the main thesis will be discussed here: Catecholaminergic polymorphic ventricular tachycardia (CPVT) and Brugada Syndrome (BrS).

1.4.1 Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT):

Catecholaminergic polymorphic ventricular tachycardia (CPVT) causes ventricular arrhythmias, triggered by emotional or physical stress (e.g. exercise) and results in syncope, and SCD in children and adolescents with a structurally normal heart. CPVT patients have a normal resting ECG but exercise stress testing can elicit the typical bidirectional or polymorphic ventricular tachycardia which is characteristic of the condition. The mean age of onset of symptoms is 8 years old, but the first syncopal event may not occur until adulthood in some instances. Approximately 30% of affected individuals have symptoms such as syncope or SCD before age 10 and nearly 60% of patients have at least one syncopal episode before age 40.

The mechanism behind the ventricular arrhythmias involves abnormal calcium homeostasis in the sarcoplasmic reticulum, with corresponding mutations in the cardiac ryanodine receptor (RyR2 – autosomal dominant) and cardiac calsequestrin (CASQ2 - autosomal recessive). Approximately 65% of CPVT index cases have a RYR2 mutation while the prevalence of CASQ2 mutations is approximately 3% to 5%. With genetic screening, up to 65% of the mutations can be identified in patients with a clinical diagnosis of CPVT. Genetic testing is recommended for index patients and their relatives.
Appendix 1A: Causes of SCD and Aborted SCD in the Young

Beta-blockers are recommended for CPVT patients with documented stress-related arrhythmias and ICD implantation plus beta-blockers for patients with aborted SCD\textsuperscript{63}.

1.4.2 Brugada Syndrome (BrS):

Brugada syndrome is an autosomal dominant inherited disease which primarily affects males\textsuperscript{31} and confers a medium to high risk of SCD\textsuperscript{31}. It is estimated to be responsible for at least 4\% of all SCDs and up to 20\% of all SCDs in young individuals with structurally normal hearts\textsuperscript{153}. This syndrome is diagnosed by characteristic ECG changes, ST elevation in leads V1-V3 followed by a negative T wave (type 1)\textsuperscript{154}. The ECG pattern can be spontaneous or elicited by fever, stress, and autonomic stimuli including sodium channel blocking drugs\textsuperscript{155}. Patients with BrS are usually asymptomatic until the third or fourth decade of life when syncope and/or SCD may occur\textsuperscript{154, 156}. The prevalence of symptomatic BrS is estimated to be 1 in 5,000 to 10,000 in Western countries and may be more prevalent in South Asia\textsuperscript{48}.

1.4.3 Commotio Cordis – A Special Case of Primary Arrhythmias:

Commotio cordis is defined as a lethal cardiac arrhythmia caused by a direct, non-penetrating blow to the chest\textsuperscript{168}. It usually occurs during sports with the most common sports projectiles being baseballs (41\%), softballs (11\%) and hockey pucks (7.8\%)\textsuperscript{169}. It is the second leading cause of death in young athletes, most commonly in young males\textsuperscript{169, 170}. The higher prevalence in children is thought to be due to their compliant chest walls, which allow greater transmission of impact energy to the myocardium, causing ventricular fibrillation and cardiac arrest instantaneously\textsuperscript{171}.
Appendix 1A: Causes of SCD and Aborted SCD in the Young

1.5 Drug Induced (Acquired) Arrhythmias:

1.5.1 Psychotropic Arrhythmia Inducing Drugs:

The following arrhythmia inducing drugs not included in the main thesis will be discussed here as they all relate to arrhythmias and SCD: antibiotics and opioids.

1.5.2 Antibiotics:

Macrolides (e.g. erythromycin, clarithromycin), fluoroquinolones, antifungals, and antimalarials have all been implicated in triggering TdP as a result of QT prolongation\textsuperscript{198-202}. In 2012, Ray et al. quantified the risk of cardiovascular death (CVD) associated with azithromycin as compared with other antibacterial drugs or non-use, in Tennessee Medicaid patients\textsuperscript{203}. The study showed that the risks of death, (all cause and CVD), associated with azithromycin were greater than those associated with amoxicillin, however, the excess risk over amoxicillin varied considerably according to cardiovascular risk factors\textsuperscript{204}; as with all observational studies, this investigation is limited by potential unknown confounders, which may be responsible for the differences observed between the 2 groups and not because of the differing drugs.

1.5.3 Opioids – Methadone:

For over 30 years, methadone, a synthetic opioid, has been used for substitution in patients with heroin addiction as well as for pain control\textsuperscript{205, 206}. Its most severe side effect is the development of life-threatening TdP in the setting of a prolonged QT-interval\textsuperscript{207}. Since drug addicts are prone to concomitant medical conditions requiring additional medication (such as antibiotics) as well as continued abuse of cocaine, they are at higher risk for developing this major complication of methadone therapy\textsuperscript{207}. Furthermore, the
Appendix 1A: Causes of SCD and Aborted SCD in the Young

Prolongation of the QT interval has been shown to be dose-dependent\textsuperscript{208, 209}, which is important since patients receiving methadone as part of a methadone maintenance program tend to have relatively high doses of 60–120 mg/day\textsuperscript{207}. Most of these case reports demonstrated that the TdP occurred in the context of methadone, with the addition to other QT-prolonging drugs, and severe electrolyte disturbances or concomitant use of cocaine\textsuperscript{207, 208}.

However, Chugh et al., observed an association between therapeutic levels of methadone and SCD in the general community\textsuperscript{210}. In this study, 22 SCD cases with therapeutic levels of methadone were compared with 106 consecutive SCD cases without evidence of methadone on toxicologic screen. Among the SCD methadone cases, a cardiac etiology was identified in only 23%, with no identifiable cause of death in the remaining 77%. In comparison, the non-methadone SCD cases had an attributable SCD cause in 60% of the cases. The authors concluded that the low prevalence of identifiable cardiac disease or structural abnormalities in the methadone SCD cases strongly suggested a causative role for methadone in the pathogenesis of SCD among this group.

Yet there are important limitations to this study; firstly the authors could not rule out that some of the patients may have experienced respiratory arrest rather than an arrhythmic event, as methadone is known to suppress breathing, particularly during sleep\textsuperscript{211}. Furthermore, other known QT-prolonging drugs such as antidepressants and antipsychotics were also found on toxicology screens in both groups of SCD patients, (albeit in therapeutics ranges), which may have contributed to these deaths.
Appendix 1A: Causes of SCD and Aborted SCD in the Young

1.5.4 Cocaine:
Cocaine is a potent sympathomimetic drug (e.g. produces physiological effects characteristic of the sympathetic nervous system), derived from the leaves of the Erythroxylon coca plant, which grows primarily in South America. It is available in 2 main formats, as the hydrochloride salt which is ingested nasally, or the free-base ‘crack' form used in smoking, with street purity ranging from 1% to over 90%. Cocaine has a half-life of between 0.5 and 1.5 h and it is metabolized to partially active metabolites called benzoylcegonine and ecgonine methyl ester. Cocaine users who ingest alcohol produce a metabolite called cocaethylene, which is associated with more toxic effects than alcohol or cocaine use alone.

1.5.5 Mechanisms of Cocaine Cardiotoxicity:
Cocaine stimulates the sympathetic nervous system by increasing the sensitivity of adrenergic nerve endings to norepinephrine and inhibiting catecholamine reuptake at sympathetic nerve terminals. These effects on the sympathetic nervous system result in the stimulation of cardiomyocyte α1- and β-adrenergic receptors, with resulting increases in heart rate, blood pressure, and contractility. Ultimately, this contributes to increased myocardial oxygen demand, while the contrasting effects on the vasculature (vasoconstriction) result in a simultaneous decrease in myocardial oxygen supply. In addition to vasoconstriction, cocaine also induces a prothrombotic state by increasing platelet coagulability and induction of von Willebrand factor from endothelial cells.
### Appendix 1B: Sudden Death and Sudden Cardiac Death Incidence Studies in the General Population – Ages 1-50 Published between 1994-2014.

<table>
<thead>
<tr>
<th>Author</th>
<th>Time</th>
<th>Location</th>
<th>Definitional equivalent</th>
<th>Age</th>
<th>Autopsy Rate (%)</th>
<th>Review Process</th>
<th>Tox</th>
<th>Estimate Annual Incidence</th>
<th>Proportion Cardiac (%)</th>
<th>Sources for Case Ascertainment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meyer</td>
<td>1980-2009</td>
<td>King County Washington</td>
<td>Confirmed or likely cardiovascular cause of OHCA</td>
<td>0-35</td>
<td>72.8%</td>
<td>Yes</td>
<td>NR</td>
<td>2.28 per 100,000</td>
<td>361/2660 (13.6%)</td>
<td>Autopsy reports, death certificates, EMS incident reports, hospital or emergency records</td>
</tr>
<tr>
<td>Donohoe*</td>
<td>2003-2007</td>
<td>London UK</td>
<td>Treated OHCA of presumed cardiac cause</td>
<td>0-35</td>
<td>NR</td>
<td>NR</td>
<td>No</td>
<td>4.5 per 100,000</td>
<td>44.9%*</td>
<td>EMS incident reports and survival outcomes</td>
</tr>
<tr>
<td>Wisten</td>
<td>1992-99</td>
<td>Sweden</td>
<td>Witnessed natural unexpected death &lt; 1 hour after symptom onset in healthy person or if unwitnessed natural unexpected death last seen &lt;24 hours</td>
<td>15-35</td>
<td>100%*</td>
<td>Yes</td>
<td>NR but reviewed</td>
<td>0.93 per 100,000</td>
<td>20.8% (181/871) of all natural deaths</td>
<td>National database of forensic medicine; forensic, clinical and police records; family interviews</td>
</tr>
<tr>
<td>Margey</td>
<td>2005-2007</td>
<td>Ireland</td>
<td>Witnessed sudden unexpected death &lt; 1 hour after symptom</td>
<td>14-35</td>
<td>73%</td>
<td>Yes</td>
<td>No</td>
<td>2.85 per 100,000</td>
<td>39.7% (116/292)</td>
<td>ICD-9 codes, post mortem and toxicology reports</td>
</tr>
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</table>
onset or if unwitnesse d sudden unexpected death last seen <24 hours with cardiac cause of death.

<table>
<thead>
<tr>
<th>Bardai</th>
<th>2005 - 2010</th>
<th>Netherlands</th>
<th>OHCA witnessed or OHCA unwitnessed &lt;24 hours. Cardiac OHCA used for this reported incidence.</th>
<th>0-21</th>
<th>NR</th>
<th>Yes</th>
<th>No</th>
<th>3.2 per 100,000</th>
<th>39% (90/233)</th>
<th>EMS records from ARREST db, coroner database, post mortems, death certificates.</th>
</tr>
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<tbody>
<tr>
<td>Eckart</td>
<td>1998 - 2008</td>
<td>US Military</td>
<td>Event resulting in death &lt; 1 hr collapse or unwitnessed but unexpected death in absence of known disease. Cardiac deaths were</td>
<td>18+</td>
<td>86.4%</td>
<td>NR</td>
<td>NR but reviewed</td>
<td>6.68 per 100,000 (all ages)</td>
<td>68.5% 715/1044</td>
<td>Dept of Defense mortality registry; post mortems; medical records.</td>
</tr>
<tr>
<td>Location</td>
<td>Years</td>
<td>Methodology</td>
<td>Autopsy Cases</td>
<td>Yes (%)</td>
<td>NR but reviewed</td>
<td>Rate per 100,000</td>
<td>Non-cardiac (%)</td>
<td>Notes</td>
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<tr>
<td>Risgaard</td>
<td>2007-2009</td>
<td>Sudden, natural unexpected death. If witnessed &lt; 1 hr or unwitnessed &lt; 24 hrs. Excluded non cardiac cases.</td>
<td>1-49</td>
<td>56%</td>
<td>Yes</td>
<td>2.3 per 100,000 (ages 1-35)</td>
<td>62%</td>
<td>Danish national pt registry, death certificates, discharge summaries, autopsies.</td>
<td></td>
<td></td>
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<tr>
<td>Chugh</td>
<td>2002-2003</td>
<td>Sudden, unexpected death. If witnessed &lt; 1 hr or unwitnessed &lt; 24 hrs. Excluded non cardiac cases.</td>
<td>0+</td>
<td>12%</td>
<td>Yes</td>
<td>NR but reviewed</td>
<td>53 per 100,000 (all ages)</td>
<td>69.6%</td>
<td>EMS records, medical examiner and hospital records, autopsy records.</td>
<td></td>
</tr>
<tr>
<td>Chugh</td>
<td>2002-2005</td>
<td>Sudden, unexpected death. If witnessed &lt; 1 hr or unwitnessed &lt; 24 hrs. Excluded non cardiac cases.</td>
<td>0-17</td>
<td>91%</td>
<td>Yes</td>
<td>NR but reviewed</td>
<td>1.7 per 100,000 (pediatric)</td>
<td>NR as non-cardiac cases excluded.</td>
<td>EMS records, medical examiner and hospital records, autopsy records.</td>
<td></td>
</tr>
<tr>
<td>Pilmer</td>
<td>2008</td>
<td>Event resulting in death &lt; 1 hr</td>
<td>2-40</td>
<td>NR</td>
<td>Yes</td>
<td>NR but reviewed</td>
<td>2.6 per 100,000</td>
<td>46.3%</td>
<td>Coroner records only which include investigative statements,</td>
<td></td>
</tr>
<tr>
<td>Pilmer</td>
<td>2005 - 2009</td>
<td>Ontario, Canada</td>
<td>Event resulting in death &lt; 1 hr collapse or unwitnessed but unexpected death in absence of known disease.</td>
<td>1-19</td>
<td>88%</td>
<td>Yes</td>
<td>NR but reviewed</td>
<td>0.78 per 100,000</td>
<td>33.0% (116/351)</td>
<td>Coroner records only which include investigative statements, post mortems and toxicology reports.</td>
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<tr>
<td>Fragkouli</td>
<td>1998 - 2008</td>
<td>Epirus, Greece</td>
<td>Sudden, natural unexpected death. If witnessed &lt; 6 hrs or unwitnessed &lt; 24 hrs.</td>
<td>1-80</td>
<td>NR</td>
<td>Yes</td>
<td>NR but reviewed</td>
<td>1.78 per 100,000 (ages 1-35)</td>
<td>54.9% (688/1254)</td>
<td>Dept of Forensic Medicine and Toxicology; EMS records, clinical records, post mortem and toxicology.</td>
</tr>
<tr>
<td>Hendrix</td>
<td>1996 - 2006</td>
<td>Netherlands</td>
<td>Sudden unexpected death due to cardiac</td>
<td>1-39</td>
<td>NR</td>
<td>No</td>
<td>No</td>
<td>1.6 per 100,000</td>
<td>NR</td>
<td>Death certificates</td>
</tr>
<tr>
<td>Study</td>
<td>Year</td>
<td>Location</td>
<td>Description</td>
<td>Timeframe</td>
<td>Witnessed</td>
<td>Excluded</td>
<td>Rate</td>
<td>Notes</td>
<td></td>
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<tr>
<td>Stecker</td>
<td>2002-2004</td>
<td>Multnomah County, Oregon US</td>
<td>Sudden, unexpected death. If witnessed &lt; 1hr or unwitnessed &lt; 24 hrs. Excluded non cardiac cases.</td>
<td>0+</td>
<td>NR</td>
<td>Yes</td>
<td>NR</td>
<td>EMS records, medical examiner and hospital records, autopsy records.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eckart</td>
<td>1977-2001</td>
<td>US Military</td>
<td>Event resulting in death &lt; 1hr collapse. Cardiac deaths were confirmed on autopsy.</td>
<td>18-35</td>
<td>97%</td>
<td>NR</td>
<td>NR but reviewed</td>
<td>Dept of Defense mortality registry; post mortems; medical records.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Winkel</td>
<td>2000-2006</td>
<td>Denmark</td>
<td>Sudden, natural unexpected death of unknown or cardiac cause. If witnessed &lt; 1hr or unwitnessed &lt; 24 hrs.</td>
<td>1-35</td>
<td>75%</td>
<td>Yes</td>
<td>82% of SUDS cases (112/136)</td>
<td>Danish national pt registry, death certificates, discharge summaries, autopsies.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Year Range</td>
<td>Country</td>
<td>Definition</td>
<td>Duration</td>
<td>%</td>
<td>Yes/No</td>
<td>% Detected</td>
<td>Rate per 100,000</td>
<td>%</td>
<td>Methodology</td>
</tr>
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</tr>
<tr>
<td>Winkel</td>
<td>2000-2006</td>
<td>Denmark</td>
<td>Sudden natural unexpected death of unknown or cardiac causes; in unwitnessed &lt;24 hr; in witnessed cases &lt;1 hr.</td>
<td>1-18</td>
<td>77%</td>
<td>Yes</td>
<td>92% (70/76)</td>
<td>1.1 per 100,000</td>
<td>76%</td>
<td>Danish national pt registry, death certificates, discharge summaries, autopsies.</td>
</tr>
<tr>
<td>Papadakis</td>
<td>2002-2005</td>
<td>England and Wales, UK</td>
<td>Definite cardiac deaths (SADS + structural heart disease)</td>
<td>1-34</td>
<td>NR</td>
<td>No</td>
<td>NR</td>
<td>1.8 per 100,000</td>
<td>NR</td>
<td>Office of National Statistics; ICD-10 codes (e.g. death certificates)</td>
</tr>
<tr>
<td>Shen</td>
<td>1960-1989</td>
<td>Olmsted County, Minnesota, US</td>
<td>Witnessed nontraumatic death &lt;1 hr after symptoms. Unwitnessed &lt; 6 hrs. “Unexpected death” was defined as death that occurred in a subject without previous</td>
<td>20-40</td>
<td>NR</td>
<td>Yes</td>
<td>16.7% (9/54) detected among SCD cases</td>
<td>6.2 per 100,000</td>
<td>57%</td>
<td>Complete list of deaths was obtained – not specified how. Death certificates, complete community outpatient and inpatient medical records, coroner’s reports, and autopsy reports were reviewed</td>
</tr>
<tr>
<td>Name</td>
<td>Year</td>
<td>Location</td>
<td>Definition</td>
<td>Age Range</td>
<td>Investigator</td>
<td>Review</td>
<td>NR</td>
<td>ICD-10 Codes</td>
<td>Rate</td>
<td>Comments</td>
</tr>
<tr>
<td>----------------</td>
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</tr>
<tr>
<td>Vaartjes</td>
<td>1996-2006</td>
<td>Netherlands</td>
<td>Unexpected natural death &lt;24 h due to cardiac cause.</td>
<td>1-40</td>
<td>NR</td>
<td>No</td>
<td>No</td>
<td>1.62 per 100,000</td>
<td>59%</td>
<td>Statistics Netherlands, ICD-10 codes (e.g. death certificates)</td>
</tr>
<tr>
<td>Bray*</td>
<td>1997-2010</td>
<td>Perth, Australia</td>
<td>OHCA of no obvious cause</td>
<td>0+</td>
<td>N/A</td>
<td>No</td>
<td>No</td>
<td>7.5 per 100,000 (ages 15-34)</td>
<td>76%</td>
<td>St John Ambulance Western Australia OHCA dataset</td>
</tr>
<tr>
<td>Hofer</td>
<td>2000-2007</td>
<td>Switzerland</td>
<td>Diseases of the cardiovascular system</td>
<td>5-39</td>
<td>47.5%</td>
<td>No</td>
<td>No</td>
<td>1.71 per 100,000</td>
<td>3.6%</td>
<td>Cantonal Statistical Research and Information Service and the University Institute of Social and Preventive Medicine, iCD-10 codes</td>
</tr>
<tr>
<td>Arzamendi**</td>
<td>2000-2006</td>
<td>Montreal, Canada</td>
<td>Natural, nonviolent, unexpected death, occurring within 24 hours of the onset of symptoms.</td>
<td>0-40</td>
<td>100%*</td>
<td>Yes</td>
<td>Review but NR</td>
<td>NR</td>
<td>39.9% (97/243)</td>
<td>All coroner autopsies of individuals &lt;40 years old who presented OHCA and referred to the Montreal Heart Institute or Maisonneuve-Rosemont Hospital.</td>
</tr>
<tr>
<td>Wang**</td>
<td>1978-2008</td>
<td>China</td>
<td>Natural, unexpected fatal events occurring &lt; 1 h from symptoms in an</td>
<td>18-80</td>
<td>100%*</td>
<td>Yes</td>
<td>12.3% of SCD cases tested</td>
<td>NR</td>
<td>10.3% of all natural deaths</td>
<td>All autopsy cases referred to the forensic medical centers and general hospitals in eight cities of China.</td>
</tr>
</tbody>
</table>
apparently healthy. Unwitnessed <24 h before the event.

<table>
<thead>
<tr>
<th>Study</th>
<th>Period</th>
<th>Location</th>
<th>Cause</th>
<th>Causality</th>
<th>Younger</th>
<th>Population Size</th>
<th>SCD Rate</th>
<th>Lower 95% CI</th>
<th>Study Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atkins*</td>
<td>2005 - 2007</td>
<td>ROC Sites (US and Canada)</td>
<td>Pediatric OHCA treated or untreated. No obvious cause was presumed cardiac.</td>
<td>1-19</td>
<td>NA</td>
<td>No</td>
<td>No</td>
<td>8.04 per 100,000*</td>
<td>EMS records, in-hospital data.</td>
</tr>
<tr>
<td>Corrado**</td>
<td>1979 - 1999</td>
<td>Veneto, Italy</td>
<td>Unexpected death as a result of natural causes in which a loss of all functions occurred &lt; 1 h of the onset of collapse symptoms. SCD if confirmed on autopsy.</td>
<td>12-35</td>
<td>NR but implies 100%</td>
<td>Yes</td>
<td>NR</td>
<td>0.7 per 100,000 (non athletes, SCD rate)</td>
<td>Prospective clinico-pathologic investigation of SD.</td>
</tr>
<tr>
<td>Corrado**</td>
<td>1979 - 2004</td>
<td>Veneto, Italy</td>
<td>Unexpected death as a result of natural causes in which a loss</td>
<td>12-35</td>
<td>NR but implies 100%</td>
<td>Yes</td>
<td>NR</td>
<td>0.81 per 100,000 (non athletes, SCD rate)</td>
<td>100% (non-cardiac excluded)</td>
</tr>
</tbody>
</table>
of all functions occurred < 1 h of the onset of collapse symptoms. SCD if confirmed on autopsy.

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Location</th>
<th>Description</th>
<th>Incidence</th>
<th>Confidence</th>
<th>Code</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doolan**</td>
<td>1994-2002</td>
<td>Sydney, Australia</td>
<td>Sudden death occurring &lt; 24 hrs of the onset of symptoms.</td>
<td>0-35</td>
<td>NR but implies 100%</td>
<td>Yes</td>
<td>Dept of Forensic Medicine at Westmead Hospital; autopsies and clinical data.</td>
</tr>
<tr>
<td>Wren**</td>
<td>1985-1994</td>
<td>Northern Health Region of England, UK</td>
<td>Deaths that occurred suddenly, out-of-hospital or arriving or within the ED.</td>
<td>1-20</td>
<td>NR but implies 100%</td>
<td>Yes</td>
<td>Office of National Statistics; death certificates and additional clinical information from hospitals, coroners or pathologists.</td>
</tr>
</tbody>
</table>

NR = not reported
*Presumed cardiac
**These studies only used autopsy cases and excluded cases without.
Dear (patient’s name):

Re: The Family Study: Assessment of the incidence, etiology and familial risk for sudden cardiac arrest in young individuals and their family members

Why are you being contacted?
I am writing to ask you to consider participating in a study called “The Family Study”. We are contacting you because our records show that you were treated by Peel Emergency Medical Services and/or Peel Fire Services personnel for an out-of-hospital cardiac arrest (sudden stopping of the heart), which involved the use of medical procedures that are called Basic or Advanced Cardiac Life Support.

