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Morbidity characteristics related to cardiovascular outcomes in French Canadian Families of the Saguenay-Lac-Saint-Jean region of Quebec

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This Master's Thesis is entitled:
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Was evaluated by a jury composed of the following people:

Lise Gauvin, Chair of the Jury
Pavel Hamet, Research Director
James Brophy, Member of the Jury

Abstract

BACKGROUND: The World Health Organization (WHO) recognizes cardiovascular diseases (CVD), such as high blood pressure (hypertension; HBP), coronary heart disease (e.g. myocardial infarction), cerebrovascular disease (stroke) and heart failure, as the major cause of death globally. Furthermore, CVD are multifactorial traits with a steeply rising prevalence worldwide, determined by a complex interplay of interactions between genome and environment, which renders their hereditary analysis a complicated task. Our previous studies in the founder population of French-Canadian families from the Saguenay-Lac-Saint-Jean (SLSJ) region of Quebec revealed the largest set of significantly linked loci to hypertension and its metabolic components [1, 2].

HYPOTHESIS AND OBJECTIVE: Since our preliminary findings suggest that early mortality from CVD has genetic and environmental factors, we hypothesize that our population will have distinct characteristics from diseases with and without fatal outcomes (FO and NFO, respectfully), especially in relation to CV cause. Our objectives are to analyze morbidity causes, their temporal characteristics and their clustering in the hypertensive families with or without obesity from the SLSJ region, using hospital, civic death registries and genealogical records from 1950 to the present. We want to describe and study FO and compare them to NFO.

RESULTS: In total, we identified 3,654 diagnosis from FO and NFO in 343 participating subjects. For FO, we report: (1) 299 participants suffered from diseases of the circulatory system with a grand total of 1,103 diagnosis, 555 outcomes and 247 first outcomes; (2) 333 of the participating subjects were affected by non-CV systems with a total of 1,536 diagnosis, 195 outcomes and 107 first outcomes; (3) all other diseases were responsible for a total of 81 diagnosis, 30 outcomes and 11 first outcomes in 62 of the participating subjects; and for NFO: (1) the circulatory system affected 105 of the participating subjects with a total of 156 diagnosis; (2) non-CVD, 53 of participating subjects with a total of 60 diagnosis; (3) all other diseases were found in 252 of participating subjects with a total of 718 diagnosis. For FO, 109 of 333 affected subjects by non-CVD and 58 of 62 by all other diseases had also a concomitant CVD. We were able to show characteristics from both FO and NFO. In both first outcomes and total outcomes, CVD predominated over non-CV and all other diseases. When examining CV co-affection with non-CV or all other diseases, 67.1% of our sample population was affected by CV FO. In fact, our sample showed a threefold risk increase in developing CVD ($p<0.0001$; $\chi^2=1,575.348$) when compared to the general population of SLSJ, while it diminished by half for non-CVD ($p=0.0006$; $\chi^2=11.834$). Finally, the relative risk for developing malignancies decreased by half in our sample in contrast to the same region.

CONCLUSION: This 11 year follow-up study provided a unique insight into affections for both FO and NFO. When looking at malignancies in conjunction with CVD, this risk grew twofold in our sample.

KEY WORDS: Cardiovascular diseases, diagnosis, outcomes, first outcomes, hypertension, cancer, diseases with mortality, disease without mortality.

Résumé

PROBLÉMATIQUE: L'Organisation Mondiale de la Santé (OMS) considère les maladies cardiovasculaires (MCVs) comme l'hypertension, la maladie coronarienne (par exemple, infarctus du myocarde), l'insuffisance cardiaque ainsi que les accidents cérébrovasculaires, parmi les principales causes de mortalité dans le monde. Les MCVs sont des maladies multifactorielles caractérisées par des interactions complexes entre le génome et l'environnement et dont la prévalence augmente rapidement dans toutes les populations du globe, ce qui vient compliquer d'autant l'étude de leurs bases héréditaires. Nos études précédentes sur la population fondatrice des familles Canadiennes-françaises de la région du Saguenay-Lac-Saint-Jean (SLSJ) au Québec ont permis d'obtenir une carte des loci significativement liés à des déterminants qualitatifs et quantitatifs de l'hypertension et ses déterminants métaboliques [1, 2].

HYPOTHÈSE ET OBJECTIF: Puisque nos données préliminaires nous suggèrent que la mort prématurée consécutive aux MCVs possède des composantes génétique et environnementale, notre hypothèse de départ est que les maladies avec occurrences fatales et non fatales (OF et ONF, respectivement) ont des caractéristiques distinctes, surtout lorsqu'en lien avec le système CV. Pour réaliser ce projet, nos objectifs sont d'analyser les causes de morbidité/mortalité d'hypertendus avec ou sans obésité chez des familles de la région du SLSJ. Nous accomplirons ceci en interrogeant les registres des hôpitaux et de l'état civil de

même que les données généalogiques de 1950 jusqu'à maintenant. Nous voulons décrire et étudier les OF pour les comparer aux NFO.

RÉSULTATS: Nous avons identifié un total de 3,654 diagnostiques appartenant aux OF et ONF chez les 343 sujets étudiés. Pour les OF, nous avons trouvé que: (1) un grand total de 1,103 diagnostiques du système circulatoire ont affecté 299 sujets avec 555 occurrences et 247 premières occurrences; (2) 333 des sujets participants ont reçu 1,536 diagnostiques non-CV avec 195 occurrences et 107 premières occurrences; (3) 62 diagnostiques de toutes autres causes chez 62 des sujets participants avec 81 occurrences et 11 premières occurrences. Pour les ONF: (1) 156 diagnostiques du système circulatoire ont affecté 105 sujets; (2) 60 diagnostiques de causes non-CV chez 53 des sujets; (3) et 718 diagnostiques de toutes autres causes chez 252 des sujets. Pour les OF, 109 des 333 sujets affectés par les maladies non-CV et 58 des 62 par toutes autres maladies étaient atteints simultanément par des MCV. Nous avons décrit les caractéristiques des maladies avec occurrences fatales et non fatales. Les MCVs prédominaient dans les résultats des premières occurrences et occurrences totales tandis que les maladies non-CV étaient les plus élevées pour les diagnostiques. De plus, les OF CV ont affecté 67.1% de notre échantillon de population, incluant les sujets co-affectés par les maladies non-CV ou de toutes autres causes. En fait, nos sujets ont un risque trois fois plus élevé de développer des MCVs ($p<0.0001$; $\chi^2=1,575.348$), tandis qu'il diminue de moitié pour les maladies non-CV comparativement au reste de la population du SLSJ ($p=0.0006$; $\chi^2=11.834$). Enfin, le risque de développer des tumeurs malignes est diminué de moitié dans notre échantillon comparativement à l'incidence régionale.

CONCLUSION: Cette étude a apporté une nouvelle perspective sur les OF et ONF chez nos sujets de la région SLSJ du Québec après 11 ans. Quand on observe ces résultats en conjonction avec les MCVs, ce risque double.

MOTS CLEFS: Maladies cardiovasculaires, diagnostiques, occurrences, premières occurrences, hypertension, cancer, occurrences fatales, occurrences non fatales.

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List Of Abbreviations

Ar	*Aortic regurgitation*
As	*Aortic stenosis*
AFG	*Abnormal fasting glucose (pre-diabetes)*
AG	*Angiography*
ARBs	*Angiotensin type II receptor blockers*
ARDS	*Adult respiratory distress syndrome*
AV	*Atrial-Ventricular*
BMI	*Body mass index*
BP	*Blood pressure*
BW	*Body Weight*
CABG	*Coronary artery bypass grafting*
CAD	*Coronary artery disease*
CAIQ	*Commission d'accès à l'information du Québec (Quebec's access to information board)*
CBC	*Complete blood count*
CBVD	*Cerebrovascular disease*
CDC	*Centers for Disease Control and Prevention*
CHADS2	*Congestive heart failure, HBP, Age, DM, and Stroke (or prior TIA)*
CHD	*Coronary heart disease*
CHOL	*Cholesterol*
CNS	*Central nervous system*
COPD	*Chronic obstructive pulmonary disease*
CPR	*Cardiopulmonary reanimation*
CV	*Cardiovascular*
CVD	*Cardiovascular disease*
DBL	*Dysbetalipoproteinemia*
DBP	*Diastolic blood pressure*
***DBP*∆	*Subject's first DBP value measured minus latest DBP*
DLP	*Dyslipidemia*
DM	*Diabetes mellitus*
DNA	*Deoxyribonucleic acid*
DVT	*Deep venous thrombosis*
ECHO	*Echocardiogram*
ECG	*Electrocardiogram*
EF	*Ejection fraction*

eGFR	*Estimated glomerular filtration rate*
FCD	*Familial combined dyslipidemia (or hyperlipidemia)*
FH	*Familial hypercholesterolemia*
FO	*Fatal outcomes*
FPG	*Fasting plasma glucose*
HALP	*Hypoalphalipoproteinemia*
HBP	*High blood pressure (hypertension)*
HDL-c	*High density lipoproteins cholesterol*
HF	*Heart failure*
HLP	*Hyperlipidemia*
DWM	*High risk mortality*
HTG	*Hypertriglyceridemia*
ICD	*International Classification of Diseases*
IFG	*Impaired fasting glucose*
ISQ	*Institut de la statistique du Québec (Quebec Institute of Statistics)*
LDL-c	*Low density lipoproteins cholesterol*
LV	*Left ventricular*
LVD	*Left ventricular dilatation*
LVDD	*Left ventricular diastolic dysfunction*
LVH	*Left ventricular hypertrophy*
LVSD	*Left ventricular systolic dysfunction*
MACCE	*Major Adverse Cerebral/Cardiovascular Event*
MI	*Myocardial Infarction*
Mr	*Mitral regurgitation*
Ms	*Mitral stenosis*
MSY	*Metabolic syndrome*
NFO	*Non-fatal outcomes*
PH	*Polygenic hypercholesterolemia*
PSVT	*Paroxystic supra-ventricular tachycardia*
PTCA	*Percutaneous trans-luminal angioplasty*
RAAS	*Renin-angiotensin-aldosterone system*
RIND	*Reversible ischemic neurological deficit*
RR	*Relative risk*
RVD	*Right ventricular dilatation*
RVSD	*Right ventricular systolic dysfunction*
Rx	*Medication*
SBP	*Systolic blood pressure*
***SBP*Δ**	*Subject's first SBP value measured minus latest SBP*
SLSJ	*Saguena-Lac-Saint-Jean*

SV	*Supra-ventricular*
SVT	*Superficial venous thrombosis*
T1D	*Type I Diabetes mellitus*
T2D	*Type II Diabetes mellitus*
TC	*Total cholesterol*
TG	*Triglycerides*
TIA	*Transient ischemia attack*
WHO	*World Health Organization*

Dedications

"I dedicate this thesis to my family and loved ones who helped me and supported me during this endeavor. You inspired me to pursue my dreams half way around the world.

...и нисам те заборавио Милице"

"I also dedicate it to my grandparents, who always pushed me to surpass my parents and myself. They will never be forgotten and will be immortal!"

"TH^{2}B"

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Since I cannot write more even if I wished, I would like to thank all the people who have helped me and supported during this project (this way I do not forget anyone). In addition, I would like to thank all the participating members of the families from Saguenay-Lac-Saint-Jean, without which none of this would be possible.

CHAPTER I:

Introduction

Introduction

Before getting into the core of this thesis, we wanted to give a brief overview of the study dealing with fatal as well as non-fatal outcomes and how they are related to cardiovascular diseases (CVD).

Both national and international statistics classify CVD as a leading cause of morbidity and mortality worldwide. This particularly refers to the founder French-Canadian population of Quebec's Saguenay-Lac-Saint-Jean (SLSJ) region. Due to its historical background, the recruited subjects from this population offer us the unique opportunity to study morbidity characteristics related to CV outcomes.

Bearing this in mind, the basis of this research will be discussed in the "Literature Review" (Chapter II). This will begin with more detailed statistics concerning CVD on a global level and focus on the SLSJ region. In addition, we will introduce and elaborate on:

(a) The concept of genes and environment interaction;

(b) Cancer and CVD;

(c) The previously mentioned major causes of morbidity and mortality;

(d) CV risk factors;

(e) Synaptic plasticity in CVD.

In fact, these concepts help to comprehend the numerous results collected during this study. Lastly, we present the description of the project, hypothesis and objectives.

In the third Chapter ("Methods") we give a detailed explanation of the project's phases. We will address the ethics behind it and detail the population of study, i.e. family cohort, phenotyping and probands. Furthermore, we show the stages involved in the design for data compilations, various disease criteria, followed by the result calculations and statistics.

Chapters IV ("Results) and V ("Discussion") will present and discuss the data gathered following a novel classification method: fatal and non-fatal outcomes. We will examine the importance of CVD, non-CVD (e.g. cancer, etc.) and all other diseases (e.g. neurological disorders, etc.) for each category. Moreover, we will address the limitations of the current study. Finally, we will show the relative risk calculated and the degree of significance with Chi square (χ^2) test for CVD versus other diseases.

We will complete this thesis with a short conclusion about our work and future perspectives (Chapter VI).

CHAPTER II:

Literature Review

Literature Review

2. CARDIOVASCULAR DISEASES (CVD)

2.1. DEFINITION

The World Health Organization (WHO) defines CVD as “caused by disorders of the heart and blood vessels, including coronary heart disease (CHD; myocardial infarction (MI), heart failure (HF)), cerebrovascular diseases (CBVD; stroke), raised blood pressure (hypertension; HBP), peripheral artery disease, rheumatic heart disease, congenital heart disease and HF” [3]. Furthermore, the WHO recognizes them as the number one cause of death globally, in both children and adults, and estimates that, by the year 2030, CVD (mainly heart disease and stroke) will kill close to 23.6 million people [4-6]. In Western Countries, such as the United States of America (USA) and Canada, the overall mortality rates caused by CVD have decreased over the last decade yet their burden remains high [7, 8]. Actually, the Public Health Agency of Canada totalized the costs for CVD at $22.2 billion while the USA estimates that, in 2010, the direct and indirect costs will amount to $503.2 billion [7-9].

2.2. STATISTICS

2.2.1. CANADA

In 2004, CVD were the first cause of Canadian deaths, amounting to 72,743 deaths or 32.1% of all deaths and surpassing neoplasms in second place with 68,322 or 30.2% (Figure 1A) [8]. During 2005-2006, they were the highest cause for patient hospitalization (16.9%) and length of stay in hospital (17.1%) compared to all diagnosis.

The 2007 statistics on the provincial deaths from CVD portrays their high prevalence throughout Canada, 30% on average, except for Nunavut, which has the lowest one with 12.4% (Figure 2A) (Statistics Canada 2010).

2.2.2. QUEBEC

The updated data of May 2010 by the *Institut de la statistique du Québec* (ISQ) in the French-Canadian Province of Quebec demonstrates, from the years 2000 to 2009, the overall number of deaths from CVD decreased by 2,305 [10]. In fact, the adjusted mortality rate went down from 400 deaths per 100,000 people in 1981 to less than 150 in 2008 [11]. Nevertheless, it is estimated that they affect more than 6% of the Quebec population. As one of the lowest CV death prevalence in Canada, Quebec maintains a favorable position when compared to the other provinces where, in contrast, an estimated 25.2% deaths are caused by CVD (n=14,421; Figure 2B) [10]. Moreover, only the neoplasms deaths surpass CVD deaths by 8.5%, making them, in the case of Quebec, the second cause of all deaths. Ischemic heart diseases were the major CVD cause with 13.2%. Notwithstanding this encouraging data, the overall mortality from CVD still amounts to an estimated 709 potential lost lives per 100,000 people, which will also have a heavy impact on cost and usage of the health care system [11].

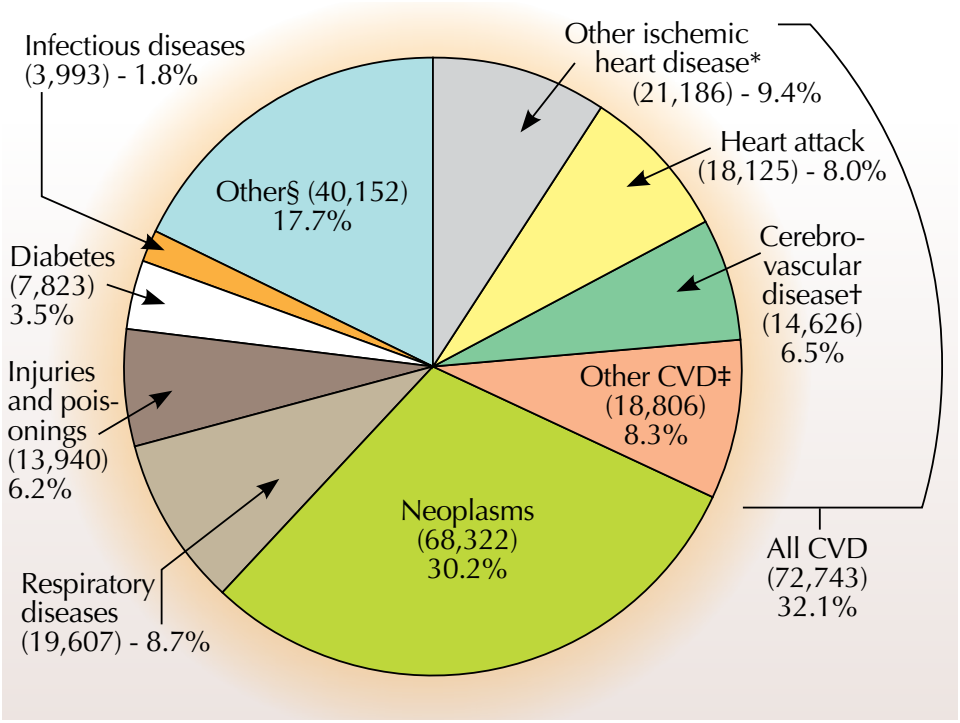
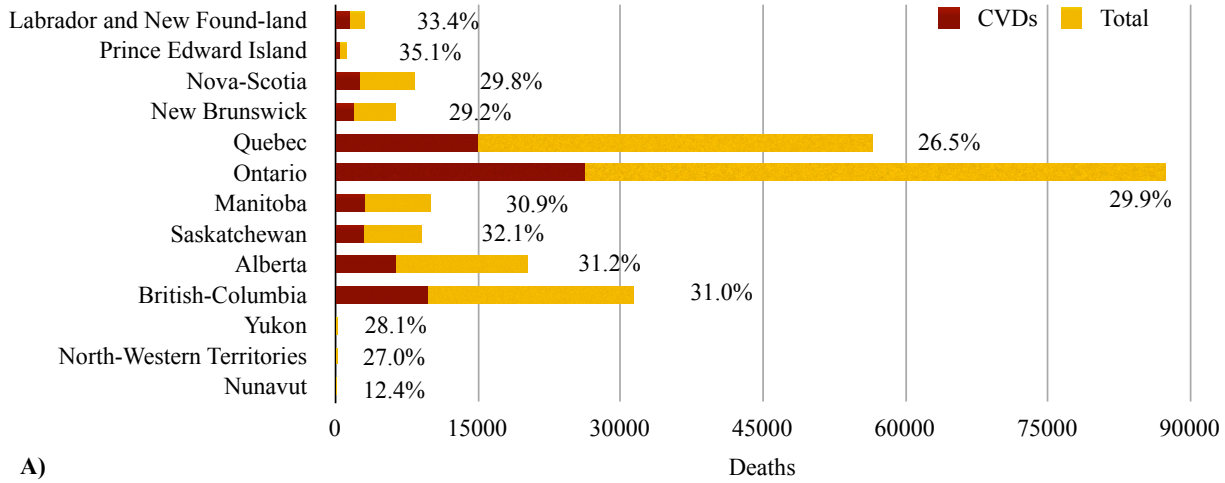


Figure 1. Leading causes of death in 2004 Canada [8]. The total number of deaths from all causes = 226,584. *Other ischemic heart disease = ischemic heart disease - heart attack. †CBVD excludes transient ischemic attacks. ‡Other CVD = circulatory disease–other ischemic heart disease–heart attack–CBVD. §Other = all causes–[respiratory disease, all CVD, accidents/poisoning/violence, neoplasms, infectious diseases, and diabetes]. **Original Source:** Chronic Disease Surveillance Division, Centre for Chronic Disease Prevention and Control, Public Health Agency of Canada, using data from the Vital Statistics Database (Statistics Canada). Reproduced with permission from the Minister of Health, 2013.



A)

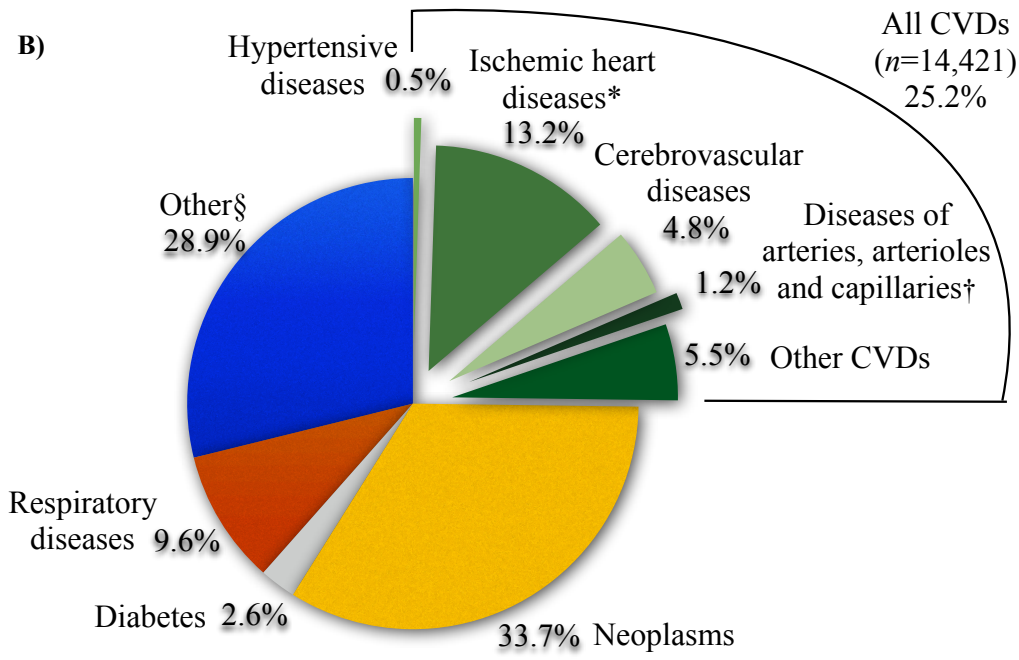


Figure 2. A) Deaths caused by CVD in each Canadian province in 2007. The total number of deaths in Canada from CVD = 69,503; from all causes = 235,217. Percentage takes into account the population sample size from each province giving a better picture of the prevalence of CVD. Small population: Yukon, North-Western Territories and Nunavut deaths from CVD = 54, 47 and 16, respectively. Original Source: Statistics Canada **[12]**. **B) Leading causes of death in Quebec, 2009.** The total number of deaths from all causes = 57,200. *Ischemic heart disease: Total deaths = 7,565—from which 4,359 are due to acute and subsequent myocardial infarction. †Diseases of arteries, arterioles and capillaries: Total deaths = 855—from which 211 are due to atherosclerosis. §Other = all causes–[respiratory diseases, all CVD, neoplasms and diabetes]. **Original Data Source:** *Institut de la statistique du Québec* **[10]**. *NOTE:* Small discrepancy in the data from Figures 2A and 2B exists due to the different dates the two organisms close their respective 'death' files for analysis (explained in a email correspondence with Miss Caroline Guillemette, *Institut de la statistique du Québec*.

2.2.3. SAGUENAY-LAC-SAINT-JEAN REGION

The extensively studied French Canadian population of the Saguenay-Lac-Saint-Jean (SLSJ) region of Quebec is at high risk for CVD [1, 13-18]. Recent statistics obtained between 2002 and 2006 concerning the mortality by cause (adjusted rate per 100,000) depict neoplasms as the first cause of death, which is followed by CVD as the second cause for this region (Table I) [19]. Even though the estimated life expectancy at birth has increased since the last census [13] (1994-1998) for men and women to 76.5 and

81.6, respectively, the ISQ estimates that these values remain amongst the lowest within the province for the years 2005-2007. The data also show a higher prevalence of death by all causes especially in SLSJ when compared to the whole Province of Quebec. Furthermore, we observe in SLSJ high onset of ischemic heart diseases and especially for CBVD and diseases of arteries, arterioles and capillaries (Table II) [19].

Table I. Adjusted mortality rate per 100,000 by cause (2002-2006) of the SLSJ region compared to the whole Province of Quebec [19].

Causes	Quebec	SLSJ	Cases/year
All	679.2	718.6	2,058
Neoplasms	221.7	247.5	726
Diseases of the circulatory system	190.0	184.9	525
Diseases of the respiratory system	58.0	64.3	181
External causes of morbidity and mortality	45.4	58.8	164
Endocrine, nutritional and metabolic diseases	28.9	27.3	79

Table II. Adjusted mortality rate per 100,000 caused by diseases of the circulatory system, CVD, (2002-2006) of the SLSJ region compared to the whole Province of Quebec [19].

Diseases of the circulatory system	Quebec	SLSJ	Cases/year
Ischemic heart disease	105.4	92.7	265
Acute and subsequent MI	59.9	52.6	152
CBVD	34.2	**40.7**	115
Diseases of arteries, arterioles and capillaries	9.9	**12.2**	35

Diseases of the circulatory system	Quebec	SLSJ	Cases/year
HF	11.6	9.7	27
Total	221	207.9	594

The epidemiological data of the SLSJ also reveal that, in the cases of morbidities, diseases of the circulatory system are the main cause of hospitalization in this region (Table III) [19].

Table III. Adjusted hospitalization rate per 10,000 by main diagnosis (2006-2009) of the SLSJ region compared to the whole Province of Quebec [19].

Causes	Quebec	SLSJ	Cases/year
All hospitalization by main diagnosis	762.3	985.3	26,872
Malignant neoplasms	60.9	74.0	2,019
Diseases of the circulatory system	123.9	142.2	3,878
Diseases of the respiratory system	54.8	68.3	1,862
Diseases of the gastrointestinal tract	76.9	123.0	3,355
Non-intentional traumas	81.7	119.5	3,258

2.3. GENES AND ENVIRONMENT

Before Sir Archibald E. Garrod proposed his theory on genetics in the early twentieth century [20], diseases were thought to affect people arbitrarily rather than having a direct or indirect cause due to genetic factors found in our deoxyribonucleic acid (DNA) blueprint [21]. In fact,

when people died of an unknown origin, their death was adjudged by the coroner as “death by natural cause”. However, we now understand that the underlying causes of a significant number of diseases are due to complex interactions such as “gene-gene” and “gene-environment”. CVD are multifactorial traits that do not display a clear Mendelian type pattern of inheritance [2, 22, 23], which has challenged the paradigms of classical genetics. Today, the notion of genetic susceptibility is firmly established and we realized that deaths by “natural causes” were heavily over-rated.

2.4. CANCER AND CVD

Neoplasms and CVD account for more than 60% of all deaths in western countries and can be referred to as “age-related diseases” (Figures 1 and 2B) [24]. After reviewing the literature until the late 1990s, Hamet explains how the previously thought “weak” association between Hypertension and Cancer is actually being revised and increasing significantly [25]. With the knowledge surrounding cellular biology and the complex genomic interactions of complex diseases increasing, the recently published “diseasome” clearly shows how overlapping pathophysiological pathways are involved in both HBP and cancer (Figure 3) [25, 26].

Furthermore, the debate whether there exists an association between cancer and HBP began more than forty years ago with Dyer *et al.*’s prospective study and continued on since [25, 27-39]. Differences in the various studies may lie in the many factors analyzed, especially differences in the population size, control and affected groups, and parallel evaluation of HBP in their subjects. In fact, it is also questionable whether hypertension may be secondary to the

carcinoma, i.e. the malignancy would be the cause of HBP, or they would just have similar risk factors [34, 40]. In some cases, this relationship would be quite difficult to determine.

In the last decade, HBP treatment with antihypertensive drugs (e.g. diuretics and Angiotensin type II receptor blockers), has been suspected to be associated with a higher risk to develop certain types of carcinomas, such as renal cell and breast [25, 28, 31, 33, 35-37, 39, 41-44], and even modestly increase the risk of new cancer diagnosis [45]. In fact, hypertension is not only associated in men (not women) with an increased risk of death from cancer but also to the risk of developing it [46, 47].

2.5. EARLY MORTALITY

The term early mortality refers to a fatal event (e.g. CVD) that occurred prematurely, *prematurely* being defined as having occurred between ages of 25 to 55 for men and 25 to 65 for women [13]. Furthermore, premature death due to CVD accounted for $9.3 billion in loss of productivity in Canada [8]. In 2004, mortality rates began to increase dramatically among men at age 45 (1 in 5) and women at age 55 (1 in 4) compared to 1 in 8 between 35 and 44 years of age [8].

2.6. RISK FACTORS FOR CVD

While the risk factors for CVD are debatable, USA's Seventh Report of the Joint National Committee classifies them in 10 major categories: hypertension, cholesterol (CHOL), age, sex, diabetes mellitus (DM), estimated glomerular filtration rate (eGFR), family history,

microalbuminuria, obesity and lifestyle [48]. Components of the metabolic syndrome (MSY) previously mentioned, such as HBP, DM and CHOL, are especially crucial when considering the risk factors for CVD. The prevalence of these predisposition elements is responsible for the CVD epidemic worldwide. In fact, the WHO considers this prevalence to lead to a higher incidence of CVD highly associated with CV mortality [4]. Unfortunately, they are rarely identified and remain untreated [49], which may lead to deadly diseases, such as stroke, ischemic heart diseases, left ventricular hypertrophy (LVH), renal dysfunction and even death [48, 50-52]. Finally, investigations on Canadian vascular health done between 1985 - 1990 revealed a staggering 41% and 33% of men and women, respectively, aged from 18 to 74 years, had at least 2 major risks factors for CVD, such as dyslipidemia (DLP) and HBP [53].

