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Familial Aggregation of Ideal Cardiovascular Health and Cardiovascular Disease Disability-Adjusted Life Years in Parent-Offspring Dyads: Analysis of the Framingham Heart Study

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FAMILIAL AGGREGATION OF IDEAL CARDIOVASCULAR HEALTH AND CARDIOVASCULAR DISEASE DISABILITY-ADJUSTED LIFE YEARS IN PARENT-OFFSPRING DYADS: ANALYSIS OF THE FRAMINGHAM HEART STUDY

A Dissertation Presented

by

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ABSTRACT

FAMILIAL AGGREGATION OF IDEAL CARDIOVASCULAR HEALTH AND CARDIOVASCULAR DISEASE DISABILITY-ADJUSTED LIFE YEARS IN PARENT-OFFSPRING DYADS: ANALYSIS OF THE FRAMINGHAM HEART STUDY

May 2019

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Background: Ideal cardiovascular health (iCVH) is defined as the simultaneous presence of seven health metrics-physical activity, not-smoking, healthy diet, healthy body weight, and blood cholesterol, blood pressure, and blood glucose levels as defined by evidence-based guidelines. Evidence suggests familial aggregation of single cardiovascular disease (CVD) risk factors but research on clustering of seven iCVH metrics and CVD disability-adjusted life years (CVD DALYs) within families is lacking.

Purpose: To examine trends and relationship of parental iCVH and offspring iCVH and CVD DALYs at similar age across the lifespan.

Methods: A secondary data analysis of the Framingham Heart Study (FHS) Dataset-Original and Offspring Cohorts. Pearson correlations and multivariate linear regressions were used to assess linear relationships of iCVH; T-test and chi-square were used to test differences

between iCVH metrics and CVD DALYs. Proportional odds model was used for assessing relationships of ordered iCVH categories. Brant test and gologit2 command in Stata©14 were used to test the parallel assumptions of the proportional odds model. CVD disability weights were derived from the Global Burden of Disease Study (GBD) 2015 DALYs and Health Adjusted Life Expectancy (HALE) Collaborators.

Results: At total of 2734 parents and 3492 offspring met inclusion criteria with 1,044 distinct families with a mean of 2 children per family. Women participants were slightly higher than men in both cohorts ($p<0.001$). Offspring iCVH was positively correlated with the parents iCVH ($r\leq0.25$). "Ideal" parental iCVH increased the odds of offspring attaining "ideal" iCVH by two-to-fourfold. Offspring of parents with high iCVH had lower mean CVD DALYs compared with offspring of parents with lower iCVH. iCVH was inversely associated with CVD DALYs. The mean CVD DALYs of Offspring Cohort was 5.5 (95% CI 5.2-5.9) compared with 1.8 (95% CI 1.6-1.9) in Original Cohort ($p<0.001$).

Conclusion: Results indicate familial clustering of iCVH metrics over the lifespan, with positive parental-offspring iCVH relationship and inverse relationship of iCVH and CVD DALYs. This study fuels the impetus for systems approaches in implementation of family-based interventions that combine multiple iCVH metrics with the ultimate goal of improving cardiovascular health for families and communities.

ACKNOWLEDGEMENTS

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DEDICATION

I thank the Almighty God for my achievements this far in life. I dedicate this work to my lovely mom and dad who taught me resilience, perseverance and hard work. Special thanks to my lovely wife Naomi for her support beyond measure. To my friends close and far, and the church community; indeed, a community of friends.

I wish to thank my dissertation committee members Drs. Laura L. Hayman, Eileen Stuart-Shor, Phil Gona and Suzanne Leveille for their remarkable guidance, support and precious time invested throughout this work and my training. Special thanks to Dr. Hayman, the chair of my dissertation for her extraordinary support and mentorship. Also, thanks to Dr. Jerry Cromwell for incredible support and the intriguing questions. To all other professors and my classmates who worked with me, inspired and mentored me, thank you so much.

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LIST OF ABBREVIATIONS

CVD: Cardiovascular disease

iCVH: Ideal cardiovascular health

YLL: Years of life lost

YLD: Years lived with disability

DALYs: Disability-adjusted life years

CVD DALYs: Cardiovascular disease disability-adjusted life years

GBD: Global Burden of Disease

CHAPTER 1

INTRODUCTION

The overall burden of cardiovascular disease (CVD) in the United States has not declined despite a reduction in deaths attributable to CVD. An estimated 92.1 million (28%) Americans have some form of CVD and about 1 in 3 deaths in the United States is due to CVD (American Heart Association [AHA], 2018b; Mozaffarian et al., 2015). Coronary heart disease (CHD) is the most prevalent form of CVD and the leading cause of death in the United States where it contributes to half of all CVD deaths (Centers for Disease Prevention and Control [CDC], 2017). Consequently, CVD leads to increased total loss of economic productivity and increased medical costs. In 2016 for instance, the total annual cost of CVD was $555 billion, and is projected to more than double to $1 trillion by 2035 (AHA, 2018a).

The AHA 2010 Impact Goals to address CVD morbidity and mortality by implementing health behavior modification aim to reduce CVD mortality in United States by 20% by 2020. These goals have been enumerated in the AHA's 2020 Impact Goals for monitoring Americans' cardiovascular health (AHA, 2013). The AHA Goals and Metrics Committee defined ideal cardiovascular health (iCVH) as simultaneous presence of recommended levels of three health behaviors (not smoking cigarettes, physical activity, eating healthy diet) and four other health factors (normal body mass index [BMI], blood pressure, total cholesterol and blood sugar) [henceforth collectively referred to as iCVH metrics] (Lloyd-Jones et al., 2010). However, extremely few people (<1%) meet all seven recommended iCVH metrics, with findings from cardiovascular health studies suggesting that only a small fraction (4%) of the American population meet at least five recommended

iCVH metrics (Lloyd-Jones et al., 2006). The 2017 AHA statistical data suggested that 17% adults meet at least five iCVH metrics and younger adults are expected to attain greater proportion of iCVH metrics than older adults (AHA, 2017a). Age and sex-adjusted estimates indicate that females tend to achieve more iCVH metrics than males. Poor diet and low physical activity largely contribute to the low attainment of iCVH both in children and adults (AHA, 2017a). A study of adults without documented CVD using the National Health and Nutrition Examination Survey (NHANES) data (1988-2014) showed that iCVH is on the decline, with the non-Hispanic whites having the largest decline of up to 15% (Brown et al., 2018).

Measurement of iCVH can be approached from the lens of self-care activities, as captured in the AHA Life Simple 7 factors (same as iCVH metrics), since the self-care management of CVD targets attainment of all the seven iCVH metrics for prevention of CVD and stroke (Riegel et al., 2017; Webber, Guo, & Mann, 2015). Chronic disease self-care is rarely quantified by clinicians as it is seen as the individual's responsibility to self-manage their diseases. The AHA recently released a scientific statement of self-care in prevention and management of CVD and stroke based on the Life Simple 7 factors that underscores the observation that CVD self-care has been ignored for a long time (Riegel et al., 2017). In the context of everyday living, the scientific statement authors noted that patient-to-provider contact is minimal with only 10 (0.1%) of 8760 hours per year with clinicians. This is a clear indicator that people engage in health promotion or management activities in the community settings (home, work, recreation) and highlights the need for more attention to empowering individuals with self-management strategies during clinician visits.

Familial aggregation is defined as clustering or occurrence of shared exposure to diseases within families attributable to genetic, environmental or infectious factors (Matthews, Finkelstein, & Betensky, 2008). In this study, a family is viewed in the context of a social cultural environment of biologically related parents and children. Familial aggregation studies are important to determine if a disease or disorder or certain behaviors occur in clusters or shared within families. The burden of CVD can be estimated quantitatively using disability-adjusted life years (DALYs) measure. Disability-adjusted life years is a measure of differences of health in a population using a normative standard, and usually represents years of life lost (YLL) and years lived with disability (YLD) (GBD 2015 DALYs and HALE Collaborators, 2016).

Individuals meeting the recommended iCVH criteria have demonstrated increased CVD-free survival and longer lifespan. Several prospective studies have indicated that healthy behaviors such as physical activity, not smoking and healthy eating reduce the incidence of CVD or myocardial infarction (Akesson, Weismayer, Newby, & Wolk, 2007; Chiuve, McCullough, Sacks, & Rimm, 2006; Li et al., 2018). In addition, healthy behaviors can significantly reduce mortality as reported in the 2016 Nurses' Health Study, where the risk of total CVD and cancer mortality was reduced by up to 61% all-cause mortality, 60% cancer and 63% CVD mortality (Veronese et al., 2016). A 2018 report from the Nurses' Health Study supports these findings that maintaining five healthy factors contributed to more than 10 years of life expectancy (Li et al., 2018). Familial studies also show that offspring whose parents had CVD have a higher propensity to develop CHD and other cardiovascular diseases, likely due to interactions of genetic predisposition, shared

environmental and behavioral factors (Bao et al., 1997; Nasir et al., 2004). Additionally, an inverse relationship between socioeconomic status (measured using an individual's age, attained level of education, and income level) and CVD occurrence has been well-established and also contributes to familial aggregation of CVD risk (P. A. Braveman, Cubbin, Egerter, Williams, & Pamuk, 2010; Min et al., 2017). This suggests that the overall burden of CVD may be increased in offspring whose parents had CVD, though little is known about parent-offspring similarity of iCVH metrics and dose-response associations between iCVH metrics and CVD burden among parents and children.

To our knowledge, there is no published study designed to examine the familial aggregation of the combined effect of all seven iCVH metrics and CVD DALYs in parent-offspring dyads. Accumulating evidence has demonstrated an inverse association between achieving an iCVH and future development of CVD and CVD mortality (Lachman et al., 2016; Ogunmoroti et al., 2017; Shah et al., 2015; Xanthakis et al., 2014); although researchers have not explicitly investigated the mechanism through which the iCVH metrics specifically reduce CVD DALYs. In addition, there is no empirical evidence quantifying the CVD burden in terms of DALYs averted at different iCVH metrics leaving clinicians and health policymakers under-informed about the impact of the iCVH metrics on individual, family or population health (Willcox et al., 2006). The Framingham Heart Study (FHS) provides such a distinct setting to study iCVH metrics in a multigenerational prospective cohort of both parents and their offspring recruited from community dwelling participants.

Aims of the Study

The main aim of this study was to determine patterns and relationship of parental iCVH and offspring's cardiovascular health and CVD disability adjusted life years. The specific aims and hypotheses are:

Specific Aim 1: To examine the association of iCVH between parents and their offspring assessed at similar mean age over a determined life course.

Hypothesis 1A. Ideal cardiovascular health for parents will be positively correlated with that of their offspring at similar mean age.

Hypothesis 1B. Accounting for age, sex, socioeconomic status, and education level, the parents' iCVH will be positively associated with that of their offspring at a similar mean age.

Specific Aim 2: To compare iCVH and the burden of CVD (CVD DALYs) between parents and offspring at exam cycles where the mean age at specific exam cycles are generally comparable.

Hypothesis 2A. Accounting for age, sex, education and income, the parents' and offspring's iCVH will be positively associated with CVD DALYs respectively.

Hypothesis 2B. Offspring of parents with low iCVH will have higher mean CVD DALYs compared to the mean CVD DALYs for offspring of parents with high iCVH.

Significance of the Study

Results of this study have potential to guide and inform patient and community based-programs that advocate for iCVH metrics in prevention of CVD and can also be used to counsel individuals on the positive impact of engaging in healthy behaviors. The study will potentially provide health policy makers with the needed actionable information that is key in life course epidemiology as well as inform the discussion on optimal allocation of resources to family-based primordial CVD prevention programs.

Conceptual Framework

The conceptual framework for this study combines and integrates Family Systems Theory (FST) as conceptualized by Vendanthan et al. (2016) and Orem's self-care framework (OSCF). The complex interaction between parents and their offspring is approached from lens of FST. Family System's Theory posits that a family exists within interconnected interactive social systems or subsystems which include parent-offspring interactions, caregiver-children and sibling interactions and that families have their own rules that guide their relationships (Fingerman & Bermann, 2000; Reiss, 1981). The theory's argument that families' rules, values and practices are shaped over time (Fingerman & Bermann, 2000) is an important addition to this study since an individual iCVH metrics and CVD outcomes are expected to be transmitted over the life course. Vendanthan and colleagues argued that family exists as a system with mutual interdependence and shared environment which interacts with parenting style or caregiver perceptions and genomics in lifespan promotion of cardiovascular health (see Figure 1.1 below) (Vedanthan et al., 2016). For this study, the concept of shared environment in FST was integrated with other OSCF concepts of self-care. Shared environment is critical

for family studies since parents and children live and interact at homes and neighborhood environments that promote or hinder access to safe places to exercise, purchase affordable healthy foods, be exposed to high density of fast food restaurants and stores that sell tobacco.

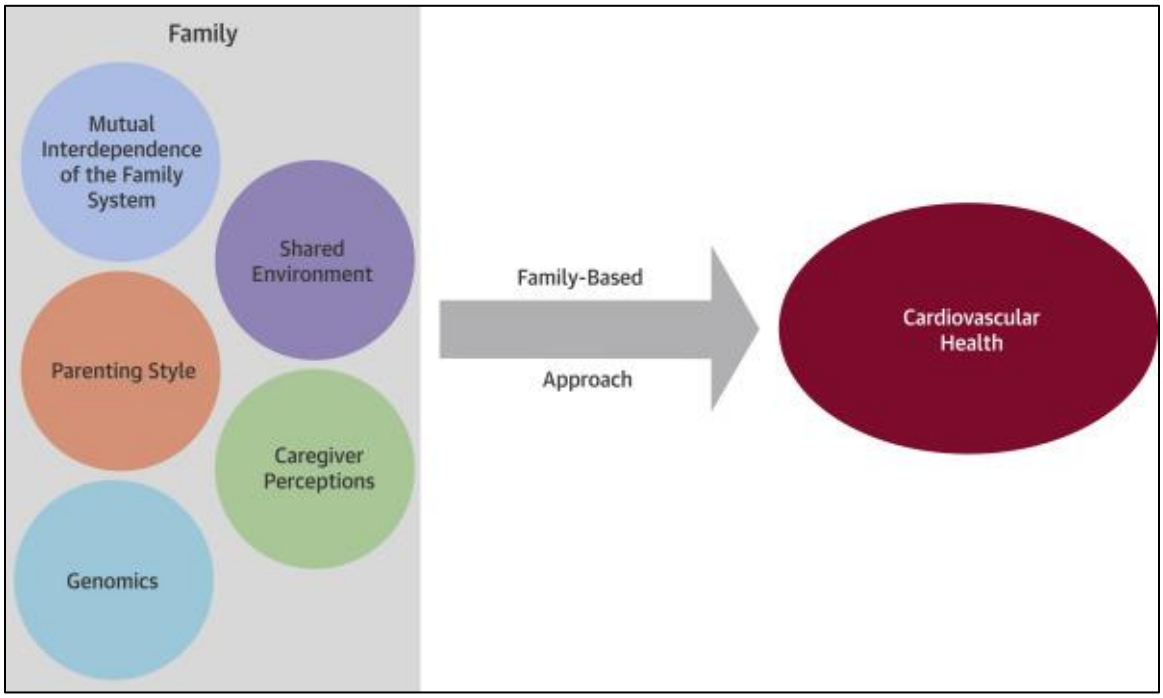

Figure 1. 1 Family-Based Factors and Cardiovascular Health Promotion. A conceptual model showing relationship between family-based factors and cardiovascular health promotion. Adapted from "Family-based approaches to cardiovascular health promotion," by R. Vedanthan, S. Bansilal, A. V. Soto, J. C. Kovacic, J. Latina, R. Jaslow… V. Fuster, 2016, *Journal of the American College of Cardiology, 67*(14), 1725–1737. https://doi.org/10.1016/j.jacc.2016.01.036

Dorothea Orem developed the self-care framework in the 1950s and the framework underwent further developments in the 1980s. The framework focuses on individuals deliberate actions to meet their own health goals or having power to meet their own health needs (Fawcett & DeSanto-Madeya, 2013; Orem, 1997). Orem's view of human beings as "multiperson unit" will be used in this study as it focuses on situations where more than one person is interacting for their self-care (Geden & Taylor, 1999; Taylor, 2001). Multiperson units are relevant for

situations where the wellbeing of one person is subject to the effects of interactions among other persons (Fawcett & DeSanto-Madeya, 2013). In this study, the well-being of the offspring is hypothesized to be influenced by that of the parents through complex interactions.

Orem' Self-Care Framework had historical transformations to address the dynamic challenges of health care (Rizzo, 1987). Multi-person units such as family and resident groups were included to provide nursing care to different populations (Rizzo, 1987). Population was defined as individual members in a whole number of people in a community or a geographic area and that the individuals' behavior is influenced by others within a population (Parker, 2006; Rizzo, 1987). The multiperson unit, as opposed to self-care which mainly focuses on an individual unit, was adopted for the framework for this proposed study as it focuses on an aggregate, rather than an individual, therefore is appropriate for studies of population health. Multiperson unit can also be viewed as a dyadic unit where two or more persons, such as parents and children, have a mutual shared relationship as operationalized in this study (Geden & Taylor, 1999).

Family System's Theory complements OSCF by explaining the possible relations that occur in families resulting in improvement or decline of cardiovascular health. The shared family environment concept is ideal for this study because parents and children interact both in physical environment (such as physical activity and food accessibility) and behavioral environment (practices such as smoking, feeding behaviors) in a complex family system (Vedanthan et al., 2016).

Parent-offspring relationship fits both FST and OSCF because children's health behaviors are interlinked with those of the parents. Parents are the primary role models for

their young children, and the shared family environment for parents and their children forms a basis for lifelong learning and may influence strong role-modeling behaviors among the children (Faith et al., 2012). Orem's theory views family as basic conditioning factor that influences self-care activities or enhances behavior change(Taylor, 2001). In this regard therefore, family acts as a resource for individuals to achieve self-care requisites and setting where children rely on their parents to model some health-associated behaviors beginning in the early stages of development.

Conceptual-theoretical-empirical (CTE) structure. In the CTE structure (Figure 1.2), shared family environment is proposed to interact with multiperson unit, therapeutic care demand and basic conditioning factors to influence individuals' cardiovascular health and burden of CVD. The physical and behavioral aspects of shared family environment align well with therapeutic care demand and basic conditioning factors from the OSCF. Multiperson unit is viewed as interaction between parents and their offspring, resulting in modification of health behaviors. Therapeutic self-care demand concept entails all required regulatory care for parents and offspring to maintain cardiovascular health. Therapeutic self-care demand is viewed as activities which the participants can perform to remain healthy, in this case, the iCVH metrics that are necessary for maintaining cardiovascular health.

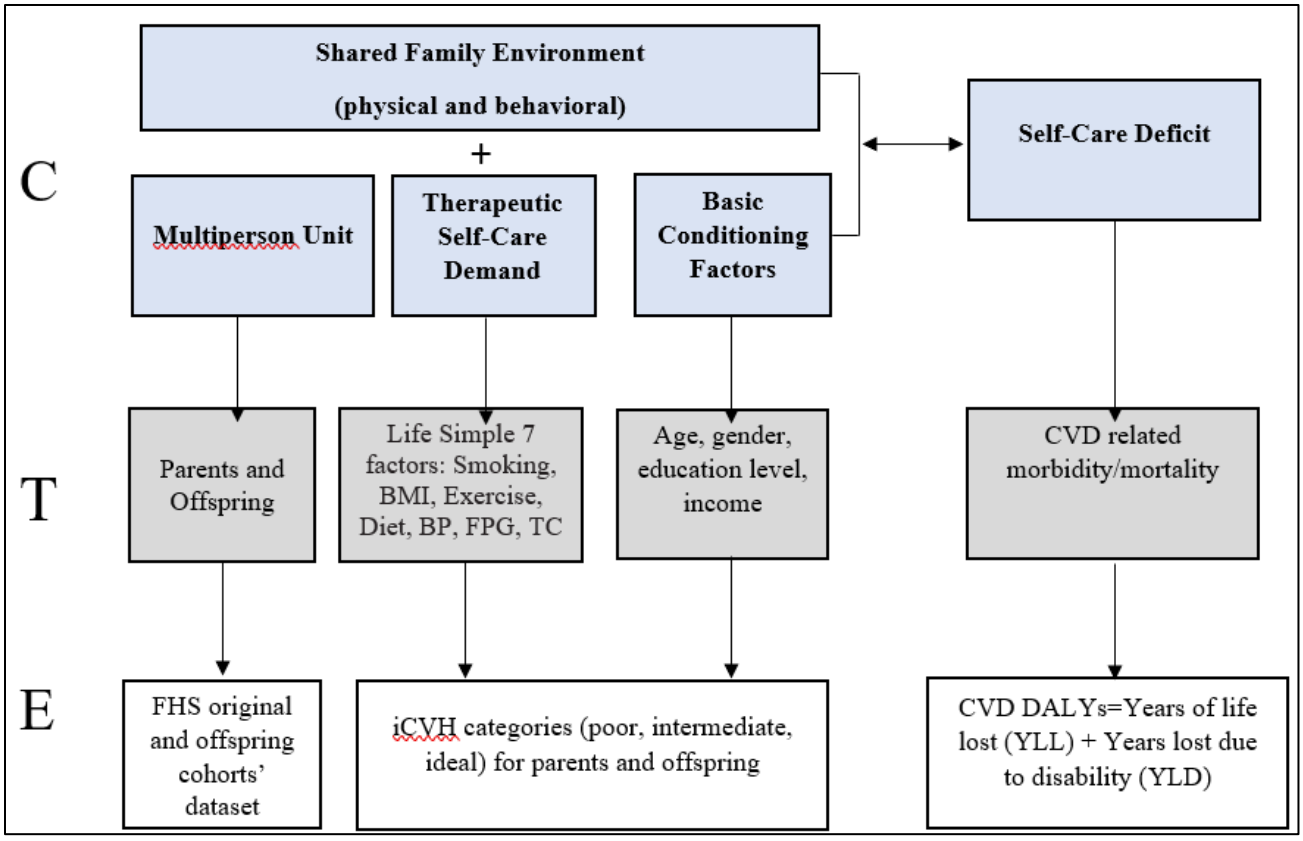

Figure 1. 2 Conceptual-theoretical-empirical structure for iCVH self-care. Key: C, conceptual; T, middle range theory; E, empirical research methods; BMI, body mass index; BP, blood pressure, TC, total cholesterol; FBS, fasting plasma glucose; FHS, Framingham Heart Study; DALYs-disability-adjusted life years

Basic conditioning factors relate to population characteristics that affect their care, including age, sex, sociocultural, and resource availability (Fawcett & DeSanto-Madeya, 2013). These therapeutic self-care demand and basic conditioning characteristics are nurtured in a shared family environment where initial self-care is learned. The process by which acquisition of behaviors among members of families occurs is not explicit. However, valuing of specific health behaviors may be modelled early in life in family settings because of strong social bonds and need to promote wellbeing of all members of the families (Taylor, 2001). Self-care deficit occurs when the individuals are not able to meet the requisite care demand such as

recommended iCVH metrics (Fawcett & DeSanto-Madeya, 2013). Deterioration of self-care deficit would lead to chronic conditions such as cardiovascular disease or even death from persistent ill-health. Chapter 2 presents a review of the literature on the state-of-science regarding iCVH and familial aggregation of CVD and highlight gaps in knowledge. Chapter 3 presents methods for closing some of the identified gaps using an established longitudinal multi-generational public use dataset.

CHAPTER 2

LITERATURE REVIEW

Background

Cardiovascular disease (CVD) continues to be the leading cause of death globally accounting for 31% (17.7 million people) of all global deaths annually (World Health Organization [WHO], 2017b). The burden of CVD is greater in the low- and middle-income countries (LMICs) which experience more than 75% of the global CVD deaths. In the United States, coronary heart disease (CHD) is the most common CVD and the leading cause of mortality (45%) followed by stroke, heart failure, high blood pressure, arterial diseases (16.5%, 8.5%, 9.1%, 3.2%, respectively). The WHO defines CVD as a constellation of heart and blood vessel disorders which include CHD, cerebrovascular disease (stroke), peripheral arterial disease, rheumatic heart disease, congenital heart disease and deep vein thrombosis and pulmonary embolism (WHO, 2017b). However, for this study, CVD is operationally defined in the methods section using the FHS criteria.

The prevalence of CVD among American adults is approximately 28%, but disproportionately affects the non-Hispanic blacks whereby nearly half (~50%) have some form of CVD (AHA, 2018b). Evidence from multiple studies consistently report racial disparities in CVD risk factors. For instance, the highest prevalence of elevated blood pressure was observed among non-Hispanic blacks; diabetes, smoking and abdominal obesity was highest among Hispanic individuals (Gasevic, Ross, & Lear, 2015). A study of iCVH among US adults in 2011 and 2012 also revealed disparities in iCVH metrics where non-Hispanic black women (iCVH difference=0.93, P=0.001) and Mexican-

American women (iCVH difference=0.71, P=0.02) had lower iCVH scores compared with non-Hispanic white women (Pool, Ning, Lloyd-Jones, & Allen, 2017). These differences are mainly attributed to social determinants of health such as access or lack of access to resources including neighborhoods with fewer grocery stores , recreation, and exercise facilities, all of which are associated with iCVH (Unger et al., 2014). Regarding socioeconomic status, studies have shown that there is an inverse relationship between socioeconomic status and CVD. Research from the Jackson Heart Study revealed that low income was a strong correlate of myocardial infarction (OR 3.53, 3.53; 95% CI, 2.31–5.40) and stroke (OR: 3.73; 95% CI, 2.32–5.97) (Min et al., 2017). In addition, attainment of higher education and higher income is linked with more favorable health outcomes and improved lifestyle behaviors which are associated with reduced CVD risk (P. A. Braveman et al., 2010; P. A. Braveman, Egerter, & Mockenhaupt, 2011; P. Braveman, Egerter, & Williams, 2011).