We understand that this letter is very likely arriving at a time that is quite difficult for you. However, we wish to provide you with information concerning a research study that is trying to figure out why certain people’s hearts stop so suddenly (cardiac arrest).

Why is the study being done?
The most common cause of unexpected, sudden death is the sudden stoppage of the heart. In the majority of cases, the heart stops pumping when it goes into a dangerous rhythm. One of the likely causes of this dangerous rhythm is a blockage in the tubes that carry blood to the heart itself, but there are also several other causes which can cause the heart to stop suddenly. We want to understand why certain people’s hearts suddenly stop functioning, causing them to die suddenly, in order to eventually prevent these events from happening in the first place.

You are being asked to participate in a research study conducted by St. Michael’s Hospital in partnership with Sunnybrook Health Sciences Centre that is looking into the medical and environmental causes (risk factors) that are associated with dangerous heart rhythms. We are asking you to take part because you have suffered a sudden, unexpected cardiac arrest, in order to help us understand more about why it occurred.

Both the Sunnybrook Health Sciences Centre and the St. Michael’s Hospital Research Ethics Boards have reviewed and given permission for this study to proceed.

What is the purpose of the study?
The main goal of this study is to try and figure out why your heart may have stopped suddenly and unexpectedly, which we will do by asking you detailed questions about your prior symptoms and medical history and by examining your medical records.
If you allow us to do so, we will contact you by telephone to discuss participating in the study. If you agree to participate, you will need to sign and date the attached consent form.

If you choose to participate in this research study, researchers from St. Michael’s Hospital will need to ask you detailed questions about you and your family’s medical history, your knowledge level and understanding of what happened to you when your heart stopped, as well as your knowledge and understanding of cardiac risk factors. These questionnaires can be done by telephone, or by face-to-face interview and will take approximately 30 minutes to complete.

What are my rights to withdraw participation in this research study?
If we do not hear back from you within the next 2 weeks, we will proceed to telephone you to discuss participating in the study. If you do not wish to be contacted you may opt out of the telephone follow-up by calling us at 416-864-5963 within the next 2 weeks; please provide your full name. You will not suffer any penalty or loss of benefits to which you are otherwise entitled by opting out.

What are my rights as a participant and where can I get more information?
A copy of the consent form, which has more detailed information about the study is included with this letter for your review. If you would like to discuss this further or would like to receive a more detailed account of the research, please do not hesitate to contact the study Primary Investigator Dr. Paul Dorian by e-mail at dorianp@smh.toronto.on.ca or by phone at 416-864-5104 or the Chair of the Research Ethics Board at Sunnybrook Health Sciences Centre 416-480-6100, ext. 88144.

We apologize for this intrusion. We appreciate how difficult this situation may be for you and your family. No action on your part is required unless you wish to receive further information or wish to discuss this further.

Kindest regards,

Sheldon Cheskes, MD  
Site Principal Investigator  
Sunnybrook Health Sciences Centre  
Family Study

Paul Dorian, MD  
Principal Investigator  
St. Michael’s Hospital  
Family Study

Katherine Allan  
Study Coordinator  
St. Michael’s Hospital  
Family Study
Dear Family Member:

Re: Assessment of the risk of family members of victims of out of hospital cardiac arrest for Coronary Artery Disease and Sudden Cardiac Death (Family Study)

**Why are you being contacted?**
I am writing to ask you to consider participating in a study called “The Family Study”. We are contacting you because our records show that your relative was treated by Toronto Emergency Medical Services and/or Toronto Fire Services personnel for an out-of-hospital cardiac arrest (sudden stopping of the heart) which involved the use of procedures that are called Basic or Advanced Cardiac Life Support.

We understand that this letter is very likely arriving at a time that is quite difficult for you. However, we wish to provide you with information concerning a research study that is trying to figure out why certain people’s hearts stop so suddenly (cardiac arrest).

**Why is the study being done?**
The most common cause of unexpected, sudden death is the sudden stoppage of the heart. In the majority of cases, the heart stops pumping when it goes into a dangerous rhythm. One of the likely causes of this dangerous rhythm is a blockage in the tubes that carry blood to the heart itself, but there are also several other causes which can cause the heart to stop suddenly. We want to understand why certain people’s hearts suddenly stop functioning, in order to eventually prevent these events from happening in the first place.

You are being asked to participate in a research study that is looking into the medical and environmental causes (risk factors) that are associated with dangerous heart rhythms. We are asking you to take part because you are a first-degree family member or partner of someone who has suffered an unexplained cardiac arrest.

The St. Michael's Hospital Research Ethics Board has reviewed and given permission for this study to proceed.

**What is the purpose of the study?**
The main goal of this study is to try and figure out why your first degree relative (i.e., parent, sibling, or offspring) or partner had an unexplained cardiac arrest (sudden stopping of the heart), which we will do by asking you detailed questions about their prior symptoms and medical history and by examining their medical records. These questionnaires can be completed over the phone, face-to-face or by mail and will take approximately 30 minutes of your time.
If by answering these questionnaires you are found to have many medical or environmental problems (risk factors) related to your heart, and you are interested in knowing more about these heart related risk factors, you will be asked to come to St. Michael’s Hospital to have a standard medical workup that will include an electrocardiogram (ECG), blood pressure and blood sugar measurements, cholesterol, height, weight and waist circumference will also be measured. This visit will take approximately 30 minutes of your time. This cardiac exam portion is a sub-study of the main registry project and you are not obligated to participate if you do not want to.

If you allow us to do so, we will contact you by telephone to discuss participating in the study. If you agree to participate, you will need to sign and date the attached consent form.

**What are my rights to withdraw participation in this research study?**

If we do not hear back from you within the next 2 weeks, we will proceed to telephone you. If you do not wish to be contacted you may opt out of the telephone follow-up by calling us at 416-864-5963 within the next 2 weeks; please provide your full name and the name of your relative who suffered the cardiac arrest. You will not suffer any penalty or loss of benefits to which you are otherwise entitled by opting out.

**What are my rights as a participant and where can I get more information?**

A copy of the consent form, which has more detailed information about the study, is included with this letter for your review. If you would like to discuss this further or would like to receive a more detailed account of the research, please do not hesitate to contact Dr. Paul Dorian by e-mail at dorianp@smh.toronto.on.ca or by phone at 416-864-5104 or the Chair of the Research Ethics Board at St. Michael’s Hospital (416) 864-6060, ext. 2557.

We apologize for this intrusion. We appreciate how difficult this situation may be for you and your family. No action on your part is required unless you wish to receive further information or wish to discuss this further.

Kindest regards,

Paul Dorian, MD
Principal Investigator
Family Study
Consent to Participate in a Research Study

TITLE OF RESEARCH STUDY:

The Family Study: Assessment of the incidence, etiology and familial risk for sudden cardiac arrest in young individuals and their family members

Study Investigators:

**Principal Investigator:** Dr. Sheldon Cheskes

**Sub-Investigators:**
- Dr. Richard Verbeek
- Dr. Laurie Morrison
- Dr. Paul Dorian
- Dr. Jack Tu
- Dr. Iqwal Mangat

**Research Coordinator:** Katherine Allan, MAsc, PhD (c)

**Research Assistant:** Cameron Landry and Golnaz Roshankar

Contact Information: Sunnybrook Health Sciences Centre
Sunnybrook Centre for Prehospital Medicine
77 Browns Line, Suite 100
Toronto, ON
M8W 3S2

Hours: 8:00 – 4:00
Tel/Fax: 416-667-2200 ext 0

Telephone: (416) 864.5963

You are being asked to consider taking part in a research study and before you make your decision it is important that you read the following information in this research consent form. It includes details we think you need to know in order to decide if you wish to take part in the study. If you have any questions, ask a study doctor or study staff. You should not sign this form until you are sure you understand the information. All research is voluntary. You may also wish to discuss the study with your family doctor, a family member or close friend.

PURPOSE OF THE STUDY

The most common cause of unexpected, sudden death is the sudden stoppage of the heart. In the majority of cases, the heart stops pumping when it goes into a dangerous rhythm. One of the likely causes of this dangerous rhythm is a blockage in the tubes that
carry blood to the heart itself, but there are also several other causes which can cause the heart to stop suddenly.

The only way to remove blockages in the heart is in hospital and most people die before they can have this done. Instead of removing these blockages in the hospital only after someone has experienced a sudden stoppage of the heart, we think that a much better idea would be for us to see if we can figure out why certain people’s hearts get blocked, causing them to die suddenly, and to see if we prevent this from happening in the first place.

We know that medical problems like having high blood pressure or high blood sugar can cause blockages in the heart and we also know that these problems tend to run in families. This means, for example, that if your mother or father or brother or sister has high blood pressure, you might too. We also know that your home environment can affect your chances of having heart blockages and dying suddenly. If, for example, you are overweight or smoke you are also likely to have heart blockages down the road. We think that many people do not know that they may be in danger of dying suddenly, or why their relative died “out of the blue”.

We are conducting this research study in order to look at and better understand the medical or environmental causes (risk factors) that are associated with the sudden stopping of the heart (cardiac arrest). You yourself may have some of these risk factors, which could have caused you to have a cardiac arrest (sudden stopping of the heart).

The main goal of this study is to try and figure out why your heart may have stopped suddenly and unexpectedly, which we will do by asking you detailed questions about your prior symptoms and medical history and by looking at your medical records.

In our case-control study, you are part of the population of interest or the group we will compare to the controls, or people who have not had a cardiac arrest. A case-control is a type of study design. In a case-control study, individuals with a defined characteristic (victims of cardiac arrest i.e. you) are matched with people who do not have the condition but are otherwise similar (the 'controls'). Further data is then collected on those individuals (cardiac arrest victims and controls) and the groups are compared to find out if other characteristics (perhaps a history of smoking) are also different between the two groups.

**STUDY DESCRIPTION**

If you choose to participate in this research study, we will need to ask you tape-recording detailed questions about you and your family’s medical history, your own knowledge level and understanding of what happened to you when your heart stopped, as well as your knowledge and understanding of cardiac risk factors using various questionnaires. We will need to transcribe the entire content of the interview for study purposes; however, you will not be identified in any way on either the transcript or audio recording.
The questionnaires can be completed over the phone or face-to-face and will take approximately 30 minutes of your time.

We are also asking you to provide consent to release your medical records to us, so that we may examine them in order to determine if you had any underlying medical or environmental problems (risk factors) that may have caused your heart to stop suddenly.

This is a registry study. That means that information from tests or procedures that are done as part of your standard clinical care will be collected and stored. There will be approximately 150 people in this research study, 30 of which will be enrolled from Sunnybrook Health Sciences Centre.

The information that we will collect includes:

1. Basic information including your age, gender, height, weight, waist circumference
2. Medical information including current/past medical illnesses, illnesses in the family, family history and family tree.
3. Results of past and current medical investigations such as blood tests, x-rays, echocardiograms, electrocardiograms, exercise tests, nuclear scans, magnetic resonance (MRI) scans, computed tomography (CT), cardiac catheterizations and electrophysiology studies.
4. Past and current medical and surgical treatments including medications.
5. Discharge summaries and clinical follow up letters.

POTENTIAL HARMs

There may be some emotional discomfort arising from the discussion about the actual event, however, you do not have to talk about anything you do not feel comfortable discussing and you may stop at any point.

Otherwise, except for the risks discussed in the part of this form that discusses what we will do to protect your and your family member’s health information, there are no risks involved with participating in the registry study as we are only collecting information from tests or procedures that are done as part of your standard clinical care.

POTENTIAL BENEFITS

This research study may identify an underlying medical or environmental problem that may cause a sudden cardiac arrest and allow for better medical management and prevention of an unexplained cardiac arrest in other individuals in the future. Participation in this study may or may not prove to be of no direct benefit to you. Regardless of whether the results we come up with in your case are normal or abnormal, we will be reporting them to your family doctor. We will also direct you to appropriate
resources and provide you with information for managing the risk factors associated with sudden cardiac arrest.

ALTERNATIVES TO STUDY PARTICIPATION

Participation in any research is voluntary. You are free to decline to participate in this study. If you decide not to participate in this study, that will not affect in any way your present or future medical care or treatment. You may also wish to follow up with your own personal physician regarding your own medical and environmental risk factors.

PROTECTING YOUR HEALTH INFORMATION

All persons associated with this study, including study investigators, coordinators, nurses and delegates (hereby referred to as “study personnel”) are committed to respecting your privacy. No other persons will have access to the transcription of the interview or any other identifying personal or health information without your consent, unless required by law. Any information collected from this interview or other information related to you will be coded by study numbers to ensure that persons outside of the study will not be able to identify you. The study personnel are in control of the study code key, which is needed to connect your information to you. Our guidelines include the following:

- All information that identifies you, audio tape recordings, paper copy and electronic information, will be kept confidential and stored and locked in a secure place that only the study personnel will be able to access.
- Electronic files will be stored securely on hospital or institutional networks or securely on any portable electronic devices.
- Any audio recordings/tapes will be maintained until the data/transcripts have been verified and after that they will be securely destroyed.
- No information identifying you will be allowed off site in any form.

It is important to understand that despite these protections being in place, there continues to be the risk of accidental, unintentional release of information. The study personnel will protect your records and keep all the information in your study file confidential to the greatest extent possible. The chance that this information will be accidentally released is small.

By signing this form, you are authorizing access to your records by the study personnel and the St. Michael’s Hospital and Sunnybrook Health Sciences Centre Research Ethics Boards. Such access will be used only for the purpose of verifying the authenticity and accuracy of the information collected for the study, without violating your confidentiality to the extent permitted by applicable laws and regulations.

Federal and Provincial Data Protection regulations, including the Personal Information Protection and Electronic Documents Act (PIPEDA 2000) and the Personal Health Information Protection Act (PHIPA 2004) of Ontario, protect your personal information. They also give you the right to control the use of your personal information (including
personal health information) and require your written permission for this personal information to be collected, used, or disclosed for the purposes of this study, as described in this consent form. You have the right to review and copy your personal information collected in this study. However, if you decide to be in this study or choose to withdraw from it, your right to look at or copy your personal information related to this study will be delayed until after the research is completed.

The study investigators will keep your study records securely stored on-site for 2 years after the end of the study. They will be kept in a locked office accessible only by approved study personnel. After 2 years, the data will be stored at Recall for 13 years. This company provides secure document management services and is compliant with Health Canada, PIPEDA, and PHIPAA regulations.

PUBLICATIONS OF RESULTS

The results of this study may be published as a scientific paper to help other doctors help their patients. However your privacy will be protected and you will never be identified by name or by a description of you.

POTENTIAL COST OF PARTICIPATION AND REIMBURSEMENT

Everything that we do as part of this study will be done at no cost to you. No payment or reimbursement will be made for you to participating in this study.

COMPENSATION FOR INJURY

If you suffer a physical injury as a result of the study procedures, medical care will be provided to you in the same manner, as you would ordinarily obtain any other medical treatment. In no way does signing this form waive your legal rights nor relieve the investigator, sponsor or involved institutions from their legal and professional responsibility.

PARTICIPATION AND WITHDRAWAL

Participation in any research is voluntary. If you choose not to participate, you and your family will continue to have access to customary care at Sunnybrook Health Sciences Centre. If you decide to participate in this study you can change your mind without giving a reason, and you may withdraw from the study at any time without any effect on the care you and your family will receive at Sunnybrook Health Sciences Centre.

NEW FINDINGS OR INFORMATION

We may learn new things during the study that you may need to know. If so, you will be notified about any new information in a timely manner. As was already mentioned, we will be sharing our results with your family physician. You may also be asked to sign a
new consent form discussing these new findings, such as any revisions to the consent forms or study protocol if you decide to continue in the research study.

RESEARCH ETHICS BOARD CONTACT

Should you have any questions about your rights as a research study participant, you may contact the Chair of the Sunnybrook Health Sciences Centre Research Ethics Board at 416-480-6100, ext. 88144.

STUDY CONTACTS

The study doctor and/or his/her colleagues are available to answer any questions you may have regarding the treatment described or the study procedures. If you have any questions regarding this research study, you may contact the site Primary Site Investigator Dr. Sheldon Cheskes by email at Sheldon.Cheskes@sunnybrook.ca or by phone at 416-667-2200 ext 0 or Dr. Paul Dorian by e-mail at dorianp@smh.toronto.on.ca or by phone at 416-864-5104 at (416) 864-5104 and/or the research coordinator, Katherine Allan at (416) 864-5963.
The Family Study: Assessment of the incidence, etiology and familial risk for sudden cardiac arrest in young individuals and their family members

CONSENT TO PARTICIPATE

I acknowledge that the research study described above has been explained to me and that any questions that I have asked have been answered to my satisfaction. I have been informed of the alternatives to participation in this study, including the right not to participate and the right to withdraw without compromising the quality of medical care at Sunnybrook Health Sciences Centre for me and for other members of my family. As well, the potential risks, harms and discomforts have been explained to me and I also understand the potential benefits of participating in this research study. Should I have any other questions about the study, I may call any of the study doctors at (416) 864-5104.

I understand that I have not waived my legal rights nor released the investigators, sponsor, or involved institutions from their legal and professional duties. I know that I may ask now, or in the future, any questions I have about the study. I have been assured that my records will be kept confidential and that no information will be released or printed that would disclose my personal identity without my permission unless required by law.

I have been given sufficient time to read and understand the above information, and I will be given a signed copy of this consent.

I would like to participate in the questionnaire portion of the study (please check the appropriate box and initial to indicate your decision):

Yes☐ _______ (Initials)    No☐ _______ (Initials)

I agree to release my health records (please check the appropriate box and initial to indicate your decision):

Yes☐ _______ (Initials)    No☐ _______ (Initials)
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<th>Participant Name <em>(Please Print)</em></th>
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<td>Date (by Participant)</td>
<td>Participant Phone Number</td>
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I certify that I have explained the contents of this Informed Consent Form to the above named individual. I have asked whether there are any questions and answered any questions that were raised by this individual.

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<th>Name of Person Conducting Informed Consent <em>(Please Print)</em> and Position</th>
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</tr>
</thead>
</table>

Date Consent Discussion
Consent to Participate in a Research Study

TITLE OF RESEARCH STUDY:
The Family Study: Assessment of the incidence, etiology and familial risk for sudden cardiac arrest in young individuals and their family members

Investigators:

Principal Investigator: Dr. Paul Dorian
Sub-Investigators:
- Dr. Laurie Morrison
- Dr. Jack Tu
- Dr. Iqwal Mangat
- Dr. Sheldon Cheskes
- Dr. Richard Verbeek

Contact Information:
- St. Michael's Hospital
- Division of Cardiology
- 30 Bond St., 6-050Q
- Toronto, ON M5B 1W8
- Hours: 8:00 – 4:00
- Tel/Fax: (416) 864.5104
- (416) 864.5963

Research Coordinator:
- Katherine Allan, MASc.
Telephone: (416) 864.5963

Research Assistant:
- Cameron Landry and Golnaz Roshankar
Telephone: (416) 864.5963

Before agreeing to take part in this research study, it is important that you read the information in this research consent form. It includes details we think you need to know in order to decide if you wish to take part in the study. If you have any questions, ask a study doctor or study staff. You should not sign this form until you are sure you understand the information. All research is voluntary. You may also wish to discuss the study with your family doctor, a family member or close friend.

PURPOSE OF THE STUDY

The most common cause of unexpected, sudden death is the sudden stoppage of the heart. In the majority of cases, the heart stops pumping when it goes into a
dangerous rhythm. One of the likely causes of this dangerous rhythm is a blockage in the tubes that carry blood to the heart itself, but there are also several other causes which can cause the heart to stop suddenly.

We want to understand why certain people’s hearts suddenly stop functioning, in order to see what can be done to prevent these events from happening in the first place.

We know that medical problems like having high blood pressure or high blood sugar can cause blockages in the heart and we also know that these problems tend to run in families. This means, for example, that if your mother or father or brother or sister has high blood pressure, you might too. We also know that your home environment can affect your chances of having heart blockages and dying suddenly. If, for example, you are overweight or smoke you are also likely to have heart blockages down the road. We think that many family members do not know that they may be in danger of dying suddenly themselves, or why their relative died “out of the blue”.

We are conducting this research study in order to look at and better understand the medical or environmental causes (risk factors) that are associated with the sudden stopping of the heart (cardiac arrest). Your family member or partner may have had these risk factors, which caused them to have an unexplained cardiac arrest (sudden stopping of the heart).

The main goal of this study is to try and figure out why your first-degree relative (father, mother, son, daughter, sibling) or partner had an unexplained cardiac arrest (sudden stopping of the heart), which we will do by asking you detailed questions about their prior symptoms and medical history and by examining their medical and autopsy records.

Another goal of the study is to try and figure out what each family member’s medical and environmental problems (risk factors) are so that we can know if they are in danger of dying suddenly.

Although you yourself have not experienced a cardiac arrest (sudden stopping of the heart), this research may detect an underlying medical or environmental problem that may put you at risk of experiencing a cardiac arrest in the future. Early detection and treatment may reduce the risk of an unexplained cardiac arrest in the future. For this reason, we will be sharing the results that we come up with in your case with your family physician, regardless of whether those results are normal or abnormal. We will also direct you to appropriate on-line resources and provide you with written information for managing the risk factors that are associated with sudden cardiac arrest.
STUDY DESCRIPTION

If you choose to participate in this research study, we will ask you tape-recorded detailed questions about you and/or your family member and/or partner’s medical history. We will need to transcribe the entire content of the interview for study purposes; however, you or your family member and/or partner will not be identified in any way on either the transcript or audio recording. These questionnaires can be completed over the phone or face-to-face and will take approximately 30 minutes of your time.

If by answering these questionnaires you are found to have any medical or environmental problems (risk factors) related to your heart, and you are interested in knowing more about these heart related risk factors you will be advised to come to St. Michael’s Hospital to have a standard medical workup (cardiac exam) as part of your clinical care that will include an electrocardiogram (ECG), blood pressure, blood sugar and cholesterol measurements. For these measurements, we will require you to come to St. Michael’s Hospital for a short visit. This visit will take approximately 30 minutes of your time. This cardiac exam is part of your standard clinical care and you are not obligated to participate if you do not want to.

To measure blood sugar and cholesterol levels, you will be asked to provide a blood sample (about 10-20 ml or 2-4 teaspoons). The blood sample will be drawn at St. Michael’s Hospital and will take 15 minutes.

As part of an additional separate sub-study, we would also like to interview some of the participants about their experiences with regards to the cardiac arrest of their first-degree relative. You may be asked to be interviewed by one of the investigators about your experience at some point in the future and will need to sign a separate consent form at that time.

In addition, the Chief Coroner of Ontario has requested that the investigating coroner follow-up with family members regarding what happened to their relative, whenever someone dies suddenly from a cardiac arrest where a coroner investigates. This means that for all such investigations in the Province of Ontario of those who die suddenly and unexpectedly from a cardiac arrest, the coroner creates a detailed file of what happened. That file includes the investigating coroner’s investigation statement, as well as the post mortem and toxicology reports.

We are asking you to provide consent to release this coroner’s report about your deceased first-degree family member or partner so that we can better understand the circumstances and causes of this cardiac arrest.
We are also asking you to provide consent to release the medical records of your first-degree family member or partner or yourself, so that we may examine them, in order to determine if they had any underlying medical or environmental problems (risk factors) that may have caused his/her heart to stop suddenly.

This is a registry study. This means that information from tests or procedures done, as part of your deceased first-degree family member’s or partner’s or your standard clinical care will be collected and stored. There will be approximately 1250 people enrolled from St. Michael's Hospital.

The information that we will collect will include:

1. Basic information including age, gender, height, weight, waist circumference.
2. Medical information including current/past medical illnesses, illnesses in the family, family history and family tree
3. Results of past and current medical investigations such as blood tests, x-rays, echocardiograms, electrocardiograms, exercise tests, nuclear scans, magnetic resonance (MRI) scans, computed tomography (CT), cardiac catheterizations and electrophysiology studies.
4. Past and current medical and surgical treatments including medications.
5. Discharge summaries and clinical follow up letters.
6. Coroner’s report including the investigation statement, post mortem and toxicology reports.