In fact, Goh, Barabasi and their colleagues have conceptualized the human genetic disorders and their corresponding disease genes to show how they might be related to one another at a higher level of cellular and organismal organization (Figures 3) [26]. This might help understand how the CVD risk factors influence each other and the outcomes of CV events and even mortality.

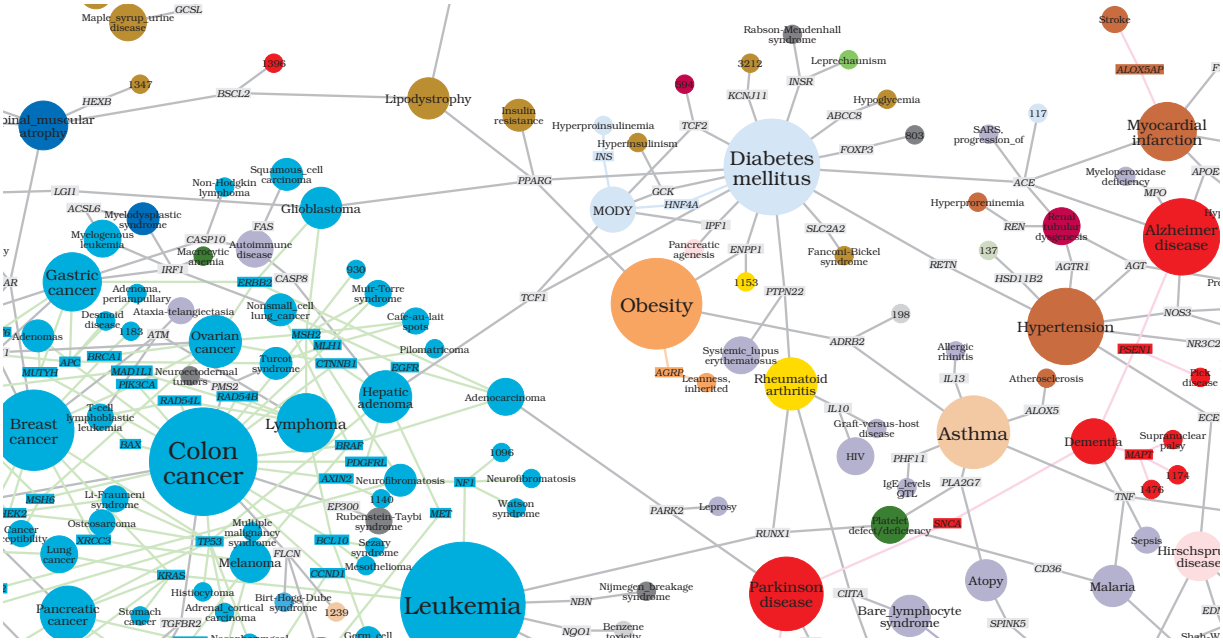


Figure 3. "The human disease network" [26]**.** Zoomed section of the original figure pertaining to this thesis. Full original figure from Goh's paper; Note: Original legend from figure - Each node corresponds to a distinct disorder, colored based on the disorder class to which it belongs. A link between disorders in the same disorder class is colored with the corresponding dimmer color and links connecting different disorder classes are gray. The size of each node is proportional to the number of genes participating in the corresponding disorder, and the link thickness is proportional to the number of genes shared by the disorders it connects. For a complete explanation of the details from the original figure with the names, colors and corresponding genes see the figure ***SI Fig. 13*** from Goh et al. referred above. Copyright (2007) National Academy of Sciences, U.S.A.

2.6.1. HYPERTENSION

As one of the leading risk factors for mortality and disability, HBP is a major worldwide public-health issue due to its high frequency and concomitant risks for CV and kidney disease [54-56]. By 2025, Kearney and her colleagues estimate that the world's adults affected by HBP will rise from 1 billion in 2000 to 1.56 billion—29% of the global population [56, 57]. Furthermore, many people remain unaware of their HBP despite the progress of detection, even in western countries, such as Canada [58]. Criteria for HBP are systolic BP (SBP)/diastolic BP (DBP) ≥ 140/90 mmHg without treatment [48, 59],

which can be managed relatively well with adequate therapy (i.e. adjustment of antihypertensive medication, etc.).

HBP is a very complex multifactorial disease, which includes both monogenic and essential sub-categories depending on the basis of the mode of inheritance. The first type, known as ‘monogenic’ or Mendelian forms of hypertension, results from a single gene defect and, as such, is inherited in a simple Mendelian manner [51]. The second one, human essential hypertension, occurs from a complex interplay of of genetic mutations and environmental factors and is the most common form found in human population. This form exhibits cases of familial aggregation without a clear pattern of Mendelian inheritance attributable to a single gene locus [51]. In fact, previous genealogical research in the geographically isolated population of French-Canadians origin provided the most detailed genome-wide set of highly significant qualitative and quantitative linkage loci of hypertension and related traits [1, 17, 18].

Historically, the initial focus has been on DBP from evidence of clinical trial before shifting to SBP from observational studies as a stronger predictor of death in middle and older-aged populations [60-64]. More specifically, SBP rises throughout life, whereas DBP peaks at the fifth and sixth decades where it plateaus or even decreases afterwards [65]. However, it is not uncommon that cases arise with patients not only affected by HBP but other systemic diseases, such as DM, DLP or kidney diseases, which complicates both their obvious health status and the complexity of their treatment. In

fact, treatment of HBP in people with DM reduces premature death and disability by up to 50% [59]. Furthermore, HBP is one of the major risk factors for CVD, such as MI and stroke, which may lead to early death (Figure 4). Hypertensive subjects, with a positive family history for CV death, are at higher risk for early mortality from CVD and specific quantitative trait loci demonstrate familial aggregation of HBP phenotypes [1, 48]. Thus, CVD are more frequent in hypertensive families than in normotensive ones.

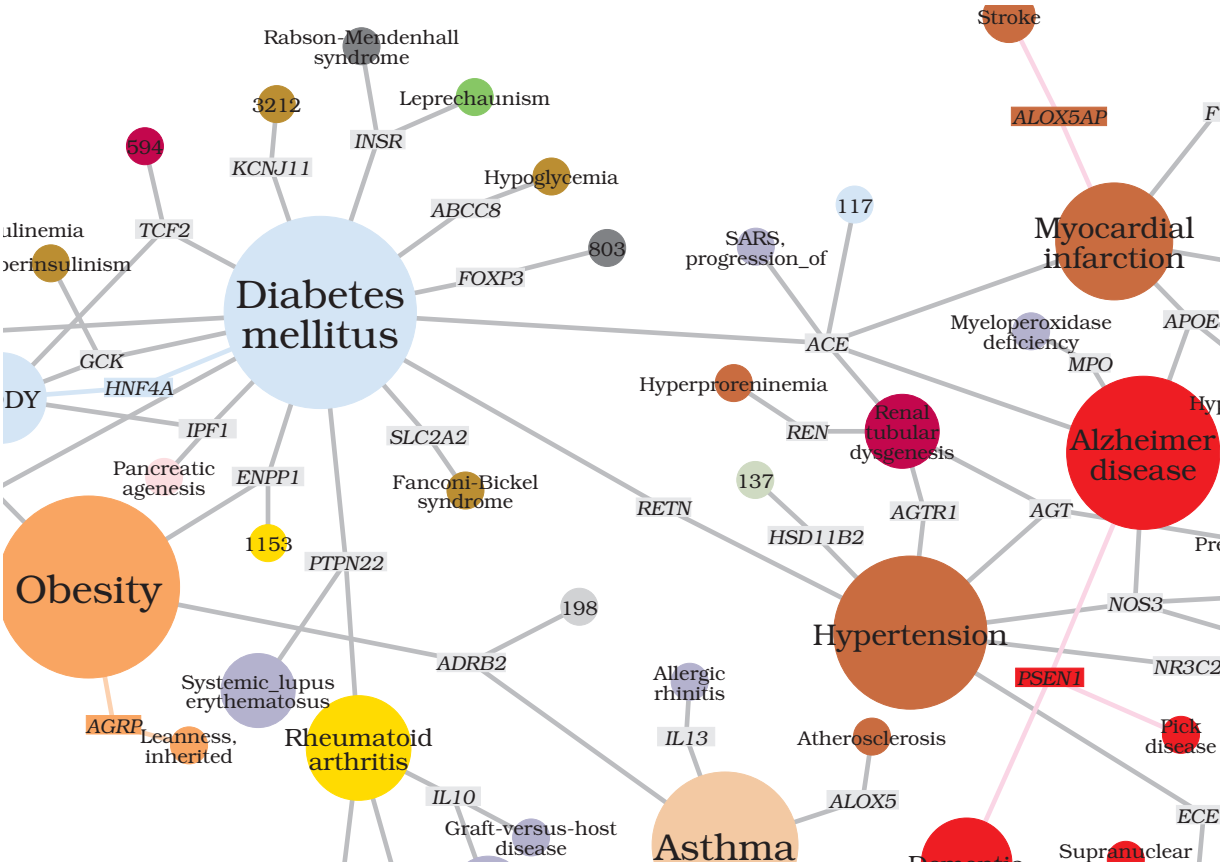


Figure 4. Close view of the original figure "The human disease network" [26]**.** Copyright (2007) National Academy of Sciences, U.S.A.

Criteria for early mortality age-classification [13, 48] do not take into account HBP, which may lead to deadly CV outcomes. Little research has been done to identify the

possible causal link between HBP and early mortality. Moreover, the age stratification criterion does not distinguish between younger and older adults. A recent review suggests this may overshadow the role of DBP in younger adults (less than 40 years of age) where high DBP predominates and the risk of death rising sharply with DBP values above 90 mm Hg [64, 66, 67]. Furthermore, ambulatory DBP and SBP measurements as a mortality predictors in young Japanese decreased the number of stroke or CV-related deaths, while a decreased nocturnal decline in SBP was associated with a higher risk of CV mortality and morbidity [68, 69]. In other words, people under 40 years of age may possibly be at high risk from early mortality due to HBP, either DBP, SBP or even both, which is not currently reflected in the early mortality age-classification criteria.

2.6.2. CHOLESTEROL

In 2010, Statistics Canada, following the Canadian Health Measures Survey, declared that over 40% and 25% of Canadians, between 20 and 79 years of age, had unhealthy levels of total CHOL and triglycerides (TG), respectively (Figure 5) [70].

DLP or dysregulation of the blood lipid levels has been recognized as major risk factors for CVD [71, 72]. Abnormally high levels of CHOL (>5.2 mmol/L for ages between 20 and 79), low density lipoproteins CHOL (LDL-c >3.36 mmol/L) and TG (>1.7 mmol/L), combined with low high density lipoproteins CHOL (HDL-c <1.3 mmol/L) elevate the risk for CHD [53, 70, 73-75]. Moreover, high blood CHOL, TG and LDL-c levels are also important risk factors for cerebrovascular diseases (CBVD) [76]. Inversely, high

plasma levels of HDL-c decreases independently and strongly the incidence of CVD and CHD mortality [77-79].

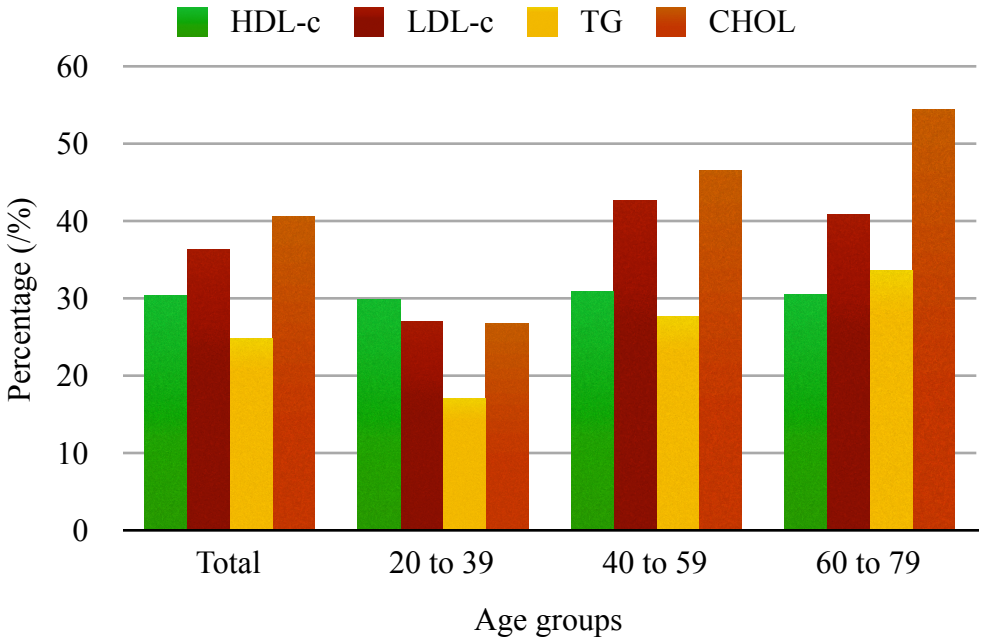


Figure 5. Canadian adults with unhealthy levels of HDL-c, LDL-c, TG and total CHOL, by age groups (from 20 to 79 years). All data presented are from fasting respondents and do not account for the impact of lipid adjusting therapy. Original data sources from the Canadian Health Measures Survey, 2007 to 2009 [70].

2.6.3. AGE AND SEX

Aging can be defined as a series of morphological and functional variations happening over time [80]. After an organism reaches its maximal reproductive potential, the deterioration of the biological functions begins. In fact, the risk of mortality and morbidity from CVD, such as atrial fibrillation, atherosclerosis, stoke, MI and HF, increases with age [81-86]. Nevertheless, CVD are sex-specific traits [18, 87]. In the Framingham Heart Study, men's incidence doubles with age for MI while it quintuples in women from the age groups of 55-65 to 85-94 [83, 86, 88]. In pathophysiological

states, heart aging can be caused by cardiomyocytes apoptosis stimulation, which can lead to poor LV remodeling and eventually HF [83].

2.7. SYNAPTIC PLASTICITY IN CVD

Stress and consumption of psychoactive substances, e.g. tobacco, coffee and alcohol is common and even encouraged in today world [89, 90]. Both stress and substance usage are involved in obesity and CVD [91]. Because all these traits arise from a multifactorial genetic and environmental background, we were not surprised to find common genes shared in the neural synapse to obesity, stress, substance use and CVD in the SLSJ population [92]. A significant number of genomic determinants overlapped for stress, obesity, substance use, heart rate and BP. This finding suggests that common pathways of synaptic plasticity with genetic variations underlie these traits. From this, we can assume that the subjects' lifestyle and/or habits can be affected by interactions from the synapses' genetic background. In turn, this lifestyle will alter body systems (e.g. CV system) which will modify the CV outcome and risk factors. This suggests that synaptic plasticity plays a predominant role in complex multifactorial disorders affected by lifestyle (Figure 6) [93]. In addition, these new findings are supported by the growing awareness of the "human disease network", which depicts interconnectivity of the complex disorders (e.g. CVD; Figure 3) [26]. For future perspectives, this will be a crucial analysis of outcomes in subjects with an increased response to stress vs. those who did not.

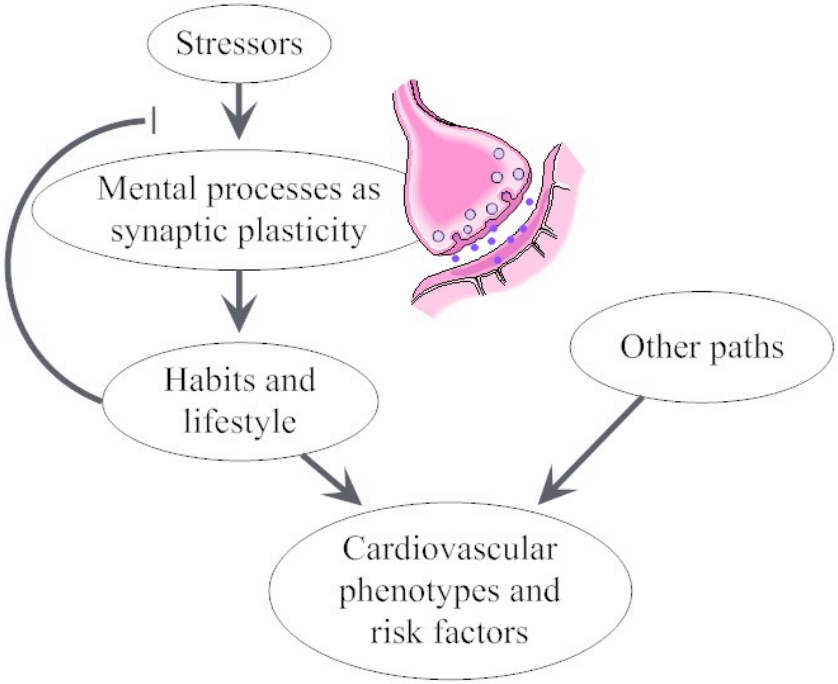


Figure 6. Hypothetical model of the interaction between stress, synaptic plasticity, substance us, obesity and related CV outcomes. Original picture from Nikpay, *et al.* **[92]**.

2.8. PROJECT DESCRIPTION

Previous genealogical research on the geographically isolated population of French-Canadians from the SLSJ region provided the most detailed genome-wide set of highly-significant qualitative and quantitative linkage loci of hypertension and related traits [1, 2, 18]. Our samples comprises of 120 hypertensive and dyslipidemic families. These findings also showed that the degree of genetic homogeneity increased by selecting families with a high prevalence of HBP. As such, we decided to characterize in the current study the families at high-risk for CVD. Some were classified as having a higher risk of early death and, others, at lower risk [13]. We propose here a multistep project to analyze the fatal and non-fatal outcomes of these French-Canadian families.

Since we have already obtained the informed consent of participants who enrolled in the study, the first step was to characterize the subsequent morbidity status, after which, treating physician charts and hospital records were reviewed. In fact, we examined their ways of living by looking at their medical history. The diseases were classified according to the International Classification of Disease (ICD) and will be grouped into fatal and non-fatal outcomes (FO and NFO, respectively). The grouping of different category of events, e.g. CV events, will be discussed in Chapter II: Methods. Adjudication and ascertainment procedure were conducted by an archivist, family physician and internist, with a specialty in cardiology (i.e. the Adjudication committee).

2.9. HYPOTHESIS

We hypothesize that our sample will demonstrate distinct characteristics in the prevalence of diseases with FO and NFO, especially in relation to CV cause, from general population. In the future, further analysis will include differences between subjects with or without obesity, with high or low body water and with low or high response to stress or insulin resistance.

2.10. OBJECTIVE

In order to appreciate the clinical relevance, we want to describe and study diseases in subjects with FO and compare them to subjects with NFO. In turn, this will lead to studying families and their respective members in relation to their risk of early mortality. This will also be achieved by comparing their phenotypic characteristics gathered here. In summary, by

examining the non-deadly outcomes of French Canadian families, we want to describe our sample population through the differences between FO and NFO at a clinical level.

CHAPTER III:

Methods

Methods

3.1. ETHICS AND ACCESS TO INFORMATION BOARDS

The Research Ethics Committees of the *Centre de santé et de services sociaux de Chicoutimi, l'Université du Québec à Chicoutimi*, and the *Centre Hospitalier de l'Université de Montréal*, reviewed and approved this study. The written consents of all subjects participating were obtained before the data collections begun. The families and their extensive phenotyping were described previously in detail [1, 17, 18]. Among the numerous phenotypes monitored in this cohort, those that are investigated in this study are described below.

In order to obtain the causes of death of proband's family members, we have written and submitted an authorization request to the *Commission d'accès à l'information du Québec* (CAIQ; Quebec's access to information board) in July 2011. However, we are still awaiting their approval concerning this matter. Once we have obtained this, we will be able to receive from the ISQ the causes of death for those members and to proceed with the analysis of the families displaying early mortality and look at the possible relation with CVD and FO (Figure 7).

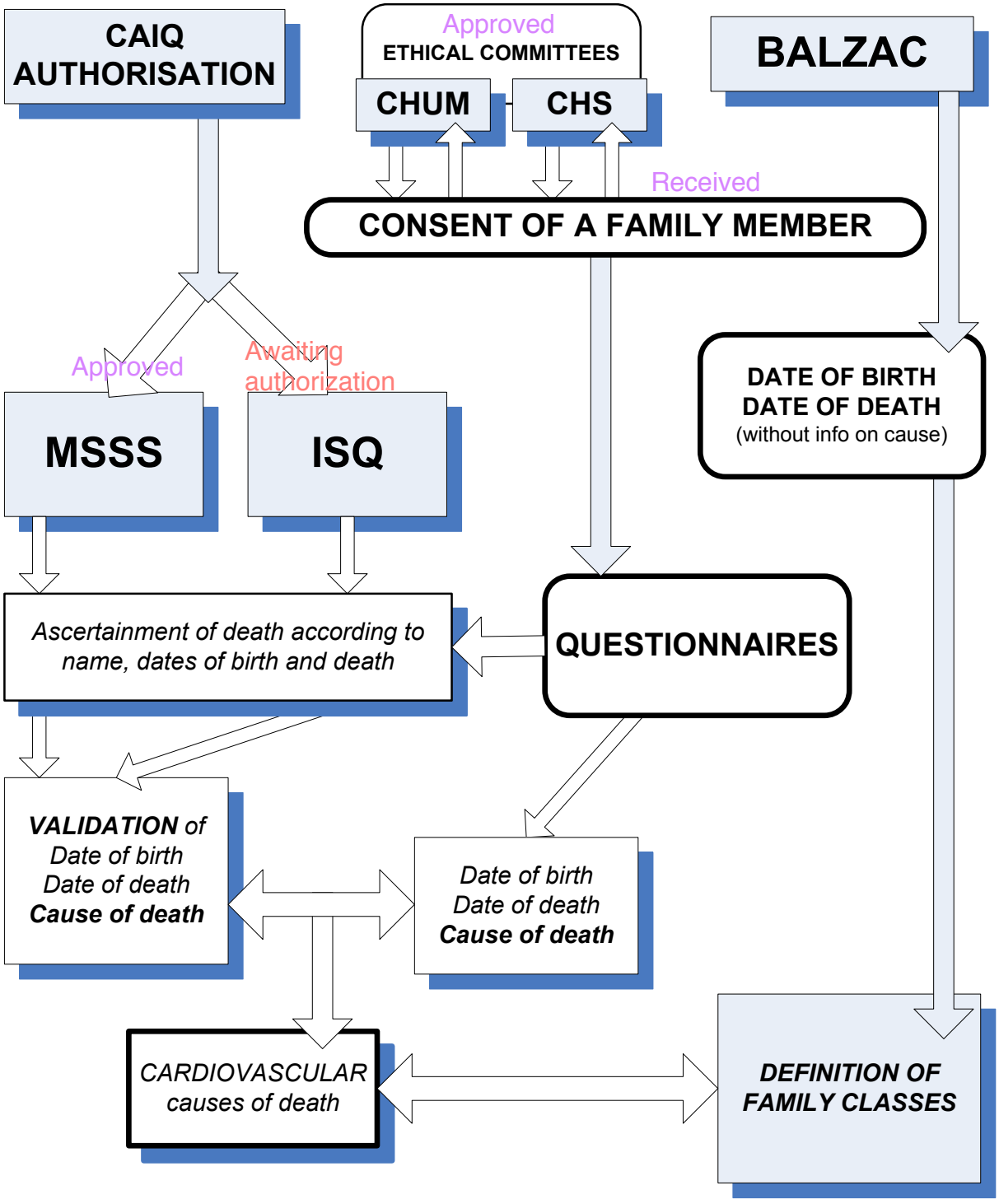


Figure 7. Flowchart depicting the multi-step procedure in retrieval and validation of the data and causes of death. CAIQ: Quebec's access to information board; CHUM: Centre Hospitalier de l'Universite de Montreal; CHS: Complexe Hospitalier de la Sagamie; MSSS: Québec Ministry of Health; ISQ: Québec Institute of Statistics. Reference: Dr. Pavel Hamet's "Search for genes of hypertension" grant application; Figure 7, by permission.

3.2. FAMILY COHORT

Extensive studies have been done on the population, i.e. analysis of founder effect, heritability estimates, genetic analyses including linkage and association and comparison between sex differences in the field of CVD, especially HBP, and associated metabolic components [1, 2, 14-18, 92, 94-100]. The probands for this study were recruited from relatively genetically differentiated families in the SLSJ area of the Canadian province of Quebec [1].

The families were ascertained by the presence of at least one sibpair with HBP and DLP. Sibship sizes ranged from 2 to 11 persons (mean 3.9; median 3). The affected sib pair–inclusion criteria were essential hypertension (SBP > 140 mmHg and/or DBP > 90 mmHg on two occasions or the use of antihypertensive medication), DLP (plasma CHOL 5.2 mmol/L and/or HDL-c 0.9 mmol/L or the use of lipid lowering medication), BMI < 35 kg/m^2 , age 18–55 years, and Catholic French Canadian origin. Exclusion criteria included secondary hypertension, DBP > 110 mmHg in spite of the use of medication, DM, renal or liver dysfunction, malignancy, pregnancy, and substance abuse. Once the affected sib pairs were selected, all first and second-degree relatives aged > 18 years were invited to participate in the study, independent of health status. The recruited population included 120 families (mean size 7.3 persons; median size 5 persons), comprising 897 subjects and 1,617 sib pairs (259 concordant-affected, 556 discordant, and 802 non-affected sib pairs) [1, 2, 18].

The SLSJ population is subjected to a founder effect that reflects its demographic history: it was shaped by its very early founders, starting in 1675 in the Charlevoix settlement, followed

by migration to the SLSJ region [1]. Since 1870, the migration rates were relatively low and the population has grown from 5,200 in 1852 to 286,649 in 1996 mostly due to the very large family sizes in each generation; after which year, this population isolate started to decline to 278,279 in 2001 and furthermore to 272,610 individuals in 2006 [17, 101, 102].

In gene finding studies, the founder effect observed in this region provides many advantages, such as lower allelic and locus heterogeneity (key features common in complex diseases that obscure association signals), environmental stratification and population stratification likelihood compared to general populations.

3.3. PHENOTYPING

All phenotyping was performed by trained personnel who followed standard operating procedures [1, 14-17]. In summary, 294 subjects without any contraindications were invited for extensive phenotyping. Their antihypertensive drugs were withdrawn for 1 week and lipid-lowering agents for 1 month. The full phenotyping was performed in a group of 159 normotensive and 135 hypertensive subjects [1, 17, 18]. The data on the current generations in our database comprise over 50,000 SNPs (single nucleotide polymorphisms), 450 microsatellites, 539 direct and derived phenotypes, history and pedigree on 16 family generations thanks to the BALSAC project, medical status and diagnostic for most family members and DNA samples [1, 14-18].

3.4. PRELIMINARY OVERVIEW OF DATA ORGANIZATIONS

In this Chapter, the data gathered from participating subjects will be presented and explained for better understanding of the undertaken study. First, all the data have been divided into to two main categories: (1) FO and (2) NFO (Figure 8).

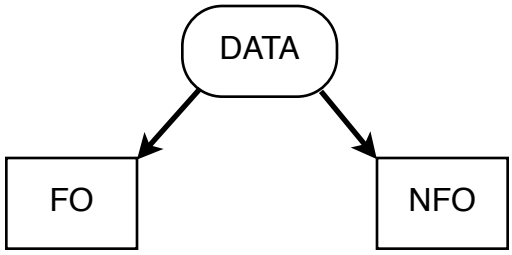


Figure 8. Main data organization from the subjects of the SLSJ region during the present study.

Following this first division, each of the categories was sub-divided into three categories: (1) CVD, (2) non CV diseases and (3) other disorders (Figure 9).

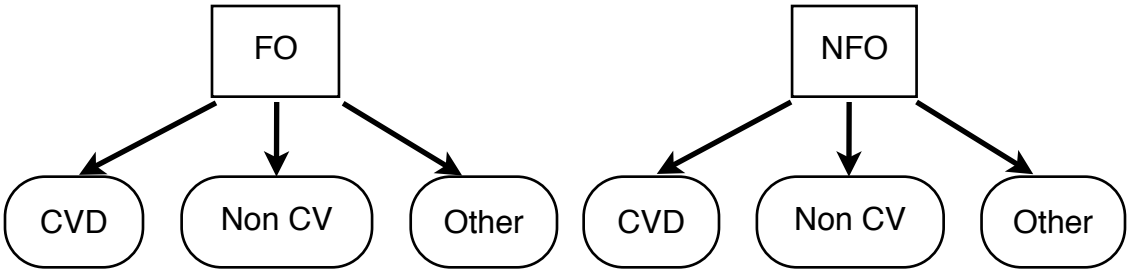


Figure 9. Organization of sub-categories in which the data gathered from the subjects of the SLSJ region has been classified.

Within each of the six subcategories, the divisions became more specific according to their risk and relation to CVD. The more detailed composition of each of them will be shown in section “Data Compilation” of this Chapter.

