# Life course socioeconomic position and ankle-brachial index

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**ABSTRACT**

The mechanisms by which life course socioeconomic position (SEP) may influence cardiovascular disease (CVD) are not well explored. Objectives were to investigate the association between cumulative life course SEP and an indicator of subclinical atherosclerosis: ankle-brachial index (ABI). Participants (n=1454) were from the Framingham Heart Study Offspring Cohort. Cumulative SEP was calculated by summing scores for childhood SEP (father's education), early adulthood SEP (own education), and active professional life SEP (own occupation). ABI was dichotomized as low (≤1.1) and normal (>1.1 to 1.4). In logistic regression analyses, cumulative SEP was associated with low ABI in men (odds ratio [OR]=2.09, 95% confidence interval [CI]: 1.24,3.51 for low vs. high cumulative SEP score) but not in women (OR=0.94, 95% CI: 0.63,1.38), after adjustment for age and CVD risk markers. This effect was largely explained by the association of own education with low ABI in men and not in women. Father's education and own occupation were not significantly associated with low ABI in men or women. In conclusion, while cumulative SEP was inversely associated with ABI in men, this effect was primarily due to own education.

**ABRÉGÉ**

Les mécanismes par lesquels la situation socio-économique (SSE) pourrait influencer les maladies cardiovasculaires (MCV) ne sont pas bien définis. Les objectifs de cette étude sont d'examiner la relation entre la SSE au cours d'une vie et l'athérosclérose sous-clinique, telle que mesurée par le "Indice de Pression Cheville Brachial ABPI", aussi connu sous le nom de "index ABPI''. Les participants (n=1454) provenaient de l'étude de cohortes *Framingham Heart Study Offspring*. La SSE cumulative a été calculée en additionnant les résultats pour la SSE durant l'enfance (scolarité du père), la SSE durant la period le jeune et l'adolescence (sa propre scolarité) et la SSE durant la vie professionnelle active (sa propre profession). L'index ABPI a été divisé en deux fractions, notamment la fraction basse (≤1.1) et normale (>1.1 à 1.4). Dans des analyses de régression logistique, la SSE cumulative a été associée à un index ABPI bas pour les hommes, mais pas pour les femmes, après l'ajustement pour le sexe et pour les facteurs risque de MCV. Ce résultat s'explique largement par l'association entre sa propre scolarité et un index ABPI bas dans le cas des hommes, mais pas dans les cas des femmes. Il n'y a pas eu d'association significative entre scolaritè du père ou sa propre profession et un index ABPI bas ni pour les hommes, ni pour les femmes. On peut donc conclure que si la SSE cumulative a été inversement proportionnelle à l'index ABPI pour les hommes, cela est principalement dû à sa propre scolarité.

# CHAPTER 1: INTRODUCTION

Cardiovascular disease (CVD) is a leading cause of disability and mortality in North America, and is on the rise in developing countries.[1, 2] CVD and many of its risk factors tend to be patterned by early life socioeconomic position (often measured as education and occupation of participants' parents), as well as by adulthood socioeconomic position (usually measured as participants own education, occupation and income), where low socioeconomic position is associated with higher risk for CVD.[3-9]

There is also increasing evidence that socioeconomic position (SEP) across the life course has important contributions to the development of cardiovascular disease (CVD) [10]. Life course SEP encompasses socioeconomic conditions, experienced at various stages of life, that can contribute to downstream health effects independently, collectively, and interactively.[11-13] Various life course SEP frameworks have been proposed, which can be used to examine the association between life course SEP and various health outcomes. The 'critical periods' framework suggests that there are certain time windows, e.g. *in utero*, in which socioeconomic exposures can have adverse or protective effects; outside this developmental window there is no excess risk for disease. Similar to the "critical periods" framework, the "sensitive periods" framework suggests that time periods exist when socioeconomic exposure has a stronger effect on subsequent disease risk than other periods in life; outside such sensitive periods any excess risk will be weaker. The 'Social Mobility' framework recognizes that people have evolving socioeconomic circumstances across their life span. Social 'trajectories' such as increasing, decreasing or stable SEP across the life course is thought to impact later disease. The 'Cumulative Risk' framework focuses on the total amount of exposure to SEP, suggesting that accumulation of negative socioeconomic experiences across the life-course contributes to later disease. Disease risk is thought to increase as the number, duration, and severity of negative experiences increase [11-13]. Numerous studies have been designed to test the association between SEP and CVD using the different proposed life-course frameworks.[10, 14] Particularly strong evidence has been provided for the 'Cumulative Risk' framework, as numerous observational studies showed that cumulative life course

SEP is inversely associated with CVD in various European countries,[10, 14] and more recently in one cohort in the United States.[15]

Although the association between life course SEP and CVD has been demonstrated in many observational studies, gaps remain in understanding the biological mechanisms by which life course SEP may influence CVD. Therefore, it is informative to consider how life course SEP influences the atherosclerotic process before clinical manifestation of CVD occurs.

Several studies to date have investigated the association between SEP and indicators of subclinical atherosclerosis.[16-30] However, almost all of these studies have been limited to SEP at one time point in the life course. Several of these studies reported inverse associations between adulthood SEP and indicators of subclinical atherosclerosis,[17, 18, 21, 22, 25-27, 30] and a smaller number of studies found that SEP during other life periods (e.g. birth or adolescence) is also associated with subclinical atherosclerosis.[23, 24, 29] Furthermore, common indicators of subclinical atherosclerosis in prior studies included coronary artery calcium (CAC) and carotid intima-media thickness (IMT). However, fewer of these studies have focused on the ankle-brachial index (ABI).[16, 19]

ABI is the ratio of systolic blood pressure at the ankle to that in the arm, and serves as a standard measure of Peripheral Arterial Disease (PAD) in the lower limbs.[31] In healthy individual without peripheral atherosclerosis, systolic blood pressure increases with greater distance from the heart, leading to higher systolic blood pressure at the ankle as compared with the arm, and consequently a ratio typically greater than 1.00.[32] However in the presence of peripheral atherosclerosis, poor circulation leads to lower ABI values observed. ABI is also increasingly recognized as an indicator of generalized subclinical atherosclerosis.[33] Recent emerging evidence has demonstrated increased risk for coronary and carotid atherosclerosis, coronary events, and CVD mortality up to ABI values of 1.1,[34, 35] consequently the Ankle Brachial Index Collaboration defined a normal or low risk ABI as 1.1 to 1.4.[34] In the only prior study to examine cumulative life course SEP in relation to ABI, Carson et al. found an inverse association between individual-level cumulative SEP and PAD, measured

as ABI < 0.9, in white men, white women, and black women from the Atherosclerosis Risk in Communities (ARIC) Study.[19] However, the association between cumulative life course SEP and low ABI, defined as ABI <1.1 has not been investigated thus far.

There is evidence that CVD begins early in life and develops over the life course,[13, 36] and it is likely that a lifetime of exposure to unfavourable socioeconomic conditions influences the course of CVD. Accordingly, examining cumulative SEP across the life course, as opposed to SEP in single time points, may be more relevant to both subclinical and clinically manifest disease. Elucidating the biological mechanisms by which cumulative life course SEP is associated with CVD adds additional support for inverse associations between life course SEP and CVD found in observational studies. In addition, Understanding how cumulative life course SEP influences subclinical atherosclerosis may inform policy on the timing and method of intervention for subclinical disease, and thus lead to prevention of progression to clinically manifest disease.

<u>The objectives of this study were:</u>

1) To investigate whether cumulative life course SEP is associated with ankle-brachial index (ABI) in the Framingham Study Offspring Cohort, a well-characterized United States prospective cohort.
2) To examine the relative contributions of SEP at three individual life course periods (childhood, early adulthood, and older adulthood), each a sub-component of cumulative life course SEP, to ABI values.
3) To assess the contribution of CVD risk markers in accounting for associations between life course SEP and ABI.

# CHAPTER 2: LITERATURE REVIEW

## 2.1. Cardiovascular Disease

Cardiovascular disease (CVD) refers to a class of disorders affecting the heart and blood vessels. The most common of these conditions are related to atherosclerosis, and include coronary artery disease (the most common form of coronary heart disease), ischemic stroke, and peripheral arterial disease (PAD).

### *2.1.1. Global Burden of Cardiovascular Disease*

The World Health Organization (WHO) recently reported that CVD is the number one cause of death globally, representing 30% of all global deaths. It is projected that by 2015, almost 20 million people will die from CVD, which will remain the single leading causes of death.[37] According to the National Vital Statistics Reports, data on deaths in 2005 revealed that heart disease is the leading cause of death for both men and women in the United States.[1]

Coronary heart disease (CHD) is the principle type of heart disease, accounting for 68.3% of all heart disease deaths in the United States.[38] Similarly in Canada, CVD accounts for the deaths of more Canadians than any other disease.[39] Based on 2004 data from Statistics Canada, ischemic heart disease, stroke, and heart attacks accounted for all of CVD deaths. Heart disease and stroke costs the Canadian economy more than $22.2 billion every year in physician services, hospital costs, lost wages and decreased productivity.[40]

Despite the persisting impact of CVD in western countries, age-adjusted CVD death rates in several developed countries have largely declined over the past 30 years. Mortality from heart disease in the United States has steadily declined since 1980.[1] Similar declines in death rates from heart disease and stroke have occurred in Canada, approximated to be 50% according to the Heart & Stroke Foundation.[41] On the contrary, rates of CVD have increased significantly in low-income and middle-income countries, with about 80% of the CVD burden now occurring in these countries. This increase is proposed to be a result of 3 main factors. First, decreasing mortality from acute infectious diseases and increasing longevity of the population results in a larger proportion of individuals reaching middle and old age, when they are subject to chronic diseases. Furthermore,

lifestyle and socioeconomic changes are resulting from increasing urbanization in developing nations. These changes translate into major impacts on diet, physical activity, and tobacco use, which in turn lead to higher levels of CVD risk factors. For example, the globalization of food production and marketing has resulted in greatly increased availability of inexpensive vegetable oils and fats, and increased consumption of energy-dense foods which may be poor in dietary fibre and nutrients. Increasing tobacco consumption observed in many of the developing countries such as china, India, and those in the Middle East and Latin America, is also contributing to an increase in CVDs. Finally, particular genetic susceptibility in certain populations in the developing world may lead to a greater impact on CVD compared to western populations.[42]

### *2.1.2. Risk Factors for Cardiovascular Disease*

In 1948, Ancel Keys pioneered the idea that atherosclerotic disease was not an inevitable consequence of aging, but was rather related to environmental factors.[43] Beginning with the Framingham Heart study in 1950, a large body of epidemiological evidence has since confirmed the primary risk factors for CVD to be cigarette smoking, hypertension, elevated serum cholesterol, physical inactivity, and diabetes.[7] The first 3 are deemed to be of most importance, and now satisfy public health criteria for causation.[44] Strong and precise findings came in 1986 from Stamler et al., who demonstrated that in a large sample of men aged 35-57 years at entry in the Multiple Risk Factor Intervention Trial (MRFIT), a 13-fold gradient in CHD death rates was found between non-hypertensive non-smokers in the lowest cholesterol level quintile (lowest-risk group) and hypertensive smokers in the highest cholesterol level quintile (highest-risk group). It was reported that 75% of CHD deaths were potentially attributed to the three classical risk factors.[45] The authors reported similar results in a later study that also included women. Significantly lower 16- and 22-year CHD and CVD mortality rates were observed among those in a low risk group as compared with those who had elevated levels of risk factors.[46] In addition, findings from epidemiological studies have contributed to important public health gains by demonstrating lowered CVD risk associated with a reduction in levels of

modifiable CVD risk factors. Law et al. reported in 1994 that based on half a million men from 10 prospective cohort studies, a long term reduction of 0.6 mmol/l in serum cholesterol concentration lowered the risk for ischemic heart disease across all age categories, ranging from 54% at age 40 to 20% at age 70. Based on 45,000 men in randomized trial studies, reduction in incidence of ischemic heart disease was estimated to be 25% after 5 years.[47] Similarly, Macmahon et al. investigated the association of diastolic blood pressure (DBP) with stroke and CHD in 42,000 individuals from nine major prospective observational studies, reporting that the combined results indicated positive, continuous, and independent associations consistently among the different studies.[48] Furthermore, in 1989 the Department of Health and Human Services (Center for Disease Control) reported that on average, cigarette smoking increases the risk for CHD death by 70% compared with not smoking.[49]

The major CVD risk factors are prevalent in both the developed and developing areas of the world, among all social classes, and are of similar public health significance in all countries.[48, 50-52] Although the global burden of CVD has increasingly shifted to low and middle income countries in the recent past, much of the current knowledge about CVD risk factors is derived from studies done in populations of European origin in developed countries. Thus, Yusuf et al. addressed whether the effects of different risk factors vary in different regions of the world, investigating 9 modifiable risk factors, including abnormal lipids, smoking, hypertension, and diabetes, in 15,000 cases and 15,000 controls from 52 countries across different continents. It was found that these risk factors accounted for most of the risk of myocardial infection worldwide in both sexes, at all ages, and in all regions, indicating that similar approaches could be taken worldwide for the prevention of premature myocardial infarction (MI).[53]

### *2.1.3. Development of Atherosclerosis*

Atherosclerosis is a cumulative and slowly progressive condition that remains asymptomatic for decades. The atherosclerotic process is initiated when low-density lipoprotein (LDL) particles invade the endothelium lining of arteries and become oxidized by free radicals beneath the endothelial cells. This initial

damage to the artery walls sets off an inflammatory response, in which monocyte-driven macrophages (specialized white blood cells) localize to the site of damage and ingest oxidized LDL. However these macrophages are not able to process oxidized LDL, and thus slowly turn into foam cells and form fatty deposits (this chronic inflammatory response is propagated when growing foam cells rupture and release a greater amount of oxidized LDL into the artery walls). This is followed by migration and proliferation of smooth muscle cells that produce a hard fibrous cap over the fatty deposits, now forming atheromatous plaques. Smooth muscle cells on the outer layer of the plaque die over time, leading to extracellular calcium deposition which further hardens the plaque.[54-56]

Atherosclerosis can develop in various arterial beds, and different conditions arise based on which arteries are affected. The accumulation of atheromatous plaques in the walls of coronary arteries over time leads to CAD. Plaque build-up causes thickening and hardening of the artery wall, and consequent narrowing (stenosis) or obstruction of the artery lumen. In addition, sudden rupture of plaques leads to the formation of blood clots, which cause further narrowing and blockage in the lumen. Obstruction of the artery reduces or completely restricts flow of oxygen-carrying blood to the myocardium, and can lead to angina (chest pain or discomfort) or the irreversible damage or death of heart tissue (myocardial infarction) [57]. Similarly, if atherosclerotic build-up occurs in arteries (e.g. carotid artery) that supply oxygen-rich blood and nutrients to brain tissue, an ischemic stroke can occur due to insufficient blood flow. Atherosclerotic build-up can also lead to altered structuring and function of arteries supplying the lower limbs, a condition defined as lower extremity Peripheral Arterial Disease (PAD). Stiffness and narrowing impedes blood flow, particularly in times of greater need such as during increased physical activity.[31, 57]

## 2.2. Socioeconomic position and cardiovascular disease

### *2.2.1. Definition, conceptualization, and indicators of socioeconomic position*

Socioeconomic position (SEP) refers to the social and economic factors that influence the relative standing of individuals within the structure of a society. SEP, along with various other terms such as social class social stratification, and socioeconomic status (SES) are often used interchangeably. However, the exact definition, theoretical bases, and interpretations of each of these terms can differ to varying degrees (for the purposes of general discussions in this literature review, SEP will be the standard term of use, however each study included in the literature review will be described using the socioeconomic term employed in that respective study).The term SEP encompasses resource-based measures, as well as status-based measures. An individual's actual resources can include an educational degree, a home, or a stable income, while status-related characteristics refer to an individual's relative position in socially ranked hierarchies in relation to access to and consumption of goods, services, and knowledge.[58] SEP is crucial to understanding inequalities in health. A vast number of studies have shown that in both industrialized and less industrialized countries, socioeconomic gradients are apparent for infant mortality, adult mortality, and infectious and non-infectious diseases.[59-62]

Some of the most common indicators of SEP are outlined below. Each of these indicators measures a different yet related aspect of SEP, and may be more or less suitable depending on the purpose, health outcome, and time period of interest in a given study. SEP can be measured meaningfully at three complementary levels: (a) individual, (b) household, and (c) neighbourhood. Each level may independently contribute to distributions of SEP and associated health outcomes.[58]