If you decide to participate in the cardiac exam as part of your standard clinical care, we would like permission to collect the information from any of the clinical tests that you may undergo. If you decide not to have the cardiac exam and your blood sample(s) collected, this will have no effect on your participation in the main study (registry). You may choose to participate only in the registry portion of the study, whereby we look at the medical and autopsy records of your first-degree family member or partner or yourself and not the cardiac exam portion. If you choose to not participate in the registry portion, you cannot participate in the cardiac exam portion.

**POTENTIAL HARMS**

If you decide to have your blood drawn for the sub-study, the blood draw will be undertaken by a qualified nurse or physician. Placing of the needle in the vein to draw blood may cause pain. On rare occasions, bruising may develop at the site of the blood draw. This may last for a few days, but will eventually completely go away. There is also a less than 0.1% risk of infection at the puncture site.
Also, there is the possibility that you may experience some emotional discomfort during the discussion of the actual event. Please understand that you do not have to talk about anything you do not feel comfortable discussing, and that you may stop at any point.

Otherwise, except for the risks discussed in the part of this form that discusses what we will do to protect your and your family member’s health information, there are no medical or physical risks associated with participating in the registry study as we are only collecting information from tests or procedures that are done as part of you or your partner’s or family member’s standard clinical care.

POTENTIAL BENEFITS

This research study may identify an underlying medical or environmental problem that may cause an unexplained cardiac arrest and allow for better medical management and prevention of an unexplained cardiac arrest in the future. Participation in this study may or may not prove to be of benefit to you. As was already mentioned, we will be sharing the results that we come up with in your case with your family physician, regardless of whether those results are normal or abnormal. We will also be directing you to appropriate on-line resources and provide you with written information for managing the risk factors that are associated with sudden cardiac arrest.

ALTERNATIVES TO STUDY PARTICIPATION

Participation in any research is voluntary. You are free to decline to participate in this study. If you decide not to participate in this study, that will not affect in any way your present or future medical care or treatment. You may also wish to follow up with your own personal physician regarding your own medical and environmental risk factors.

PROTECTING YOUR HEALTH INFORMATION

All persons associated with this study, including study investigators, coordinators, nurses and delegates (hereby referred to as "study personnel") and the study sponsor are committed to respecting your privacy. No other persons will have access to the transcription of the interview or any other identifying personal or health information without your consent, unless required by law. Any information collected from this interview or other information related to you will be coded by study numbers to ensure that persons outside of the study (i.e., sponsors) will not be able to identify you. The study personnel are in control of the study code key, which is needed to connect your information to you. Our guidelines include the following:
All information that identifies you, audio tape recordings, paper copy and electronic information, will be kept confidential and stored and locked in a secure place that only the study personnel will be able to access.

- Electronic files will be stored securely on hospital or institutional networks or securely on any portable electronic devices.
- Any audio recordings/tapes will be maintained until the data/transcripts have been verified and after that they will be securely destroyed.
- No information identifying you will be allowed off site in any form.

It is important to understand that despite these protections being in place, there continues to be the risk of accidental, unintentional release of information. The study personnel will protect your records and keep all the information in your study file confidential to the greatest extent possible. The chance that this information will be accidentally released is small.

By signing this form, you are authorizing access to your records by the study personnel and the St. Michael’s Hospital Research Ethics Board. Such access will be used only for the purpose of verifying the authenticity and accuracy of the information collected for the study, without violating your confidentiality to the extent permitted by applicable laws and regulations.

Federal and Provincial Data Protection regulations, including the Personal Information Protection and Electronic Documents Act (PIPEDA 2000) and the Personal Health Information Protection Act (PHIPA 2004) of Ontario, protect your personal information. They also give you the right to control the use of your personal information (including personal health information) and require your written permission for this personal information to be collected, used, or disclosed for the purposes of this study, as described in this consent form. You have the right to review and copy your personal information collected in this study. However, if you decide to be in this study or choose to withdraw from it, your right to look at or copy your personal information related to this study will be delayed until after the research is completed.

The study investigators will keep your study records securely stored on-site for 2 years after the end of the study. They will be kept in a locked office accessible only by approved study personnel. After 2 years, the data will be stored at Recall for 13 years. This company provides secure document management services and is compliant with Health Canada, PIPEDA, and PHIPAA regulations.

**PUBLICATIONS OF RESULTS**

The results of this study may be published as a scientific paper to help other doctors help their patients. However you and your family member’s privacy will be protected and you/he/she will never be identified by name or by a description of you/him/her.
POTENTIAL COST OF PARTICIPATION AND REIMBURSEMENT

Everything that we do as part of this study will be done at no cost to you. No payment or reimbursement will be made to you for participating in this study.

COMPENSATION FOR INJURY

If you suffer a physical injury as a result of the study procedures, medical care will be provided to you in the same manner, as you would ordinarily obtain any other medical treatment. In no way does signing this form waive your legal rights nor relieve the investigator, sponsor or involved institutions from their legal and professional responsibility.

PARTICIPATION AND WITHDRAWAL

Participation in any research is voluntary. If you choose not to participate, you and your family will continue to have access to customary care at St. Michael’s Hospital. If you decide to participate in this study you can change your mind without giving a reason, and you may withdraw from the study at any time without any effect on the care you and your family will receive at St. Michael’s Hospital.

NEW FINDINGS OR INFORMATION

We may learn new things during the study that you may need to know. If so, you will be notified about any new information in a timely manner. As was already mentioned, we will be sharing our results with your family physician. You may also be asked to sign a new consent form discussing these new findings, such as any revisions to the consent forms or study protocol if you decide to continue in the research study.

RESEARCH ETHICS BOARD CONTACT

Should you have any questions about your rights as a research study participant, you may contact the Chair of the St. Michael’s Hospital Research Ethics Board at (416) 864-6060, ext. 2557.

STUDY CONTACTS

The study doctor and/or his/her colleagues are available to answer any questions you may have regarding the study procedures. If you have any questions regarding this research study, you may contact Dr. Paul Dorian at (416) 864-5104 and/or the research coordinator, Katherine Allan at (416) 864-5963.
The Family Study: Assessment of the incidence, etiology and familial risk for sudden cardiac arrest in young individuals and their family members

CONSENT TO PARTICIPATE

I acknowledge that the research study described above has been explained to me and that any questions that I have asked have been answered to my satisfaction. I have been informed of the alternatives to participation in this study, including the right not to participate and the right to withdraw without compromising the quality of medical care at St. Michael's Hospital for me and for other members of my family. As well, the potential risks, harms and discomforts have been explained to me and I also understand the potential benefits of participating in this research study. Should I have any other questions about the study, I may call any of the study doctors at (416) 864-5104.

I understand that I have not waived my legal rights nor released the investigators, sponsor, or involved institutions from their legal and professional duties. I know that I may ask now, or in the future, any questions I have about the study. I have been assured that my family member’s records will be kept confidential and that no information will be released or printed that would disclose my or my family member’s personal identity without my permission unless required by law.

I have been given sufficient time to read and understand the above information, and I will be given a signed copy of this consent.

I would like to participate in the questionnaire portion of the study (please check the appropriate box and initial to indicate your decision):

Yes☐ ________ (Initials) No☐ ________ (Initials)

I ___________________________ (print your name) agree to release the health records and/or coroner’s report of my partner and/or first-degree relative ___________________________ (name of relative) (please check the appropriate box and initial to indicate your decision):

Yes☐ ________ (Initials) No☐ ________ (Initials)

I agree to release my health records (please check the appropriate box and initial to indicate your decision):

Yes☐ ________ (Initials) No☐ ________ (Initials)

I would like to participate in the clinical cardiac exam (please check the appropriate box and initial to indicate your decision):

Yes☐ ________ (Initials) No☐ ________ (Initials)
Participant Name (*Please Print*)

Participant Signature

Date (by Participant)

Participant Phone Number

I certify that I have explained the contents of this Informed Consent Form to the above named individual. I have asked whether there are any questions and answered any questions that were raised by this individual.

Name of Person Conducting Informed Consent (*Please Print*) and Position

Signature of Person Conducting Informed Consent

Date Consent Discussion
Consent to Participate in a Research Study

TITLE OF RESEARCH STUDY:
The Family Study: Assessment of the risk of family members of victims of out of hospital cardiac arrest for Coronary Artery Disease and Sudden Cardiac Death

Investigators:

Principal Investigator:  
Dr. Paul Dorian  
Contact Information:  
St. Michael’s Hospital

Sub-Investigators:  
Dr. Laurie Morrison  
Dr. Jack Tu  
Dr. Iqwal Mangat  
Division of Cardiology  
30 Bond St., 6-050Q  
Toronto, ON M5B 1W8  
Hours: 8:00 – 4:00  
Tel/Fax: (416) 864.5104

Research Coordinator:  
Katherine Allan, MASc.  
Telephone:  
(416) 864.5963

Before agreeing to take part in this research study, it is important that you read the information in this research consent form. It includes details we think you need to know in order to decide if you wish to take part in the study. If you have any questions, ask a study doctor or study staff. You should not sign this form until you are sure you understand the information. All research is voluntary. You may also wish to discuss the study with your family doctor, a family member or close friend.

PURPOSE OF THE STUDY

The most common cause of unexpected, sudden death is the sudden stoppage of the heart. In the majority of cases, the heart stops pumping when it goes into a dangerous rhythm. One of the likely causes of this dangerous rhythm is a blockage in the tubes that carry blood to the heart itself, but there are also several other causes which can cause the heart to stop suddenly. We want to
understand why certain people’s hearts suddenly stop functioning, in order to see what can be done to prevent these events from happening in the first place.

We know that medical problems like having high blood pressure or high blood sugar can cause blockages in the heart and we also know that these problems tend to run in families. This means for example that if your mother or father or brother or sister has high blood pressure, you might too. We also know that your home environment can affect your chances of having heart blockages and dying suddenly. If, for example, you are overweight or smoke you are also likely to have heart blockages down the road. We think that many people do not know that they may be in danger of dying suddenly themselves, or why their relative died “out of the blue”.

We are conducting this research study in order to look at and better understand the medical or environmental causes (risk factors) that are associated with the sudden stopping of the heart (cardiac arrest).

Although you yourself have not experienced a cardiac arrest (sudden stopping of the heart) but this research may detect an underlying medical or environmental problem that may put you at risk of experiencing a cardiac arrest in the future. Early detection and treatment may reduce the risk of an unexplained cardiac arrest in the future. For this reason, we will be sharing the results that we come up with in your case with your family physician, regardless of whether those results are normal or abnormal. We will also direct you to on-line resources and provide you with written information about managing the risk factors that are associated with sudden cardiac arrest.

In our case-control study, you are part of the control population or comparison group that we will be using for the victims who have had cardiac arrests. A case-control is a type of study design. In a case-control study, individuals with a defined characteristic (victims of cardiac arrest) are matched with people who do not have the condition but are otherwise similar (the ‘controls’ i.e. you). Further data is then collected on those individuals (cardiac arrest victims and controls) and the groups are compared to find out if other characteristics (perhaps a history of smoking) are also different between the two groups.

**STUDY DESCRIPTION**

If you choose to participate in this research study, we will need to ask you tape-recorded detailed questions about your medical history. We will need to transcribe the entire content of the interview for study purposes; however, you will not be identified in any way on either the transcript or audio recording. These questionnaires can be completed over the phone, face-to-face, mail or by email and will take approximately 30 minutes of your time.
This is a registry study. This means that information from tests or procedures that are done as part of your standard clinical care will be collected and stored. There will be approximately 1250 people enrolled from St. Michael’s Hospital.

The information that we will collect includes:
1. Basic information including age, gender, height, weight, waist circumference
2. Medical information including current/past medical illnesses, illnesses in the family, family history and family tree
3. Results of past and current medical investigations such as blood tests, x-rays, echocardiograms, electrocardiograms, exercise tests, nuclear scans, magnetic resonance (MRI) scans, computed tomography (CT), cardiac catheterizations and electrophysiology studies.
4. Past and current medical and surgical treatments including medications.
5. Discharge summaries and clinical follow up letters.

POTENTIAL HARMs

There are no medical or physical risks associated with participating in the registry study as we are only collecting information from tests or procedures that are done as part of you or your partner’s or family member’s standard clinical care. Otherwise, except for the risks mentioned in the part of this form that discusses what we will do to protect your health and your family member’s information, there are no other risks associated with your participating in this study.

POTENTIAL BENEFITS

This research study may identify an underlying medical or environmental problem that may cause a sudden cardiac arrest and allow for better medical management and prevention of an unexplained cardiac arrest of other individuals in the future. Participation in this study may or may not prove to be of direct benefit to you. As was already mentioned, we will be sharing the results that we come up with in your case with your family physician, regardless of whether those results are normal or abnormal. We will also direct you to on-line resources and provide you with written information about managing the risk factors that are associated with sudden cardiac arrest.

ALTERNATIVES TO STUDY PARTICIPATION

Participation in any research is voluntary. If you choose not to participate, you and your family will continue to have access to customary care at St. Michael’s Hospital. If you decide to participate in this study you can change your mind.
without giving a reason, and you may withdraw from the study at any time without any effect on the care you and your family will receive at St. Michael's Hospital.

PROTECTING YOUR HEALTH INFORMATION

All persons associated with this study, including study investigators, coordinators, nurses and delegates (hereby referred to as “study personnel”) and the study sponsor are committed to respecting your privacy. No other persons will have access to the transcription of the interview or any other identifying personal or health information without your consent, unless required by law. Any information collected from this interview or other information related to you will be coded by study numbers to ensure that persons outside of the study (i.e., sponsors) will not be able to identify you. The study personnel are in control of the study code key, which is needed to connect your information to you. Our guidelines include the following:

- All information that identifies you, audio tape recordings, paper copy and electronic information, will be kept confidential and stored and locked in a secure place that only the study personnel will be able to access.
- Electronic files will be stored securely on hospital or institutional networks or securely on any portable electronic devices.
- Any audio recordings/tapes will be maintained until the data/transcripts have been verified and after that they will be securely destroyed.
- No information identifying you will be allowed off site in any form.

It is important to understand that despite these protections being in place, there continues to be the risk of accidental, unintentional release of information. The study personnel will protect your records and keep all the information in your study file confidential to the greatest extent possible. The chance that this information will be accidentally released is small.

By signing this form, you are authorizing access to your records by the study personnel and the St. Michael’s Hospital Research Ethics Board. Such access will be used only for the purpose of verifying the authenticity and accuracy of the information collected for the study, without violating your confidentiality to the extent permitted by applicable laws and regulations.

Federal and Provincial Data Protection regulations, including the Personal Information Protection and Electronic Documents Act (PIPEDA 2000) and the Personal Health Information Protection Act (PHIPA 2004) of Ontario, protect your personal information. They also give you the right to control the use of your personal information (including personal health information) and require your written permission for this personal information to be collected, used, or disclosed for the purposes of this study, as described in this consent form. You have the right to review and copy your personal information collected in this study. However, if you decide to be in this study or choose to withdraw from it,
your right to look at or copy your personal information related to this study will be delayed until after the research is completed.

The study investigators will keep your study records securely stored on-site for 2 years after the end of the study. They will be kept in a locked office accessible only by approved study personnel. After 2 years, the data will be stored at Recall for 13 years. This company provides secure document management services and is compliant with Health Canada, PIPEDA, and PHIPAA regulations.

PUBLICATIONS OF RESULTS

The results of this study may be published as a scientific paper to help other doctors help their patients. However your privacy will be protected and you will never be identified by name or by a description of you.

POTENTIAL COST OF PARTICIPATION AND REIMBURSEMENT

Everything that we do as part of this study will be done at not cost to you. If you choose to participate in the study, you will receive a small coffee gift card in the amount of $5 as thanks for your participation.

COMPENSATION FOR INJURY

If you suffer a physical injury as a result of the study procedures, medical care will be provided to you in the same manner, as you would ordinarily obtain any other medical treatment. In no way does signing this form waive your legal rights nor relieve the investigator, sponsor or involved institutions from their legal and professional responsibility.

PARTICIPATION AND WITHDRAWAL

Participation in any research is voluntary. If you choose not to participate, you and your family will continue to have access to customary care at St. Michael’s Hospital. If you decide to participate in this study you can change your mind without giving a reason, and you may withdraw from the study at any time without any effect on the care you and your family will receive at St. Michael’s Hospital.

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We may learn new things during the study that you may need to know. If so, you will be notified about any new information in a timely manner. As was already mentioned, we will be sharing our results with your family physician. [You may also be asked to sign a new consent form discussing these new findings, such as
any revisions to the consent forms or study protocol if you decide to continue in the research study.

RESEARCH ETHICS BOARD CONTACT

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STUDY CONTACTS

The study doctor and/or his/her colleagues are available to answer any questions you may have regarding the study procedures. If you have any questions regarding this research study, you may contact Dr. Paul Dorian at (416) 864-5104 and/or the research coordinator, Katherine Allan at (416) 864-5963.
The Family Study: Assessment of the risk of family members of victims of out of hospital cardiac arrest for Coronary Artery Disease and Sudden Cardiac Death

CONSENT TO PARTICIPATE

I acknowledge that the research study described above has been explained to me and that any questions that I have asked have been answered to my satisfaction. I have been informed of the alternatives to participation in this study, including the right not to participate and the right to withdraw without compromising the quality of medical care at St. Michael's Hospital for me and for other members of my family. As well, the potential risks, harms and discomforts have been explained to me and I also understand the potential benefits of participating in this research study. Should I have any other questions about the study, I may call any of the study doctors at (416) 864-5104.

I understand that I have not waived my legal rights nor released the investigators, sponsor, or involved institutions from their legal and professional duties. I know that I may ask now, or in the future, any questions I have about the study. I have been assured that my family member's records will be kept confidential and that no information will be released or printed that would disclose my or my family member's personal identity without my permission unless required by law.

I have been given sufficient time to read and understand the above information, and I will be given a signed copy of this consent.

I would like to participate in the questionnaire portion of the study (please check the appropriate box and initial to indicate your decision):

Yes☐ _______ (Initials)   No☐ _______ (Initials)

I agree to release my health records (please check the appropriate box and initial to indicate your decision):

Yes☐ _______ (Initials)   No☐ _______ (Initials)
Participant Name (Please Print)  Participant Signature

Date (by Participant)  Participant Phone Number

I certify that I have explained the contents of this Informed Consent Form to the above named individual. I have asked whether there are any questions and answered any questions that were raised by this individual.

Name of Person Conducting Informed Consent (Please Print) and Position  Signature of Person Conducting Informed Consent

Date Consent Discussion
The Family Study: Assessment of the incidence, etiology and familial risk for sudden cardiac arrest in young individuals and their family members

Study ID:      Date:       Start Time:       Current Age:       Sex: M/F
First 3 Digits Postal Code: Height: cm/inches (circle one) Weight: lbs/kg (circle one)
Waist Circumference: cm/inches (circle one)

Relationship to patient:
Family Doctor information: Name:
Telephone:
Intersection/City:

Before starting:
The following questions are about your own behaviours or habits that may relate to your risk for heart disease. If I ask you anything that you’d rather not talk to me about, you just tell me you don’t want to talk about it. Is that all right?

1. When was the last time you had a routine medical check-up, undertaken by a doctor or a nurse? (A medical check-up is a physical exam that usually includes at least a blood pressure measurement)
   - Less than 6 months ago
   - 6 months to less than 1 year ago
   - 1 year to less than 2 years ago
   - 2 years to less than 3 years ago
   - 3 or more years ago
   - Never
   - Don’t know
   - Prefer not to answer

2. Prior to the event, had he/she ever had an ECG done in the last year? □ Yes □ No □ Don’t know
   (a) If yes, when? _____ months
   (b) What were the results? (i.e. did the doctor tell him/her what the test results were? For example some changes on the ECG can indicate you may have had a heart attack in the past or that you have a rhythm problem with your heart. Did your doctor mention anything like that?)

3. Are you a: □ current smoker □ ex-smoker (quit >30 days ago) □ non smoker (never smoked)
   If yes to current smoker or ex-smoker, how long have you/have you previously smoked? _____ (years)
   - How many packs per day do you/did you smoke? _____ (packs) Total Pack years: _____
     (Pack years = (packs smoked per day) x (years as a smoker), 20 cigarettes = 1 pack)
   If yes to ex-smoker, how long have you quit smoking? _____ (years)

4. Do you get any regular recreational exercise defined as 30 minutes, one time per week performing a sport or recreational activity? □ Yes □ No □ Don’t know
The Family Study: Assessment of the incidence, etiology and familial risk for sudden cardiac arrest in young individuals and their family members

Please describe:

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5. What is the highest level of education that you have?
   - primary (up to grade 8)
   - secondary (9-12)
   - undergraduate degree/college diploma
   - graduate degree
   - post graduate degree

6. Choose all that apply:
   - Do you live alone or with your
   - spouse
   - partner
   - child(ren)
   - roommate(s)
   - parent(s)
   - sibling(s)
   - in-laws?

7. What is your ethnic background? Choose all that apply:
   - Aboriginal (e.g., First Nations, Métis, Inuit)
   - Arab (e.g., Egypt, Iraq, Jordan, Lebanon)
   - Black (African or Caribbean descent)
   - Chinese
   - Filipino
   - Japanese
   - Korean
   - Latin American/Hispanic
   - South Asian (e.g., India, Sri Lanka, Pakistan, Bangladesh)
   - Southeast Asian (e.g., Malaysia, Indonesia, Vietnam, Cambodia)
   - West Asian (e.g., Turkey, Iran, Afghanistan)
   - White (European descent)
   - Other ethnic group (not listed above); Please describe:
   - Don't know
   - Prefer not to answer

8. Do you ever consume alcohol?  
   - Yes  
   - No  
   - Don't know
   If yes, how many times per week do you consume alcohol? ___/week (If less than once per week, write 0)
   How much alcohol do you consume at each sitting? ____
   How many years have you been consuming alcohol? ___

Details:
_____________________________________________________________________________________
_____________________________________________________________________________________
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The Family Study: Assessment of the incidence, etiology and familial risk for sudden cardiac arrest in young individuals and their family members

Before starting:
The following questions are about your own medical history. If I ask you anything that you’d rather not talk to me about, you just tell me you don’t want to talk about it. Is that all right?

Medical History:
Screening for heart risk factors:

If yes for the following questions, please write in the age you were diagnosed, the number of events (where applicable) and describe the event.

9. Are you currently taking any medications prescribed to you by a doctor or nurse?
   □ Yes  □ No  □ Don’t know

   If yes, what are your cardiac medications that you take on a regular basis?
   □ ACE inhibitor  □ ARB  □ beta-blocker  □ calcium channel blocker  □ cholesterol medication
   □ anticoagulant  □ diabetes medication  □ diuretic  □ antiplatelet  □ antirhythmic  □ nitrate

10. Have you ever fainted (lost consciousness) suddenly or unexpectedly? □ Yes  □ No  □ Don’t know
   Was it a cardiac syncope? □ Yes  □ No  □ Don’t know  □ N/A
   If yes, please describe:
   __________________________________________________________________________
   __________________________________________________________________________
   __________________________________________________________________________
   __________________________________________________________________________

11. Has your doctor ever said you have one of the following and/or are you currently taking any medications for the following conditions (If yes, please indicate the age of diagnosis):
(a) Chest pain (angina)? Dx: □ Yes  □ No  □ Don’t know  Age: ____
(b) Has anyone ever told you that you have an irregular heartbeat (arrhythmia)? □ Yes  □ No  □ Don’t know
(c) High blood pressure? Dx: □ Yes  □ No  □ Don’t know  Age: ____
(d) High blood sugar (diabetes)? Dx: □ Yes  □ No  □ Don’t know  Age: ____
(e) High cholesterol? Dx: □ Yes  □ No  □ Don’t know  Age: ____

12. Did you ever see a heart specialist? □ Yes  □ No  □ Don’t know

   Have you ever been hospitalized because of your heart?
   □ Yes, for less than 24 hours  □ Yes, for more than 24 hours  □ No  □ Don’t know  Age: ____
   If yes, can you please tell me why you were hospitalized on the next page?