3.5. SUBJECTS STUDIED

Here, we will try to explain as clearly as possible the differences between the participating and analyzed subjects in this study [1]. All Chicoutimi subject's have received care at the *Centre de santé et des services sociaux de Chicoutimi* where the data were gathered for more than 3 months. Together, a total of 896 subjects have participated in the initial study. However, several factors have influenced the final number of subjects that are actually presented in this thesis (Figure 10).

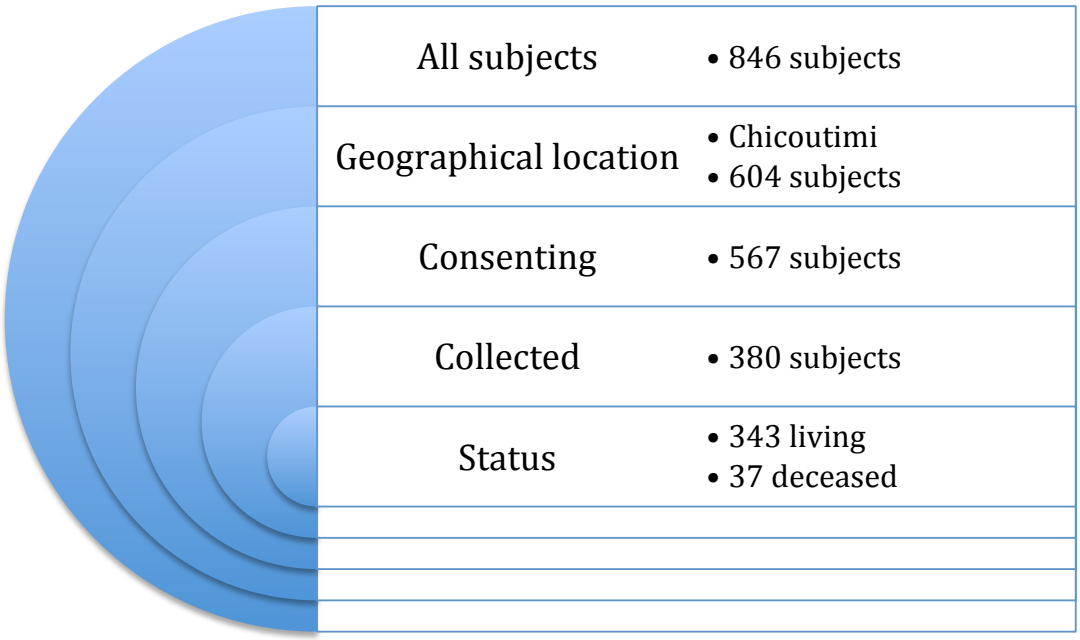


Figure 10. Summary of the subjects' recruitment.

3.5.1. CONSENT

Each participating subject has given their consent to participate in the initial study. However, not all participant wanted their data to be used in sub-sequent studies. The

following table depicts this information (Table IV). In summary, 567 subject could be analyzed immediately at the time of data gathering but, due to other limiting factors (e.g. requirement for re-consenting, CAIQ etc.), 380 were analyzed at the time of the writing of this thesis.

Table IV. Representation of the consent status from the participating subjects. Other category refers to consents that remain to be found (n=65) and subjects from Chicoutimi living in Montreal (n=227) that remain to be gathered. Note: n = number of subject.

Consent status	n
Consenting subjects from Chicoutimi	567
Non-consenting subjects from Chicoutimi	37
Other	292
Total	896

3.5.2. DATA SOURCES FOR THE PRESENT STUDY

In order to ascertain subjects' diagnosis and outcomes, we have examined each of their medical chart and hospital records at *Centre de santé et des services sociaux de Chicoutimi*, the largest in the SLSJ region (http://www.csss-chicoutimi.qc.ca). A total of 380 subjects were examined and their medical history pertaining to the mortality risk was recorded. All of these subjects have received their care at the site aforementioned. During the data gathering, it is to be noted that 26 subjects were hospitalized and their charts unavailable at that time. They will be analyzed in the future. To comply with the

ethic committee approval, there was no direct contact with subjects, only their hospital or clinic charts were examined.

In addition, 121 patients of the 380 have been seen in a specialized clinic, Lipid Clinic (*Clinique des Lipides)*, of the *Centre de santé et des services sociaux de Chicoutimi*. This helped improve the selection and information for those 121 subjects since more in depth testing and questioning was performed on these subjects. In other words, it helped confirm some diagnosis (e.g. hypertension, type of DLP, DM, etc.) and even 'diagnosing' (in terms of data collecting) a disease for a given subject. For example, Subject B had two charts (1 at the Hospital, 1 at the Clinic). The hospital chart showed lab results suggesting type 2 diabetes (T2D) diagnosis (high fasting glucose) but no physician 'official' mention (see criteria in Table XVII). On the other side, the clinic chart for the same patient gave the information that a physician had in fact diagnosed T2D following appropriate testing.

3.6. DIAGNOSIS ASCERTAINMENT AND CLASSIFICATION

Dr. Milenko Petrovich, an Internist with a special background in cardiology was consulted during this study and ascertained all diagnostic findings. For the purpose of this study, the consulting specialist has examined in depth each patient's diagnosis (and undiagnosed diseases) in order to confirm the data and check for false positive or negative results for this study (e.g. misdiagnosis of DM with documented laboratories meeting criteria or undiagnosed CVD). This will be discussed more in length in the "Discussion" Chapter.

The definitions used to classify the diseases in their respective categories are discussed in the following sections. They were chosen after lengthy discussion with the Adjudication Committee in order to have as much as possible an objective system to stratify the subjects. The dichotomous distinction of diagnosis into FO and NFO is based on the potential severity of the diseases in relation to their risk of mortality (Figure 11). Here, we will explain our reasoning while the limitations themselves will be discussed later in the Discussion Chapter.

FO are high-risk diseases, which could put at risk for mortality and serious complications. NFO are low-risk conditions, which usually do not result in death or serious complications. Following this train of thought, we have decided to further subdivide the seriousness of the diseases from the circulatory system by using the Major Adverse Cerebral and/or Cardiovascular Event (MACCE) score (discussed in Section 3.18; Table XV). In summary, the advantages of this novel grading systems are (1) that it was adapted to include CBVD and (2) measured the degree of severity.

For example, lets discuss the case of first degree AV block. This pathology has been associated in both healthy patients and those with underlying CHD with a higher risk of morbidity and mortality [173, 174]. In most situations, it is benign and is attributed a MACCE score of 1/4. Nevertheless, in rare situations, a patient can develop a high-grade first degree AV block. Being potentially deadly, this is a recommendation for a pacemaker and would be classified as MACCE 3/4 [174].

Another example is sinus bradycardia. In the great majority of cases, it is also a benign condition, which can be caused by medication or physiological consequence of training [175]. However, in some situations, low cardiac output and symptomatic hypotension can cause sinus bradycardia to be potentially deadly, which absolutely requires permanent pacemaker implantation. This situation is relatively frequent in clinical practice. Thus, FO (high-risk diseases) have in addition the MACCE scoring while NFO (or with low-risk) do not.

3.7. DEFINING DIAGNOSIS AND OUTCOMES

In this present analysis, we made a distinction between a diagnosis and an outcome.

Diagnosis comprise all the health events that have occurred to the subject before the current analysis but since enrolling in the study, i.e. over the last 11 years.

Outcomes we define an 'outcome' as an event with high risk of morbidity that has occurred to a given subject after the time (year) he/she entered the study. *Note:* for a known and documented outcome without a specific date, the year of the patient's enrollment will be taken into account (e.g. as if the outcome occurred right after his/hers enrollment).

First outcome is the term used to define the very first event that affected the subject following his/her enrollment.

Here is an example of a subject's medical history (Figure 11). Subject A enrolled in the study in 1995 and has suffered from three events: the first in 1980, the second in 1995 and the third in 2010; this patient had three diagnosis (1980) but only two of them are considered outcomes (1995 and 2010). In this case the first outcome would be in 1995.

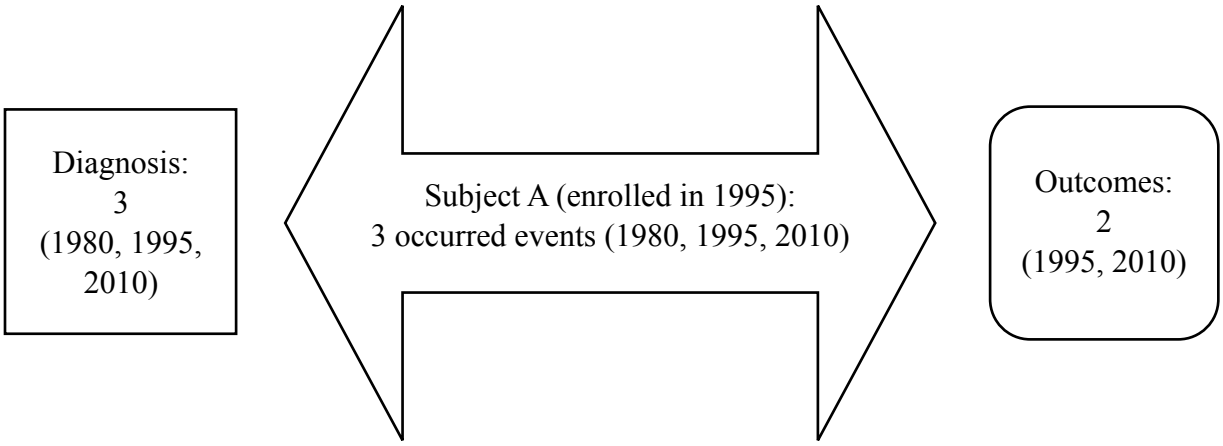
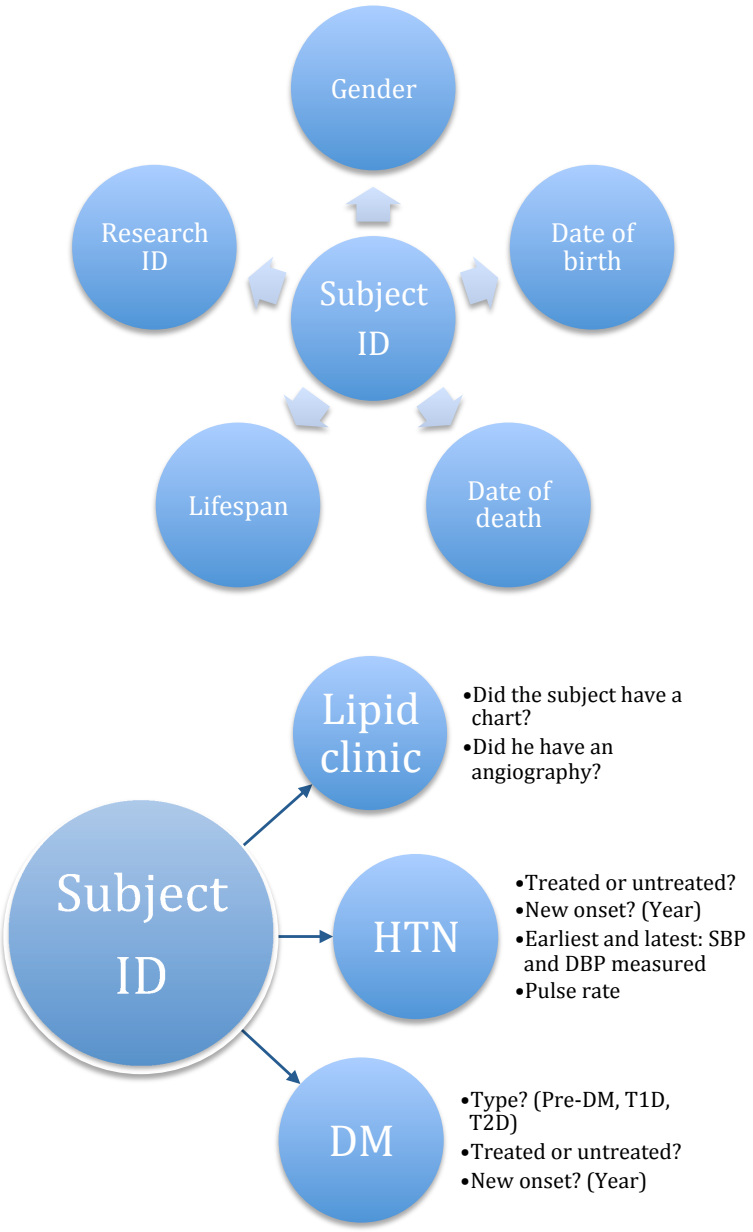


Figure 11. Schematic explanation of the medical history classification in outcomes and diagnosis for hypothetical Subject A.

3.8. FIRST STAGE: SUBJECT IDENTIFICATION

A total of 380 subjects were examined through their medical records at the Hospital or Lipid Clinic at the *Centre de santé et des services sociaux de Chicoutimi*. In the following figure, we will show the basic information ascertained for each subject's identification and medical history in cases of both fatal and non-fatal outcomes (Figure 12). This pertains to the subject's identification and global affections related to DM and HBP. More detailed information about each criteria and ICD used will be discussed later in this Chapter.



Figures 12. Subjects' primary data used for identification and analysis of FO and NFO.
Note: date of death was only given when appropriate. ID=Identification

3.9. SECOND STAGE: FATAL OUTCOMES

As previously mentioned, the morbidity and mortality data gathered comprise common data designs, e.g. for living and deceased subjects. The following figure depicts the diagnosis organization for CV FO (Figure 13).

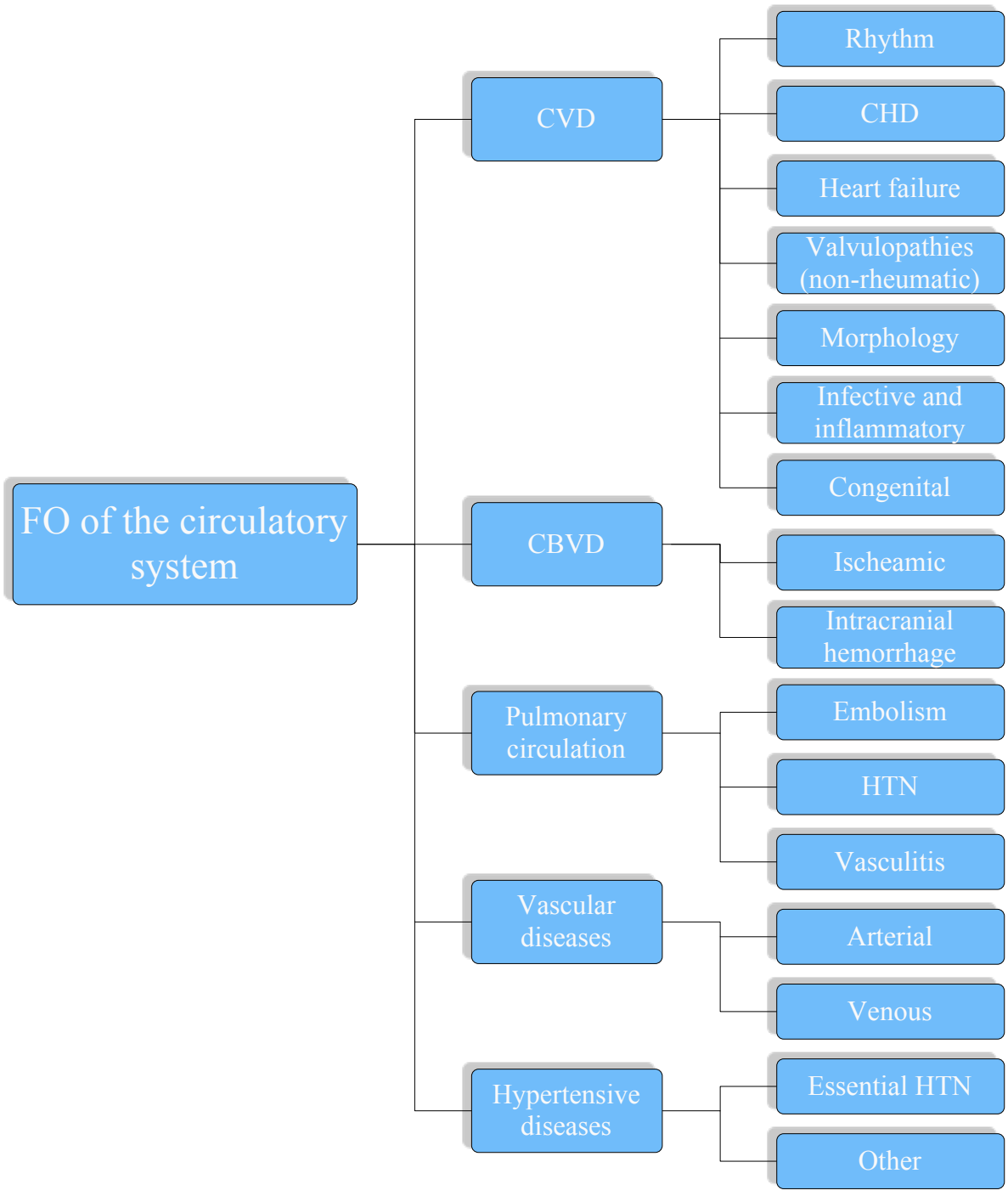


Figure 13. Second stage: FO of the circulatory system. It is to be noted that renal failure from CV origin has also been classified in this category, under "Hypertensive diseases - other".

Each of the sub-categories of Figure 12 encompasses different diseases, which will be detailed in the section "Data compilations" of this Chapter. The following figures depict the FO organization for non-CV origin and all other causes (Figures 14 and 15, respectively).

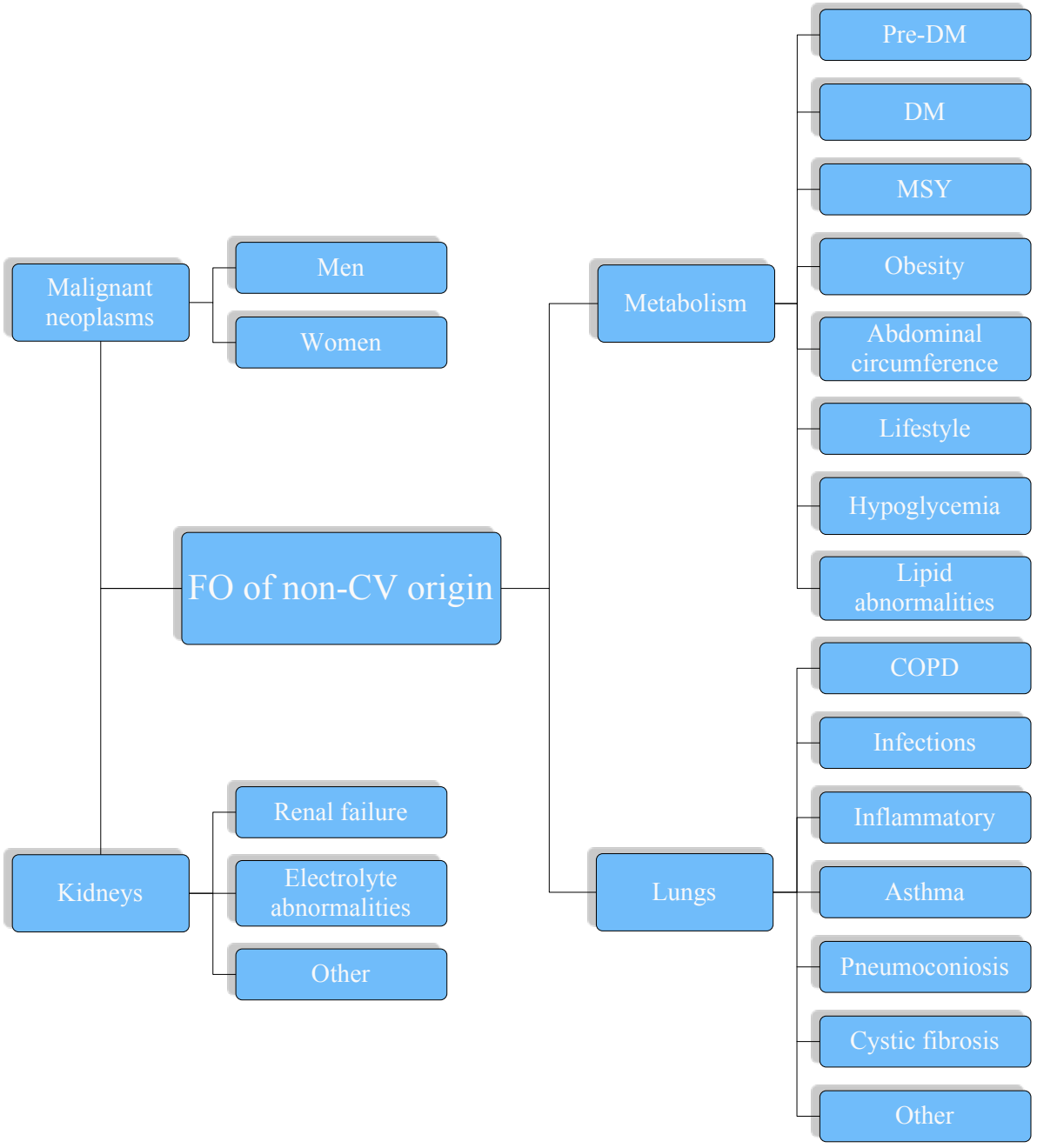


Figure 14. Second stage: FO of non-CV origin.

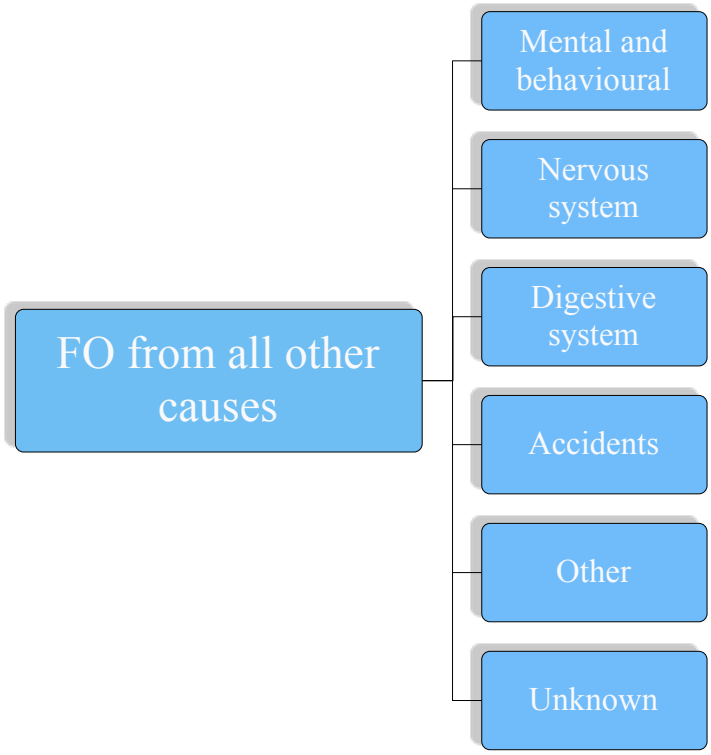


Figure 15. Second stage: FO from all other causes.

3.10. THIRD STAGE: NON-FATAL OUTCOMES

As previously mentioned, the morbidity and mortality data gathered comprise common data designs, e.g. for living and deceased subjects. The following figure depicts the organization of NFO from the circulatory system, as well as non-CV and all other causes (Figure 16, 17 and 18, respectively).

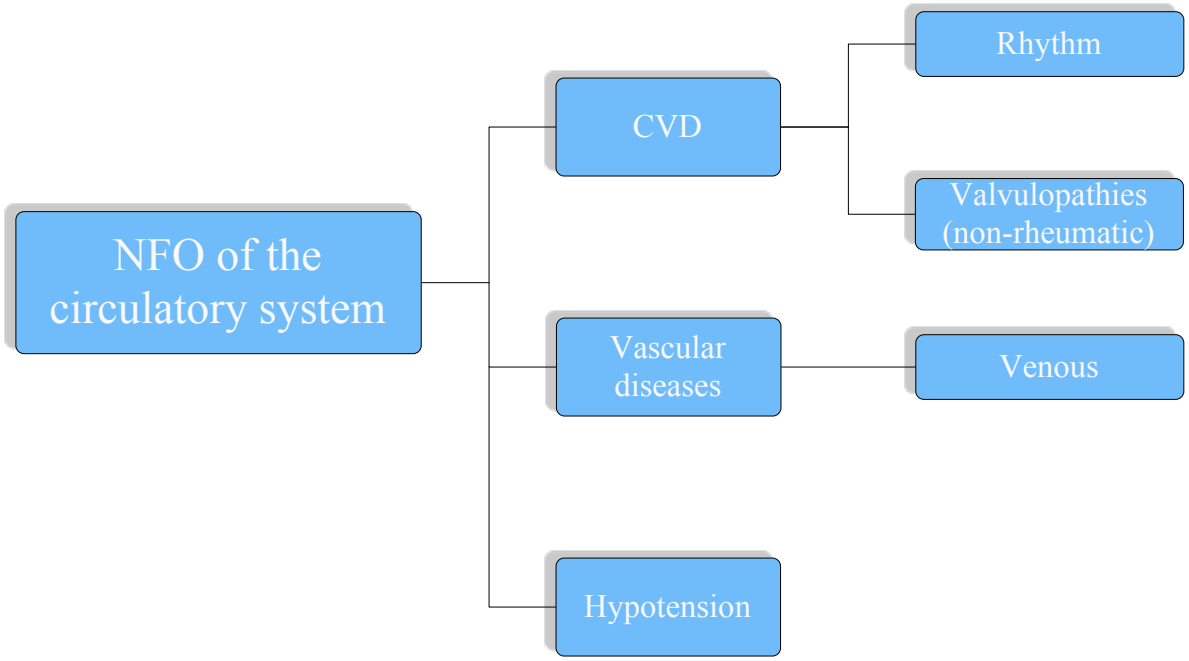


Figure 16. Third stage: NFO of the circulatory system.

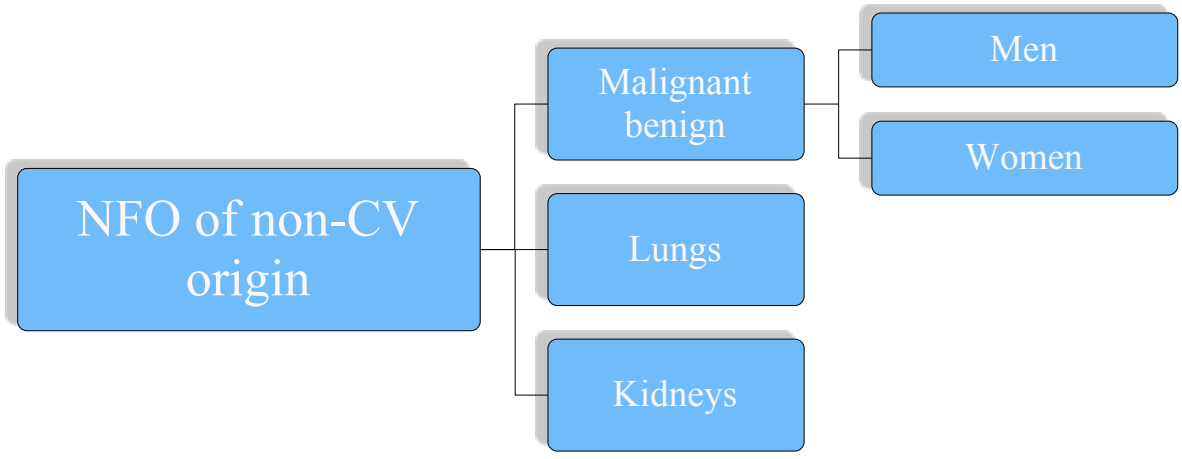


Figure 17. Third stage: NFO of non-CV origin.

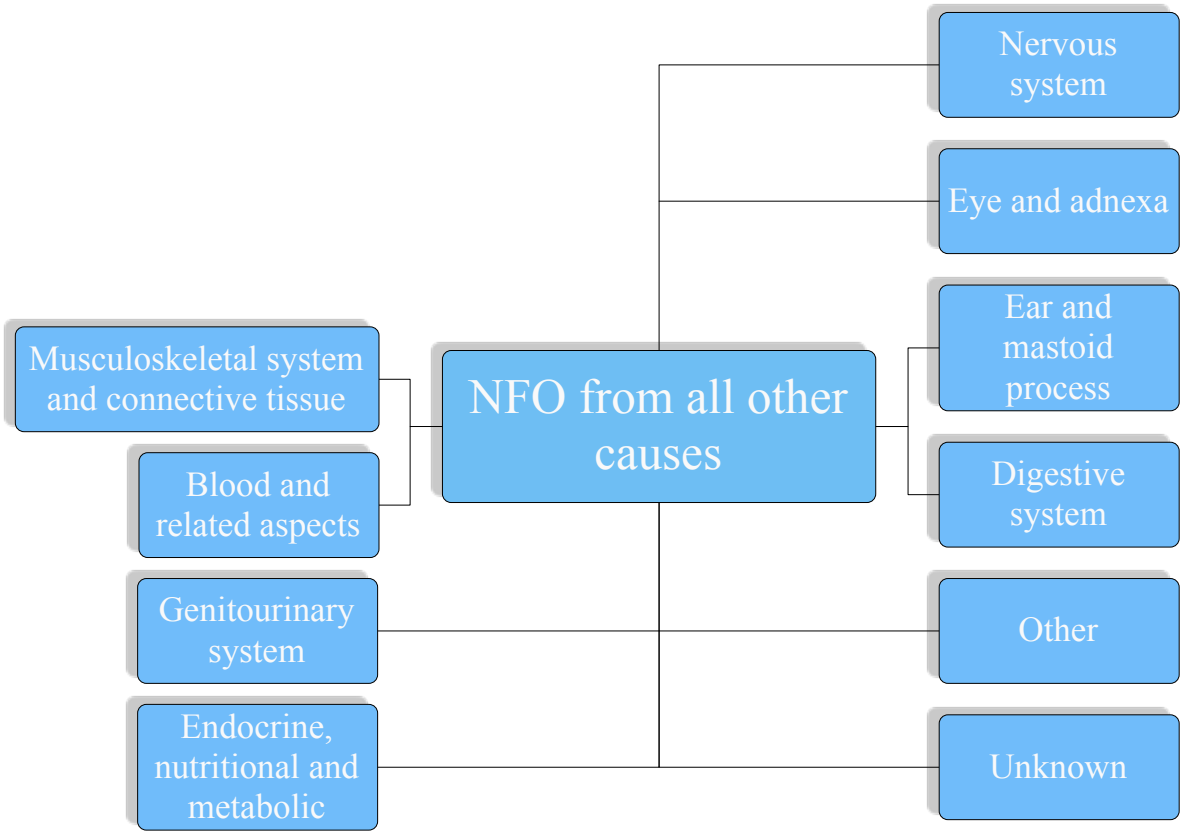


Figure 18. Third stage: NFO from all other causes.