Disparities of CVD DALYs in the United States are also evident. A recent study investigating the burden of CVD in the United States between 1990 and 2016 showed that CVD DALYs were twice as prevalent in men compared with women and largely attributed to ischemic heart disease (Global Burden of Cardiovascular Diseases Collaboration et al., 2018). Of all the states, Mississippi had the highest age- standardized CVD DALYs (4982 DALYs per 100 000 persons) and the lowest was Minnesota (2352 age-standardized DALYs per 100000 persons). Unhealthy diet, high systolic blood pressure, BMI, total cholesterol, fasting plasma glucose, tobacco smoking and physical inactivity were the leading risk factors for high CVD DALYs. As expected, the CVD

DALYs increased after age 40 years and reached peak by age 65 (Global Burden of Cardiovascular Diseases Collaboration et al., 2018).

Approached from the lens of life-course epidemiology, cardiovascular disease risk factors such as smoking cigarettes and physical inactivity are potentially modifiable. Even in individuals who are genetically predisposed to developing CVD, healthy lifestyle factors such as consumption of healthy diet throughout the lifespan has been associated with lower risk of developing CVD (Khera et al., 2016). Consistent with this assertion, Life Simple 7 factors are recommended for maintaining iCVH; however, it remains elusive how to attain or maintain all the recommended iCVH levels over time.

The exceedingly high economic burden due to CVD contributes to loss of optimal health and substantial human suffering for affected populations. To address this crisis, the WHO has recommended cost-effective interventions, popularly known as "best buys" interventions, to be implemented in all settings including the under-resourced countries. These interventions implemented at the national population level include smoking control policies, availing public spaces for physical activity, raising taxation for salt, fat and sugar-rich foods and providing healthy diets for school children (WHO, 2017a). Similarly, the AHA recommends attainment of the iCVH metrics with main messages emphasizing maintenance of smoke -free lifestyles, healthy patterns of physical activity and dietary intake and maintenance of a healthy weight blood pressure, cholesterol and blood glucose at specified levels (AHA, 2013). The WHO's global action plan targets prevention and control of non-communicable diseases (NCDs) by the year 2020, specifically to reduce by 25% premature deaths from CVD and other NCDs (WHO, 2017a). This target approximates the AHA's 2020 Impact Goals which targets a 20% improvement of

cardiovascular health and reduction of CVD and stroke mortality by 20% by the year 2020 (AHA, 2013).

The United Nations (UN) also advocates for achieving an optimal health across the life span (United Nations, 2016). This is documented in the UN Sustainable Development Goal (SDG) 3 which targets achievement of health and well-being and 25% reduction of premature mortality from NCDs by 2030. A significant portion (75%) of premature mortality due to NCDs globally is attributed to CVD and cancer; hence, this is also an important SDG issue (United Nations, 2016). The Global Burden of Disease (GBD) study 2016 has embarked on tracking health-related SDGs to advise governments on the health situation of their populations (GBD 2016 SDG Collaborators, 2017). The efforts to track iCVH metrics on a global level is a novel way for assessing the attainment of health-related SDGs across different countries and impacts on policies that address health problems faced in those countries. Health-related SDGs may be quantitatively measured differently from iCVH, but one salient finding is that both iCVH and most of SDGs are associated with sociodemographic factors (GBD 2016 SDG Collaborators, 2017).

History and Definition of Ideal Cardiovascular Health (iCVH)

The AHA Strategic Planning Task Force commissioned the concept of iCVH in June 2007 with the aim of developing and implementing the 2020 Impact Goal (Lloyd-Jones et al., 2010). The focus of AHA Impact Goal for 2010 targeted reducing CHD and stroke risk factors and mortality rates. The AHA committee defined iCVH using the Life Simple 7 factors (as defined earlier in chapter 1) for prevention of CVD, and that definition was

adopted in 2010 by AHA (Lloyd-Jones et al., 2010). The AHA approved the recommendation to improve the cardiovascular health for Americans by 20% and reduce by 20% the incidence of CVD and stroke deaths by the year 2020. To meet the AHA criteria for iCVH, an individual must attain all the seven components at ideal levels. These ideal components are highlighted in Table 3.3 in the methods section.

Ideal Cardiovascular Health and Relation to the AHA's Strategic Impact Goal Through 2020 and Beyond

Using data from the cross-sectional National Health and Nutrition Examination Surveys (NHANES), the AHA tracks the iCVH metrics and targets to report the attainment of iCVH by the year 2020. These goals can be evaluated and monitored using studies focused on iCVH metrics and CVD incidence and mortality. Large prospective cohort studies have shown comparable trends that participants with iCVH experience significantly reduced incidence of heart failure, even among different racial-ethnic groups (Lachman et al., 2016; Ogunmoroti et al., 2017; Shah et al., 2015; Xanthakis et al., 2014). The Honolulu Heart Program/Honolulu Asia Aging Study demonstrated that most of ideal health factors were associated with longevity and reduction in disability, but questions still exist on the specific implications of the health factors in shaping and informing health care policy (Willcox et al., 2006). Other studies focusing on one or more health behaviors such as not smoking cigarettes, having normal BMI, engaging in physical activity for at least 30 minutes daily, drinking not more than 2 glasses of wine per day, a low glycemic diet with low fat content, serve to cumulatively reduce the incidence of CHD or myocardial infarction by up to 92% (Akesson et al., 2007; Chiuve et al., 2006; Kyu et al., 2016; Reid et al., 2014).

The association of lifestyle factors on life-expectancy and incident CVD has been widely investigated. Examples include studies conducted by Veronese and colleagues (2016), the Health Professionals Follow-up Study (HPFS) (n=74, 582 men) and the Nurses' Health Study (NHS) (n=39, 284 women). These prospective cohort studies focused on the association of diet, physical activity, alcohol use, smoking and BMI and CVD mortality. Risk reducing factors were defined as avoidance of cigarette smoking, engaging in moderate- to -vigorous physical activity (MVPA) for ≥30 min/day, limiting alcohol consumption to 5-15 g/day for women, or limiting to 5-30 g/day for men, and an alternate healthy eating index (AHEI) diet score in the upper 40%. The AHEI diet score is derived from the recommended servings of fruits, vegetables, whole grains, nuts and unsaturated fats, processed meats, sugars and sodium and multivitamins (Veronese et al., 2016). Findings from a 32-year follow-up study accounting for the three protective lifestyle factors stated above and low BMI (18.5-22.4 kg/m^2) indicated that the hazard for CVD mortality was significantly reduced (hazard ratio [HR] 0.37, 95% CI: 0.29-0.46) (Veronese et al., 2016). Another most recent 34-year longitudinal Nurses' Health Study found that five-low risk health factors defined as no smoking, normal BMI (18.5-24.9 kg/m2) physical activity (moderate- to- vigorous ≥30minutes/day) moderate alcohol intake and healthy diet (upper 40% diet score) resulted in reduced all-cause mortality (HR 0.26, 95% CI, 0.22-0.31) and CVD mortality (HR 0.18, 95% CI 0.12-0.26), and lead to an average increase of 14 more years of life (Li et al., 2018). This points to the impact of combined CVD risk factors in prevention or reduction of CVD burden.

Further examination of healthy behavioral-lifestyle factors demonstrates a strong protective association with incident CVD. In a 16-year prospective US study of 42, 487 male

health professionals aged 45-75 years, five healthy indicators (smoking abstinence, limiting alcohol consumption, healthy diet, physical activity as defined above and BMI <25 kg/m^2) were associated significantly with an 87% reduced risk of CHD (Chiuve et al., 2006). The risk of CHD was not altered by antihypertensive or cholesterol drugs pointing to the importance of lifestyle in prevention of CHD. Similar associations were observed among older populations in other parts of the world. In Europe for instance, an 11-country longitudinal study involving 2, 339 individuals aged 70-90 years of age observed that the 10-year survival rate from all causes was higher for those with four healthy factors (related to physical activity, smoking, limited alcohol consumption, and diet) compared with individuals who reported 0-1 healthy behaviors (75% and 50% respectively) (Knoops et al., 2004).

Behavioral-lifestyle health factors are also associated with disability. Growing evidence from prospective cohort studies suggests that participants with favorable health factors manifest with reduced disability as age increases. In a Taiwan longitudinal study of 1940 men and 1247 women aged 60 years and older, the combined effect of health factors on functional disability attributed to one or more healthy behaviors contributed 15% to 75% reduction in functional disability (Liao et al., 2011). Functional disability was defined as the inability to perform activities of daily living (ADL) comprised of unassisted bathing and ability to walk for 200-300 meters. Healthy behaviors were defined as not smoking, none or moderate alcohol consumption, regular exercise and maintaining 6 to 8 hours per day of sleep (Liao et al., 2011). In another cohort study (1986–2005) of 2327 college alumni, lifestyle risk factors were found to predict disability and mortality among healthy aging adults with mean baseline age of 68 (SD 3.6) years (Chakravarty et al., 2012). Three risk

groups were created based on the number of baseline characteristics as no risk factors (low-risk), one risk factor (medium), two or more risk factors (high-risk); the risk factors measured were BMI, cigarette smoking, and physical inactivity. Individuals 65 years of age and older at no risk at baseline experienced 8.3 years delayed onset of moderate disability compared to those at high-risk. Mortality rates were 384 per 10, 000 person- years compared with 247 per 10, 000 person-years for high-risk and low-risk groups respectively (Chakravarty et al., 2012).

Similarly, in another longitudinal study, the onset of disability was delayed by five or more years among middle-aged participants with favorable health behaviors (Vita, Terry, Hubert, & Fries, 1998). No gender differences were observed in the trends for time to disability onset. Vita et al. (1998) investigated the relationship between health behaviors (smoking, BMI, and exercise) at a mean age of 43 years and cumulative disability later in life from 66 to 74 years (n=1741). Risk scores were calculated using smoking, BMI and exercise variables where subjects were assigned risk level depending on the total score (0 to 2: low-risk; 3 to 4: moderate risk; 5 to 9: high-risk). Among those with favorable health behaviors compared with those with least favorable health behaviors, the disability index was 0.49 versus 1.02 respectively (Vita et al., 1998). In addition, disability index was similar among the offspring where individuals with the least favorable health behaviors had double the disability index compared to those with favorable health behaviors (Vita et al., 1998).

Combination of iCVH metrics at the recommended levels could synergize overall cardiovascular health achievement throughout the lifespan as demonstrated in the Atherosclerosis Risk in Communities (ARIC) study where four combined factors defined as untreated cholesterol (<200mg/dl), blood pressure (<120/80 mmHg), no diabetes and never

smoked were investigated (Hozawa, Folsom, Sharrett, & Chambless, 2007). Results of this study showed that individuals with optimum combined health factors were 88% less likely to die due to CVD (HR 0.12, 95% CI 0.04-0.31) compared with those with any elevated risk factors; while borderline attainment of combined health factors reduced CVD mortality risk by 72% (HR 0.28, 95% CI 0.21-0.37). Also, combined optimum risk factors reduced all-cause mortality by up to 74% (HR 0.26, 95% CI 0.17-0.38) among all races. Population attributable fraction (PAF) results indicated that having at least 1 elevated and borderline risk factors accounted for 84.7% CVD mortality among all races, 100% among African American men and women, 88.6% in White women and 72.1% in White men (Hozawa et al., 2007).

Several implications for having iCVH exist, such as increased longevity and morbidity-free survival, improved health-related quality of life even in old age and lower treatment costs in old age (Chakravarty et al., 2012; Hozawa et al., 2007). Taken together, these results indicate that such benefits are not currently fully realized by the American population since only extremely small proportion of Americans (5%) [other studies show even lower prevalence of <2% (AHA, 2017a)] attain all seven iCVH metrics (Chiuve et al., 2006; Ford, Li, Zhao, Pearson, & Capewell, 2009; Lloyd-Jones et al., 2006). In addition, collective results indicate the need for urgent measures to address the main factors that lead to poor iCVH metrics and the roles of lifestyle activities in addition to genetic predisposition to CVD.

Prevalence of Cardiovascular Disease Risk Factors (Life's Simple 7) in the United States

Smoking. The prevalence of smoking among persons aged 18 years and older in the United States is 15% (males 16.7% versus 13.7% females) (CDC, 2016). In 2015, Non-Hispanic American Indians or Native males had the highest smoking rates of 22%, while Hispanics and Asians were least likely to smoke at 10% and 7% respectively (American Heart Association, 2018b). In 2015, about 1 in 5 deaths (480, 000) among Americans was attributed to cigarette smoking. These estimates were taken from individuals who reported smoking more than 100 cigarettes at any point in their life and currently smoking either daily or some days (CDC, 2016).

Physical activity. The AHA recommends moderate activity of at least 30 minutes per day for five days per week or 150 minutes a week or 75 minutes of vigorous activity per week (AHA, 2017b, 2018b). About 30.4% of the US population is physically inactive (American Heart Association, 2018b). In 2015, only 21.5% of American adults and 27.1% of American adolescents achieved recommended leisure-time aerobic and muscle-strengthening levels of physical activity (Benjamin et al., 2018).

Healthy Diet. The prevalence of healthy diet between 2003 and 2012 among children and adults using the ideal health score increased from 0.2% to 0.6% and 0.7% and 1.5%, respectively (American Heart Association, 2018b). This marginal improvement in healthy diet from 2003 to 2012 could be attributed to an increase in whole grain consumption and reduced consumption of sugary drinks; however, substantial improvement is warranted since achievement of a healthy diet in both adults and children remains quite low. In general, the AHA recommends (for adults) a healthy diet comprised

of vegetables and fruits (4-5 servings/day), whole grains rich in fibers (6-8 servings/day), nuts and legumes (4-5 servings/week), poultry, meat and eggs (8-9 servings/week) and fish (less than 6 oz/day), skimmed or low fat (1%) milk and unsaturated fats (2-3 servings per day or 27g/day for oils or 20g/day for saturated fats for a 2,000-calorie level (U.S. Department of Health and Human Services and U.S. Department of Agriculture, 2015). In addition, the diet should be low in sodium (not more than 2400mg per day) and low added sugar (5 or fewer servings/week, for instance, 1 serving of sugar= 1 Tbsp sugar; 1 serving of lemonade=1 cup lemonade) (AHA, 2018b; Eckel et al., 2013). Similarly, WHO recommends a healthy diet that is rich in fruits, vegetables, legumes, unprocessed nuts and whole grains. At least five servings of fruits and vegetables are required per day, not more than 10% and 30% of total energy intake from sugars and fats respectively and salt intake of less than 5 grams per day (WHO, 2015).

Body mass index. The prevalence of obesity among adults in the United States increased from 30.5 % in 1999 to 2000 to 37.7% in 2013 to 2014 (AHA, 2018b). The prevalence of obesity and overweight among adults in the United States is on the increase from 65.1% in 1999-2002 to 70.9 in 2013-2016 (Centers for Disease Prevention and Control, 2017a). Among adult Americans aged 20 years and above, racial and ethnic differences exist where Mexican Americans had the highest prevalence of obesity and overweight (83.8%) in 2013-2016 compared with Hispanic American (80.4%), African American (76.1%) and Whites (75.3%) and lowest in Asian Americans (42.7%) (Centers for Disease Prevention and Control, 2017a). Among children and adolescents, the prevalence of obesity was 9.4%, 17.4% and 20.6% among children aged 2-5 years, 6-11 years and adolescents aged 12-19 years, respectively in 2014 (AHA, 2018b), which points

to increased future risk of CVD if this trend continues and prevention of overweight is not addressed early in life.

Cholesterol. The prevalence of total blood cholesterol greater than 200mg/dL among US adults is 39.7% and highest in non-Hispanic White females (43.4%) and lowest in non-Hispanic black males (32.6%) and children 7% (AHA, 2018b; CDC, 2017). In 2012, about 37% of American adults had high levels of low-density lipoprotein (a well-established risk factor for heart disease and stroke) while 18.7% had the appropriate, gender and age-specific levels of cardioprotective high-density lipoprotein (AHA, 2018b; CDC, 2017). Between 2011-2014, the prevalence of high total cholesterol (≥200 mg/dL) among US children and adolescents aged 6–19 was 7.4%; girls had higher prevalence (8.9%) compared to boys (5.9%); non-Hispanic Asians had the highest prevalence (10.9%) while Hispanics had the lowest (6.3%) (Centers for Disease Prevention and Control, 2015a).

Blood pressure. The most recent 2017 American College of Cardiology (ACC)/AHA guidelines define hypertension as blood pressure of 130/80 mm Hg and above, a 10 mm Hg lower than previous classification of 140/90 mm Hg and above (AHA, 2017a). This lower value increases the proportion of individuals who meet the criteria for hypertension and has implications for practice regarding new treatment guidelines and lifestyle changes. Approximately 46% of American adults have high blood pressure using the most recent 2017 ACC/AHA guidelines and about 78, 862 deaths were attributed to high blood pressure in 2015, a rise by 37.5% from 2005 (AHA, 2018b). Similarly, new blood pressure guidelines for pediatrics were developed to align with adult guidelines, where the term “prehypertension” was replaced with “elevated blood pressure”

(Flynn et al., 2017). Currently pediatric blood pressure is classified in three categories by age and sex: (1) elevated blood pressure ≥90th percentile, (2) stage 1 hypertension ≥95th percentile, and (3) stage 2 hypertension ≥95th percentile+12 mm Hg. These guidelines estimate the US prevalence of pediatric hypertension at 2-5%; however, estimates suggest that 75% of the hypertension cases in children are undiagnosed (Flynn et al., 2017).

Diabetes. The 2015 prevalence of type 2 diabetes among American adults was 9.1%, with non-Hispanic black males having the highest prevalence and among non-Hispanic white females the lowest (14.1%; 7.4% respectively) (AHA, 2018b). These precise estimates of the US burden of diabetes are further confounded by the high proportion of individuals with undiagnosed diabetes (7.6 million adults) and an additional 81.6 million prediabetic adults (33.9%) (AHA, 2018b). Between 2002 and 2012, the incidence of type 2 diabetes among youth aged 10-19 years increased by 7.1% annually (9.0 cases/100, 000 youths in 2002 to 12.5 cases/100, 000 youths in 2012) (Mayer-Davis et al., 2017). By race, adjusted annual incidence of type 2 diabetes increased by 8.9% for Native Americans, 8.5% for Asian/Pacific Islander, 6.3% for non-Hispanic blacks, 3.1% for Hispanics and 0.6% for non-Hispanic whites (Mayer-Davis et al., 2017).

Familial Aggregation of Cardiovascular Disease and Ideal Cardiovascular Health Metrics

There is evidence of familial clustering of adverse health behaviors, that also contributes to familial aggregation of CVD (Imes & Lewis, 2014). The majority of studies of familial aggregation suggest the existence of positive parent-offspring correlations of single CVD risk factors such as elevated BMI, physical inactivity and poor diet (Fuemmeler,

Anderson, & Mâsse, 2011; Johnson et al., 2012; Massarani et al., 2015). In addition, there is substantial evidence that atherosclerotic and hypertensive processes begin early in life and are influenced over time by modifiable risk factors (Hayman & Worel, 2015; Juonala et al., 2010; Loria et al., 2007). In addition, favorable iCVH metrics in childhood are cumulatively associated with lower incidence of hypertension, metabolic syndrome, low-density lipoprotein, and carotid artery intima-media thickness in adulthood (Laitinen et al., 2012; Pulkki-Råback et al., 2015). These findings suggest that iCVH in childhood can help reduce future burden of CVD later in the life course.

Familial transmission of cardiovascular health benefits from parents to children through behavioral-lifestyle factors holds promise and potential for intergenerational prevention of CVD morbidity and mortality. The precise pathway for intergenerational influence of health behaviors is complex. However, studies suggest that socioeconomic factors such as education and household income contribute positively to that pathway (Martin, Van Hook, & Quiros, 2015) as demonstrated by cumulative evidence from multiple studies linking educational attainment and higher income to favorable health outcomes throughout the life course (P. A. Braveman et al., 2010; P. A. Braveman, Egerter, & Mockenhaupt, 2011; P. Braveman, Egerter, & Williams, 2011). Parental educational attainment has also been linked to increased knowledge, increased health literacy and improved health behaviors as these individuals tend to make more informed health-related choices for themselves and their families (P. Braveman et al., 2011; Sanders, Federico, Klass, Abrams, & Dreyer, 2009). In a study of 1480 parent-offspring dyads, higher parental educational attainment was associated with healthier clusters, and positively related to

improved physical activity and healthy diet (Rodenburg, Oenema, Kremers, & van de Mheen, 2013). Similarly, educational attainment is a major contributor to employment opportunities, whereas individuals with lower educational attainment face higher rates of unemployment, which, in turn, is a risk factor for more adverse CVD outcomes (Walter, Glymour, & Avendano, 2014).

Research on iCVH metrics is important in family-based studies since parents serve as powerful role models for observed behaviors which would consequently impact their children's health behaviors. For instance, a family healthy feeding cluster-randomized trial in London, United Kingdom, showed positive parent-offspring correlations, with significant associations in fruit or vegetable intake ($r = 0.52$, $P < 0.001$) and healthy drinks or water ($r = 0.54$, $P < 0.001$) (McGowan et al., 2013). Children's intake of fruits, consumption of saturated fats, and physical activity and other health behaviors were correlated with the parents' or caregivers' practices (Isgor, Powell, & Wang, 2013; Martin et al., 2015). However, the effect of familial aggregation of combined iCVH metrics has not been empirically quantified. Most studies on familial aggregation of health factors investigated only a single or few iCVH metrics with limited attention paid to the intergenerational transmission of iCVH from parents to children and the corresponding future burden of CVD in offspring that is attributed to iCVH metrics.

Shared Common Family Environment and Ideal Cardiovascular Health

Offspring living with their parents in childhood years share common parental socioeconomic status, practices or values, living conditions such as housing or neighborhood (Kjøllesdal, Ariansen, Mortensen, & Næss, 2017). However, it is assumed that parents and

children shared early life environment not withstanding if some parents separated early in children's life (or moved to another location out of Framingham area, which is beyond the scope of this study). Since the causes of most familial diseases are complex, and influenced by an interaction of genetic and environmental factors, most family-based studies have attempted to account for the hereditability of diseases from the genetics view point; however, these studies can only explain a fraction of family factors associated with disease (Muñoz et al., 2016). The UK Biobank study investigating the role of genetics and familial shared environment showed that the "missing hereditability" of the common chronic diseases such as CVD is attributable to family lifestyle or environmental effect, which most studies do not take into account (Muñoz et al., 2016).

It is well established that offspring of parents with CVD are more likely to develop CVD in adulthood (Bao et al., 1997), which is mainly linked to genetic interplay between parents and children. However, other studies report that parent-offspring concordance in phenotypic expression of selected CVDs and associations with other CVD risk factors such as obesity are also moderated substantially by family environmental factors such as exercise, diet, smoking (Nielsen, Nielsen, & Holm, 2015). The attributable risk of genetic factors to potentially modifiable health factors has been examined extensively. For instance, the contribution of hereditability to waist circumference ranges from 39-79%, fasting glucose 7-77%, diastolic blood pressure 20-66%, total cholesterol 8-72% (Elder et al., 2009). However, most of these studies included monozygotic or dizygotic twins, not representative of the general population and may overestimate hereditability or variance of the inherited factors due to their limited genetic heterogeneity. In addition, most of the studies did not account for shared familial lifestyle or environmental and behavioral factors such as smoking, exercise, diet, neighborhood

type, among others, which are known to substantially influence such phenotypic expression of inherited CVD risk factors (Elder et al., 2009; Sun et al., 2013). Taken together, accumulated evidence from twin-family studies and population based epidemiological studies suggest that parents' health behaviors , patterns of dietary intake, smoking and physical activity as well as socioeconomic factors influence intergenerational transmission of CVD risk factors, and point to the important role of the shared common family environment in CVD manifestation across generations (Sun et al., 2013).

Definition of Disability-Adjusted Life Years (DALYs)

The burden of a particular disease is usually calculated from disability-adjusted life years (DALYs) for that specific disease and can be directly estimated from specific health behaviors or interventions (Lopez, Mathers, Ezzati, Jamison, & Murray, 2006). Disability-adjusted life years are the sum of two quantities: (1) the number of years of healthy life lost (YLLs) due to premature death, and (2) the number of years lived with disability (YLDs) as demonstrated in Figure 2.1 below (WHO, 2017c). For example, assume the life-expectancy of Country X is 80 years. If an otherwise healthy individual die suddenly in an accident at age 60 years, their YLD is 0, and their YLL=20 (80-60 years); therefore, contribution to DALYs is 20 years. On the other hand, if the individual is diagnosed with CVD at age 55 and dies at 60 years, their YLD=5 (60-55), their YLL=80-60=20, therefore their DALYs= YLD + YLL=5+20=25. A region, country, or population with a low burden of a particular disease will have few DALYs associated with that disease. However, elevated DALYs are associated with a high burden of a disease or when life expectancy is short, or disease treatment and management is suboptimal.