#### *Income*

Income is the indicator that most directly measures the resource-based component of SEP, and has been argued to be the best single indicator of material

recourses and living standards. The influence of income on material circumstances has direct implications for health, often in a 'dose-response' manner.[63, 64] United States data indicates that even simple measures of annual personal and family income at one point in time are strongly associated with numerous health outcomes.[65-67] Studies also show that small differences in income are associated with much larger changes in health status among those that are poor, as compared to wealthy families.[68, 69] In a large prospective study based on data from the Panel Survey of Income Dynamics (PSID), a 30% increase in risk of mortality was observed among individuals who experienced a sharp income drop during a five-year period, with risk increasing to 70% when two or more sharp drops in income occurred.[70]

Income is a multifaceted and dynamic variable, and there are certain complexities associated with the measurement of income in health and epidemiological studies. First, measures of gross income or annual family income may not reflect the disposable or net income that a given individual or family can actually spend, after deductions due to taxes or interest. Similarly, a measure of 'annual family income' does not take into account the number of persons supported by this income. The health consequences of an annual family income of 15,000 may greatly differ for a family of two adults vs. a family of two adults and two children.[58] Furthermore, using annual family income or household income to apply to all people in a given household assumes and even distribution of income according to the needs of all individuals within a household, which may not necessarily be the case.[71]Thus, it would be most useful to incorporate additional information on the number of dependant family members, as well as their age and gender, into measures of household income.[58] thus creating a 'standardized' measure of income.[72, 73] Income is also an unstable measure and can fluctuate considerably from one time period to the next. Consequently, measures of income at one point and time may fail to capture health impacts related to income at other periods of life, or the health impact of income fluctuations itself.[71] Finally, income is considered a 'sensitive' indicator and thus particularly subject to non-response, in comparison to other measures of SEP. There is evidence that in the

US, poor reporting and non-response to questions of income is often high. Researchers have developed various techniques such as response cards, bracketing, and imputation in order to increase accurate reporting of income.[74, 75] However, there are greater costs associated because of the need for more time and space for data collection when using these more sophisticated measures.[71]

***Education***

Education is one of the most commonly used indicators of SEP in public health research. There is extensive evidence that an individual's educational level is an important predictor of mortality and morbidity in the United States,[69, 76-78] as well as in less industrialized countries.[59, 61] Education is greatly influenced by parental characteristics, and is also a strong determinant of future employment and income. Therefore, it captures the impact of both early life and adult-life circumstances on health. The knowledge and skills attained through education may influence an individual's health by making them more receptive to health education messages, more likely to adopt healthy life behaviours, and more able to communicate with and access appropriate health services.[58]

Education is the preferred measure of SEP in many studies for several reasons. It is relatively stable over the life span, and as a result it is not subject to downward mobility due to changes in health status. In the event of a serious illness, individuals may be forced to work at jobs below the level of their normal occupations or they may experience a decline in income, however their level of educational attainment is not affected. Furthermore, education is easily measured, and high response rates are usually achieved regardless of what method is used to collect information on education (self-administered questionnaires, personal interviews, etc.). It is also applicable to person who may not be in the active labour force (e.g. homemakers, unemployed, retired) at the time education is assessed.[58]

Despite its numerous advantages, several limitations of education as a measure of SEP are of important consideration. First, the stability of the education measure may work to its disadvantage, as it is unable to capture how changes in

individuals' economic well-being later in adulthood may alter health status. Capturing socioeconomic fluctuations may be particularly important in the coming future, in light of increasing job insecurity and changing occupational structures associated with growing economic instability.[58] In addition, because the span of education level is less than that for other SEP measures such as income, education level may be a less sensitive measure for evaluating the magnitude of social inequalities in health.[79] Finally, the meaning of a given educational level and health implications associated with it can vary according to birth cohort, race/ethnicity, gender, and location. For example, educational level in the US has risen in successive cohorts during the twentieth century.[58, 63] Consequently, results from studies on education that include participants from different birth cohorts may be biased if such cohort effects are not taken into account, as older cohorts would be over-represented among those classified as less educated.[80]

***Occupation***

Occupation- based indicators of SEP have been widely used in a vast number of health studies to date. Both European and United States data have provided evidence of socioeconomic disparities in health status and mortality by occupational groups.[62, 81, 82] Occupation reflects a person's social standing, and can have an impact on health on many different yet interconnected levels. For example, income and tangible rewards associated with a given occupational positions can directly influence an individual's material living standards, which in turn can translate into downstream health effects. Various factors related to the work environment, such as social networks, work-based stress, and employer-employee relationships, may also effect health outcomes through psychosocial processes. A given occupation may also have a direct physical impact on health due to unfavourable work conditions (toxic environment, lack of job safety, draining physical demand). Information on occupation is often readily available through routine census data and death certificates.[83]

A major limitation of occupational indicators is that they can not be readily assigned to people outside the workforce at the time of data collection (e.g. retired

people, students, homemakers). As a result, using occupation as a measure of SEP to assess health may lead to biased results due to exclusion of some people in the population. Similarly, people who are self-employed can be difficult to classify. Efforts have been made to alleviate some of these problems by assigning the last occupation held to those who are retired or temporarily unemployed, or using husband's occupation as a measure of women's SEP.[83]

Several occupation-based classification schemes have been developed and used in various studies. Among the best known is the British Occupation based Social Class Scale (known as the Registrar General's Social Class prior to 1990), which is based on the prestige or social standing that a given occupation has within a society. Occupations are categorized into six classes, ranked from higher to lower prestige, which can also be collapsed into two broader categories of manual and non-manual occupations.[83] This classification scheme has proven to be powerfully predictive of inequalities in morbidity and mortality.[62, 81, 82] Similar to the British Occupation-based social class scheme is Edward's socioeconomic scheme, which is used in the US census and in North American studies.[63] It is based on the educational and income level required for each occupation, classifying occupation into 13 categories that are often collapsed into a smaller number of major socioeconomic categories.[21, 84] Other examples include Wright's classification scheme.[83] the Cambridge Social Interaction and Stratification Scale,[85] the Erikson and Goldthorpe Schema,[86, 87] and Treiman's standard international occupational prestige scale.[63]

### *2.2.2. The Association between socioeconomic position and cardiovascular disease*

(As noted previously, SEP is the standard term of use in this literature review, however each study included in the literature review will be described using the socioeconomic term employed in that respective study).

An inverse association between SEP and CVD is well established today, however it began to emerge only several decades ago. Beginning in the 1960s, studies conducted in male populations from the US and England provided initial evidence of emergent SEP disparities in CVD. Hinkle et al. investigated the

association of education and occupation with coronary disease in a 5-year prospective survey among 270,000 men employed by the Bell System throughout the US, reporting that men who entered with a college degree had a lower incidence and mortality rate from coronary disease at every age, in every part of the country, and in all departments.[88] Similarly in 1971, Cassel et al. examined the association of SES with CHD in the Evans County Georgia Heart Study, and found that among men aged 35-54 the 7-year incidence of CHD for workers in lower SES categories was approximately twice those of professional workers.[89] One of the most influential studies on the association between SEP and CVD was the Whitehall Study, based on 17,530 middle-aged civil servants. Rose and Marmot reported that in 1968, the baseline age-adjusted prevalence of angina pectoris was 53% higher for men in the lowest employment grade than for those in the top administrative grade, and ischemic-type electrocardiogram abnormalities were 72% higher in the lower than in the top grades. At follow-up, the 10-year coronary mortality rate was found to be 3.6 times higher in the lowest employment grade, as compared with the top grade.[90] Early in the 1980s, Evidence of socioeconomic disparities in CVD further came from three Chicago epidemiological studies, in which an inverse relation between education and long-term risk of CHD, CVD, and all-cause mortality were observed.[91] Emerging SEP disparities in CVD were also evident among black men. In 1984 it was reported that after 14 years of follow-up, acute MI and CHD rates among black men of high SES recruited in the Charleston Heart Study were half in comparison to other black men in the study, who were almost entirely of lower SES.[92]

An inverse association between SEP and CVD is also well documented in women, with many studies indicating that associations are in fact stronger in women than in men. In 1984, Heller et al. found that in England and Wales, SES gradients for ischemic heart disease were much more pronounced in women as compared with men.[93] Similarly, in 1992 Rogot et al. reported that among different race-gender groups in the US National Longitudinal Mortality Study, inverse association observed between education and mortality from ischemic heart disease was strongest in white women.[94] Eaker et al. found an inverse association

between education and 20-year incidence of MI or coronary death among women in the Framingham Study, with lower rates observed in women who held white-collar jobs as compared with blue-collar workers.[95] Results from studies conducted most recently are also in line with previous findings. Petrelli et al. evaluated the association of educational level, job status, and median income with CHD in men and women (n=523,755) residing in Turin, Italy. Marked education gradients in incident coronary events and mortality were observed in men, while all three socioeconomic indicators were inversely associated with coronary events and mortality in women.[96] Thurston et al. evaluated gender differences in the relation between SEP and CHD in 6,913 men and women from the First National Health and Nutrition Examination Survey, a longitudinal representative sample of the US population. Having less than a high school education was associated with a stronger risk for CHD in women than in men, with associations remaining significant in women after adjustment for various CVD risk factors but not in men.[97]

### *2.2.3. Mediators of the association between socioeconomic position and cardiovascular disease*

A considerable amount of research has focused on determining the mediators of the association between SEP and CVD. In particular, traditional CVD risk factors are proposed to explain, at least in part, the effect of SEP on CVD. This is primarily driven by the fact that several early studies and reports have established an inverse association between various SEP indicators and individual CVD risk factors. Using data from the National Health Interview Survey, Pierce et al. reported in 1987 that the prevalence of smoking among those who had not graduated from high school was more than twice that among college graduates. Examining data from 1974-1985 also revealed that quitting rates, as well as decrease in smoking prevalence, were considerably higher among those with more education.[49, 98] Several more recent studies have also shown that considerable differences in smoking rates exist between individual with the highest vs. lowest level of education. [5, 99, 100] According to the Surgeon's General Report in1989, occupational status and employment status were also shown to be strongly

associated with smoking rates. [49] There is also consistent and substantial evidence that low SES is related to both the prevalence and incidence of hypertension.[7] In a narrative systematic review of studies published from 1966-1996, Colhoun et al. reported that lower SES was associated with higher mean blood pressure in almost all studies in developed countries.[3] Early studies that examined multiple risk factors in relation to SEP also provide evidence of strong associations. Among adults aged 20-69 in the Canadian Health and the Canada Fitness survey, the prevalence of smoking, overweight, obesity, elevated diastolic blood pressure, physical inactivity, elevated serum cholesterol, and diabetes mellitus tended to be higher in men and women with a lower level of education, as compared with high.[101] Similar results were observed in a sample of 12,368 Norwegian men and women, comparing those with the highest level of education to those with the lowest.[102] Length of school education was also negatively associated with prevalence of most CVD risk factors according to 1984-1986 data from the First National Health Examination Survey of the German Cardiovascular Prevention Study.[103]

Given the considerable amount of evidence linking various CVD risk factors to SEP as well as CVD outcomes, a logical conclusion is that socioeconomic differences in CVD are mostly explained by established CVD risk factors. Accordingly, statistical adjustment for various CVD risk factors is a typical approach used in studies in order to assess their potential role as mediators of the association between SEP and CVD. Although considerable attenuation of the association between SEP and CVD is observed in some cases,[104, 105] many studies have found that adjustment for CVD risk factors has at most only a modest impact on observed association.[106-109] According to Lynch et al,[110] the idea that conventional risk factors do not explain social inequalities in CHD has been widely accepted. The authors explained that one main reason for this so called 'paradox' is epidemiological emphasis on and interest in looking at relative social inequalities in CHD, as apposed to absolute social inequalities. Using data from a large cohort of Eastern Finnish men, they showed that conventional risk factors explained the vast majority of CHD cases in the population and accounted for

72% of absolute social inequalities in CHD. However, adjustment for conventional risk factors reduced the relative social inequality by only 24%. It was concluded that an absolute risk approach to understanding social inequalities in CHD focuses attention on those risk factors that cause most cases of disease attributable to social inequality, and that reducing conventional risk factors will accomplish the goal of decreasing the overall population health burden of CHD and the disproportionate population health burden associated with the social inequalities in CHD. Other methodological issues can also arise when statistical adjustment for CVD risk factors are carried out, which may also explain why adjustment for CVD risk factors does not necessarily impact the association of SEP with CVD. Cole and Hernan explained that adjusting for an intermediate variable (mediators or confounder) on a pathway between an exposure and outcome may lead to spurious associations observed, due to unknown or unmeasured confounders of the intermediate variable and exposure, as well as the intermediate variable and outcome.[111] Furthermore, 'regression dilution bias' may occur if only a single measure of risk factors are included in a study. Single measures have a large variance and as a result, are only moderately correlated with subsequent measurements of the same risk factor in the same population. Therefore, relating a single (as opposed to multiple) measure of a risk factor to an outcome leads to substantial underestimation of the strength of association.[112]

Despite all methodological considerations, the fact that CVD risk factors do not fully account for the association of SEP with CVD is thought to suggest that other mechanisms involving other types of risk factors may also be at work. For example, inflammatory and hemostatic factors, often referred to as 'novel risk factors', are increasingly being considered as potential mediators, given the understanding of the crucial role of inflammation in the pathogenesis of atherosclerotic disease.[113-116] Several studies have found strong associations between SEP and various novel risk factors such as C-creative protein, plasma fibrinogen, intercellular adhesion molecule-1, homocysteine, and interleukin-6 [114, 117-119]. These associations were shown to persist even after adjustment for conventional CVD risk factors.[114, 118, 120]

Psychosocial factors are also proposed as potential mediators between SEP and CVD. Initially, several studies showed associations between various psychosocial factors and CVD.[7] For example, Falk et al. reported in 1992 that a high relative mortality risk of 1.7 was found among men, born in 1914 and living in Malmo, Sweden, who were exposed to job strain. The combination of job strain and seven different measures of a weak social network and social support was associated with further increased relative risks ranging from 2.1 to 4.6.[121] In 2004, Yusuf et al. assessed the impact of various potentially modifiable risk factors in a standardized case-control study of MI in 52 countries, and showed that the population attributable risk for psychosocial factors for acute MI was 32.5%.[53] In men and women of the Whitehall II study, Marmot et al. assessed the contribution of various psychosocial and coronary risk factors to social gradients in incident CHD, and found that the greatest contribution was from job control at work.[122]

## 2.3. Life course socioeconomic position and cardiovascular disease

### *2.3.1. A life course approach to chronic disease epidemiology: background and frameworks*

A life course approach is increasingly being adopted in studies of chronic diseases, offering a way to conceptualize how the interaction and accumulation of various biological and social factors may shape the course of disease. A life course approach recognizes that the chronic conditions such as CVD usually develop early, progresses over time, and manifest after long latency periods.[13] For example, autopsy studies have revealed precursors of atherosclerosis in the arteries of children,[36, 123] and demonstrated a high prevalence of atherosclerosis and narrowing in the arteries of young male U.S. war fatalities.[124, 125] In parallel, several lines of evidence highlight the importance of life course exposures and experiences, and their contribution to chronic disease development. Early in the 1970s, Forsdahl demonstrated that infant mortality rates early in the 20th century correlated strong with CHD mortality rates 70 years later,[126] suggesting that exposure to adverse conditions in early life could increase the risk of CHD in

adult life. Early life anthropometry and growth are also linked to CHD in adulthood. Based on results from 11 studies examining the association of birth size with CHD, Lawlor et al. concluded that there was generally an inverse association between birth weight and CHD.[11] Similarly, various studies have also found inverse associations between height and CHD in both men and women,[127-129] and these associations appear to be independent of birth weight.[128] In addition, many important risk factors for chronic disease observed in adulthood trace across the life course. CHD Risk factors such as cholesterol, blood pressure, and overweight are already present during childhood and adolescence, and carry on into adulthood.[130-133] CHD risk factors measured in adolescence have also shown to be predictive of subclinical atherosclerosis[134] and CHD up to 50 years later.[13]

Given the importance of considering life course processes, there is increasing focus on the contributions of life course SEP to the development of CVD. Life course SEP encompasses socioeconomic experiences and conditions, experienced at various stages of life, that can contribute to downstream health effects independently, collectively, and interactively.[12, 13] Several life course frameworks have been developed, and can be used conceptualize the different processes by which socioeconomic experiences across the life course may influence disease risk.