3.11. FOURTH STAGE: SUPPORTING INFORMATION FOR FATAL OUTCOMES

In order to assess a subject's state or FO, i.e. for the morbidity and mortality causes, a rigorous and consistent documentation sources have to be observed. All diagnostics and causes of death have been documented according to the available proof in the subject's medical records (Table V). In case of contradiction between diagnostic and medical test results, the consulting internist on the research project decided the final marked diagnostics. For example, diagnosed angina with normal stress test and angiography is dismissed according to the specific tests done to the patient.

Table V. Supporting documentation for FO.

Outcomes	Supporting documentation (if available)
Non-fatal stroke	Clinical notes (e.g. Discharge summary) CT report MRI report Any other relevant documentation
Non-fatal myocardial infarction	Clinical notes (e.g. Discharge or admission summary) Laboratory reports of biochemical markers of myocardial Injury (e.g. Creatine kinase and/or troponins) ECG reports Any other relevant documentation
Death	Clinical notes Death certificate Autopsy report Any documentation supporting the diagnosis if autopsy not performed Any other relevant documentation
New or worsening nephropathy	Clinical notes Laboratory reports of urinalysis Note: Microalbuminuria must be confirmed on two separate specimens. Laboratory reports clearly indicating the change in serum creatinine during study follow-up.
New or worsening eye disease	Ophthalmologist or other report, which may include reference to: Retinal photographs Fundoscopy Visual acuity Any other relevant documentation
Fatal accidents caused by cardiovascular defects	Autopsy report Death certificate Medical history records Discussion with physicians

3.12. FOURTH STAGE: SUPPORTING INFORMATION FOR DIAGNOSIS

Diagnosis recorded were supported, when possible, with laboratories and specialized medical tests (Table VI). This information was referred to by the Adjudication Committee when discussion about subjects' diagnosis. The specialist, also, used this information in order to

confirm each diagnosis or not. It is to be noted that not all the following information was available systematically for each patient. Nevertheless, depending on the subject's affection, these were usually enough to support the diagnosis.

Table VI. Fourth stage: supporting information for diagnosis of FO and NFO.

Clinical exams and questioning	
Personal Habits	**Anthropometric data**
Smoking	Weight (kg)
Degree of physical activity	Height (cm)
Drinking status (alcohol use)	BMI (kg/(cm^2))
Drug abuse	Body composition
Medications	Abdominal circumference
Laboratories	
Blood sugar level (random, fasting, etc.)	Iron profile (TIBC, iron, ferritin, transferrin)
Coagulogram (PT (INR), PTT, bleeding time, fibrinogen)	Liver profile (e.g. AST, ALT, GGT, bilirubin, alkaline phosphatase, LDH)
Cardiac profile (CK, CK-MB, TnI, TnT)	CBC (leucocytes, erythrocytes, hemoglobin, hematocrit, etc.)
Renal profile (BUN, creatinine, eGFR, urinalysis, electrolytes—Na^+, K^+, Cl^- and bicarbonates)	Lipid profile (e.g. total CHOL, HDL-c, LDL-c, TG, CHOL/HDL ratio)
TSH	Albumin (g/L)
Globulin (g/L)	Total proteins (g/L)
A.C.E. antigen	Oxygen saturation
Other labs	
Specific Medical Exam	
Resting ECG	ECHO
Exercise tolerance (STRESS) test	Holter monitoring

Clinical exams and questioning	
Radionuclide myocardial perfusion imaging (exercise and dipyridamole)	Coronary angiography
Other angiography	Arterial and venous Doppler
Left ventricular catheterization, ventriculography and selective coronary angiography	
All other relevant reports (e.g. lung X-rays, CT scan, MRI, etc.)	

A.C.E.=Angiotensin converting enzyme
ALT=Alanine amino-transaminase
AST=Aspartate amino-transaminase
BUN=Blood urea nitrogen
CBC=Complete blood count
CK=Creatinine kinase
CK-MB=Creatinine kinase myoglobin band
CT=Computerized tomography
ECG=Electrocardiogram
ECHO=Echocardiogram
eGFR=Estimated glomerular filtration rate
GGT=Glutamine amino-transaminase
INR=International normalized ratio
LDH=Lactic dehydrogenase
MRI=Magnetic resonance imaging
PT=Prothrombin time
PTT=Partial thromboplastin time
TIBC=Total iron binding capacity
TnI=Troponin I
TnT=Troponin T

3.13. DATA COMPILATIONS

Bearing in mind the basic overview of the six subcategories (Figure 9) and the data sections for FO and NFO (Figures 13 to 18), we decided on the following design for the data compilations for all subjects. As such, we show in the following tables how our complex data were finally organized and classified (Table VII to XII). After this strategic approach, each sub-group was organized following the WHO's ICD 10 (www.who.org; ICD will be discussed later in this Chapter). *Note:* Tables correspond to their respective figures (i.e. Table VII and Figure 13; VIII and 14; IX and 15; X and 16; XI and 17; XII and 18).

Table VII. Classification of the circulatory system FO. MACCE score is adjusted if necessary for each patient. ICD10 coding is also specified individually for each disease.

FO of the circulatory system				***ICD***	***MACCE***
Rhythm pathologies	*Atrial*	*Bradycardia*	Sinus or atrial	R00.1	1-3
		Sinus pathologies	Pauses <3 seconds long	I45.5	1
			Pauses >3 seconds long	I45.5	2

FO of the circulatory system				***ICD***	***MACCE***
			Sinus arrest	I45.5	3
			Sick sinus syndrome	I49.5	2
		Non sinus pathologies	Fibrillation and flutter (with CHADS 2)	I48	1
			Multifocal atrial rhythm		
	AV	*AV-Bloc 1'*		I44.0	1-3
		AV-Bloc 2'	Wenckebach (Mobitz 1)	I44.1	1
			Mobitz 2	I44.1	3
			High grade 2' block	I44.1	3
		AV-Bloc 3'	Complete	I44.2	3
		AV dissociation		I45.8	3
		Accessory pathway		I45.6	1
		PSVT		I47.1	1
	Ventricular	*Left bundle branch block*		I44.7	3
		Ventricular tachycardia	Non-sustained	I47.2	3
			Sustained	I47.2	3
			Torsade de points	I47.2	3
		Ventricular flutter		I49.0	3
		Ventricular fibrillation		I49.0	3
		Cardiac arrest		I46	3
	Other	*Electromechanical dissociation*		R94.3	
		Diagnosis and outcomes			
		Subjects			
		First outcome (/%)			
CHD	*Angina*	*Unstable angina*	Angina: - crescendo - de novo effort - worsening effort Intermediate coronary syndrome Pre-infarction syndrome and post-MI	I20.0	3
		Angina pectoris with documented spasm	Angina: - angiospastic - Prinzmetal - spasm-induced - variant	I20.1	3
		Other forms of angina pectoris	Angina of effort Stenocardia	I20.8	3
		Angina pectoris, unspecified	Angina: -non otherwise specified -cardiac Anginal syndrome Ischeamic chest pain	I20.9	0-3
	MI	*Transmural*	Anterior wall	I21.0	3
			Inferior wall	I21.1	3
			Other sites	I21.2	3

FO of the circulatory system				***ICD***	***MACCE***
			Unspecified sites	I21.3	3
		Sub-endocardial		I21.4	3
		Unspecified		I21.9	3
		Old		I25.2	3
		Multiple MI		I21	3
		Total MI		I21	3
	Other CHD			I25.9	3
	AG	*Normal*	Coronary arteries without any stenosis	I25.1	1
		Mild CAD	Stenosis <70%	I25.1	2
		Single vessel disease	One major CAD	I25.1	3
		Two vessel disease	Two major CAD or isolated left main CAD	I25.1	3
		Three vessel disease	All major CAD or right and left main CAD	I25.1	3
		Terminal CAD	Stenosis non amenable to CABG or PTCA	I25.1	3
		Grafts	Bypass grafts' stenosis	I25.1	3
	Treatment	*CABG*	2 grafts	Z95.1	3
			3 grafts	Z95.1	3
			≥4 grafts	Z95.1	3
			Unspecified	Z95.1	3
		PTCA	Low risk—No high risk features	Z95.5	2
			High risk—Multiple stents, long lesions, bifurcation lesion	Z95.5	3
			Unspecified	Z95.5	-
		Diagnosis and outcomes Subjects First outcome (/%)			
HF (cardiac insufficiency)	*LVSD*	Mild	EF 40-49%	I50.1	1
		Moderate	EF 30-39%	I50.1	2
		Severe	EF ≤ 29%	I50.1	3
		Unspecified		I50.1	0
	RVSD	Mild		I50.0	1
		Moderate		I50.0	2
		Severe		I50.0	3
	LVDD	Mild	Abnormal relaxation	I50.1	1
		Moderate	Pseudo-normalization	I50.1	2
		Severe	Restricted	I50.1	3
		Diagnosis and outcomes Subjects First outcome (/%)			
Valvulopathies (non-rheumatic valve disorders)	*Ar*	Mild		I35.1	1
		Moderate			2
		Severe			3
	As	Mild		I35.0	1
		Moderate			2
		Severe			3
	Mr	Mild		I34.0	1

FO of the circulatory system			***ICD***	***MACCE***
		Moderate		2
		Severe		3
		Unclassified		-
	Ms	Mild	I34.2	1
		Moderate		2
		Severe		3
		Unclassified		-
	Tricuspid regurgitation/ stenosis	Mild	I36.0,I	1
		Moderate	36.1	2
		Severe		3
	Pulmonary stenosis, regurgitation or congenital anomaly	Mild	I37.0,	1
		Moderate	I37.1,	2
		Severe	Q22.1	3
		Diagnosis and outcomes		
		Subjects		
		First outcome (/%)		
Morphologic abnormalities	*LVH*	By ECHO	I51.7	2
		By ECG		1
	RVD and LVD		I51.7	3
	Other	Auricular dilatation, etc.	I51.9	1-3
		Diagnosis and outcomes		
		Subjects		
		First outcome (/%)		
Infective and inflammatory heart disease	*Endocarditis*		I39	3
	Myocarditis		I40	3
	Pericarditis		I30.1	3
	Other	Unspecified, Carditis, Rheumatic fever, etc.	I51.8, I01	2
		Diagnosis and outcomes		
		Subjects		
		First outcome (/%)		
Congenital defects			Q20-Q28	1, 2, 3
		Diagnosis and outcomes		
		Subjects		
		First outcome (/%)		
All cardiac events		Diagnosis and outcomes		
		Subjects		
		First outcome (/%)		
Ischeamic	*TIA*		G45	3
	RIND		I63.5	3
	Stroke (Cerebral infarction)	*Thrombotic infarct*	I63.3	3
		Embolic infarct	I63.4	3
		Diagnosis and outcomes		
		Subjects		
		First outcome (/%)		

FO of the circulatory system			***ICD***	***MACCE***
Intracranial hemorrhage	*Epidural*	Chronic	I62.1	2
		Acute		3
	Subarachnoid	Chronic	I60	2
		Acute		3
	Intracerebral		I61	3
		Diagnosis and outcomes		
		Subjects		
		First outcome (/%)		
All CBVD events		Diagnosis and outcomes		
		Subjects		
		First outcome (/%)		
Diseases of the pulmonary circulation	*Embolism*	Chronic	I26	3
		Acute		3
	Hypertension	Mild	I27	1
		Moderate		2
		Severe		3
	Vasculitis	Without alveolar hemorrhage	I77.6	2
		With alveolar hemorrhage		3
All events of the pulmonary circulation		Diagnosis and outcomes		
		Subjects		
		First outcome (/%)		
Vascular disease - Arterial	*CBVD*	Atherosclerosis and unspecified hemorrhage	I60.9, I67.2	3
	Thoracic aorta	Atherosclerosis (including embolism and thrombosis)	I70.0, I74.1	3
		Aneurism	I71.1, I71.2	1-3
		Dissection	I71.0	1-3
	Abdominal aorta	Atherosclerosis	I70.0	3
		Aneurism	I71.3,I 71.4	1-3
		Dissection	I71.0	1-3
	Renovascular disease	Atherosclerosis of renal artery and arterioles	I70.1	3
		Renal ischemia and infarction	N28.0	
	Intestinal vascular disease	Mesenteric ischemia and/or necrosis	K55.1	1-3
		Atherosclerosis	I70.8	3
	Peripheral vascular disease	Atherosclerosis and aneurisms of arteries of extremities	I70.2, I73,	3
		Multiple arterial embolisms and thrombosis	I74	
		Other peripheral vascular disease (ischemia, etc.)		
Vascular disease - Venous	*SVT*		I80,	1
	DVT		I82	3
All vascular disease		Diagnosis and outcomes		
		Subjects		
		First outcome (/%)		
Essential (primary) hypertension	*Controlled*		I10	1
	Uncontrolled			3
	Unspecified			0

FO of the circulatory system				*ICD*	*MACCE*
	Mean BP measurements	SBPΔ DBPΔ	2.00 -6.79		- -
Other hypertensive diseases	*Hypertensive heart disease* *Hypertensive renal disease* *Hypertensive heart and renal diseases* *Secondary hypertension*			I11 I12 I13 I4	3 3 3 3
All hypertensive diseases		Diagnosis and outcomes Subjects First outcome (/%)			
	Total	**Participating ♀ subjects** **Participating ♂ subjects** **Subjects affected** **Subjects with outcomes** **Outcomes** **First outcome (/%)** **Diagnosis**			

AG=Angiography
Ar=Aortic regurgitation
As=Aortic stenosis
AV=Atrial-ventricular
CAD=Coronary artery disease
CABG=Coronary artery bypass grafting
CHADS 2=Congestive HF, HBP, Age, DM, and Stroke (or prior TIA)
CBVD=Cerebrovascular diseases
DVT=Deep venous thrombosis
EF=Ejection fraction
ECG=Electrocardiogram
ECHO=echocardiogram
EF=Ejection fraction
LVD=Left ventricular dilatation
LVDD=Left ventricular diastolic dysfunction
LVH=Left ventricular hypertrophy
LVSD=Left ventricular systolic dysfunction
Mr=Mitral regurgitation
Ms=Mitral stenosis
PSVT=Paroxystic supra-ventricular tachycardia
RIND=Reversible ischemic neurological deficit
RVD=Right ventricular dilation
RVSD=Right ventricular systolic dysfunction
SVT=Superficial venous thrombosis
TIA=Transient ischemia attack

Table VIII. Classification of non-CV FO. ICD10 coding is also specified individually for each disease.

Non-CV FO			*ICD*
Malignant neoplasms	*Men*	Lip, oral cavity and pharynx	C00-C14
		Digestive organs	C15-C26, D01
		Respiratory and intrathoracic organs	C30-C39
		Bone and articular cartilage	C40-C41
		Skin	C43-C44
		Mesothelial and soft tissue	C45-C49
		Breast	C50
		Male genital organs	C60-C63
		Urinary tract	C64-C68
		Eye, brain and other parts of CNS	C69-C72
		Thyroid and other endocrine glands	C73-C75
		Ill-defined, secondary and unspecified sites	C76-C80

Non-CV FO				***ICD***
		Lymphoid, hematopoietic and related tissue		C81-C96
		Independent multiple sites		C97
		Diagnosis and outcomes		
		Subjects		
		First outcome (/%)		
	Women	Lip, oral cavity and pharynx		C00-C14
		Digestive organs		C15-C26
		Respiratory and intrathoracic organs		C30-C39
		Bone and articular cartilage		C40-C41
		Skin		C43-C44
		Mesothelial and soft tissue		C45-C49
		Breast		C50
		Female genital organs		C51-C58
		Urinary tract		C64-C68
		Eye, brain and other parts of CNS		C69-C72
		Thyroid and other endocrine glands		C73-C75
		Ill-defined, secondary and unspecified sites		C76-C80
		Lymphoid, haematopoietic and related tissue		C81-C96
		Independent multiple sites		C97
		Diagnosis and outcomes		
		Subjects		
		First outcome (/%)		
All neoplasm events		Diagnosis and outcomes		
		Subjects		
		First outcome (/%)		
Metabolic causes	*Pre-DM*	AFG and IFT		E74.3, R73.0
		Diagnosis and outcomes		
		Subjects		
		First outcome (/%)		
	DM	Type I		E10
		Possible Type II (not confirmed by 2nd test)	Diet	E11
			Oral Rx	
		Type II	Treated with diet	E11
			Oral Rx	
			Insulin Rx	
		Unspecified	Treated with diet	E14
			Oral Rx	
			Insulin Rx	
		Diagnosis and outcomes		
		Subjects		
		First outcome (/%)		

Non-CV FO				***ICD***
	Metabolic syndrome	Previously undiagnosed Criteria		E88.81
		Diagnosis		
	Obesity	Underweight	BMI<18.00	R62.8
		Normal	BMI 18.00-24.99	-
		Overweight	BMI 25.00-29.99	E66.9
		Mild	BMI 30.00-34.99	E66.8
		Moderate	BMI 35.00-39.99	E66.8
		High	BMI>40.00	E66.8
		Diagnosis		
	Abdominal circumference	Men	Abnormal>94 cm	-
			Average (/cm)	-
		Women	Abnormal>80 cm	-
			Average (/cm)	-
		Diagnosis		
	Lifestyle	Smoking		Z72.0
		Alcohol		Z72.1
		Drugs		Z72.2
		Diagnosis		
	Hypoglycemia			E16.2
		Diagnosis and outcomes		
		Subjects		
		First outcome (/%)		
	Lipid abnormalities	PH		E78.0
		FCD		E78.4
		DBL		E78.2
		Heterozygous FH		E78.0
		Homozygous FH		E78.0
		HTG	Borderline high	E78.1
			High	E78.1
			Severe	E78.1
		HALP		E78.6
		Unclassified		E78.8, E78.9
		Diagnosis and outcomes		
		Subjects		
		First outcome (/%)		
All metabolic events		Diagnosis and outcomes		
		Subjects		
		First outcome (/%)		
Lung diseases	*COPD*			J44
	Infection	Pneumonia and Influenza		J09-J18
		Collagen vascular diseases		J84.17

Non-CV FO				***ICD***
	Inflammatory			J20-22
	Asthma			J45
	Pneumoconiosis			J60-J65
	Cystic fibrosis			E84
	Other	ARDS, etc.		J80 [J00-J99]
All lung events		Diagnosis and outcomes Subjects First outcome (/%)		
Kidney disorders	*Renal failure*	Pre-renal		-
		Renal		-
		Post-renal		-
		Unspecified Ex		N19
		Acute		N17
		Chronic		N18
	Electrolyte abnormalities	Sodium (Na+)	High	E87.0
			Low	E87.1
		Potassium (K+)	High	E87.5
			Low	E78.6
	Other			N00-N29
All kidney events		Diagnosis and outcomes Subjects First outcome (/%)		
	Total	**Participating ♀ subjects** **Participating ♂ subjects** **Subjects affected** **Subjects with outcomes** **Outcomes** **First outcome (/%)** **Diagnosis**		

ARDS=Adult respiratory distress syndrome Rx=Medication

Table IX. Classification of all other FO. ICD10 coding is also specified individually for each disease.

FO from all other causes		***ICD***
Mental and behavioral		F00-F99
Nervous system	Alzheimer's disease, etc.	G00-G99
Digestive system	Other (e.g. sub-occlusion/ileum)	K00-K93
Accidents		V01-X59
Other	Bleeding, Enterocolitis due to *Clostridium difficile*, etc.	
Unknown		R69
Total	**Participating ♀ subjects**	

FO from all other causes	*ICD*
Participating ♂ subjects	
Subjects affected	
Subjects with outcomes	
Outcomes	
First outcome (/%)	
Diagnosis	

Table X. Classification of NFO from the circulatory system. MACCE score is considered as 1/4 for all diseases in the category. ICD10 coding is also specified individually for each disease.

NFO of the circulatory system—MACCE 1					*ICD*
Cardiac diseases	*Rhythm pathologies*	*Atrial*	Sinus pathologies	Premature depolarization (ES)	*I49.1*
				Tachycardia	*I47.1*
				Arrhythmia	*I49*
			Non sinus pathologies	Multifocal rhythm	*I49*
				Multifocal tachycardia	*I49*
		AV	Junctional tachycardia		*I47.1*
			Junctional premature contractions		*I49.2*
		Ventricular	Premature depolarization	(Extrasystole)	*I49.3*
			Hemiblock		*I44.6, I45.4*
			Bundle branch block		*I44.7*
	Non-rheumatic valve disorders	*Aortic*	Sclerosis, calcification and thickening		*I35.8*
		Mitral	Sclerosis, calcification and thickening		*I34.8*
			Prolapse		*I34.1*
		Tricuspid	Sclerosis, calcification and thickening		*I36.8*
		Pulmonary	Sclerosis, calcification and thickening		*I37.8*
Subtotal	Subjects Diagnosis				
Vascular diseases	*Venous*		Varicose veins, Hemorrhoids, etc.		*I83, I84, I87.2*
Subtotal	Subjects Diagnosis				
Hypotension		*Low risk* *High risk* *Unclassified*			*I95*
Subtotal	Subjects Diagnosis				

NFO of the circulatory system—MACCE 1		*ICD*
Total	**Participating ♀ subjects**	
	Participating ♂ subjects	
	Subjects affected	
	Diagnosis	

Table XI. Classification of non-CV NFO. ICD10 coding is also specified individually for each disease.

Non-CV NFO			*ICD*
Benign neoplasms	*Men*	Lip, oral cavity and pharynx	D10, D11
		Digestive organs	D12, D13
		Respiratory and intrathoracic organs	D14, D15
		Bone and articular cartilage	D16
		Skin	D23
		Mesothelial and soft tissue	D19-D21
		Breast	D24
		Male genital organs	D29
		Urinary tract	D30
		Eye, brain and other parts of CNS	D31-D33
		Thyroid and other endocrine glands	D34, D35
		Lymphoid, haematopoietic and related tissue	D36
		Other	D17, D18, D36
		Independent multiple sites	
	Women	Lip, oral cavity and pharynx	D10, D11
		Digestive organs	D12, D13
		Respiratory and intrathoracic organs	D14, D15
		Bone and articular cartilage	D16
		Skin	D23
		Mesothelial and soft tissue	D19-D21
		Breast	D24
		Female genital organs	D25-D28
		Urinary tract	D30
		Eye, brain and other parts of CNS	D31-D33
		Thyroid and other endocrine glands	D34, D35
		Lymphoid, hematopoietic and related tissue	D36
		Other	D17, D18, D36
		Independent multiple sites	
Subtotal		Diagnosis	

Non-CV NFO			*ICD*
Lung diseases			J00-J99
Kidney disorders			N00-N99
Total		***Participating ♀ subjects***	
		Participating ♂ subjects	
		Subjects affected	
		Diagnosis	

Table XII. Classification of all other NFO. ICD10 coding is also specified individually for each disease.

NFO from all other causes		*ICD*
Mental and behavioral	Anxiety	F00-F99
	Other	
Nervous system		G00-G99
Eye and adnexa	Cataracts, etc.	H00-H59
Ear and mastoid process		H60-H95
Digestive system		K00-K93
Genitourinary system		N00-N99
Endocrine, nutritional and metabolic	Hypothyroidism	E00-E90
	Hyperthyroidism	
Blood and blood-forming organs and certain disorders involving the immune mechanism	Anemia, etc.	D50-D89
	Other	
Musculoskeletal system and connective tissue		M00-M99
Accidents		V01-X59
Other		
Unknown		R69
Total	**Participating ♀ subjects**	
	Participating ♂ subjects	
	Subjects affected	
	Diagnosis	

3.14. RESULT CALCULATIONS

In each of the detailed tables for FO and NFO sub-categories, results were organized to show (1) the number of events or '*n*' (e.g. the number of affections for a given diseases), and (2) the *n* subtype percentage (%) compared to all events of the disease type it belongs to (e.g.

bradycardia importance in rhythm pathologies, and total percentage (%) of the event's weight in the whole sub-category of diseases: e.g. bradycardia in CV FO). The following table explains all the results calculated within each sub-category (Table XIII). Also, each percentage for a sub-category is compared to its respectful type, i.e. diagnosis % vs. all diagnosis %, outcome % vs. all outcomes %, first outcome % vs. all first outcomes % of each given subcategory.

Table XIII. Explanation of the result calculations.

FO of the circulatory system			***n***	***Subtype %***	***Total %***
Rhythm pathologies	*Atrial*	Bradycardia	A	= (A/C) × 100	= (A/P) × 100
		Sinus pathologies	B	= (B/C) × 100	= (B/P) × 100
		...	...		
	...	...			
		Diagnosis	C	= (C/G) × 100	= (C/N) × 100
		Subjects with outcomes	D	= (D/G) × 100	= (D/N) × 100
		Outcomes	E	= (E/G) × 100	= (E/N) × 100
		First outcomes	F	= (F/G) × 100	= (F/G) × 100
Cardiac diseases		Diagnosis	G	-	= (G/N) × 100
		Subjects with outcomes	H	-	= (H/K) × 100
		Outcomes	I	-	= (I/L) × 100
		First outcomes	J	-	= (J/M) × 100
Total	**...**		**...**		
	Subjects with outcomes		**K**		
	Outcomes		**L**		
	First outcome		**M**		
	Diagnosis		**N**		

3.15. RELATIVE RISK

The basis of our relative risk (RR) calculation is a ratio between proportions of cases with a positive outcome in two groups [103]:

$$RR = \frac{\frac{a}{(a+b)}}{\frac{c}{(c+d)}} = \frac{a}{(a+b)}\ x\ \frac{(c+d)}{c}$$

$where$:
$a - number\ of\ positive\ outcomes\ of\ exposed\ group$
$b - number\ of\ negative\ outcomes\ of\ exposed\ group$
$c - number\ of\ positive\ outcomes\ of\ control\ group$
$d - number\ of\ negative\ outcomes\ of\ control\ group$

A RR of 1 signifies that there is no difference between the two groups. However, if RR is < 1, it means the event is less likely to occur in the exposed than the control group. Inversely, if RR is > 1, the experimental group is more susceptible to develop the disease than the control. We used our analyzed subjects as the 'exposed group' and compared them to the general population of SLSJ, 'control group'. The data used for the control group has been presented in Chapter II from the *Agence de la santé et des services sociaux du Saguenay– Lac-Saint-Jean* [19]. Here is a calculated RR:

$$RR = \frac{a}{(a+b)}\ x\ \frac{(c+d)}{c} = \frac{1{,}103}{(1{,}103+1{,}617)}\ x \frac{(3{,}878+22{,}994)}{3{,}878} = 2.8100$$

where: *a = total CV FO in our probands = 1,103*

b = total non-CV FO in our probands = 1,617

c = total CV FO in SLSJ = 3,878

d = total non-CV FO in SLSJ = 22,994

Lastly, calculations were checked through the Belgium MedCalc Software for statistics and significance (http://www.medcalc.org/calc/relative_risk.php). In addition, it calculates a 95% confidence interval (CI) and Z statistic (which indicates the outcome's relationship to the mean in the outcome's group of values). A P-value was also considered and statistically significant if $p \leq 0.05$. Here is an example of the same data previously used for RR calculation but through the aforementioned program (Figure 19):

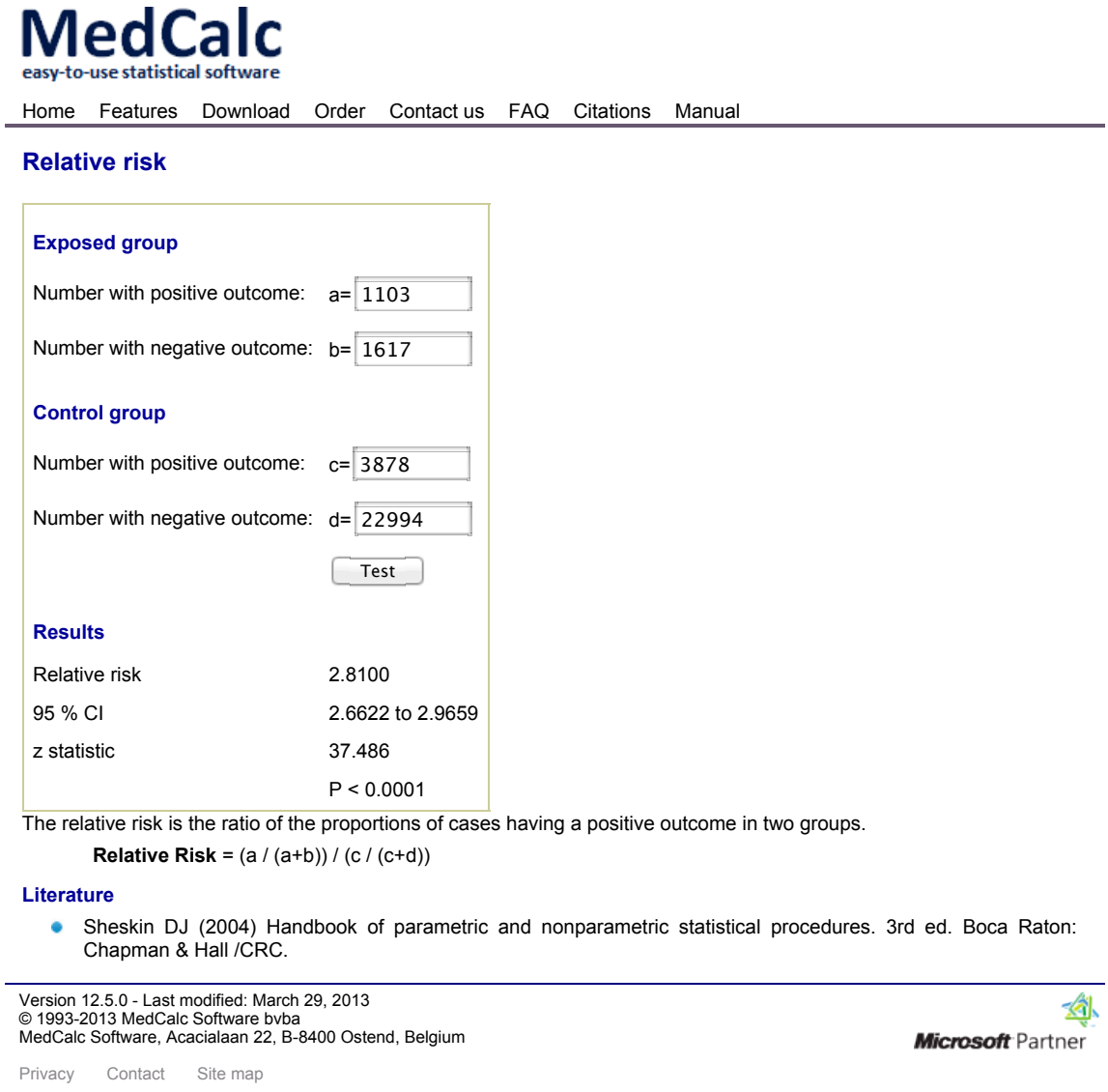


Figure 19. RR calculation with the MedCalc Software 2012, by permission.