   Has anyone ever told you that you have blocked arteries in your heart (CAD)?
   □ Yes  □ No  □ Don’t know  Age: ____  If yes, can you please describe on the next page?

   Have you ever had a procedure called Percutaneous Coronary Intervention or PCI (an angiogram or angioplasty)? □ Yes  □ No  □ Don’t know  Age: ____ (procedure where they look at the arteries in your heart for blockages)

   Have you ever had a heart bypass (CABG)? □ Yes  □ No  □ Don’t know  Age: ____
   If yes, can you please describe on the next page?
**The Family Study**: Assessment of the incidence, etiology and familial risk for sudden cardiac arrest in young individuals and their family members

Have you ever had a heart failure?  □ Yes  □ No  □ Don’t know  Age: ___
If **yes**, can you please describe on the next page?

Have you ever had any congenital heart issues?  □ Yes  □ No  □ Don’t know  Age: ___
If **yes**, can you please describe on the next page?

Have you ever had valvular heart disease (problems with your heart valves)?  □ Yes  □ No  □ Don’t know  Age: ___  If **yes**, can you please describe on the next page

Please describe:
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If more, please use the pages at the end of questionnaire and label as question 12:

13. Have you ever had a stroke?  □ Yes  □ No  □ Don’t know
If **yes**, number of strokes: ____  Age(s) of each stroke: _________________

Please describe:
____________________________________________________________________________________
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If more, please use the pages at the end of questionnaire and label as question 13:

14. Have you ever had a non fatal heart attack (non fatal MI)?  □ Yes  □ No  □ Don’t know
If **yes**, number of attacks: ____  Age(s) of each attack: ______________

Please describe:
____________________________________________________________________________________
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____________________________________________________________________________________
If more, please use the pages at the end of questionnaire and label as question 14:
**The Family Study:** Assessment of the incidence, etiology and familial risk for sudden cardiac arrest in young individuals and their family members

**Before starting:**
The following questions are about your family’s medical history i.e. if they have a history of heart problems. If I ask you anything that you’d rather not talk to me about, you just tell me you don’t want to talk about it. Is that all right?

Please indicate the age of each of your siblings, do not include yourself. For deceased relatives, please include a “D” next to the age.

<table>
<thead>
<tr>
<th>Relationship</th>
<th>Age</th>
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<tbody>
<tr>
<td>Brother 1</td>
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<td>Sister 1</td>
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<td>Brother 2</td>
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<td>Maternal Sister 2</td>
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</table>

**Family History:**

15. **Are any of your first degree relatives (parents, siblings, children) being treated for or have received a diagnosis for or are taking any medications for:**

Please use the chart from the previous page to fill in relationship, i.e. bro1 for Brother 1, or p-bro1 for Paternal Brother 1.

(a) **high blood pressure**

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<tr>
<th>Relationship</th>
<th>Age of diagnosis</th>
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If more, please use the pages at the end of questionnaire and label as question 15 (a):

(b) **high blood sugar**

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<th>Relationship</th>
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If more, please use the pages at the end of questionnaire and label as question 15 (b):

16. **heart disease** (for example has anyone ever had an angiogram or been hospitalized because of their heart or sees a heart specialist on a regular basis).

<table>
<thead>
<tr>
<th>Relationship</th>
<th>Age of diagnosis; circle all applicable and list if not mentioned; please describe.</th>
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Family Study: Control Medical History
SMH version Dec 30, 2013
The Family Study: Assessment of the incidence, etiology and familial risk for sudden cardiac arrest in young individuals and their family members

__________________________  Age: ____, saw heart specialist, hospitalization for less than 24 hours, hospitalization for more than 24 hours, CAD (blocked arteries), PCI (angiogram and/or angioplasty), CABG (heart bypass), heart failure, congenital heart issues, valvular heart disease, please describe each item.

___________________________________________________________________________________
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__________________________  Age: ____, saw heart specialist, hospitalization for less than 24 hours, hospitalization for more than 24 hours, CAD (blocked arteries), PCI (angiogram and/or angioplasty), CABG (heart bypass), heart failure, congenital heart issues, valvular heart disease; please describe each item.

___________________________________________________________________________________
___________________________________________________________________________________
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__________________________  Age: ____, saw heart specialist, hospitalization for less than 24 hours, hospitalization for more than 24 hours, CAD (blocked arteries), PCI (angiogram and/or angioplasty), CABG (heart bypass), heart failure, congenital heart issues, valvular heart disease; please describe each item.

___________________________________________________________________________________
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If more, please use the pages at the end of questionnaire and label as question 16:

17. stroke □ Yes □ No □ Don't know  **If yes:**
   Relationship  Number of strokes, age(s) of each stroke
   ____________________  ____________________
   ____________________  ____________________
   ____________________  ____________________
   ____________________  ____________________
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If more, please use the pages at the end of questionnaire and label as question 17:

18. **non fatal heart attack (non fatal MI)** By non fatal heart attack we mean: when the arteries to the heart become blocked and require intervention in a hospital setting and the person does not die.
   □ Yes □ No □ Don't know  **If yes:**
   Relationship  Number of attacks, age(s) of each attack
   ____________________  ____________________
   ____________________  ____________________
   ____________________  ____________________
   ____________________  ____________________
   ____________________  ____________________
   ____________________  ____________________
The Family Study: Assessment of the incidence, etiology and familial risk for sudden cardiac arrest in young individuals and their family members

Completed By (Initials):_________

19. Have there been any non sudden cardiac deaths in his/her relative’s first degree relatives (parents, siblings, children). By this we mean: when the arteries to the heart become blocked and require intervention in a hospital setting and the person dies as a result (i.e. deaths due to MI which occur in hospital; deaths due to Heart Failure or other cardiovascular deaths)

☐ Yes  ☐ No  ☐ Don't know  If yes:
Relationship  Age at death, please describe

If more, please use the pages at the end of questionnaire and label as question 18:

20. Have there been any sudden cardiac deaths in your first degree relatives (parents, siblings, children)? By sudden cardiac death we mean: person dies suddenly and unexpectedly within one hour of the onset of symptoms or were in their normal state of health in the 24 hours prior to being found dead.

☐ Yes  ☐ No  ☐ Don’t know  If yes:
Relationship  Age at death; circle all applicable and list if not mentioned; please describe.

If more, please use the pages at the end of questionnaire and label as question 19:
The Family Study: Assessment of the incidence, etiology and familial risk for sudden cardiac arrest in young individuals and their family members

If more, please use the pages at the end of questionnaire and label as question 20:

21. After answering all of the questions in this questionnaire, is there anything relevant about your heart health or family’s heart health that you think I should know?
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22. In the future, would it be possible for us to get a blood sample from you? ☐Yes ☐No

End Time:                                          Duration:
WHAT IS THE PURPOSE OF THIS STUDY?

We are conducting this research study in order to look at and better understand the medical or environmental causes (risk factors) that are associated with the sudden stopping of the heart (cardiac arrest). The main goal of the study is to try and figure out what each person’s medical and environmental problems (risk factors) are, using questionnaires, so that we will know if they are in danger of dying suddenly.

WHY IS THE STUDY BEING DONE?

The most common cause of unexpected, sudden death is the sudden stoppage of the heart. In the majority of cases, the heart stops pumping when it goes into a dangerous rhythm. The most likely cause of this dangerous rhythm is a blockage in the tubes that carry blood to the heart itself. We want to understand why certain people’s hearts suddenly stop functioning, causing them to die suddenly, in order to eventually prevent these events from happening in the first place.

We know that medical problems like having high blood pressure or high blood sugar can cause blockages in the heart and we also know that these problems tend to run in families. This means for example that if your mother or father or brother or sister has high blood pressure, you might too. We also know that your home environment can affect your

WHERE CAN I GET MORE INFORMATION?

If you would like to receive a more detailed account of the research, please do not hesitate to contact the study coordinator Katherine Allan by e-mail at allank@smh.ca or by phone at 416.864.5963.
chances of having heart blockages and dying suddenly. If, for example, you are overweight or smoke you are also likely to have heart blockages down the road.

Although you yourself have not experienced a cardiac arrest (sudden stopping of the heart) this research may detect an underlying medical or environmental problem that may put you at risk of experiencing a cardiac arrest in the future. Early detection and treatment may reduce the risk of an unexplained cardiac arrest in the future. For this reason, we will be sharing the results that we come up with in your case with your family physician, regardless of whether those results are normal or abnormal. We will also direct you to on-line resources and provide you with written information about managing the risk factors that are associated with sudden cardiac arrest.

In our case-control study, you are part of the control population or comparison group that we will be using for the victims who have had cardiac arrests. A case-control is a type of study design. In a case-control study, individuals with a defined characteristic (victims of cardiac arrest) are matched with people who do not have the condition but are otherwise similar (the ‘controls’ i.e. you). Further data is then collected on those individuals (cardiac arrest victims and controls) and the groups are compared to find out if other characteristics (perhaps a history of smoking) are also different between the two groups.

**WHAT AM I REQUIRED TO DO TO PARTICIPATE?**

If you choose to participate in this research study, we will need to ask you detailed questions about your medical history. These questionnaires can be completed over the phone or face-to-face and will take approximately 30 minutes of your time. You are part of the control population or comparison group that we will be using for the victims who have had cardiac arrests.

If you allow us to do so, we will contact you by telephone to discuss participating in the study. If you agree to participate, you will need to sign and date a consent form.

All persons associated with this study, including study investigators, coordinators, nurses and delegates (hereby referred to as “study personnel”) and the study sponsor are committed to respecting your privacy. No other persons will have access to your personal health information or other identifying personal information without your consent, unless required by law.

Any personal health information collected from your medical records, laboratory samples or other information related to you will be coded by study numbers to ensure that persons outside of the study (i.e., sponsors) will not be able to identify you. The study personnel are in control of the study code key, which is needed to connect your personal health information to you.

**POTENTIAL COST OF PARTICIPATION AND REIMBURSEMENT**

Everything that we do as part of this study will be done at no cost to you. No payment or reimbursement will be made to you for participating in this study.

**WHAT ARE MY RIGHTS TO WITHDRAW PARTICIPATION IN THIS RESEARCH STUDY?**

Participation in any research is voluntary. If you choose not to participate, you and your family will continue to have access to customary care at St. Michael’s Hospital. If you decide to participate in this study you can change your mind without giving a reason, and you may withdraw from the study at any time without any effect on the care you and your family will receive at St. Michael’s Hospital.

**WHAT ARE MY RIGHTS AS A PARTICIPANT?**

If you would like to discuss this further, please contact the Chair of the Research Ethics Board at St. Michael’s Hospital 416.864.6060 x2557.
Assessment of the risk of family members of victims of out of hospital cardiac arrest for Coronary Artery Disease and Sudden Cardiac Death

(FAMILY STUDY)

You may be eligible for this clinical research study if you:

1. Are 18 years of age or older

2. Are healthy with no major medical problems.

3. Do not have any heart disease that you know of

Please Contact:

Principal Investigator:
Dr Paul Dorian

Study Coordinator:
Katherine Allan, pager 416-685-4974, ext 5963
Hello Mrs./Mr. (participants name), this is (research team member’s name) calling from St. Michael’s Hospital regarding the FAMILY study. Our records show that (patient’s name) was recently treated by Toronto Emergency Medical Services and/or Toronto Fire Services personnel for an out-of-hospital cardiac arrest (sudden stopping of the heart). I understand this phone call is coming at a time that is very difficult for you and your family. However, I wish to provide you with information concerning a research study, which is trying to figure out why certain people’s hearts stop so suddenly (cardiac arrest).

We provided or couriered a study notification letter to you and in that letter we indicated that we would be giving you a call. Do you have a copy of this study notification letter? If you do not have a copy, I’ll gladly resend you another one. I’m calling today just to ask how you are doing and to ask you if you would like to participate in this research study. Your participation is completely voluntary and you can choose to opt out at any time. Also if you wish to opt out of the study at a future date, please call 416-864-5963 and provide your full name and the name of your relative who had the cardiac arrest. Is it O.K. if I begin describing the study? (if not, is there another time that would be convenient for you to call back?)
Hello Mrs./Mr. (participants name), this is (research team member’s name) calling from St. Michael’s Hospital regarding the FAMILY study. Our records show that (patient’s name) was recently treated by Toronto Emergency Medical Services and/or Toronto Fire Services personnel for an out-of-hospital cardiac arrest (sudden stopping of the heart). I understand this phone call is coming at a time that is very difficult for you and your family. Please accept our sincerest condolences. However, I wish to provide you with information concerning a research study, which is trying to figure out why certain people’s hearts stop so suddenly (cardiac arrest).

We provided or couriered a study notification letter to you and in that letter we indicated that we would be giving you a call. Do you have a copy of this study notification letter? If you do not have a copy, I’ll gladly resend you another one. I’m calling today just to ask how you are doing and to ask you if you would like to participate in this research study. Your participation is completely voluntary and you can choose to opt out at any time. Also if you wish to opt out of the study at a future date, please call 416-864-5963 and provide your full name and the name of your relative who had the cardiac arrest. Is it O.K. if I begin describing the study? (If not, is there another time that would be convenient for you to call back?)
The Family Study: Assessment of the risk of family members of victims of out of hospital cardiac arrest for Coronary Artery Disease and Sudden Cardiac Death

Study ID: Date: Start Time: Current Age: Sex: M/F
First 3 Digits Postal Code: Height: cm/inches (circle one) Weight: lbs/kg (circle one)
Waist Circumference: cm/inches (circle one)
Family Doctor information: Name:
Telephone:
Intersection/City:

Before starting:
The following questions are about your own behaviours or habits that may relate to your risk for heart disease. If I ask you anything that you’d rather not talk to me about, you just tell me you don’t want to talk about it. Is that all right?

1. Prior to the event, when was the last time you had a routine medical check-up, undertaken by a doctor or a nurse? (A medical check-up is a physical exam that usually includes at least a blood pressure measurement)
   - [ ] Less than 6 months ago
   - [ ] 6 months to less than 1 year ago
   - [ ] 1 year to less than 2 years ago
   - [ ] 2 years to less than 3 years ago
   - [ ] 3 or more years ago
   - [ ] Never
   - [ ] Don’t know
   - [ ] Prefer not to answer

2. Prior to the event, have you ever had an ECG done in the last year? [ ] Yes [ ] No [ ] Don’t know
   (a) If yes, when? _____ months
   (b) What were the results? (i.e. did the doctor tell you what the test results were? For example some changes on the ECG can indicate you may have had a heart attack in the past or that you have a rhythm problem with your heart. Did your doctor mention anything like that?)
   
   ____________________________________________________________________________________
   ____________________________________________________________________________________
   ____________________________________________________________________________________
   ____________________________________________________________________________________

3. Prior to the event, were you a:
   - [ ] current smoker
   - [ ] ex-smoker (quit >30 days ago)
   - [ ] non smoker (never smoked)
   If yes to current smoker or ex-smoker, how long had you previously smoked? _____ (years)
   How many packs per day did you smoke? _____ (packs) Total Pack years: _____
   (Pack years = (packs smoked per day) x (years as a smoker), 20 cigarettes = 1 pack)
   If yes to ex-smoker, how long had you quit smoking? _____ (years)

4. Prior to the event, what was your weight? lbs/kg (circle one)
5. Prior to the event, did you get any regular recreational exercise defined as 30 minutes, one time per week performing a sport or recreational activity? □ Yes  □ No  □ Don’t know

Please describe:

____________________________________________________________________________________
____________________________________________________________________________________
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6. What is the highest level of education that you have?
   □ primary (up to grade 8)  □ secondary (9-12)  □ undergraduate degree/college diploma
   □ graduate degree  □ post graduate degree

7. Choose all that apply: Prior to the event, did you live □ alone or with your □ spouse □ partner
   □ child(ren)  □ roommate(s)  □ parent(s)  □ sibling(s)  □ in-laws?

8. What is your ethnic background? Choose all that apply:
   □ Aboriginal (e.g., First Nations, Métis, Inuit)
   □ Arab (e.g., Egypt, Iraq, Jordan, Lebanon)
   □ Black (African or Caribbean descent)
   □ Chinese
   □ Filipino
   □ Japanese
   □ Korean
   □ Latin American/Hispanic
   □ South Asian (e.g., India, Sri Lanka, Pakistan, Bangladesh)
   □ Southeast Asian (e.g., Malaysia, Indonesia, Vietnam, Cambodia)
   □ West Asian (e.g., Turkey, Iran, Afghanistan)
   □ White (European descent)
   □ Other ethnic group (not listed above); Please describe:
   □ Don’t know
   □ Prefer not to answer

9. Prior to the event, did you ever consume alcohol? □ Yes  □ No  □ Don’t know
If yes, how many times per week did you consume alcohol? ___/week (If less than once per week, write 0)
   How much alcohol did you consume at each sitting? ___
   How many years had you been consuming alcohol? ___

Details:

____________________________________________________________________________________
____________________________________________________________________________________
____________________________________________________________________________________
____________________________________________________________________________________
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Before starting:
The following questions are about your own medical history. If I ask you anything that you’d rather not talk to me about, you just tell me you don’t want to talk about it. Is that all right?

Medical History:
Screening for heart risk factors:

If yes for the following questions, please write in the age you were diagnosed, the number of events (where applicable) and describe the event.

10. (a) Prior to the event, were you taking any medications prescribed to you by a doctor or nurse?
   □ Yes  □ No  □ Don’t know
   If yes, what were your cardiac medications that you took on a regular basis?
   □ ACE inhibitor  □ ARB  □ beta-blocker  □ calcium channel blocker  □ cholesterol medication
   □ anticoagulant  □ diabetes medication  □ diuretic  □ antiplatelet  □ antirhythmic  □ nitrate

10. (b) What are your current medications?
   □ ACE inhibitor  □ ARB  □ beta-blocker  □ calcium channel blocker  □ cholesterol medication
   □ anticoagulant  □ diabetes medication  □ diuretic  □ antiplatelet  □ antirhythmic  □ nitrate

11. (a) Prior to the event, have you ever fainted (lost consciousness) suddenly or unexpectedly?
   □ Yes  □ No  □ Don’t know
   Was it a cardiac syncope? □ Yes  □ No  □ Don’t know  □ N/A  If yes, please describe:
   __________________________________________________________
   __________________________________________________________
   __________________________________________________________

(b) After the event, have you ever fainted (lost consciousness) suddenly or unexpectedly?
   □ Yes  □ No  □ Don’t know
   Was it a cardiac syncope? □ Yes  □ No  □ Don’t know  □ N/A  If yes, please describe:
   __________________________________________________________
   __________________________________________________________
   __________________________________________________________
   __________________________________________________________

12. Prior to the event, has your doctor ever said you have one of the following and/or are you currently taking any medications for the following conditions (If yes, please indicate the age of diagnosis):

(a) Chest pain (angina)? Dx: □ Yes  □ No  □ Don’t know  Age: ____
(b) Has anyone ever told you that you have an irregular heartbeat (arrhythmia)? □ Yes  □ No  □ Don’t know. If yes please describe:

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(c) High blood pressure? Dx: □ Yes □ No □ Don’t know Age: ____
(d) High blood sugar (diabetes)? Dx: □ Yes □ No □ Don’t know Age: ____
(e) High cholesterol? Dx: □ Yes □ No □ Don’t know Age: _____

13. (a) Prior to the event, has anyone ever told you that you have blocked arteries in your heart (CAD)?
   □ Y □ N □ Don’t know Age: ___ If yes, can you please describe on the next page?

Prior to the event, have you ever had a procedure called Percutaneous Coronary Intervention or PCI (an angiogram or angioplasty)? □ Yes □ No □ Don’t know Age: ____ (procedure where they look at the arteries in your heart for blockages)

Prior to the event, have you ever had a heart bypass (CABG)? □ Yes □ No □ Don’t know Age: ____
   If yes, can you please describe on the next page?

Prior to the event, did you ever see a heart specialist? □ Yes □ No □ Don’t know

Prior to the event, have you ever been hospitalized because of your heart?
□ Yes, for less than 24 hours □ Yes, for more than 24 hours □ No □ Don’t know Age: ____
   If yes, can you please tell me why you were hospitalized on the next page?

Prior to the event, have you ever had a heart failure? □ Yes □ N □ o Don’t know Age: ____
   If yes, can you please describe on the next page?

Prior to the event, have you ever had any congenital heart issues? □ Yes □ No □ Don’t know Age: ____
   If yes, can you please describe on the next page?

Prior to the event, have you ever had valvular heart disease (problems with your heart valves)?
□ Yes □ No □ Don’t know Age: ____
   If yes, can you please describe on the next page?

If yes to any of the above, please describe:
____________________________________________________________________________________
____________________________________________________________________________________
____________________________________________________________________________________
____________________________________________________________________________________
____________________________________________________________________________________

If more, please use the pages at the end of questionnaire and label as question 13a:

(a) After the event, has anyone ever told you that you have blocked arteries in your heart (CAD)?
   □ Y □ N □ Don’t know Age: ___ If yes, can you please describe on the next page?

After the event, have you ever had a procedure called Percutaneous Coronary Intervention or PCI (an angiogram or angioplasty)? □ Yes □ No □ Don’t know Age: ____ (procedure where they look at the arteries in your heart for blockages)
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After the event, have you ever had a heart bypass (CABG)? □ Yes □ No □ Don’t know Age: ___
If yes, can you please describe on the next page?

After the event, did you ever see a heart specialist? □ Yes □ No □ Don’t know

After the event did you have a device implanted called an internal defibrillator?
□ Yes □ No □ Don’t know
If yes please describe:

If yes to ICD, ask: Have you ever had any shocks from your defibrillator?
□ Yes □ No □ Don’t know
If yes please describe:

After the event, have you ever been hospitalized because of your heart?
□ Yes, for less than 24 hours □ Yes, for more than 24 hours □ No □ Don’t know Age: ___
If yes, can you please tell me why you were hospitalized on the next page?

After the event, have you ever had a heart failure? □ Yes □ No □ Don’t know Age: ___
If yes, can you please describe on the next page?

After the event, have you ever had any congenital heart issues? □ Yes □ No □ Don’t know Age: ___
If yes, can you please describe on the next page?

Prior to the event, have you ever had valvular heart disease (problems with your heart valves)?
□ Yes □ No □ Don’t know Age: ___
If yes, can you please describe on the next page?

If yes to any of the above, please describe:
____________________________________________________________________________________
____________________________________________________________________________________
____________________________________________________________________________________
____________________________________________________________________________________
____________________________________________________________________________________
____________________________________________________________________________________
____________________________________________________________________________________

If more, please use the pages at the end of questionnaire and label as question 13b:

14. Prior to the event, have you ever had a stroke? □ Yes □ No □ Don’t know
If yes, number of strokes: ____ Age(s) of each stroke: _________________

Please describe:
____________________________________________________________________________________
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If more, please use the pages at the end of questionnaire and label as question 14:

15. Prior to the event, have you ever had a non fatal heart attack (non fatal MI)?
   - Yes
   - No
   - Don’t know
   If yes, number of attacks: ____ Age(s) of each attack: __________

   Please describe:

   ______________________________________________________________________

   ______________________________________________________________________

   ______________________________________________________________________

If more, please use the pages at the end of questionnaire and label as question 15:

Before starting:
The following questions are about your family’s medical history i.e. if they have a history of heart problems. If I ask you anything that you’d rather not talk to me about, you just tell me you don’t want to talk about it. Is that all right?

Please indicate the age of each of your siblings, do not include yourself. For deceased relatives, please include a “D” next to the age.