***'Sensitive Periods' and 'Critical Periods' frameworks***

The 'Critical Periods' framework suggests that there are certain time windows, e.g. *in utero*, in which a given exposure can have adverse or protective effects on subsequent disease or health outcome; outside of this limited time window, there is no excess risk for disease associated with the exposure. Similar to the 'Critical Periods' framework, the 'Sensitive Periods' framework suggests that time periods exist, such as early childhood or adolescence, when exposure to a socioeconomic condition has a stronger effect on subsequent disease, as compared to the same exposures occurring in another time period.[10, 12, 13]

***'Social Mobility' framework***

The 'Social Mobility' framework recognizes that people likely have varying social circumstances across their life span, and hypothesizes that social 'trajectories' such as increasing, decreasing or stable SEP across the life course can impact later disease. For example, Forsdahl proposed that the combination of deprivation in early life followed by affluence later in life can increase risk for CHD mortality, partly mediated by adult cholesterol levels.[135] Others propose that such trajectories occur through 'health selection', wherein less healthy individual tend to experience downward social mobility, while those healthier tend to be upwardly mobile.[136, 137]

***'Cumulative risk' framework***

The 'Cumulative Risk' framework posits that the accumulation of various exposures and experiences over the life course may influence later disease, and that the impact on health or disease increases as the number, duration, and severity of these experiences increase.[11-13] Accumulation of risk for disease may occur when negative socioeconomic exposures cluster with other types of exposures (e.g. environmental, behavioural, and physiological) that also affect health. For example, those living in a low socioeconomic environment are more likely to have poor eating habits, live in polluted neighbourhoods, and experience work stress, all of which can increase risk for disease. Additionally, negative socioeconomic exposures may form chains of risk, where one negative socioeconomic exposure increases the likelihood of a subsequent one.[13] For example, living in low income conditions during childhood may create circumstances that lead to low income or low education obtained during adulthood. Some evidence indicates that cardiovascular diseases such as CHD and ischemic stroke are influenced by factors acting across the entire life course, and thus they may conform more to 'Cumulative Risk' frameworks [138-141].

### *2.3.2. The association between life course socioeconomic position and cardiovascular disease*

#### *'Sensitive Periods' life course SEP and CVD*

The 'Sensitive Periods' life course SEP design has been utilized in several studies of SEP and CVD to date, with the childhood period representing the 'sensitive' time window in most cases. In 2006, Galobardes et al. conducted a systematic review of 40 individual studies of morbidity and mortality from CVD and specific CVD subtypes linked to early life SEP.[4] Studies were from the United Kingdom, United States, Czech Republic, and various northern European countries. In the 24 prospective studies included, father's occupational class was the indicator most often used to measure socioeconomic circumstances during childhood. Other measures used were parental education, farm size, housing conditions (e.g., having running water, type of toilet, ventilation, and cleanliness), crowding, number of siblings, living in a single-parent family, mother's marital status, inadequate food intake, parent's unemployment, self-reported economic problems during childhood, family without car, and sibling mortality. In 19 of 24 prospective studies, indicators of less favourable socioeconomic conditions during childhood were associated with a greater risk for developing or dying of CVD. Adjusting for adult SEP and risk factors often diminished the effect of childhood circumstances on CHD, but this had little or no effect on the association with stroke in several studies. Seven of 11 case-control studies found an association of poor childhood socioeconomic circumstances and risk for MI, angina, or stroke. Of the 5 cross-sectional studies that were included, all reported an inverse association of childhood conditions with prevalence of CHD. Overall, it was concluded from this systematic review that those who experienced worse socioeconomic conditions in their childhood, independently of their circumstances during adult life, were generally at greater risk for developing and dying of CVD.

A few other studies of Childhood SEP and CVD were published after the aforementioned Systematic review. Lawlor et al. argued that prior studies lacked sufficient power to assess associations between early life SEP and cause-specific mortality, thus they examined associations of early life SEP measured as parental

social class at age 0-16 years, with adult mortality from various conditions in a study of 1,824,064 Swedish men and women. Those from manual compared with non-manual childhood social classes were more likely to die from a variety of chronic conditions, including CVD. The authors noted that adjustment for adult SEP measures resulted in attenuations of the associations observed, particularly when adjustments were made for educational attainment.[142] Naess et al. found similar associations between childhood SEP measured as parental occupational class and CHD in a large prospective cohort of Norwegian men and women.[143]

***'Social Mobility' life course SEP and CVD***

The 'Social Mobility' framework has also been employed in studies of life course SEP and CVD. In a recent systematic review, Pollitt et al. evaluated 49 observational studies in the biomedical literature on the association of life course SES with CVD outcomes and risk factors.[10] The social mobility life course model was tested by 11 of the studies included, with inter-generational social mobility usually determined by contrasting the participant's father's occupational SEP to the participant's, and intra-generational SES typically defined as a change in occupational SES from early adulthood to later adulthood. Seven of these studies evaluated CVD mortality or CHD as the outcome, and all reported the suggestion of inverse, although not always statistically significant, relationships between social mobility CVD-related outcomes. Three reported that individuals with stable low-SES trajectories had a greater CVD risk than stable high-SES trajectory individuals; while another reported a marginally significantly greater risk. However, one study reported increased CVD risk among the upwardly mobile, and another reported no associations between upward or downward mobility and CVD, when compared to stable low-SES or high-SES trajectories.

***'Cumulative Risk' life course SEP and CVD***

Pollitt et al. summarized 7 studies in their systematic review that tested the 'Cumulative Risk' life course SES framework in relation to CVD.[10] These studies typically measured cumulative life course SES by summing the number of times

participants experienced unfavourable SES situations during early, middle or later life, and creating SES indices representing the accumulation of these experiences All studies reported that participants' cumulative life course exposure to low SES conditions was associated with increases in CVD outcome. Four of these studies indicated that cumulative SES was a more powerful predictor of CVD morbidity and/or mortality than adult or early-life SES alone. In studies that adjusted for CVD risk factors, associations were attenuated but remained strong in two studies and were greatly attenuated in another. Davey-Smith et al. employed a unique cumulative measure, combining two indicators of socioeconomic risk (early and later-life occupational class experience) with two CVD behavioural risk factors (smoking and heavy alcohol consumption).[144] They reported a marked difference in risk of CVD mortality between the group with the most favourable and least favourable life course exposures. Most recently, Loucks et. al investigated whether cumulative life course SEP was associated with CHD incidence in the Framingham Study Offspring Cohort. Similar to other prior studies, cumulative SEP was measured by summing measures of childhood and adulthood (early as well as later adulthood) SEP measures to create a cumulative SEP index. The authors reported that cumulative SEP was associated with incident CHD, however adjustment for CHD risk factors reduced the magnitude of associations.[15]

### *2.3.3. Measuring life course socioeconomic position: Methodological concerns*

The measurement of life course SEP presents several methodological and analytical challenges concerning study design, data collection, and interpretation. Some of the major methodological issues regarding measurement of each life course SEP framework, as well as measurement of life course SEP in general, are outlined below.

#### *Methodological concerns: 'Sensitive Periods'/ 'Critical Periods' life course SEP framework*

Lynch et al. noted that testing critical and sensitive-period exposures requires that a given exposure is measured at multiple points spanning the hypothesized time period. However, such repeated measurements are rare and expensive to

collect.[13] For example, studies of early life SEP and CVD generally have a single measure of childhood SEP at a given time point. Most studies also adjust for adult SEP in statistical models for the association of childhood SEP with CVD, in order to draw conclusions regarding the independent effect of childhood SEP. This may be problematic for several reasons. First, attempting to determine the "direct", adjusted effect of early life SEP on CVD risk may incorrectly estimate this effect, due to unmeasured or unknown variables that influence both adulthood SEP (the "mediator" or "confounder" adjusted for in this context) as well as the outcome.[111, 145, 146] Furthermore, childhood SEP may be poorly indexed in comparison to adulthood measures in studies relying on adulthood recall of childhood circumstances. Thus, due to greater measurement error in childhood indicators, mutual statistical adjustment will tend to favour adulthood measures.[4] Galobardes et al. reported that studies that measured SEP in childhood generally showed stronger associations with CVD outcomes than those using adult recall of childhood SEP, suggesting that recalled socioeconomic measures of childhood tended to underestimate the true association.[4] An updated analyses by Kauhanen et al. revealed that objective measures of childhood SEP collected during childhood were in fact more accurate than those recalled from adulthood.[147] Nevertheless, even if it is the case that adulthood SEP entirely explains risk for a given disease, adulthood circumstances are in part an outcome of circumstances earlier in life (i.e. childhood), thus adjusting for adulthood SEP may be an over-adjustment regardless of the presence or absence of measurement error.[10]

***Methodological concerns: 'Social Mobility' life course SEP framework***

In studies examining the 'Social Mobility' life course framework, the unit of analysis is a trajectory, in an attempt to capture the impact of change over time. However, Pollitt et al. noted that socioeconomic trajectories in most of these studies were limited to two time points, and groups compared tended to share the same SEP at one of these time points. This may partly explain why the weak and somewhat inconsistent associations reported by such studies. Social trajectories incorporating SEP at three ore more time points are more informative than those

evaluating SEP at only two time points. Nevertheless, analyses can become difficult and strenuous when measuring SEP at more than two or three levels and at three different time points. Additionally, certain trajectories (e.g. downward) are uncommon and typically comprise of a small number of individuals, making the assessment of these trajectories difficult due to the lack of power.[10]

***Methodological concerns: 'Cumulative Risk' life course SEP framework***

According to the 'Cumulative Risk' framework, SEP is thought to affect the outcome through accumulation, and thus entails that SEP be measured at multiple time points. However, multiple measures present analytical challenges in how to best represent their accumulation.[13] In life course studies, cumulative SEP is typically measured by summing values for SEP from each life course period (e.g. childhood, early adulthood, etc.), with equal weights given to SEP from each time periods. This approach makes two critical assumptions: a) that a specific socioeconomic experience has the same impact regardless of when it occurs in an individual's lifetime, and that b) different types of socioeconomic experiences at different life course periods equally affect the outcome in question. Finally, measures of cumulative SEP may conflate the effect of SEP measures at individual life course periods with that of SEP over the life course, thus it is unclear as to which time period may be particularly important in its impact on disease.[10]

***General methodological concerns with measuring life course SEP***

Investigating socioeconomic life course processes for chronic diseases such as CVD requires measuring data at multiple time points in the lifespan, and even across generations. Loss to follow-up, selective survival, measurement error due to recall of earlier life experiences, and changing socioeconomic status are some common obstacles when adopting a life course approach. However, life course studies are increasingly using cohorts followed from birth or early life, with multiple measures of socioeconomic and other risk factors often available. Accordingly, concerns regarding issues such as selection bias or measurement

error are decreasing.[10] Studies of life course SEP and CVD to date have generally provided strong support for the 'Cumulative Risk' framework, moderate support for the 'Critical Period'/ 'Sensitive Periods' framework, and less support for the 'Social Mobility' framework. However, it is important to note that different methodological issues of each study design make direct comparisons of the relative support for each conceptual framework difficult [10]. In addition, teasing out one particular life course model from another is rather problematic and not necessarily feasible, as there is strong correlation between each of these frameworks.[148, 149]

According to Pollitt et al., the most informative and complete conclusions regarding the impact of life course SEP on CVD may be drawn from incorporating multiple life course frameworks within the same study. In 2006, Rosvall et al. used all 3 life course frameworks to assess the association between life course SEP and 12-year risk of premature CVD mortality and all-cause mortality in a large population sample of men and women in Scania, Sweden. The authors found that there was a strong relation between SEP and cardiovascular mortality as well as all-cause mortality, irrespective of the conceptual framework used. In a statistical comparison of the life-course frameworks examined (using the Akaike Information Criterion (AIC)), all 3 showed the same fit to the data, and no single framework could be pointed out as "the best". It was argued that even though strong correlation between the effects of each life course framework makes it hard to separate the observed effects, it is not obviously necessary to do so. Rather, each conceptual framework can provide useful and complementary information, which can be combined to build a more comprehensive picture of the relation between life course SEP and CVD.[14]

## 2.4 Understanding the biological mechanisms between socioeconomic position and cardiovascular disease

### *2.4.1. Focus on subclinical atherosclerosis*

Despite abundant evidence linking SEP to CVD endpoints, the biological mechanisms by which SEP may influence CVD are not fully understood. It is

proposed that a deeper understanding of these potentially causal mechanisms may be reached by focusing on earlier and clinically latent stages of the disease. Accordingly, studies are increasingly turning focus to investigating the association of SEP with subclinical indicators of CVD. Focusing on subclinical measures of CVD offers several additional opportunities. Importantly, it makes it possible to differentiate the association of SEP with the underlying atherosclerotic process from associations with later stages of the disease process.[150, 151] For example, SEP may reduce the risk of clinical disease through factors related specifically to overt disease, such as access to treatment, disease care-seeking behaviours, health literacy, and adherence to medical treatment advice.[152-154] Physicians may have potentially different reactions and treatment patterns for overt disease toward patients of different socioeconomic backgrounds.[155] On the other hand, any association between SEP and subclinical disease is not confounder by these factors. Thus, focusing on subclinical atherosclerosis allows one to determine whether socioeconomic factors are important in their contribution to CVD, even before symptoms of the disease appear.[156] In addition, the risk of misclassifying SEP because of downward mobility following manifest disease is minimized by using a subclinical measure.[157] Concerns of such misclassification stem from the 'drift' or 'selection' hypothesis, which posits that any association between SEP and health may occur because sick individuals "drift down" the social hierarchy, so that lower socioeconomic position is a consequence of the disease process.[158] Finally, focusing on the association of SEP with subclinical disease has important implications in terms of disease prevention. Focusing on the subclinical stage of disease may be useful for identifying subgroups of individuals with low SEP who are at highest risk for later CVD events.[22]

### *2.4.2. Indicators of subclinical atherosclerosis*

The presence of atherosclerosis at the subclinical stage can be detected and quantified using various non-invasive indicators. The additional use of these indicators increases the predictive risk of developing clinical CVD beyond

traditional risk factor assessment alone.[159] Outlined below are some of the more established non-invasive measures of subclinical atherosclerosis.

***Carotid intima-media thickness***

Carotid intima-media thickness (IMT) is defined as the distance between the lumen-intima surface and the media-adventitia interface of the carotid artery wall, and reflects diffuse thickening of the intimal layer due to atherosclerotic build-up. It is measured with high-resolution B-mode ultrasonography, and is a standard and reliable measure of carotid atherosclerosis. It is also used to assess the extent and severity of atherosclerosis.[159] In a systemic review and meta-analysis of eight studies examining the association between carotid IMT and vascular events, the relative risk of a myocardial and stroke per one standard deviation difference in carotid artery IMT was 1.26 (95% CI: 1.21,1.30) and 1.32 (95% CI: 1.27,1.38), respectively. The authors concluded that the meta-analysis provided strong evidence for carotid IMT as a strong and valid predictor of vascular events.[160] Several clinical trials have also demonstrated that greater IMT is related to the prevalence of clinical CAD and clinical coronary events.[161-163] Generally, IMT measurements ≥1.20 mm are considered abnormal; however, a thickness of 1.00 mm is considered highly abnormal in a young individual.