3.16. CHI SQUARE TEST

We used the Chi square test (χ^2) to validate our results. With the result for χ^2, we can obtain the p-value by referring to widely available pre-existing tables (on the Internet or statistical books) and identify the corresponding score for the χ^2 obtained. The formula is as follows:

$$\chi^2 = \sum \frac{(O - E)^2}{E}$$

$$\begin{aligned} where \quad \chi^2 &= Chi\ square \\ \sum &= the\ sum\ of \\ O &= observed\ outcomes \\ E &= expected\ outcomes \end{aligned}$$

This test was used to verify the null hypothesis; the observed data frequencies could be predicted from the sample population. In fact, the P-value will answer if the data observe can actually generate a large discrepancy between the expected and observed results. Thus, the smaller is the P-value, the stronger statistical evidence that the values are not sampled from the expected distribution.

The results generate an χ^2 value with its degrees of freedom, and states a P-value. It is to be noted that the same criteria were applied for the P-value ($p \leq 0.05$) as for the RR. We used the California's GraphPad Software founded in 1984 to ascertain calculation for χ^2 test (http://graphpad.com/quickcalcs/chisquared1/). Here is an example of a χ^2 result from this program (Figure 20):

QuickCalcs

1. Select category | 2. Choose calculator | **3. Enter data** | 4. View results

Compare observed and expected frequencies

This calculator compares observed and expected frequencies with the chi-square test. Read an example with explanation.

Enter the names of the categories into the first column (optional). Enter the actual number of objects or individuals or events observed in the second column. Then enter the expected number, fraction or percent expected in the third column.

1. Choose data entry format

- (•) Enter up to 20 categories (rows).
- ( ) Enter or paste up to 2000 categories (rows).

Caution: Changing format will erase your data.

2. How will you enter the expected values?

- (•) Actual number expected
- ( ) Percent expected
- ( ) Fraction expected

Even if you enter the expected values as fractions or percentages, you must enter the the actual number of objects or individuals or events into the Observed column.

3. Enter data

	Category	Observed #	Expected
1:			
2:			

4. View the results

Calculate now

Clear the form

A

QuickCalcs

1. Select category | 2. Choose calculator | 3. Enter data | **4. View results**

Chi-square test results

P value and statistical significance:

Chi squared equals 1575.348 with 1 degrees of freedom.

The two-tailed P value is less than 0.0001

By conventional criteria, this difference is considered to be extremely statistically significant.

The P value answers this question: If the theory that generated the expected values were correct, what is the probability of observing such a large discrepancy (or larger) between observed and expected values? A small P value is evidence that the data are not sampled from the distribution you expected.

Review your data:

Row #	Category	Observed	Expected #	Expected
1	CVD affected	1103	383	14.081%
2	CVD unaffected	1617	2337	85.919%

B

Figure 20. χ^2 test with the GraphPad Software, by permission. A) Inputing the necessary data; B) Results of data inputed in A.

3.17. INTERNATIONAL CLASSIFICATION OF DISEASES

The FO and NFO were meticulously categorized following the ICD from the WHO: ICD version 9 (ICD9) for ones prior to 2000 and ICD version 10 (ICD10) for those from year 2000 onwards, depending on data available. However, for the purpose of reporting in this work, we converted all available ICD9 coding to ICD10 version using the ICD9-ICD10 Conversion Database (http://www.icd10data.com/Convert) and simultaneously consulting the Archives' department of the *Centre de services sociaux de Chicoutimi* in order to limit bias results and confusion between all the coding. Only ICD10 coding was used in the final results presented here (www.who.org; Table XIV).

Table XIV. ICD 10 codes used (www.who.org).

Diseases	ICD10
Circulatory system	
Acute rheumatic fever	I00-I02
Chronic rheumatic heart diseases	I05-I09
Hypertensive diseases	I10-I15
Ischemic heart diseases	I20-I25
Pulmonary heart disease and diseases of pulmonary circulation	I26-I28
Other forms of heart disease	I30-I52
Cerebrovascular diseases	I60-I69
Diseases of arteries, arterioles and capillaries	I70-I79
Diseases of veins, lymphatic vessels and lymph nodes, not elsewhere classified	I80-I89
Other and unspecified disorders of the circulatory system	I95-I99
Neoplasms	
Malignant neoplasms	C00-D48

Diseases	ICD10
Malignant neoplasms, stated or presumed to be primary, of specified sites, except of lymphoid, hematopoietic and related tissue	C00-C75
Lip, oral cavity and pharynx	C00-C14
Digestive organs	C15-C26
Respiratory and intrathoracic organs	C30-C39
Bone and articular cartilage	C40-C41
Skin	C43-C44
Mesothelial and soft tissue	C45-C49
Breast	C50
Female genital organs	C51-C58
Male genital organs	C60-C63
Urinary tract	C64-C68
Eye, brain and other parts of central nervous system	C69-C72
Thyroid and other endocrine glands	C73-C75
Malignant neoplasms of ill-defined, secondary and unspecified sites	C76-C80
Malignant neoplasms, stated or presumed to be primary, of lymphoid, hematopoietic and related tissue	C81-C96
Endocrine, nutritional and metabolic	
Disorders of thyroid gland	E00-E07
Insulin-dependent diabetes mellitus	E10
Non-insulin-dependent diabetes mellitus	E11
Unspecified diabetes mellitus	E14
Obesity and other hyperalimentation	E65-E68
Of the respiratory system	
Acute upper respiratory infections	J00-J06
Influenza and pneumonia	J09-J18
Other acute lower respiratory infections	J20-J22
Other diseases of upper respiratory tract	J30-J39

Diseases	ICD10
Chronic lower respiratory diseases	J40-J47
Other diseases of the respiratory system *(Including lung diseases due to external agents, other respiratory diseases principally affecting the interstitium, suppurative and necrotic conditions of lower respiratory tract and other diseases of pleura)	J60-J99
Of the genitourinary system	
Acute renal failure	N17
Chronic renal failure	N18
Unspecified renal failure	N19

3.18. MACCE

A standard definition for MACE (Major Adverse Cardiovascular Events) does not exist, since it varies from individual outcomes and studies. In this report, we propose an alternate grading system that includes CBVD. To do so, we quantified the diseases from the circulatory system with the MACCE score. This helped us distinguish clinically subjects at a higher or a lower risk within the FO category. More specifically, it helped stratify more accurately the diseases affecting the subjects (Table XV).

Table XV. MACCE grading system.

MACCE Grading System		
Score	***Rank***	***Description***
0	Null	○Unspecified risk
1	Low	○Diseases or conditions that result in death on rare or exceptional occasions and considered generally to have a benign clinical course ○Low risk of death, heart arrest, CPR, malignant arrhythmia, stroke, RIND, TIA, intra-cranial bleeding and major vessel rupture or occlusion
2	Moderate	○Diseases or conditions that do not meet criteria for MACCE 0, 1, 3 or 4.

MACCE Grading System		
Score	***Rank***	***Description***
3	High	○Moderate risk of death, heart arrest, CPR, malignant arrhythmia, stroke, RIND, TIA, intra-cranial bleeding and major vessel rupture or occlusion ○Diseases or conditions that result in death or serious morbidity on frequent occasions and considered generally to have a malignant clinical course ○High risk of death, heart arrest, CPR, malignant arrhythmia, stroke, RIND, TIA, intra-cranial bleeding and major vessel rupture or occlusion
4	Terminal	○No possible chances for improvement with imminent death in the near future. Life expectancy measured at the maximum in few months.

CPR= Cardiopulmonary reanimation

3.19. HYPERTENSION

HBP in subjects was determined by the diagnosis found in their medical records. The treating physician has previously identified this disorder, and related tests and medical notes were found to support this information. In the cases where patients were taking anti-hypertensive medication but no HBP diagnosis was mentioned in their file, we referred to their measured BP to identify criteria for HBP (Table XVI) [104]. In addition, HBP of our subjects was also related to HBP when initially enrolled in the study.

Table XVI. Hypertension criteria [104, 105].

Target groups	***Optimal BP values***
Hospital/Office BP	<140/90
Home BP	<135/85
Patients <80 years	<140/90
Patients ≥80 years	<145/90
DM and/or nephropathy	<130/80

3.20. DIABETES MELLITUS

DM in subjects was determined by the diagnosis found in the medical records. Similarly for other diagnosis, the treating physician, related tests and medical notes were sought to support this information (Table XVII). In the case where patients were taking diabetic medication but no DM was mentioned in their chart, we referred to the consulting specialist to ascertain and identify which type of DM was affecting the subject.

Table XVII. DM criteria were based on the American Diabetes Association Guidelines 2010 (www.diabetes.org).

Tests	***Values***	
	IFG	***DM***
Hemoglobin A1c or glycated hemoglobin (HbA1c; /%)	5.5-6.4	≥6.5
FPG (/mmol/L)	5.5-6.9	≥7
Random plasma glucose (/mmol/L) with symptoms of hyperglycaemia (e.g. polyuria and polydypsia)	-	≥11.1
Glucose tolerance test (/mmol/L; 75g glucose/2 hours)	7.8-11	≥11.1

IFG=Impaired fasting glucose

3.21. METABOLIC SYNDROME AND LIPID ABNORMALITIES

The lipid abnormalities and MSY of the subjects were assessed according to the 2004 International Diabetes Federation Guidelines, Harrison's Manuel of Medicine (17th Edition) and the 2011 American Heart Association guidelines (Tables XVIII and XIX)[106, 107]. It is to be noted that if the subject had a MSY when first seen prior to the enrollment (e.g. in 1995), and, by beginning a healthy lifestyle, resolved his MSY after enrollment (e.g. in 2008), he was still considered as having a MSY by the specialist and the Adjudication Committee. The rationale was that the subject was at risk of having sustained a certain degree of "health

damage" from that condition. The same applied inversely if the patient developed a MSY subsequently to the start of the study. In addition, lipid disorders were diagnosed following the subjects' lipid status without medication (previously phenotyped by Hamet and his colleagues [1]) and complemented with their latest status, if available, in the patient's hospital record.

Table XVIII. MSY criteria according to the International Diabetes Federation [108].

MSY Criteria		***Values***
1st (obligatory) inclusion	Abdominal waist circumference (/cm) **AND** at least two of the following criteria:	♀≥80; ♂≥94
2nd	BP (/mmHg)	>130/85 (or treated HBP)
3rd	FPG (/mmol/L)	>5.6 (or diagnosed DM)
4th	HDL (/mmol/L)	♀<1.29; ♂<1.03 (or treated for low HDL)
5th	TG (/mmol/L)	>1.7 (or treated for high TG)

Table XIX. Lipid disorders according to the American Heart Association and Harrison's Manual of Medicine [106, 107].

Criteria for lipid abnormalities					
Affection	***TC (/mmol/L)***	***HDL-c (/mmol/L)***	***LDL-c (/mmol/L)***	***TG (/mmol/L)***	***Notes***
PH	6.5-8.9		3.36-7.76		Elevated TC or LDL-c; Normal value for LDL-c ≤3.34
FCD	6.5-8.9		3.36-7.76	1.7-8.5	Elevated TG + LDL-c and/or TC
DBL	6.5-8.9		≤3.34	2.8-5.6	Elevated TG and TC
Heterozygous FH	9.0-14.0				Elevated TC
Homozygous FH	14.1-26.0				
HTG Normal				<1.7	Very high or elevated TG without concomitant MSY diagnosis
Borderline high				1.7-2.2	
High				2.3-5.6	
Very high				≥5.7	
HALP		0.4-0.9			Decreased HDL-c
Unclassified	Requiring more testing to decide the type of abnormality				

3.22. KIDNEY FAILURE

Kidney function was assessed using laboratory results found in subjects' medical charts. Values of eGFR were referenced with the National Kidney Foundation Guidelines to assess the renal health status.

Table XX. The five stages of chronic kidney disease of the National Kidney Foundation Kidney Disease Outcome Quality Initiative guidelines (www.kidney.org) [109]. Chronic kidney disease = kidney damage or eGFR<60 mL/min/1.73 m^2 for 3 months. Kidney damage=pathologic abnormalities (including blood or urine tests or imaging studies) or markers of damage.

Stage	Description	eGFR (mL/min/1.73 m^2)
1	Kidney damage with normal or ↑ GFR	≥ 90
2	Kidney damage with mild ↓ GFR	60-89
3	Moderate ↓ GFR	30-59
4	Severe ↓ GFR	15-29
5	Kidney failure	< 15 (or dialysis)

3.23. OBESITY

Most commonly, the degree of adiposity is evaluated through the body mass index (BMI), which correlates with body fat and body fat mass [110-112]. The calculated value for a given person is then compared to the predicted age/sex-independent values in order to assess the degree of obesity (Table XXI) (WHO; www.who.org). In addition, waist circumference is associated with abdominal obesity (♀> 80 cm; ♂> 94) [108] and, as previously mentioned, was used to ascertain MSY diagnosis.

Table XXI. The International Classification of the degree of obesity in adults (both sexes together) according to BMI and their relative risk of CV death (www.who.org) [113].

Classification	BMI (/kg/m^2)	CV mortality risk
Underweight	<18.50	Low
Normal range	[18.50, 25[	None or very little
Overweight (pre-obese)	**[25.00, 30[**	**Low**
Obese (Classes I to III)	**≥30.00**	**Moderate to very high**

3.24. SPECIFIC TESTING: TREADMILL OR STRESS TEST

The degree of CV fitness was considered a complementary measure, and reflected the physical activity. This was best ascertained with the stress test, measured in metabolic equivalents (METs), which ascertains the subjects' fitness on a treadmill. In fact, studies have shown a 12% survival improvement with every METs increase in exercise capacity and a high correlation of increased CV fitness with CHD reduction and overall and CV mortality [171-176]. This very important specific test was used to detect or confirm underlying CHD.

3.25. DATA TO BE COLLECTED

The remaining data from 516 subjects will be gathered and analyzed in the future, while the data from deceased family members is pending approval from the CAIQ. We will discuss this aspect at the end of the Discussion Chapter.

CHAPTER IV:

Results

Results

4.1. OVERVIEW

Our study represents an average follow-up of 11 years of the 343 participants. The Results will be presented according to the final data classifications (Figures 9, 13 to 18 and their corresponding Tables VII to XII). In other words, each of the six sub-categories will be analyzed in detail in the next sections followed by sections summarizing both FO and NFO (Table XIII). At any point, please refer to Chapter III for more details on the explanation, organization and presentation of the data. Finally, the relative risk calculations and statistics will be presented in the last section of this Chapter.

4.2. CARDIOVASCULAR DISEASES WITH FATAL OUTCOMES

In the following section, we analyze results from 343 subjects with CV affections from FO (Table XXII, Figures 13 and 21 A to C). We can see that circulatory system with FO, which include cardiac disease, CBVD, diseases of the pulmonary circulation, vascular diseases and hypertensive diseases, affect 299 out of the 343 participating subjects. In addition, a grand total of 1,103 diagnosis have been identified. Furthermore, 555 of those 1,103 are considered outcomes, of which 247 are first outcomes for these subjects.

Table XXII. FO of the circulatory system identified in 343 participating subjects of the SLSJ region.

FO of the Circulatory system			*n*	*Subtype %*	*Total %*
Rhythm pathologies	*Atrial*	Bradycardia	97	62.6	8.8
		Sinus pathologies	2	1.3	0.2
		Non sinus pathologies	21	13.5	1.9
	AV	AV-Bloc 1', 2' and 3'	28	18.1	2.5
		AV dissociation			
		Accessory pathway			
		PSVT			
	Ventricular	Left bundle branch block	7	4.5	0.6
		Ventricular tachycardia			
		Ventricular flutter			
		Ventricular fibrillation			
		Cardiac arrest			
	Other	Electromechanical dissociation	0		
		Diagnosis	155	23.4	14.1
		Subjects with outcomes	84	58.7	46.4
		Outcomes	103	26.1	18.6
		First outcomes	47	27.0	19.0
CHD	*Angina*	Unstable angina	24	7.5	2.2
		Angina pectoris with documented spasm	1	0.3	0.1
		Other forms of angina pectoris	57	17.7	5.2
		Angina pectoris, unspecified	15	4.7	1.4
	MI	Transmur Anterior wall al	6	1.9	0.5
		Inferior wall	21	6.5	1.9
		Other sites	3	0.9	0.3
		Unspecified	0		
		Sub-endocardial	5	1.6	0.5
		Unspecified	6	1.9	0.5
		Old	3	0.9	0.3
		Multiple MI	11	3.4	1.0
		Total MI	70	21.7	6.3
	Unspecified CHD		0		
	AG	Normal	4	1.2	0.4
		Mild	7	2.2	0.6
		CAD			
		Single vessel disease	9	2.8	0.8
		Two vessel disease	11	3.4	1.0
		Three vessel disease	36	11.2	3.3
		Terminal	1	0.3	0.1
		CAD			
		Grafts (stenosis)	11	3.4	1.0
	CABG treatment	2 grafts	9	2.8	0.8
		3 grafts	17	5.3	1.5
		≥4 grafts	8	2.5	0.7
		Unspecified	0		
	PTCA treatment	Low risk	3	0.9	0.3

FO of the Circulatory system			***n***	***Subtype %***	***Total %***
		High risk	28	8.7	2.5
		Unspecified	0		
		Diagnosis	322	48.7	29.2
		Subjects with outcomes	86	60.1	47.5
		Outcomes	141	35.7	25.4
		First outcomes	59	33.9	23.9
HF (cardiac insufficiency)	*LVSD*	Mild	11	26.8	1.0
		Moderate	2	4.9	0.2
		Severe	3	7.3	0.3
		Unspecified	1	2.4	0.1
	RVSD	Mild	1	2.4	0.1
		Moderate	0		
		Severe	0		
	LVDD	Mild	19	46.3	1.7
		Moderate	3	7.3	0.3
		Severe	1	2.4	0.1
		Diagnosis	41	6.2	3.7
		Subjects with outcomes	29	20.3	16.0
		Outcomes	30	7.6	5.4
		First outcome	13	7.5	5.3
Valvulopathies (non-rheumatic valve disorders)	*Ar*	Mild	11	16.4	1.0
		Moderate	4	6.0	0.4
		Severe	1	1.5	0.1
	As	Mild	8	11.9	0.7
		Moderate	0		
		Severe	4	6.0	0.4
	Mr	Mild	19	28.4	1.7
		Moderate	5	7.5	0.5
		Severe	1	1.5	0.1
		Unclassified	2	3.0	0.2
	Ms	Mild	2	3.0	0.2
		Moderate	0		
		Severe	0		
		Unclassified	1	1.5	0.1
	Tricuspid regurgitation/ stenosis	Mild	7	10.4	0.6
		Moderate	1	1.5	0.1
		Severe	1	1.5	0.1
	Pulmonary stenosis, regurgitation or congenital anomaly	Mild	0		
		Moderate	0		
		Severe	0		
		Diagnosis	67	10.1	6.1
		Subjects with outcomes	34	23.8	18.8
		Outcomes	61	15.4	11.0
		First outcomes	25	14.4	10.1
Morphologic abnormalities	*LVH*	By ECHO	20	29.0	1.8
		By ECG	25	36.2	2.3
	RVD and LVD		8	11.6	0.7
	Other	Auricular dilatation, etc.	16	23.2	1.5

FO of the Circulatory system			***n***	***Subtype %***	***Total %***
		Diagnosis	69	10.4	6.3
		Subjects with outcomes	46	32.2	25.4
		Outcomes	56	14.2	10.1
		First outcomes	28	16.1	11.3
Infective and inflammatory heart disease	*Endocarditis*		0		
	Myocarditis		0		
	Pericarditis		1	25.0	0.1
	Other	Unspecified, Carditis, Rheumatic fever, etc.	3	75.0	0.3
		Diagnosis	4	0.6	0.4
		Subjects with outcomes	2	1.4	1.1
		Outcomes	2	0.5	0.4
		First outcomes	0		
Congenital defects			3	100.0	0.3
		Diagnosis	3	0.5	0.3
		Subjects with outcomes	1	0.7	0.6
		Outcomes	2	0.5	0.4
		First outcomes	2	0.8	0.8
Cardiac diseases		Subjects affected	173		57.9
		Diagnosis	661		59.9
		Subjects with outcomes	143		79.0
		Outcomes	395		71.2
		First outcomes	174		70.4
Ischeamic	*TIA*		17	53.1	1.5
	RIND		0		
	Stroke (Cerebral infarction)	Thrombotic infarct	13	40.6	1.2
		Embolic infarct	2	6.3	0.2
		Diagnosis	32	94.1	2.9
		Subjects with outcomes	18	100.0	9.9
		Outcomes	23	100.0	4.1
		First outcome	12	100.0	4.9
Intracranial hemorrhage	*Epidural*		0		
	Subarachnoid		2	100.0	0.2
	Intracerebral		0		
		Diagnosis	2	5.9	0.2
		Subjects	0		
		Outcomes	0		
		First outcome	0		
CBVD diseases		Subjects affected	27		9.0
		Diagnosis	34		3.1
		Subjects with outcomes	18		9.9
		Outcomes	23		4.1
		First outcome	12		4.9
Pulmonary	*Embolism*		9	45.0	0.8
	Hypertension	Mild	6	30.0	0.5
		Moderate	3	15.0	0.3
		Severe	2	10.0	0.2

FO of the Circulatory system			***n***	***Subtype %***	***Total %***
	Vasculitis	Without alveolar hemorrhage	0		
		With alveolar hemorrhage			
Diseases of pulmonary circulation		Subjects affected	16		5.4
		Diagnosis	20		1.8
		Subjects with outcomes	14		7.7
		Outcomes	17		3.1
		First outcome	3		1.2
Arterial	*Cerebrovascular disease*	Atherosclerosis and unspecified hemorrhage	23	21.5	2.1
	Thoracic aorta	Atherosclerosis (including embolism and thrombosis)	16	15.0	1.5
		Aneurism	6	5.6	0.5
		Dissection	0		
	Abdominal aorta	Atherosclerosis	13	12.1	1.2
		Aneurism	2	1.9	0.2
		Dissection	0		
	Renovascular disease	Atherosclerosis of renal artery and arterioles	7	6.5	0.6
		Renal ischemia and infarction	0		
	Intestinal vascular disease	Mesenteric ischemia and/or necrosis	2	1.9	0.0
		Atherosclerosis	1	0.9	0.1
	Peripheral vascular disease	Atherosclerosis and aneurisms of arteries of extremities	23	21.5	2.1
		Multiple arterial embolisms and thrombosis			
		Other peripheral vascular disease (ischemia, etc.)			
Venous	*SVT*		6	5.6	0.5
	DVT		8	7.5	0.7
Vascular diseases		Subjects affected	74		24.7
		Diagnosis	107		9.7
		Subjects with outcomes	65		35.9
		Outcomes	89		16.0
		First outcome	36		14.6
Essential (primary) Hypertension	*Controlled*		125	44.5	11.3
	Uncontrolled		115	40.9	10.4
	Unspecified		34	12.1	3.1
	Mean BP measurements	SBPΔ = 2.00	-		
		DBPΔ = -6.79	-		
Other	*Hypertensive*	Heart disease	1	0.4	0.1
		Renal disease	5	1.8	0.5
		Heart and renal diseases	1	0.4	0.1
		Secondary hypertension	0		
Hypertensive diseases		Subjects affected	274		91.6
		Diagnosis	281		25.5
		Subjects with outcomes	31		17.1
		Outcomes	31		5.6
		First outcome	22		8.9
Total	**Participating ♀ subjects**		**184**		

FO of the Circulatory system	*n*	*Subtype %*	*Total %*
Participating ♂ subjects	**159**		
Participating ♀ ♂ together	**343**		
Subjects affected	**299**		
Subjects with outcomes	**181**		
Outcomes	**555**		
First outcome	**247**		
Diagnosis	**1103**		

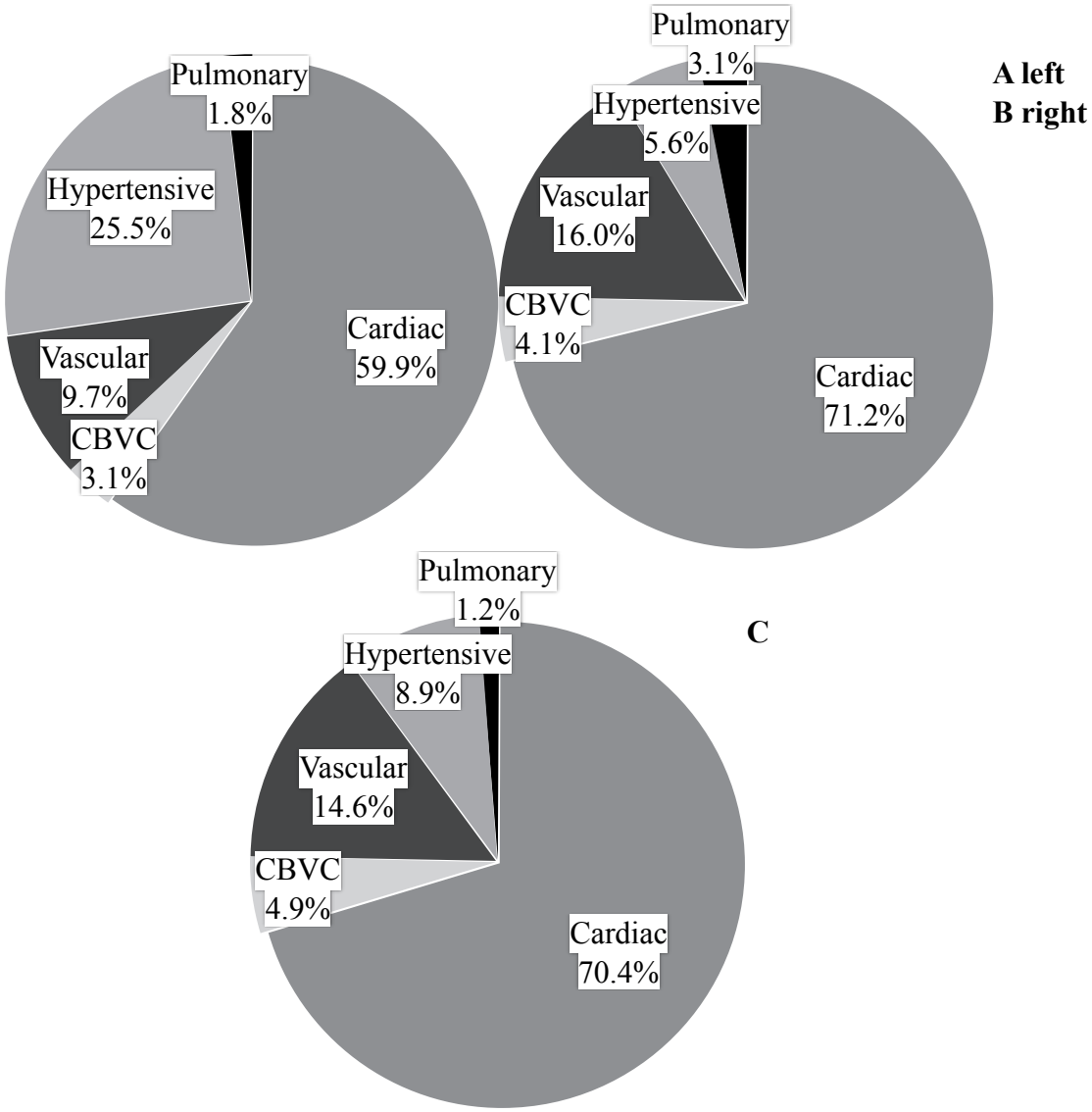
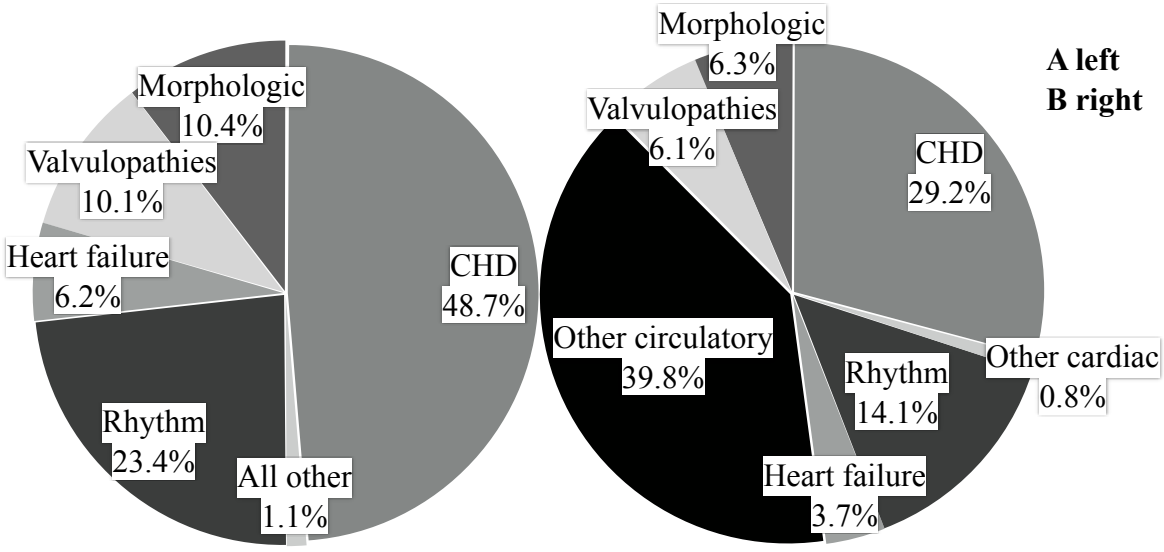


Figure 21. FO of the circulatory system results for the main sub-types from 299 affected subjects of the SLSJ region: A) Diagnosis, B) Outcomes and C) First outcomes.