☐ Brother1 ___ (age) ☐ Sister1 ___ (age) ☐ Son1 ___ (age) ☐ Daughter1 ___ (age)
☐ Brother2 ___ (age) ☐ Sister2 ___ (age) ☐ Son2 ___ (age) ☐ Daughter2 ___ (age)
☐ Brother3 ___ (age) ☐ Sister3 ___ (age) ☐ Son3 ___ (age) ☐ Daughter3 ___ (age)
☐ Brother4 ___ (age) ☐ Sister4 ___ (age) ☐ Son4 ___ (age) ☐ Daughter4 ___ (age)
☐ Brother5 ___ (age) ☐ Sister5 ___ (age) ☐ Son5 ___ (age) ☐ Daughter5 ___ (age)
☐ Paternal Brother1 ___ (age) ☐ Maternal Brother1 ___ (age) ☐ Paternal Sister1 ___ (age) ☐ Maternal Sister1 ___ (age)
☐ Paternal Brother2 ___ (age) ☐ Maternal Brother2 ___ (age) ☐ Paternal Sister2 ___ (age) ☐ Maternal Sister2 ___ (age)

Family History:
16. Are any of your first degree relatives (parents, siblings, children) being treated for or have received a diagnosis for or are taking any medications for:

Please use the chart on the previous page to fill in relationship, i.e. bro1 for Brother1, or p-bro1 for Paternal Brother1.

(a) high blood pressure ☐ Yes ☐ No ☐ Don’t know
   If yes:
   Relationship
   Age of diagnosis
   __________
   __________
   __________

If more, please use the pages at the end of questionnaire and label as question 16 (a):
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(b) high blood sugar ☐ Yes ☐ No ☐ Don’t know If yes:
   Relationship Age of diagnosis
   __________ ______________________________
   __________ ______________________________
   __________ ______________________________
   __________ ______________________________
If more, please use the pages at the end of questionnaire and label as question 16 (b):

17. heart disease (for example has anyone ever had an angiogram or been hospitalized because of their heart or sees a heart specialist on a regular basis).
   ☐ Yes ☐ No ☐ Don’t know If yes:
   Relationship Age of diagnosis; circle all applicable and list if not mentioned; please describe.
   __________ Age: ____, saw heart specialist, hospitalization for less than 24 hours, hospitalization for more than 24 hours, CAD (blocked arteries), PCI (angiogram and/or angioplasty), CABG (heart bypass), heart failure, congenital heart issues, valvular heart disease; please describe each item.
   __________ Age: ____, saw heart specialist, hospitalization for less than 24 hours, hospitalization for more than 24 hours, CAD (blocked arteries), PCI (angiogram and/or angioplasty), CABG (heart bypass), heart failure, congenital heart issues, valvular heart disease; please describe each item.
   __________ Age: ____, saw heart specialist, hospitalization for less than 24 hours, hospitalization for more than 24 hours, CAD (blocked arteries), PCI (angiogram and/or angioplasty), CABG (heart bypass), heart failure, congenital heart issues, valvular heart disease; please describe each item.
If more, please use the pages at the end of questionnaire and label as question 17:

18. stroke ☐ Yes ☐ No ☐ Don’t know If yes:
   Relationship Number of strokes; age(s) of each stroke
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19. **non fatal heart attack** (non fatal MI) By non fatal heart attack we mean: when the arteries to the heart become blocked and require intervention in a hospital setting and the person does not die.

□ Yes  □ No  □ Don’t know  **If yes:**

Relationship  Number of attacks; age(s) of each attack

__________________________________________________________________________________
__________________________________________________________________________________
__________________________________________________________________________________
__________________________________________________________________________________

If more, please use the pages at the end of questionnaire and label as question 19:

20. Have there been any **non sudden cardiac deaths** in his/her relative’s first degree relatives (parents, siblings, children). **By this we mean:** when the arteries to the heart become blocked and require intervention in a hospital setting and the person dies as a result (i.e. deaths due to MI which occur in hospital; deaths due to Heart Failure or other cardiovascular deaths)

□ Yes  □ No  □ Don’t know  **If yes:**

Relationship  Age at death, please describe

__________________________________________________________________________________
__________________________________________________________________________________
__________________________________________________________________________________

If more, please use the pages at the end of questionnaire and label as question 20:

21. Have there been any **sudden cardiac deaths** in your first degree relatives (parents, siblings, children)? By sudden cardiac death we mean: person dies suddenly and unexpectedly within one hour of the onset of symptoms or were in their normal state of health in the 24 hours prior to being found dead.

□ Yes  □ No  □ Don’t know  **If yes:**

Relationship  Age at death; circle all applicable and list if not mentioned; please describe.

______________
Age: ____, collapsed at home, 911 called, person went to hospital, conscious/unconscious on way to hospital, died in emergency, died later in hospital, died in field (at location), survived; please describe each item.

__________________________________________________________________________________
__________________________________________________________________________________
__________________________________________________________________________________
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____________  Age: ____, collapsed at home, 911 called, person went to hospital, conscious/unconscious on way to hospital, died in emergency, died later in hospital, died in field (at location), survived; please describe each item.

___________________________________________________________________________________
___________________________________________________________________________________
___________________________________________________________________________________

____________  Age: ____, collapsed at home, 911 called, person went to hospital, conscious/unconscious on way to hospital, died in emergency, died later in hospital, died in field (at location), survived; please describe each item.

___________________________________________________________________________________
___________________________________________________________________________________
___________________________________________________________________________________

If more, please use the pages at the end of questionnaire and label as question 21:

Before starting:
We are trying to learn more about why certain people’s hearts stop suddenly (cardiac arrest). This will involve me asking you some questions about what you remember happening in the minutes right before your cardiac arrest as well as further back, say in the weeks to months before. If I ask you anything that you’d rather not talk to me about, you just tell me you don’t want to talk about it. Is that all right?

Event History:

22. Please describe the event:
___________________________________________________________________________________
___________________________________________________________________________________
___________________________________________________________________________________
___________________________________________________________________________________
___________________________________________________________________________________
___________________________________________________________________________________
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If you have more details, please use the pages at the end of questionnaire and label as question 22:

23. Choose all that apply: Who provided information about the event?
☑ Patient  ☐ Spouse  ☐ Parent(s)  ☐ Sibling(s)  ☐ Child(ren)  ☐ Doctor/Registered Nurse  ☐ EMS  ☐ Coroner  ☐ Other: ______________________

Total number of sources: ______________________

Did one or more of the above individuals witness the event? Were they told about the event by a third party?  ☐ Witness  ☐ Told

24. In the 60 minutes prior to the event, did you experience any new symptoms? By new symptoms we mean any symptoms that you would not normally feel in your current state of health.  ☐ Yes  ☐ No  ☐ Don’t know

(If you filled out No, please fill in: 25. N/A, 26. 0 minutes)

If yes, in the 60 minutes prior to the event, did you experience any of the following new symptoms:
☐ shortness of breath/air hunger/can’t catch your breath/gasping for air
☐ chest pain/discomfort/squeezing/dull ache/tightness
☐ arm pain/discomfort/ache
☐ leg pain/discomfort/ache
☐ back pain/discomfort/ache
☐ stomach pain/discomfort/ache/ nausea
☐ neck/head pain/discomfort
☐ palpitations/heart racing/fluttering
☐ vomiting
☐ dizziness/ light headed/impending loss of consciousness/inability to stand up
☐ sweating
☐ fatigue/weakness/tiredness
☐ hot flash/cold flash/tingling/numbness

Please Describe:
____________________________________________________________________________________
____________________________________________________________________________________
____________________________________________________________________________________
____________________________________________________________________________________

25. Did you complain to anyone about your symptoms?  ☐ Yes  ☐ No  ☐ Don’t know  ☐ N/A (no symptoms)

26. When did these symptoms start prior to your collapse?  ___ minutes  ☐ Don’t know

27. What was he/she doing in the hour prior to the onset of his/her symptoms?
☐ Rest
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☐ Vigorous physical exertion _____ minutes prior to event ☐ Don’t know
☐ Moderate physical exertion _____ minutes prior to event ☐ Don’t know

Rest (sitting or standing, does not cause a change in breathing)

Vigorous physical activities refer to activities that take hard physical effort and make you breath much harder than normal (heavy lifting, digging, aerobics or fast bicycling)

Moderate physical activities refer to activities that take moderate physical effort and make you breathe somewhat harder (carrying light loads, bicycling at a regular pace or doubles tennis)

Please Describe:
___________________________________________________________________________________
___________________________________________________________________________________
___________________________________________________________________________________

28. (a) Were you under any stress? ☐ Yes ☐ No ☐ Don’t know

(b) Were you under any acute emotional stress in the hour prior to the onset of your symptoms? By this we mean an emotional state or stressor that started within 60 minutes of your event. For example, this could mean you were in conflict with someone at the time of your arrest or that you received news of something that caused you to become very angry/sad/happy/excited. A chronic emotional stress refers to something ongoing such as work/health related stress.

☐ Yes ☐ No ☐ Don’t know ☐ N/A
How long before? ____ minutes prior to event ☐ Don’t know
Emotion experienced: ☐ Anger ☐ Sadness ☐ Grief ☐ Excitement ☐ Happiness ☐ Other ☐ N/A

Please Describe:
___________________________________________________________________________________
___________________________________________________________________________________
___________________________________________________________________________________
___________________________________________________________________________________

29. In the 60 minutes to 24 hours prior to the event, did you experience any new symptoms? By new symptoms we mean any symptoms that you would not normally feel in your current state of health.

☐ Yes ☐ No ☐ Don’t know

(If you filled out No, please fill in: 30. N/A, 31. N/A)

If yes, in the 60 minutes to 24 hours prior to the event, did you experience any of the following new symptoms:

☐ shortness of breath/air hunger/can’t catch your breath/gasping for air
☐ chest pain/discomfort/squeezing/dull ache/tightness
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☐ arm pain/discomfort/ache
☐ leg pain/discomfort/ache
☐ back pain/discomfort/ache
☐ stomach pain/discomfort/ache/ nausea
☐ neck/head pain/discomfort
☐ palpitations/heart racing/fluttering
☐ vomiting
☐ dizziness/ light headed/impending loss of consciousness/inability to stand up
☐ sweating
☐ fatigue/weakness/tiredness
☐ hot flash/cold flash/tingling/numbness

Please Describe:
____________________________________________________________________________________
____________________________________________________________________________________
____________________________________________________________________________________
____________________________________________________________________________________
____________________________________________________________________________________

30. Did you seek medical care for any new symptoms? ☐ Yes ☐ No ☐ Don't know ☐ N/A

31. Did you complain to anyone about these symptoms? ☐ Yes ☐ No ☐ Don't know ☐ N/A
If yes, to whom? ☐ Family members ☐ Family doctor ☐ Friend ☐ Co-worker ☐ Other: __________

32. In the 24 hours to 7 days prior to the event, did you experience any new symptoms? By new symptoms we mean any symptoms that you would not normally feel in your current state of health.
☐ Yes ☐ No ☐ Don't know

(If you filled out No, please fill in: 33. N/A)

If yes, in the 24 hours to 7 days prior to the event, did you experience any of the following new symptoms:
☐ shortness of breath/air hunger/can’t catch your breath/gasping for air
☐ chest pain/discomfort/squeezing/dull ache/tightness
☐ arm pain/discomfort/ache
☐ leg pain/discomfort/ache
☐ back pain/discomfort/ache
☐ stomach pain/discomfort/ache/ nausea
☐ neck/head pain/discomfort
☐ palpitations/heart racing/fluttering
☐ vomiting
☐ dizziness/ light headed/impending loss of consciousness/inability to stand up
☐ sweating
☐ fatigue/weakness/tiredness
☐ hot flash/cold flash/tingling/numbness
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Please Describe:
____________________________________________________________________________________
____________________________________________________________________________________
____________________________________________________________________________________
____________________________________________________________________________________
____________________________________________________________________________________
____________________________________________________________________________________
____________________________________________________________________________________

33. Did you seek medical care for any new symptoms? □ Yes □ No □ Don’t know □ N/A

If **yes**, choose all that apply: □ Saw family doctor □ Went to Hospital
□ Received a new diagnosis from ____________ □ Other: ____________

34. In the **weeks to months** prior to the event, did you experience any **new** symptoms? By new symptoms we mean any symptoms that you would not normally feel in your current state of health.
□ Yes □ No □ Don’t know

(If you filled out No, please fill in: 35. N/A)

If **yes**, in the **weeks to months** prior to the event, did you experience any of the following **new** symptoms:
□ shortness of breath/air hunger/can’t catch your breath/gasping for air
□ chest pain/discomfort/squeezing/dull ache/tightness
□ arm pain/discomfort/ache
□ leg pain/discomfort/ache
□ back pain/discomfort/ache
□ stomach pain/discomfort/ache/ nausea
□ palpitations/heart racing/fluttering
□ vomiting
□ dizziness/ light headed/impending loss of consciousness/inability to stand up
□ sweating
□ fatigue/weakness/tiredness
□ hot flash/cold flash/tingling/numbness/

Please Describe:
____________________________________________________________________________________
____________________________________________________________________________________
____________________________________________________________________________________
____________________________________________________________________________________
____________________________________________________________________________________
____________________________________________________________________________________
____________________________________________________________________________________

35. Did you seek medical care for any new symptoms? □ Yes □ No □ Don’t know □ N/A
The Family Study: Assessment of the risk of family members of victims of out of hospital cardiac arrest for Coronary Artery Disease and Sudden Cardiac Death

If yes, choose all that apply: □ Saw family doctor  □ Went to Hospital
□ Received a new diagnosis from ____________  □ Other: __________

36. What was the etiology (cause) for your cardiac arrest? i.e. What did the doctors tell you caused your heart to stop? (Example – CAD, inherited arrhythmia structural HD, etc - se)
____________________________________________________________________
____________________________________________________________________
____________________________________________________________________
____________________________________________________________________
____________________________________________________________________
____________________________________________________________________

37. What sort of medical tests or procedures did you have after your arrest and what were the results? (e.g. angiogram, PCI, CABG, MRI, ECHO, EP study, ICD, Pacemaker, ECG, Holter, Drug Infusion – circle all that apply)
____________________________________________________________________
____________________________________________________________________
____________________________________________________________________
____________________________________________________________________
____________________________________________________________________
____________________________________________________________________

38. After answering all of the questions in this questionnaire, is there anything relevant about your heart health or family’s heart health that you think I should know?
____________________________________________________________________
____________________________________________________________________
____________________________________________________________________
____________________________________________________________________
____________________________________________________________________
____________________________________________________________________
The Family Study: Assessment of the risk of family members of victims of out of hospital cardiac arrest for Coronary Artery Disease and Sudden Cardiac Death

End Time: Duration:

39. **Underlying cause of Event: as adjudicated by reviewer after all information reviewed**

Reviewer’s initials: ________________

___ **Cardiac:** Structural heart disease- non coronary/infiltrative/infectious → abnormalities of the myocardium
   (ie. ARVC, HCM, DCM, valvular, hypertensive, LV non-compaction sarcoidosis, myocarditis)
   **Specify type:** __________________

___ **Cardiac:** Ischemic

___ **Cardiac:** Non structural Heart disease/primary arrhythmic
   (ie LQTS, Brugada, CPVT, commotion cordis, WPW)
   **Specify type:** __________________

___ **Cardiac (other)**
   (ie. Anomalous origin of coronary artery, aortic dissection/Marfan’s syndrome, coronary arteritis, LV rupture, pericarditis)
   **Specify type:** __________________

___ **Non cardiac:** Vascular event
   (ie. CVA, acute hemorrhage, PE, etc)
   **Specify type:** __________________

___ **Non cardiac:** Non vascular event
   (ie drowning, trauma, cancer, overdose)
   **Specify type:** __________________

___ **Cannot determine:** Explanation: ______________________________________________________

Additional notes:
The Family Study: Assessment of the risk of family members of victims of out of hospital cardiac arrest for Coronary Artery Disease and Sudden Cardiac Death

Study ID: Date: Start Time: Age: Sex: M/F
First 3 Digits Postal Code: Height: cm/inches (circle one) Weight: lbs/kg (circle one)
Waist Circumference: cm/inches (circle one)
Relationship to patient:
Family Doctor information: Name:
Telephone:
Intersection/City:

Before starting:
The following questions are about your loved one’s behaviours or habits that may have related to his/her risk for heart disease/cardiac arrest. If I ask you anything that you’d rather not talk to me about, you just tell me you don’t want to talk about it. Is that all right?

1. Prior to the event, when was the last time he/she had a routine medical check-up, undertaken by a doctor or a nurse? (A medical check-up is a physical exam that usually includes at least a blood pressure measurement)
   □ Less than 6 months ago  □ 6 months to less than 1 year ago  □ 1 year to less than 2 years ago
   □ 2 years to less than 3 years ago  □ 3 or more years ago  □ Never  □ Don’t know
   □ Prefer not to answer

2. Prior to the event, had he/she ever had an ECG done in the last year? □ Yes  □ No  □ Don’t know
   (a) If yes, when? _____ months
   (b) What were the results? (i.e. did the doctor tell him/her what the test results were? For example some changes on the ECG can indicate you may have had a heart attack in the past or that you have a rhythm problem with your heart. Did your doctor mention anything like that?)
   ___________________________________________________________________
   ___________________________________________________________________
   ___________________________________________________________________
   ___________________________________________________________________

3. Prior to the event, was he/she a:
   □ current smoker  □ ex-smoker (quit >30 days ago)  □ non smoker (never smoked)
   If yes to current smoker or ex-smoker, how long had he/she previously smoked? _____ (years)
   How many packs per day did he/she smoke? _____ (packs)  Total Pack years: _____
   (Pack years = (packs smoked per day) x (years as a smoker), 20 cigarettes = 1 pack)
   If yes to ex-smoker, how long had he/she quit smoking? _____ (years)

4. Prior to the event, what was his/her weight? lbs/kg (circle one)
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5. Prior to the event, did he/she get any regular recreational exercise defined as 30 minutes, one time per week performing a sport or recreational activity? □ Yes □ No □ Don’t know
Please describe:
___________________________________________________________________________________
___________________________________________________________________________________
___________________________________________________________________________________

6. What was the highest level of education that he/she had?
□ primary (up to grade 8) □ secondary (9-12) □ undergraduate degree/college diploma
□ graduate degree □ post graduate degree

7. Choose all that apply: Prior to the event, did he/she live □ alone or with his/her □ spouse □ partner □ child(ren) □ roommate(s) □ parent(s) □ sibling(s) □ in-laws?

8. What was his/her ethnic background? Choose all that apply:
□ Aboriginal (e.g., First Nations, Métis, Inuit)
□ Arab (e.g., Egypt, Iraq, Jordan, Lebanon)
□ Black (African or Caribbean descent)
□ Chinese
□ Filipino
□ Japanese
□ Korean
□ Latin American/Hispanic
□ South Asian (e.g., India, Sri Lanka, Pakistan, Bangladesh)
□ Southeast Asian (e.g., Malaysia, Indonesia, Vietnam, Cambodia)
□ West Asian (e.g., Turkey, Iran, Afghanistan)
□ White (European descent)
□ Other ethnic group (not listed above); Please describe: □ Don’t know □ Prefer not to answer

9. Prior to the event, did he/she ever consume alcohol? □ Yes □ No □ Don’t know
If yes, how many times per week did he/she consume alcohol? ___/week (If less than once per week, write 0)
How much alcohol did he/she consume at each sitting? ___
How many years had he/she been consuming alcohol? ___
Details:
___________________________________________________________________________________
___________________________________________________________________________________

Before starting:
The following questions are about your loved one’s medical history. If I ask you anything that you’d rather not talk to me about, you just tell me you don’t want to talk about it. Is that all right?
The Family Study: Assessment of the risk of family members of victims of out of hospital cardiac arrest for Coronary Artery Disease and Sudden Cardiac Death

Medical History:
Screening for heart risk factors:

If yes for the following questions, please write in the age he/she were diagnosed, the number of events (where applicable) and describe the event.

10. Prior to the event, was he/she taking any medications prescribed to him/her by a doctor or nurse?
   □ Yes  □ No  □ Don’t know  □ N/A

   If yes, what were his/her cardiac medications that he/she took on a regular basis?
   □ ACE inhibitor  □ ARB  □ beta-blocker  □ calcium channel blocker  □ cholesterol medication
   □ anticoagulant  □ diabetes medication  □ diuretic  □ antiplatelet  □ antirhythmic  □ nitrate

11. Prior to the event, had he/she ever fainted (lost consciousness) suddenly or unexpectedly?
   □ Yes  □ No  □ Don’t know
   Was it a cardiac syncope?  □ Yes  □ No  □ Don’t know  □ N/A  If yes, please describe:
   ______________________________________________________________________
   ______________________________________________________________________

12. Prior to the event, to your knowledge, had his/her doctor ever said he/she had one of the following and/or was he/she currently taking any medications for the following conditions (If yes, please indicate the age of diagnosis):
   (a) Chest pain (angina)?  Dx: □ Yes  □ No  □ Don’t know  Age: _____
   (b) Has anyone ever told him/her that he/she had an irregular heartbeat (arrhythmia)?
      □ Yes  □ No  □ Don’t know
   (c) High blood pressure?  Dx: □ Yes  □ No  □ Don’t know  Age: _____
   (d) High blood sugar (diabetes)?  Dx: □ Yes  □ No  □ Don’t know  Age: _____
   (e) High cholesterol?  Dx: □ Yes  □ No  □ Don’t know  Age: _____

13. Prior to the event, had anyone ever told him/her that he/she has blocked arteries in his/her heart (CAD)?
   □ Yes  □ No  □ Don’t know  Age: ____  If yes, can you please describe on the next page?

   Prior to the event, had he/she ever had a procedure called Percutaneous Coronary Intervention or PCI (an angiogram or angioplasty)?  □ Yes  □ No  □ Don’t know  Age: ____ (procedure where they look at the arteries in your heart for blockages)

   Prior to the event, had he/she ever had a heart bypass (CABG)?  □ Yes  □ No  □ Don’t know  Age: ____  If yes, can you please describe on the next page?

   Prior to the event, did he/she ever see a heart specialist?  □ Yes  □ No  □ Don’t know
   Prior to the event, had he/she ever been hospitalized because of his/her heart?
   □ Yes, for less than 24 hours  □ Yes, for more than 24 hours  □ No  □ Don’t know  Age: ____
   If yes, can you please tell me why you were hospitalized on the next page?

   Prior to the event, had he/she ever had a heart failure?  □ Yes  □ No  □ Don’t know  Age: ____
   If yes, can you please describe on the next page?
The Family Study: Assessment of the risk of family members of victims of out of hospital cardiac arrest for Coronary Artery Disease and Sudden Cardiac Death

Prior to the event, had he/she ever had any congenital heart issues? □ Yes  □ No  □ Don’t know
Age: ___  If yes, can you please describe on the next page?

Prior to the event, had he/she ever had valvular heart disease (problems with your heart valves)?
□ Yes  □ No  □ Don’t know  Age: ___  If yes, can you please describe on the next page?

If yes, please describe test results:
____________________________________________________________________________________
____________________________________________________________________________________
____________________________________________________________________________________
____________________________________________________________________________________
____________________________________________________________________________________
____________________________________________________________________________________
If more, please use the pages at the end of questionnaire and label as question 13:

14. Prior to the event, had he/she ever had a Stroke? □ Yes  □ No  □ Don’t know
If yes, number of strokes: ____  Age(s) of each stroke: _________________
Please describe:
___________________________________________________________________________________
___________________________________________________________________________________
___________________________________________________________________________________
If more, please use the pages at the end of questionnaire and label as question 14:

15. Prior to the event, had he/she ever had a previous non fatal heart attack (non fatal MI)?
□ Y  □ N  □ Don’t know  If yes, number of attacks: ____  Age(s) of each attack: _________________
Please describe:
___________________________________________________________________________________
___________________________________________________________________________________
___________________________________________________________________________________
If more, please use the pages at the end of questionnaire and label as question 15:

Before starting:
The following questions are about [insert name of deceased] family’s medical history i.e. if he/she had a family history of heart problems – parents, siblings, children. If I ask you anything that you’d rather not talk to me about, you just tell me you don’t want to talk about it. Is that all right?