***Coronary artery calcium***

Coronary artery calcium (CAC) refers to the calcium deposits on atheromatous plaques within the coronary vessel wall.[164] Because calcium deposits are related to the lipid and apoptotic remnants of the plaque, the amount of CAC directly correlates with both the extent and severity of angiographically documented atherosclerosis. CAC is visualized with electron-beam computed tomagraphy (EBCT), a standard non-invasive scanning technique that detects the location and quantity (score, mass, volume) of coronary calcium.[165] In 2000, A meta-analysis of 5 independent studies showed that there was an increased risk of MI or sudden death if calcium scores were above a median score (summary risk ratio 4.2, 95% CI: 1.6, 11.3).[166] Several more recent epidemiological studies have

also shown CAC to be an independent predictor of cardiac events.[167-171] Coronary calcium quantity and prevalence increases with age, and is also related to major cardiovascular risk factors, including hypertension, hypercholesterolemia, and cigarette smoking.[172]

***Pulse wave velocity***

Pulse-wave velocity (PWV) is a measure of arterial stiffness, based upon the principle that the velocity of pressure waves travelling down the aorta increases with stiffer vessels. Doppler flow probes are used to measure signals from two sites in the arterial tree, commonly the carotid and femoral arteries. PWV is then calculated as the distance between the carotid and femoral arteries (measured using tape over the surface of the body), divided by the time interval between carotid and femoral waveforms. PWV is expressed in meters per second, with higher PWV indicating stiffer arteries.[173, 174] Given that atherosclerotic build-up leads to stiffening of the arteries, PWV is considered to be a marker of early disease, and has been prospectively linked to future CVD events.[29, 173, 175] For example, in a recent study it was shown that the risk of CVD increased with increasing aortic PWV in 2,835 subjects from the Rotterdam Study. Hazard ratios and corresponding 95% CIs of CHD for subjects in the second and third tertiles of the aortic PWV index compared with subjects in the reference category were 1.72 (CI: 0.91,3.24) and 2.45 (CI: 1.29,4.66), respectively, after adjustment for age, gender, mean arterial pressure, and heart rate. Estimates decreased only slightly after further adjustment for CVD risk factors, other measures of atherosclerosis, and pulse pressure.[173]

***Ankle-brachial index***

The ankle brachial index (ABI) is the ratio of systolic blood pressure at the ankle to that in the arm, and has been used for many years in vascular practice as standard measure for the diagnosis of lower extremity peripheral arterial disease (PAD).[31, 34] The ABI is commonly calculated by measuring the systolic blood pressure in the posterior tibial and/or the dorsalis pedis arteries either in both legs

or one leg chosen at random (using a Doppler probe or alternative pulse sensor), with the lowest ankle pressure then divided by the brachial pressure.[34] In healthy individuals without peripheral atherosclerosis, arterial pressure increases with greater distance from the heart, resulting in a higher systolic blood pressure at the ankle than that in the arm.[32] Accordingly, persons without PAD typically have an ABI greater than 1.00. Impaired circulation in persons with peripheral atherosclerosis causes the systolic blood pressure at the ankle to be lower than in the arm, thus lower ABI values are observed.[35] ABI is also increasingly being recognized as an indicator of generalized subclinical atherosclerosis. In population cohort studies in the United States[176-179] and Europe,[180-182] a low ABI has been related to an increased incidence of CVD, MI, and stroke. These increased relative risks have been shown to be independent of baseline CVD and risk factors, suggesting that the ABI might have an independent role in predicting cardiovascular events. In a recent systematic review of 11 studies comprising subjects from six different countries,[33] a low ABI ( <0.9) was associated with an increased risk of cardiovascular mortality (pooled RR 1.96, 95% CI: 1.46,2.64), CHD (pooled RR 1.45, 95% CI: 1.08,1.93), and stroke (pooled RR 1.35, 95% CI: 1.10,1.65) after adjustment for age, sex, conventional CVD risk factors, and prevalent CVD.

### *2.4.3. The association between socioeconomic position and subclinical atherosclerosis*

Numerous studies have investigated the association between SEP and various measures of subclinical atherosclerosis. Findings have generally varied across SEP indicators and across measures of subclinical atherosclerosis.

SEP has been investigated in relation to subclinical atherosclerosis most often measured by IMT of the carotid artery. Diez-roux et. al. investigated the cross-sectional association of social class indicators with CHD prevalence and carotid IMT among 15,800 individuals from four US communities between 1987 and 1989.[21] In race-specific analyses among persons free of clinically manifest atherosclerotic disease, IMT increased with decreasing income and education,

although trends by education were clearer in Whites than in Blacks. Lower occupational categories were also associated with increased IMT. Associations did not persist after adjustment for CVD risk factors. Similarly in 2008, Lutsey et al. investigated whether SEP was related to internal carotid IMT and carotid plaque in 6,716 older adults from the Multi-Ethnic Study of Atherosclerosis (MESA), and whether the relation may differ across racial/ethnic groups.[25] Comparable to previous findings from Diez-roux et al., greater educational attainment was associated with lower mean internal carotid IMT among Whites but not among the Chinese, Blacks, or Hispanics.

Several other studies have looked at the association between SEP and IMT by sex. In 1995, Lynch et al. investigated the association of education, income, and occupation with IMT in a population-based sample of Eastern Finnish men.[26] It was reported that the age-adjusted mean IMT for those with primary schooling or less, some high school, and completed high school or more was 0.96, 0.94, and 0.82 mm, respectively. The difference in mean IMT between the most extreme categories of education corresponded to a 15.4% increase in the risk of MI. Similar patterns were found for other measures of SES, although the differences between the highest and lowest levels of SES were often attenuated by adjustment for atherosclerotic risk factors. Importantly, it was found that in men who had no carotid stenosis or non-stenotic plaque and in men who had no indication of prevalent CVD, a graded, inverse association between SES and IMT persisted, even after risk factor adjustment. This was strongly indicative of SES differences in the very early stages of atherosclerosis. In 2003, Gallo et al. examined the level of cardiovascular risk in 362 pre-menopausal women aged 42-50 years from the Healthy Woman Study (HWS).[183] Risk-factors were measured pre-menopausally at baseline and measures of IMT were obtained approximately 11 years later. Clerical workers had significantly greater IMT relative to blue-collar and white-collar workers, and adjustment for behaviour risk factors, physical risk factors, and workplace characteristics did not effect associations observed. Rosvall et al. investigated the association of educational level and occupational status with mean carotid IMT in 4,176 Swedish men and women from a sample of the general

population. No association was observed between education and IMT in men.[17] Age-adjusted IMT decreased with increasing educational level for women; however this trend was no longer significant after adjustment for lifestyle factors and biologic risk factors. Age-adjusted IMT decreased with increasing occupational status in men, however adjustment for risk factors turned this gradient statistically non-significant. In women, results for occupational status were surprising. For women with IMT below the median value, IMT tended to be thicker among those with higher occupational status. However, in women with IMT above the median value, IMT was thinner among those with higher occupational status, as expected. The authors noted that such findings may be an indication that mean IMT is not a valid or specific enough measure of the atherosclerotic process when examining socioeconomic differences in carotid wall thickness in women.

Some studies have also further investigated whether SEP is associated with *progression* of IMT. Lynch et al. were the first to examine prospectively the association of income and education with 4-year IMT progression, measured as maximum IMT as well as mean IMT.[158] Compared with the lowest SES group, men with the highest SES had 14% to 29% less atherosclerotic progression, depending on the SEP measure used. Similarly, Rosvall et al. looked at the association of SEP with progression of IMT in 1016 men and women from the Malmo Diet and Cancer Study (MDCS) cohort.[156] In age, sex- and baseline IMT-adjusted analyses, those in unskilled manual occupations showed a significantly higher yearly progression of carotid IMT in the bifurcation area compared to those in high- or medium-level non-manual occupations. Similar results were observed for education. Further adjustment for lifestyle, biological, and psychosocial risk factors somewhat attenuated associations observed. Ranjit et al. looked at the association of income, education, and neighbourhood characteristics with 9-year progression of carotid IMT in a middle-aged black and white men and women from the Atherosclerosis Risk in Communities (ARIC) study.[27] A moderate inverse association of SEP with IMT progression was observed in Whites, however this gradient was reversed in Blacks, such that lower SEP was

associated with a lower rate of progression from baseline IMT. Patterns of associations observe were not accounted for by baseline cardiovascular risk factors.

SEP has also been investigated in relation to subclinical atherosclerosis measured as CAC, and to a lesser extent, aortic calcification. Among elderly people from the Rotterdam Study, aortic atherosclerosis was found to be more common among women in the lower educational and occupational strata, however no associations were observed between income and aortic calcification.[184] No relation emerged between SEP measures and aortic calcification among men. Gallo et al. evaluated the association of educational attainment with aortic as well as coronary calcification in 308 post-menopausal women from the Healthy Women Study.[22] Similar to findings in the Rotterdam study, marginally significant trends were observed for coronary and aortic calcification, with the more educated groups showing lower calcification than the less educated groups. The authors reported that although biologic, behavioural, and psychosocial factors risk factors measured were associated with education and with the calcification outcomes, they explained little of the associations between educational attainment and coronary or aortic calcification. Kop et al. assessed the relation of multiple psychosocial variables, including social network, SES, and depressive symptoms with CAC in 783 men and women enrolled in the EISNER study.[185] Indicators of SES, measured by education level and income, did not display associations with the severity or presence of CAC. Diez-roux et al. investigated whether any relations of SEP with coronary calcification would differ by race/ethnicity, using data from 2,553 non-Hispanic Whites, 1,734 non-Hispanic Blacks, 1,457 Hispanics, and 797 Chinese as part of the Multi-Ethnic Study of Atherosclerosis (MESA).[20] Similar to findings for carotid IMT in MESA,[25] low education was independently and significantly associated with increased probability of calcification in whites. In blacks, income appeared to be inversely associated with calcification. In contrast, low education appeared to be associated with lower probability of calcification among Hispanics. Inverse associations observed in Blacks and Whites were reduced by approximately 50% after CVD risk factor

adjustment. Among persons with detectable calcium, the association between SEP and amount of coronary calcification was also investigated. Low education was associated with more calcium in Blacks, and low income was associated with more calcium in both whites and blacks. Similar to the reverse pattern of associations observed for education and probability of calcification in Hispanics, low education was associated with less, as apposed to more calcium in Hispanics. Dragano et al. examined the relation between SES and CAC in the Heinz Nixdorf Recall Study, an on-going cohort study based on the three large German cities.[157] After adjustment for age, men and women with 10 or less years of formal education had a 70% and 80% increase in calcification score as compared with men and women with high education, respectively. Associations observed for income were weaker, with a 20% and 50% increase in calcification score for the lowest compared with the highest quartile among men and women, respectively. Consecutive adjustment for cardiovascular risk factors significantly attenuated the observed association. Yan et al. assessed the relation between education and CAC,[30] reporting results consistent with other studies. In a sample of black and white men and women from the Coronary Artery Risk Development in Young Adults (CARDIA) study, there was a significant inverse and graded relationship between educational level and prevalence of CAC after adjustment for age, race, and sex. Similar associations were observed within each of the 4 race-sex groups. In addition to adjustment for baseline CVD risk factors, the authors also adjusted for 15-year changes in risk factors, reporting that adjustment for baseline risk factors attenuated associations observed but adjustment for 15-year changes in risk factors had minimal effect. As stated by the authors, this was the first study to demonstrate a relationship between education and CAC among young and early middle-aged individual.

Fewer studies to date have utilized ABI as a measure of subclinical atherosclerosis in relation to SEP. In 1991, Fowkes et al. reported on a cross-sectional survey conducted on an age-stratified sample of men and women aged 55-74 in the Edinburgh Artery Study.[186] PAD was assessed by means of the WHO questionnaire on intermittent claudication, measurement of the ankle brachial

systolic pressure index (ABPI), and change in ankle systolic pressure during reactive hyperaemia. Mean ABPIs differed significantly between social class groups, showing a consistent decreasing trend from social class I to V. This trend was stronger in males than in females. In men but not in women, Mean ABPI decreased consistently from those who attended university to those who only attended primary school. Rooks et al. investigated the relation of race and SES with CVD indicators in the Health, Aging, and Body Composition Study, a longitudinal research study of well-functioning older adults in Tennessee and Pennsylvania.[16] Aside from including education and family income in their measure of SES, they also included measures of home ownership and ownership of other financial assets, proposing that these latter measures may be more relevant to older age groups. The authors reported that being black was significantly associated with elevated systolic blood pressure (men only), low ankle-arm index (AAI), and left ventricular hypertrophy (LVH). These racial associations with CVD were reduced the most by income for elevated SBP in men, and other financial assets for low AAI (men and women) and LVH (men only). However, all associations remained significant after accounting for each SES measure. In analyses of SES in relation to CVD indicators after adjustment for race, family income remained associated with low AAI in women, while education, home ownership, and other financial assets remained associated with low AAI in men. In 2006, Woo et al. examined the prevalence of atherosclerosis, measured as ABI < 0.9, and associated socioeconomic and lifestyle factors in a sample of 3,999 male and female elderly Chinese volunteers in Hong Kong.[187] SES was obtained by asking participants about their standing in the community, and their perception of status regarding money, education, and respectable jobs. A higher status in the community was associated with low ABI, but no significant associations were observed for the other socioeconomic measure (money, education, respectable job).

### *2.4.4. The association between life course socioeconomic position and subclinical atherosclerosis*

Only a handful of studies have included life course measures in their investigation of SEP and subclinical disease. Some of these studies have tested the 'Sensitive Periods' framework by looking at how SEP at stages other than adulthood influences risk for subclinical disease. Lamont et al. assessed the effect of fetal life, childhood, and adult life on risk for CVD in 154 males and 193 females from the "Newcastle thousand families" cohort.[23] Early life factors considered were family history, birth weight, and SEP at birth, while childhood factors included SEP during childhood, growth, illness, and adverse life events during childhood. Proportions of variance in carotid IMT that were accounted for by each of these life course stages were examined. The authors found that social class at birth, measured by father's occupational social class, displayed a strong negative association with carotid IMT in women and not in men. The association observed in women remained statistically significant after adjustment for adult lifestyle and biological risk markers. SEP at ages 5 and 10 years, measured by social class of the main wage-earner of the household, were unrelated to carotid IMT. Thus, the authors concluded that other than social class at birth in women, adult lifestyle and biological risk markers were the most important determinants of cardiovascular health in the study members. Thurston et al. examined socioeconomic and racial disparities in IMT and PWV among 81 African American and 78 Caucasian adolescents (mean age 17.8) from two schools in Pittsburgh, USA.[29] SES indices included parental education, family income, family assets, subjective social status, and census-derived neighbourhood SES. Analyses revealed that High school parental education, low (vs. high,) or medium family income (vs. high), and lower neighbourhood SES were associated with higher PWV, controlling for age, gender, BMI, and SBP. Of the SES indicators, only fewer household assets were significantly associated with higher IMT, controlling for age, BMI, SBP, and gender. When objective individual-level SES variables (education, income) were included with race in relation to PWV, only family income remained significantly associated with PWV, and family assets

remained associated with lower IMT. Stratified by race, low income was associated with PWV among African Americans, whereas low education was associated with higher PWV among Caucasians. The authors concluded that findings support the hypothesis that racial and socioeconomic disparities in arterial stiffness and IMT begin early in life, and that low SES African American adolescents may be at particular risk. Lemelin et al. examined childhood SEP, adulthood SEP, and 20-year average exposure to neighbourhood poverty in relation to prevalence of subclinical atherosclerosis in participants from MESA.[24] After adjustment for age, neighbourhood SEP (obtained by geo-coding and linking residential addresses to census data), childhood SEP (measured as father or caretaker's education) and adulthood SEP (a summary score of income, education, and wealth) were all inversely and independently associated with IMT in women, while Childhood SEP and adulthood SEP but not exposure to neighbourhood poverty were associated with IMT in men. Associations were somewhat reduced after adjustment for CVD risk factors. Heterogeneity in effects of adulthood SEP by race/ethnicity was also noted. Among black men, higher adulthood SEP was associated with slightly greater, rather than lower, IMT. This was similar to findings from Ranjit et al. in the Kuopio Ischemic Heart Disease Risk Factor Study, where lower SEP was associated with a lower rate of IMT progression from baseline. No associations of adulthood SEP and IMT was observed in Hispanics, comparable to findings from Lutsey et al. in the same study population. A much stronger association between neighbourhood SEP and IMT was observed for black women, as compared with white women. The association of neighbourhood SEP and IMT in Hispanic women was in the opposite direction as that observed in black and white women, similar to findings by Diez-roux et al. in the MESA population. The authors concluded that the link between childhood SEP and IMT in adulthood, even after controlling for adults measures, suggests that the early childhood socioeconomic environment has a long-lasting effect on the development of atherosclerosis.

Two studies to date have included cumulative measures of SEP in their assessment of life course SEP in relation to subclinical atherosclerosis. In addition

to examining the relation of childhood and adulthood SES with carotid stenosis, Rosvall et al. also assessed the impact of life-course SES by using a cumulative measure of one's combined SES during childhood and adulthood.[28] Childhood SES was assessed as father's occupational status, while the subject's own occupational status was used as a measure of adulthood SES. A cumulative measure of SES during childhood and adulthood was taken by means of a total SES life-course score ranging from 2 to 8, a combination of the father's and the subject's occupational status scores: high- or medium-level non-manual employees were given 1 point; low-level non-manual employees, 2 points; skilled manual workers, 3 points; and unskilled manual workers, 4 points. Primary analyses considered the effects of father's occupational status as well as own occupational status simultaneously. Among women, the age-adjusted carotid stenosis prevalence odds were significantly higher for those in unskilled manual occupations than for those in high- or medium-level non-manual occupations, this being observed for both father's occupational status as well as own occupational status . Such a pattern of linkage could be discerned only for the association with adult occupational status in men. Adjustment for atherosclerotic risk factors did not change the magnitude of the association with father's occupation found in women, whereas the association with the subject's own occupation was attenuated and turned statistically non-significant. In analyses examining the cumulative effect of SES, there was a clear trend in women, with the odds of carotid stenosis rising with an increasing SES life course score. Again, no clear pattern could be seen between the SES life course score and carotid stenosis in men. The authors took their findings to indicate that total life-course exposure to low SES, with contributions from childhood and adulthood, seems to play a role in atherogenesis in women.