4.2.1. CARDIAC DISEASES

A more in depth examination of the Table XXII data indicates that cardiac disease (rhythm pathologies, CHD, HF, valvulopathies of non-rheumatic nature, morphologic abnormalities, infective and inflammatory heart disease and congenital defects), affect 173 of 343 (50.4%) examined subjects or 173 of 299 subjects affected by CV FO (57.9%). The diagnosis, outcomes and first outcomes data for cardiac FO are reflected below (Figures 22 to 24). This group comprises of 661 out of 1,103 diagnosis (59.9%), of which 395 are outcomes (71.2%) and 174 first outcomes (70.4%). It is to be noted that, as previously explained in the Methods Chapter, all percentages (%) are relate to their own type.



Figures 22. Diagnosis A) within cardiac disease and B) in comparison to all FO of CV origin in 299 affected subjects of the SLSJ region.

Our results show 155 diagnosed rhythm pathologies (23.4%), comprising 103 outcomes (26.1%) and 47 first outcomes (27.0%). Moreover, 322 diagnosis of CHD (48.7%), comprising 141 outcomes (35.7%) and 59 first outcomes (33.9%).

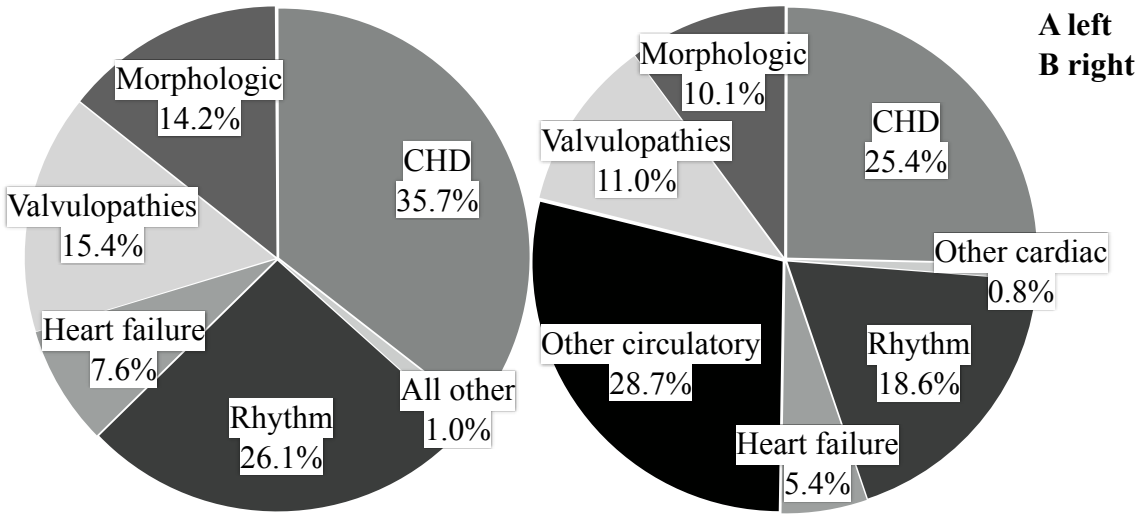


Figure 23. Outcomes A) within cardiac disease and B) in comparison to all FO of CV origin in 299 affected subjects of the SLSJ region.

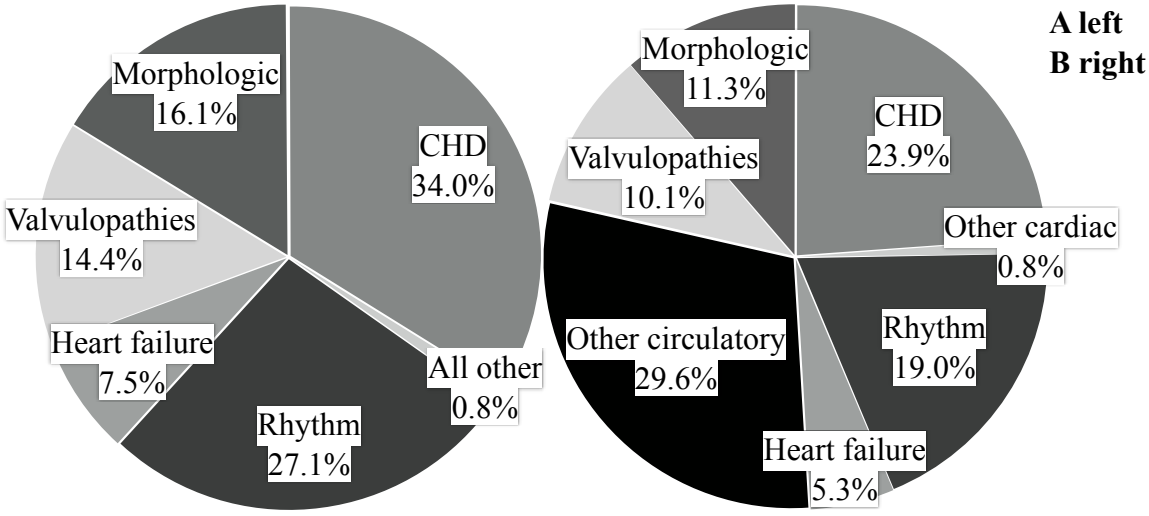
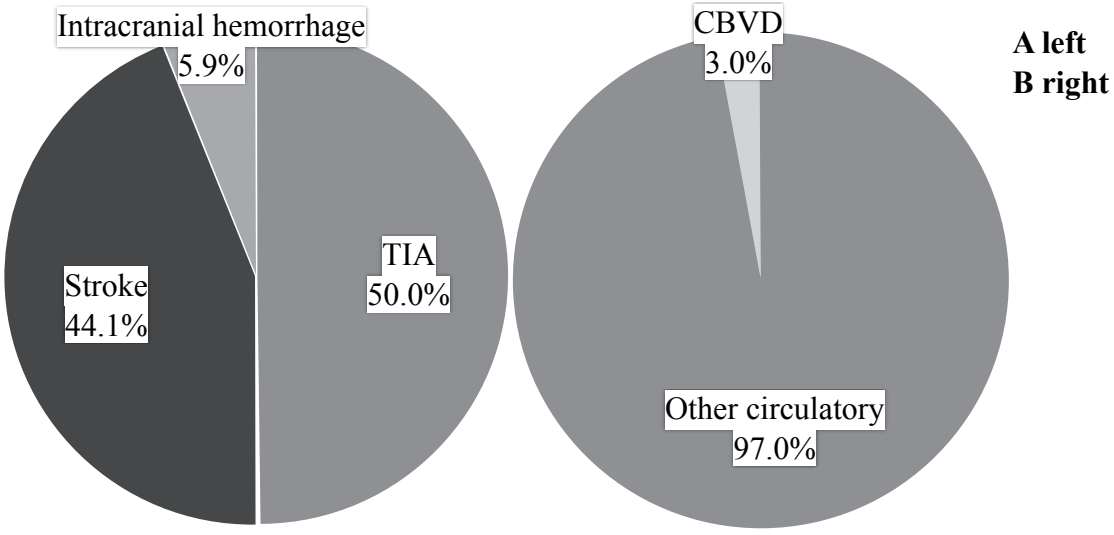


Figure 24. First outcomes A) within cardiac disease and B) in comparison to all FO of CV origin in 299 affected subjects of the SLSJ region.

Following this, 41 diagnosis of HF (6.2%), comprising 30 outcomes (7.6%) and 13 first outcomes (7.5%). Next, 67 diagnosis of valvulopathies (10.1%), comprising 61 outcomes (15.4%) and 25 first outcomes (14.4%). In addition, 69 diagnosis of morphologic abnormalities (10.4%), comprising 56 outcomes (14.2%) and 28 first outcomes (16.1%). Finally, there were 1 diagnosis of pericarditis of infective and inflammatory heart diseases and 3 diagnosis of congenital defects.

4.2.2. CEREBROVASCULAR DISEASES

Looking closely now at the data of CBVD, comprised of ischemic diseases and intracranial hemorrhage, these affected 27 of 299 affected subjects (9.0%) (Table XXII; Figure 25).



Figures 25. Diagnosis A) within CBVD and B) in comparison to all FO of CV origin in 299 affected subjects of the SLSJ region.

This group comprises of 34 out of 1,147 diagnosis (3.1%). More specifically, our results show only 2 diagnosis from subarachnoid hemorrhaging (0.2%). Thus, the rest originated from ischemic CBVD. In fact, 17 diagnosis originated from TIA (1.5%) and 15 from stroke (1.2%). Together, they hold 23 outcomes (4.1%), of which 12 were first outcomes (4.9%; Figures 21 and 26).

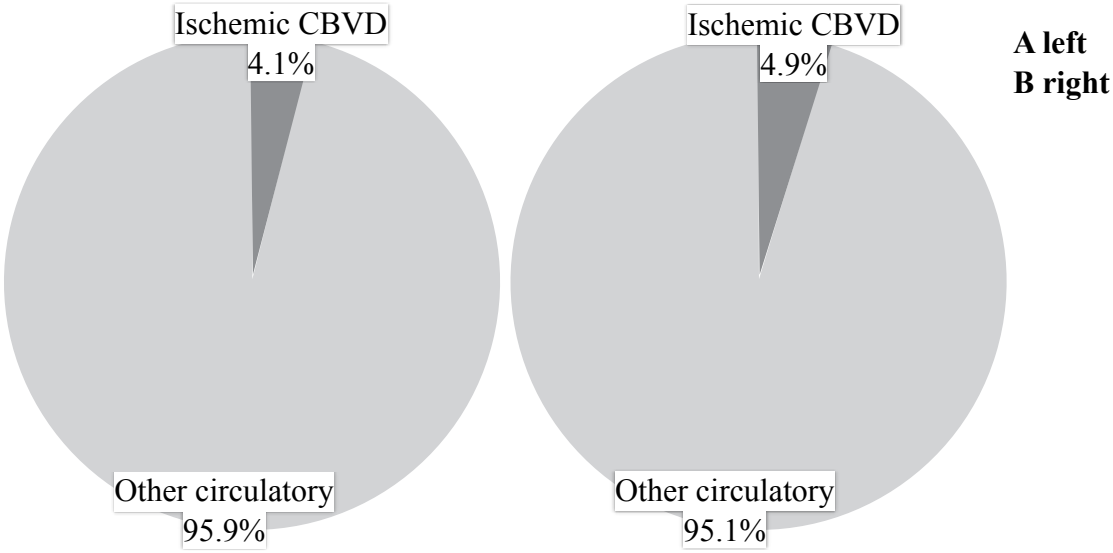


Figure 26. CBVD A) outcomes and B) first outcomes in comparison to all FO of CV origin in 299 affected subjects of the SLSJ region.

4.2.3. PULMONARY CIRCULATION DISEASES

When looking at the data for diseases of the pulmonary circulation, we see that they resulted in 20 of the total diagnosis (1.8%), of which 17 were outcomes (3.1%) and 3 first outcomes (1.2%; Table XXII; Figures 27). More specifically, 9 diagnosed embolisms (0.8%) and 11 pulmonary hypertension (1.0%).

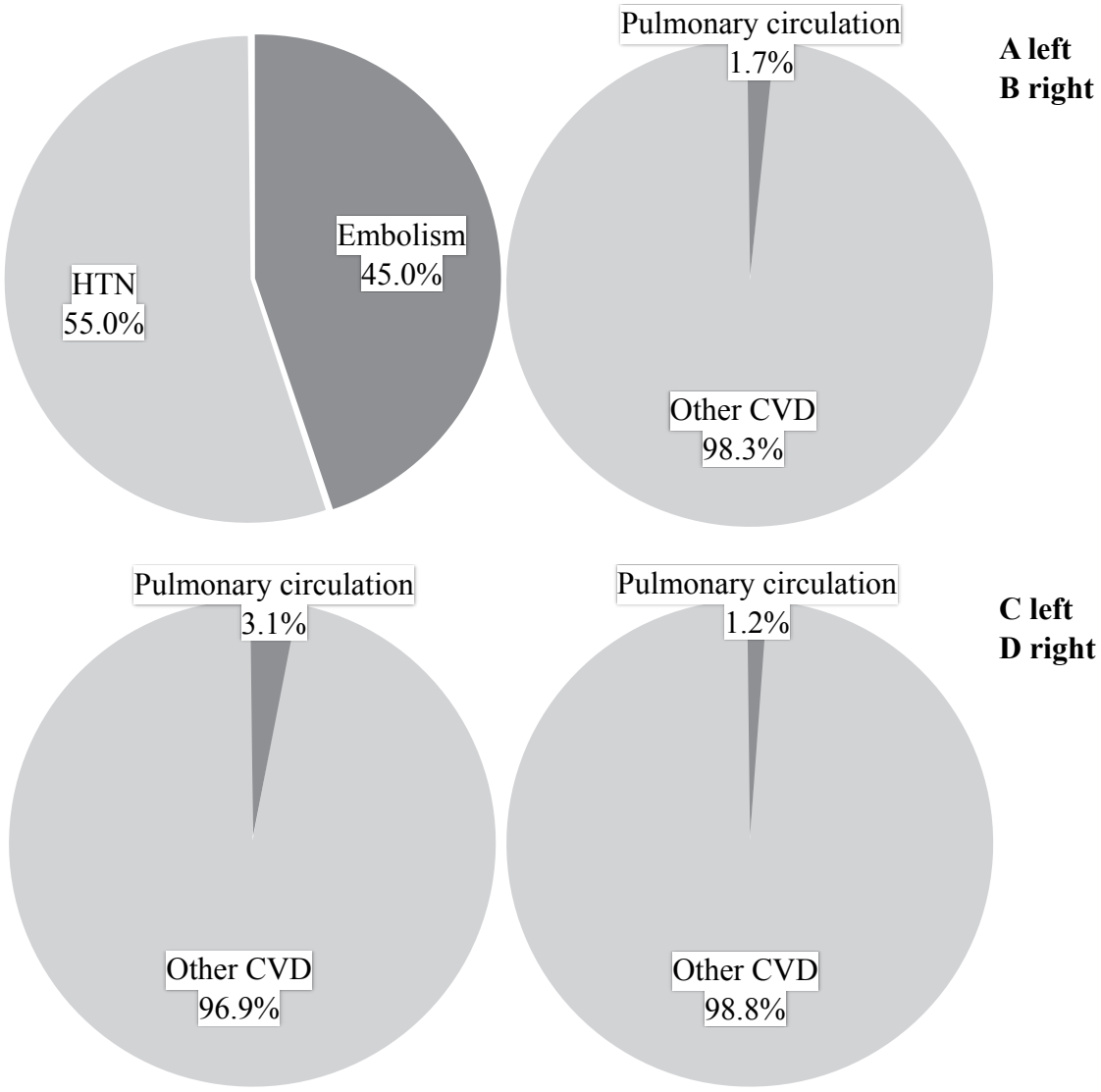


Figure 27. Pulmonary circulation A) diagnosis and B) in comparison to all FO of CV origin; C) outcomes and D) first outcomes in comparison to all FO of CV origin in 299 affected subjects of the SLSJ region.

4.2.4. VASCULAR DISEASES

The data for vascular diseases show that arterial and venous diseases accounted for 107 diagnosis (9.7%), of which 89 were outcomes (16.0%) and 36 first outcomes (14.6%; Table XXII; Figures 28).

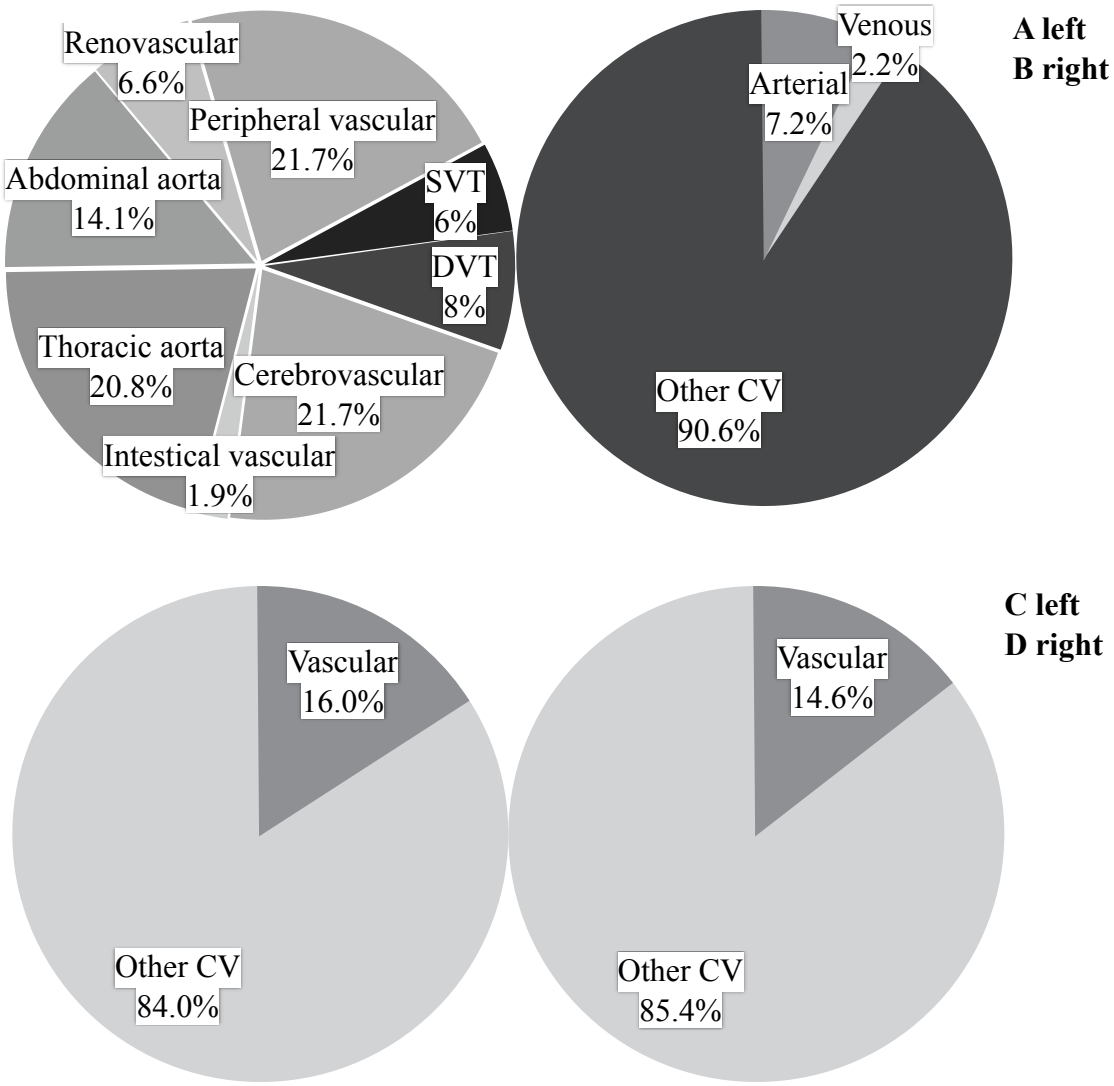


Figure 28. Vascular A) diagnosis and B) in comparison to all FO of CV origin; C) outcomes and D) first outcomes in comparison to all FO of CV origin in 299 affected subjects of the SLSJ region.

More specifically, arterial vascular diseases were responsible for 93 of 107 diagnosis: cerebrovascular made up 23 of those diagnosis (2.1%), thoracic aorta 22 (2.0%), abdominal aorta 13 (1.4%), renovascular 7 (0.6%), intestinal vascular 3 (0.3%) and peripheral vascular diseases 23 (2.1%). On the other hand, venous vascular diseases

were mainly due to SVT, responsible for 6 diagnosis (0.5%), and DVT, responsible for 8 diagnosis (0.7%).

4.2.5. HYPERTENSIVE DISEASES

The last segment that can be observed pertains to hypertensive diseases. Essential HBP is a condition found in 274 of 299 affected subjects with CV FO (91.6%). Moreover, it encompasses 281 of 1,147 diagnosis (25.5%), 31 outcomes (5.6%) and 22 first outcomes (8.9%). In addition, 6 subjects have other connective hypertensive diseases such as hypertensive heart, renal or both diseases.

4.3. NON-CARDIOVASCULAR DISEASES WITH FATAL OUTCOMES

In the following section, we analyze results from 343 subjects with affections from non-CV FO (Table XXIII, Figures 14 and 29). These include malignant neoplasms, metabolic, lung and kidney diseases and affect 333 out of the 343 participating subjects. A grand total of 1,536 diagnosis have been identified. Furthermore, 195 of those 1,536 are considered outcomes and 107 first outcomes for these subjects.

Table XXIII. Non-CV FO results found in 343 participating subjects of the SLSJ region.

Non-CV FO		***n***	***Subtype %***	***Total %***
Malignant neoplasms—Men	Lip, oral cavity and pharynx	0		
	Digestive organs	3	12.5	0.2
	Respiratory and intrathoracic organs	2	8.3	0.1
	Bone and articular cartilage	0		
	Skin	2	8.3	0.1
	Mesothelial and soft tissue	2	8.3	0.1

Non-CV FO		*n*	*Subtype %*	*Total %*
	Breast	0		
	Male genital organs	5	20.8	0.3
	Urinary tract	3	12.5	0.2
	Eye, brain and other parts of CNS	1	4.2	0.1
	Thyroid and other endocrine glands	1	4.2	0.1
	Ill-defined, secondary and unspecified sites	3	12.5	0.2
	Lymphoid, hematopoietic and related tissue	1	4.2	0.1
	Independent multiple sites	1	4.2	0.1
	Diagnosis	24	46.2	1.6
	Subjects affected	20	44.4	6.0
	Subjects with outcomes	21	63.6	14.8
	Outcomes	18	39.1	9.2
	First outcome (/%)	6	30.0	5.6
Malignant neoplasms—Women	Lip, oral cavity and pharynx	0		
	Digestive organs	4	14.3	0.3
	Respiratory and intrathoracic organs	2	7.1	0.1
	Bone and articular cartilage	0		
	Skin	1	3.6	0.1
	Mesothelial and soft tissue	0		
	Breast	6	21.4	0.4
	Female genital organs	3	10.7	0.2
	Urinary tract	2	7.1	0.1
	Eye, brain and other parts of CNS	0		
	Thyroid and other endocrine glands	0		
	Ill-defined, secondary and unspecified sites	1	3.6	0.1
	Lymphoid, hematopoietic and related tissue	3	10.7	0.2
	Independent multiple sites	6	21.4	0.4
	Diagnosis	28	53.8	1.8
	Subjects affected	25	55.6	7.5
	Subjects with outcomes	25	75.8	17.6
	Outcomes	21	45.7	10.8
	First outcome (/%)	14	70.0	13.1
Malignant neoplasms	Diagnosis	52	-	3.4
	Subjects affected	45	-	13.5
	Subjects affected also with CVD	40	88.9	12.0
	Subjects affected by HBP	38	84.4	11.4
	Subjects with outcomes	33	82.5	23.2
	Outcomes	46	-	23.6
	First outcome (/%)	20	-	18.7
Pre-DM	AFG and IFT	103	100.0	6.7
	Diagnosis	103	8.0	6.7
	Subjects affected	103	30.9	30.9
	Subjects affected also with CVD	95	92.2	28.5
	Subjects with outcomes	43	44.8	30.3

Non-CV FO			*n*	*Subtype %*	*Total %*
	Outcomes		43	42.6	22.1
	First outcome (/%)		36	54.5	33.6
DM	Type I		2	2.1	0.1
	Possible Type II (not confirmed by 2nd test)	Diet	1	1.0	0.1
		Oral Rx	0		
	Type II	Treated with diet	33	34.0	2.1
		Oral Rx	44	45.4	2.9
		Insulin Rx	13	13.4	0.8
	Unspecified	Treated with diet	3	3.1	0.2
		Oral Rx	0		
		Insulin Rx	1	1.0	0.1
	Diagnosis		97	7.6	6.3
	Subjects affected		94	28.2	28.2
	Subjects affected also with CVD		90	95.7	27.0
	Subjects with outcomes		43	44.8	30.3
	Outcomes		43	42.6	22.1
	First outcome (/%)		26	39.4	24.3
Metabolic syndrome	Previously undiagnosed Criteria		160	100.0	10.4
	Diagnosis		160	12.5	10.4
Obesity	Underweight		5	2.0	0.3
	Normal		92		
	Overweight		141	56.2	9.2
	Mild		66	26.3	4.3
	Moderate		26	10.4	1.7
	High		13	5.2	0.8
	Diagnosis		251	19.6	16.3
Abdominal circumference	*Men*	*Abnormal >94 cm*	96	47.3	6.3
		Average (/cm)	98.3		
	Women	*Abnormal >80 cm*	107	52.7	7.0
		Average (/cm)	85.4		
	Diagnosis		203	15.9	13.2
Lifestyle	Smoking		101	85.6	6.6
	Alcohol		13	11.0	0.8
	Drugs		4	3.4	0.3
	Subjects affected		109	32.7	32.7
	Diagnosis		118	9.2	7.7
Hypoglycemia			4	100.0	0.3
	Diagnosis		4	0.3	0.3
	Subjects affected		4	1.2	1.2
	Subjects with outcomes		0		
	Outcomes		1	1.0	0.5
	First outcome (/%)		1	1.5	0.9

Non-CV FO			*n*	*Subtype %*	*Total %*
Lipid abnormalities	PH		85	24.7	5.5
	FCD		95	27.6	6.2
	DBL		3	0.9	0.2
	Heterozygous FH		16	4.7	1.0
	Homozygous FH		2	0.6	0.1
	HTG	Borderline high	9	2.6	0.6
		High	9	2.6	0.6
		Severe	20	5.8	1.3
	HALP		85	24.7	5.5
	Unclassified		20	5.8	1.3
	Diagnosis		344	26.9	22.4
	Subjects affected		273	82.0	82.0
	Subjects affected also with CVD		246	90.1	73.9
	Subjects with outcomes		14	14.6	9.9
	Outcomes		14	13.9	7.2
	First outcome (/%)		3	4.5	2.8
Metabolic causes	Diagnosis		1280		83.3
	Subjects affected		333		100.0
	Subjects with outcomes		96		67.6
	Outcomes		101		51.8
	First outcome (/%)		66		61.7
COPD			32	39.5	2.1
Infection	Pneumonia and Influenza		14	17.3	0.9
	Collagen vascular diseases		0		
Inflammatory			1	1.2	0.1
Asthma			18	22.2	1.2
Pneumoconiosis			0		
Cystic fibrosis			0		
Other	ARDS		16	19.8	1.0
Lung diseases	Diagnosis		81		5.3
	Subjects affected		62		18.6
	Subjects with outcomes		32		22.5
	Outcomes		35		17.9
	First outcome (/%)		14		13.1
Renal failure	Pre-renal		1	0.8	0.1
	Renal		8	6.5	0.5
	Post-renal		0		
	Unspecified Ex		25	20.3	1.6
	Acute		9	7.3	0.6
	Chronic		26	21.1	1.7
Electrolyte	*Sodium (Na+)*	*High*	9	7.3	0.6