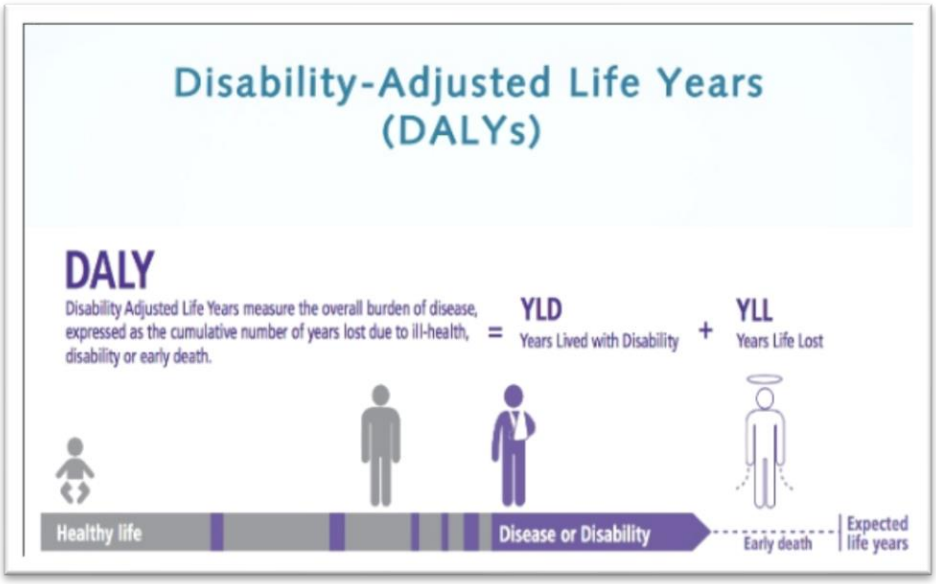

Figure 2. 1. Diagram to show components of disability-adjusted life years. Adapted from https://www.slideshare.net/souravgoswami11/burden-of-disease-analysis

The DALYs concept was initiated in 1993 in the first Global Burden of Diseases (GBD) study (GBD 2015 DALYs and HALE Collaborators, 2016). Use of DALYs is simple but powerful in terms of estimating the progress and difficulties in achieving a certain health status and can be used to monitor disease burden and healthy life over time and therefore captures the health gap of the population against a standard ideal health status. The GBD study has been instrumental in providing advice to countries on priority areas in the allocation of healthcare resources. Without considering the magnitude of DALYs, it is quite difficult to deliver effective and timely high-quality health care interventions without understanding the key disease burdens and tracking population health status trends (Murray & Lopez, 2013).

Importance of Cardiovascular Disease DALYs

Epidemiologic studies have demonstrated the association between some iCVH metrics and incident CVD and CVD mortality, but most have not attempted to quantify the impact of all seven iCVH metrics in the reduction of CVD DALYs (Veronese et al., 2016). It has been shown that a health-gap exists between the recommended iCVH status and the prevailing health situation which needs to be addressed. World Health Organization has recommended use of GBD methods such as DALYs for national or sub-national level to study needs specific to each country (WHO, 2018b). One DALY represents the loss of the equivalent of one year of complete health. About 60% of global DALYs arise from premature mortality. In 2004, the global average burden of disease was 237 per 1,000 population (World Health Organization, 2008). In 1990, global CVD DALYs loss was 85 million and was predicted to nearly double to 150 million by 2020 (Vilahur, Badimon, Bugiardini, & Badimon, 2014). In the United States, ischemic heart disease is the number one cause of death (21.1%), years of life lost (15.9%), years lived with disability 1.9%) and DALYs of 7, 850 (9.6%) per 10, 000 population (Murray & Lopez, 2013).

Due to the increased demand for health resources in the society, strategic planning is needed to attain certain health goals using the available limited resources. Policy makers would not be well informed to make rational decisions for health resources allocation if such comparative burden of disease is not known. The AHA strategic planning committee recommended monitoring of iCVH metrics from 2010-2020. The health-related quality of life (HRQOL) was recommended to be done as a secondary measure for AHA 2020 impact goals due to the availability of disease-specific HRQOL measures in the literature (Lloyd-

Jones et al., 2010). However, it is known that use of HRQOL scales may not be adequate in most national databases and may also not be feasible to measure in all datasets (Karimi & Brazier, 2016). Health-related quality of life scales are also subjective as they involve individual's perception of their quality of life and may not indicate comparable standards across different populations (Karimi & Brazier, 2016).Therefore, DALYs may serve as a valuable tool for measuring the impact of iCVH on CVD as it captures population's health gap against an established normative standard (GBD 2015 DALYs and HALE Collaborators, 2016); this is important to the policy makers to quantify how much iCVH contributes to the reduction of CVD burden.

Benefits and Controversies of DALYs in Estimating Disease Burden

Although widely used in the measurement of global burden of disease literature (GBD 2015 DALYs and HALE Collaborators, 2016; GBD 2016 SDG Collaborators, 2017; Murray & Lopez, 2013; WHO, 2018b), critics fault the assumptions and value judgments, conceptual and technical basis for DALYs (Anand & Hanson, 1997). For example, disability weights for calculating societal preferences at different health states may not necessarily be in tandem with the lived experiences with or without disability since it simply implies societal preferences for such health states (Anand & Hanson, 1997). Another limitation is that a diagnosis of CVD does not necessarily impact quality of life the same way in all individuals. Note that disability weights denote severity of a disease on a continuum scale from 0 (perfect health) to 1 (death) (WHO, 2018b).

In addition, the 5% annual discount rate has been suggested to be reduced to 3% by the environmentalists and renewable energy stakeholders, therefore politicizing DALYs. The

concept of discounting presupposes that there is a social preference of a healthy year lived now than in the future (in other words, a year lived now is better than a year lived in the future), and this is achieved by decreasing the value of life years gained annually at that fixed percentage (World Health Organization, n.d.). The environmentalists and renewable energy advocates argue for this rate discounting in order to align with World Bank Disease Control Priorities Study and GBD, which uses 3%, as well as US Panel on Cost-Effectiveness in Health and Medicine which also support the use of 3% to discount for cost and health outcomes (World Health Organization, n.d.). The WHO recommends a 3% annual discounting (World Health Organization, 2017c).

Research Gaps and Innovation

Findings of most studies conducted to date are consistent with familial aggregation of some iCVH metrics, but no known study has investigated the relationships of all the seven iCVH metrics, especially among paired parent-offspring dyads. This is one gap this study attempted to address. Furthermore, there is lack of data on quantification of iCVH to reduce incident CVD or CVD disability-adjusted life years. Most studies have focused on the clinical occurrence of CVD or mortality using a single examination of few health factors at baseline. This has limitations in that iCVH tends to decline with age (Shah et al., 2015) and hence examining trend of iCVH metrics over time might yield more accurate estimations of CVD impact. This is another gap this study attempted to address.

Ideal cardiovascular health has received much attention since the term was coined in 2010. To increase uptake of self-care programs by the policy makers and the patients, convincing evidence is needed on the extent to which health factors impact the health of

populations. As much as there is increasing evidence to show how atherosclerosis originates in childhood (Hayman & Worel, 2015; Juonala et al., 2010; Loria et al., 2007), there lacks specific data on familial aggregation of combined iCVH metrics and CVD outcomes (Loria et al., 2007). Because most behavioral factors such as dietary patterns and physical activity patterns are formed in childhood, and may worsen in adolescence (CDC, 2011), there is need for familial aggregation studies to inform parents and policy makers on how best to increase health behaviors in the general population by targeting family environments. Improving iCVH among the parents has potential to improve iCVH in children and eventually improve cardiovascular health, reduce the burden of CVD mortality (CDC, 2011). To address this gap, the burden of CVD attributed to iCVH metrics for parents and children was estimated.

CHAPTER 3

METHODOLOGY

Since iCVH metrics were first introduced in the literature in 2010, Chapter 2 above highlighted several gaps in knowledge regarding familial aggregation and the relationships with iCVH metrics. Scientific evidence in the last decade suggests that development of atherosclerosis begins in childhood (Hayman & Worel, 2015; Juonala et al., 2010; Loria et al., 2007), however, specific cross-sectional and longitudinal data on the association of familial aggregation of combined iCVH metrics and CVD outcomes (Loria et al., 2007) is currently lacking. Moreover, there has not been studies of parent-offspring dyads to empirically quantify the association of iCVH longitudinally in reducing the burden of incident CVD and CVD-DALYs. This dissertation examined time trends of iCVH metrics and burden of CVD with the goal of informing the association of familial aggregation of iCVH using FHS data (Feinleib, Kannel, Garrison, McNamara, & Castelli, 1975; Kannel, Dawber, Kagan, Revotskie, & Stokes, 1961).

Data from the Original and Offspring Cohorts of the FHS were analyzed to elucidate intergenerational patterns of health behaviors between parents and their offspring. Framingham Heart Study is a unique epidemiological study that has contributed substantially to the current knowledge of cardiovascular diseases, enrolling and meticulously following three generations of Framingham residents in Massachusetts (see Figure 3.1). The FHS has contributed to a cutting-edge understanding of CVD risk factors and heart disease treatment due to its comprehensive recording of physical, phenotypic and biological traits (Tsao & Vasan, 2015). The design of FHS is described in detail

elsewhere and is one of the longest multi-generation studies (Kannel et al., 1961). The Original Cohort was recruited in 1948 with a sample size of 5209 persons aged 28-62 years (Dawber, Meadors, & Moore, 1951). The second-generation cohort, Offspring Cohort, is comprised of children and spouses of children from the Original Cohort. The Offspring Cohort was enrolled in 1971 and included 5124 participants (Feinleib et al., 1975). Further in 2002, the third generation of 4095 adults having at least one parent in the Offspring Cohort was started to explore contributions of inheritance or genetic patterns to CVD development (Tsao & Vasan, 2015).

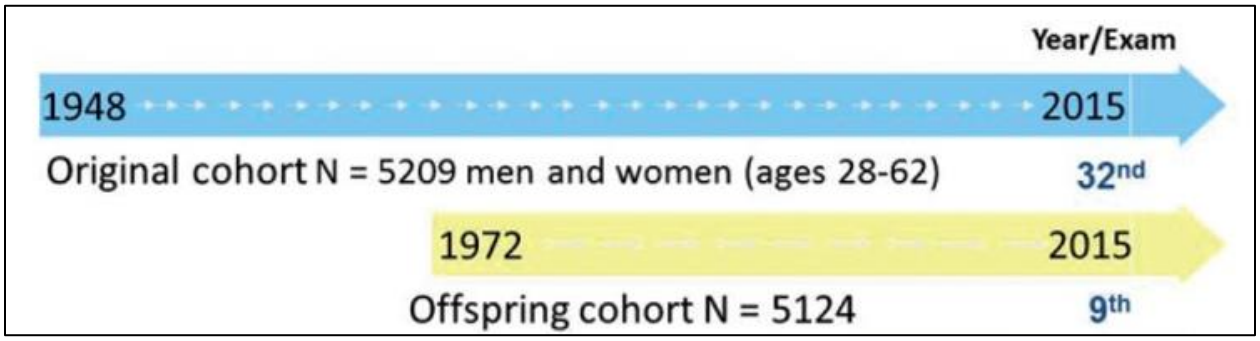

Figure 3. 1. Time course of enrollment of the cohorts within the FHS. Adapted from "Cohort Profile: The Framingham Heart Study (FHS): overview of milestones in cardiovascular epidemiology," by C. W. Tsao, and R. S. Vasan, 2015, *International Journal of Epidemiology*, *44*(6), 1800–1813. https://doi.org/10.1093/ije/dyv337

Study Population

Framingham Heart Study participants are community dwelling; most of whom were selected using systematic random sampling of residents of Framingham, Massachusetts, with a population of 10, 000 at its inception. Individuals or selected households and all family residents were invited to participate. A response of 4, 469 (68.7%) was achieved and n=888

volunteers were included to achieve the desired sample size. More than one half of the Original Cohort participants were women (Mahmood, Levy, Vasan, & Wang, 2014).

More than two out of three (~ 66%) of the Offspring Cohort participants are biologic offspring of the Original Cohort (Feinleib et al., 1975). These parent-offspring dyads were the focus of this analysis. At enrollment, Offspring Cohort participants, the children of 1644 spouse pairs were aged 12-60 years. Framingham residents were exclusively white at the time of initiation. The lack of ethnic diversity of Framingham has been recognized as a limitation of the study; therefore, the study is not representative of the general population. However, FHS has contributed to science that is applicable among diverse multiethnic groups and some of the findings such as CVD risk factors are similar to other multiethnic cohort studies (Tsao & Vasan, 2015). Regarding social diversity, the participants were from all social classes (Northwestern University, 2013; Tsao & Vasan, 2015). Framingham city was selected for this epidemiological study after many considerations; one indicated that the region had successfully completed a six-year country's first community study of tuberculosis which began in 1917. The Framingham community had also demonstrated a goodwill for population-based research and was accustomed to group approach for solving their problems. Taken together, the characteristics of Framingham provided such an environment and one with strong potential to enroll sufficient participants in a long-term study (Dawber et al., 1951).

Standardized and Systematic Data Collection

Most of the examination cycles in the FHS are done every 2 years which is coordinated by a team of staff including examining physicians, clinic nurses, statisticians,

imaging and laboratory technicians, among others (Dawber et al., 1951). Family and medical history, physical examination targeting CVD, smoking history, dietary intake, physical activity, anthropometrics, blood pressure, hemoglobin A1c, lipids and CVD imaging and pulmonary function test are systematically collected using standardized protocols, usually at onsite locations such as elderly, home- or nursing homes (Tsao & Vasan, 2015). Interim questionnaires regarding medical and family history are usually mailed in between examinations, while further information is obtained via phone calls. Regular surveillance of the subjects is done to identify specific CVD events such as angina pectoris, myocardial infarction, heart failure and stroke or cerebrovascular disease. The 22-year lapse between the two cohorts strategically places the offspring to be examined at approximately the same ages as their parents (Feinleib et al., 1975; Tsao & Vasan, 2015).

Selection of Exam Cycles for Familial Aggregation Analysis

Table 3.1 below shows the mean age distributions for each exam cycle for the Original and Offspring Cohorts as well as the number of participants attending each exam cycle. The rationale for selecting exam cycles was to achieve approximate similarity in the mean age between the two cohorts at the paired exam cycles. The exam periods selected for this study are as follows: (1) Original Cohort's exams 1, 3, 5, 7, 9, 11 (mean ages 44, 48, 52, 55, 59, 62 years, respectively), and (2) Offspring's Cohort's exams 2, 3, 4, 5, 6, 7 (mean ages 44, 48, 52, 55, 59, 62 years, respectively) with a mean age range of 3-4 years between the exam periods. Notable, the distribution of age at specific-exam

cycles was generally comparable and is important for parent-offspring comparison of different CVD profiles.

Table 3. 1
Framingham Heart Study Exam Dates and age ranges

Original Cohort					Offspring Cohort				
Exam	**Exam Dates**	**Age Range**	**Mean Age**	**Attendees**	**Exam**	**Exam Dates**	**Age Range**	**Mean Age**	**Attendees**
Exam1	1948-1953	28-74	44	5209	Exam2	1979-1983	17-77	44	3863
Exam3	1952-1956	32-67	48	4416	Exam3	1983- 1987	18-77	48	3873
Exam5	1956-1960	37-70	52	4421	Exam4	1987- 1991	22-81	52	4019
Exam7	1960-1964	40-74	55	4191	Exam5	1991- 1995	26-84	55	3799
Exam9	1964-1968	44-78	59	3893	Exam6	1995-1998	29-86	59	3532
Exam11	1968-1971	49-81	62	2955	Exam7	1998-2001	33-90	62	3539

Table on matched exam pairs of FHS-Original and Offspring Cohorts. Adapted from the "Framingham Heart Study-Cohort (FHS-Cohort)" by American Heart Association, 2017. Retrieved from https://www.framinghamheartstudy.org/researchers/description-data/data/tableofexams.pdf

Familial Aggregation Analysis

The final sample size for the familial aggregation analysis of iCVH was determined from the number of 1644 father and mother pairs with biological children also enrolled in the Offspring Cohort Study (see Table 3.2). A parent in this dissertation was therefore a biological father and/or mother of an offspring. Family members were linked using a family identification (famID) number and each participant has their own unique ID number linking their individual data across exams as well as to the CVD events and survival files in FHS.

Table 3. 2
Sampling Frame of the Offspring Cohort

Total spouse pairs in Original Cohort	1644
Spouse pairs with ≥1 children	1387
Spouse pairs with no children	227
Unknown pairs	30
Individuals with no spouse in Original Cohort	1921
Individuals with CHD/lipid abnormality &≥1 child	330
Individuals with ≥1 offspring volunteer	163

Adapted from "The Framingham Offspring Study. Design and preliminary data," by Feinleib, M., Kannel, W. B., Garrison, R. J., McNamara, P. M., & Castelli, W. P.,1975. *Preventive Medicine*, *4*(4), 518–525

Data for Analyzing Cardiovascular Disease Burden

Cardiovascular disease burden (CVD-DALYs), CVD-survival free period, CVD events and mortality rates were derived from the FHS Sequence of Events (SOE), and Survival Files and Follow-up for Cardiovascular Events files (BioLINCC, 2017), and the U.S official life expectancy data and disability weights were derived from the GBD 2016 study and the National Center for Health Statistics (GBD 2016 SDG Collaborators, 2017; National Center for Health Statistics, 2017).

Table 3. 3

Ideal Cardiovascular Health Metrics using AHA criteria for adults ≥20 years

Blood Pressure	Ideal [2]	<120/<80 mmHg
	Intermediate [1]	SBP 120–139 or DBP 80–89 mmHg
	Poor [0]	SBP≥l40 or DBP≥90mmHg
Physical Activity	Ideal [2]	≥150 min/wk M or ≥75 min/wk V or ≥150 min/wk M+V
	Intermediate	1–149 min/wk M or 1–74 min/wk V or 1–149 min/wk M+V
	Poor [0]	None
Cholesterol	Ideal [2]	<200 mg/dL
	Intermediate [1]	200–239 mg/dL
	Poor [0]	≥240 mg/dL
Healthy Diet	Ideal [2]	4–5 components
	Intermediate [1]	2–3 components
	Poor [0]	0–1 component
Healthy Weight	Ideal [2]	<25 kg/m2
	Intermediate [1]	25–29.9 kg/m2
	Poor [0]	≥30 kg/m2
Smoking Status	Ideal [2]	Never or quit > 12 months
	Intermediate [1]	Former ≤12 months
	Poor [0]	Current smoker
Fasting/Random Blood Glucose	Ideal [2]	<100 mg/dL OR <140 mg/dL
	Intermediate	100–125 mg/dL OR 140-199 mg/dL
	Poor [0]	≥ 126 mg/dL OR ≥ 200 mg/dL

Key: SBP, Systolic blood pressure; DBP, diastolic blood pressure; wk, week; M, moderate; V, vigorous; Adapted from "2017 Statistical Fact Sheet: Cardiovascular health" by AHA, 2017. Retrieved from https://healthmetrics.heart.org/wp-content/uploads/2017/06/2017-Statistical-Fact-Sheet-ucm_492104.pdf

Inclusion and Exclusion Criteria

Participants were included if aged 20 years and older at the first eligible exam period. Offspring were required to be biological children of the parents even though it was not a requirement that the parents should be married to each other or live together for the entire offspring's childhood (≤18 years). Participants were included if they had at least five of the following variables recorded at each of the exams for deriving of iCVH metrics: (1) smoking, (2) body mass index, (3) physical activity, (4) dietary intake of vegetables and fruits or other recommended dietary components, (5) total cholesterol, (6) blood pressure and (7) blood glucose as shown in Table 3.3 below. It is recommended to conduct multiple imputation if

more than 10% but less than 25% of the participants had missing covariates to preserve power (Lodder, 2013; Mukaka et al., 2016; Pedersen et al., 2017); however, most of the variables had less than 10% missing values necessitating a complete case analysis (see appendix for table of missing values).

Independent Variables and Operational Definitions

The main exposure variable was the iCVH metric for the parents derived from seven (or five depending on which variables were missing) variables, namely; smoking, body mass index, physical activity, healthy diet, total cholesterol, blood pressure and blood glucose (AHA, 2017b). Idela cardiovascular health was defined using the seven metrics on a score of 0=poor, 1= intermediate, 2=ideal (Lloyd-Jones et al., 2010) as shown in Table 3.3 and operationalized as described in the inclusion criteria. Smoking and physical activity and diet were self-reported in FHS using a technician-administered questionnaire. Cigarette smoking history was collected for most exams and was mainly recorded as current smoker if smoked within a year and not a smoker if quit for more than a year or never smoked (BioLINCC, 2017). The smoking variables were generated from questionnaire data regarding the participants' smoking history and classified using iCVH criteria. Participants who answered as currently smoking cigarettes were classified as "poor", former smokers or who quit smoking in less than 12 months were classified as "intermediate", those who never smoked or quit smoking more than 12 months were classified as "ideal".

Physical activity questions were based on hours spent sleeping, resting, in slight, moderate or heavy activity on an average day. Physical activity score was calculated using previously suggested methods for use in FHS physical activity data (Kannel et al., 1961).

Minutes spent on each activity was multiplied by the oxygen requirement or metabolic cost for that activity as described by Kannel (Kannel et al., 1961). This method assigns weights for different activities such as sleep (1.0), sedentary (1.1), slight activity (1.5), moderate activity (2.4), heavy activity (5) in the formula: Physical activity score= $(1.0 \times h_{sleep}) + (1.1 \times h_{sedentary}) + (1.5 \times h_{slight}) + (2.4 \times h_{moderate}) + (5.0 \times h_{heavy})$ to derive a physical activity score (on a continuous scale, with no SI units). This methodology on calculating physical activity has been used elsewhere in other studies involving FHS data (Jonker et al., 2006; Shortreed, Peeters, & Forbes, 2013). Physical activity score was collapsed into three categories less than 30 for poor, 30-33 for intermediate and greater than 33 for ideal physical activity levels as used elsewhere (Jonker et al., 2006; Shortreed et al., 2013). This scale has been used effectively among FHS participants and has been shown to be appropriate for physical activity score derivation in this population (Shortreed et al., 2013).

A healthy diet was defined as the top 40% of a dietary score and is composed of low glycemic load, high cereal fiber, high folate, high marine omega-3 fatty acid, a high polyunsaturated to saturated fat ratio, and low trans-fat content (Lloyd-Jones et al., 2010). Data for diet as defined in this study was available in exams 20, 21, 22 for Original Cohort (parents) and exams 3, 5, 6, 7 for Offspring Cohort. Healthy diet was derived from five food groups according to AHA criteria as follows: (1) dairy products, (2) meats, (3) saturated fats, (4) vegetable or fruit intake and (5) cereals (AHA, 2018c). The dietary components were collected using the Framingham Diet Composite Table and entered in the FHS dataset (Mann, Pearson, Gordon, & Dawber, 1962). If no dietary components were available in any

of the study exams, only the available iCVH metrics (mostly five metrics) were used to calculate iCVH.

Three blood pressure readings were taken (using Baumanometer 300 model and Litman stethoscope: Classic II 3M) on each participant, initial one by the nurse on admission and the two-final blood pressure measurements by the examining physician as recorded in the FHS 30-year protocol section. Blood pressure categories were calculated from an average of the three blood pressure readings (one by the nurse on admission and the two-final blood pressure measurements by the examining physician) for each exam cycle. The participants were seated with arm at the heart level (National Heart, Lung, and Blood Institute, 2017). Normal blood pressure ("ideal") was defined as ≤120/80mm Hg to be consistent with the current hypertension guidelines and iCVH definition (AHA, 2017c, 2017b). Body weight was measured using Detecto Worcester scale, Co, Inc. and recorded in pounds. Participant's height was measured using a Stadiometer, barefoot or wearing thin socks and recorded in inches (BioLINCC, 2017). Body mass index was calculated in FHS, similar to other epidemiological studies, as weight in kilograms divided by height in meters-squared (kg/m^2).

Serum cholesterol was determined using colorimetric method but the measurement method was later changed after exam 2 in 1952 to use the Abell-Kendall method (BioLINCC, 2017). Blood was collected in oxalate tube and centrifuged at 5000 rpm for hematocrit and hemoglobin measurement. Blood glucose was recorded in mg/100ml, as the amount of glucose present in whole blood from the oxalate potassium solution using Nelson method (BioLINCC, 2017; National Heart, Lung, and Blood Institute, 2017). Blood glucose measures were recorded as fasting and/or random blood sugar. In this case, blood glucose

was not necessarily required to have been entered in fasting status for calculation of iCVH, but fasting blood glucose values were preferred where available.

Other covariates included were offspring age at the exam cycle, sex, education and level of income. All self-reported data were collected using a technician-administered questionnaire (BioLINCC, 2017). Parental and offspring education and occupation has been previously used in FHS to calculate the relationship between socioeconomic position (SEP) and incidence of coronary heart disease among the Offspring Cohort (Loucks et al., 2009). Inclusion of education and income in this intergenerational study is important because the two factors (education and income) have been implicated as the main socio-determinants of health that are involved in the transfer of health from parents to offspring (Loucks et al., 2009). Low level of education and low income in this case are viewed as cumulative exposures to socioeconomic disadvantage over the lifespan that leads to CVD later in life, for individuals and/or from one generation to another.

Dependent Variables and Operational Definitions

Offspring iCVH and CVD DALYs were the main dependent variables. Ideal cardiovascular metrics for offspring were operationalized as described for parents. Cardiovascular disease was defined using the FHS criteria to include SOE codes for coronary heart disease, intermittent claudication, congestive heart failure, stroke or transient ischemic attack (BioLINCC, 2017). Diagnosis of coronary disease in FHS was adjudicated based on medical records and agreed upon by a panel of three cardiologists. Stroke events were confirmed if participants demonstrated abrupt onset hemiparesis or aphasia, computed tomography scan (CT) scan was used to confirm the diagnosis (Tsao & Vasan, 2015).

Intermittent claudication was mostly subjectively diagnosed when reported as cramping discomfort in calf muscles with walking and relieved by rest and then physician physical examination was completed to confirm diagnosis. Diagnosis of congestive heart failure in FHS was made using criteria of two major episodes of: either paroxysmal nocturnal dyspnea, jugular vein distention, acute pulmonary edema, or one major and two minor events of bilateral ankle edema, night cough, dyspnea on ordinary exertion, hepatomegaly, pleural effusion (BioLINCC, 2017; Tsao & Vasan, 2015).

Disability-adjusted life years were used to estimate the burden of CVD for parents and offspring as described later in this chapter. The baseline visit was the first selected exam cycleof each cohort (i.e exam 1 for parents and exam 2 for offspring). Cardiovascular disease DALYs (see Figure 3.9) of each cohort was calculated for each exam and stratified by iCVH metrics. Trend of DALYs lost due to CVD for each cohort were presented at each exam cycle (Tables 4.13a&b). Further details for DALYs calculation are provided in the data analysis section.