In 2007, Carson et al. investigated the relation between cumulative individual-level SES across the life course, neighbourhood-level SES across the life course, and PAD, defined as ABI < 0.9.[19] Participants were from the ARIC prospective study, a middle-aged cohort of black and white men and women. A cumulative life course SES score was created by summing values for various SES indicators

(education, occupation, occupational role, home ownership, and income) at each of 3 different life course periods (childhood, young adulthood, and older adulthood). In order to measure neighbourhood-level life course SES, childhood and adulthood residential data were linked to country level census data. Race-specific z-scores were then obtained for each census variable, from which a summary z score for neighbourhood-level life course SES was created, with greater summary z score values reflecting higher neighbourhood-level SES. Sex- and race-specific age-adjusted analyses revealed an inverse association between cumulative individual-level SES and PAD in white men, white women, and black women, but not black men. A lack of association observed for black men was attributed to lack of power. Adjustment for numerous CVD risk factors attenuated the associations observed; however the authors noted that when changes in parameter estimates were evaluated to assess the potential mediating role of each CVD risk factor, none of the risk factors tested was a strong or moderate mediator of the association between SEP and PAD. In analyses for neighbourhood-level life course SES, the lowest tertile as compared with the highest tertile of neighbourhood-level life course SES was not associated with PAD for whites or blacks.

#### *2.4.4. Summary*

This literature review evaluated evidence on the association between SEP and CVD, recognized several decades ago and consistently observed today. As the inverse relation between SEP and CVD is widely accepted, studies are increasingly turning focus on to understanding the mechanistic pathways that may link SEP with CVD. Furthermore, it is increasingly recognized that chronic diseases such as CVD are the result of life course processes that are likely complex. Thus, a better understanding of the association between SEP and CVD can be gained by adopting a life course perspective.

# CHAPTER 3: MANUSCRIPT

## Cumulative Life course Socioeconomic Position and Ankle-brachial Index

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**ABSTRACT WORD COUNT:** 248

**MANUSCRIPT WORD COUNT:** 4,362

## 3.1. Abstract

Socioeconomic position (SEP) across the life course is inversely associated with cardiovascular disease (CVD); however, the biological mechanisms are poorly understood. Our objective was to investigate whether cumulative life course SEP is associated with a measure of subclinical atherosclerosis: the ankle-brachial index (ABI). The study was a prospective analysis of 1454 participants from the Framingham Heart Study Offspring Cohort (mean age 57 years, 53% women). Cumulative SEP was calculated by summing scores for 3 individual measures of SEP: father's education, own education, and own occupation. ABI was dichotomized as low (≤1.1) and normal (>1.1 to 1.4), due to increased risk for CVD events with values ≤1.1. After adjustment for age, smoking, systolic blood pressure, antihypertensive medication, fasting glucose, total:HDL cholesterol ratio, cholesterol-lowering medication, diabetes, and depression score, cumulative life course SEP was associated with low ABI in men (odds ratio [OR]=2.09, 95% confidence interval [CI]: 1.24,3.51 for low vs. high cumulative SEP score), but not in women (OR=0.94, 95% CI: 0.63,1.38 ). This effect was largely explained by the association of own education with low ABI in men (OR=4.15, 95% CI: 1.87,9.22 for <high school vs. >high school) and not in women (OR = 1.12, 95% CI:0.62,2.01), after adjustment for other individual SEP measures and CVD risk factors. Father's education and own occupation were not significantly associated with low ABI in men or women. In conclusion, cumulative SEP was inversely associated with ABI in men and not women; however associations in men were largely due to own education.

## 3.2. Introduction

There is increasing evidence that life course socioeconomic position (SEP) has important contributions to the development of cardiovascular disease (CVD). Various life course SEP frameworks have been developed, which propose that socioeconomic circumstances experienced at various stages of life may independently, collectively, and interactively contribute to downstream health effects. In particular, the *cumulative risk* life course SEP framework suggests that negative socioeconomic exposures accumulated over the life course may influence later disease, and that disease risk increases as the number, duration, and severity of these exposures increase.[12, 13] Accumulation of risk may occur when negative socioeconomic exposures cluster with other types of exposures (e.g. environmental, behavioural, and physiological) that also affect health. Additionally, negative socioeconomic exposures may form chains of risk, where one negative exposure increases the likelihood of a subsequent one.[13] Cumulative life course SEP is usually measured by summing negative socioeconomic exposures an individual has experienced at various stages of life, and creating SEP indices that represent the accumulation of these exposures across the life course. Numerous observational studies showed that cumulative life course SEP is inversely associated with CVD in various European countries.[10, 14] and in the United States.[15]

In order to better understand the biological mechanisms by which cumulative SEP may influence CVD, it is informative to consider how cumulative SEP influences the atherosclerotic process before clinical manifestation of CVD occurs. Several studies reported inverse associations between adulthood SEP and indicators of subclinical atherosclerosis,[17, 18, 21, 22, 25-27, 30] and a smaller number of studies have found that SEP during other life periods (e.g. birth or adolescence) is also associated with subclinical atherosclerosis.[23, 24, 29] Common measures of subclinical atherosclerosis in these studies include coronary artery calcium (CAC) and carotid intima-media thickness (IMT), while ankle-brachial index (ABI) was examined to a lesser extent. In addition, prior investigations of SEP in relation to subclinical atherosclerosis were limited to SEP measured at one time point in the

life course. We are aware of only two prior studies which examined life course SEP in relation to subclinical atherosclerosis using a cumulative measure of SEP [19, 28]; only one of these two studies examined subclinical atherosclerosis using the ABI measure, reporting inverse associations between cumulative SEP and low ABI (ABI $\leq$0.9).[19]

The objective of this study was to investigate whether cumulative life course SEP is associated with ankle-brachial index (ABI) in the Framingham Study Offspring Cohort, taking into account other risk markers for CVD.

## 3.3. Methods

### *Study Population*

The Framingham Heart Study is a community-based, observational cohort study that was initiated in 1948 to investigate risk factors for coronary heart disease (CHD). The present investigation was based on participants in the Framingham Offspring Study which began in 1971 with recruitment of 5,124 US men and women who were offspring (or offspring's spouses) of the original cohort of the Framingham Heart Study. The design and selection criteria of the Framingham Offspring Study have been described elsewhere.[188] Participants were examined every 4-8 years, undergoing medical history, physical examination, anthropometry, and laboratory assessment of CHD risk factors at each examination, as previously described.[188] Framingham Study participants signed informed consent and the Framingham Study is reviewed annually by the Boston University Medical Center Institutional Review Board.

### *Measures of Socioeconomic Position*

*Childhood SEP:* Childhood SEP was measured by father's educational attainment, obtained directly from the participants' fathers who were enrolled in the Framingham Heart Study original cohort between 1948 and 1950 (mean age 44, range 28-62 years). Father's education was initially ascertained as a 6-category variable: 8th grade or less, some high school (i.e. did not graduate from high school), high school graduate, some college (i.e. did not graduate from college), college graduate, and a final category including post graduate, business

college, nursing school, music school and art school. For analyses, father's education was categorized as 3 levels: <high school, completed high school, and >high school.

*Young Adulthood SEP:* Young adulthood SEP was measured by own educational attainment, obtained directly from the Framingham Offspring Study participants at Examination 3 (1984-1987); if Examination 3 education was missing, the Examination 2 assessment (1979-1982) was used. Education was initially ascertained as years of education completed, divided into 6 categories: 0-4, 5-8, 9-11, 12, 13-16 and ≥17 years. For analyses, education was categorized as 3 levels: ≤12, 13-16 and ≥17 years of education.

*Active Professional Life SEP:* Active professional life SEP was measured as own occupation, and was ascertained at Examination 2 (1979-1982) by asking what kind of work the participants did, categorized as professional, executive, supervisory, technical, laborer, clerical, sales and homemaker. For analyses, occupation was categorized as 3 levels: Laborer, Homemaker/Clerical/Sales, and Professional/Executive/ Supervisory/Technical.

*Cumulative Life course SEP:* Analyses testing the *accumulation of risk* framework used a cumulative SEP score, created by summing values for SEP at three successive life course periods: childhood SEP (measured as father's education: <high school=0, high school=1, >high school=2), young adulthood SEP (measured as own education: ≤12 years=0, 13-16 years=1, ≥17 years=2), and active professional life SEP (measured as own occupation: laborer=0, clerical/sales/homemaker=1, executive/professional/supervisory/technical=2). Higher cut points were used for educational categories of offspring, compared with fathers, to account for secular trends of increased normative levels of education across generations. Lower scores indicate accumulation of low SEP across the life course, while higher scores indicate higher SEP attatinment through the life course.

***Measure of subclinical atherosclerosis: Ankle Brachial Index***

ABI is the ratio of systolic blood pressure at the ankle to that in the arm, and serves as a standard measure of Peripheral Arterial Disease (PAD) in the lower

limbs[31] In healthy individuals without peripheral atherosclerosis, systolic blood pressure (SBP) increases with greater distance from the heart, leading to higher SBP at the ankle as compared with the arm,[32] and consequently a ratio typically greater than 1.00. However in the presence of peripheral atherosclerosis, poor circulation leads to lower ABI values observed.[189] ABI is also recognized as an indicator of generalized subclinical atherosclerosis, as lower levels of ABI have been shown to be predictive of an increased risk of CVD events and mortality, over and above conventional CVD risk factors.[33]

Measurements of ABI were obtained at Offspring examination 6 (1995-1998). Ankle-brachial systolic blood pressure measurements were performed by trained technicians according to standardized protocols.[190] Systolic blood pressure was measured using an 8-MHz Doppler pen probe and an ultrasonic Doppler flow detector (Parks Medical Electronics, Inc., Aloha, Oregon). For each limb (right arm, left arm, right ankle, left ankle), the cuff was inflated to the maximum inflation level then deflated at 2 mmHg per second until systolic blood pressure was audible. Two measures of all limb blood pressures were obtained. ABI was calculated for each leg as the ratio of average systolic blood pressure in the ankle divided by average systolic blood pressure in the arm with the higher blood pressure. The lower of the ABI values calculated for the left and right ankle was used for analyses. If ABI was missing for one ankle, data from the non-missing ankle was used.

Emerging evidence has demonstrated increased risk for coronary and carotid atherosclerosis, coronary events, and CVD mortality up to ABI values of 1.1,[34, 35] consequently the Ankle Brachial Index Collaboration defined a normal or low risk ABI as 1.1 to 1.4.[34] Therefore, ABI was dichotomized as low (ABI $\leq$1.1) *vs.* normal (ABI=1.1-1.4) for the present investigation. However, additional analyses were carried out for women, using a lower cut point of 1.0 to define low ABI. This was done in light of some recent evidence suggesting that normal ABI values may be intrinsically lower in healthy women than men, and that using a single threshold to define low ABI in both men and women can distort population estimates of disease burden.[191] Participants with an ABI value $\geq$1.4 were excluded

from analyses (as ABI values may be inaccurate in these individuals, due to poor arterial compressibility). Due to a very low number of people (n=41) with an ABI value ≤0.9 (i.e. definite PAD), there was inadequate statistical power to carry out analyses with ABI dichotomized as ≤0.9 *vs.* >0.9-1.4 (for example, power (1-β) was equal to 25.6% for a low ABI (≤0.9) outcome rate of 2% vs. 0.5% for own education ≤12 years (n=229) vs. ≥17 years (n=191), with α=0.05).

***Covariates***

All covariates were measured at Offspring Examination 6. Smoking status (current, former, or never) was determined by self report. Systolic blood pressure was calculated as the average of the clinic physician's two seated systolic blood pressure measurements. Body mass index (BMI) was calculated as the weight in kilograms divided by the square of the height in meters ($kg/m^2$). Fasting glucose was measured with a hexokinase reagent kit (A-gent glucose test, Abbott, South Pasadena, California). Glucose assays were run in duplicate, and the intra-assay coefficient of variation ranged from 2% to 3%, depending on the assayed glucose concentration. High density lipoprotein and total cholesterol concentrations were measured by automated enzymatic techniques.[192] Depressive symptomatology was measured by using the Center for Epidemiologic Studies Depression (CES-D) scale and was adjusted for in analyses as a continuous variable (range: 0-51). Medication use was self-reported. CVD events were identified in participants since the onset of the Framingham Offspring study (1971-1975), and included recognized myocardial infarction, coronary insufficiency, cerebrovascular events (including cerebral atherothrombotic infarction, cerebral embolism, intracerebral hemorrhage, subarachnoid hemorrhage, and other cerebrovascular accident), and congestive heart failure.

***Exclusion Criteria***

There were 3,413 participants in the dataset who completed offspring examination 6 (1995-1998), on which this present investigation was based. After implementation of exclusion criteria (**Figure 1**), the final sample size was 1454 (782 women and 672 men). Comparisons of excluded (n=1913) vs. included (n= 1454) participants demonstrated that those excluded were more likely to be older

(mean age at 60.0 vs. 57.2 years, respectively, p<0.0001), to be taking anti-hypertensive medication (31.6% vs. 23.5%, p<0.0001), cholesterol lowering medication (15.2% vs. 10.0%, p<0.0001), and to be diabetic (11.3% vs. 8.4%, p=0.006). Included and excluded participants did not differ significantly for other variables including sex, BMI, fasting glucose, HDL: total cholesterol ratio, depression score, and current smoking.

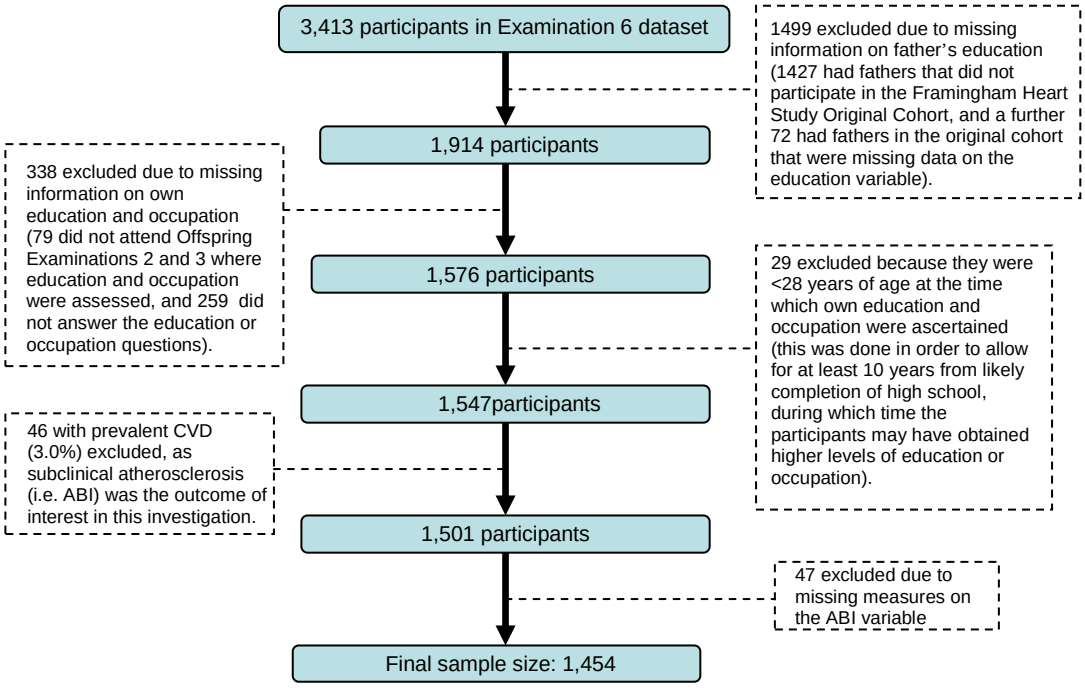


**Figure 1.** Exclusion criteria and final sample size for the present investigation.

***Statistical Analyses***

Multivariable logistic regression analyses evaluated the association between cumulative SEP and ABI. Analyses were initially adjusted for age only, followed by additional adjustment for CVD risk markers described above.