Please indicate the age of each of his/her siblings, do not include himself/herself. For deceased relatives, please include a “D” next to the age.

□Brother1 ___ (age)  □Sister1 ___ (age)  □Son1 ___ (age)  □Daughter1 ___ (age)
□Brother2 ___ (age)  □Sister2 ___ (age)  □Son2 ___ (age)  □Daughter2 ___ (age)
□Brother3 ___ (age)  □Sister3 ___ (age)  □Son3 ___ (age)  □Daughter3 ___ (age)
□Brother4 ___ (age)  □Sister4 ___ (age)  □Son4 ___ (age)  □Daughter4 ___ (age)
□Brother5 ___ (age)  □Sister5 ___ (age)  □Son5 ___ (age)  □Daughter5 ___ (age)
□Paternal Brother1 ___ (age)  □Maternal Brother1 ___ (age)  □Paternal Sister1 ___ (age)  □Maternal Sister1 ___ (age)
□Paternal Brother2 ___ (age)  □Maternal Brother2 ___ (age)  □Paternal Sister2 ___ (age)  □Maternal Sister2 ___ (age)
The Family Study: Assessment of the risk of family members of victims of out of hospital cardiac arrest for Coronary Artery Disease and Sudden Cardiac Death

Family History:

16. Are any of his/her first degree relatives (parents, siblings, children) being treated for or have received a diagnosis for or are taking any medications for:

Please use the chart from the previous page to fill in relationship, i.e. bro1 for Brother1, or p-bro1 for Paternal Brother1.

(a) high blood pressure □ Yes □ No □ Don’t know If yes:

<table>
<thead>
<tr>
<th>Relationship</th>
<th>Age of diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
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</tbody>
</table>

If more, please use the pages at the end of questionnaire and label as question 16 (a):

(b) high blood sugar □ Yes □ No □ Don’t know If yes:

<table>
<thead>
<tr>
<th>Relationship</th>
<th>Age of diagnosis</th>
</tr>
</thead>
<tbody>
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</tbody>
</table>

If more, please use the pages at the end of questionnaire and label as question 16 (b):

17. heart disease (for example has anyone ever had an angiogram or been hospitalized because of their heart or sees a heart specialist on a regular basis).

□ Yes □ No □ Don’t know If yes:

<table>
<thead>
<tr>
<th>Relationship</th>
<th>Age of diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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</tbody>
</table>

Age: ____, saw heart specialist, hospitalization for less than 24 hours, hospitalization for more than 24 hours, CAD (blocked arteries), PCI (angiogram and/or angioplasty), CABG (heart bypass), heart failure, congenital heart issues, valvular heart disease; please describe each item.

___________________________________________________________________________________

___________________________________________________________________________________

___________________________________________________________________________________

___________________________________________________________________________________

<table>
<thead>
<tr>
<th>Relationship</th>
<th>Age of diagnosis</th>
</tr>
</thead>
<tbody>
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</tbody>
</table>

Age: ____, saw heart specialist, hospitalization for less than 24 hours, hospitalization for more than 24 hours, CAD (blocked arteries), PCI (angiogram and/or angioplasty), CABG (heart bypass), heart failure, congenital heart issues, valvular heart disease; please describe each item.

___________________________________________________________________________________

___________________________________________________________________________________

___________________________________________________________________________________

___________________________________________________________________________________
The Family Study: Assessment of the risk of family members of victims of out of hospital cardiac arrest for Coronary Artery Disease and Sudden Cardiac Death

________________________
Age: ____, saw heart specialist, hospitalization for less than 24 hours, hospitalization for more than 24 hours, CAD (blocked arteries), PCI (angiogram and/or angioplasty), CABG (heart bypass), heart failure, congenital heart issues, valvular heart disease; please describe each item.

___________________________________________________________________________________
___________________________________________________________________________________
___________________________________________________________________________________
___________________________________________________________________________________
If more, please use the pages at the end of questionnaire and label as question 17:

18. **stroke** □ Yes □ No □ Don't know **If yes:**
   Relationship
   Number of strokes, age of stroke
   ____________  ________________________________________________________
   ____________  ________________________________________________________
   ____________  ________________________________________________________
   ____________  ________________________________________________________
   If more, please use the pages at the end of questionnaire and label as question 18:

19. **non fatal heart attack** (non fatal MI) By non fatal heart attack we mean: when the arteries to the heart become blocked and require intervention in a hospital setting and the person does not die.
   □ Yes □ No □ Don’t know **If yes:**
   Relationship
   Number of attacks, age of attack
   ____________  ________________________________________________________
   ____________  ________________________________________________________
   ____________  ________________________________________________________
   ____________  ________________________________________________________
   ____________  ________________________________________________________
   If more, please use the pages at the end of questionnaire and label as question 19:

20. Have there been any **non sudden cardiac deaths** in his/her relative’s first degree relatives (parents, siblings, children). **By this we mean:** when the arteries to the heart become blocked and require intervention in a hospital setting and the person dies as a result (i.e. deaths due to MI which occur in hospital; deaths due to Heart Failure or other cardiovascular deaths)
   □ Yes □ No □ Don't know **If yes:**
   Relationship
   Age at death, please describe
   ____________  ________________________________________________________
   ____________  ________________________________________________________
   ____________  ________________________________________________________
   ____________  ________________________________________________________
   If more, please use the pages at the end of questionnaire and label as question 20:
21. Have there been any sudden cardiac deaths in his/her relative’s first degree relatives (parents, siblings, children)? By sudden cardiac death we mean: person dies suddenly and unexpectedly within one hour of the onset of symptoms or were in their normal state of health in the 24 hours prior to being found dead.

☐ Yes  ☐ No  ☐ Don’t know  If yes:

Relationship Age at death; circle all applicable and list if not mentioned; please describe.

___________  
Age: ____, collapsed at home, 911 called, person went to hospital, was conscious/unconscious on way to hospital, died in emergency, died later in hospital, died in field (at location), survived; please describe each item.

___________________________________________________________________________________  
___________________________________________________________________________________  
___________________________________________________________________________________  
___________________________________________________________________________________  

___________  
Age: ____, collapsed at home, 911 called, person went to hospital, was conscious/unconscious on way to hospital, died in emergency, died later in hospital, died in field (at location), survived; please describe each item.

___________________________________________________________________________________  
___________________________________________________________________________________  
___________________________________________________________________________________  
___________________________________________________________________________________  

___________  
Age: ____, collapsed at home, 911 called, person went to hospital, was conscious/unconscious on way to hospital, died in emergency, died later in hospital, died in field (at location), survived; please describe each item.

___________________________________________________________________________________  
___________________________________________________________________________________  
___________________________________________________________________________________  
___________________________________________________________________________________

If more, please use the pages at the end of questionnaire and label as question 21:

Before starting:
We are trying to learn more about why certain people’s hearts stop suddenly (cardiac arrest). This will involve me asking you some questions about what you remember happening in the minutes right before your loved one’s cardiac arrest as well as further back, say in the weeks to months before. If I ask you anything that you’d rather not talk to me about, you just tell me you don’t want to talk about it. Is that all right?

Event History:

22. Please describe the event:

___________________________________________________________________________________  
___________________________________________________________________________________  
___________________________________________________________________________________  
___________________________________________________________________________________
The Family Study: Assessment of the risk of family members of victims of out of hospital cardiac arrest for Coronary Artery Disease and Sudden Cardiac Death

If you have more details, please use the pages at the end of questionnaire and label as question 22:

23. Choose all that apply: Who provided information about the event?
   □ Patient  □ Spouse  □ Parent(s)  □ Sibling(s)  □ Child(ren)  □ Doctor/Registered Nurse  □ EMS
   □ ACR  □ Coroner  □ Other: ______________________

   Total number of sources: ______________________

   Did one or more of the above individuals witness the event? Were they told about the event by a third party?
   □ Witness  □ Told

24. In the 60 minutes prior to the event, did he/she experience any new symptoms? By new symptoms we mean any symptoms that he/she would not normally feel in his/her current state of health.
   □ Yes  □ No  □ Don’t know
   (If you filled out No, please fill in: 25. N/A, 26. 0 minutes)

   If yes, in the 60 minutes prior to the event, did he/she experience any of the following new symptoms:
   □ shortness of breath/air hunger/can’t catch your breath/gasping for air
   □ chest pain/discomfort/squeezing/dull ache/tightness
   □ arm pain/discomfort/ache
   □ leg pain/discomfort/ache
   □ back pain/discomfort/ache
   □ stomach pain/discomfort/ache/ nausea
   □ neck/head pain/discomfort
   □ palpitations/heart racing/fluttering
   □ vomiting
   □ dizziness/ light headed/impending loss of consciousness/inability to stand up
   □ sweating
   □ fatigue/weakness/tiredness
   □ hot flash/cold flash/tingling/numbness
The Family Study: Assessment of the risk of family members of victims of out of hospital cardiac arrest for Coronary Artery Disease and Sudden Cardiac Death

Please Describe:
____________________________________________________________________________________
____________________________________________________________________________________
____________________________________________________________________________________
____________________________________________________________________________________
____________________________________________________________________________________

25. Did he/she complain to anyone about his/her symptoms?
   □ Yes   □ No   □ Don’t know   □ N/A (no symptoms)

26. When did these symptoms start prior to his/her collapse? _____ minutes □ Don’t know

27. What was he/she doing in the hour prior to the onset of his/her symptoms?
   □ Rest
   □ Vigorous physical exertion _____ minutes prior to event □ Don’t know
   □ Moderate physical exertion _____ minutes prior to event □ Don’t know

Please Describe:
____________________________________________________________________________________
____________________________________________________________________________________
____________________________________________________________________________________
____________________________________________________________________________________
____________________________________________________________________________________

Rest (sitting or standing, does not cause a change in breathing)

Vigorous physical activities refer to activities that take hard physical effort and make you breathe much harder than normal (heavy lifting, digging, aerobics or fast bicycling)

Moderate physical activities refer to activities that take moderate physical effort and make you breathe somewhat harder (carrying light loads, bicycling at a regular pace or doubles tennis)

28. (a) Was he/she under any stress? □ Yes   □ No   □ Don’t know

(b) Was he/she under any acute emotional stress in the hour prior to the onset of his/her symptoms? By this we mean an emotional state or stressor that started within 60 minutes of your event. For example, this could mean he/she was in conflict with someone at the time of his/her arrest or that he/she received news of something that caused him/her to become very angry/sad/happy/excited. A chronic emotional stress refers to something ongoing such as work/health related stress.

   □ Yes   □ No   □ Don’t know   □ N/A
   How long before? _____ minutes prior to event □ Don’t know
   Emotion experienced: □ Anger □ Sadness □ Grief □ Excitement □ Happiness □ Other

Please Describe:
____________________________________________________________________________________
____________________________________________________________________________________
____________________________________________________________________________________
____________________________________________________________________________________
29. In the 60 minutes to 24 hours prior to the event, did he/she experience any **new** symptoms? By new symptoms we mean any symptoms that he/she would not normally feel in his/her current state of health.

- [ ] Yes
- [ ] No
- [ ] Don’t know

(If you filled out No, please fill in: 30. N/A, 31. N/A)

If **yes**, in the 60 minutes to 24 hours prior to the event, did he/she experience any of the following **new** symptoms:

- [ ] shortness of breath/air hunger/can’t catch your breath/gasping for air
- [ ] chest pain/discomfort/squeezing/dull ache/tightness
- [ ] arm pain/discomfort/ache
- [ ] leg pain/discomfort/ache
- [ ] back pain/discomfort/ache
- [ ] stomach pain/discomfort/ache/ nausea
- [ ] neck/head pain/discomfort
- [ ] palpitations/heart racing/fluttering
- [ ] vomiting
- [ ] dizziness/ light headed/impending loss of consciousness/inability to stand up
- [ ] sweating
- [ ] fatigue/weakness/tiredness
- [ ] hot flash/cold flash/tingling/numbness/

**Please Describe:**

___________________________________________________________________________________
___________________________________________________________________________________
___________________________________________________________________________________
___________________________________________________________________________________
___________________________________________________________________________________

30. Did he/she seek medical care for any new symptoms?  

- [ ] Yes
- [ ] No
- [ ] Don’t know
- [ ] N/A

31. Did he/she complain to anyone about these symptoms?  

- [ ] Yes
- [ ] No
- [ ] Don’t know
- [ ] N/A

If **yes**, to whom?  

- [ ] Family members
- [ ] Family doctor
- [ ] Friend
- [ ] Co-worker
- [ ] Other: _________

32. In the 24 hours to 7 days prior to the event, did he/she experience any **new** symptoms? By new symptoms we mean any symptoms that he/she would not normally feel in his/her current state of health.

- [ ] Yes
- [ ] No
- [ ] Don’t know

(If you filled out No, please fill in: 33. N/A)

If **yes**, in the 24 hours to 7 days prior to the event, did he/she experience any of the following **new** symptoms:

- [ ] shortness of breath/air hunger/can’t catch your breath/gasping for air
- [ ] chest pain/discomfort/squeezing/dull ache/tightness
- [ ] arm pain/discomfort/ache
- [ ] leg pain/discomfort/ache

Family Study: Symptom Questionnaire – 1st degree relative/spouse of deceased victim

SMH version June 12 2013
The Family Study: Assessment of the risk of family members of victims of out of hospital cardiac arrest for Coronary Artery Disease and Sudden Cardiac Death

- back pain/discomfort/ache
- stomach pain/discomfort/ache/nausea
- palpitations/heart racing/fluttering
- vomiting
- dizziness/light headed/impending loss of consciousness/inability to stand up
- sweating
- fatigue/weakness/tiredness
- hot flash/cold flash/tingling/numbness/

Please Describe:
___________________________________________________________________________________
___________________________________________________________________________________
___________________________________________________________________________________
___________________________________________________________________________________
___________________________________________________________________________________
___________________________________________________________________________________

33. Did he/she seek medical care for any new symptoms? ☐ Yes ☐ No ☐ Don’t know ☐ N/A

If yes, choose all that apply: ☐ Saw family doctor ☐ Went to Hospital
☐ Received a new diagnosis from ____________ ☐ Other: ___________

34. In the weeks to months prior to the event, did he/she experience any new symptoms? By new symptoms we mean any symptoms that he/she would not normally feel in his/her current state of health.

☐ Yes ☐ No ☐ Don’t know
(If you filled out No, please fill in: 35. N/A)

If yes, in the weeks to months prior to the event, did he/she experience any of the following new symptoms:
- shortness of breath/air hunger/can’t catch your breath/gasping for air
- chest pain/discomfort/squeezing/dull ache/tightness
- arm pain/discomfort/ache
- leg pain/discomfort/ache
- back pain/discomfort/ache
- stomach pain/discomfort/ache/nausea
- palpitations/heart racing/fluttering
- vomiting
- dizziness/light headed/impending loss of consciousness/inability to stand up
- sweating
- fatigue/weakness/tiredness
- hot flash/cold flash/tingling/numbness/

Please Describe:
___________________________________________________________________________________
The Family Study: Assessment of the risk of family members of victims of out of hospital cardiac arrest for Coronary Artery Disease and Sudden Cardiac Death

35. Did he/she seek medical care for any new symptoms? □ Yes □ No □ Don’t know □ N/A

If yes, choose all that apply: □ Saw family doctor □ Went to Hospital
□ Received a new diagnosis from ____________ □ Other: __________

36. What was the etiology for your cardiac arrest? i.e. What did the doctors tell you was the cause of your arrest? (Example – CAD, inherited arrhythmia structural HD, etc)

37. What sort of medical tests or procedures did you have after your arrest and what were the results? (e.g. angiogram, PCI, CABG, MRI, ECHO, EP study, ICD, Pacemaker, ECG, Holter, Drug Infusion – circle all that apply)

38. After answering all of the questions in this questionnaire, is there anything relevant about your heart health or family’s heart health that you think I should know?
The Family Study: Assessment of the risk of family members of victims of out of hospital cardiac arrest for Coronary Artery Disease and Sudden Cardiac Death

39. Underlying cause of Event: as adjudicated by reviewer after all information reviewed

Reviewer’s initials: ______________

___ Cardiac: Structural heart disease- non coronary/infiltrative/infectious → abnormalities of the myocardium
   (ie. ARVC, HCM, DCM, valvular, hypertensive, LV non-compaction sarcoidosis, myocarditis)
   Specify type: __________________

___ Cardiac: Ischemic

___ Cardiac: Non structural Heart disease/primary arrhythmic
   (ie LQTS, Brugada, CPVT, commotion cordis, WPW)
   Specify type: __________________

___ Cardiac (other)
   (ie. Anomalous origin of coronary artery, aortic dissection/Marfan’s syndrome, coronary arteritis,
   LV rupture, pericarditis)
   Specify type: __________________

___ Non cardiac: Vascular event
   (ie. CVA, acute hemorrhage, PE, etc)
   Specify type: __________________

___ Non cardiac: Non vascular event
   (ie drowning, trauma, cancer, overdose)
   Specify type: __________________

___ Cannot determine: Explanation: ______________________________________________________

Additional notes:

Completed By (Initials): __________
A) Patient Details:

Date of birth (dd/mm/yr): Date of event: Date of death:

Age at event: ___________ Sex: M / F Ethnicity: 

Past medical history (recorded from coroner’s reports):

____ None Recorded
____ Healthy

i) Cardiac:
____ Hypertension
____ Hypercholesterolemia
____ Diabetes mellitus
____ Obesity
____ Cerebrovascular accident/transient ischemic attack
____ Previous myocardial events

____ Percutaneous coronary intervention
____ Coronary artery bypass grafting
____ Valvular
____ Arrhythmia
____ Pacemaker/ICD

Additional Cardiac Hx/Tests:
___________________________________________________________________________________
___________________________________________________________________________________
___________________________________________________________________________________
___________________________________________________________________________________
___________________________________________________________________________________
___________________________________________________________________________________

Smoking history
____ Cigarettes (if current smoker)
____ Marijuana (specify)

ii) Neurologic:
____ Epilepsy/seizure disorder
____ Other (specify)

iii) Psychiatric
____ Mood disorder (specify)
____ Psychosis (specify)
____ Drug use (check all that apply)

____ Prescription drugs (list types of drugs)
____ Recreational (list types of drugs)
____ EtoH abuse (circle one: known or suspected)

iv) Other:
___________________________________________________________________________________
___________________________________________________________________________________
___________________________________________________________________________________

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Medications:
(Free text): ___ None ___ Not specified

Family history (only cardiac illnesses with death at age <65, record relationship and age):
____ None Recorded ____ No relevant hx

Referral of first degree kin to specialist? (circle one if known) Yes No

Details: _____________________________________________________________________________

B) Circumstances of event:

Brief Description:
___________________________________________________________________________________
___________________________________________________________________________________
___________________________________________________________________________________
___________________________________________________________________________________
___________________________________________________________________________________
___________________________________________________________________________________
___________________________________________________________________________________
___________________________________________________________________________________
___________________________________________________________________________________
___________________________________________________________________________________
___________________________________________________________________________________
___________________________________________________________________________________
___________________________________________________________________________________
___________________________________________________________________________________

___ Witnessed ____ Unwitnessed Found by whom: __________________________

Environment:
____ Private residence ____ Public (non-recreational) ____ Recreational area

Circumstances:
____ At rest (sitting or standing, does not cause a changed in breathing)
      ____ In bed
____ During exercise (specify intensity)
      _____ Light to moderate activities of daily living \(< 3\) metabolic equivalents (ie. housework, driving)
      _____ Moderate activities of daily living \(\geq 3\) metabolic equivalents (ie. sporting or fitness activities
         or strenuous physical work or chores, ex: snow shoveling = 7 mets)
      _____ Unknown

____ Immediate to 1-hr post exercise (specify time and degree of exercise, see above)
Acute Emotional Stress:
_______ within 60 minutes of the event
_______ within 60 min-24 hours from event
Specify stressor:
___________________________________________________________________________________
___________________________________________________________________________________

Symptoms prior to event (specify timing if known i.e. within 60 minutes, 1-24 hrs; past week; weeks to months, etc):
___________________________________________________________________________________

___ Recently seen MD or hospitalized ___ < 24 hours ___ 1-7 days ___ 7-30 days
Diagnosis given (if available)___________________________________________________________
Therapies given (include medication, followup) _____________________________________________

C) Coroners statements:
Medical cause of death:___________________________________________________________
Due to/as a consequence of:___________________________________________________________
Contributing factors:_______________________________________________________________
Assessment notes:_______________________________________________________________

D) Researchers statements:
Immediate cause of death:_______________________________________________________
Antecedent causes (indicate linkages):________________________________________________
_______________________________________________________________________________
Other significant conditions:_______________________________________________________
Assessment notes:_______________________________________________________________

Autopsy performed
____ Yes   ____ No

If yes, cardiac gross/histologic findings:
Muscular
Hypertrophy (LV____ cm) ___ Valvular
Dilatation/enlargement (____ g) ___ Valve involved____________________________________
Signs of acute ischemia/past MI ___ Pericardial
___ Coronary artery
(circle:thrombus/occlusion/stenosis/calcification)
specify # of arteries:
Max stenosis in any coronary artery: (RCA___, LMain___, LAD___, LCx___),
Max troponin level (if available): _________________________
___ All Normal

Normal Measurements (LV: 0.6 to 1.1 cm; normal heart weight: males: 325g; females 275g)
Additional Cardiac Description:____________________________________________________
Non cardiac relevant autopsy findings: ______________________________________________________

Toxicology (in-hospital or autopsy):

_____ Positive  _____ Negative  _____ Not done

If positive, specify: ________________________________________________________________

Molecular autopsy (N/A prior to 2012):

___ Completed: results ________________________________________________________________

___ Not done

___ Pending

E) Underlying cause of Event: as adjudicated by reviewer after all information reviewed

Reviewer’s initials: ______________________

___ Cardiac: Structural heart disease- non coronary/infiltrative/infectious → abnormalities of the myocardium
  (ie. ARVC, HCM, DCM, valvular, hypertensive, LV non-compaction sarcoidosis, myocarditis)
  
  Specify type: ______________________

___ Cardiac: Ischemic

___ Cardiac Nonstructural Heart disease/primary arrhythmic
  (ie LQTS, Brugada, CPVT, commotion cordis, WPW)
  
  Specify type: ______________________

___ Cardiac (other)
  (ie. Anomalous origin of coronary artery, congenital heart disease)
  
  Specify type: ______________________

___ Non cardiac: Vascular event
  (ie. CVA, acute hemorrhage, aortic dissection/Marfan’s syndrome PE, etc)
  
  Specify type: ______________________

___ Non cardiac: Non vascular event
  (ie infectious, metabolic, SUDEP, etc)
  
  Specify type: ______________________

___ Cannot determine: Explanation: ______________________________________________________
Appendix 3N: Autopsy Criteria for Cardiac and Non-Cardiac Categories

A: Cardiac Unexpected Etiologies:

1. **Ischemic Structural Heart Disease**, 1) Moderate to severe atherosclerosis in ≥1 major coronary artery (e.g. stenosis ≥ 70%), 2) thrombosis or plaque hemorrhage in one or more major coronary arteries, or 3) acute or healed/chronic myocardial infarction.1, 2

2. **Structural Non Ischemic Heart Disease** was one of:

3. **Hypertrophic Cardiomyopathy**, left ventricular wall thickness ≥15 mm and/or heart weight ≥500g with significant myocyte disarray and hypertrophy in the left ventricle with/without interstitial fibrosis and/or microvasculature pathology.1, 3

4. **Non-Specific Cardiomyopathy**, heart weight increased over value predicted for normal body weight, LHV or both right and left ventricular wall hypertrophy, dilation of both atria and ventricles4.

5. **Fibrotic Cardiomyopathy**, interstitial, diffuse or patchy myocardial fibrosis without LVH, or other structural abnormalities4.