Non-CV FO			*n*	*Subtype %*	*Total %*
abnormalities		*Low*	14	11.4	0.9
	Potassium (K+)	*High*	8	6.5	0.5
		Low	15	12.2	1.0
Other			8	6.5	0.5
Kidney disorders	Diagnosis		123		8.0
	Subjects affected		68		20.4
	Subjects affected also with CVD		28		8.4
	Subjects with outcomes		17		12.0
	Outcomes		20		10.3
	First outcome (/%)		7		6.5
Total	**Participating ♀ subjects**		**184**		
	Participating ♂ subjects		**159**		
	Participating ♀ ♂ subjects		**343**		
	Subjects affected		**333**		
	Subjects affected also with CVD		**109**		
	Subjects with outcomes		**142**		
	Outcomes		**195**		
	First outcome (/%)		**107**		
	Diagnosis		**1536**		

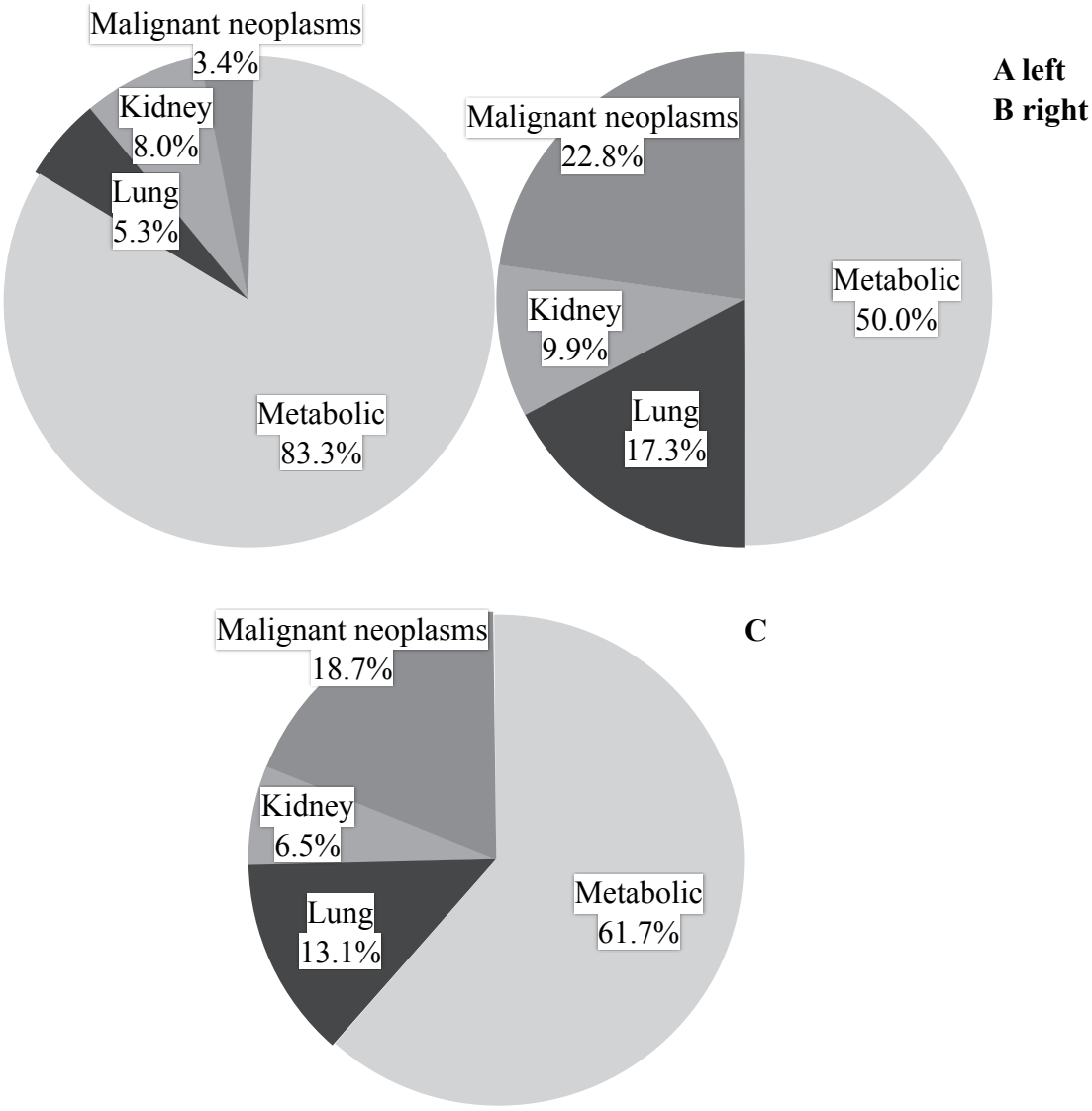


Figure 29. Non-CV FO results identified in the main sub-types for 333 affected subjects of the SLSJ region: A) Diagnosis, B) Outcomes and C) First outcomes.

4.3.1. MALIGNANT NEOPLASMS

Looking closely now at the data from malignant neoplasms, men have 24 diagnosis (1.6%) and women 28 (1.8%), accounting for 52 diagnosis together. Amongst these, 46 are outcomes (23.6%), of which 20 are first outcomes (18.7%) In total of 45 subjects were affected (13.5%), of which 40 were also affected by CV FO (88.9%) and 33 of those 45 by HBP (84.4%; Figure 30).

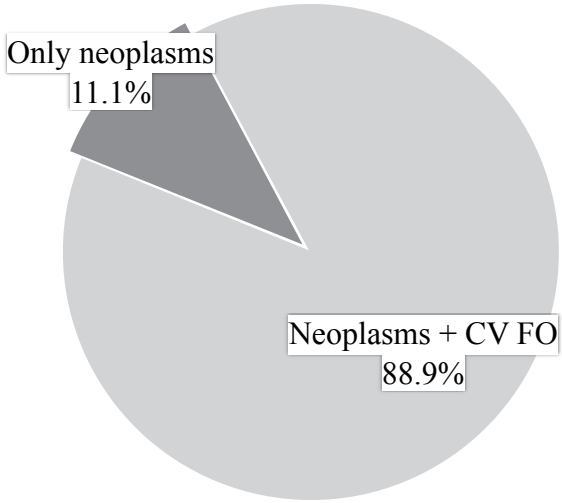


Figure 30. Neoplasm affected subjects with and without underlying CV FO.

4.3.2. METABOLIC DISORDERS

We found that 103 subjects were at the pre-DM stage with diagnosed IFT and AFG with 43 outcomes (22.1%) and 36 first outcomes (33.6%; Table XXIII, Figure 31).

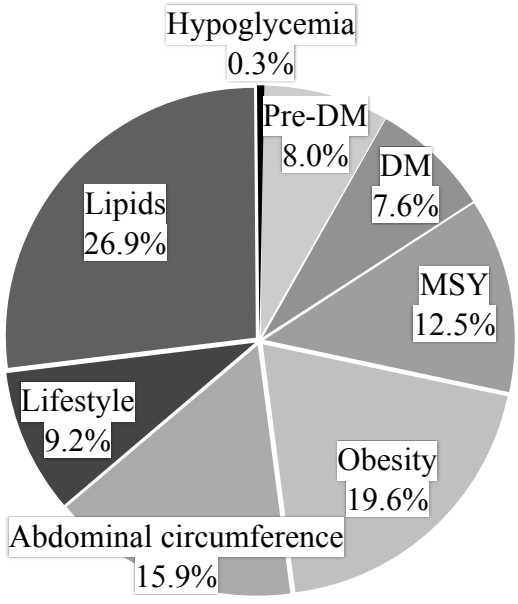


Figure 31. Metabolic diagnosis amongst 333 subjects affected by non-CV FO from the SLSJ region.

More than 92% of the diagnosis were for T2D with 90 subjects while only 2 were diagnosis with type 1 diabetes (T1D) and 5 with unspecified DM. In addition, none of the subjects were previously diagnosed with MSY while, in fact, 50% (160 subjects out of 343) were found to meet the criteria for MSY. MSY diagnosis represents 12.5% of metabolic disorders and 10.4% of all non-CV FO diagnosis.

Moreover, 251 probands were found to have an unhealthy weight amongst all participating subjects (Figure 32). Normal BMI subjects have not been considered in the calculations of metabolic disorder in non-CV FO. About 50% of men (96) and women (107) were over their normal limit for abdominal circumference of 94 cm and 80 cm, respectfully. The average abdominal circumference for men was 98.3 cm and for women 85.4 cm.

In addition, an unhealthy lifestyle was reported in 109 subjects (31.8%). More specifically, there were 101 subjects that actively smoke or that have smoked, 13 of them are alcoholics (0.8%) and 4 taking drugs or narcotics (0.3%). Furthermore, 4 subjects had hypoglycemia (0.3%) and 1 of those four was a first outcome (0.9%). Lastly, lipid abnormalities affect 273 subjects (82.0%), 14 of them are outcomes (13.9%) and 3 are first outcomes (2.8%; Figure 33).

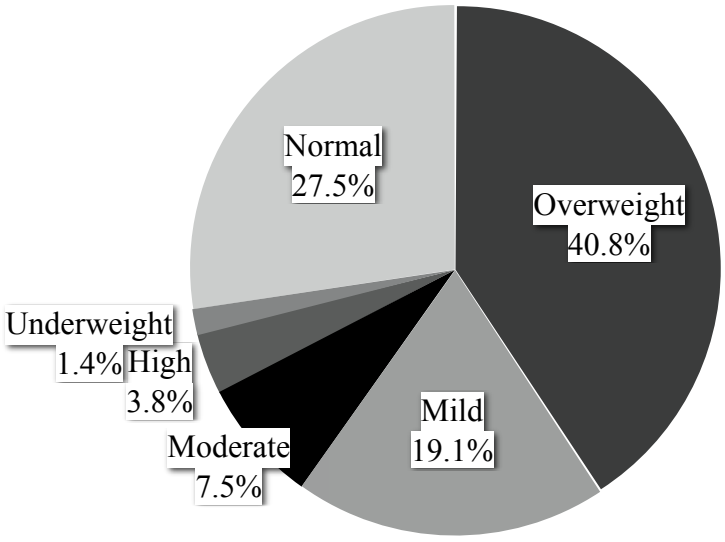


Figure 32. Abnormal weight diagnosis amongst 333 subjects affected by non-CV FO from the SLSJ region. Percentages conducted here within the category of obesity and reflect the normal weight % in addition to all others. Note that the normal weight calculation is not included in Table XXIV.

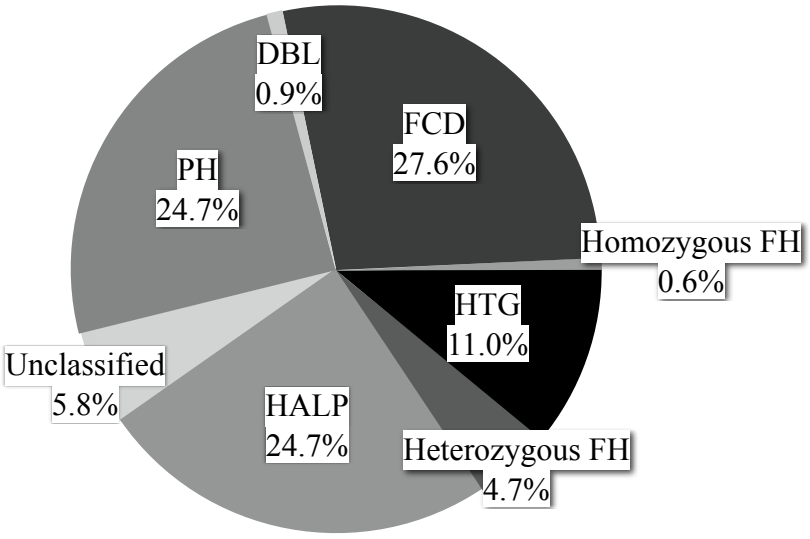


Figure 33. Lipid abnormalities within metabolic disorders amongst 333 subjects affected by non-CV FO from the SLSJ region.

4.3.3. LUNG DISEASES

The data for lung diseases comprise of 81 diagnosis (5.3%), of which 35 are outcomes (17.9%) and 14 first outcomes (13.1%; Table XXIII, Figure 34).

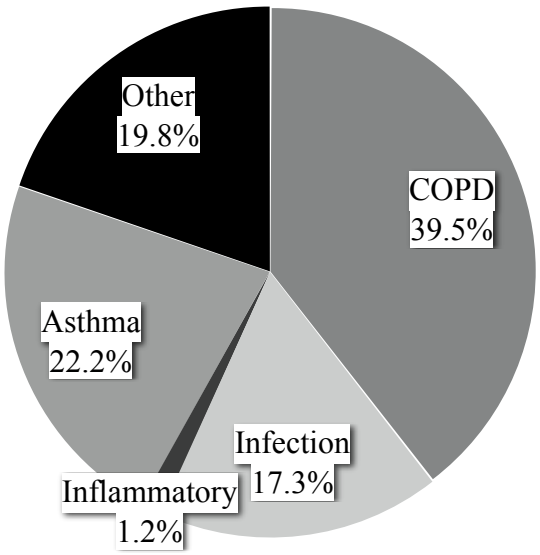


Figure 34. Lung diseases amongst 333 subjects affected by non-CV FO from the SLSJ region.

They affect 62 subjects; COPD represented 40% of all lung diagnosis and infections and asthma each 20%.

4.3.4. KIDNER DISORDERS

The last family of diseases that can be observed from Table XXIII pertains to kidney disorders, which affect 68 subjects (20.4%). Together, they have 123 diagnosis (8.0%), of which 20 are outcomes (10.3%) and 7 first outcomes (6.5%). Renal failure comprises of 69 diagnosis (4.5%), while electrolyte abnormalities form 46 diagnosis (3.0%). Finally, there are 8 diagnosis (1.5%) from other kidney disorders.

4.4. ALL OTHER FATAL OUTCOMES

In the following section, we analyze results from 343 subjects with affections from all other FO (Table XXIV, Figure 15 and 35). These include disorders of mental and behavioral,

nervous, digestive, accidental, other and unknown origins, and affect 62 out of the 343 participating subjects. In addition, a grand total of 81 diagnosis have been identified. Furthermore, 30 of those 81 are considered outcomes and, 11 are first outcomes. There were 6 mental and behavioral disorders (7.4%), 18 of the nervous system (22.2%), 17 of the digestive system (21.0%), 9 accidents (11.1%) and 31 of other known causes (38.3%).

Table XXIV. All other FO results from 343 participating subjects of the SLSJ region.

All other FO		***n***	***%***
Mental and behavioral		6	7.4
Nervous system	Alzheimer's disease, etc.	18	22.2
Digestive system	Other (e.g. sub-occlusion/ileum)	17	21.0
Accidents		9	11.1
Other	Bleeding, Enterocolitis due to *Clostridium difficile*, etc.	31	38.3
Unknown		0	
Total	**Participating ♀ subjects**	**184**	
	Participating ♂ subjects	**159**	
	Participating ♀ ♂ subjects	**343**	
	Subjects affected	**62**	
	Subjects with outcomes	**27**	
	Outcomes	**30**	
	First outcome (/%)	**11**	
	Diagnosis	**81**	

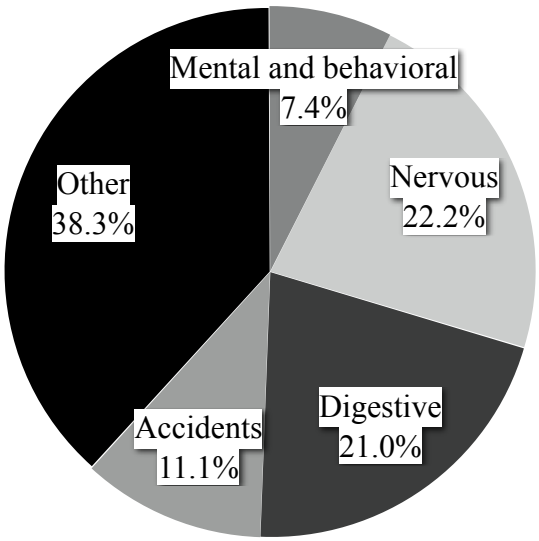


Figure 35. All other FO in 62 affected subjects from the SLSJ region.

4.5. SUMMARY OF FATAL OUTCOMES

The following table and figures depict the summary of FO in participating subjects (Table XXV, Figures 36 and 37). In summary, a grand total of 337 subjects (98.3%) were affected by all three causes, 236 of them had 780 outcomes, of which 365 were first outcomes. Lastly, a grand total of 2,720 diagnosis were identified in the participating subjects. As such, there were 299 subjects affected by CVD, 333 from non-CVD and 62 by all other diseases. In addition, 109 of those affected by non-CVD (32.3%) and 58 by all other diseases (17.2%) have concomitant CV FO. Lastly, there were 181 subjects with CV outcomes (76.7%), 142 from non-CV (60.2%) origin and 27 all other causes (11.4%; Figure 37 B).

Diagnosis from CV FO totalized 1,103 (55.9%), from non-CV 1,536 (41.8%) and from all other causes 81 (3.0%; Figure 37 A). Furthermore, outcomes from CVD totalized 555 (71.2%), from non-CVD 195 (25.0%) and from all other causes 30 (3.8%) (Figure 37 C).

Finally, first outcomes from CVD totalized 247 (67.7%), from non-CVD 107 (29.3%) and from all other causes 11 (3.0%; Figure 37 D).

Table XXV. FO summary for 343 participating subjects of the SLSJ region (total *n* = 343; 184 ♀and 159 ♂).

DWM		**CV**		**Non-CV**		**Other**	
		n	**%**	***n***	**%**	***n***	**%**
Subjects	•Affected	299	88.7	333.0	98.8	62.0	18.4
	•+ CVD			109.0	32.3	58.0	17.2
	•Outcomes	181	76.7	142.0	60.2	27.0	11.4
Outcomes		555	71.2	195.0	25.0	30.0	3.8
First outcomes		247	67.7	107.0	29.3	11.0	3.0
Diagnosis		1103	40.6	1536.0	56.5	81.0	3.0
Total		**Subjects affected**				**337**	**98.4**
		Subjects with outcomes				**236**	
		Outcomes				**780**	
		First outcome %				**365**	
		Diagnosis				**2720**	

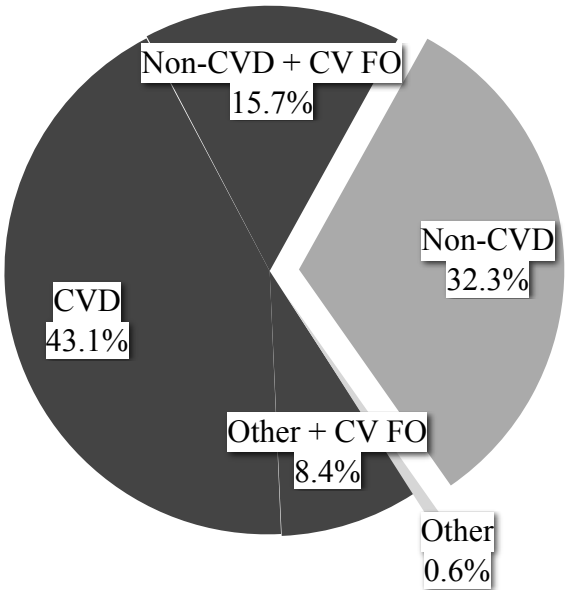


Figure 36. Subjects affected by all FO, focussing on their concomitance with CV FO.

In summary, non-CV FO had the most diagnosis. Nevertheless, CV FO had the most impact when it came to the most subjects with outcomes, outcomes themselves and first outcomes (Figure 37).

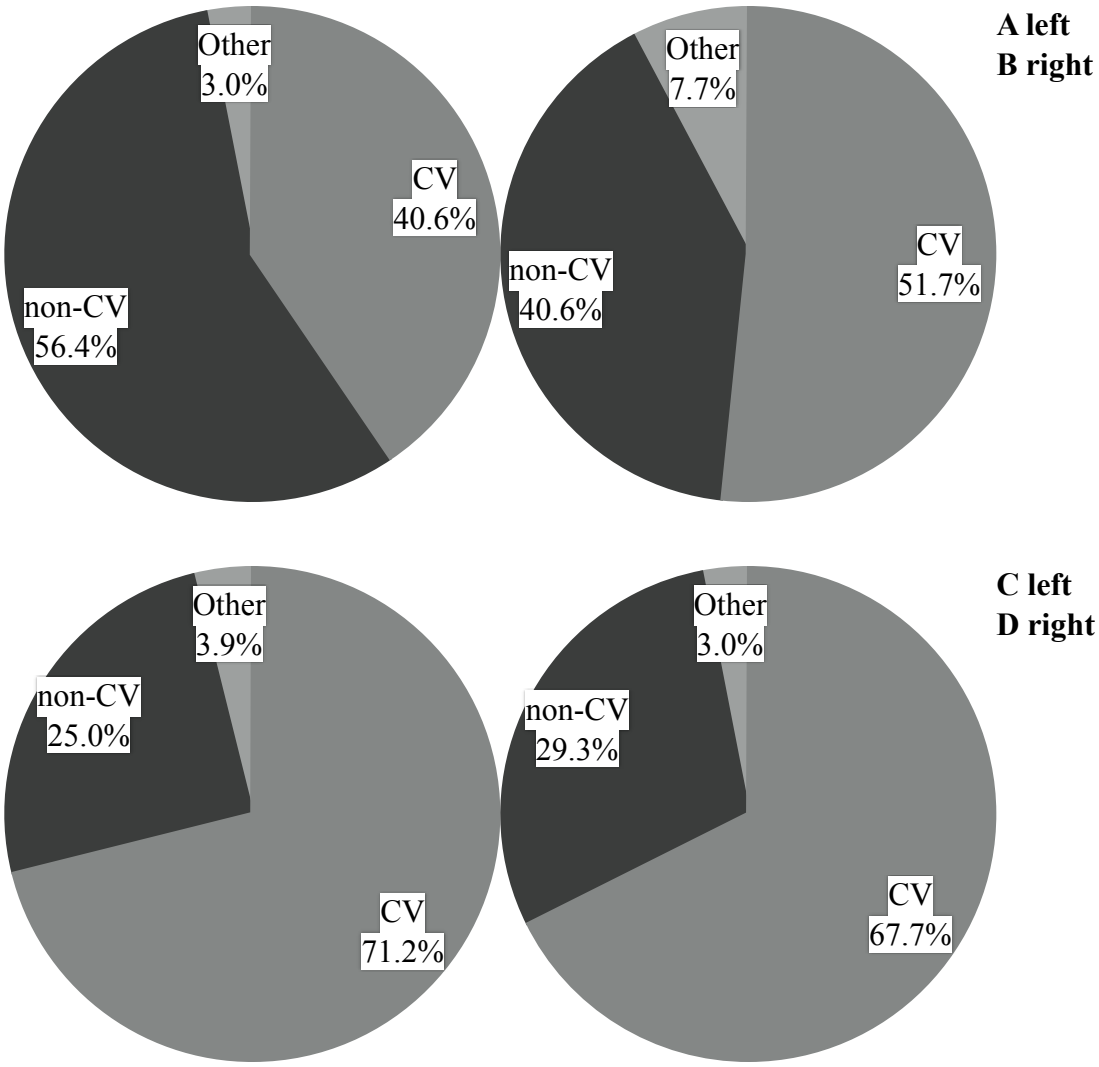


Figure 37. Summary of A) diagnosis, B) subjects with outcomes, C) outcomes and D) first outcomes for FO in 337 affected subjects of the SLSJ region.

4.6. CARDIOVASCULAR DISEASES WITHOUT FATAL OUTCOMES

In the following section, we analyze results from 343 subjects with affections from CV NFO (Table XXVI, Figure 16). There are three main diseases in the sub-category: cardiac diseases, vascular diseases and hypotension. Cardiac diseases, which included rhythm pathologies and non-rheumatic valve disorders affected 98 of 105 affected subjects (93.3%), venous vascular diseases 10 (6.4%) and hypotension 7 (6.7%). Moreover, cardiac diagnosis represented 14.9%, venous vascular diseases 1.1% and hypotension 0.7% of the 934 total diagnosis from NFO. In summary, a total of 156 diagnosis have been identified affecting 105 subjects.

Table XXVI. NFO of the circulatory system identified in 343 participating subjects of the SLSJ region.

NFO of the circulatory system			***n***	***Subtype %***	***Total %***
Cardiac diseases	*Rhythm pathologies*	Atrial	59	42.4	37.8
		AV	2	1.4	1.3
		Ventricular	56	40.3	35.9
	Non-rheumatic valve disorders	Aortic	17	12.2	10.9
		Mitral	5	3.6	3.2
		Tricuspid	0		
		Pulmonary	0		
	Subjects affected		98		62.8
	Diagnosis		139		89.1
Vascular diseases	*Venous*		10		6.4
	Subjects affected		10		9.5
	Diagnosis		10		6.4
Hypotension		Low risk	2	28.6	1.3
		High risk	1	14.3	0.6
		Unclassified	4	57.1	2.6
	Subjects affected		7		6.7
	Diagnosis		7		4.5
Total	**Participating ♀ subjects**		**284**		
	Participating ♂ subjects		**159**		
	Participating ♀ ♂ subjects		**343**		
	Subjects affected		**105**		
	Diagnosis		**156**		

4.7. NON-CARDIOVASCULAR DISEASES WITHOUT FATAL OUTCOMES

343 subjects were affected with non-CV NFO (Table XXVII, Figure 17). There are three main diseases in the sub-category: benign neoplasms, lung and kidney diseases. We can see that benign neoplasms, for both, men and women, totalized 44 (73.3%), lung diseases 7 (11.7%) and kidney disorders 5 (8.3%). In summary, a total of 60 diagnosis have been identified affecting 53 subjects.

Table XXVII. Non-CV NFO found in 343 participating subjects of the SLSJ region.

Non-CV NFO			***n***	***Subtype %***	***Total %***
Benign neoplasms	*Men*	Lip, oral cavity and pharynx	0		
		Digestive organs	4	9.1	6.7
		Respiratory and intrathoracic organs	1	2.3	1.7
		Bone and articular cartilage	0		
		Skin	6	13.6	10.0
		Mesothelial and soft tissue	1	2.3	1.7
		Breast	0		
		Male genital organs	0		
		Urinary tract	1	2.3	1.7
		Eye, brain and other parts of CNS	0		
		Thyroid and other endocrine glands	0		
		Lymphoid, hematopoietic and related tissue	0		
		Other	0		
		Independent multiple sites	0		
	Women	Lip, oral cavity and pharynx	0		
		Digestive organs	5	11.4	8.3
		Respiratory and intrathoracic organs	0		
		Bone and articular cartilage	0		
		Skin	5	11.4	8.3
		Mesothelial and soft tissue	1	2.3	1.7
		Breast	5	11.4	8.3
		Female genital organs	6	13.6	10.0
		Urinary tract	1	2.3	1.7
		Eye, brain and other parts of CNS	0		
		Thyroid and other endocrine glands	2	4.5	3.3

Non-CV NFO			*n*	*Subtype %*	*Total %*
		Lymphoid, hematopoietic and related tissue	0		
		Other	3	6.8	5.0
		Independent multiple sites	3	6.8	5.0
Subtotal		Diagnosis	44		100.0
Lung diseases			7		15.9
Kidney disorders			5		11.4
Total	**Participating ♀ subjects**		**184**		
	Participating ♂ subjects		**159**		
	Participating ♀ ♂ subjects		**343**		
	Subjects affected		**53**		
	Diagnosis		**60**		

4.8. ALL OTHER DISEASES WITHOUT FATAL OUTCOMES

In the following section, we analyze results from 343 subjects with affections from all other NFO (Table XXVIII, Figure 18). In summary, a total of 718 diagnosis have been identified affecting 252 subjects. Details of each disease are found below.

Table XXVIII. All other NFO identified in 343 participating subjects of the SLSJ region.

All other NFO		*n*	*%*
Mental and behavioral	Anxiety	15	2.1
	Other	6	0.8
Nervous system		8	1.1
Eye and adnexa	Cataracts, etc.	75	10.4
Ear and mastoid process		8	1.1
Digestive system		141	19.6
Genitourinary system		96	13.4
Endocrine, nutritional and metabolic	Hypothyroidism	51	7.1
	Hyperthyroidism	2	0.3
Blood and blood-forming organs and certain disorders involving the immune mechanism	Anemia, etc.	93	13.0
	Other	9	1.3
Musculoskeletal system and connective tissue		144	20.1
Accidents		14	1.9
Other		55	7.7
Unknown		1	0.1

All other NFO		*n*	*%*
Total	**Participating ♀ subjects**	**184**	
	Participating ♂ subjects	**159**	
	Participating ♀ ♂ subjects	**343**	
	Subjects affected	**252**	
	Diagnosis	**718**	

4.9. SUMMARY OF DISEASES WITHOUT FATAL OUTCOMES

The following table and figures depict the summary of NFO in participating subjects (Table XXIX, Figures 38). A grand total of 273 subjects (79.6%) were affected, totalizing 934 diagnosis. As such, 92.3% of subjects (718) were affected by all other diseases, while only 38.5% (105) by CVD and 19.4% (53) by non-CVD. Similarly, 76.9% of diagnosis (718) originated from all other diseases, but only from 16.7% (156) from CVD and 6.4% (60) from non-CVD.

Table XXIX. Summary for NFO in 343 participating subjects of the SLSJ region (total *n* = 343; 184 ♀and 159 ♂).