Analyses of individual SEP measures (each representing a different life course period) in relation to ABI were also carried out, in order to evaluate whether SEP at any of these 3 life course periods particularly contributed to cumulative SEP risk for low ABI. Analyses were initially adjusted for age only, followed by further adjustment for other individual SEP measures, and finally

additional adjustment for CVD risk markers. All analyses performed were sex-specific, as there was evidence of effect modification by sex (p=0.003 for interaction between own education and sex and p=0.01 for interaction between cumulative SEP score and sex). Generalized Estimating Equations (GEE), extension of multiple logistic regression with exchangeable covariance structure, were used to account for clustering of outcomes by family.[193]

Pearson correlation coefficients and variance inflation factors (VIFs) were used to evaluate co-linearity, and evidence of even moderately strong correlations was not found (all pair-wise Pearson's correlation coefficients were less than 0.40 and all VIFs were below 3.0). The three SEP variables (father's education, own education and own occupation) also had minimal variance inflation (pair-wise correlation coefficients ranged from 0.25 to 0.51), and were not correlated highly enough to be of concern when simultaneously including all three in a single multivariable model Power analyses were performed using PS Power and Sample Size Calculation Version 3.0.2, according to methods for an independent prospective study design, with data analyzed using an uncorrected chi-squared test.[194] The null hypothesis was tested with respect to a two-sided alternative hypothesis, with the alternative hypothesis being specified in terms of outcome probabilities.

## 3.4. Results

Participants in the study sample had a mean age of 57 years (range 38–80 years) and 53.7% were women. Mean ABI was 1.16 (standard deviation (SD) 0.1) in men and 1.09 (SD 0.1) in women. The prevalence of low ABI defined as $\leq$1.1 was 21% in men, as compared with 49 % in women; low ABI defined as $\leq$1.0 demonstrated a prevalence of 4.8% in men and 16% in women. In age-adjusted analyses in men, lower father's education was associated with higher body mass index, systolic blood pressure, total: HDL cholesterol ratio, and depression score, and more frequent use of anti-hypertensive medication (**Table 1**). Own education was inversely associated with mean ABI, body mass index, total: HDL cholesterol ratio, cholesterol-lowering medication use, current smoking, diabetes, and

depression score. Finally, men in lower occupation categories had significantly higher body mass index (**Table 1**).

In women, father's education was inversely associated with body mass index, total: HDL cholesterol ratio, anti-hypertensive medication use, current smoking, and depression score (**Table 2)**. Own education was inversely associated with mean ABI, body mass index, systolic blood pressure, total: HDL cholesterol ratio, fasting glucose, anti-hypertensive medication use, cholesterol-lowering medication use, diabetes, current smoking, diabetes, and depression score. Women in lower occupation categories had significantly higher body mass index and depression score, and were more likely to be current smokers and on anti-hypertensive medication (**Table 2**).

**Table 1. Males - age-adjusted characteristics according to socioeconomic position (SEP) measures**

| | Father's education | | |
|---|---|---|---|
| | **<High School** (n = 331 ) | **High School** (n = 157 ) | **>High School** (n = 184 ) |
| Age, years* | 58.9 (58.0,59.8) | 53.2 (51.9,54.5) | 55.8 (54.6,57.0) |
| Mean ABI | 1.16 (1.15,1.17) | 1.16 (1.13,1.17) | 1.17 (1.15,1.18) |
| Body mass index, kg/m$^2$ | 29.2 (28.7,29.6) | 28.2 (27.5,28.9) | 28.2 (27.5,28.8) |
| Systolic blood pressure, mmHg | 129.1 (127.4,130.7) | 130.5 (128.1,132.9) | 126.5 (124.3,128.7) |
| Total:HDL cholesterol ratio† | 5.3 (5.0,5.6) | 5.0 (4.6,5.4) | 4.6 (4.2,4.9) |
| Fasting glucose, mg/dL | 106.8 (103.8,109.7) | 108.0 (103.8,112.3) | 104.8 (100.9,108.6) |
| Anti-hypertensive medication use, % | 24.7 (20.2,29.9) | 30.8 (23.6,39.2) | 16.2 (11.4,22.5) |
| Cholesterol-lowering medication, % | 11.3 (8.3,15.3) | 12.8 (8.2,19.4) | 9.7 (6.2,14.9) |
| Diabetes, % | 8.6 (6.0,12.3) | 8.5 (4.9,14.5) | 7.8 (4.7,12.6) |
| Current smoker, % | 14.0 (10.6,18.3) | 17.3 (12.2,24.2) | 11.8 (7.9,17.2) |
| Depression Score | 4.9 (4.2,5.7) | 5.1 (4.1,6.2) | 3.8 (2.9,4.8) |
| | **Own Education** | | |
| | **≤12 years** (n = 216 ) | **13-16 years** (n = 270) | **≥17 years** (n = 186) |
| Age, years* | 58.4 (57.2,59.6) | 56.9 (54.8,57.0) | 55.9 (54.8,57.0) |
| Mean ABI | 1.15 (1.14,1.17) | 1.15 (1.14,1.16) | 1.19 (1.17,1.20) |
| Body mass index, kg/m$^2$ | 28.6 (28.0,29.1) | 29.2 (28.7,29.8) | 27.9 (27.3,28.6) |
| Systolic blood pressure, mmHg | 128.3 (126.2,130.3) | 129.1 (127.3,130.9) | 128.6 (126.4,130.8) |
| Total:HDL cholesterol ratio† | 5.3 (5.0,5.6) | 5.0 (4.7,5.3) | 4.7 (4.3,5.0) |
| Fasting glucose, mg/dL | 106.5 (102.9,110.0) | 108.2 (105.1,111.4) | 104.0 (100.2,107.9) |
| Anti-hypertensive medication use, % | 24.3 (18.9,30.7) | 25.5 (20.5,31.3) | 20.8 (15.5,27.4) |
| Cholesterol-lowering medication, % | 11.5 (7.9,16.5) | 13.9 (10.2,18.6) | 6.9 (4.0,11.6) |
| Diabetes, % | 10.7 (7.2,15.6) | 8.4 (5.6,12.4) | 5.7 (3.1,10.0) |
| Current smoker, % | 18.5 (13.8,24.4) | 16.7 (12.7,21.8) | 5.7 (3.2,9.9) |
| Depression score | 5.1 (4.2,6.1) | 4.9 (4.1,5.7) | 3.9 (2.9,4.8) |
| | **Own Occupation** | | |
| | **Laborer** (n = 234 ) | **Housewife/ Clerical/ Sales** (n = 84) | **Supervisory/ Professional / Executive/ Technical** (n = 354 ) |
| Age, years* | 57.7 (56.6,58.9) | 58.0 (56.1,59.9) | 55.8 (54.9,56.6) |
| Mean ABI | 1.15 (1.14,1.17) | 1.15 (1.13,1.17) | 1.17 (1.16,1.18) |
| Body mass index, kg/m$^2$ | 29.2 (28.6,29.8) | 28.7 (27.7,29.6) | 28.3 (27.8,28.8) |
| Systolic blood pressure, mmHg | 127.9 (126.0,130.0) | 130.5 (127.3,133.8) | 128.8 (127.2,130.4) |
| Total:HDL cholesterol ratio† | 5.0 (4.7,5.4) | 5.1 (4.5,5.6) | 5.0 (4.7,5.2) |
| Fasting glucose, mg/dL | 106.2 (102.7,109.6) | 102.6 (96.9,108.3) | 107.7 (104.9,110.4) |
| Anti-hypertensive medication use, % | 24.2 (19.0,30.3) | 22.3 (14.6,32.5) | 23.9 (19.6,28.8) |
| Cholesterol-lowering medication, % | 11.3 (7.8,16.0) | 13.0 (7.4,21.8) | 10.7 (7.9,14.5) |
| Diabetes, % | 9.6 (6.4,14.2) | 5.8 (2.5,12.6) | 8.1 (5.7,11.5) |
| Current smoker, % | 15.7 (11.5,21.0) | 16.4 (9.9,26.0) | 12.6(9.6,16.6) |
| Depression score | 5.2 (4.3,6.1) | 5.3 (3.8,6.7) | 4.2 (3.5,4.9) |

*Calculated using univariate analyses.

†HDL, high density lipoprotein.

Data are expressed as means or percent prevalence (95 percent confidence intervals), Framingham Heart Study Offspring Cohort, United States (1971-1975).

**Table 2. Females - age-adjusted baseline characteristics according to socioeconomic position (SEP) measures**

| | Father's education | | |
|---|---|---|---|
| | **<High School** | **High School** | **>High School** |
| | (n = 388 ) | (n = 203 ) | (n = 191 ) |
| Age, years* | 60.0 (59.1,60.9) | 53.9 (52.8,55.1) | 56.2 (54.9,57.4) |
| Mean ABI | 1.09 (1.08,1.10) | 1.09 (1.08,1.10) | 1.09 (1.07,1.10) |
| Body mass index, kg/m$^2$ | 27.8 (27.2, 28.3) | 27.2 (26.4, 28.0) | 26.7 (25.9,27.5) |
| Systolic blood pressure, mmHg | 126.2 (124.4,128.0) | 124.7 (122.2,127.2 | 125.3 (122.8,127.8) |
| Total:HDL cholesterol ratio† | 4.1 (3.9,4.2) | 3.9 (3.7,4.1) | 3.8 (3.6,3.9) |
| Fasting glucose, mg/dL | 100.6 (97.9,103.2) | 99.5 (95.8,103.2) | 98.5 (94.8,102.2) |
| Anti-hypertensive medication, % | 22.8 (18.7,27.5) | 18.8 (13.7,25.2) | 17.8 (12.9,24.1) |
| Cholesterol-lowering medication, % | 7.4 (5.1,10.6) | 7.0 (4.1,11.8) | 6.4 (3.7,10.9) |
| Diabetes, % | 7.3 (5.0,10.5) | 6.6 (3.7,11.2) | 5.6 (3.0,9.9) |
| Current smoker, % | 19.2 (15.5,23.5) | 17.7 (13.0,23.6) | 13.5 (9.4,19.1) |
| Depression score | 7.5 (6.7,8.4) | 6.5 (5.3,7.7) | 5.3 (4.0,6.5) |
| | **Own Education** | | |
| | **≤12 years** | **13-16 years** | **≥17 years** |
| | (n = 333) | (n = 355) | (n = 94 ) |
| Age, years* | 59.2 (58.3,60.2) | 56.7 (55.8,57.7) | 54.2 (52.3,56.1) |
| Mean ABI | 1.08 (1.07,1.09) | 1.09 (1.08,1.10) | 1.10 (1.08,1.12) |
| Body mass index, kg/m$^2$ | 27.8 (27.2,28.4) | 27.1 (26.5,27.7) | 26.6 (25.4,27.8) |
| Systolic blood pressure, mmHg | 126.5 (124.6,128.4) | 125.6 (123.7,127.4) | 122.5 (118.9,126.2) |
| Total:HDL cholesterol ratio† | 4.0 (3.8,4.1) | 4.0 (3.8,4.1) | 3.7 (3.4,3.9) |
| Fasting glucose, mg/dL | 100.5 (97.6,103.3) | 99.8 (97.1,102.6) | 97.2 (91.8,102.5) |
| Anti-hypertensive medication, % | 25.6 (21.0,30.7) | 18.5 (14.7,23.0) | 10.3 (5.4,18.7) |
| Cholesterol-lowering medication, % | 8.9 (6.2,12.5) | 6.0 (4.0,9.0) | 4.4 (1.7,11.3) |
| Diabetes, % | 8.5 (5.9,12.2) | 5.8 (3.8,8.8) | 3.4 (1.1,10.0) |
| Current smoker, % | 22.4 (18.2,27.3) | 14.1 (10.8,18.1) | 12.5 (7.3,20.6) |
| Depression score | 8.1 (7.2,9.1) | 5.9 (5.0,6.8) | 5.0 (3.2,6.7) |
| | **Own Occupation** | | |
| | **Laborer** | **Housewife/ Clerical/ Sales** | **Supervisory/ Professional/ Executive/ Technical** |
| | (n = 65 ) | (n = 532) | (n = 185 ) |
| Age, years* | 61.0 (58.7,63.3) | 58.0 (57.2,58.7) | 55.0 (53.6,56.3) |
| Mean ABI | 1.09 (1.06,1.11) | 1.09 (1.08,1.10) | 1.10 (1.09,1.12) |
| Body mass index, kg/m$^2$ | 28.5 (27.1,29.9) | 27.3 (26.8,27.8) | 27.0 (26.2,27.8) |
| Systolic blood pressure, mmHg | 125.8 (121.4,130.1) | 126.2 (124.7,127.8) | 123.7 (121.1,126.3) |
| Total:HDL cholesterol ratio† | 4.0 (3.7,4.4) | 4.0 (3.9,4.1) | 3.9 (3.7,4.1) |
| Fasting glucose, mg/dL | 100.5 (94.1,106.9) | 99.3 (97.0,101.5) | 101.0 (97.2,104.8) |
| Anti-hypertensive medication, % | 27.9 (18.4,40.0) | 21.1 (17.8,24.9) | 16.3 (11.5,22.7) |
| Cholesterol-lowering medication, % | 7.2 (3.3,15.2) | 8.0 (5.9,10.8) | 4.2 (2.1,8.3) |
| Diabetes, % | 5.6 (2.2,13.3) | 7.4 (5.4,10.1) | 4.9 (2.5,9.2) |
| Current smoker, % | 32.6 (22.1,45.2) | 17.7 (14.7,21.2) | 11.3 (7.5,16.7) |
| Depression score | 9.9 (7.9,12.0) | 6.4 (5.7,7.2) | 6.3 (5.1,7.6) |

*Calculated using univariate analyses.

†HDL, high density lipoprotein.

Data are expressed as means or percent prevalence (95 percent confidence intervals), Framingham Heart Study Offspring Cohort, United States (1971-1975).

Age-adjusted logistic regression models showed that lower cumulative SEP across the life course was associated with higher prevalence of low ABI in men (odds ratio [OR]=2.00, 95% confidence interval [CI]:1.28, 3.14 for low vs. high cumulative SEP score) and not in women (OR=0.94, 95% CI:0.63,1.38) (**Table 3**). Further adjustment for CVD risk factors did not attenuate the association in men (OR=2.09, 95% CI: 1.24, 3.51). In analyses of individual SEP measures in relation to ABI, own education was associated with low ABI in men (OR=4.82, 95% CI: 2.57,9.05 for ≤ 12 years of education vs. ≥17 years) after adjustment for age only (**Table 4**). Further adjustment for other SEP measures and CVD risk markers did not attenuate the impact of the low education category (OR=4.15, 95% CI: 1.87,9.22). No association between own education and ABI was observed in women (OR=1.23, 95% CI: 0.77,2.00). Own occupation was also inversely associated with ABI in men (OR= 1.55, 95% CI: 1.02,2.35 for occupation as Laborer vs. occupation in a professional/Executive/Supervisory/Technical position). However, the association became statistically non-significant after adjustment for other SEP measures and CVD risk markers (OR=1.24, 95% CI: 0.71,2.16). Own occupation was not associated with ABI in women (OR= 1.36, 95% CI: 0.76,2.41). No significant associations were observed between father's education and ABI in either men or women (**Table 4**).

In additional analyses using ABI dichotomized as ≤1.0 (low) vs. >1.0–1.4 (normal) in women, the point estimate for cumulative SEP were somewhat higher than when an ABI cut point of 1.1 was used to dichotomize ABI (OR= 1.52, 95% CI: 0.88, 2.60 for low vs. high cumulative SEP score), however it still did not reach statistical significance as indicated by wide 95% CIs **(Appendix Table A1).** Similarly, associations of own education and own occupation with ABI using a cut point of 1.0 in women demonstrated slightly higher point estimates than for the standard cut point of 1.1; **(Appendix Table A2)**.