6. **Hypertensive Heart Disease**, presence of macroscopic concentric hypertrophy of left ventricle, with a wall thickness (>13mm) and/or a cardiac weight considered excessive for the subject’s body size, in the absence of CAD, valvular or congenital heart disease, and without microscopic evidence of myocardial disarray. Patient also has a history of hypertension or evidence of renovascular hypertensive changes at autopsy.2, 3

7. **Arrhythmogenic right ventricular cardiomyopathy**, Right ventricular thinning or aneurysms, fatty replacement, fibrosis and microscopically fat and fibrosis of the wall of the right and/or left ventricle.1, 3

8. **Myocarditis**, multiple foci of interstitial inflammatory infiltrate with/without myocyte necrosis in the myocardium.2

   **Dilated cardiomyopathy**, Cardiomegaly with dilated ventricles and in the absence of hypertension, valve disease, or significant coronary artery disease.3, 5, 6

9. **Valvular Heart Disease** evidence of valvular disease on autopsy (e.g. stenosis, thickening, fibrosis, etc.) and in the absence of CAD and any other cardiac findings and considered causative for the SD event.

10. **Sarcoidosis**: macroscopically replacement tissue with non-necrotizing granulomatous inflammatory processes; microscopically interstitial lymphocytic infiltration7

11. **Suspected Primary Arrhythmic Syndrome**: no anatomical or toxicological cause of death established after autopsy with circumstances or medical history supporting an arrhythmic event.8

12. **Congenital Cardiac Diseases**: e.g. anomalous origin of coronary vessels, ASD, VSD, repaired CHD, etc., considered causative when autopsy reveals no other cause of death.

13. **Undetermined Cardiac**: where there were 2 competing cardiac etiologies (e.g. atherosclerosis and hypertensive heart disease) or lack of autopsy to determine the exact cardiac mechanism.
Appendix 3N: Autopsy Criteria for Cardiac and Non-Cardiac Categories

Non-Cardiac Unexpected Categories

1. **Non-cardiac, vascular etiology** was one of: ruptured aneurysm, pulmonary embolism, acute hemorrhage (e.g. intercranial hemorrhage, upper gastrointestinal bleed, hemoperitoneum) as diagnosed on autopsy and considered causative.

2. **Sudden unexplained death in epilepsy** (SUDEP): is defined as "the sudden, unexpected, witnessed or unwitnessed, non-traumatic, and non-drowning death of patients with epilepsy with or without evidence of a seizure, excluding documented status epilepticus, and in which postmortem examination does not reveal a structural or toxicological cause of death." 

3. **Infectious** included any of sepsis, peritonitis, pneumonia, bronchitis or tuberculosis, diagnosed at autopsy and with circumstances/history supporting death due to these mechanisms.

4. **Metabolic**: included cases of diabetic or alcoholic ketoacidosis with levels of acetone ≥ 8 mg/100mL, Beta-hydroxybutyrate (BHB) ≥ 250 mg/mL. Alcoholic acidosis includes BHB and acetone plus the presence of alcohol.

5. **Respiratory**: when cause of death was attributed to respiratory arrest such as during an acute asthma attack with evidence of hyperinflated lungs and mucous plugging on autopsy and with circumstances/history which supported this diagnosis.

6. **Anaphylaxis**: signs of mucous plugging and/or hyperinflated lungs, pulmonary congestion or edema, rash, elevated levels of tryptase and IgE in combination with circumstances/history which supported this diagnosis.

7. **Undetermined Non-Cardiac**: where there were 2 competing non-cardiac etiologies or lack of autopsy to determine the exact non-cardiac mechanism.

Expected Deaths Cardiac and Non-Cardiac:

1. **Drug Overdose**: death was attributed to an acute drug overdose (accidental or suicidal) as per toxicology testing and post-mortem results.

2. **Trauma**: was defined as cause of death due to penetrating or blunt trauma caused by motor vehicle accidents, drowning, hanging, electrocution, choking, stabbing, etc. and where cardiac arrest causing trauma (e.g. fall, single vehicle MVA, drowning, was deemed unlikely).

3. **Cancer**: when death was attributed and or expected due to cancer as per the post mortem report or when the ambulance call report indicated past medical history of terminal cancer with or without the presence of a DNR.

4. **Complex Chronic Care**: defined as patients who resided in a long term care facility and/or home and were in need of chronic care with expected death (e.g. severe cerebral palsy, complex genetic disorders) with or without the presence of a DNR.

5. **Congestive Heart Failure**: defined as patients with a documented clinical history of congestive heart failure with worsening symptoms and a decline in physical health.

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*aNote in some or all SUDEP cases the etiology may be cardiac.*
Appendix 3N: Autopsy Criteria for Cardiac and Non-Cardiac Categories

Undetermined Etiologies
1. Undetermined Decomp: where there was no anatomical or toxicological cause of death identifiable because of advanced decomposition.
2. Undetermined: where the cause of death was unclear due to lack of information or autopsy.
3. Lack of Info: cases with incomplete information.

References
Appendix 3N: Autopsy Criteria for Cardiac and Non-Cardiac Categories


Died Inhospital/Survivor Data Collection Form

1. Inhospital Disposition:

<table>
<thead>
<tr>
<th>1st Hospital Admit name:</th>
<th>1st unit:</th>
<th>2nd Hospital Admit name:</th>
<th>2nd unit</th>
<th>Discharge Status</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

0=no symptoms; 1=no disability despite symptoms; 2=slight disability; 3=moderate disability; 4=moderate severe disability; 5=severe disability

MRS (0-5):

1=good cerebral performance; 2=moderate cerebral disability; 3=severe cerebral disability; 4=coma or vegetative state

CPC (0-3):

If death occurred:

Discharge Summary Conditions:

2. ROSC:

Course in Hospital: ☐ Intubation, ☐ DNR, ☐ bleeding:

Site Classification of Etiology:

Contributing Factors:

3. Cooling:

Pt cooled (Y/N)?

4. Past History?

5. Procedures?

☐ CPR ☐ Fibrinolysis ☐ Cath ☐ PCI ☐ CABG ☐ ICD ☐ Other
4.0 Appendix 4A– Sudden Unexpected Non-Cardiac Cases (n=410)

4.1 Incidence and Event Characteristics for Sudden Unexpected Non-Cardiac Cases:

Table 1 shows incidence rates, baseline subject and event characteristics for the entire non-cardiac cohort (n=410). Cases were similarly divided into 3 age groups to compare event and subject characteristics. The average annual incidence for sudden non-cardiac death for the entire study cohort was 2.48 (95% CI, 2.25-2.74) per 100,000 in those ages 2-45. Age stratified incidence rates were 0.77 (95% CI, 0.57-1.05) per 100,000 in children ages 2-17, 2.21 (95% CI, 1.88-2.61) per 100,000 in younger adults ages 18-34 and 4.88 (95% CI, 4.28-5.56) per 100,000 in older adults ages 35-45.

Table 1: Sudden Death Incidence Rates of Non-Cardiac Cases Ages 2-45 from 2009-2012

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Ages 2-17</th>
<th>Ages 18-34</th>
<th>Ages 35-45</th>
<th>Ages 2-45</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population at Risk from 2009-2012</td>
<td>5,434,520</td>
<td>6,465,080</td>
<td>4,614,680</td>
<td>16,514,280</td>
</tr>
<tr>
<td>Total Sudden Cardiac Death Events</td>
<td>42</td>
<td>143</td>
<td>225</td>
<td>410</td>
</tr>
<tr>
<td>Incidence Rate per 100,000 persons annually (95% CI)</td>
<td>0.77 (0.57-1.05)</td>
<td>2.21 (1.88-2.61)</td>
<td>4.88 (4.28-5.56)</td>
<td>2.48 (2.25-2.74)</td>
</tr>
<tr>
<td>Relative Risk</td>
<td>1.0</td>
<td>2.87 (2.03-4.04)</td>
<td>6.34 (4.54-8.77)</td>
<td>N/A</td>
</tr>
</tbody>
</table>
The mean age of non-cardiac cases was slightly lower than in cardiac cases, 33.2 ± 10.4 (Table 2, Figure 1) and occurred less in males (61.0% non-cardiac vs. 76.4% cardiac). Children were significantly more likely to receive treatment from EMS than adults (83.3%; 35/42 children vs. 51%; 73/143 younger adults or 49.3% 111/225 older adults; p=0.002). Fewer cases were witnessed by bystanders (18.2%; 65/357) or received bystander CPR (19.5%; 80/410). Similarly to cardiac cases, children were more likely to receive bystander CPR than their adult counterparts (31.0% ages 2-17 vs. 18.2% ages 18-45). As expected, most non-cardiac cases had a non-shockable initial rhythm (93.9%; 202/215), with a small percentage having a shockable rhythm (6.5%; 14/215). Of the cases with a shockable rhythm, almost half had a non-cardiac vascular event as the underlying etiology (6/14, 42.8%) while the rest had underlying metabolic imbalances (3/14; 21.4%), infectious diseases (3/14; 21.4%) or were SUDEP cases (2/14; 14.3%).
Table 2: EMS Baseline Characteristics of Non-Cardiac Cases Ages 2-45 from 2009-2012

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Ages 2-17</th>
<th>Ages 18-34</th>
<th>Ages 35-45</th>
<th>Ages 2-45</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male Gender (%)</td>
<td>18/42 (42.9)</td>
<td>85 (59.4)</td>
<td>147/225 (65.3)</td>
<td>250/410 (61.0)</td>
<td>0.21</td>
</tr>
<tr>
<td>Age ± SD</td>
<td>11.1 ± 5.1</td>
<td>27.5 ± 4.5</td>
<td>41.0 ± 2.9</td>
<td>33.2 ± 10.4</td>
<td>N/A</td>
</tr>
<tr>
<td>Treated By EMS (%)</td>
<td>35/42 (83.3)</td>
<td>73/143 (51.0)</td>
<td>111/225 (49.3)</td>
<td>219/410 (53.4)</td>
<td>0.002 ¹³</td>
</tr>
<tr>
<td>Bystander CPR (%)</td>
<td>13/42 (31.0)</td>
<td>26/143 (18.2)</td>
<td>41/225 (18.2)</td>
<td>80/410 (19.5)</td>
<td>0.14</td>
</tr>
<tr>
<td>Bystander Witnessed (%)</td>
<td>14/37 (37.8)</td>
<td>23/129 (17.8)</td>
<td>28/191 (14.7)</td>
<td>65/357 (18.2)</td>
<td>0.004 ¹²</td>
</tr>
<tr>
<td>EMS Witnessed (%)</td>
<td>4/42 (9.5)</td>
<td>10/143 (7.0)</td>
<td>25/225 (11.1)</td>
<td>39/410 (9.5)</td>
<td>0.42</td>
</tr>
<tr>
<td>Initial Rhythm %</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.54</td>
</tr>
<tr>
<td>VF/VT (%)*</td>
<td>1/33 (3.0)</td>
<td>6/72 (8.3)</td>
<td>7/110 (6.4)</td>
<td>14/215 (6.5)</td>
<td>0.64</td>
</tr>
<tr>
<td>PEA/Asystole (%)</td>
<td>29/33 (88.0)</td>
<td>53/72 (79.2)</td>
<td>83/110 (75.5)</td>
<td>165/215 (76.7)</td>
<td>0.25</td>
</tr>
<tr>
<td>Not shockable/AED no shock (%)</td>
<td>3/33 (9.0)</td>
<td>13/72 (18.1)</td>
<td>21/110 (19.1)</td>
<td>37/215 (17.2)</td>
<td>0.40</td>
</tr>
<tr>
<td>Shocks Given** (%)</td>
<td>4/42 (9.5)</td>
<td>14/143 (9.8)</td>
<td>22/225 (9.8)</td>
<td>40/410 (9.8)</td>
<td>0.99</td>
</tr>
<tr>
<td>Location of Arrest (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.89</td>
</tr>
<tr>
<td>Public (%)</td>
<td>4/42 (9.5)</td>
<td>7/143 (4.9)</td>
<td>15/225 (6.7)</td>
<td>26/410 (6.3)</td>
<td>0.53</td>
</tr>
<tr>
<td>Private (%)</td>
<td>37/42 (88.1)</td>
<td>133/143 (93.0)</td>
<td>207/225 (92.0)</td>
<td>377/410 (92.0)</td>
<td>0.58</td>
</tr>
<tr>
<td>Other (%)</td>
<td>1/42 (2.4)</td>
<td>3/143 (2.1)</td>
<td>3/225 (1.3)</td>
<td>7/410 (1.7)</td>
<td>N/A</td>
</tr>
<tr>
<td>Prehospital ROSC (%)</td>
<td>13/42 (31.0)</td>
<td>18/143 (12.6)</td>
<td>18/225 (8.0)</td>
<td>49/410 (12.0)</td>
<td>0.0001 ¹²</td>
</tr>
<tr>
<td>Admitted (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Died at Scene (%)</td>
<td>9/42 (21.4)</td>
<td>92/143 (64.3)</td>
<td>157/225 (69.8)</td>
<td>258/410 (62.9)</td>
<td>&lt;0.0001 ¹³</td>
</tr>
<tr>
<td>Died ED (%)</td>
<td>24/42 (57.1)</td>
<td>35/143 (24.5)</td>
<td>45/225 (20.0)</td>
<td>104/410 (25.4)</td>
<td>&lt;0.0001 ¹³</td>
</tr>
<tr>
<td>Admitted (%)</td>
<td>9/42 (21.4)</td>
<td>16/143 (11.2)</td>
<td>23/225 (10.2)</td>
<td>48/410 (11.7)</td>
<td>0.11</td>
</tr>
<tr>
<td>Survived to Hospital Discharge (%)</td>
<td>3/42 (7.1)</td>
<td>2/143 (1.4)</td>
<td>4/225 (1.8)</td>
<td>9/410 (2.2)</td>
<td>0.07</td>
</tr>
</tbody>
</table>

*VF/VT cases include: 6 non-cardiac vascular cases; 3 metabolic imbalances; 3 infectious diseases and 2 SUDEP cases.
**Shockable cases include: 19 non-cardiac vascular cases; 3 metabolic; 8 infectious diseases; 6 SUDEP; 1 undetermined.
¹Significant Regression Coefficient comparison across 3 age categories.
²Regression Residual comparison for linear trend is significant indicating a linear dose response.
³Regression Residual comparison for linear trend is non-significant indicating a non-linear dose response.
⁴Pearson χ²/Fisher’s Exact Test comparison across 3 age categories.
Most patients died at the scene (62.9%; 258/410) or in the ED (25.4%; 104/410), with fewer non-cardiac cases being admitted to hospital versus their cardiac counterparts (11.7% vs. 26.4%). Overall survival from non-cardiac events was very poor, 2.2% (9/410) and was higher in children ages 2-17 (7.1%; 3/42) than in adults ages 18-45 (1.6%; 6/368). Most events happened at home (92.0%; 377/410) than in public (6.3%; 26/410).

4.2 Comparison of EMS and Rescu Data Guardian Classification of Sudden Unexpected Non-Cardiac Cases:

When comparing EMS and Rescu Data Guardian classification of the sudden unexpected non-cardiac cases (Table 3), both EMS and Rescu Data Guardians classified these cases as “no obvious cause” (e.g. presumed cardiac cause) in most cases (83.4% vs. 96.6%).
Table 3: EMS and Data Guardian Utstein Designation of Non-Cardiac Cases 2009-2012 Ages 2-45

<table>
<thead>
<tr>
<th>EMS Utstein Designation</th>
<th>Ages 2-17 (n=42)</th>
<th>Ages 18-34 (n=143)</th>
<th>Ages 35-45 (n=225)</th>
<th>Ages 2-45 (n=410)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Obvious Cause (%)</td>
<td>39 (92.9)</td>
<td>117 (81.8)</td>
<td>186 (82.7)</td>
<td>342 (83.4)</td>
</tr>
<tr>
<td>Obvious Cause (%)</td>
<td>0</td>
<td>4 (2.8)</td>
<td>5 (2.2)</td>
<td>9 (2.2)</td>
</tr>
<tr>
<td>Not Determined (%)</td>
<td>3 (7.1)</td>
<td>22 (15.4)</td>
<td>34 (15.1)</td>
<td>59 (14.4)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Data Utstein Guardian Designation</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Obvious Cause (%)</td>
</tr>
<tr>
<td>Obvious Cause (%)</td>
</tr>
<tr>
<td>Not Determined (%)</td>
</tr>
</tbody>
</table>

4.3 Etiologies of Sudden Unexpected Non-Cardiac Cases:

In the overall non-cardiac study population (n=410), the predominant etiology was vascular non-cardiac (28.0%; 115/410), followed by metabolic imbalances (19.0%; 78/410), sudden unexplained death in epilepsy (SUDEP) at 17.1% (70/410) and infectious conditions (17.8%; 73/410). A small percentage of non-cardiac cases had other non-cardiac etiologies such as anaphylaxis or asthma (9.3% (38/410) or could not be determined due to competing non-cardiac causes or lack of autopsy (8.8%; 36/410).
Table 4: Types of Non-Cardiac Disease in Non-Cardiac Cases by Age Category 2009-2012

<table>
<thead>
<tr>
<th>Type of Non-Cardiac Disease</th>
<th>Ages 2-17 (n=42)</th>
<th>Ages 18-34 (n=143)</th>
<th>Ages 35-45 (n=225)</th>
<th>Ages 2-45 (n=410)</th>
<th>P value¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vascular*</td>
<td>7 (16.7)</td>
<td>35 (24.5)</td>
<td>73 (32.4)</td>
<td>115 (28.0)</td>
<td>0.02³</td>
</tr>
<tr>
<td>SUDEP</td>
<td>10 (23.8)</td>
<td>35 (24.5)</td>
<td>25 (11.1)</td>
<td>70 (17.1)</td>
<td>0.001²</td>
</tr>
<tr>
<td>Infectious**</td>
<td>11 (26.2)</td>
<td>20 (14.0)</td>
<td>42 (18.7)</td>
<td>73 (17.8)</td>
<td>0.76</td>
</tr>
<tr>
<td>Metabolic</td>
<td>3 (7.1)</td>
<td>32 (22.4)</td>
<td>43 (19.1)</td>
<td>78 (19.0)</td>
<td>0.33</td>
</tr>
<tr>
<td>Other***</td>
<td>9 (21.4)</td>
<td>13 (9.1)</td>
<td>16 (7.1)</td>
<td>38 (9.3)</td>
<td>0.01²</td>
</tr>
<tr>
<td>Undetermined-Non-Cardiac****</td>
<td>2 (4.8)</td>
<td>8 (5.6)</td>
<td>26 (11.6)</td>
<td>36 (8.8)</td>
<td>0.04²</td>
</tr>
</tbody>
</table>

¹Includes aortic dissection, upper gastrointestinal bleeds, cerebral vascular accident, pulmonary embolism, subarachnoid hemorrhage, intracranial bleed and hemoperitoneum.

²Includes pneumonia, bronchitis, sepsis, tuberculosis, and peritonitis.

***Includes anaphylaxis, respiratory arrest due to asthma and congestive heart failure.

****Includes cases with competing non-cardiac etiologies or those cases without autopsy were the etiology is clearly non-cardiac in nature.

¹Regression Coefficient comparison across 3 age categories.

²Regression Residual comparison for linear trend is significant indicating a linear dose response.

³Regression Residual comparison for linear trend is non-significant indicating a non-linear dose response.

⁴Pearson χ²/Fisher’s Exact Test comparison across 3 age categories.

Specific types of vascular non-cardiac disease were determined from autopsy for each age category and the overall study population (Table 5). Pulmonary embolism accounted for 42.6% (49/115) of SCD and aborted SCD events in the entire cohort, followed by intracranial or subarachnoid hemorrhage (19.1%; 22/115), upper gastrointestinal bleed (14.8%; 17/115) and aortic dissection (13.0%; 15/115). The rest consisted of cerebral vascular events (0.87%; 1/115), hemoperitoneum (4.3%; 5/115) and undetermined due to lack of autopsy (5.2%; 6/115).
<table>
<thead>
<tr>
<th>Type of Non Cardiac Disease</th>
<th>Ages 2-17 (n=7)</th>
<th>Ages 18-34 (n=35)</th>
<th>Ages 35-45 (n=73)</th>
<th>Ages 2-45 (n=115)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aortic Dissection</td>
<td>1 (14.3)</td>
<td>3 (8.6)</td>
<td>11 (15.1)</td>
<td>15 (13.0)</td>
</tr>
<tr>
<td>Cerebral Vascular Event</td>
<td>0</td>
<td>1 (2.9)</td>
<td>0</td>
<td>1 (0.87)</td>
</tr>
<tr>
<td>Hemoperitoneum</td>
<td>0</td>
<td>1 (2.9)</td>
<td>4 (5.6)</td>
<td>5 (4.3)</td>
</tr>
<tr>
<td>ICH/SAH*</td>
<td>2 (28.6)</td>
<td>6 (17.1)</td>
<td>14 (19.2)</td>
<td>22 (19.1)</td>
</tr>
<tr>
<td>Pulmonary Embolism</td>
<td>3 (42.9)</td>
<td>18 (51.4)</td>
<td>28 (38.3)</td>
<td>49 (42.6)</td>
</tr>
<tr>
<td>Upper GI Bleed</td>
<td>0</td>
<td>3 (8.6)</td>
<td>14 (19.2)</td>
<td>17 (14.8)</td>
</tr>
<tr>
<td>Vascular Undermined</td>
<td>1 (14.3)</td>
<td>3 (8.6)</td>
<td>2 (2.7)</td>
<td>6 (5.2)</td>
</tr>
</tbody>
</table>

*ICH = intracranial hemorrhage; SAH=subarachnoid hemorrhage.

Fisher’s Exact Test comparison across 3 age categories = 8.8, p=0.62.
Appendix 4B: Age and Gender Comparisons of Patient Characteristics for Sudden Unexpected Cardiac Cases:

Sudden unexpected cardiac cases were further subdivided by gender as well as age to compare incidence rates, etiologies, event and subject characteristics (Tables 1, 2, 3 Females and 4, 5, 6 Males).