Human Subject Consideration (Institutional Review Board-IRB)

Institutional ethics approval was granted by the University of Massachusetts Boston under the definition of a human subject research at 45 CFR 46.102. In addition, further approval was granted by the National Heart, Lung, and Blood Institute (NHLBI) and signed relevant Research Distribution Agreement (RMDA) materials. Framingham Heart Study is an existing public dataset of individuals who have provided informed consent. The data of this study are de-identified so that no information such as name or any other personally identifiable information can be accessed.

Statistical Analysis

The path diagram or schematic analytic model below (Figure 3.2) is used to depict the conceptual framework of how parental iCVH metrics influence those of their offspring.

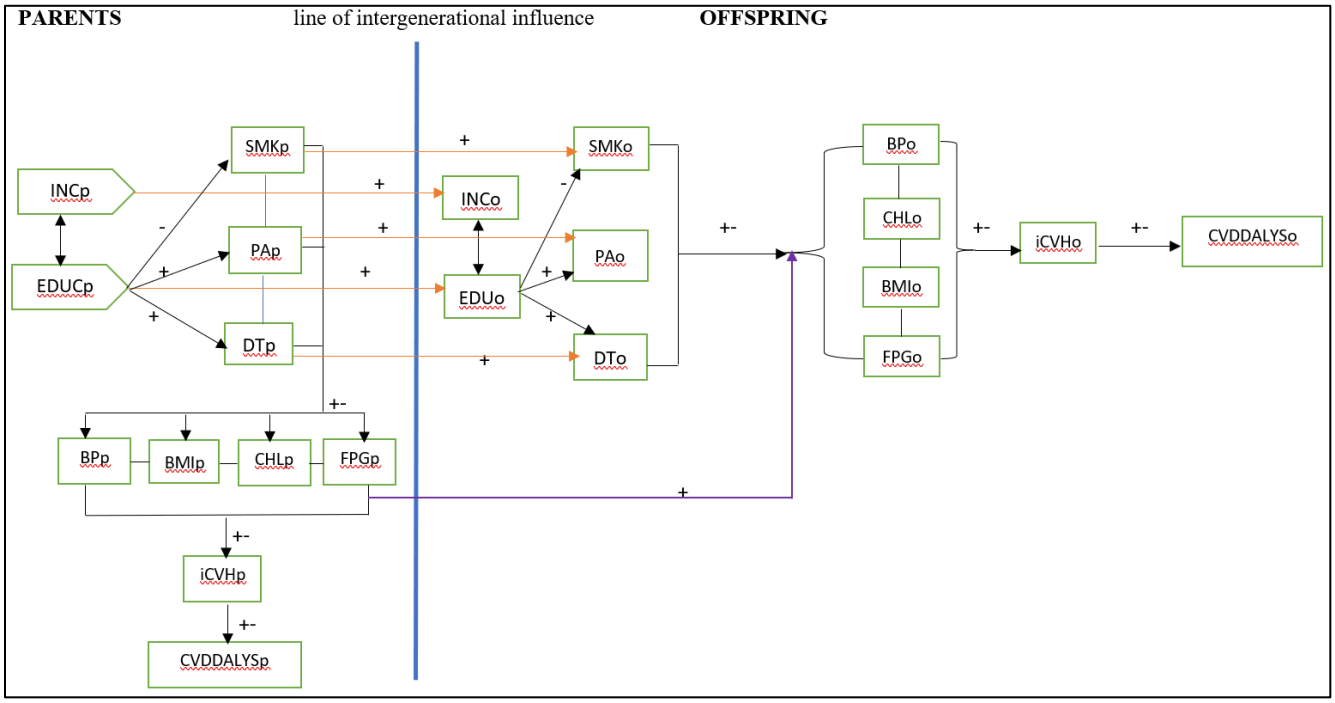

Figure 3. 2 Path diagram showing intergenerational association of iCVH metrics between parents to offspring.
Key: variables=EDU (education), INC (income), PA (physical activity), DT (diet), SMK (smoking), BMI (body mass index), BP (blood pressure), FPG (blood glucose), CHOL (cholesterol); "X" o Offspring); "X" p (Parents), iCVH (iCVH).

The model includes two main exogenous variables namely education and income (assessed anytime between exams 1-7 in both cohorts). Education variable is the main driving force, with some modifying effect on income. The emphasis of this model is the influence of parent's health behaviors (assessed at exam periods 1, 3, 5, 7, 9, 11) and those of their offspring (assessed at exam periods 2, 3, 4, 5, 6, 7). Parent's smoking status (SMKp), physical activity

(PAp) and diet (DTp) are hypothesized to directly influence respective offspring health behaviors [smoking behavior (SMKo), physical activity (PAo) and diet (DTo), with the main driving factor being parents' education status (EDUp). Progressively, the model hypothesizes that offspring's behaviors [smoking behavior (SMKo), physical activity (PAo) and diet (DTo)] influence their own physiological factors (BMIo, BPo, CHLo, FPGo). There is a complex interrelationship among offspring's physiological factors, but for the ease of illustrating the relationships, an abbreviated explanation is provided below. Combined effect of offspring's blood pressure (BPo), blood glucose (FPGo), body mass index (BMIo) and cholesterol levels (CHLo) contribute directly to the offspring's iCVH status (iCVHo), which further influences their total cardiovascular disease burden (CVD DALYSo). Additively, the role of familial genetics is depicted through the parental physiological factors (BMIp, BPp, CHLp, FPGp) which directly influence the offspring's physiological factors (BMIo, BPo, CHLo, FPGo). This effect modulates the risk of CVD by either increasing or reducing offspring iCVH, with subsequent effects on offspring CVD DALYs. In summary, the probability of achieving an iCVH (seven health metrics) among the offspring is primarily a function of parental iCVH metrics (behavioral and biomarkers) and socioeconomic status 1) $iCVHk = a + biCVHp + cEDUo + \Sigma offspring\{age; sex\} + \varepsilon k$, where offspring's iCVH health (iCVHo) hypothetically depends on parents' iCVHp and the offspring's education (EDUo), controlling for age and sex of the offspring.

Statistical analysis of specific aim 1. Aim 1 examined the association of offspring's iCVH and their parents at comparable mean age for the selected exam cycles (where offspring iCVH dependent variable and parent iCVH as the main explanatory variable). Both

offspring and parent iCVH were categorized as poor (0), intermediate (1) and ideal (2) as shown in Table 3.3 and as a continuous iCVH variable on a scale of 0 to 14, meaning than each iCVH metric contributes a maximum of two points, multiplied by the seven to make 14 as maximum point. Testing of normality assumption of the linear regression model was conducted using Q density plot and Q-Q plot of residuals in STATA.

Statistical analysis for aim 1 hypothesis 1A. Hypothesis 1A was to determine whether iCVH metrics for parents will be positively correlated with that of their offspring at similar mean age. Pearson correlation coefficients were used to assess linear patterns of iCVH at each examination to determine whether the correlation between parent iCVH and offspring iCVH becomes stronger or weaker with time and check the similarities of correlations at each exam cycle. A correlation coefficient matrix table was generated as shown in sample Table 3.4, one matrix for parents (mother and/or father), offspring with their mothers and another matrix for offspring with their father with direct correlation coefficients r12, r33, r54, r75, r96 and r117 as period specific coefficients and off-diagonal partial correlations r14, r35, r56 and r77.

While the interpretation of diagonal correlation coefficients r12, r33, r54, r75, r96 and r117 is straightforward, they represent “age-contemporaneous” exam cycles when each cohort had similar age distribution. On the other hand, off-diagonal partial correlations r14, r35, r56 and r77 represent the nature of the correlation when the Original Cohort and Offspring Cohort are mismatched for age distribution, i.e., when the cohorts are “age non-congruent”. This hypothesis generating analysis was designed to reveal whether correlations

are unstructured, remain constant, or decline with widening age gap between parent and offspring, i.e., constant, autoregressive, compound symmetric (Kincaid, n.d.).

Table 3. 4
Pearson Correlation coefficient matrix for parents and offspring iCVH

	Mean iCVH Father/Mother					
Offspring iCVH at exam	iCVH exam 1	iCVH exam 3	iCVH exam 5	iCVH exam 7	iCVH exam 9	iCVH exam 11
iCVH exam 2	r12					
iCVH exam 3	r13	r33				
iCVH exam 4	r14	r34	r54			
iCVH exam 5	r15	r35	r55	r75		
iCVH exam 6	r16	r36	r56	r76	r96	
iCVH exam 7	r17	r37	r57	r77	r97	r117
	Mean iCVH Mother					
Offspring iCVH at exam	iCVH exam 1	iCVH exam 3	iCVH exam 5	iCVH exam 7	iCVH exam 9	iCVH exam 11
iCVH exam 2	r12					
iCVH exam 3	r13	r33				
iCVH exam 4	r14	r34	r54			
iCVH exam 5	r15	r35	r55	r75		
iCVH exam 6	r16	r36	r56	r76	r96	
iCVH exam 7	r17	r37	r57	r77	r97	r117
	Mean iCVH Father					
	iCVH exam 1	iCVH exam 3	iCVH exam 5	iCVH exam 7	iCVH exam 9	iCVH exam 11
iCVH exam 2	r12					
iCVH exam 3	r13	r33				
iCVH exam 4	r14	r34	r54			
iCVH exam 5	r15	r35	r55	r75		
iCVH exam 6	r16	r36	r56	r76	r96	
iCVH exam 7	r17	r37	r57	r77	r97	r117

Power and sample size for aim 1 hypothesis 1A. Studies have shown some parent-offspring Pearson correlations between some iCVH metrics such as diet, physical activities ranging from 0.24-0.52 (McGowan et al., 2013; Storti, Kristi Leigh, 2007; Wang, Beydoun, Li, Liu, & Moreno, 2011; Yee, Lwin, & Ho, 2017). It is assumed that relationship between parents and children will follow a similar pattern**.** Table 3.5 below shows different power estimations for detecting a Cohen' d of 0.10 using samples ranging from 800 to 1500 at 0.05

and 0.01 significance levels. Using two-tailed t-test for correlation, a sample size of 800 parents and offspring will detect significant correlations between parents and offspring, with power of 81% and at a small effect size of 0.1. An excellent power of 82% and small effect size of 0.10 will also be achieved with a sample of N=1200 at a lower significance level of 0.01.

Table 3. 5
Power calculation for hypothesis 1A

α/cohen's d	n=800	n=1000	n=1200	n=1500
0.05/0.10	Power=0.81	Power=0.89	Power=0.94	Power=0.97
0.01/0.10	Power=0.60	Power=0.72	Power=0.82	Power=0.91

Statistical analysis for aim 1 hypothesis 1B. Hypothesis 1B examined the relationship between Parent iCVH and Offspring iCVH at similar mean age using linear regressions with the Offspring iCVH as the dependent variable and the Parent iCVH as the main exposure variable. Exploratory data analysis was used to determine whether iCVH was normally distributed or skewed. Model 1 was comprised of a simple linear regression analysis of the Offspring's iCVH as dependent variable and the iCVH for the parents as the independent variable. Model 2 was comprised of the same model as Model 1 but adjusted for the offspring's exam-specific covariates (age, sex, income, education level), with a general regression equation: $iCVHo = a + \beta_1 iCVHp + \beta_2 Education + \{\beta_2 Sex; \beta_3 Age\} + \varepsilon k$. This model asserts that an offspring's iCVH (iCVHo) depends on the parents' iCVH (iCVHp) and offspring's education, controlling for age and sex of the offspring. Testing of normality assumption of the linear model was done using Q density plot and Q-Q plot of residuals. Income variable was dropped from the model since it did not yield any significant

relationship. All regression equations were run with complete case analysis since most of the variables had more than 25% missing values.

Supplemental Statistical analysis for aim 1 hypothesis 1B. As a supplement to linear regression, Models 1 and 2 were similarly implemented using ordered logit model also known as the proportional odds model (Peterson & Harrell, 1990). In proportional odds modeling, the Offspring's iCVH (dependent variable) and Parents' iCVH (independent variable) were transformed to an ordinal variable to conform to AHA classification of iCVH into three levels, coded as "poor" [0], "intermediate" [1] and "ideal" [2]. The proportional odds model is suited for the analysis of ordinal response variables, assuming that the slopes among the ordered levels are parallel. This assumption was assessed in preliminary analyses, using Brant test and consequently confirmed using gologit2 command in STATA (Williams, 2018). The tests showed that overall, there was no violation of the parallel regression assumption. Details on the statistical theory behind the partial proportional odds model can be found in several sources (Ananth & Kleinbaum, 1997; Williams, 2018). The STATA command *ologit* was used to fit the proportional odds model (Williams, 2006), which set the "poor" iCVH category as the referent category as opposed to the *gologit2* command which set "ideal" category as referent category. Results were however checked to determine if there were substantial differences between the two estimation commands. Model 1 was not adjusted for any covariates, but Model 2 was adjusted for the offspring's covariates (age, sex, education level). To account for correlation due to familial clustering, regression models were run using the 'cluster' option in STATA with Family ID as the cluster variable.

Power and sample analysis for aim 1 hypothesis 1B. Previous studies have documented positive linear relationships between some of the iCVH metrics among parents and offspring. For instance, in one study, regression coefficients for offspring and parent were 0.213, 0.144, 0.231, 0.038 for BMI, systolic blood pressure, total cholesterol, glucose, respectively (Vik, Romundstad, Carslake, Smith, & Nilsen, 2014). To be able to detect a Cohens d of 0.10 using a two-tailed t-test for correlation at $\alpha = 0.05$ significance level, a minimum sample size of 800 parents and offspring is required to detect statistically significant correlations between parents and offspring achieves 81% power. A sample size of 1200 achieves 82% power at a conservative significance level of $\alpha = 0.01$ can also be achieved with a sample of 1200 (see Table 3.6 below).

Table 3. 6
Power calculation for hypothesis 1B

α/cohen's d	n=800	n=1000	n=1200	n=1500
0.05/0.10	Power=0.81	Power=0.89	Power=0.94	Power=0.97
0.01/0.10	Power=0.60	Power=0.72	Power=0.82	Power=0.91

Statistical analysis of specific aim 2. Aim 2 compared iCVH and CVD DALYs between parents and offspring at exam cycles where distribution of age at specific exam cycles are generally comparable. The following hypotheses were tested: (1) Hypothesis 2A, accounting for age, sex, education and income, the parents' and offspring's iCVH metrics will be positively associated with CVD DALYs respectively and (2) Hypothesis 2B, offspring of parents with lower iCVH will have higher mean CVD DALYs compared to the mean CVD DALYs for offspring of parents with higher iCVH.

Statistical analysis of hypothesis 2A. Hypothesis 2A proposes that parents' and offspring's iCVH metrics will be positively associated with their respective CVD DALYs at each exam cycle. Separate regressions were run for the parents and for the offspring at each of the six exam cycles: (1) Model 1=simple regression for CVD DALYs as outcome variable and iCVH (continuous variable), (2) Model 2=multivariate model as in 1 above controlling for age, education, sex and income, and (3) iCVH as categorical ("poor" [0], "intermediate" [1] and "ideal" [2]) as follows: Model 1=simple regression for CVD DALYs as outcome variable; iCVH adjusted for age and Model 2=multivariate model as in 1 above controlling for age, education, sex and income. Linear trends regarding the effect of iCVH were assessed across exam cycles by plotting the regression coefficients of iCVH over time.

Statistical power and sample size for hypothesis 2A. No study was identified to describe the relationship between heart-healthy behaviors and CVD DALYs averted. However, it is assumed that for every one-unit increase in iCVH, there will be a reduction on CVD DALYs based on prior research on disease burden (Global Burden of Cardiovascular Diseases Collaboration et al., 2018). Table 3.7 below shows different power estimations for detecting a Cohen' d of 0.10 using samples ranging from 800 to 1500 at α =0.05 and α =0.01 significance levels. For example, a sample size of 800 will achieve 81% power for detecting a Cohen's d of 0.10 at α =0.05.

Table 3. 7
Power calculation for hypothesis 2A

α/cohen's d	n=800	n=1000	n=1200	n=1500
0.05/0.10	Power=0.81	Power=0.89	Power=0.94	Power=0.97
0.01/0.10	Power=0.60	Power=0.72	Power=0.82	Power=0.91

Statistical analysis for aim 2 hypothesis 2B. To assess whether offspring of parents with lower iCVH will have higher mean CVD DALYs compared to the mean CVD DALYs for offspring of parents with higher iCVH, the following was done. A two-sample t-test was used to compare the means for parents vs. offspring: iCVH and CVD DALYs. Additionally, two-sample t-test was used to analyze subgroups of CVD DALYs for offspring of parents with high (>7) and low (≤7) iCVH [or high (>5) versus low (≤5) parental iCVH if missing two iCVH variables).

Calculation of DALYs, YLDs, and YLLs. First, sex-individual-specific CVD DALYs, YLDs, and YLLs were calculated for each eligible parents and offspring. The relation of DALYs to YLDs and YLLs is DALYs=YLD+YLL (see Figure 3.1). In this equation individual YLD is calculated as the number of cases=1 (since the outcome event is only "CVD" for each individual) multiplied by years lived until death, then multiplied by CVD disability weights (1X years until death X CVD disability weight); YLL was calculated as the age at death due to CVD multiplied by remaining years if someone reached the maximum life expectancy (i.e age at death X remaining life expectancy at the age of death) (Devleesschauwer et al., 2014). The aggregate CVD disability weight of 0.276 was derived from Global Burden of Disease Study 2017, and calculated as an average of disability weights of five most common CVDs (myocardial infarction, DW=0.432; stroke, DW=0.588; heart failure=0.179, intermittent claudication=0.014; angina, 0.167) (GBD 2017, 2017).

The 2016 age-standardized maximum life expectancy for US population at birth was used to calculate the maximum expected life expectancy for each cohort, i.e 81 years for females and 76 years for males (National Center for Health Statistics, 2018). Rationale for

using 2016 life expectancy is given at the analysis section of CVD DALYs. Exploratory data analysis was used to determine whether DALYs are normally distributed. Four hypothetical examples as shown in Table 3.8 below illustrate the calculation of DALYS assuming the 2016 US life expectancy. The four hypothetical individuals are assumed to experience CVD events at different ages. Years of Life Lost (YLLs)=Life Expectancy (LE)-Age died; Years Lived with Disability (YLDs)= (1 X [years until death] X [CVD disability weight]); and CVD DALYs =YLLs +YLDs.

Table 3. 8
Example of DALYs calculation using CVD disability weights (DW) of 0.276

Female	YOB (I)	YR CVD DX (II)	YR CVD death (III)/end f/up	Expected LE (I+81) (IV)	YLL (IV-III)	YLD= [III-II] *DW	DALYs= YLL+YLD
A	1900	1956	1975	1981	6	5.2	11.5
B	1922	1970	1991	2003	12	5.8	17.5
C	1890	1948	1990	1971	0	11.5	11.5
D	1950	1988	1991	2031	0	3	3

*LE, life expectancy; Equations: YLL= Life Expectancy (LE)- Year died/end of follow-up; YLD=1 X duration with CVD till death X disability weight; DALYs=YLD+YLL.
Note end of follow-up for parents=1991, for offspring is 2014; YLLs less than zero were coded as zero

The DALYs calculations were done in way that it would be possible to compare equal follow-up times for parents and offspring. Considering the available CVD events follow-up time for the offspring of 43 years (1971-2014), parents follow-up time was truncated at the year 1991 (meaning parents alive at 1991 mark was coded as end of follow-up even if they continued to be followed-up for CVD events). Decision to use this balanced method was based from Struijk and colleagues (method 4 pg.3) who recommended an elaborate method

of calculating individual-specific life expectancies in a cohort data as opposed to the most common method of calculating population-based life expectancy (Struijk et al., 2013). This method is appropriate as it estimates life expectancy at attained age (age of death or end of follow up) and was found to be most accurate for calculating the number of years lost giving a variable age and variable reference year for individual participants a cohort dataset expectancy (Struijk et al., 2013).

Statistical power and sample size for hypothesis 2B. Previous studies have reported that the mean CVD DALYs in the United States was 6231 per 100, 000 in 2005 and 5178 per 100, 000 in 2015 (GBD 2015 DALYs and HALE Collaborators, 2016). Assuming a sample ratio of 1:1 between parents and offspring, alpha of 0.05 and a Cohens d of 0.10, a sample size of 1612 can detect a significant mean CVD DALYs differences with a power of 81% and SD of 0.5.

Table 3. 9
Power calculation for hypothesis 2B

α/cohen's d	n=1612	n=2032	n=2472	n=2952
0.05/0.10	Power=0.81	Power=0.89	Power=0.94	Power=0.97

Sensitivity Analysis

This study employed several levels of sensitivity analysis. The most outstanding sensitivity analyses include running several regression equations at each exam cycle for Original and Offspring Cohorts using iCVH as continuous variables. Conversion of iCVH metrics into binary variables 0 or 1 (low iCVH≤5=0 and high iCVH>7=1) and ordered 0, 1, 2 categories also provided comparative analysis. Burden of CVD calculated from DALYs averted or incurred from each increment of iCVH also provided information on how iCVH

metrics drive CVD burden and compared CVD DALYs results with and without disability weights.

In this chapter, the FHS and how the study is an ideal setting for the proposed analysis was described. Exam cycles at which the Offspring and Original Cohort had similar age distribution were identified. The outcome variable for Aim 1, iCVH for offspring as well as the iCVH for the parents and their derivations were described. The outcome variable for Aim 2, CVD DALYs and their derivations were also described. Proposed statistical method for addressing Aims 1 and 2 were provided together with a sensitivity analysis. Next, in Chapter 4, statistical results for Aims 1 and 2 will be summarized and discussed in Chapter 5.

CHAPTER 4

RESULTS

Chapter 4 presents statistical results for Aims 1 and 2. Aim 1 examined the association of iCVH health between parents and offspring assessed at selected exam cycles at which both cohorts had similar age distribution. Aim 2 compared iCVH and CVD DALYs between parents and offspring at paired exam cycles (Table 3.1). Offspring participants were recruited from 1644-spouse pairs of Original Cohort at the onset. In preparing the data before statistical analysis, the family ID was used to link the data for each offspring to the data of the parents. Each record in the analysis dataset represents a unique offspring participant. The parents' data was merged to each corresponding offspring such that in families with multiple children, the data for the parents was replicated in the records for all their children. Original Cohort participants [parents' cohort] with no offspring were excluded.

Paired exam cycles were selected such that mean age of parent cohort was similar to the Offspring Cohort, a total of six exam cycles for each cohort were paired as shown in Table 1 in the Methods section. Note that the parent/offspring exam cycles (1/2 [mean ages 44/44], 3/3 [mean ages 48/48], 5/4 [mean ages 52/52], 7/5 [mean ages 55/55], 9/6 [mean ages 59/59], 11/7 [mean ages 62/62], were selected where mean age of Original Cohort were similar to the mean age of the Offspring Cohort (Table 3.1). Figure 4.1 is a flowchart showing participants who were retained and excluded after inclusion criteria was applied. Participants who were recorded as "attended" at any given exam cycle was used as the

denominator for the exam cycle.

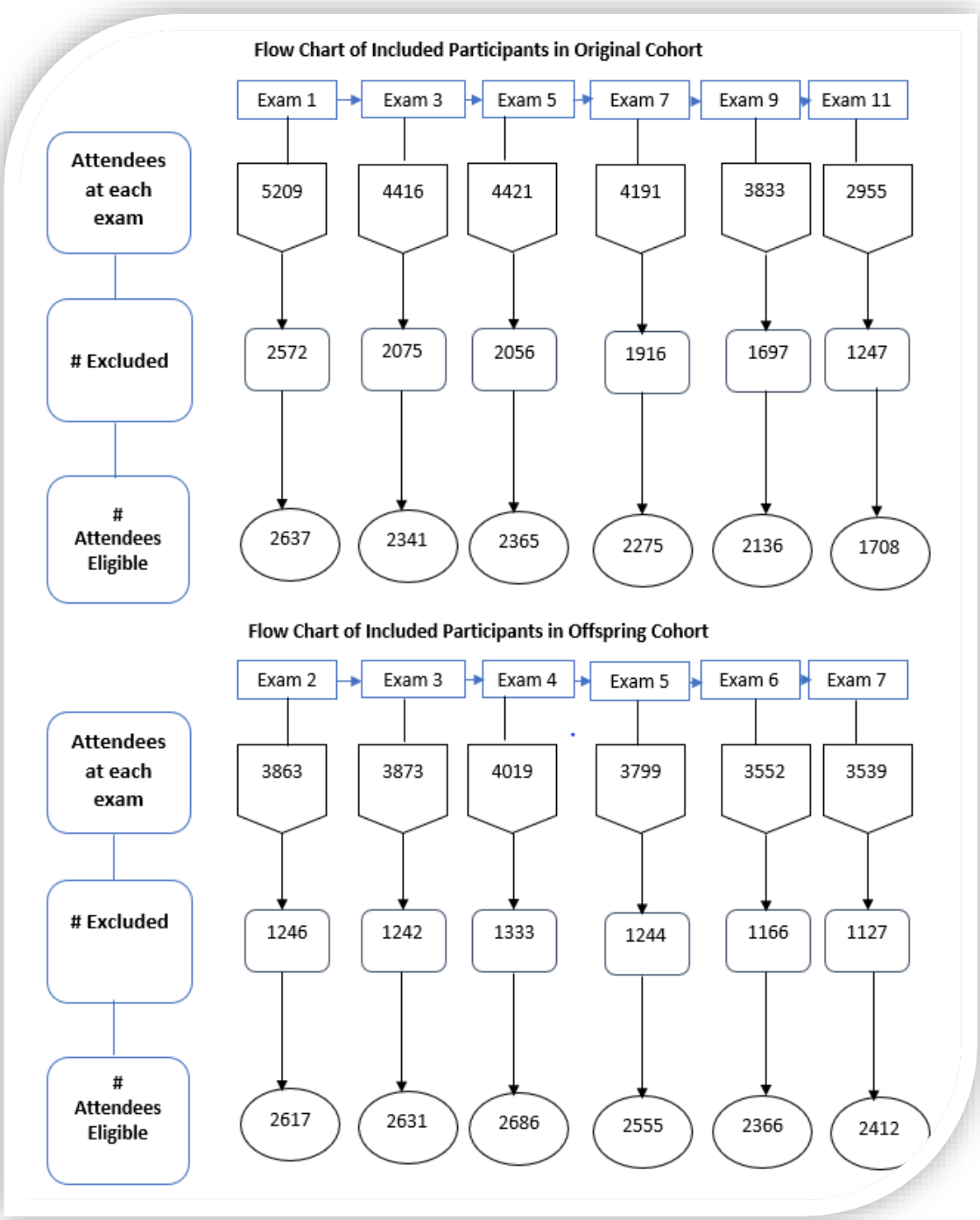

Figure 4. 1 Flowchart showing selection of eligible number participants and those excluded from the study after pairing offspring to their parents.