**Table 3. Odds ratios for the association between life course socioeconomic position (SEP) and low ankle-brachial index (ABI), defined as ABI ≤1.10**

| | Men | | | | Women | | | |
|---|---|---|---|---|---|---|---|---|
| | | | Model Adjustment | | | | Model Adjustment | |
| | | | Age | Age, CVD Risk Markers* | | | Age | Age, CVD Risk Markers* |
| Cumulative SEP Score | N | No. of events (ABI ≤1.1) | OR (95% CI) | OR (95%CI) | N | No. of events (ABI ≤1.1) | OR (95% CI) | OR (95%CI) |
| 0 or 1 | 192 | 52 | 2.00 (1.28,3.14) | 2.09 (1.24,3.51) | 230 | 117 | 0.94 (0.63,1.38) | 0.87 (0.57,1.34) |
| 2 or 3 | 189 | 45 | 1.81 (1.13,2.92) | 1.54 (0.89,2.68) | 318 | 153 | 0.93 (0.67,1.31) | 0.94 (0.65,1.37) |
| 4 - 6 | 291 | 42 | 1.00 | 1.00 | 234 | 117 | 1.00 | 1.00 |

*Cardiovascular disease (CVD) risk markers include smoking, body mass index, systolic blood pressure, total:HDL cholesterol ratio, fasting glucose, antihypertensive medication , cholesterol-lowering medication, depressive symptomatology and diabetes.

**Table 4. Odds ratios for the association between socioeconomic position (SEP) measures and low Ankle-brachial index (ABI), defined as ABI ≤1.10**

| | | Men | | | | | Women | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Model Adjustment | | | | | Model Adjustment | | |
| | | | | Age | Age, other SEP measures* | Age, other SEP, CVD risk markers† | | | Age | Age, other SEP measures* | Age, other SEP, CVD risk markers† |
| SEP Measure | SEP Level | N | No. of events (ABI ≤1.1) | OR (95%CI) | OR (95%CI) | OR (95%CI) | N | No. of events (ABI ≤1.1) | OR (95%CI) | OR (95%CI) | OR (95%CI) |
| Father's Education | <High School | 331 | 72 | 1.07 (0.69,1.66) | 0.75 (0.45,1.23) | 0.67 (0.38,1.18) | 388 | 185 | 0.71 (0.49,1.01) | 0.62 (0.43,0.91) | 0.65 (0.43,0.99) |
| | High School | 157 | 32 | 1.20 (0.71,2.04) | 0.96 (0.54,1.71) | 0.98 (0.51,1.89) | 203 | 99 | 0.86 (0.58,1.29) | 0.85 (0.56,1.28) | 0.95 (0.61,1.48) |
| | >High School | 184 | 35 | 1.00 | 1.00 | 1.00 | 191 | 103 | 1.00 | 1.00 | 1.00 |
| Own Education | ≤12 years | 216 | 59 | 4.82 (2.57,9.05) | 5.82 (2.86,11.83) | 4.15 (1.87,9.22) | 333 | 173 | 1.23 (0.76,2.00) | 1.19 (0.68,2.11) | 1.12 (0.62,2.01) |
| | 13-16 years | 270 | 67 | 4.53 (2.45,8.38) | 4.59 (2.44,8.64) | 3.22 (1.61,6.44) | 355 | 172 | 1.11 (0.70,1.78) | 1.05 (0.63,1.75) | 1.00 (0.60,1.67) |
| | ≥17 years | 186 | 13 | 1.00 | 1.00 | 1.00 | 94 | 42 | 1.00 | 1.00 | 1.00 |
| Own Occupation | Laborer | 234 | 57 | 1.55 (1.02,2.35) | 0.92 (0.57,1.50) | 1.24 (0.71,2.16) | 65 | 34 | 1.36 (0.76,2.41) | 1.42 (0.75,2.68) | 1.13 (0.57,2.24) |
| | Homemaker, Clerical or Sales | 84 | 24 | 1.91 (1.10,3.32) | 1.40 (0.79,2.51) | 1.97 (1.04,3.73) | 532 | 275 | 1.40 (1.00,1.96) | 1.43 (0.98,2.10) | 1.34 (0.89,2.02) |
| | Professional, Executive, Supervisory or Technical | 354 | 58 | 1.00 | 1.00 | 1.00 | 185 | 78 | 1.00 | 1.00 | 1.00 |

*"Other SEP measures" refers to adjustment for measures of SEP other than the exposure of interest. For example analyses on father's education are adjusted for own education and own occupation.

†CVDrisk markerss include smoking, body mass index, systolic blood pressure, total:HDL cholesterol ratio, fasting glucose, antihypertensive medication , cholesterol-lowering medication, depressive symptomatology and diabetes

## 3.5. Discussion

Life course Cumulative SEP was inversely associated with subclinical atherosclerosis, measured as ABI, in men. This effect appeared to be largely due to early adulthood SEP measured as participants' education, as opposed to childhood SEP or active professional life SEP. Adjustment for CVD risk markers did not attenuate the associations, suggesting these may not be explanatory mechanisms for the observed associations. Cumulative life course SEP and individual SEP measures were not associated with ABI in women.

***Prior Literature***

Very few studies have investigated associations of SEP in relation to ABI. Carson et al. reported an inverse association between cumulative individual-level SEP and PAD (ABI < 0.9) in middle-aged white men (n=4,284) and women (n= 5,170) of the Atherosclerosis Risk in Communities Study.[19] Associations were attenuated and no longer significant after adjustment for CVD risk factors. Similar to our findings, they found that SEP in the young adulthood period was associated more strongly with PAD than that in the childhood or older adulthood periods. However, it was also reported that magnitudes of association for each life course period were less than that observed for the cumulative SEP measure, while we found that the association between early adulthood SEP and low ABI was stronger than that observed for cumulative life course SEP. Furthermore, in that study associations of SEP with PAD were found in both men and women, while our study did not find associations in women. A more extensive measure of cumulative life course SEP (which included measures of occupational role, home ownership, and income, in addition to education and occupation) may be one reason for their findings of an association in women. Other studies have only investigated associations of adulthood SEP with ABI. In an elderly Chinese sample (n=3999), adulthood SEP (measured as participants' perception about their standing in the community, and status regarding money, education, and respectable jobs) was not associated with ABI.[187] Other studies that examined SEP in relation to ABI reported findings on gender fairly similar to ours. Fowkes

et al. reported on the distribution of symptomatic and asymptomatic PAD in a cross-sectional survey of individuals aged 55 to 74 years in the Edinburgh Artery Study [186]. Mean ABI decreased consistently from those who attended university to those who only attended primary school, these differences being observed in men and not in women. Rooks et al. found inverse associations between various measures of adulthood SEP (education, income, home ownership, and financial assets) and ABI in an elderly population of black and white men and women (n=3075). However, it was reported that after adjustment for race, age, household family size, marital status, and study site, the association between education and low ABI persisted in men but not in women.[16] Another study of 1,025 individuals in the Chianti area of Italy reported significantly lower age-adjusted mean ABI in men but not women with low education vs. high education [195]. Several other studies reported inverse associations of SEP with subclinical atherosclerosis indicators other than ABI, including CAC and IMT.[17, 19, 21, 24, 25, 27-30, 196] Of the few that were stratified by gender, some found associations in both men and women,[19, 24] while others observed significant associations in women but not in men.[17, 28, 184]

Our findings of an association in men but not in women are in line with most of the prior evidence with respect to ABI, nevertheless the lack of significant associations in women was surprising, considering there were large SEP gradients in some of the strongest risk factors for PAD (smoking and diabetes). One explanation is that the use of inappropriate cut points for defining low ABI in women may have contributed to null findings. There is evidence that ABI values are intrinsically lower in women as compared with men. Lower ABI values were observed in women as compared with men in a healthy non-smoking subgroup without glucose intolerance, high blood pressure, or any CVD history, as well as in a healthy subgroup without PAD or major risk factors.[191, 197] Evidence of these differences in normal ABI between men and women exist even after adjustment for height (which is suggested to contribute to the lower ABI observed in women).[186] Furthermore, McDermott et al. found that in the Multi-Ethnic Study of Atherosclerosis (MESA), there was evidence of excess coronary and carotid

atherosclerosis up to an ABI value of 1.1 in men, but only up to an ABI value of 1.0 in women [35] . In our analyses, Using lower ABI cut points (1.0 instead of 1.1) to define low ABI somewhat increased effect sizes for associations of SEP and ABI in women. However, effects would still be considered very weak or null, suggesting these different cut points are not the primary explanation for weak associations among women found in this study. A second potential explanation is that atherosclerosis typically develops at earlier ages in men than women, and that stronger gradients may be observed in men given the mean age of the study population was 57. However, the prevalence of subclinical atherosclerosis (as defined by ABI values below 1.1 or 1.0 in this case) was in fact higher in women than in men in this study population.

To the best of our knowledge, the association between childhood SEP and subclinical atherosclerosis measured as ABI has not been previously investigated however a few studies have investigated this association using other indicators of subclinical atherosclerosis. One study reported that social class at birth was associated with carotid IMT in women, while SEP at ages 5 and 10 (measured by father's occupational social class and the social class of the main wage-earner in the household, respectively) were unrelated to carotid IMT in men and women.[23] Another study found an inverse association between father's occupational status and carotid stenosis in women but not in men, with no change in the magnitude of the association in women after adjustment for atherosclerotic risk factors.[28] Similarly, a third study showed that childhood SEP (measured by father or caretaker's education) was inversely and independently associated with carotid IMT in women and not men.[24]

Associations of childhood SEP with clinically manifest CVD are more established. In their systematic review, Galobardes et al. reported that 31 of 40 studies found a robust inverse association between childhood SEP and risk for various CVD outcomes.[4] Father's occupational class was the indicator most often used to measure childhood SEP in studies included in the systematic review. It is possible that father's education is an imperfect or incomplete proxy for childhood social environment in this study population, which may be one reason for the lack

of association between childhood SEP and low ABI, even in analyses adjusted for age only. However, in a recent study in the Framingham Offspring cohort, father's education was inversely associated with CVD incidence after adjustment for age and sex.[15] In the present investigation persons with clinically manifest CVD were excluded from analyses, in keeping with the study's objective of examining early stages of CVD. Sensitivity analyses revealed that those excluded due to CVD were likely to have lower childhood SEP as well as low ABI (data not shown), thus exclusion of these persons may have led to an underestimation of an association between childhood SEP and low ABI in the study sample.

***Potential Mechanisms***

There is evidence suggesting that the effect of SEP on subclinical and clinically manifest CVD is partly mediated through CVD risk factors [30, 104, 157, 198]. In this investigation, there were strong SEP gradients in several CVD risk factors (particularly some the strongest risk factors for PAD: smoking and diabetes). However, adjustment for these risk factors did not attenuate point estimates for the association of SEP measures with ABI. Several prior studies have similarly reported that adjustment for traditional CVD risk factors did not attenuate statistically significant associations between SEP and subclinical atherosclerosis.[22, 25, 27, 158] Carson et. al. found that adjustment for CVD risk factors attenuated associations between SEP and PAD (ABI < 0.9) However, it was reported that when the potential mediating role of CVD risk factors were assessed , none of the risk factors tested were a strong or moderate mediator of the association between SEP and PAD.[19] It is important to note that methodological biases may arise due to statistical adjustment for potential mediators and confounders.[111] Therefore, results after such adjustments should be interpreted in light of these limitations.

Other potential risk factors, not accounted for in this study, may also explain the association between SEP and atherosclerosis development. For example, novel CVD risk factors (interleukin-6, fibrinogen, homocysteine, D-dimer) were shown to be significantly associated with PAD measured as ABI $\leq$ 0.9, after

adjustment for traditional CVD risk factors.[199] SEP could be related to the development of atherosclerosis through mechanisms involving such novel CVD risk factors . Other important factors that may mediate or modify the association between SEP and subclinical atherosclerosis include psychosocial stressors (poor family function, stressful working conditions, social isolation)[13] and genetic susceptibility.[200]

***Strengths and Limitations***

A major strength of this investigation was that childhood SEP (father's education) was assessed directly from the participants' parents themselves. Thus, this measure was less likely to be subject to measurement error, as compared with studies that obtained measures of childhood SEP retrospectively through personal recall by participants.[4] Furthermore, rigorous quality assurance and quality control methods were used in this study to ensure high quality measures of outcomes and covariates.

Several limitations of this study should be noted. Due to a smaller number of women in certain SEP categories, there was limited statistical power for detecting potential associations(for example, power (1-β) was equal to 28.7% for 34 events observed in 65 women with occupation as a Laborer vs. 78 events observed in 185 women with a professional/Executive/Supervisory/Technical position, with $\alpha$=0.05). Furthermore, individuals in this study population were of European descent (representing the demographics of the city of Framingham at study onset) residing in the Northeastern United States, consequently results from this study are not necessarily generalizable to other communities, races and ethnicities. In addition, individuals with clinically manifest CVD were excluded from analyses, in keeping with the study's objective of examining early stages of CVD. Lastly, there are methodological issues in measuring cumulative SEP. Individual SEP measures, each from a different life course period, are typically weighted equally when creating cumulative SEP indices. This implies that a given socioeconomic experience has the same impact regardless of when it occurs in an individual's lifetime. Furthermore, measures of cumulative SEP conflate SEP measures at

individual life course periods, thus it is unclear as to which time period may be particularly important in its impact on disease.[10] We examined the relative contribution of the SEP in childhood, early adulthood, and later adulthood, each a sub-component of the cumulative SEP index, in order to better understand the contributions of SEP in each of these life periods.

***Conclusions and Implications***

Cumulative life course SEP was inversely associated with low ABI, an indicator of peripheral atherosclerosis, in men and not women of the Framingham Offspring study, however investigation of individual life course periods indicated that socioeconomic conditions in early adulthood were of most importance. This study provides complementary mechanistic evidence supportive of inverse associations found in men between life course SEP and cardiovascular disease in observational studies.[10, 14, 15]

## 3.6. Manuscript Appendix

**Table A1. Odds ratios for the association between cumulative life course socioeconomic position (SEP) and low ankle-brachial index (ABI), defined as ABI ≤1.00, in women.**

| | | | Model Adjustment | |
|---|---|---|---|---|
| | | | Age | Age, CVD Risk Markers* |
| Cumulative SEP Score | N | No. of events (ABI ≤1.0) | OR (95% CI) | OR (95% CI) |
| 0 or 1 | 230 | 49 | 1.52 (0.88, 2.60) | 1.22 (0.68,2.19) |
| 2 or 3 | 318 | 47 | 1.23 (0.73,2.07) | 1.07 (0.62,1.82) |
| 4- 6 | 234 | 30 | 1.00 | 1.00 |

*CVD (cardiovascular disease) risk markers include smoking, body mass index, systolic blood pressure, total:HDL cholesterol ratio, fasting glucose, antihypertensive medication , cholesterol-lowering medication, depressive symptomatology, and diabetes

**Table A2. Odds ratios for the association between socioeconomic position (SEP) and low ankle-brachial index (ABI), defined as ABI ≤1.0, in women.**

| | | | | Model Adjustment | | |
|---|---|---|---|---|---|---|
| | | | | Age | Age, other SEP measures* | Age, other SEP, CVD risk markers† |
| SEP Measure | SEP Level | N | No. of events (ABI ≤ 1.0) | OR (95% CI) | OR (95% CI) | OR (95% CI) |
| Father's Education | <High School | 388 | 69 | 0.96 (0.58,1.58) | 0.78 (0.45,1.34) | 0.81 (0.46,1.4) |
| | High School | 203 | 27 | 0.91 (0.50,1.65) | 0.87 (0.47,1.62) | 1.10 (0.57,2.10) |
| | >High School | 191 | 30 | 1.00 | 1.00 | 1.00 |
| Own Education | ≤12 years | 333 | 68 | 1.45 (0.71,2.99) | 1.36 (0.57,3.24) | 1.13 (0.47,2.69) |
| | 13-16 years | 355 | 46 | 0.93 (0.45,1.94) | 0.88 (0.40,1.96) | 0.77 (0.35,1.70) |
| | ≥17 years | 94 | 12 | 1 | 1 | 1 |
| Own Occupation | Laborer | 65 | 14 | 1.75 (0.81,3.80) | 1.4 (0.57,3.51) | 1.06 (0.40,2.79) |
| | Homemaker, Clerical or Sales | 532 | 91 | 1.46 (0.85,2.50) | 1.30 (0.68,2.50) | 1.19 (0.63,2.24) |
| | Professional, Executive, Supervisory or Technical | 185 | 21 | 1.00 | 1.00 | 1.00 |

*"Other SEP measures" refers to adjustment for measures of SEP other than the exposure of interest. For example analyses on father's education are adjusted for own education and own occupation.