NFO	CVD		Non-CVD		Other diseases	
	n	***%***	***n***	***%***	***n***	***%***
Subjects affected	105	38.5	53	19.4	252	92.3
Diagnosis	156	16.7	60	6.4	718	76.9
Total	**Subjects affected**		**273**	**79.6%**		
	Diagnosis		**934**			

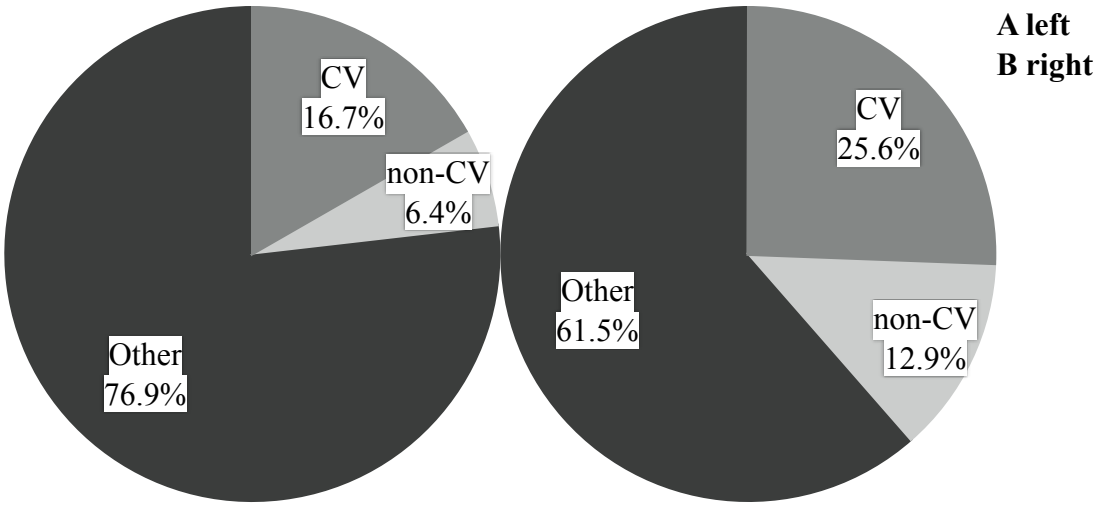


Figure 38. Summary of A) diagnosis and B) subjects affected for NFO in 273 affected subjects of the SLSJ region.

4.10. RELATIVE RISK

In this section, we evaluate the RR for diseases in our 'exposed' subjects versus the 'control' population of SLSJ region (Table XXX). If necessary, please refer to Chapter III for more detailed specifications on the calculations involved. Interestingly, we observe that there is a threefold risk increase in our subjects to develop disease from the circulatory system compared to the general population of SLSJ, and this is statistically significant. Furthermore, the risk of developing isolated malignancies significantly decreased by half in our sample while it almost doubled when taken into account with CVD. In addition, the risk for HBP was one and a half higher.

Table XXX. RR calculated for various diseases in our study. Note that the reference values for 'c' and 'd' come from Lapierre *et al.* **[19]**.

Disease	a[ϕ]	b[ϕ]	c[ϕ]	d[ϕ]	RR	Z[ϕ]	P-value
Circulatory system**	1,103	1,617	3,878	22,994	2.810	23.545	<0.0001
Hypertension**	281	822	44,874	221,054	1.510	7.971	<0.0001
HBP with CVD**	274	69	88	255	3.114	11.853	<0.0001
DM	97	1,439	15,313	239,266	1.050	0.494	0.62
Malignant neoplasms**	52	1,484	2,019	24,853	0.451	5.778	<0.0001
Malignant neoplasms + HBP**	38	52	7,474	19,398	1.518	3.375	0.0007
Malignant neoplasms + circulatory system**	1,155	1,565	5,897	20,975	1.935	26.289	<0.0001
Obesity with CVD**	246	97	172	171	1.430	5.624	<0.0001
Non-CV**	1,536	1,184	5,374	8,998	1.510	20.616	<0.0001
All other**	81	2,639	5,120	9,252	0.084	22.558	<0.0001
All non-CV and other**	1,617	1,103	10,494	14,372	1.409	19.592	<0.0001

Legend[ϕ]:
** = highly significant
a = affected individuals in our study
b = unaffected individuals in our study
c = affected individuals in SLSJ region 2006-2007
d = unaffected individuals in SLSJ region 2006-2007
Z = Z test (Z statistics) performed

4.11. CHI SQUARE TEST

We used the Chi square (χ^2) test if the large differences in observed between exposed outcomes are probable in our sample (see Chapter III). As such, our results show a high degree of significance for all data tested (Table XXXI). In fact, we obtained a χ^2 value of 1,575.348

for data of diseases of the circulatory system ($p<0.0001$), while this value decreased a 100 times for Non-CV diseases ($p<0.0006$). As for malignant neoplasm, when considered with malignant neoplasm the χ^2 value increases tenfold.

Table XXXI. Chi square (χ^2) test results with their degrees of freedom (ν) and a two-tailed P-value for various diseases in our study. Note that the expected values were calculated from Lapierre *et al.* **[19]**.

Disease	w^{ϕ}	x^{ϕ}	y^{ϕ}	z^{ϕ}	χ^2	ν	P-value
Circulatory system**	1,103	383	1,617	2,337	1,575.348	1	<0.0001
Hypertension**	281	69	62	274	815.392	1	<0.0001
HBP with CVD**	274	88	69	255	528.807	1	0.0001
Malignant neoplasms**	52	125	1484	1411	46.409	1	<0.0001
Malignant neoplasms + HBP**	38	15	15	38	49.188	1	<0.0001
Malignant neoplasms + circulatory system**	1155	597	1565	2123	668.210	1	<0.0001
Obesity with CVD**	246	172	97	171	63.861	1	0.0001
Non-CV**	1,536	1,624	1,184	1,096	11.834	1	0.0006
All other**	81	1,505	2,639	1,215	3,016.311	1	0.0001
All non-CV and other**	1,617	1,986	1,103	734	254.066	1	0.0001
Smokers with CVD**	70	50	30	50	16.000	1	0.0001

Legend$^{\phi}$:
** = highly significant
w = observed affected individuals in our study
x = expected affected individuals in our study
y = observed unaffected individuals in our study
z = expected unaffected individuals in our study

CHAPTER V:

Discussion

Discussion

5.1. OVERVIEW

Our study represents an average follow-up of 11 years of the 343 participants. In this Chapter, we will discuss the relevance and importance of the reported results. In doing so, we hope to paint a CV portrait in order to eventually identify the risk factors for patients with similar familial and phenotypic characteristics (dyslipidemia +/- obesity). A descriptive overview of the population sample can give an idea of the group morbidities and possible mortality causes. We will see what affections are found in our segment of population. As previously mentioned, it is hard to isolate the different components of CVD. They are multifactorial traits with complex interactions from both genetic and environmental factors. Previous findings showed that the degree of genetic homogeneity increased by selecting families with a high prevalence of HBP and even more in a subset with high and low risks of early mortality [13].

In summary, we will start by discussing the overall data for FO, NFO and RR, following result organization. Finally, we will address the limitations of the present study and its techniques.

5.2. DISEASES WITH FATAL OUTCOMES

5.2.1. CARDIOVASCULAR VS. NON-CARDIOVASCULAR DISEASES

The mortality rates from CVD in Canada and Quebec are 32.1% and 25.2%, respectively, which ranks them first and second of mortality causes [8, 11]. Interestingly, we notice that 59.9% of the diagnosis in our subjects (661 of 1,103 CV FO diagnosis)

come from cardiac diseases, the most frequent cardiac disease being CHD representing 48.7% (322 of 661 cardiac FO diagnosis). High elevation of this type of diseases in our cohort seems to explain the high elevation of mortality events from CVD. This also can suggest that our FO classification was valid, but this will be discussed later on.

The depth of CV FO affection is vast. In fact, CV FO affect purely 43% of subjects, while 109 of 333 affected subjects with non-CVD FO have also a concomitant CV FO (Figure 36). Furthermore, 58 out of the 62 subjects from other FO also suffer from a CV FO. Thus, 67.1% of all subjects from this category have a CV FO. This highlights the importance of CVD in this sample of 343 subjects from SLSJ. While no statistical testing has been done, the real number of affected participants gives an idea of the importance of CVD. It would be interesting to compare the number of participants affected with only CVD to those with concomitant CVD to those without CVD.

In fact, our sample showed a threefold risk increase in developing CVD ($p<0.0001$; $\chi^2=1,575.348$), while it diminished by half when compared to non-CVD ($p=0.0006$; $\chi^2=11.834$) in the population of SLSJ. This is very interesting since it supports our finding that CVD predominated in the number of outcomes and first outcome over all other causes (discussed in the following section).

5.2.2. DIAGNOSIS VS. OUTCOMES VS. FIRST OUTCOMES

As previously stated, CV and non-CV FO are the leading causes of morbidity and mortality in North America [3, 5, 8]. Our classification into three subcategories of FO showed that CVD accounted for 40.6% of all diagnosis, non-CVD for 56.4% and all other diseases 3.0% (Figure 38). This seems to suggest that our sample is mainly affected by non-CV FO. However, as mentioned in the previous section, CV FO seemed to affect more subjects when looking at combinations of CV and other diseases. As such, our outcomes and first outcomes reflect this tendency and highlight the difference between our category of diagnosis vs. outcomes and first outcomes. In fact, there is a complete reversal in importance: (1) 71.2% of all outcomes are from CVD (elevation of almost 30% from CVD diagnosis; drop of almost 31% for non-CVD) and (2) 67.7% of all first outcomes from CVD (elevation of almost 27% from CVD diagnosis; drop of almost 27% for non-CVD).

The reason why the importance of CVD rises might come from our definitions of diagnosis, outcomes and first outcomes. The fact that outcomes and first outcomes only appear at the entry of the study gives us the opportunity to see what diseases developed during the last 11 years of this follow-up. At the same time, it distinctly focuses on these diseases without having middle ground for affection with both CV and non-CV/other FO. In other words, this pre-selecting criterion also seems to elevate the degree of homogeneity for CVD and may be considered as a possible guideline when analyzing with proper statistical testing, this population in future studies.

Finally, the average age for outcomes occurrence in men was 55, while for women was 61. Following the criteria for early onset of CVD and risk of early mortality, men from this sample are at the borderline for early onset or early mortality since the age interval of early risk is between 25 to 55 years of age [48, 105]. On the other hand, women fall directly into their respective interval for early onset or early mortality (from 25 to 65 years of age). These results support literature findings that post-menopausal women are more at risk towards CVD and that men are more at risk towards CVD than pre-menopausal women [87]. These preliminary data also raise the question of the stringency and validity of the age criteria for early onset of CVD and risk for early mortality.

5.2.3. CARDIOVASCULAR RISK FACTORS

Historically, it is only during the last half century, with the beginning of the Framingham Heart Study, that the scientific community and general population have started to be aware of the importance of prevention and treatment of CV risk factors before the disease onset [114]. These have been discussed in length in the Chapter II. Unless otherwise specified, the results discussed in this section relate to Table XXIII (non-CV FO).

5.2.3.1. HYPERTENSION AND OBESITY

The dangers and deleterious effects of HBP are well known as well as the reason why it is one of the main risk factors for CVD morbidity and mortality [50, 105]. In our sample, 274 out of 343 subjects were affected by hypertensive diseases

(79.9%; Table XXII). Moreover, 6 of them had HBP in conjunction with heart, renal or both diseases. As simple compilation of the affected subject showed how important this disease is in our population, and was previously reported [1]. Obesity is another crucial risk factor for CVD. Statistic Canada reports that 68% of men and 53% of women are overweight or obese [115]. In fact, we report that only 92 of 343 participating subjects had a normal BMI (27.5%), indicating that 71.5% were at least overweight (only 1.4% are underweight; Figure 32).

Furthermore, previous research on the French-Canadian families SLSJ region of Quebec showed that the genetic entities for HBP and obesity were distinct [2, 17]. Together, we identified 210 subject both with both HBP and obesity yet they only had 59 CV FO (28.1%). However, our results showed that, separately, 60.6% of affected subjects with HBP (χ^2=528.807, p=0.0001) and 59.8% with obesity had an also an underlying CV FO. In addition, the RR was high in both cases in combination with CVD in our sample compared to the rest of SLSJ region: threefold for HBP ($p<0.0001$) and one and a half for obesity ($p<0.0001$).

Abdominal obesity is the first obligatory criteria for MSY and an additional risk for CVD by itself [112, 116] and also contributed to the risk factors for CV FO. Our subjects had abnormal or elevated average abdominal circumferences for 96 out 159 men, and 107 out of 184 women (98.3 cm and 85.4 cm, respectively). To

conclude, our study sample had already risk factors for CVD that might explain previous results for diagnosis, outcomes and first outcomes for CV FO.

5.2.3.2.PRE-DIABETES AND DIABETES MELLITUS

Until the 1800s, DM was to be treated by the Rollo diet, consisting mainly of meat [117]. Subjects at the stage of pre-diabetes, e.g. IFG or AFG, are at high risk to develop DM and even CVD [118]. After consulting with a specialist, we identified between 50 to 60% of the subjects previously undiagnosed with DM with laboratory results confirming the pre-DM stage, or T2D (not mentioned in the hospital charts or untreated). Nevertheless, it is quite possible that the subject(s) was/were made aware of their medical situation but the diagnosis was not recorded properly in their hospital chart. Notwithstanding this information, we have found that 103 of 343 participating subjects (30.0%) were classified as pre-DM affected, and 43 of these (42.6%) were outcomes. More specifically, 95 out of the 103 subjects (91.3%) had concomitant CV FO, which contributed to the CV impact mentioned above.

Furthermore, we identified 2 T1D subjects, 93 T2D and 4 with unspecified DM (could not be confirmed by hospital notes). DM had also 43 outcomes (22.1% of all non-CV outcomes), of which 26 were first outcomes (24.3% of all non-CV first outcomes). In addition, 7 of the 93 subjects with T2D were previously undiagnosed for DM in their hospital charts but were classified as diabetics

according to their laboratory results and medication. Similarly to the pre-diabetes subjects, 94.7% with DM were affected also by CV FO. In comparison, in the subjects without diabetes, the percentage of affected subjects by also CV FO dropped to 60.9%, supporting the literature indicating that people with DM have a higher prevalence of CVD [119]. However, this will be done in the future study and will have to be supported by appropriate statistical testing.

5.2.3.3.CHOLESTEROL

Cholesterol is another risk factor for CV FO that may contribute to the high number of outcomes and first outcomes. In fact, DLP is a major risk factor for CVD [71, 72]. It is important in CV prevention to detect early cholesterol-related health problems, since they can be treated quite efficiently with medication and the counter gain is significant in avoiding or slowing down the onset of CVD. This is especially important in rarer cases of heterozygous or homozygous FH where subjects might be at risk of dying even before the age of 25 years from CVD. In addition to very high CHOL in both FH forms, there can be concomitant severe HTG, which aggravates a subject's health situation and requires fast treatment.

We noted 344 diagnosis of lipid abnormalities out of 1,536 total diagnosis for non-CV FO (22.4%). These were affecting 273 out of 343 subjects (79.6%). When cross-referencing those subjects to the ones with CV FO, we obtain a total of 246 subjects (71.7% of participating subjects) with both CV and non-CV FO. This

again may contribute to the CV importance mentioned above. Moreover, we found 16 cases of heterozygous FH and 2 cases homozygous FH, which are rarer but potentially deadly as previously mentioned.

5.2.3.4.KIDNEY DISORDERS

Renal disorders, e.g. diminished GFR, have been known to be associated to an increased prevalence of prior CVD, CV risk factors and overall death [109, 120, 121]. Within our study, we found 35 diagnosis of chronic and acute renal failure for 29 subjects. Amongst those diagnosis, we also found 20 outcomes and 7 first outcomes for 17 subjects. In addition, we have 13 subjects with renal atherosclerosis, 5 subjects with renal hypertensive diseases and 1 with both heart and renal hypertensive diseases. Lastly, 28 out of the 68 subjects also have concomitant DWM from CVD within the segment of kidney failure.

5.2.3.5.LIFESTYLE AND CARDIOVASCULAR DISEASES

An unhealthy lifestyle has been known to increase the risk of CV FO [116, 119, 122, 123]. In addition, tobacco use is imbedded in the global socio-cultural and economic dimensions and Tobacco Industry lobbying targets ideologies and way of thinking of young adults and/or adolescence [90, 124, 125]. This reflects the importance of prevention and roles of physicians in our society to make their patients aware of the risks. However, the problem lies in the patient's will to change. Another issue is the popular urban myths of people who led very

unhealthy lifestyle, excessive smoking, eating and alcoholism, and lived a long 'healthy' life. Nevertheless, it is important to look at this with objective and critical thinking. In all statistics, there are exceptions, but this might apply only to a small segment of the population possibly due to a strong 'defensive' genetic background protecting against FO, such as CVD.

In fact, our sample showed that 101 of 343 participating subjects smoked (29.4%), and 109 (31.8%) had an unhealthy lifestyle, such as smoking, alcoholism and drug abuse. Interestingly, about half of the non-smokers were affected by FO CV, while this rose to 70% in smokers (χ^2=16.000, p<0.0001). This supports the previously mentioned literature that smoking puts subjects at risk for CVD.

5.2.4. CANCER AND CARDIOVASCULAR DISEASES

CVD may be linked to malignancies [46, 47, 126]. The rationale for coexistence of CVD and cancer risk is not yet fully understood. Nonetheless, overstimulation and even higher proliferation of smooth muscle cells in HBP creates a bigger cell turnover [25, 127-129]. In doing so, mutations occur more frequently, which in itself is a risk for cancer.

In the case of non-CV FO, malignant neoplasms account for 52 diagnosis affecting 45 of 333 affected subjects. At first look, it may be argued that this ratio of subjects compared to other diseases of the same group is not that high. Nevertheless, our results show that 88.9% of these subjects are also affected by CVD. More interestingly, 84,4%

of cancer subjects suffer from also from HBP. In fact, our results show a 1.5 increased risk ($p=0.0007$) in our sample to suffer both from HBP and cancer ($p<0.0001$, $\chi^2=49.188$) than from cancer alone, which was actually diminish by half ($p<0.0001$). Thus, this might hold a partial explanation to the higher outcomes and first outcomes that might be linked to overall death from cancer and/or developing it, but further data collection and statistical testing will be required.

Lastly, the RR for developing malignancies yielded a twofold decrease in occurrence in our sample in contrast in to the general population of SLSJ ($p<0.0001$, $\chi^2=46.409$). Interestingly, this result changed when we examined the combination of malignant neoplasms with CVD. In fact, it grew twice as much in our sample ($p<0.0001$, $\chi^2=668.210$). As such, this would support the literature that there exist a link between CVD and cancers.

5.3. DISEASES WITHOUT FATAL OUTCOMES

We also analyzed NFO in comparison to FO. Among these, we note a complete reversal of importance which was to be expected (Table XXIX; Figure 38). The results showed that the importance of CVD fell to 16.7% and non-CV to 6.4% while all others rose to 77%. This may suggest that CVD (and non-CVD) are more often FO than NFO and when they occur, they put the subject at a rising risk over time. While there are many NFO, the patient can be treated and

managed more efficiently, which diminishes the overall risk on the subject's morbidity and mortality.

5.4. LIMITATIONS OF THE CURRENT STUDY

In this last section, we will discuss some variables that influenced the development of this study.

5.4.1. DATA COLLECTION

5.4.1.1. COMMITTEE APPROVALS

Approval from the CAIQ has been previously been obtained but had expired in 2006. A new submission has been sent in July 2011 after contacting the CAIQ on numerous occasions because we were assured that this would be the most efficient way to proceed. At the moment of the writing of this thesis, we are still awaiting the approval to contact the ISQ and pursue the study of mortality events to determine early mortality within each family of the participating subjects.

The fatal outcomes deserve further analysis, pending the permission from the CAIQ. It is to be noted that the data from deceased subjects that were enrolled directly in the study have not been showed in this thesis. It will be relevant to analyze the nature of these lethal outcomes in relation to early mortality. In fact, this initial exploration of the data may result in re-examining the age criteria for

early mortality (25 to 55 years of age for men and 25 to 65 for women). The presented data will assist us at determining more objectively those criteria.

5.4.1.2.GATHERING PROCESS

When examining the subject at the *Centre de santé et des services sociaux* of the Chicoutimi Hospital in the SLSJ region, not all the hospital charts contained a systematic coding of ICD. Many of them were not yet coded following this system during the data gathering of July 2010. For those that were, some were coded by ICD9 and converted to ICD10 while others directly by ICD10 (as explained in Chapter III: Methods).

In addition, many subjects had their records destroyed by the archives, limiting the availability of laboratory results and specific tests for several cases. This was unfortunate since much information could have been gathered from those data. On a more positive note, after consulting and explaining this problem in length to the Chicoutimi Research Center' law representative, a request was sent the Hospital's Archives to stop the chart destruction process for the participating subjects for the next 25 years. The request was approved by the competent authorities.

During the data gathering, we noted that 37 patients did not consent to continue this study and 65 had missing consent. Those consents were kept at the Chicoutimi Research Center and were, unfortunately, not all found. Further clarification and

investigation is required for these. When leaving the collection site in July 2010, an order was issued to find these consents and clarify the status of the subjects' who did not consent with the Chicoutimi Ethics Committee. In fact, it was unclear if they actually refused their data to be used in further studies or just to be contacted for new procedures in the future. However, the Center's Administrative Coordinator decided they were not to be included until further clarification.

In addition, there were 4 out of 380 analyzed subjects that were not associated to any families in our database but were participating in the study. It will be important to find out where these 4 subjects fall in the families in order to elevate the statistical value of the present and future studies on the data gathered. This also might have been a clerical error on the subjects' ID.

Finally, the geographical location of the Chicoutimi site limited the time for data collections and will have to be completed in the future. On the other hand, the data from the subjects that have moved to Montreal (second collection site) have not been gathered yet. It was planned to first finish with the Chicoutimi subjects before starting the second group. Also, these two groups have not received care at the same Hospital sites, which may lead to selection and information bias. Montreal subjects are not presented in the current study. Furthermore, if the subjects from Chicoutimi had received care elsewhere, hospital charts can be transferred for review, which limits the information bias. Moreover, the *Centre de*

santé et de services sociaux de Chicoutimi is the largest hospital system in the SLSJ region and offers the possibility for advance testing (both clinical and laboratory), which is not available in smaller cities of the region. This is another aspect to be worry about for future data collection(s).

5.4.2. DATA CLASSIFICATIONS AND DIAGNOSIS

As previously mentioned in Chapter III: Methods, our dichotomous data classifications have been decided with the help of an Adjudication Committee and the recommendation of a specialist. Each diagnosis, has been examined in depth by the consulting specialist in order to verify the data and check for false positive or negative results for the purpose of this study. In conjunction, the diagnosis were validated by the Adjudication Committee. However, a potential misclassification of the diseases cannot be excluded. Fortunately, the impact would not be as important as it could be because the data were not separated randomly into FO and NFO categories. It followed experienced advisement and was done according to the potential severity of diseases. In the end, some disease are life threatening (e.g. malignant neoplasm, etc.) while others are not (e.g. benign neoplasm, etc.).

Furthermore, a second degree of classification for CV FO, i.e. MACCE score, has been added to help quantify if the diagnosis was at high or lower risk within the category of FO. The data may also suggest that CVD are more often FO than NFO. When this occurs, it would put the subject more at risk over time, which would yield false positive

results. In other words, this additional measure helped differentiate between patients with severe CV (e.g. CHD, HF, etc., with MACCE≥3/4) and non-CV FO (e.g. malignant neoplasms, DM, etc.), from patients with 'milder' CV (e.g. bradycardia, etc., MACCE≤1) and non-CV FO. In summary, we tried to objectively separate and distinguish diseases into qualifying categories in order to better understand and describe this sample population.

5.4.3. MACCE SCORING SYSTEM

The MACCE score system has been adapted for the present study from the MACE grading system. In addition to the CVD, we combined them to CBVD to obtain the MACCE scoring system. In fact, this is why we computed a total MACCE score and an individual MACCE score for each disease. These assisted us in stratifying individuals with multiple CV FO for further analyses

The cumulative MACCE score was used to give an idea of the relative importance of CV FO in each subject. In fact, this may also show that some individuals with an elevated cumulative risk for CVD are at higher risk of outcomes. This may be illustrated by two individual examples:

Subject A is a 69-year-old woman with a total MACCE score of 3. She has HBP with MACCE=3/4. As HBP is a CV FO, we classify this subject in CV FO, because HBP can have many deleterious effects on several organs, e.g. heart, brain, kidney and lung;

Subject B is an 80-year-old woman with a total MACCE score of 11. If we examine only her CV status, she has bradycardia with MACCE=1/4, ischemic heart disease with MACCE=3/4 (multiple MI, PTCA with multiple stents and three vessel disease), mild HF with MACCE=1, mitral valve regurgitation with MACCE=1, LVH with MACCE=2 and HBP with MACCE=3. As such, this individual is considered as CV FO because her multiple and severe CVD put her at very high risk of deleterious effects and possibly even death.

Now, both of these patients have CV FO. Nevertheless, the Subject B is clearly more affected and thus 'more' at risk for mortality from CVD. This is why a total MACCE score was introduced into this study to allow for quantification of different CVD of each subject. Eventually, it may be relevant to see if these total MACCE scores are more frequent in specific families. This will allow the characterization of transmission patterns of different CVD within each family. Lastly, this new paradigm of a total MACCE score will be helpful in creating an update classification of subjects affected by severe CVD, e.g. subjects with two or more CV FO (e.g. Subject A) vs. those with three and more CV FO (e.g. Subject B).

5.4.4. STATISTICAL ANALYSIS

The main limitation of this study is that not all 896 subjects were examined. This leaves room for adding those to be collected in a later study and perform the statistical analyses

that will help to interpret these results. However, even these collected subjects give a good idea and description to stratify the current sample population. We can see exactly how each disease, reported diagnosis, outcome and first outcome affects our subjects. As such, relative risk and chi square tests were performed to ascertain the validity of our findings.

CHAPTER VI:

Conclusion And Future Perspectives

Conclusion And Future Perspectives

This study provided an insight into affections, of both FO and NFO, in subjects of SLSJ region of Quebec. We describe the predominant importance of CV FO in both first outcomes and total outcomes when compared to all other diseases, both on the level of subject affections and the number of diagnosed outcomes in this specific cohort. When examining CV co-affection with non-CV or all other diseases, 67.1% of our sample population was affected by CV FO. In fact, our sample showed a threefold risk increase in developing CVD ($p<0.0001$; $\chi^2=1{,}575.348$), while it diminished by half when compared to non-CVD ($p=0.0006$; $\chi^2=11.834$) in the population of SLSJ. Finally, the RR for developing malignancies was twice as unlikely to occur in our sample in contrast with the same region. Nevertheless, when looking at them in conjunction with CVD, this risk grows twofold in our sample. As such, these results may eventually help physicians in their patient approach, and a more effective health system.

In the future, it will be important to pursue the morbidity data collection for the remaining participating subjects, both in Chicoutimi and Montreal. Moreover, once the approval from the CAIQ has been obtained, it will be necessary to obtain from the ISQ the mortality data from the families of the participating subject. Thus, we can classify and move ahead with the current study by associating high risk of early death to the actual rate of mortality of these families. In fact, it will be crucial to link the morbidity and mortality data with each family and observe the prevalence of FO. Furthermore, genetic studies will be necessary in order to

link the present phenotypic observation on a genetic level. In fact, genetic predisposition may help identify which subjects are more at risk than others.

The mortality analysis will be ascertained firstly by collecting directly obtained information. In order to complete this project to the fullest extent, causes of death will be directly obtained from the ISQ according to ICD 9 and ICD 10. The next step will comprise the validation with the health registry data from the Ministry of Health and Social Services, contained in the summary sheets of all hospitalizations. As for morbidities, the questions raised about consents will have to be resolved. Moreover, we will continue doing what was started in this study by looking at their medical history in a similar way as for mortalities.

We plan to analyze these mortalities and morbidities, their temporal characteristics and their clustering in hypertensive French-Canadian families with or without obesity, using hospital, civic death registries and genealogical records from 1950 up to the present. We want to describe and study the families and their respective members at high risk of early mortality. This will also be achieved by comparing their phenotypic characteristics within those families and also with the families at low risk of early mortality.

Preliminary data on early mortality appeared to be more prevalent in specific families, as previously shown in this population [13]. As discussed above, it may be relevant to review the criteria for early mortality. Are the age intervals for men and women to stringent for analysis?

Do they actually qualify as a segment of population with 'very' early mortality? These are important question that should be addressed in the future.

By examining the lethal and non-leathal outcomes of French Canadian families, we want to identify the connection between CVD and early mortality on a clinical and even genetic level. This may lead in the future to develop predictive biomarkers, such as genes, to identify the people at risk. Clinical implication may involve a novel development of techniques for the patients at risk and a possible orientation towards individualized medicine.

Since our preliminary findings suggest that early mortality from CVD includes both genetic and environmental factors, we will have to test in the future if subjects with FO, especially from CV cause, are more at risk of early mortality than subjects with NFO. If this proves to be true, we will try to find the genetic determinants responsible for early mortality due to FO. With a genetic test, we could one day be able to identify the subjects at risk sooner and treat them more efficiently. In fact, this might make the difference between life and death.

To conclude, the study aims to be a foundation for future analysis, both phenotypic and genetic. The data gathered were compiled and we created a database component of the participating subjects. Furthermore, we were able to calculate the RR for our sample to develop CVD and it was statistically significant. We expect to use it for modeling future results for better understanding of CVD risk with a goal to improve prevention and therapy in most exposed families.

CHAPTER VII:

References

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