Sample Characteristics of Original and Offspring Cohorts

At total of 3,492 offspring were paired with 2,734 unique parents (mothers [n=1, 416] and/or fathers [n=1,318]) derived from 1,044 distinct families with a mean of 2 children per family (minimum 1, maximum 9). Each exam had a different number of offspring and parents which represents the participants who attended that exam cycle. Out of the 1, 044 families, 399 (38.2%) had one child, 347 (33.2%) had 2 children, 183 (17.5%) had 3 children, 81 (7.8%) had 4 children, 17 (1.6%) had 5 children, 12 (1.2%) had 6 children, 4 (0.4%) had 7 children and 1 (0.1%) had 9 children.

Table 4.1 shows summary demographic characteristics of Original and Offspring Cohorts who attended each exam cycle. Gender was equally distributed in either cohort, although the proportions of women were slightly higher than men in both cohorts ($p<0.001$). Women were slightly younger than men in Original Cohort ($p<0.05$) except last exams 9 and 11. However, no statistically significant differences in mean ages of women and men in Offspring Cohort except in older age where women were slightly older than men. Most (35.6% parents vs 33.3 offspring) participants were aged 35-44 years at the first eligible inclusion exam. In each age group of the Original Cohort, the proportion of mothers aged 55 years and above was significantly lower than of fathers ($p<0.05$) except at exams 9 and 11. No statistically significant differences noted among age categories for the offspring male and female participants (Table 4.3). In Table 4.1, nearly a half (45%) of the Original Cohort participants had not completed high school education while more than 93% of the offspring participants had attained at least high school education. Noteworthy among the two cohorts was that there was remarkable difference in the proportion of housewives in the Offspring

Cohort compared with their parents (20.4% vs 43.4%), with the offspring occupying most of the professional jobs.

Table 4. 1
Sample characteristics of Original and Offspring Cohorts by sex in each matched exam cycle

FHS Original Cohort n=2734					FHS Offspring Cohort n=3492				
Characteristic	**Total n%**	**Male n%**	**Female n%**	**P value**	**Characteristic**	**Total n%**	**Male n%**	**Female n%**	**P value**
Sex	2637(100)	1290(48.9)	1347(51.1)	0.000	**Sex**	2617(100)	1246(47.6)	1371(52.4)	0.000
Age (mean/SD)					**Age (mean/SD)**				
Exam1 n=2637	43.1 (8.3)	44.3 (8.4)	43.0 (8.2)	0.000	Exam2 n=2617	43.1(10.2)	42.8 (10.3)	43.3 (10.1)	0.147
Exam3 n=2341	47.4 (8.3)	48.0 (8.3)	47.0 (8.2)	0.002	Exam3 n=2631	47.2(10.2)	46.8 (10.2)	47.2 (10.3)	0.062
Exam5 n=2365	51.2 (8.3)	51.7 (8.2)	50.8 (8.2)	0.008	Exam4 n=2686	50.3(10.2)	49.9 (10.1)	50.6 (10.2)	0.058
Exam7 n=2275	55.0 (8.2)	55.3 (8.2)	54.6 (8.1)	0.030	Exam5 n=2555	53.7(10.1)	53.3 (10.1)	54.1 (10.2)	0.049
Exam9 n=2136	58.7 (8.1)	58.9 (8.1)	58.4 (8.1)	0.127	Exam6 n=2366	57.6(10.0)	57.0 (9.8)	58.1 (10.1)	0.004
Exam11n=1708	62.0 (7.8)	62.3 (7.8)	61.8 (7.8)	0.182	Exam7 n=2412	60.6 (9.9)	60.0 (9.7)	61.1 (10.0)	0.005
Marital status (n= 2365) (Exam 5)					**Marital status (n=2617) (Exam 2)**				
Married	2294(97.0)	1124(99.4)	1170(94.8)		Married	1984(75.8)	1033(79.5)	999 (69.7)	
Single	0 (0.0)	1 (0.08)	6 (0.7)		Single	319 (12.2)	134 (10.3)	159 (11.1)	
Widowed	53 (2.2)	4 (0.4)	49 (4.0)	0.000	Widowed	61 (2.3)	16 (1.2)	101 (7.1)	0.000
Divorced/ Separated	17 (0.89)	3 (0.3)	14 (1.1)		Divorced/ Separated	253 (9.7)	94 (7.2)	152 (10.6)	
Education level (n=2543) (Exam 1-7)					**Education level (n=2611) (Exam 2)**				
<High school	1132(44.5)	585 (47.3)	547 (41.9)		<High school	172 (6.6)	87 (7.0)	85 (6.2)	
High school	730 (28.7)	307 (24.8)	423 (32.4)	0.000	High school	875 (33.5)	368 (29.6)	507 (37.0)	0.000
Some college	204 (8.0)	99 (8.0)	105 (8.0)		Some college	725 (27.8)	292 (23.5)	433 (31.6)	
≥College grad	477 (18.8)	246 (19.9)	231 (17.7)		≥College grad	839 (32.3)	495 (39.9)	344 (25.1)	
Type of work (n=2208) (Exam 6)					**Type of work (n=2506) (Exam 2)**				
Professional	122 5.5)	104 (10.0)	18 (1.5)		Professional	486 (19.4)	267 (22.6)	219 (16.5)	
Executive	21 (1.0)	21 (2.0)	0 (0.0)		Executive	27 (1.1)	23 (2.0)	4 (0.3)	
Supervisory	292 (13.2)	273 (26.4)	19 (1.6)		Supervisory	188 (7.5)	152 (12.9)	36 (2.7)	
Technical	130 (5.9)	124 (12.0)	6 (0.5)	0.000	Technical	175 (7.0)	124 (10.5)	51 (3.9)	0.000
Laborer	521 (23.6)	400 (38.6)	121 (10.3)		Laborer	594 (23.7)	468 (39.6)	126 (9.5)	
Clerical	74 (3.4)	37 (3.5)	37 (3.2)		Clerical	401(16.0)	42 (3.6)	359 (27.1)	
Sales	89 (4.0)	77 (7.4)	12 (1.0)		Sales	125 (5.0)	103 (8.7)	22 (1.7)	
Housewife	959 (43.4)	0 (0.0)	959 (81.8)		Housewife	510 (20.4)	0 (0.0)	510 (38.5)	

Note: Sample size in each exam include only eligible participants that attended the specific exam; eligible participants are unique individuals in each cohort

Comparison of Body Mass Index for Original versus Offspring Cohorts

All descriptive tables present eligible participants' iCVH metrics for unique individual Original and Offspring participants. Note that according to the iCVH classification "ideal" metric is the most desirable and "poor" is undesirable cardiovascular health status. In all the seven iCVH metrics, "poor", "intermediate" and "ideal" metrics are coded as 0, 1 and 2 respectively. Table 4.2 presents descriptive statistics for BMI by Cohort at each exam categorized using iCVH classification criteria (Table 4.2). Two-sample t-test comparing mean BMI showed the Offspring Cohort had a significantly higher mean BMI in most of the paired exam cycles compared with Original Cohort ($p<0.05$) except at younger ages. Overall BMI trend for all exam cycles showed that the Offspring Cohort had a higher proportion of "poor" BMI status compared with the Original Cohort.

Table 4. 2 Original and Offspring Cohorts body mass index metric by ideal cardiovascular health classification

FHS Original (Parents) Cohort					FHS Offspring Cohort					
Exam #	Mean/SD	Poor	Intermediate	Ideal	Exam #	Mean/SD	Poor	Intermediate	Ideal	P value
Exam 1					Exam 2					
n=2634	25.8 (4.2)	371 (14.1)	1056 (40.1)	1207 (45.8)	n=2616	25.6 (4.5)	380 (14.5)	926 (35.4)	1310 (50.1)	0.217
Exam 3					Exam 3					
n=2338	26.0 (4.0)	302 (13.0)	1043 (44.6)	993 (42.5)	n=2582	25.8 (4.6)	464 (18.0)	1022 (39.6)	1096 (42.5)	0.204
Exam 5					Exam 4					
n=2356	26.0 (4.0)	323 (13.7)	1016 (43.1)	1017 (43.2)	n=2672	26.4 (4.8)	568 (21.3)	1091 (40.8)	1013 (37.9)	0.000
Exam 7					Exam 5					
n=2210	26.1 (4.0)	312 (14.1	959 (43.4)	939 (42.5)	n=2534	26.9 (4.9)	622 (24.6)	1050 (41.4)	862 (34.0)	0.000
Exam 9					Exam 6					
n=2070	26.1 (4.0)	289 (14.0)	901 (43.5)	880 (42.5)	n=2331	27.5 (4.9)	684 (29.3)	984 (42.2)	663 (28.4)	0.000
Exam11					Exam 7					
n=1683	26.5 (4.1)	272 (16.2)	767 (45.6)	644 (38.3)	n=2281	27.9 (5.2)	711 (31.2)	953 (41.8)	617 (27.1)	0.000

BMI classification: Poor; ≥30, Intermediate; 25-29.9, Ideal;<25; p values calculated from ttest for mean parent-offspring BMI

Comparison of Blood Pressure for Original versus Offspring Cohorts

Table 4.3 presents descriptive statistics for blood pressure by Cohort at each cycle. Blood pressure was derived as shown in Table 4.3 from systolic blood pressure (SBP) and

diastolic blood pressure (DBP). Blood pressure measurements for parents compared with offspring were statistically different in all matched exam cycles ($p<0.05$). Parents had higher proportion of high blood pressure at each exam cycle. For instance, parents with poor blood pressure (SBP≥140 or DBP≥90mmHg) compared with offspring in paired exams 1 versus 2 and exams 11 versus 7 was 37.9% vs. 17.6% ($p<0.001$) and parents in exam 11 versus offspring exam 7 was 45.9% vs. 22.3% ($p<0.001$) respectively.

Table 4. 3
Original and Offspring Cohorts blood pressure metric by ideal cardiovascular health classification

FHS Original (Parents) Cohort				FHS Offspring Cohort				
Exam #	Poor	Intermediate	Ideal	Exam #	Poor	Intermediate	Ideal	P value
Exam 1				Exam 2				
n=2637	998 (37.9)	1101 (41.8)	538(20.4)	n=2617	460 (17.6)	971 (37.1)	1186 (45.3)	0.000
Exam 3				Exam 3				
n=2341	662 (28.3)	917 (39.2)	762(32.6)	n=2631	532 (20.2)	1021 (38.8)	1078 (41.0)	0.000
Exam 5				Exam 4				
n=2365	841 (35.6)	907 (38.4)	617(26.1)	n=2686	656 (24.4)	1061 (39.5)	969 (36.1)	0.000
Exam 7				Exam 5				
n=2275	1030(45.3)	854 (37.5)	391(17.2)	n=2555	502 (19.7)	1013 (39.7)	1040 (40.7)	0.000
Exam 9				Exam 6				
n=2136	980 (45.9	798 (37.4)	358(16.8)	n=2365	527 (22.3)	963 (40.7)	875 (37.0)	0.000
Exam11				Exam 7				
n=1696	887 (52.3)	597 (35.2)	212(12.5)	n=2408	580 (24.1)	984 (40.9)	844 (35.1)	0.000

Ideal blood pressure Poor: SBP≥140 or DBP≥90mmHg; Intermediate=SBP 120–139/DBP 80–89 mmHg; Ideal:<120/<80mmHg; P values computed from $\chi 2$ test for blood pressure categories of parents and offspring

Comparison of Smoking Patterns for Original versus Offspring Cohorts

Table 4.4 presents descriptive statistics of cigarette smoking between the two cohorts. A higher proportion of parents were "current" ("poor" category) smokers compared with their offspring at similar mean age in all exams ($p<0.001$) and consequently offspring had higher attainment of ideal smoking status (no smoking). For instance, 58.5% (n=1533) of the

parents at exam 1 had "poor" category smoking status, compared with the corresponding 39.5% (n=1033) offspring ($p<0.001$) and the gap continue to widen with age.

Table 4. 4 *Original and Offspring Cohorts smoking status by ideal cardiovascular health classification*

FHS Original (Parents) Cohort				FHS Offspring Cohort				
Exam #	**Poor**	**Intermediate**	**Ideal**	**Exam #**	**Poor**	**Intermediate**	**Ideal**	**P value**
Exam 1				Exam 2				
n=2619	1533 (58.5)	166 (6.3)	920 (35.1)	n=2617	1033 (39.5)	63 (2.4)	1521 (58.1)	0.000
Exam 3				Exam 3				
n=2216	1216 (54.9)	40 (1.8)	960 (43.3)	n=2628	789 (30.2)	07 (0.3)	1832 (69.7)	0.000
Exam 5				Exam 4				
n= 2361	1293 (54.8)	286 (12.1)	782 (33.1)	n=2679	670 (25.0)	13 (0.5)	1996 (74.5)	0.000
Exam 7				Exam 5				
n=2233	1134 (50.8)	4 (0.2)	1095 (49.0)	n=2552	495 (19.4)	35 (1.4)	2022 (79.2)	0.000
Exam 9				Exam 6				
n=2136	839 (39.3)	177 (8.3)	1120 (52.4)	n=2358	339 (14.4)	36 (1.5)	1983 (84.1)	0.000
Exam11				Exam 7				
n=1018	610 (36.1)	61 (3.6)	1018 (60.3)	n=2408	317 (13.2)	21 (0.9)	2070 (86.0)	0.000

Smoking categories, Poor: current smoker; Intermediate: former ≤12 months; Ideal: Never/quit >12 months; P value computed from Chi-square of cigarette smoking categories for parents and offspring

Comparison of Blood Glucose Patterns for Original versus Offspring Cohorts

Table 4.5 presents descriptive statistics for blood glucose metric by cohort for offspring matched to their parents at each exam period. Blood glucose was measured using random blood glucose (RBG) for the Offspring Cohort while fasting blood glucose (FBG) for the Offspring Cohort. Therefore, the mean/SD for blood glucose may not be comparable since different test units were used but the iCVH categorization (poor, intermediate, ideal) is comparable as it takes into consideration the respective FBG or RBG categorizations. Offspring Cohort have higher proportion of abnormal/high blood glucose (poor blood glucose score) compared to their parents in all exam periods ($p<0.01$), consequently, offspring had a higher prevalence of diabetes than their parents.

Table 4. 5
Original and Offspring Cohorts blood glucose metric by ideal cardiovascular health classification

FHS Original (Parents) Cohort					FHS Offspring Cohort					
Exam #	Mean/SD	Poor n%	Intermediate n%	Ideal n%	Exam #	Mean/SD	Poor n%	Intermediate n%	Ideal n%	P value
Exam 1 n=2576	82.0 (22.6)	18 (0.7)	19 (0.7)	2539 (98.6)	Exam 2 n=2509	98.6 (18.5)	84 (3.4)	840 (33.5)	1585 (63.2)	0.000
Exam 3 n=2304	83.1 (21.8)	19 (0.8)	18 (0.8)	2267 (98.4)	Exam 3 n=2437	94.1 (22.3)	80 (3.3)	403 (16.5)	1954 (80.2)	0.000
Exam 5 n=2240	81.6 (25.1)	19 (0.8)	28 (1.2)	2240 (98.0)	Exam 4 n=2481	95.6 (26.5)	106 (4.3)	381 (15.4)	1994 (80.4)	0.000
Exam 7 n=2200	81.6 (24.2)	18 (0.8)	26 (1.2)	2156 (98.0)	Exam 5 n=2489	00.2 (26.8)	149 (6.0)	666 (26.8)	1674 (67.3)	0.000
Exam 9 n=2095	86.6 (29.6)	29 (1.4)	46 (2.2)	2020 (96.4)	Exam 6 n=2275	03.3 (27.3)	183 (8.0)	765 (33.6)	1327 (58.3)	0.000
Exam11 n=1673	17.3 (45.3)	85 (5.1)	309 (18.5)	1279 (76.5)	Exam 7 n=2228	03.7 (26.1)	195 (8.8)	773 (34.7)	1260 (56.6)	0.000

Original Cohort:Random Blood Glucose Poor= ≥ 200 mg/dL, Intermediate=140-199 mg/dL, Ideal= <140 mg/dL; Offspring: Fasting Blood Gluose: Poor= ≥ 126 mg/dL, Intermediate=100-125 mg/dL, Ideal= <100 mg/dL; p values computed from $\chi 2$ comparing blood glucose categories for parents and offspring

Comparison of Blood Cholesterol Trends for Original versus Offspring Cohorts

Table 4.6 presents descriptive statistics for non-fasting total blood cholesterol by cohort for offspring matched to biological parents for each exam period. Total blood cholesterol ("poor" category score ≥240 mg/dl) was significantly higher for parents compared with their offspring in all observation exam periods. At exam 5 for example, 47.3% (n=1104) of the parents had poor cholesterol score compared with 19.2% (n=502) in the matched offspring exam 4 ($p<0.001$). In other words, a higher proportion of offspring achieved ideal cholesterol score compared with their parents in all matched exam cycles.

Table 4. 6

Comparing Original and Offspring Cohorts total cholesterol trends by ideal cardiovascular health classification

FHS Original (Parents) Cohort					FHS Offspring Cohort					
Exam #	Mean/SD	Poor n%	Intermediate n%	Ideal n%	Exam #	Mean/SD	Poor n%	Intermediate n%	Ideal n%	P value
Exam 1 n=2567	224.6 (45.1)	852 (33.2)	885 (34.5)	830 (32.3)	Exam 2 n=2612	200.6 (38.8)	380 (14.6)	828 (31.7)	1404 (53.8)	0.000
Exam 3 n= 2311	230.2 (44.5)	894(38.7)	860 (37.2)	557 (24.1)	Exam 3 n=2542	209.6 (41.5)	552 (21.7)	895 (35.2)	1095 (43.1)	0.000
Exam 5 n= 2336	241.1 (45.2)	1104 (47.3)	834 (35.7)	398 (17.0)	Exam 4 n=2615	207.3 (39.8)	502 (19.2)	959 (36.7)	1154 (44.1)	0.000
Exam 7 n= 2251	252.3 (50.5)	1293 (57.4)	720 (32.0)	238 (10.6)	Exam 5 n=2535	203.9 (36.8)	402 (15.9)	937 (37.0)	1196 (47.2)	0.000
Exam 9 n= 2118	242.2 (46.1)	1019 (48.1)	774 (36.5)	325 (15.3)	Exam 6 n=2332	207.0 (40.6)	438 (18.8)	839 (36.0)	1055 (45.2)	0.000
Exam11 n= 1673	233.8 (42.6)	697 (41.7)	631 (37.7)	345 (20.6)	Exam 7 n=2279	200.2 (37.1)	320 (14.0)	757 (33.2)	1202 (52.7)	0.000

Total blood cholesterol poor=>=240; intermediate=200-239; ideal= <200 mg/dl; p values signifant $\alpha<0.05$ for both ttest for means and $\chi 2$ for categorical cholesterol for parents and offspring

Comparison of Physical Activity Trends for Original versus Offspring Cohorts

Table 4.7 presents descriptive statistics for physical activity for offspring and their parents for each exam period. However, physical activity data for iCVH classification was only available in only two exams for each cohort (exams 4 & 11 for Original Cohort and exams 2 &4 for Offspring Cohort). Most of the offspring (>50%) attained higher levels of ideal physical activity compared with their parents (<40%). Physical activity score was collapsed into three categories less than 30 representing “poor” category, 30-33 for “intermediate” category and greater than 33 for “ideal” category physical activity levels as described in the methods section. Notably, physical activity in the FHS data was recorded as duration in number of hours spent doing a particular task per day.

Table 4. 7

Original and Offspring Cohorts physical activity metric by ideal cardiovascular health classification

FHS Original (Parents) Cohort				FHS Offspring Cohort			
Exam #	**Poor**	**Intermediate**	**Ideal**	**Exam #**	**Poor**	**Intermediate**	**Ideal**
Exam 4				Exam 2			
n=2147	632 (29.4)	903 (42.1)	612 (28.5)	n=2614	422 (16.1)	886 (33.9)	1306 (50.0)
Exam11				Exam 4			
n= 395	327 (82.8)	34 (8.6)	33 (8.6)	n=2587	289 (11.2)	511 (19.8)	1787 (69.0)

Physical activity categorized using physical activity score <30=poor; 30-33= intermediate; >33= ideal, calculated using the formula: Physical activity score= (1.0 x $_{hr}$sleep) + (1.1 x $_{hr}$sedentary) + (1.5 x $_{hr}$slight) + (2.4 x $_{hr}$moderate) + (5.0 x $_{hr}$heavy). Adapted from "Estimating the effect of long-term physical activity on cardiovascular disease and mortality: evidence from the Framingham Heart Study" by Shortreed, Peeters, & Forbes, 2013, *Heart (British Cardiac Society)*, 99(9), 649–654. https://doi.org/10.1136/heartjnl-2012-303461 and "Factors of risk in the development of coronary heart disease--six-year follow-up experience. The Framingham Study" by Kannel, Dawber, Kagan, Revotskie, & Stokes, 1961, *Annals of Internal Medicine*, 55, 33–50.

Comparison of five food components for Original versus Offspring Cohorts

Table 4.8 presents descriptive statistics for dietary components by Cohort for offspring (exams 3, 5, 6, 7) and parents (exam 20, 21, 22). Data in Table 4.8 was used to calculate the ideal diet score in Table 4.9. Achievement of recommended servings of food categories was low for both Original Cohort and Offspring Cohort, overall less than 25% achievement of recommended levels of any of the five food groups, with the lowest attainment for fruits and vegetable intake. Offspring had an overall poor dietary pattern with the lowest proportions of recommended servings of all the five food groups.

Table 4. 8

Five food categories for computing ideal diet metrics as recommended by the American Heart Association (AHA)

FHS Original (parents) cohort (n%)			FHS Offspring Cohort (n%)		
1. Fruits & vegetables-servings/day (recommended ≥4 servings/day)					
Exam	<4 servings/day (n%)	≥4 servings/day (n%)	**Exam**	<4 servings/day (n%)	≥4 servings/day (n%)
Exam 20 n=548	543 (99.1)	5 (0.9)	Exam 3 n=2530	2,517 (99.5)	13 (0.5)
Exam 21 n=418	409 (97.9)	6 (2.2)	Exam 5 n=2298	2,286 (99.5)	12 (0.5)
Exam 22 n=342	341 (99.7)	1 (0.3)	Exam 6 n=2104	2,095 (99.6)	9 (0.4)
			Exam 7 n=2076	2,064 (99.4)	12 (0.6)
2. Whole grains servings/day (recommended ≥6 servings/day)					
	<6 servings/day	≥6 servings/day		<6 servings/day	≥6 servings/day
Exam 20 n=548	536 (97.8)	12 (2.2)	Exam 3 n=2531	2,427 (95.9)	104 (4.1)
Exam 21 n=418	407 (97.4)	11 (2.7)	Exam 5 n=2298	2,243 (97.6)	55 (2.4)
Exam 22 n=342	333 (97.4)	9 (2.6)	Exam 6 n=2104	2,079 (98.8)	25 (1.2)
			Exam 7 n=2076	2,050 (98.8)	26 (1.3)
3. Nuts/Legumes-servings/week (recommended ≥4 servings/week)					
	<4 servings/wk	≥4 servings/wk		<4 servings/wk	≥4 servings/wk
Exam 20 n=548	526 (96.0)	22 (4.0)	Exam 3 n=2527	2,136 (84.5)	391 (15.5)
Exam 21 n=418	404 (96.7)	14 (3.4)	Exam 5 n=2298	1,848 (80.4)	450 (19.6)
Exam 22 n=342	323 (94.4)	19 (5.6)	Exam 6 n=2104	2,079 (98.8)	25 (1.2)
			Exam 7 n=2076	2,050 (98.8)	26 (1.3)
4. Meat/Poultry-servings/week (recommended ≤9 servings/wk)					
	>9 servings/wk	≤9 servings/wk		>9 servings/wk	≤9 servings/wk
Exam 20 n=548	121 (22.1)	427 (77.9)	Exam 3 n=2536	2,395 (94.4)	141 (5.6)
Exam 21 n=418	213 (51.0)	205 (49.0)	Exam 5 n=2298	2,202 (95.8)	96 (4.2)
Exam 22 n=342	165 (48.2)	177 (51.8)	Exam 6 n=2104	1,889 (89.8)	215 (10.2)
			Exam 7 n=2076	1,821 (87.7)	255 (12.3)
5. Low fats/milk-servings/day (recommended ≤3 servings/day)					
	>3 servings/day	≤3 servings/wk		>3 servings/day	≤3 servings/wk
Exam 20 n=548	404 (73.7)	144 (26.3)	Exam 3 n=2596	2,246 (88.8)	283 (11.2)
Exam 21 n=418	317 (75.8)	101 (24.2)	Exam 5 n=2297	2,012 (87.6)	285 (12.4)
Exam 22 n=342	278 (81.3)	64 (18.7)	Exam 6 n=2103	1,810 (86.1)	293 (13.9)
			Exam 7 n=2076	1,804 (86.9)	272 (13.1)

Ideal Diet for Original versus Offspring Cohorts

Table 4.9 shows that offspring had a lower attainment of recommended dietary requirements than the parents. No test of statistical significance was done since the available dietary data for Original and Offspring Cohorts were derived from exams where parents-offspring were not similar by mean age as with other phenotypes in this study. Most of the Offspring Cohort had high proportion of poor dietary scores ranging from 80.4% to 99.5% across exam periods. Ideal diet score was defined using the number of achieved dietary components as shown in Table 4.9. Of note, no parent in Original Cohort achieved ideal" diet category or attained 4-5 dietary components. This pattern was similar to that for Offspring, except for just one offspring achieved an "ideal" diet category at exam 5 cycle.