4.1 Age and Gender Comparisons of Incidence Rates for Sudden Unexpected Cardiac Cases:

Total sudden cardiac death annualized incidence rates (e.g. combined SCD and aborted SCD cases) were higher in males versus females (6.15 per 100,000 vs. 1.84 per 100,000; ages 2-45) across all age categories, with the most significant differences observed between older males and females (ages 35-45). Older males had combined SCD incidence rates almost 4-fold higher than their female counterparts. When comparing only SCD events (e.g. patients who died from their events), older males had almost 6-fold higher SCD incidence rates compared to older females. These differences were somewhat lower when comparing rates of aborted SCD events between the genders (only 2.5-fold difference). (Tables 1, 2).
# Table 1: SCD and Aborted SCD Incidence Rates Female Cardiac Cases Ages 2-45 from 2009-2012

<table>
<thead>
<tr>
<th>Variable</th>
<th>Ages 2-17</th>
<th>Ages 18-34</th>
<th>Ages 35-45</th>
<th>Ages 2-45</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Female Population at Risk from 2009-2012</td>
<td>2,640,140</td>
<td>3,291,300</td>
<td>2,401,540</td>
<td>8,332,980</td>
</tr>
<tr>
<td>Total Unexpected Cardiac Events¹</td>
<td>9</td>
<td>51</td>
<td>93</td>
<td>153</td>
</tr>
<tr>
<td>Incidence Rate per 100,000 annually (95% CI)</td>
<td>0.03 (0.02-0.07)</td>
<td>1.55 (1.18-2.04)</td>
<td>3.87 (3.16-4.75)</td>
<td>1.84 (1.57-2.15)</td>
</tr>
<tr>
<td>Relative Risk</td>
<td>1.0</td>
<td>51.7</td>
<td>129.0</td>
<td>N/A</td>
</tr>
<tr>
<td>Total Unexpected Cardiac Deaths²</td>
<td>7</td>
<td>35</td>
<td>73</td>
<td>115</td>
</tr>
<tr>
<td>Incidence Rate per 100,000 annually (95% CI)</td>
<td>0.03 (0.001-0.006)</td>
<td>1.06 (0.76-1.48)</td>
<td>3.04 (2.40-3.82)</td>
<td>1.38 (1.15-1.66)</td>
</tr>
<tr>
<td>Relative Risk</td>
<td>1.0</td>
<td>35.3</td>
<td>101.3</td>
<td>N/A</td>
</tr>
<tr>
<td>Total Unexpected Aborted Cardiac Deaths³</td>
<td>2</td>
<td>16</td>
<td>20</td>
<td>38</td>
</tr>
<tr>
<td>Incidence Rate per 100,000 annually (95% CI)</td>
<td>0.01 (0.0002-0.003)</td>
<td>0.49 (0.30-0.79)</td>
<td>0.83 (0.54-1.29)</td>
<td>1.84 (1.57-2.15)</td>
</tr>
<tr>
<td>Relative Risk</td>
<td>1.0</td>
<td>49.0</td>
<td>83.0</td>
<td>N/A</td>
</tr>
</tbody>
</table>

¹Includes both unexpected cardiac deaths and unexpected aborted cardiac deaths.
²Includes only unexpected cardiac deaths.
³Includes only unexpected aborted cardiac deaths.
### Table 2: SCD and Aborted SCD Incidence Rates of Male Cardiac Cases Ages 2-45 from 2009-2012

<table>
<thead>
<tr>
<th>Variable</th>
<th>Ages 2-17</th>
<th>Ages 18-34</th>
<th>Ages 35-45</th>
<th>Ages 2-45</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Incidence Rates per 100,000 persons annually</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total Male Population at Risk from 2009-2012</td>
<td>2,794,400</td>
<td>3,173,760</td>
<td>2,213,180</td>
<td>8,181,340</td>
</tr>
<tr>
<td>Total Unexpected Cardiac Events¹</td>
<td>26</td>
<td>144</td>
<td>333</td>
<td>503</td>
</tr>
<tr>
<td>Incidence Rate per 100,000 annually (95% CI)</td>
<td>0.93 (0.63-1.37)</td>
<td>4.54 (3.85-5.34)</td>
<td>15.10 (13.5-16.8)</td>
<td>6.15 (5.63-6.71)</td>
</tr>
<tr>
<td>Relative Risk</td>
<td>1.0</td>
<td>4.88</td>
<td>16.23</td>
<td>N/A</td>
</tr>
<tr>
<td>Total Unexpected Cardiac Deaths²</td>
<td>14</td>
<td>115</td>
<td>395</td>
<td>414</td>
</tr>
<tr>
<td>Incidence Rate per 100,000 annually (95% CI)</td>
<td>0.5 (0.30-0.85)</td>
<td>3.62 (3.02-4.35)</td>
<td>17.9 (16.2-19.7)</td>
<td>5.06 (4.6-5.57)</td>
</tr>
<tr>
<td>Relative Risk</td>
<td>1.0</td>
<td>7.24</td>
<td>35.8</td>
<td>N/A</td>
</tr>
<tr>
<td>Total Unexpected Aborted Cardiac Deaths³</td>
<td>12</td>
<td>29</td>
<td>48</td>
<td>89</td>
</tr>
<tr>
<td>Incidence Rate per 100,000 annually (95% CI)</td>
<td>0.43 (0.24-0.76)</td>
<td>0.91 (0.63-1.31)</td>
<td>2.17 (1.63-2.88)</td>
<td>1.09 (0.88-1.34)</td>
</tr>
<tr>
<td>Relative Risk</td>
<td>1.0</td>
<td>2.12</td>
<td>5.04</td>
<td>N/A</td>
</tr>
</tbody>
</table>

¹Includes both unexpected cardiac deaths and unexpected aborted cardiac deaths.
²Includes only unexpected cardiac deaths.
³Includes only unexpected aborted cardiac deaths.

### 4.2 Age and Gender Comparisons of Etiologies for Sudden Unexpected Cardiac Cases:

In females ages 2-45, the predominant underlying cardiac etiologies were structural, with 33.3% (51/153) having non-ischemic heart disease and 31.4% (48/153) having ischemic heart disease. Of the 153 cases, 20.3% (31/153) had structurally normal hearts and were presumed to represent the primary arrhythmic syndromes. A small proportion died from congenital heart disease (3/153; 2.0%) and 13.1% (20/153) had undetermined cardiac etiologies due to competing cardiac causes of death or lack of autopsy (Table 3).
Table 3 Female Cardiac Etiologies Ages 2-45 from 2009-2012

<table>
<thead>
<tr>
<th>Etiology Type†</th>
<th>Ages 2-17 (n=9)</th>
<th>Ages 18-34 (n=51)</th>
<th>Ages 35-45 (n=93)</th>
<th>Ages 2-45 (n=153)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Structural Heart Disease</td>
<td>4 (44.4)</td>
<td>16 (31.4)</td>
<td>31 (33.3)</td>
<td>51 (33.3)</td>
<td>0.74†</td>
</tr>
<tr>
<td>Ischemic Heart Disease</td>
<td>0</td>
<td>7 (13.7)</td>
<td>41 (44.1)</td>
<td>48 (31.4)</td>
<td>0.0001¹²</td>
</tr>
<tr>
<td>Primary Arrhythmic</td>
<td>4 (44.4)</td>
<td>19 (37.3)</td>
<td>8 (8.6)</td>
<td>31 (20.3)</td>
<td>&lt;0.0001¹²</td>
</tr>
<tr>
<td>Other*</td>
<td>0</td>
<td>2 (3.9)</td>
<td>1 (1.1)</td>
<td>3 (2.0)</td>
<td>0.45</td>
</tr>
<tr>
<td>Undetermined-Cardiac**</td>
<td>1 (11.1)</td>
<td>7 (13.7)</td>
<td>12 (12.9)</td>
<td>20 (13.1)</td>
<td>0.97</td>
</tr>
</tbody>
</table>

†Significant association across age categories (Pearson χ²=30.8; p<0.0001)
*Other includes congenital HD, anomalous coronary arteries, endocarditis, tamponade and commotio cordis.
**Undetermined-Cardiac includes patients with competing cardiac etiologies or those without autopsy in whom the etiology was considered to be cardiac.
†Pearson χ²/Fisher’s Exact Test comparison across 3 age categories.
¹Significant Regression Coefficient comparison across 3 age categories.
²Regression Residual comparison for linear trend is significant indicating a linear dose response.

Similar to females, males ages 2-45 died more frequently from non-ischemic structural heart disease (26.6%; 134/503) and ischemic heart disease (43.3%; 218/503), with fewer males than females dying from presumed arrhythmias (13.9% vs. 20.3%). A small proportion died from congenital heart disease (13/503; 2.6%) and 13.5% (68/503) had undetermined cardiac etiologies due to competing cardiac causes of death or lack of autopsy (Table 4).
Table 4: Male Cardiac Etiologies Ages 2-45 from 2009-2012

<table>
<thead>
<tr>
<th>Etiology Type†</th>
<th>Ages 2-17 (n=26)</th>
<th>Ages 18-34 (n=144)</th>
<th>Ages 35-45 (n=333)</th>
<th>Ages 2-45 (n=503)</th>
<th>P Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Structural Heart Disease (%)</td>
<td>10 (38.5)</td>
<td>47 (32.6)</td>
<td>77 (23.1)</td>
<td>134 (26.6)</td>
<td>0.04¹,²</td>
</tr>
<tr>
<td>Ischemic Heart Disease (%)</td>
<td>0</td>
<td>31 (21.5)</td>
<td>187 (56.2)</td>
<td>218 (43.3)</td>
<td>&lt;0.0001¹,²</td>
</tr>
<tr>
<td>Primary Arrhythmic (%)</td>
<td>9 (34.6)</td>
<td>40 (27.8)</td>
<td>21 (6.3)</td>
<td>70 (13.9)</td>
<td>&lt;0.0001¹,²</td>
</tr>
<tr>
<td>Other* (%)</td>
<td>2 (7.7)</td>
<td>7 (4.9)</td>
<td>4 (1.2)</td>
<td>13 (2.6)</td>
<td>0.02¹,²</td>
</tr>
<tr>
<td>Undetermined-Cardiac** (%)</td>
<td>5 (19.2)</td>
<td>19 (13.2)</td>
<td>44 (13.2)</td>
<td>68 (13.5)</td>
<td>0.83</td>
</tr>
</tbody>
</table>

*Other includes congenital HD, anomalous coronary arteries, endocarditis, tamponade and commotio cordis.

**Undetermined-Cardiac includes patients with competing cardiac etiologies or those without autopsy in whom the etiology was considered to be cardiac.

†Pearson χ²/Fisher’s Exact Test where appropriate.

¹Regression Coefficient comparison across 3 age categories.

²Regression Residual comparison for linear trend is significant indicating a linear dose response.

Female children were more likely to die from non-ischemic heart disease than their male counterparts (44.4% females vs. 38.5% males). Younger females were also more likely to die from a primary arrhythmic syndrome than their male counterparts (44.4% females vs. 34.6% males ages 2-17) and (37.3% females vs. 27.8% males ages 18-34). This trend was reversed when comparing rates of ischemic heart disease between genders: (21.5% males vs. 13.7% females ages 18-34) and (56.2% males vs. 44.1% females ages 35-45).

4.3 Age and Gender Comparisons of Medical History for Sudden Unexpected Cardiac Cases:

Across the entire age cohort (2-45), males and females (Tables 5, 6) had similar rates of no past medical health history (12.9% vs. 11.3%) and having past medical histories (85.1% vs. 88.7%, p=0.6). Rates of cardiac risk factors such as hypertension (19.0% vs. 27.9%, p=0.02) and diabetes (12.1% vs. 19.4%; p=0.08) were significantly higher in
females than males. Smoking (23.8% males vs. 21.6% females; p=0.6), hyperlipidemia (9.3% males vs. 5.7% females, p=0.4) and obesity rates (15.5% males vs. 22.1% females, p=0.3) were similar between the sexes while significantly more males than females had a history of a diagnosed seizure disorder (6.7% vs. 2.2%, p=0.06).

Both rates of diagnosed arrhythmias (7.1% males vs. 4.3% females, p=0.2) and implantable cardioverter defibrillators were relatively similar (2.2% males vs. 3.6% females, p=0.3).
<table>
<thead>
<tr>
<th>Variable¹</th>
<th>Ages 2-17</th>
<th>Ages 18-34</th>
<th>Ages 35-45</th>
<th>Ages 2-45</th>
<th>P Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Medical History</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No past medical history (e.g. healthy) (%)</td>
<td>4/8 (50.0)</td>
<td>6/45 (13.3)</td>
<td>6/88 (6.8)</td>
<td>16/141 (11.3)</td>
<td>0.01¹²</td>
</tr>
<tr>
<td>Past Medical Hx (%)</td>
<td>4/8 (50.0)</td>
<td>39/45 (86.7)</td>
<td>82/88 (93.2)</td>
<td>125/141 (88.7)</td>
<td>0.01¹²</td>
</tr>
<tr>
<td>HTN (%)</td>
<td>0</td>
<td>7/45 (15.6)</td>
<td>32/87 (36.8)</td>
<td>39/140 (27.9)</td>
<td>&lt;0.007¹³</td>
</tr>
<tr>
<td>Lipid (%)</td>
<td>0</td>
<td>1/45 (2.2)</td>
<td>7/87 (8.0)</td>
<td>8/140 (5.7)</td>
<td>0.43</td>
</tr>
<tr>
<td>Diabetes Mellitus (%)</td>
<td>0</td>
<td>6/45 (13.3)</td>
<td>21/86 (24.4)</td>
<td>27/139 (19.4)</td>
<td>0.11¹³</td>
</tr>
<tr>
<td>Obesity (%)</td>
<td>0</td>
<td>10/45 (22.2)</td>
<td>21/87 (24.1)</td>
<td>31/140 (22.1)</td>
<td>0.29</td>
</tr>
<tr>
<td>Prior MI (%)</td>
<td>0</td>
<td>1/45 (2.2)</td>
<td>10/87 (11.5)</td>
<td>11/140 (7.4)</td>
<td>0.18</td>
</tr>
<tr>
<td>Arrhythmia (%)</td>
<td>0</td>
<td>4/45 (8.9)</td>
<td>2/86 (2.3)</td>
<td>6/139 (4.3)</td>
<td>0.26</td>
</tr>
<tr>
<td>ICD/Pacemaker (%)</td>
<td>1/8 (12.5)</td>
<td>4/45 (8.9)</td>
<td>0</td>
<td>5/140 (3.6)</td>
<td>0.006¹²</td>
</tr>
<tr>
<td>Smoking (%)</td>
<td>0</td>
<td>6/44 (13.6)</td>
<td>24/87 (27.6)</td>
<td>30/139 (21.6)</td>
<td>0.06</td>
</tr>
<tr>
<td>Seizure Disorder (%)</td>
<td>0</td>
<td>1/44 (2.3)</td>
<td>2/87 (2.3)</td>
<td>3/139 (2.2)</td>
<td>0.91</td>
</tr>
<tr>
<td><strong>Mental Health</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mood Disorder* (%)</td>
<td>0</td>
<td>11/44 (25.0)</td>
<td>11/87 (12.6)</td>
<td>22/139 (15.8)</td>
<td>0.08</td>
</tr>
<tr>
<td>Psychosis (%)</td>
<td>0</td>
<td>1/44 (2.3)</td>
<td>6/87 (6.9)</td>
<td>7/139 (5.0)</td>
<td>0.61</td>
</tr>
<tr>
<td>Other Psych** (%)</td>
<td>0</td>
<td>2/44 (4.5)</td>
<td>5/87 (5.7)</td>
<td>7/139 (5.0)</td>
<td>0.76</td>
</tr>
<tr>
<td>Illicit Drug Use (%)</td>
<td>0</td>
<td>6/44 (13.6)</td>
<td>7/87 (8.0)</td>
<td>13/139 (9.4)</td>
<td>0.46</td>
</tr>
<tr>
<td>Etoh Abuse (%)</td>
<td>0</td>
<td>2/43 (4.7)</td>
<td>6/86 (7.0)</td>
<td>8/137 (5.8)</td>
<td>0.82</td>
</tr>
<tr>
<td><strong>Medications</strong>*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac (%)</td>
<td>1/8 (12.5)</td>
<td>9/38 (23.7)</td>
<td>34/74 (45.9)</td>
<td>44/120 (36.7)</td>
<td>0.02¹²</td>
</tr>
<tr>
<td>Diabetic (%)</td>
<td>0</td>
<td>5/38 (13.2)</td>
<td>14/74 (18.9)</td>
<td>19/120 (15.8)</td>
<td>0.45</td>
</tr>
<tr>
<td>Antibiotic (%)</td>
<td>0</td>
<td>4/38 (10.5)</td>
<td>4/74 (5.4)</td>
<td>8/120 (6.7)</td>
<td>0.58</td>
</tr>
<tr>
<td>Antipsychotic (%)</td>
<td>0</td>
<td>2/38 (5.2)</td>
<td>3/74 (4.1)</td>
<td>5/120 (4.2)</td>
<td>0.78</td>
</tr>
<tr>
<td>Antidepressant (%)</td>
<td>0</td>
<td>9/38 (23.7)</td>
<td>14/74 (18.9)</td>
<td>23/120 (19.2)</td>
<td>0.38</td>
</tr>
<tr>
<td>Anticonvulsant (%)</td>
<td>0</td>
<td>3/38 (7.9)</td>
<td>5/74 (6.8)</td>
<td>8/120 (6.7)</td>
<td>0.72</td>
</tr>
<tr>
<td>Opioid (%)</td>
<td>0</td>
<td>10/38 (26.3)</td>
<td>13/74 (17.6)</td>
<td>23/120 (19.2)</td>
<td>0.20</td>
</tr>
</tbody>
</table>

¹Includes one of depression, anxiety, bipolar, schizoaffective disorder or manic depressive.
**Includes one of OCD, borderline personality disorder or suicide attempt.
***Medications are assessed per drug not per patient. E.g. patients could have been taking multiple medications and thus categories are not additive.
†Pearson χ²/Fisher’s Exact Test comparison across 3 age categories.
¹Significant Regression Coefficient comparison across 3 age categories.
²Regression Residual comparison for linear trend is significant indicating a linear dose response.
³Regression Residual comparison for linear trend is non-significant indicating a non-linear dose response.
4.4 Age and Gender Comparisons of Mental Health History for Sudden Unexpected Cardiac Cases:

Rates of depression were non-significantly higher in females (15.8% females vs. 10.6% males, \( p=0.1 \)), particularly younger females ages 18-34 than males (25.0% vs. 7.1%) while rates of psychosis did not differ by gender (5.8% males vs. 5.0% females, \( p=0.7 \)). Rates of drug abuse (14.1% males vs. 9.4% females, \( p=0.1 \)) and ethanol abuse (13.4% males vs. 5.8% females, \( p=0.05 \)) were non-significantly higher among males than females (Tables 5 and 6).
<table>
<thead>
<tr>
<th>Variable</th>
<th>Ages 2-17</th>
<th>Ages 18-34</th>
<th>Ages 35-45</th>
<th>Ages 2-45</th>
<th>P Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical History</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No past medical history (e.g. healthy) (%)</td>
<td>7/24 (29.2)</td>
<td>20/136 (14.7)</td>
<td>35/317 (11.0)</td>
<td>62/483 (12.9)</td>
<td>0.05</td>
</tr>
<tr>
<td>Past Medical Hx (%)</td>
<td>17/24 (70.8)</td>
<td>112/136 (82.3)</td>
<td>282/317 (89.0)</td>
<td>411/483 (85.1)</td>
<td>0.05</td>
</tr>
<tr>
<td>HTN (%)</td>
<td>0</td>
<td>9/127 (7.1)</td>
<td>79/313 (25.2)</td>
<td>88/464 (19.0)</td>
<td>&lt;0.0001¹²</td>
</tr>
<tr>
<td>Lipid (%)</td>
<td>0</td>
<td>3/127 (2.4)</td>
<td>40/313 (12.8)</td>
<td>43/464 (9.3)</td>
<td>&lt;0.002¹²</td>
</tr>
<tr>
<td>Diabetes Mellitus (%)</td>
<td>0</td>
<td>7/127 (5.5)</td>
<td>49/313 (15.7)</td>
<td>56/464 (12.1)</td>
<td>&lt;0.0001¹²</td>
</tr>
<tr>
<td>Obesity (%)</td>
<td>1/24 (4.2)</td>
<td>20/127 (15.7)</td>
<td>51/313 (16.3)</td>
<td>72/464 (15.5)</td>
<td>0.31</td>
</tr>
<tr>
<td>Prior MI (%)</td>
<td>0</td>
<td>4/127 (3.1)</td>
<td>25/313 (8.0)</td>
<td>29/464 (6.3)</td>
<td>0.08</td>
</tr>
<tr>
<td>Arrhythmia (%)</td>
<td>1/24 (4.2)</td>
<td>10/127 (7.9)</td>
<td>22/312 (7.1)</td>
<td>33/463 (7.1)</td>
<td>0.94</td>
</tr>
<tr>
<td>ICD/Pacemaker (%)</td>
<td>0</td>
<td>3/127 (2.4)</td>
<td>7/313 (2.2)</td>
<td>10/464 (2.2)</td>
<td>0.75</td>
</tr>
<tr>
<td>Smoking (%)</td>
<td>1/24 (4.2)</td>
<td>19/125 (15.2)</td>
<td>90/313 (28.8)</td>
<td>110/462 (23.8)</td>
<td>0.001³³</td>
</tr>
<tr>
<td>Seizure Disorder (%)</td>
<td>3/24 (12.5)</td>
<td>14/126 (11.1)</td>
<td>14/313 (4.5)</td>
<td>31/463 (6.7)</td>
<td>0.02³²</td>
</tr>
<tr>
<td>Mental Health</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mood Disorder* (%)</td>
<td>0</td>
<td>9/126 (7.1)</td>
<td>40/313 (12.8)</td>
<td>49/463 (10.6)</td>
<td>0.05</td>
</tr>
<tr>
<td>Psychosis (%)</td>
<td>0</td>
<td>10/126 (7.9)</td>
<td>17/313 (5.4)</td>
<td>27/463 (5.8)</td>
<td>0.37</td>
</tr>
<tr>
<td>Other Psych** (%)</td>
<td>0</td>
<td>5/126 (4.0)</td>
<td>13/313 (4.2)</td>
<td>18/463 (3.9)</td>
<td>0.93</td>
</tr>
<tr>
<td>Illicit Drug Use (%)</td>
<td>2/24 (8.3)</td>
<td>19/125 (15.2)</td>
<td>44/313 (14.1)</td>
<td>65/462 (14.1)</td>
<td>0.75</td>
</tr>
<tr>
<td>Etoh Abuse (%)</td>
<td>0</td>
<td>9/126 (7.1)</td>
<td>53/312 (17.0)</td>
<td>62/462 (13.4)</td>
<td>0.002³³</td>
</tr>
<tr>
<td>Medications***</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac (%)</td>
<td>3/24 (12.5)</td>
<td>15/102 (14.7)</td>
<td>99/258 (38.4)</td>
<td>117/384 (30.5)</td>
<td>&lt;0.0001³³</td>
</tr>
<tr>
<td>Diabetic (%)</td>
<td>0</td>
<td>3/102 (2.9)</td>
<td>28/258 (10.9)</td>
<td>31/384 (8.1)</td>
<td>0.02¹²</td>
</tr>
<tr>
<td>Antibiotic (%)</td>
<td>0</td>
<td>9/102 (8.8)</td>
<td>10/257 (3.9)</td>
<td>19/383 (5.0)</td>
<td>0.09</td>
</tr>
<tr>
<td>Antipsychotic (%)</td>
<td>0</td>
<td>13/102 (12.7)</td>
<td>23/258 (8.9)</td>
<td>36/503 (7.2)</td>
<td>0.14</td>
</tr>
<tr>
<td>Antidepressant (%)</td>
<td>0</td>
<td>8/102 (7.8)</td>
<td>30/258 (11.6)</td>
<td>38/503 (7.6)</td>
<td>0.14</td>
</tr>
<tr>
<td>Anticonvulsant (%)</td>
<td>2/24 (8.3)</td>
<td>10/102 (9.8)</td>
<td>20/258 (7.8)</td>
<td>32/384 (8.3)</td>
<td>0.76</td>
</tr>
<tr>
<td>Opioid (%)</td>
<td>0</td>
<td>7/102 (6.9)</td>
<td>37/257 (14.4)</td>
<td>44/383 (11.5)</td>
<td>0.03¹²</td>
</tr>
</tbody>
</table>

*Includes one of depression, anxiety, bipolar, schizoaffective disorder or manic depressive.
**Includes one of OCD, borderline personality disorder or suicide attempt.
***Medications are assessed per drug not per patient. E.g. patients could have been taking multiple medications and thus categories are not additive.
†Pearson χ²/Fisher’s Exact Test where appropriate.
¹Regression Coefficient comparison across 3 age categories.
²Regression Residual comparison for linear trend is significant indicating a linear dose response.
³Regression Residual comparison for linear trend is non-significant indicating a non-linear dose response.
4.5 Age and Gender Comparisons of Prescribed Medication History for Sudden Unexpected Cardiac Cases:

Over a third of males (30.5%; 117/384) and females (36.7%; 44/120) were prescribed cardiac medications (p=0.2) while significantly more females (15.8%; 19/120) than males (8.1%; 31/384) were prescribed diabetic medications (p=0.01). Rates of prescribed antibiotics and anticonvulsants were similar between the sexes, while females were prescribed significantly higher rates of antidepressants (19.2% females vs. 7.6% males, p=0.04) and opioids (19.2% females vs. 11.5% males, p=0.03). More males (7.2%; 36/503) than females (4.2%; 5/120) were prescribed antipsychotics (p=0.3).