Table 4. 9
Ideal diet score for Original and Offspring Cohorts by ideal cardiovascular health classification

FHS Original (Parents) Cohort				FHS Offspring Cohort			
Exam #	**Poor**	**Intermediate**	**Ideal**	**Exam #**	**Poor**	**Intermediate**	**Ideal**
Exam 20				Exam 3			
n=548	416 (75.9)	132 (24.1)	0 (0.0)	n=2517	2389 (94.9)	128 (5.1)	0 (0.0)
Exam 21				Exam 5			
n=418	361 (86.4)	57 (13.6)	0 (0.0)	n=2297	1948 (84.8)	348 (15.2)	1 (0.04)
Exam 2				Exam 6			
n=342	296 (86.6	46 (13.5)	0 (0.0)	n=2103	1949 (92.7)	154 (7.3)	0 (0.0)
				Exam 7			
				n=2076	1894 (91.2)	182 (8.8)	0 (0.0)

Ideal diet score poor=0-1 components, intermediate=2-3 components, ideal=4-5 components; Dietary components include: 1. diet-fruits/veg, 2. whole grains, 3. nuts/legumes, 4. unsaturated fat/milk, 5. lean meat

Comparison of iCVH trends for Original versus Offspring Cohorts

Table 4.10 presents descriptive statistics for an aggregate of all the seven iCVH metrics (BMI, blood pressure, smoking, blood sugar, cholesterol, physical activity and diet) calculated using data from Tables 4.2-4.9 and stratified by cohorts whereby for offspring's iCVH scores were matched to the iCVH scores of parents at each exam cycle. The iCVH

categories were coded as “poor” =0, “intermediate” =1, “ideal” =2. Note that since not all iCVH metrics were available for all exam cycles, iCVH categories were generated in two ways: (1) Using five iCVH metrics available in both cohorts (this excludes diet and physical activity which were only available for few exams). Maximum iCVH score using 5-iCVH metrics classification was 10 (i.e., 2x5) for continuous iCVH variable using five metrics, and (2) Using seven iCVH metrics (this includes criteria 1 above plus “ideal” diet and physical activity scores at available exams cycles). For uniformity, the available diet and physical activity metrics were each averaged to create one composite score applied to all exam cycles for each cohort. This means, the same diet and physical activity score was used for all the exam cycles in the respective cohorts. Maximum iCVH score for this classification was 14 (i.e 2x7) for continuous iCVH variable using seven metrics.

As shown in Table 4.10, none of the cohort attained an “ideal” iCVH score of all seven metrics (iCVH 7 metrics). However, few participants in both Cohorts (<5%) achieved least five iCVH metrics. No statistically significant difference was noted for achieving 7 iCVH metrics for parents and offspring in all included exams ($p>0.05$ at all exams cycles). However, the Offspring Cohort had a higher mean iCVH metrics at all exam cycle for both 5 and 7 metrics. In addition, parents had a higher trend of having poor iCVH metrics (for both 5 or 7 iCVH metrics) compared to offspring. The mean iCVH scores for offspring (range 6.6-6.8) were slightly higher than the parents (range 5.6-6.1) at all the paired exam cycles. Notably, mean iCVH score remained fairly constant throughout for both cohorts. No statistically significant differences between parents’ and offspring’s iCVH in four out of six exam cycles using the 7-metric criteria ($p>0.05$) were observed.

Table 4. 10

Original and Offspring ideal cardiovascular health score by ideal cardiovascular health classification

FHS Original (parents) Cohort					FHS Offspring Cohort					
Exam 1	**Mean/SD**	**Poor (n%)**	**Intermediate (n%)**	**Ideal (n%)**	**Exam 2**	**Mean/SD**	**Poor (n%)**	**Intermediate (n%)**	**Ideal (n%)**	**P value**
5metrics n=2540	5.9 (1.7)	556 (21.9)	1930 (78.9)	54 (2.1)	n=2501	6.7 (2.0)	367 (14.6)	1909 (76.2)	231 (9.2)	0.000
7metrics n=620	7.8 (2.0)	158 (25.5)	462 (74.5)	0 (0.0)	n=2339	8.4 (2.2)	466 (19.9)	1873 (80.1)	0 (0.0)	0.094
Exam 3					**Exam 3**					
5metrics n=2171	6.1 (1.7)	408 (18.8)	1712 (78.9)	51 (2.4)	n=2421	6.8 (2.0)	328 (13.6)	1849 (76.4)	244 (10.1)	0.000
7metrics n=562	7.9 (2.0)	130 (23.1)	432 (76.9)	0 (0.0)	n=2314	8.4 (2.2)	435 (18.8)	1879 (81.2)	0 (0.0)	0.040
Exam 5					**Exam 4**					
5metrics n=2265	5.7 (1.7)	560 (24.7)	1681 (74.2)	24 (1.1)	n=2466	6.8 (2.0)	335 (13.6)	1886 (76.5)	245 (9.9)	0.000
7metrics n=617	7.4 (2.0)	198 (32.1)	419 (67.9)	0 (0.0)	n=2389	8.4 (2.2)	466 (19.5)	1923 (80.5)	0 (0.0)	0.020
Exam 7					**Exam 5**					
5metrics n=2114	5.5 (1.6)	560 (26.5)	1539 (72.8)	15 (0.7)	n=2476	6.8 (1.9)	277 (11.2)	1987 (80.3)	212 (8.6)	0.000
7metrics n=606	7.1 (1.9)	240 (39.6)	366 (60.4)	0 (0.0)	n=2381	8.4 (2.1)	406 (17.1)	1975 (83.0)	0 (0.0)	0.072
Exam 9					**Exam 6**					
5metrics n=2031	5.8 (1.6)	454 (22.4)	1557 (76.7)	20 (1.0)	n= 2263	6.6 (1.8)	309 (13.7)	1831 (80.9)	123 (5.4)	0.000
7metrics n=613	7.2 (1.9)	206 (33.6)	407 (66.4)	0 (0.0)	n= 2196	8.2 (2.0)	452 (20.6)	1744 (79.4)	0 (0.0)	0.295
Exam 11					**Exam 7**					
5metrics n=1626	5.6 (1.7)	417 (25.7)	1199 (73.7)	10 (0.6)	n=2220	6.7 (1.8)	251 (11.3)	1833 (82.6)	136 (6.1)	0.000
5metrics n=544	7.0 (1.9)	214 (39.3)	330 (760.7)	0 (0.0)	n=2136	8.2 (2.0)	416 (19.5)	1729 (80.5)	0 (0.0)	0.978

Note: 5 and 7 metrics denote iCVH score computed using 5 and 7 iCVH metrics, namely-BMI, cholesterol, blood glucose, blood pressure, smoking, (physical activity and diet); P values computed using χ^2 to test differences between parents and offspring iCVH scores

Figures 4.2 and 4.3 below show the proportions of iCVH categories of parents and offspring over time using AHA criteria 5-metrics. Neither parents nor offspring attained "ideal" iCVH level at any exam cycle.

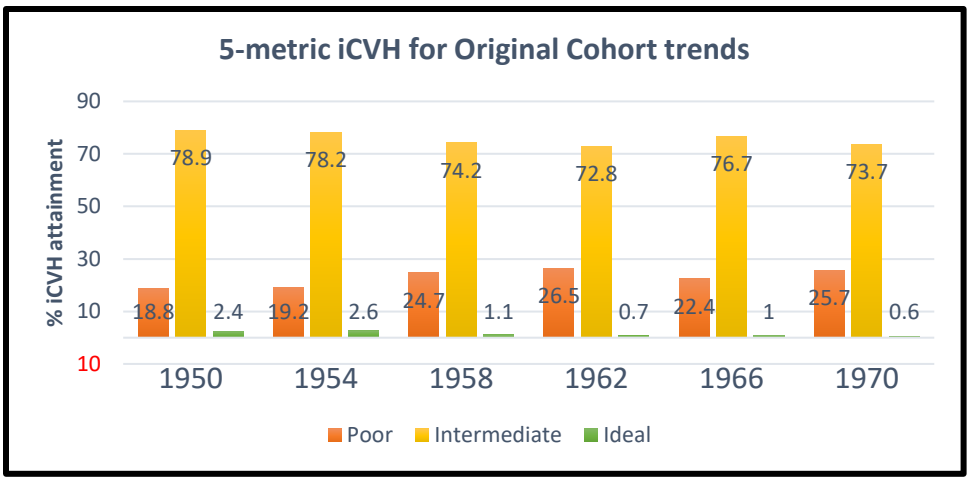

Figure 4. 2. FHS parents' iCVH metrics over time (1948-1971)

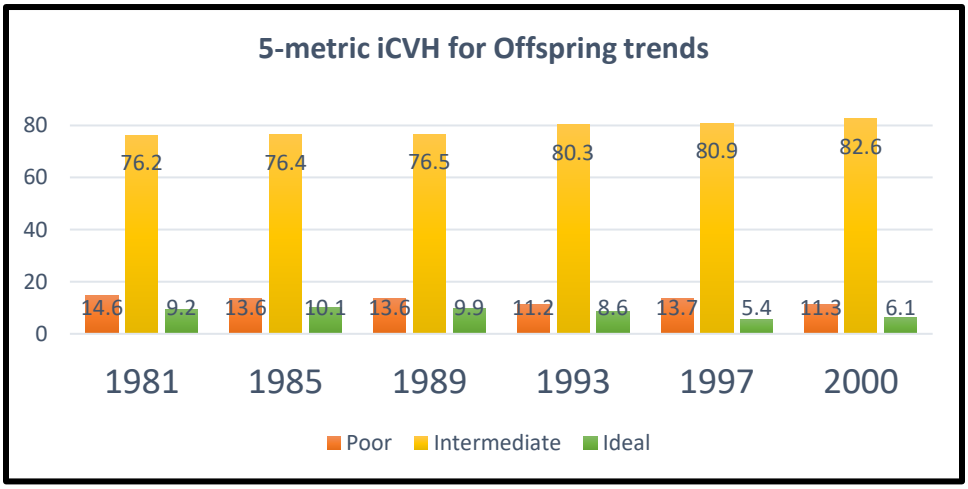

Figure 4. 3. FHS offspring iCVH metrics over time (1971-2001)

Cardiovascular Disease Events and DALYs

Cardiovascular disease was defined using the FHS criteria comprising of one or more heart or blood vessel conditions including coronary heart disease, intermittent claudication, congestive heart failure, stroke or transient ischemic attack (TIA). The date of the first CVD event was used as the overall date the individual was diagnosed with CVD regardless of multiple future CVD events. The events were recorded were coded using International Classification of Diseases, ninth edition (ICD-9). Table 4.11 presents exam-specific incidence of CVD events. The table shows that parents had a higher incidence of CVD than the offspring except at the third matched exam cycles, p=0.812). Incidence of CVD in parents increased more with increasing age-group ranging from 3.5%-16.4% in Original Cohort, and from 3.6%-5.3% in offspring. Incidence rate was lowest at exam cycles at which Original and Offspring Cohorts were younger particularly at exams when either cohort had a mean age younger than 50 years.

Table 4. 11
Incidence of cardiovascular disease events for Original and Offspring Cohort at each paired exam cycle

Original Cohort				Offspring Cohort				
Exam/Year	Number at risk	#CVD events	Incidence %	Exam/Year	Number at risk	#CVD events	Incidence %	p value
Exam 1 (1948-1953)	2637	219	8.3	Exam 2 (1979-1983)	2617	101	3.9	0.001
Exam 3 (1954-1956)	2122	75	3.5	Exam 3 (1984-1987)	2530	92	3.6	0.812
Exam 5 (1957-1960)	2071	137	6.6	Exam 4 (1988-1991)	2493	103	4.1	0.001
Exam 7 (1961-1964)	1844	157	8.5	Exam 5 (1991-1995)	2259	107	4.7	0.000
Exam 9 (1965-1968)	1548	220	14.2	Exam 6 (1995-1998)	1963	84	4.3	0.000
Exam11 (1969-1971)	900	148	16.4	Exam 7 (1998-2001)	1925	102	5.3	0.000
Total CVD events		956		Total CVD events		589		

Note: %Incidence= [Number (#) of CVD events (at each exam)/number of persons at risk]x100.; # at risk=number of eligible participants at each exam-#CVD events in previous exams; p value computed from $\chi 2$, significant at $\alpha<0.05$

Table 4.12 shows mean CVD DALYs for the two Cohorts. For comparable exposure duration for CVD between cohorts, maximum follow-up period was capped at 43 years corresponding to 1948-1991 for the Original Cohort and 1971-2014 for the Offspring Cohort. The Offspring Cohort had significantly higher mean CVD DALYs compared to the Original Cohort [5.5 (95% CI: 5.2-5.9), vs. 1.8 (95% CI: 1.6-1.9), $p<0.001$]. With respect to YLLs, the Offspring Cohort lost 4.6 years (95% CI: 4.3-5.0) due to early CVD death versus 1.1 years (95% CI 1.0-3.2) in Original Cohort. To determine the age CVD diagnosis, the participant's date of birth was first approximated by subtracting their age (in years) from the date of exam cycle 1. This estimation of date of birth was necessary since the real date of birth was masked in the FHS database to protect against identification of participants. Age at first CVD diagnosis was therefore estimated by subtracting the approximate date of birth from the date of first CVD event. This estimation is not perfect, but the best approach given the circumstances. The approximated mean age at CVD diagnosis for the Original Cohort was 72.5 years (SD=10), which was statistically significantly higher than the mean age at CVD diagnosis for the Offspring Cohort of 51.0 years (SD=11.7), $p<0.001$. The consequence of approximating date of birth in the manner described above is that any over-estimation or under-estimation CVD diagnosis age were carried forward to the calculation of CVD DALYs. The Offspring Cohort had a total of 17,163 CVD DALYs (mean 5.5) compared with 4, 656 CVD DALYs (mean 1.8) for the Original Cohort. These CVD DALY rates translate to 550, 273 and 176, 564 per 100,000 population for Offspring and Original Cohorts, respectively.

Table 4. 12

Mean CVD YLLs, CVD YLDs, and CVD DALYS for Original and Offspring Cohorts

	Original Cohort (Parents)			Offspring Cohort			
	n	Mean/SE	95% CI	N	Mean/SE	95% CI	P value
CVD YLLs	2,637	1.1 (0.06)	0.98-3.24	3,119	4.6 (0.16)	4.30-4.92	0.000
CVD YLDs	2,637	0.7 (0.03)	0.61-0.96	3,119	0.9 (0.03)	0.82-0.96	0.000
CVD DALYs	2,637	1.8 (0.07)	1.62-1.91	3,119	5.5 (0.18)	5.15-5.85	0.000
Total CVD DALYs		4, 656			17,163		

YLL= years of life lost; YLD= years lived with disability; DALYs=YLD+ YLL; P value computed using t-test for means, significant at $\alpha<0.05$; CVD DALYs per 100, 000= (total CVDDALYsx100, 000)/n

Statistical Analysis of Hypothesis 1A

Hypothesis 1A postulates that exam cycle-specific iCVH metrics for the two Cohorts will be positively linearly correlated. Table 4.13 presents a correlation matrix for iCVH of offspring matched to biological parents at each exam cycle. These correlations were generated using five iCVH metrics (i.e, excluded physical activity and diet because these variables were not available in most exam cycles). The table presents correlation coefficients for Offspring with (1) a mean iCVH for parents (mean for mother and/or father), (2) correlation coefficient for Offspring with mothers only and (3) correlation coefficient for offspring with fathers only. Diagonal correlation coefficients (in bold) represents linear associations when both cohorts had similar mean age. Other off-diagonal partial correlation coefficients represent non-congruent exam cycles when the parents and offspring are mismatched for age distribution.

Results of the diagonal Pearson correlations coefficients show that offspring's iCVH was positively linearly correlated with that of their parents at each exam cycle where mean age was similar. Correlation coefficients ranged from 0.17-0.25 and declined slightly with increasing age-group at all exam cycle pairs. The correlation coefficients were stronger

earlier exams when both the Offspring and Original Cohort participants were younger ranging from 40-50 years old. Correlation coefficients for iCVH in offspring-mother dyads were slightly higher than those of the offspring-father dyads.

Table 4. 13
Pearson correlation coefficients matrix for iCVH metrics for Original and Offspring matched/mismatched at different exam periods

	Parents (mother and/or father)					
Offspring iCVH at exam	iCVH exam 1	iCVH exam 3	iCVH exam 5	iCVH exam 7	iCVH exam 9	iCVH exam 11
iCVH exam 2 n=2029	**0.24**					
iCVH exam 3 n=2111	0.24	**0.25**				
iCVH exam 4 n=2269	0.23	0.24	**0.23**			
iCVH exam 5 n=2197	0.20	0.21	0.20	**0.18**		
iCVH exam 6 n=1968	0.24	0.23	0.22	0.20	**0.21**	
iCVH exam 7 n=1669	0.18	0.16	0.17	0.17	0.16	**0.17**
	Mothers iCVH					
Offspring iCVH at exam	iCVH exam 1	iCVH exam 3	iCVH exam 5	iCVH exam 7	iCVH exam 9	iCVH exam 11
iCVH exam 2 n=2037	**0.27**					
iCVH exam 3 n=1737	0.26	**0.28**				
iCVH exam 4 n=1800	0.23	0.26	**0.25**			
iCVH exam 5 n=1736	0.18	0.22	0.20	**0.21**		
iCVH exam 6 n=1554	0.20	0.21	0.20	0.21	**0.20**	
iCVH exam 7 n=1319	0.13	0.14	0.14	0.13	0.13	**0.17**
	Fathers iCVH					
Offspring iCVH at exam	iCVH exam 1	iCVH exam 3	iCVH exam 5	iCVH exam 7	iCVH exam 9	iCVH exam 11
iCVH exam 2 n=1945	**0.18**					
iCVH exam 3 n=1598	0.19	**0.17**				
iCVH exam 4 n=1715	0.17	0.15	**0.16**			
iCVH exam 5 n=1625	0.18	0.14	0.16	**0.13**		
iCVH exam 6 n=1422	0.20	0.16	0.18	0.14	**0.13**	
iCVH exam 7 n=1123	0.17	0.14	0.16	0.16	0.14	**0.13**

Note: sample size for each exam is for paired exam cycles, the outmost diagonal correlations

Statistical Analysis for Hypothesis 1B

All linear regression analyses were conducted after merging the offspring-parents' dyads. Table 4.14 shows raw and multivariable-adjusted linear regression coefficients (β) at each exam cycle. BMI, blood pressure, smoking, blood glucose and total cholesterol were the dependent variables. The parents iCVH was the main independent variable. The regression coefficient β represents the change in Offspring iCVH for each unit increase in parental iCVH. Ideal cardiovascular health, which ranges from 0-10, was modeled as a continuous variable. The hypothesis proposed that was parental iCVH would be a positive predictor of offspring iCVH. Notably, all the slopes for iCVH for parents paired with their offspring were positive and statistically significant at $p<0.001$ in both raw and multivariable models, meaning that an increase in parents iCVH is associated with an increase in the offspring iCVH. To put this in perspective using Model 2 regression coefficients/slope (β) for paired exams 3 was 0.3 (95% CI=0.18-0.33, $p<0.001$), meaning that for every 1-unit increase in parent iCVH (on a iCVH score of 0-10), offspring iCVH was increased by 0.3 units, accounting for age, sex and education level. In the same model (not shown in table), the higher the offspring age, the lower the iCVH (β=-0.05, 95% CI= -0.06 to -0.04, $p< 0.001$), female offspring had 15% lower iCVH than male offspring counterpart ($p< 0.001$), and offspring with college education had 31% higher iCVH compared with those with less than a college degree.

Stratifying offspring iCVH relationships by parents' gender revealed slightly contrasting results in raw and adjusted models. For instance, in Model 1 (unadjusted), offspring-mother dyads had a higher iCVH (β=0.31, 95% CI=0.27-0.37, $p<0.001$) than the

offspring-fathers' dyads (β=0.21, 95% CI=0.16-0.27, p<0.001). However, in Model 2 (adjusted for age, sex and education), offspring-father had a higher relationship (β=0.18, 95% CI=0.13-0.22, p<0.001) than offspring-mother dyads (β=0.17, 95% CI=0.12-0.22, p<0.000).

Table 4. 14
Linear regression coefficients showing the relationship between parents iCVH and offspring iCVH at each paired exam cycle

	Model 1				Model 2			
Parent/offspring exams	**N**	**B**	**95% CI**	**P value**	**n**	**β**	**95% CI**	**P value**
iCVH exam 1/2	2429	0.34	0.28-0.39	0.000	2423	0.22	0.17-0.27	0.000
iCVH exam 3/3	2111	0.34	0.27-0.42	0.000	1876	0.26	0.18-0.33	0.000
iCVH exam 5/4	2269	0.32	0.24-0.39	0.000	1991	0.23	0.16-0.30	0.000
iCVH exam 7/5	2197	0.25	0.17-0.32	0.000	1917	0.20	0.13-0.27	0.000
iCVH exam 9/6	1968	0.27	0.21-0.33	0.000	1724	0.23	0.17-0.29	0.000
iCVH exam 11/7	1669	0.21	0.14-0.27	0.000	1404	0.19	0.12-0.26	0.000

Note: Model 1, unadjusted; Model 2, adjusted for offspring age, sex, education

Overall, offspring regression coefficients for iCVH analyzed as a continuous variable were largely similar by gender of the parent. The coefficient of determination (R^2), i.e., the proportion of variability explained by the model explanatory variables was highest in the earlier exam cycles (i.e., R^2>0.25 when both parents and offspring were younger) indicating the strength of parents-offspring's iCVH strength of relationship is stronger during younger age exam cycles. Correlation due to familial clustering was accounted for in all regression models. Bootstrapping using multiple repetitions of 50-1000 random samples were used to confirm whether there was deviation between estimates with and without accounting for familial clustering.

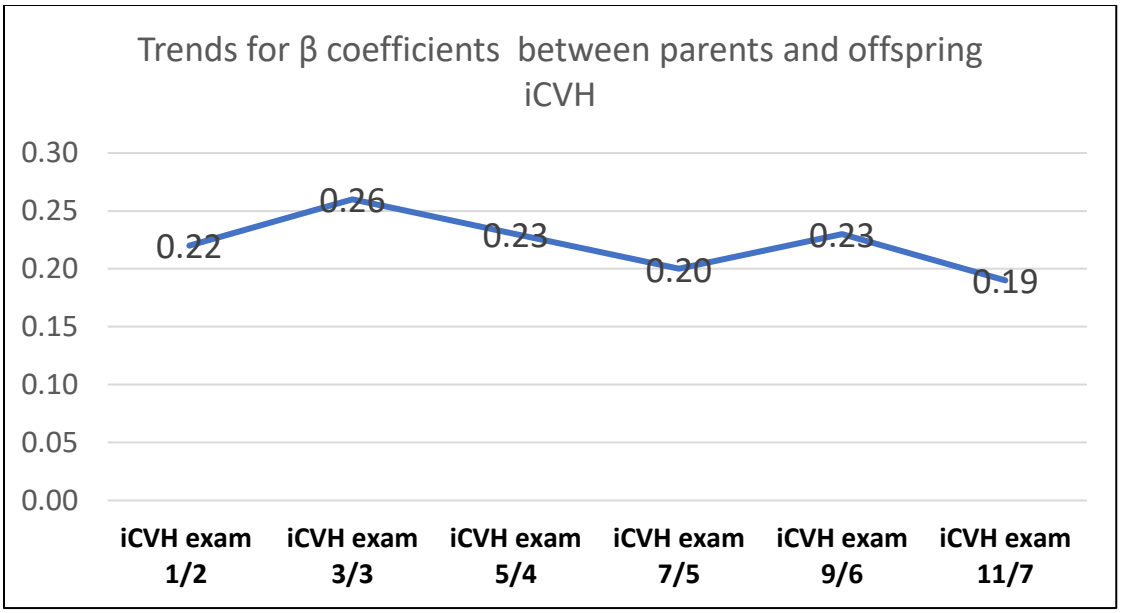

Figure 4. 4. Line graph to show trends of iCVH multivariable regression coefficients for offspring and parent iCVH across exam cycles

Supplemental statistical analysis for aim 1 hypothesis 1B. Additional analysis of iCVH as an ordinal variable using AHA criteria "poor" [0], "intermediate" [1] and "ideal" [2]). are presented in the next Table 4.15. Figure 4.4 below shows linear trends of iCVH for the relationship of parents and Offspring. Proportional odds model, also known as cumulative logit model for ordered logistic regression was used to assess the relationship between offspring and parents iCVH. Prior to statistical analysis, the proportional odds assumption that the slopes for each outcome across each level of response variable are similar was assessed (Hedeker, 2015). The Brant test of parallel regression assumption was not statistically significant (i.e., paired exam 2-1, p= 0.732) providing evidence that the assumption of proportional odds model was not violated (Williams, 2018). Analysis was conducted similar to that for hypothesis 1B where Model 1 was not adjusted for confounding, but Model 2 was adjusted for offspring demographic characteristics, age, sex, educational

level attained. To account for correlation due to familial clustering, regression models were run using the 'cluster' option in STATA with Family ID as the cluster variable.

Table 4.15 presents proportion odds model results examining the relationships between ordinal offspring and parents' iCVH coded in three levels of "poor" (score of≤4) "intermediate" (score of 4-9), and "ideal" (score of ≥10) using a mathematical formula $\mathbf{P(Y \geq j|}\boldsymbol{X_1}\mathbf{)} = \frac{1}{1+\exp\left[-(\boldsymbol{\alpha_j} + \boldsymbol{\beta_1}\, \boldsymbol{X_1})\right]}$ (Kleinbaum & Klein, 2010), where **P(Y≥j|X₁)** is probability of ordinal outcome (Y) with j levels (0,1,2) and independent variables (X_1). See substituted model $\boldsymbol{P(offiCVH =}$

$$\frac{1}{1+\exp\left[-(\boldsymbol{\alpha_{o,1,2}} + \boldsymbol{\beta_1}\mathbf{PiCVH} + \boldsymbol{\beta_i}\, \boldsymbol{off}\ (\boldsymbol{age,sex,educ})\right]}$$

Note that only iCVH with five metrics (BMI, blood sugar, blood pressure, blood cholesterol and smoking) was considered for this analysis (as explained previously) and excluded physical activity and diet variables since they were not available for all exam periods.

Table 4. 15
Proportional odds model for relationship of parents and offspring 5-metric iCVH by AHA classification

	Model 1				Model 2			
Parent/offspring exams	**N**	**Odds R**	**95% CI**	**P value**	**n**	**Odds R**	**95% CI**	**P value**
iCVH exam 1/2		Ref (poor iCVH)						
Intermediate	2429	1.65	1.33-2.03	0.000*	2423	1.63	1.31-2.01	0.000*
Ideal		5.61	3.18-9.90	0.000*		3.51	1.91-6.45	0.000*
iCVH exam 3/3		Ref (poor iCVH)						
Intermediate	2111	1.75	1.38-2.23	0.000*	1876	1.71	1.31-2.22	0.000*
Ideal		3.65	2.00-6.68	0.000*		2.12	1.10-4.36	0.026*
iCVH exam 5/4		Ref (poor iCVH)						
Intermediate	2269	1.83	1.45-2.32	0.000*	1991	1.85	1.45-2.36	0.000*
Ideal		1.50	0.65-3.44	0.343		0.63	0.25-1.58	0.325

iCVH exam 7/5		Ref (poor iCVH)						
Intermediate	2197	1.57	1.23-2.01	0.000*	1917	1.75	1.36-2.26	0.000*
Ideal		6.93	2.81-17.08	0.000*		3.57	1.25-10.26	0.018*
iCVH exam 9/6		Ref (poor iCVH)						
Intermediate	1968	1.90	1.46-2.48	0.000*	1724	2.16	1.61-2.89	0.000*
Ideal		5.44	2.46-12.03	0.000*		2.50	1.20-5.23	0.015*
iCVH exam 11/7		Ref (poor iCVH)						
Intermediate	1669	1.63	1.23-2.15	0.001*	1453	1.61	1.20-2.17	0.002*
Ideal		4.30	1.63-11.37	0.003*		4.34	1.46-12.94	0.008*

Note: Model 1, unadjusted; Model 2, adjusted for offspring age, sex, education, 5-metric iCVH used to run models; *p values significant at $p<0.05$

Table 4.15 above shows proportional odds ratios for ordered categorical iCVH for offspring (dependent variable with 'poor' iCVH as the referent category) and parents matched by exam cycle. The odds ratio results consistently show the increased likelihood of offspring achieving higher iCVH ("intermediate" or "ideal") when the parents have similar level of iCVH levels. The odds of offspring of parents with ideal iCVH attaining ideal iCVH is two-to-fourfold accounting for age, sex and education. In Table 4.15 in matched parents' exam cycle 1 and offspring exam cycle 2: among offspring of parents with ideal iCVH, the odds of offspring having ideal iCVH was 3.51 times higher compared with offspring of parents with "poor" iCVH, after adjusting for age, sex and education. In other words, the higher the parental iCVH metric, the higher the odds of offspring achieving a higher iCVH across different exam periods in the lifespan. The odds ratios reveal a notable pattern that ideal parental iCVH contributes higher offspring iCVH than intermediate iCVH.

Statistical Analysis of Hypothesis 2A

It was hypothesized that iCVH metrics were important predictors of CVD DALYs. Model 1 and Model 2 were fitted at each exam cycle, where Model 1 was comprised of a simple regression regressing CVD DALYs with iCVH coded as a continuous predictor. Model 2 expanded Model 1 to additionally adjust for age, education, sex and income [see Tables 4.16 & 4.17].

Table 4.16 show that for the parents, DALYs and iCVH were inversely associated. For every one-unit increase in iCVH, there was a reduction in CVD DALYs. For instance, at exam cycle 1, CVD DALYs decreased by at least 0.4 years for every one unit increase in iCVH adjusted for age, sex and education. The analysis revealed a stronger inverse association between iCVH and CVD DALYs at earlier exam cycles when the parent participants were younger in age than later exam cycles. At exam cycles 1 and 11, β coefficients were larger at exam cycle 1, β (SE)=0.4(SE=0.04) $p<0.001$; vs. 0.2(SE=0.04) years, $p<0.001$, corresponding to a 50% reduction in the regression slope. Notably, both raw and multivariable models for parents iCVH β coefficients were statistically significant ($p<0.001$) in all exam cycles.

Table 4. 16
Linear regression coefficients for the relationship between iCVH and CVD DALYS for Original Cohort

	Model 1				Model 2			
Parent exam	**n**	**β**	**SE**	**P value**	**n**	**β**	**SE**	**P value**
iCVH exam 1	2540	-0.36	0.04	0.000	2478	-0.44	0.04	0.000
iCVH exam 3	2171	-0.35	0.04	0.000	2121	-0.44	0.04	0.000
iCVH exam 5	2265	-0.27	0.04	0.000	2203	-0.33	0.04	0.000
iCVH exam 7	2114	-0.21	0.04	0.000	2060	-0.25	0.04	0.000
iCVH exam 9	2031	-0.22	0.04	0.000	1978	-0.24	0.04	0.000
iCVH exam11	1626	-0.15	0.04	0.000	1579	-0.16	0.04	0.000

Note: Model 1, unadjusted; Model 2, adjusted for parents age, sex, education

Table 4.17 results show even more robust iCVH slopes for offspring compared with the slopes for the parents in Table 4.16 above. As a predictor for DALYs in offspring exam cycle 1, for every one-unit increase in iCVH, DALYS decreased by 1.2 (SE=0.11), p <0.001 while accounting for age, sex and education. More robust slopes were observed in earlier exam cycles than latter cycles. All β-coefficients for multivariable models for offspring were statistically significant (p<0.001). Offspring iCVH, age and sex were significant predictors for CVD DALYs (p<0.05) in all exam cycles.

Table 4. 17
Linear regression coefficients for the association of iCVH and CVD DALYS among Offspring Cohort

	Model 1				Model 2			
Offspring exam	**N**	**β**		**P value**	**n**	**β**	**SE**	**P value**
iCVH exam 2	2507	-1.40	0.09	0.000	2501	-1.23	0.11	0.000
iCVH exam 3	2421	-1.34	0.09	0.000	2146	-1.23	0.11	0.000
iCVH exam 4	2466	-1.34	0.09	0.000	2159	-1.20	0.11	0.000
iCVH exam 5	2476	-1.18	0.09	0.000	2150	-1.09	0.10	0.000
iCVH exam 6	2263	-1.12	0.10	0.000	1983	-1.08	0.11	0.000
iCVH exam 7	2220	-0.84	0.10	0.003	1932	-0.72	0.11	0.000

Note: Model 1, unadjusted; Model 2, adjusted for offspring age, sex, education

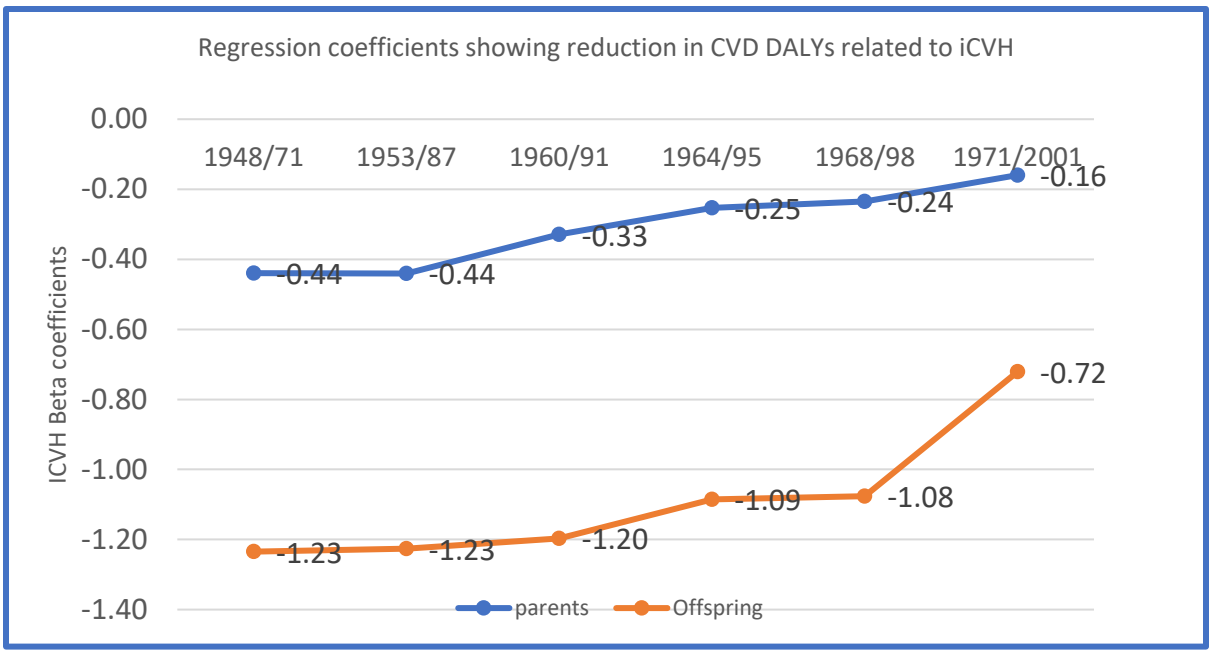

Figure 4. 5. Multivariable-adjusted linear regression coefficients comparing relationship of iCVH and CVD DALYs for parents and offspring participants
Note: Dependent variable, CVD DALYs; independent variable, iCVH; other covariates age, sex, education for each cohort

Figure 4.5 comparing β-coefficients for multivariable models show a similar pattern of iCVH relationship with CVD DALYs for parents and offspring, with a higher reduction in CVD DALYs observed among the offspring. Further analysis using categorical iCVH variables showed that those with ideal iCVH had higher reduction in CVD DALYs than those with intermediate iCVH. For instance, a multivariable adjusted linear regression model in offspring's exam 2, having ideal iCVH was associated with a reduction in CVD DALYs by 5 years (95% CI -6.92 to -3.09) compared with 2 years (95% CI -3.80 to-1.4) associated with intermediate iCVH, $p<0.001$.

Statistical Analysis of Hypothesis 2B

A t-test was used to examine whether offspring of parents with low iCVH will have higher mean CVD DALYs compared to the mean CVD DALYs for offspring of parents with high iCVH. Table 4.18 below presents mean differences of CVD DALYs for offspring of parents with high and low iCVH. The 10-point iCVH for parents was transformed into a binary classification, i.e high iCVH (≥6 scores) versus low iCVH (≤5 scores). The null hypothesis was rejected since there was a statistically significant relationship between mean CVD DALYs of offspring of parents with high iCVH versus mean CVD DALYs of offspring of parents with low iCVH in two exams (exam 2 and 4). Offspring of parents with high iCVH had lower mean CVD DALYs compared with offspring of parents with low iCVH. Even where there was no statistical significance, offspring of parents with low iCVH had higher CVD DALYs compared with offspring of parents with high iCVH.

Table 4. 18
Mean CVDDALYS for offspring of parents with high versus low iCVH

Offspring of Parents with Low vs High iCVH		Offpsring (n)	Mean (SE) DALYS	95% CI	p value
Exam 2	Low iCVH	1426	6.1 (0.3)	5.5-6.6	0.001*
	High iCVH	1111	4.7 (0.3)	4.2-5.3	
Exam 3	Low iCVH	1190	5.8 (0.3)	5.2-6.4	0.078
	High iCVH	1101	5.1 (0.3)	4.5-5.7	
Exam 4	Low iCVH	1531	5.6 (0.3)	5.1-6.1	0.006*
	High iCVH	938	4.5 (0.3)	4.0-5.1	
Exam 5	Low iCVH	1446	4.9 (0.2)	4.4-5.4	0.733
	High iCVH	813	4.8 (0.3)	4.1-5.4	
Exam 6	Low iCVH	1159	5.0 (0.3)	4.4-5.5	0.106
	High iCVH	896	4.3 (0.3)	3.8-4.9	
Exam 7	Low iCVH	1083	4.8 (0.3)	4.3-5.3	0.109
	High iCVH	717	4.1 (0.3)	3.5-4.7	

*P value computed from ttest, significant at α <0.05

CHAPTER 5

DISCUSSION OF FINDINGS

The main aim of this study was to describe the familial or intergenerational clustering and relationship between parents-offspring iCVH and CVD DALYs. Chapter 5 presents the major findings of this dissertation study. An account of the importance of the findings as well as extrapolating the findings to similar previous studies is presented. Particular focus is given to results on familial aggregation or clustering of iCVH and CVD DALYs that were examined when Original and Offspring Cohorts had similar mean age distribution. Data analyzed were derived from an eligible sample of Original (n=2,734) and Offspring (n=3,492) Cohorts of FHS both with mean age at baseline of 43 years in both cohorts. Both cohorts were balanced for the proportion of women and men, though the proportion of women was slightly larger than the proportion of men.

Summary of Major Findings

It was hypothesized that iCVH of a parent is a predictor for iCVH of the offspring and that attainment of higher levels of iCVH was associated with fewer CVD DALYs for both parents and offspring. This study showed that offspring iCVH were significantly linearly related to iCVH of parents at similar age. This study revealed that offspring of parents with ideal iCVH had increased odds of achieving "ideal" iCVH by up to four times compared with offspring of parents with "poor" iCVH. CVD DALYs were associated with lower levels of iCVH categories for both Original and Offspring Cohorts. Offspring of parents with high iCVH had lower mean CVD DALYs compared with offspring of parents

with low iCVH, indicating a desired intergenerational effect of parents' transference of cardiovascular health benefits to their children.

Interpretation and Significance of the Findings

To our knowledge, this is the first study that has investigated whether long term trends of how parental iCVH, as classified by AHA, are clustered with biological offspring who were examined at similar ages throughout most of the adult lifespan. The study adds new insights on the protective association of high iCVH on CVD DALYs, a desirable trait in individuals in a population and policy makers in behavioral medicine. We studied the association of iCVH metrics such as normal BMI, physical activity, healthy diet, non-smoking, normal blood pressure, blood cholesterol and blood glucose. The study showed that a small proportion of individuals attained the recommended levels of iCVH in both Original and Offspring Cohorts. Most importantly, the attainment or lack of attainment of iCVH thereof followed similar patterns within paired parent-offspring dyads over identical life-time which indicates familial clustering of identical iCVH scores between parents and offspring.

Similarities of iCVH metrics within the family clusters (familial aggregation of iCVH) is significant in CVD epidemiology suggesting that CVD prevention efforts can yield positive results if implemented within family environments to strengthen CVD prevention efforts targeting parents and their children. As observed in this study, the seven iCVH were strongly associated with CVD DALYs for each cohort and at each exam cycle. Indeed, the higher the iCVH, the lower the CVD DALYs for the observed participants. This inverse relationship between iCVH and CVD DALYs for parents and offspring respectively shows that addressing health behaviors or risk factors could help increase CVD-free survival. It is

encouraging to note that higher iCVH scores of parents (either having "intermediate" or "ideal" iCVH scores) were positively related to similar higher iCVH among the offspring. This indicates that offspring could achieve higher iCVH if their parents achieved similar levels of iCVH. These findings are fundamental for promoting parental involvement in their offspring cardiovascular health. Efforts to track iCVH metrics are in line with the AHA's 2020 Impact Goals of improving cardiovascular health and reducing stroke mortality (AHA, 2013).

Evidence from Literature on Attainment of iCVH Metrics

This dissertation study revealed that participants of the Framingham Original and Offspring Cohorts had a very low prevalence of iCVH [i.e, attaining either all five (0.6-10% for both Cohorts) or all seven iCVH metrics (0% for both Cohorts) at recommended levels]. Despite several FHS cohort participants being born several decades ago, results of attaining ideal iCVH does not differ from those of the general American population in recent studies which have estimated that only small proportion of Americans (<2%) attain all seven iCVH metrics (AHA, 2017a). BMI was one of the iCVH metrics investigated. The mean BMI and AHA BMI categories revealed a consistent pattern suggesting offspring had a higher mean BMI and lower proportion attaining "ideal" category of BMI. There was a general tendency of mean BMI increasing with increasing age-group across exam cycles for each cohort. These findings are not surprising. Several studies have consistently shown that the general trend of BMI increased for all age groups since the 1960s to date (Centers for Disease Prevention and Control, 2016b) . As much as there was lack of data on national surveys on

BMI studies before 1960s (von Hippel & Nahhas, 2013), it is evident that overweight and obesity prevalence was notably lower than current estimates.

In the current study, the prevalence of obesity (i.e. "poor" BMI category) at each exam cycle for parents and offspring was considerably lower (13-31%) than 2016 estimates (39.6%). Studies report that the high prevalence of obesity (including childhood obesity) is a recent phenomenon starting in the early1990s where prevalence of adult obesity among the U.S population rose from 13.4% in 1960s to 30.5% in 1999 and 39.6% in 2016 (Centers for Disease Prevention and Control, 2016b). Notably, there has been an upward shift in socioeconomic status since the 1960s. Original Cohort participants had lower levels of educational attainment than the Offspring Cohort as shown Table 1; a huge shift reflecting the social structure then when most mothers did not work outside of the home. Parents had lower socioeconomic status (SES) than offspring as evidenced by high proportion having low cadre jobs (Table 1). A possible explanation why a larger proportion of FHS Original Cohort participants achieved "ideal" BMI than the Offspring Cohort could be that Offspring Cohort had a higher SES than their parents. Studies have shown that up to mid-20th century in the US, being overweight was positively associated with wealth status. This association then could explain the lower proportion of Original Cohort attaining "ideal" BMI compared to Offspring Cohort. This pattern has since shifted as demonstrated by Hruby and Hu (2015) who reported that individuals with lower SES had higher obesity rates compared to higher levels of SES (Hruby & Hu, 2015).

Analysis of blood pressure shown in Table 4.3 revealed striking differences between the proportions of parents and Offspring Cohort with high blood pressure. Up to 37.9% (95%

CI: 36-40%) of parents in exam 1 had high blood pressure (SBP ≥140 or DBP ≥90mmHg "poor") compared with only 17.6% (95% CI: 16-20%) offspring with high blood pressure even though blood pressure was assessed at exam cycles at which both cohorts had similar age. The proportion of parents with hypertension would even be higher for parents (>60%) if the current standards of hypertension (SBP≥130 or DBP≥80mmHg) were applied, but this criterion of hypertension was not in place during the Cohorts' selected exam cycles. Attainment of most of the iCVH metrics at "ideal" levels declined with age, similar to the patterns observed in other observational studies showing that attainment of most ideal health factors especially blood pressure, glucose and cholesterol declined prominently with age (Shah et al., 2015).

Findings that offspring had lower proportions of high blood pressure are counterintuitive. It was expected that offspring would have higher blood pressure than the Original Cohort owing to epidemiological evidence suggesting that hypertension clusters within families and the risk of hypertension is higher for offspring of hypertensive parents genetic link and associated markers for hypertension (Andersson et al., 2016; Lieb Wolfgang et al., 2008). However, awareness, screening, diagnosis and treatment of hypertension has made major strides in the last 50 years, especially with the significant knowledge generated from the FHS. Since little was known about hypertension epidemiology in the 1950s (Dawber et al., 1951), it is expected that parents in the FHS would have higher blood pressure than their offspring regardless of whether offspring of parents with hypertension might have higher risk of having hypertension (Andersson et al., 2016; Lieb Wolfgang et al., 2008). It is not surprising that the proportion of parents who smoked was higher than the

proportion among offspring (Table 4.6) in all exam cycles, and consequently conferring a higher risk of hypertension given that smoking is a significant risk factor for hypertension and CVD (Messner Barbara & Bernhard David, 2014; Virdis, Giannarelli, Neves, Taddei, & Ghiadoni, 2010). It is established that adult prevalence of smoking in the 1950s (53%) to 70s (38%) was similar to the proportion of smoking among parents' cohort ("poor" category) (Table 4.6). However, the prevalence of smoking declined significantly since 1970s (National Institutes of Health, 1979). In addition, similar patterns of declining prevalence of total cholesterol were observed. Parents had higher mean total cholesterol compared with the Offspring Cohort, i.e., a higher proportion [>40%] of Offspring Cohort achieved "ideal" levels of total cholesterol at all exam cycles compared with <40% among parents. These observations can be explained by higher risk factors for CVD among parents versus Offspring Cohort in the FHS which, as described above, could be attributed to poor awareness and treatment of CVD management in the early mid-20th century.

The prevalence of diabetes in both cohorts was low (0.7-8.8%) and increased with increasing age (i.e. at later exam cycles; Table 4.5). While this increase is to be expected, offspring had significantly higher blood glucose than the parents in all exam cycles suggesting that there might have been amplified effects of offspring of parents with high blood glucose as revealed by Wang and Colleagues (2015) who found that parental history of diabetes was associated with presence of type 2 diabetes among the offspring (C. Wang et al., 2015). Physical activity data available at two exam cycles showed that Original and Offspring Cohorts were more physically active at younger age, i.e. at earlier exam cycles, but the proportion of "ideal "activity levels declined with age as shown in Table 4.7. Notably,

FHS participants were more physically active compared with today's standards (Shortreed et al., 2013). Diet data were the most intriguing amongst all other iCVH metrics. Parents' diet data comprising of five food groups- fruits/vegetables, whole grains, nuts/legumes, low-fat milk/unsaturated fat, and meats/poultry, were collected later in the Original Cohort exam cycles not included in the analysis. However, we assumed that dietary patterns did not substantially change over time; thus, it was decided to include diet data not collected at the selected exam cycles. A review of multisite longitudinal and cross-sectional studies suggests that dietary patterns of individuals may not change so much with increasing age. Some studies suggest that individuals aged 65 years and older might have more healthy eating habits consisting of consuming less red meats, more fruits and vegetables than younger individuals (Produce for Better Health Foundation, 2015; Wakimoto & Block, 2001). While use of averaged diet variable at all exams cycles is justifiable, some studies suggest that older adults have reduced intake of total energy and protein (Yannakoulia et al., 2018).

As expected from multiple studies on dietary patterns in the United States, vegetable and fruits intake "ideal" category was the least achieved metric in both Original and Offspring Cohorts. For instance, in 2007-2010, 76% and 87% of the US population did not meet recommended vegetable and recommended fruit consumption, respectively (Centers for Disease Prevention and Control, 2015b). More than 98% of FHS participants did not meet recommended vegetable and fruits consumption (Table 4.8). Other studies found that poor diet is attributable to the low attainment of iCVH in children and adults in the US (American Heart Association, 2017c). Not achieving ideal diet score in both Cohorts (Table 4.9) is comparable to findings in other studies which showed consistently very low (<1%)

attainment of the seven iCVH metrics at "ideal" levels (American Heart Association, 2018b; Folsom et al., 2011).

Attainment of Ideal Cardiovascular Health and Familial Aggregation

There is evidence that the proportion attaining all the seven iCVH metrics is extremely low in US adult and children. This dissertation examined the proportion attaining all seven and five iCVH metrics for parents and offspring separately. While no participant in any cohort attained all the seven iCVH at "ideal" levels, the proportion achieving all five recommended iCVH metrics at ideal levels was higher among the Offspring than the Original Cohort (for instance, 9.2% vs. 2.1%, $p<0.001$, first paired exam cycle). This finding is not surprising since most studies have shown that less than 2% of the US population meet all seven iCVH metrics at the "ideal" levels (American Heart Association, 2017c; Folsom et al., 2011; Shah et al., 2015; Yang et al., 2012). A study of 12,744 participants aged 45-65 years estimated iCVH of participants in 1987 to 1989 using Atherosclerosis Risk in Communities Study cohort reported that a very small proportion, (0.1%) of the participants, met the seven iCVH metrics (Folsom et al., 2011). Using data from NHANES 2013-2014, the AHA reported even lower iCVH attainment with a negligible proportion of US adults attaining seven iCVH at "ideal" levels (American Heart Association, 2017c). Other studies looking at trends have shown that iCVH is declining in most US adults although some studies reported small increases (Ogunmoroti et al., 2016; Yang et al., 2012). Trends of iCVH between 2011 and 2014 among employees of a large health care organization in South Florida (n=34,746) showed improvement in diet, physical activity, and blood pressure but a decline in BMI, total cholesterol, and blood glucose (Ogunmoroti, et al, 2016). That study revealed small increase

in “ideal” iCVH ranging from 0.3% in 2011 to 0.6% in 2014, [p<0.001] (Ogunmoroti et al., 2016).

Correlation and regression analysis of familial aggregation of iCVH for paired parents and offspring revealed a positive linear relationship between Offspring Cohort iCVH with those of the Original Cohort using five-iCVH metric score (Table 4.13, 4.14), suggesting presence of familial clustering of iCVH. Patterns of achieving “poor”, “intermediate” and “ideal” iCVH score were similar in each cohort (Table 4.10) whether using five-or seven-iCVH metrics, a finding that shows that iCVH is clustered within families and that parents may influence their offspring attainment of iCVH. A matrix of Pearson correlations of parents and offspring iCVH over the exam cycles revealed positive correlations coefficients ranging between r=0.2 and r=0.3. Similar correlation coefficients were observed when the Offspring Cohort was correlated with mothers and fathers separately (Table 4.13). The linear correlations observed are similar to linear correlations observed in other studies which reported parent-offspring correlations coefficients ranging from r=0.24 to r=0.52 for single iCVH metrics such as diet, physical activity. There are no studies which assessed correlations coefficients for all five or seven iCVH metrics (McGowan et al., 2013; Storti, Kristi Leigh, 2007; Y. Wang, Beydoun, Li, Liu, & Moreno, 2011; Yee, Lwin, & Ho, 2017).

Comparison of findings for correlations analysis and multivariate linear regressions yielded similar patterns for parent-offspring iCVH associations. Proportional odds regression analysis using the AHA classification of iCVH metrics (“poor”, “intermediate”, “ideal”) revealed that parental iCVH was associated with a two-to-fourfold the odds for attaining

"intermediate" or "ideal" iCVH levels in the Offspring Cohort, suggesting, as has been shown in other studies, that parents influence the health of their offspring. This finding is consistent with the evidence showing that the CVD health of parents and offspring are intricately associated (Vedanthan et al., 2016). It was also intriguing to note that relative to mothers, the iCVH for fathers at older ages had a larger effect on the Offspring Cohort iCVH metrics, whereas the iCVH for mothers had strongest effect on the Offspring iCVH at younger ages. However, it is important to note that this dissertation did not examine the iCVH for Offspring Cohort in childhood; an age range during which the mothers are likely to have stronger effect on offspring health habits (Dhana et al., 2018; Lawlor et al., 2007). The FHS was not designed to collect data for either parents or offspring during their early childhood years. Furthermore, in this analysis the mean age for Offspring Cohort at first eligible exam cycle (Exam 2) was 40 years.

Very minimal data exist on comparisons of paternal-offspring versus maternal-offspring iCVH differences. A population-based study in Norway (Hunt Study n=36, 538 of father-mother-offspring trios) compared CVD risk factors of offspring and their parents and found positive parent-offspring correlation with respect to blood pressure, blood lipids and glucose and resting heart rate (Vik, Romundstad, Carslake, Smith, & Nilsen, 2014). An important question to ask here is which parent (mother or father) would strongly influence offspring iCVH of their offspring, for instance if mothers influence would be stronger while in utero or fathers through genetic effects or the influence is mainly due to epigenetic effects. Epigenetic effects in offspring are known to be caused by shared family environment and lifestyle while some maternal-offspring theories such as the fetal overnutrition hypothesis, though contradictory, postulates that mothers directly influence fetal environment including

predisposition of offspring to CVD (Lawlor et al., 2007; Veena, Krishnaveni, Karat, Osmond, & Fall, 2013). The design of FHS could not establish intergenerational transmission of iCVH due to fetal overnutrition or exposure to other adverse factors in the intrauterine environment since maternal and paternal factors were not measured during or anytime close to pregnancy. In addition, most familial studies support shared family environment, lifestyle and epigenetic factors for parent-offspring CVD risk (Veena et al., 2013).

There is growing scientific evidence suggesting parent-offspring linear correlations of CVD risk factors such as BMI, physical inactivity and poor diet (Fuemmeler et al., 2011; Johnson et al., 2012; Massarani et al., 2015). This evidence, combined with findings from other studies, that suggest that development of atherosclerotic and hypertensive processes start early in life (Hayman & Worel, 2015; Juonala et al., 2010; Loria et al., 2007) underscoring the need for increased studies focusing on familial iCVH over the lifespan. As explained above, the pathway for parent-offspring CVD is complex. Socioeconomic factors such as parental education and household income have been shown to effect that pathway (Martin et al., 2015). Parental and/or individual offspring attainment of higher education and income, have been shown to be associated with favorable health outcomes throughout the life course (P. A. Braveman et al., 2010, 2011; P. Braveman et al., 2011). Results of this study point to some influence of socioeconomic factors on iCVH. Father-offspring clustering of iCVH was found to be more robust than clustering for mother-offspring dyads. While household income is inseparable within family units, it was observed that fathers were more educated and with a higher income than their mothers. Epidemiological studies that measure childhood socioeconomic status often use fathers' education as the proxy for the childhood socioeconomic status and observe that parental socioeconomic status is an important

predictor of offspring CVD (Galobardes, Lynch, & Smith, 2008; Loucks et al., 2009). To demonstrate the robustness of parental education in intergenerational transfer of health, a study involving 1480 parent-offspring dyads in Netherlands revealed that higher parental educational attainment was associated with healthier family clusters, with notable improvements in physical activity and healthy diet (Rodenburg et al., 2013). In this dissertation, it was hypothesized that parental education was the main predictor for intergenerational transmission of iCVH from parents to offspring.

Relationship Between CVD DALYs and iCVH

The health benefits to the individual for attaining iCVH should not be underestimated. Several studies continue to provide evidence that having certain iCVH metrics such as consumption of healthy diet, engaging in physical exercise, not smoking throughout lifespan can promote longevity and morbidity-free survival, health-related quality of life even in old age, and lower costs of healthcare in old age (Chakravarty et al., 2012; Hozawa et al., 2007); A Taiwan longitudinal study of men and women aged 60 years and older showed that the combined effect of health factors on functional disability attributed to one or more healthy behaviors contributed 15% to 75% reduction in functional disability (Liao et al., 2011) while another study on participants aged 65 years of age had 8.3 years delayed onset of moderate disability (Chakravarty et al., 2012). In the Atherosclerosis Risk in Communities (ARIC) study with four combined health factors (total cholesterol, blood pressure, no diabetes and never smoked) documented that participants with optimum combined health factors were 88% less likely to die due to CVD (HR 0.12, 95% CI 0.04-0.31) compared with those with any elevated risk factors (Hozawa et al., 2007). Another

study designed to evaluate the relationship between iCVH score and CVD biomarkers among the FHS Offspring Cohort concluded that participants with higher iCVH score had more favorable CVD biomarkers such as higher circulating concentrations of natriuretic peptides (Xanthakis et al., 2014). The study also found an inverse relationship between iCVH and subclinical disease, where those with higher iCVH score had a lower risk of CVD. All these studies support the premise that iCVH score if favorable for increasing CVD-free life span and reduction of CVD risk.

Results of CVD burden in this study was reported as number of CVD events per exam cycle and CVD DALYs for a fixed period for parents and offspring. The incidence of CVD events for parents were higher than their offspring (see Table 4.11). It was expected that the offspring would have equal or higher proportion of CVD events than their parents. However, it is notable that FHS parents lived as adults during a period when cardiovascular medicine had just started to receive more attention. In fact, the rise of CVD prevalence in the US during early 20th century necessitated National Heart, Lung and Blood Institute to design and establish the FHS, a location at which they previously had conducted a successful Tuberculosis screening project (Matson, 1924). There were limited scientific studies on the diagnosis and treatment of heart disease and other CVDs in early 1900s to 1950s. Coronary atherosclerosis was the leading cause of unprecedented coronary heart disease mortality with prevalence of coronary atherosclerosis up to 77% in 1950 (Dalen, Alpert, Goldberg, & Weinstein, 2014). During that period, CVD was diagnosed using autopsies because CVD was often not assessed or detected and treated during ones' life due to lack of sophisticated technology currently used to diagnose and treat CVD. The Surgeon General's report in 1950

reported that the prevalence of cigarette smoking, major risk factor for CVD, peaked at 53% (Dalen et al., 2014; National Institutes of Health, 1979). It would therefore be expected that FHS Original Cohort (parents) which was recruited in 1948, a period with high prevalence of undiscovered CVD risk factors such as smoking and coronary atherosclerosis would consequently have a higher CVD incidence than Offspring Cohort participants who enjoyed a more advanced CVD management.

The follow-up period for estimating CVD DALYs for both Cohorts extends over a longer time period than the selected iCVH exam cycles to obtain a longer follow-up time of 43 years. The events follow-up period of 43 years was used since the events files had CVD events recorded up to the year 2014. Most of the parents' life expectancy was considerably longer than the current life expectancy for (81 years for females and 76 years for males). According to trend data on US life expectancy (National Center for Health Statistics, 2018), the life expectancy of persons born in 1900, such as the FHS parents cohort was 47.3 years meaning by 1948, about half of the Framingham sample should have been dead and presumably could not join the study. The mean age of this initial Exam 1 group of 5209 was 44 years, producing a mean birth year of 1906. It is possible the original estimates of life expectancy in 1900s were inaccurate given that most of the Framingham subjects were still alive, having survived all the natural and manmade disasters and disease outbreaks that had occurred. This informed the decision not to use life expectancies of 1900s and use the current 2016 across the board for parents and offspring, so that the cohorts' DALYs could be compared with DALYs calculated from recent data.

The burden of CVD as was measured using CVD DALYs. Results suggest that for both parents and the offspring, iCVH was significantly negatively associated with CVD DALYs. This association was found at most of the exam cycles. This finding was expected since, as explained earlier in the discussion section, combination of healthy factors are negatively associated with incident CVD and CVD mortality over lifespan (Akesson et al., 2007; Hozawa et al., 2007; Ogunmoroti et al., 2017). Overall, offspring had higher CVD DALYs rate per 100, 000 population compared with parental rate (offspring had 550, 273 CVD DALYs vs.176, 564 for parents). Compared with a recent study, these rates are much lower than estimates from the Global Burden of Disease which showed Texas had the highest CVD DALYs rate of 874, 588 DALYs in 1990 (2018 Global Burden of Cardiovascular Diseases Collaboration et al., 2018). The mean age of onset of CVD disease for most parents was higher for parents than offspring. This possibly indicates why offspring had higher CVD DALYs even though they had fewer number of CVD events overall since DALYs are usually driven by the number of years someone lives with a condition or dies prematurely. However, the main differences in CVD DALYs rates for FHS participants and the US GBD study are not comparable since the study was conducted non-contemporaneously versus the FHS (1990-2016 for US GBD study vs. 1948-2014 for FHS). FHS participants lived in a period when CVD morbidity and mortality was higher than recent and current trends. It is important to also note that both Cohorts did not receive identical CVD treatment or care at the exam cycles studied. This could possibly explain some of the differences in the CVD DALYs. Interestingly, most of the parents in the FHS, by a huge margin, outlived the prevailing the life expectancy of their time of 47 years for1900 and 68.2 years for 1950 (Health, United States, 2016). This phenomenon whereby a substantial proportion of parents in FHS outlived

the expected life expectancy of 81 years for women and 76 years for men has been reported elsewhere (Terry et al., 2007). In that 2007 study of 1697 offspring, the proportion with one, or both parents surviving to 85 years or older was 47%, and 11%, respectively. In the current study, however, there was no way to account for non-overlapping of treatment and care of CVD in exam periods that were not at the same time, and the effects due to aging of the cohort with added benefits of receiving advanced cardiovascular care that was not comparable to the population not in the FHS.

One of the possible explanations the FHS Original Cohort had longer than expected life expectancy or had lower CVD DALYs compared with the general population, as noted above, might be due to age-period-cohort effects. Age effects refer to the changes that are bound to happen as individual progresses through their life course; cohort effects refer to changes of health status of a society especially due to new interventions and period effects refer to changes in health care by the virtue of lapse in time (Burton-Jeangros, Cullati, & Sacker, 2015). It is expected that age-period-cohort effects serve as potential confounders for an intergenerational study such as FHS. The confounding is influenced via socioeconomic shifts and medical discoveries and other historical and health-related events such as obesity epidemic or disease outbreaks that could potentially contribute to either optimal or suboptimal cardiovascular health over time. Statistically accounting for age-period-cohort effects is difficult to implement, in fact, many authors cast fundamental doubts on robustness and accuracy of various methods proposed to address age-period-cohort effects (Bell & Jones, 2013; Burton-Jeangros et al., 2015).

Findings of this dissertation support that development of CVD is multifactorial characterized by interplay of genetic, genomic and environmental factors (Vedanthan et al., 2016). Unlike single-gene disorders such as cystic fibrosis or sickle-cell disease, CVD manifests as polygenic or multiple-gene disorder. Genome-wide studies have shown that 10% of the variation of CVD disorders like coronary artery disease is genetic (Bjorkegren, Kovacic, Dudley, & Schadt, 2015). Studies have established that polygenic disorders like CVD are significantly affected by complex interactions of both genetic and potentially modifiable environmental factors (Bjorkegren et al., 2015). These studies report that more than 90% of remaining hereditability of polygenic disorders would be explained by certain environmental factors, a concept known as systems genetics which integrates genomic measures such as DNA, clinical measures such as blood chemistry and environmental factors such as health behaviors (Vedanthan et al., 2016). Thus said, systems genetics provides an advantage of assessing the combined effects of genetics and environmental factors in disease pathways.

The Family Systems Theory is the conceptual model used in this dissertation. Family Systems Theory addresses the two main tenets of systems genetics (clinical measures and environmental factors), which explain a substantial variance of offspring CVD DALYs even in this study. This theory has been used to study intergenerational transfer of iCVH health from parents to offspring, in the understanding of interplay of clinical and environmental factors. The family-systems model, as explained in the methods sections, was triangulated with self-care theory of multiperson units which means that family units are viewed as systems (multiperson units) for interactions to yield certain behaviors that lead to healthy or unhealthy outcomes. Principles of self-care theory for individuals' deliberately actions to meet

their own health goals can be applied to enhance systems theory in sustaining the acquired health behaviors over time (Geden & Taylor, 1999; Taylor, 2001). Very low prevalence of iCVH scores for both parents and offspring, positive linkage of iCVH and CVD DALYs emphasize the importance of implementing family-oriented interventions specifically targeting combined iCVH metrics.

Limitations and Strengths

This dissertation study has several limitations related to the contemporaneousness of the ages of the Original and the Offspring Cohorts at the selected exam cycles. Firstly, it was not possible to compare Original and Offspring Cohorts when they were younger than 20 years old, or parents at child rearing years, and offspring's childhood behavioral patterns. It was assumed that such behavioral interactions of parents and offspring during childhood years would persist in adulthood. However, a study involving younger than 20 years of age would not generate enough CVD events for investigating the role of iCVH on CVD over time. Secondly, unavailability of data on two key variables, physical activity (only available 2 exam for each cohort) and dietary data (3 exam cycles available for Original Cohort outside the matched exam cycle time-period) was a major limitation for deriving 7-metric iCVH. Third, FHS Original and the Offspring Cohorts samples were recruited from a single geographic location of principally middle-class, white individuals hence it is not possible to study racial differences. However, the FHS setting does include several widely separated areas simultaneously, so that the various socioeconomic groups were represented hence includes participants with both high and low SES (Northwestern University, 2013; Tsao & Vasan, 2015). In addition, FHS has contributed to science that is applicable among diverse

multiethnic groups and some of the findings such as CVD risk factors are similar to other multiethnic cohort studies (Tsao & Vasan, 2015). Other limitations include inability to account for other factors in the built and social environment and social desirability associated with self-reported behaviors.

There are several strengths associated with this study. Specifically, it is noteworthy that the FHS has made major contributions to the science of CVD prevention and management and was implemented in a period when epidemiological research was not advanced, lacked the modern comforts of technology and medical inventions. The longitudinal nature of FHS and follow up of participants up to 43 years is helpful to reveal temporal trends of iCVH and CVD. The extended follow up made it possible to observe intergenerational iCVH differences for parents and offspring at similar age in lifespan. This study therefore unveils systematic iCVH patterns of parents and their offspring over a defined life span. Prospective cohort study designs such as the FHS are important to determine the temporal sequence, examine multiple disease outcomes and calculate incident rates over time (Song & Chung, 2010). More importantly, the FHS has pioneered efforts to collect data on the relationship between parental and offspring CVD. In this dissertation we optimized data from two Framingham cohorts, treating the Offspring Cohort as children of the Original Cohort. The FHS, which was designed to determine "expression" or "natural history" of CVD in a free-living, community population provides a unique opportunity and high-quality data to longitudinally examine these questions. The study setting is a stable, well-characterized population. During the adjudication process in the FHS, the underlying, immediate, and contributing causes of death are determined. The CVD events files

meticulously records diagnoses as they occur among participants. Disease conditions are systematically coded using an expanded ICD-9 coding system. The CVD outcomes are adjudicated by a 3-physician panel. The adjudication process limits chances for misclassification.

Conclusion and Implications

This dissertation has elucidated the relationship between parents and offspring's iCVH and how this relationship can be used for advancing CVD risk reduction strategies. Since CVD is a complex disease involving genomic measures such as DNA, clinical measures such as blood chemistry and environmental factors, systems approach to implementation of family-based interventions have potential to increase the information yield through examination of the combined effect of modifiable clinical, behavioral and environmental factors in CVD disease pathways. This study highlights the role of individuals to self-manage their cardiovascular health given the importance of attaining ideal iCVH, as well as the role of policies in addressing key barriers of attaining ideal iCVH.

It is evident that clinicians spend very little time with their clients in one's life span. Thus, emphasis has been placed on efforts to develop individually-tailored, self-sustaining interventions that address specific health needs of different individuals in a population, given different health needs as well as resources of different people. It is well-established that individuals benefit from close associates in attempts to achieve ideal heart health; hence, feasible family-based approaches need to be developed to support primary prevention efforts. These efforts need to be intensified with increasing focus such as is devoted to other secondary prevention efforts as well as integrating health promotion interventions that

achieve similar objectives. It is clear that policies like smoking cessation implemented in the 1960s, as demonstrated in this study, helped reduce incident CVD. These trends of CVD risk factors tell an important story that if a positive health intervention is implemented, long term health effects may be realized, some of which may be intergenerational health benefits. There is a dire need for policies that support primordial CVD prevention efforts, designed to prevent the development of the risk factor in the first place. Such policies would address improving access to healthy food and physical activity environments for children, adolescents and adults. With emphasis on promoting ideal cardiovascular health for all, such policies would enable provision of healthy, nutrient rich food to families, particularly for those who live in marginalized communities. Other policies might include access to built environments conducive to physically active lifestyles with play/recreational spaces. These measures will be acting synergistically to enhance achievement of most of the iCVH metrics. Findings that parents influence their children's attainment of iCVH, reduce CVD DALYs and that iCVH is clustered within families provides health policy makers with the needed actionable information to inform the discussion on optimal allocation of resources to family-based primordial CVD prevention programs. Future research should involve longitudinal follow up of units of families with particular emphasis on nutrition and physical activity data and examine the magnitude of each iCVH metric's contribution to cardiovascular health and CVD DALYs for individuals of the same family.

APPENDIX

A. ANNUAL PERSONAL INCOME IN $ FOR OFFSPRING

Income	n%	Male (n%)	Female (n%)	p value
No Income	132 (6.4)	8 (0.8)	124 (11.9)	0.000
≤ $19,000	715 (34.4)	146 (14.1)	569 (54.5)	
$20,000 TO $39,000	841 (40.5)	535 (51.7)	306 (29.3)	
≥ $40,000	390 (18.7)	345 (33.4)	45 (4.3)	

P value for t-test for male and female personal income, Exam 3, 1983-1987

B. GROUPED AGE FOR EACH COHORT BY EXAM CYCLE

Exam	Sex	n	25-34	35-44	45-54	55-64	65+	P value	n	25-34	35-44	45-54	55-64	65+	P value
Exam 1/2	Male	1290	185 (14.3)	507 (39.3)	417 (32.3)	181 (14.0)	0 (0.0)	0.008	1246	289 (23.2)	421 (33.8)	352 (28.3)	173 (13.9)	11 (0.9)	0.687
	Female	1347	243 (18.0)	552 (41.0)	403 (30.0)	149 (11.1)	0 (0.0)		1371	300 (21.9)	443 (32.3)	405 (29.5)	209 (15.4)	14 (1.0)	
Exam 3/3	Male	1134	17 (1.5)	442 (39.0)	370 (32.6)	300 (26.5)	5 (0.4)	0.008	1247	137 (11.0)	419 (33.6)	358 (28.7)	297 (23.8)	36 (2.9)	0.217
	Female	1207	20 (1.7)	519 (43.0)	398 (33.0)	255 (21.1)	15 (1.2)		1364	127 (9.3)	436 (32.0)	415 (30.4)	330 (24.2)	56 (4.1)	
Exam 5/4	Male	1131	0 (0.0)	278 (24.6)	440 (39.0)	316 (28.0)	97 (8.6)	0.033	1285	80 (6.2)	345 (26.9)	416 (32.4)	330 (25.7)	114 (8.9)	0.192
	Female	1234	0 (0.0)	357 (29.0)	458 (37.1)	341 (27.6)	78 (6.3)		1401	66 (4.7)	371 (26.5)	428 (30.6)	397 (28.3)	139 (9.9)	
Exam 7/5	Male	1065	0 (0.0)	88 (8.3)	442 (41.5)	345 (32.4)	190 (17.8)	0.110	1196	31 (2.6)	209 (17.3)	429 (38.9)	338 (28.3)	189 (15.8)	0.178
	Female	1210	0 (0.0)	112 (9.3)	540 (44.6)	383 (31.7)	175 (14.5)		1359	20 (1.3)	234 (15.4)	509 (33.5)	437 (28.8)	320 (21.1)	
Exam 9/6	Male	987	0 (0.0)	2 (0.2)	357 (36.2)	351 (35.6)	277 (28.1)	0.453	1104	0 (0.0)	111(10.1)	366 (33.2)	356 32.3)	271 (24.6)	0.002
	Female	1149	0 (0.0)	2 (0.2)	451 (39.3)	402 (35.0)	294 (25.6)		1262	0 (0.0)	109 (8.8)	393 (31.1)	386 (30.6)	374 (29.6)	
Exam11/7	Male	771	0 (0.0)	0 (0.0)	148 (19.2)	336 (43.6)	287 (37.2)	0.546	1113	0 (0.0)	59 (5.3)	284 (25.5)	395 (35.5)	375 (33.7)	0.013
	Female	937	0 (0.0)	0 (0.0)	199 (21.2)	405 (43.2)	333 (35.5)		1299	0 (0.0)	44 (3.4)	333 (25.6)	418 (32.2)	375 (33.7)	

C. NUMBER OF INCLUDED AND MISSING PARTICIPANTS FOR 5-ICVH METRICS

1 Missing values for blood sugar for parents and offspring

Original Cohort					Offspring Cohort				
Exam	**# included**	**# BG missing**	**% BG missing**	**# BG nonmissing**	**Exam**	**# included**	**# BG missing**	**% BG missing**	**# BG nonmissing**
Exam 1	2637	61	2.3	2576	Exam 2	2617	108	4.1	2509
Exam 3	2341	37	1.6	2304	Exam 3	2631	194	7.4	2437
Exam 5	2365	78	3.3	2287	Exam 4	2686	205	7.6	2481
Exam 7	2275	75	3.3	2200	Exam 5	2555	66	2.6	2489
Exam 9	2136	41	1.9	2095	Exam 6	2366	91	3.8	2275
Exam 11	1708	35	2.0	1673	Exam 7	2412	184	7.6	2228

2. Missing values for BMI for parents and offspring

Original Cohort					Offspring Cohort				
Exam	**# included**	**# BMI missing**	**% BMI missing**	**# BMI nonmissing**	**Exam**	**# included**	**# BMI missing**	**% BMI missing**	**# BMI nonmissing**
Exam 1	2637	3	0.1	2634	Exam 2	2617	1	0.0	2616
Exam 3	2341	3	0.1	2338	Exam 3	2631	49	1.9	2582
Exam 5	2365	9	0.4	2356	Exam 4	2686	14	0.5	2672
Exam 7	2275	65	2.9	2210	Exam 5	2555	21	0.8	2534
Exam 9	2136	66	3.1	2070	Exam 6	2366	35	1.5	2331
Exam 11	1708	25	1.5	1683	Exam 7	2412	131	5.4	2281

3. Missing values for blood cholesterol for parents and offspring

Original Cohort					Offspring Cohort				
Exam	**# included**	**# CHOL missing**	**% CHOL missing**	**# CHOL nonmissing**	**Exam**	**# included**	**# CHOL missing**	**% CHOL missing**	**# CHOL nonmissing**
Exam 1	2637	70	2.7	2567	Exam 2	2617	5	0.2	2612
Exam 3	2341	30	1.3	2311	Exam 3	2631	89	3.4	2542
Exam 5	2365	28	1.2	2337	Exam 4	2686	71	2.6	2615

Exam 7	2275	24	1.1	2251	Exam 5	2555	20	0.8	2535
Exam 9	2136	18	0.8	2118	Exam 6	2366	34	1.4	2332
Exam 11	1708	35	2.0	1673	Exam 7	2412	133	5.5	2279

4. Missing values for blood pressure for parents and offspring

	Original Cohort					Offspring Cohort			
Exam	**# included**	**# BP missing**	**% BP missing**	**# BP nonmissing**	**Exam**	**# included**	**# BP missing**	**% BP missing**	**# BP nonmissing**
Exam 1	2637	0	0.0	2637	Exam 2	2617	0	0.0	2617
Exam 3	2341	0	0.0	2341	Exam 3	2631	0	0.0	2631
Exam 5	2365	0	0.0	2365	Exam 4	2686	0	0.0	2686
Exam 7	2275	0	0.0	2275	Exam 5	2555	0	0.0	2555
Exam 9	2136	0	0.0	2136	Exam 6	2366	1	0.0	2365
Exam 11	1708	12	0.7	1696	Exam 7	2412	4	0.2	2408

5. Table of missing values for smoking for parents and offspring

	Original Cohort					Offspring Cohort			
Exam	**# included**	**# SMK missing**	**% SMK missing**	**# SMK nonmissing**	**Exam**	**# included**	**# SMK missing**	**% SMK missing**	**# SMK nonmissing**
Exam 1	2637	18	0.7	2619	Exam 2	2617	0	0.0	2617
Exam 4	2341	125	5.3	2216	Exam 3	2631	3	0.1	2628
Exam 5	2365	4	0.2	2361	Exam 4	2686	7	0.3	2679
Exam 7	2275	42	1.8	2233	Exam 5	2555	3	0.1	2552
Exam 9	2136	0	0.0	2136	Exam 6	2366	8	0.3	2358
Exam 11	1708	19	1.1	1689	Exam 7	2412	4	0.2	2408

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