† cardiovascuar disease (CVD) risk markers include smoking, body mass index, systolic blood pressure, total:HDL cholesterol ratio, fasting glucose, antihypertensive medication , cholesterol-lowering medication, depressive symptomatology and diabetes

# CHAPTER 4: CONCLUSION

## 4.1. Summary

This study demonstrated that cumulative life course SEP, a composite measure of SEP at 3 different life course periods, was inversely associated with subclinical atherosclerosis, measured as ABI <1.1, in men of the Framingham Offspring cohort. Analyses of SEP at single life periods revealed that early adulthood SEP, measured as participants' own education, primarily accounted for associations observed between cumulative SEP and low ABI in men. Although several CVD risk factors (such as smoking and diabetes) were associated with own education, these risk factors did not appear to account for associations between own education and low ABI.

Cumulative life course SEP and individual SEP measures were not associated with ABI <1.1 in women. When a lower cut point (1.0 instead of 1.1) was used to define low ABI, there was some indication of an association between SEP measures and ABI in women, however results were still not statistically significant. This may have been due to lack of power, as there were a small number of events (ABI<1.0) in certain SEP categories.

## 4.2. Strengths

This study examined multiple SEP indicators in relation to ABI as a measure of subclinical atherosclerosis. In light of recent evidence showing increased risk for atherosclerosis and CVD events up to ABI values of 1.1, this is the first study to investigate SEP in relation to ABI using a higher risk cut point of 1.1 to define low ABI (as apposed to ABI <0.9, which indicates definite PAD).

A major strength of this investigation was that childhood SEP (father's education) was assessed directly from the participants' fathers themselves. Thus, this measure was less likely to be subject to measurement error, as compared with studies that obtained measures of childhood SEP retrospectively through personal recall by participants.[4] Furthermore, rigorous quality assurance and quality control methods were used in this study to ensure high quality measures of outcomes and covariates.

## 4.3. Limitations

Due to stringent exclusion criteria, the sample size for this study was greatly reduced. Particularly, there was substantial missing data on childhood SEP in this study, as 1,427 of the 3,413 participants who completed examination 6 had fathers that were not in the original Framingham cohort. In order to be eligible for the Framingham Offspring study, participants needed to be offspring of a male or female Original Framingham Study participant, or a spouse of that offspring. Consequently many participants in the Offspring cohort had either only a mother in the Original cohort (and not a father), or were a spouse of an Offspring cohort participant and consequently did not have a mother or father as part of the Original cohort. Consequently, there was limited statistical power for detecting potential associations in certain cases (for example, in women). In addition, associations of SEP with ABI defined using lower cut points (for example, 0.9) could not be explored, as there were a limited number of persons with ABI values lower than such cut points.

Furthermore, individuals with clinically manifest CVD were excluded from analyses, as the study's objectives were to investigate SEP in relation to early stages of CVD. Given that those with CVD are likely to have both lower SEP and earlier presentations of subclinical disease, excluding these persons may have led to an underestimation of associations between SEP and low ABI.

In addition, those excluded were more likely to be on anti-hypertensive and cholesterol-lowering medication, and to be diabetic. Systematic differences between those included and excluded, particularly with respect to missing SEP exposure variables, may have lead to biased results.

There was also a lack of heterogeneity in occupation for women, as approximately 70% of the women in the study sample indicated their occupation to be in the 'Homemaker/Clerical/Sales' category. This may have contributed to the lack of association between own occupation and low ABI in women.

In addition, measures of CVD risk markers included in this study were obtained at the same time point as the outcome measure. Thus, the direction of the association between CVD risk markers and the outcome could not be ascertained

with certainty. Taking measures of CVD risk markers as a proxy for intermediate processes between SEP and subclinical atherosclerosis may have produced misleading results. It is also noted that adjusting for potential mediators in order to measure the 'direct' effect of exposure on the outcome may lead to spurious associations observed, due to unmeasured or unknown confounders of both the mediator and the outcome.

Finally, individuals in this study population were of European descent (representing the demographics of the city of Framingham at study onset) residing in the Northeastern United States, consequently results from this study are not necessarily generalizable to other communities, races and ethnicities.

## 4.4. Directions for future research

As noted previously, methodological concerns regarding measurement of cumulative life course SEP (e.g., equal weighting of life course periods, conflation of current and life-course SEP) need to be considered when investigating and interpreting findings between Cumulative SEP and health outcomes. Future studies should work towards creating an optimal measure of cumulative SEP, in order to better capture the dynamic processes by which socioeconomic exposures may accumulate over the life course and contribute to later health outcomes.

Results from this study, as well as evidence from some prior studies, suggest that there may be gender differences in the association between SEP and low ABI. Future studies should explore these potential differences and further investigate the mechanisms by with the association between SEP and low ABI may differ in men vs. women. In addition, careful consideration should be given to any ABI cut point used to indicate low ABI in men vs. women, as a single ABI threshold may not be appropriate for defining low ABI in both genders.

It has also been noted recently that minority groups remain underrepresented in most life course studies.[10] As described in the literature review, some studies found that the direction of association between SEP and subclinical atherosclerosis differed according to race/ethnicity.[20, 27] This suggests that the

impact of SEP on the development of atherosclerosis may vary to a certain degree across different race/ethnicity groups. Accordingly, different ethnic/racial groups should be incorporated into future studies of life course SEP and subclinical CVD more frequently.

Finally, future studies should consider designing interventions to evaluate whether policies and programs aimed at improving socioeconomic conditions translate into beneficial effect on health.

## 4.5. Implications of the study

This study's findings indicate that socioeconomic factors have an impact on CVD, even before clinical symptoms of the disease appear. Such findings have important implications with respect to prevention efforts. For example, focusing on the subclinical stage of disease may help to identify subgroups of individuals with low SEP who are at highest risk for later CVD events. Unlike other common measures of subclinical atherosclerosis such as CAC and IMT (which require expensive equipment and may not be readily available for clinical use), ABI measurement is quick, inexpensive, and clinically accessible.[190] Future preventive efforts would benefit from routine use of this screening tool for detection of asymptomatic disease and prediction of cardiovascular risk .

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# APPENDICES

## Appendix 1: List of acronyms and abbreviations

**SEP:** socioeconomic position

**SES:** socioeconomic status

**CVD:** cardiovascular disease

**CAD:** coronary artery disease

**CHD:** coronary heart disease

**MI:** myocardial infarction

**PAD:** peripheral arterial disease

**IMT:** intima-media thickness

**CAC:** coronary artery calcium

**PWV:** pulse-wave velocity

**ABI:** ankle-brachial index

**ABPI:** ankle-brachial pressure index

**AAI:** ankle-arm index

**DBP:** diastolic blood pressure

**SBP:** systolic blood pressure

**LVH:** left ventricular hypertrophy

**LDL:** low-density lipoprotein

**VIF:** variance inflation factor

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August 28, 2007

Dr. Eric Loucks
Department of Psychiatry
Douglas Hospital Research Centre
6875 LaSalle Blvd, Room E-4116
Montreal, Quebec
H4H 1R3

**RE: IRB Initial Review Number A08-M90-06B**

Dear Dr. Loucks,

We are writing in response to your request for continuing review for the study **A08-M90-06B** entitled "*Gender-Specific Associations Between Life Course Socioeconomic Position and Longitudinal Cardiovascular Disease Risk*".

The progress report was reviewed and we are pleased to inform you that full Board re-approval for the study was provided on **August 27, 2007,** valid until **August 26, 2008**. The certification of annual review has been enclosed.

We ask that you take note of the investigator's responsibility to assure that the current protocol and consent document are deposited on an annual basis with the Research Ethics Board of each hospital where patient enrolment or data collection is conducted.

Should any modification or unanticipated development occur prior to the next review, please advise the IRB promptly.

Yours sincerely,

Serge Gauthier, MD
Chair
Institutional Review Board

cc: A08-M90-06B

McGill Faculty of Medicine

**Institutional Review Board**

**- Continuing Review Form -**

DATE OF I.R.B. APPROVAL

AUG 27 2007

Faculty of Medicine
McGill University

Principal Investigator: Eric B. Loucks

Department/Institution: Departments of ~~Psychiatry and~~ Epidemiology, Biostatistics and Occupational Health. McGill University, Douglas Mental Health University Institute.

IRB Review Number **A08-M90-06B** Study Number (*if any*): Review Interval: 1 year

Title of Research Proposal: **Gender-Specific Associations Between Life Course Socioeconomic Position and Longitudinal Cardiovascular Disease Risk**

**INTERIM REPORT** (PLEASE CHECK OR SPECIFY)

Current Status of Study : Active Study ☒ On Hold ☐ Closed to Enrolment ☐

Interim Analysis ☒ Final Analysis ☐ Study Not Activated ☐**

**If the study has not become active at McGill, please enclose correspondence to explain or provide explanation:

McGill hospital(s) where study is being conducted and has received acceptance of local Research Ethics Board(s) (*if applicable*):

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MUHC/MNH-MNI: ☐ MUHC/RVH: ☐ Shriners Hospital ☐ SMH: ☐ Other: ☐

McGill hospital(s) where study is being conducted and has NOT received acceptance of local Research Ethics Board(s) (*if applicable*): N/A

In the case of a clinical trial, has the lead sponsor registered the study in the WHO Clinical Trials Registry http://isrctn.com/ Yes ☐ No ☐ or the NIH Clinical Trials Registry http://www.clinical.trials.gov ? Yes ☐ No ☐

If study sponsorship or financial support has changed, please provide correspondence to explain; enclosed:

Total number of subjects to be enrolled in the study: N/A Number of subjects to be enrolled at McGill sites: N/A

Number of subjects enrolled by McGill PI to date: n/a Number of subjects enrolled by McGill PI since the last review: N/A

Have any of these subjects withdrawn from the study, and if yes, how many? Yes ☐ No ☐

Has the study been revised since the last review? Yes ☐ No ☒

Has the consent form been revised since the last review? Yes ☐ No ☒ Date of current consent form

Have the study and consent form revisions been submitted and approved by the IRB? Yes ☐ No ☐

Are there any new data since the last review that could influence a subject's willingness to provide continuing consent?: NO

Have there been any Serious Adverse Experiences (SAEs)?: Yes ☐ No ☒

Have all Serious Adverse Experiences (SAEs) and Safety Reports relevant to the study been reported to the IRB?: Yes ☐ No ☐

**SIGNATURES:**

Principal Investigator: _____ Date: Aug 2/07

IRB Chair: _____ Date: Aug-27, 2007

THIS FORM MUST BE TYPED:

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Student No. Program/Option

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MSc Department of Epidemiology, Biostatistics & Occupational Health
Degree Unit*

**Thesis Title:** Life course socioeconomic position and ankle brachial index

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| 1) Dr. Gilles Paradis / Professor<br>Tel: (514) 398 /1418 / (extension)<br>Fax: (514) 398 /4503<br>E-mail: gilles.paradis@mcgill.ca | Department of Epidemiology, Biostatistics & Occupational Health<br>Purvis Hall, McGill University<br>1020 Pine Avenue West<br>Montreal, Quebec H3A 1A2 |
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## Unit* Acknowledgement and Signatures:

*I certify that the above nominations of examiners have been approved by members of the unit* or by a committee authorized for this purpose. To the best of my knowledge, there is **no conflict of interest** between the candidate or the supervisor and the proposed examiners. I understand that there is to be **no contact** with the external examiners with regard to the evaluation of this thesis and, in the case of doctoral students, the set up of the Oral Defense Committee.*

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## Graduate and Postdoctoral Studies Office
# Thesis Submission Form

**To be completed by the student:**

**TYPE OR PRINT CLEARLY**

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2. **PLEASE NOTE THAT YOUR NAME WILL APPEAR IN THE CONVOCATION BOOKLET AND ON YOUR DIPLOMA AS IT APPEARS ON YOUR OFFICIAL REGISTRATION AT McGILL** (Note: The family name must be identical to the name under which you are registered. Official name changes must be submitted, in writing, and with supporting documents to the Admissions, Recruitment, and Registrar's Office, James Administration Building, Room 205, two months before convocation. If you wish to change only the appearance of your name (i.e. to add accents, uppercase/lowercase letters, hyphen or apostrophe), you must do this on the web at http://www.mcgill.ca/minerva-students by the Convocation deadlines at http://www.mcgill.ca/convocations.

**NAME:** Agha (Family Name) / Golareh (Given Name(s)) M ☐ F ☑

3. **DEGREE:** M.Sc.
(M.A., M.Sc., M.Eng., LL.M., Ph.D., D.C.L., etc.)

4. **UNIT*:** Epidemiology, Biostatistics, and Occupational Health

5. **PROGRAM/OPTION (if applicable):** Epidemiology

6. **THESIS SUPERVISOR(S):** Loucks E. B.
(e.g. Fraser F.L., Poli. Sci.)

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8. **DOES YOUR THESIS INCLUDE MANUSCRIPTS PREVIOUSLY PUBLISHED OR TO BE PUBLISHED?:**

Yes ☑ No ☐
If yes, the contribution of co-authors must be explicitly stated in the thesis.

9. **EXACT TITLE OF YOUR THESIS** (N.B.: Please capitalize proper nouns only; e.g. *The politics and economics of the Free Trade deal.* Please use words rather than symbols, e.g. "carbon dioxide" instead of $CO_2$.):

Life course socioeconomic position and ankle-brachial index

It is the responsibility of the student and department to ensure that all degree requirements have been met.

We certify that the above information is correct.

Golareh Agha
Student's Signature

Unit* Head's Signature

I certify that I have read the thesis and find it acceptable for review.

Supervisor's Signature

Date: Aug 3/09

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Revised: October 2007

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UNIT*: Epidemiology, Biostatistics, and Occupational Health DEGREE SOUGHT: Master of Science

TITLE OF THESIS: Life course socioeconomic position and ankle-brachial index

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Thornhill, ON

L3T 6T3

Date: August 11, 2009

Author's Date of Birth: March 30, 1983

Signature of Author: Golareh Agha

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5. Your name on all forms must be shown as you are registered. Official name changes must be submitted, in writing, and with supporting documents to Enrolment Services, James Administration Building, Room 205. ☑

6. The "Thesis Submission Form" has been carefully completed. The thesis title is written in lowercase letters except for proper nouns. Sub-and superscripts, chemical abbreviations and other symbols, such as Greek letters, have been written out in full for the title. e.g.: Legal education in Scotland and Québec. ☑

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8. Research Compliance Certificates
All compliance certificates that were necessary to obtain to conduct the thesis research, such as human ethics approval, animal subject use approval, radiation license or biohazardous material use approval, must be included with the library waivers. If you no longer have a copy, you must contact the appropriate committee from which it was originally obtained. Contact information is contained on the GPS Research Ethics and Safety web-site at http://www.mcgill.ca/gps/policies/ ☑

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11. Inform Graduate and Postdoctoral Studies by memo signed by yourself and your supervisor of any extenuating circumstances (i.e., NSERC, student visa) at the time of your submission. ☑

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Student's signature

Bring the following to Graduate and Postdoctoral Studies (Room 400, James Administration Building):

1. Thesis Submission Checklist
2. Nomination of Examiners Form signed by you, your supervisor and the Chair of your unit*.
3. Submission form signed by you, your supervisor and the chair of your unit*
4. Completed Library and Archives Canada, UMI and McGill Library waiver forms.
5. Research Compliance Certificates and copyright/co-author permissions, if applicable
6. Thesis:
   - 1 copy of Master's (2 copies to your unit* for distribution to supervisor[s]/internal examiner)
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Epidemiology, Biostatistics, and Occupational Health

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|---|---|
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Life course socioeconomic position and ankle-brachial index

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Golareh Agha

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Primary Subject Code 0766 Secondary Subject Codes 0534 ____

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### COMMUNICATIONS AND THE ARTS

0729 Architecture
0377 Art History
0900 Cinema
0378 Dance
0389 Design and Decorative Arts
0357 Fine Arts
0723 Information Science
0391 Journalism
0390 Landscape Architecture
0399 Library Science
0708 Mass Communications
0413 Music
0459 Speech Communication
0465 Theater

### EDUCATION

0515 General
0514 Administration
0516 Adult and Continuing
0517 Agricultural
0273 Art
0282 Bilingual and Multicultural
0688 Business
0275 Community College
0727 Curriculum and Instruction
0518 Early Childhood
0525 Educational Psychology
0524 Elementary
0277 Finance
0519 Guidance and Counseling
0680 Health
0745 Higher
0520 History of
0278 Home Economics
0521 Industrial
0279 Language and Literature
0280 Mathematics
0522 Music
0998 Philosophy of
0523 Physical
0535 Reading
0527 Religious
0714 Sciences
0533 Secondary
0534 Social Sciences
0340 Sociology of
0529 Special
0530 Teacher Training
0710 Technology
0288 Tests and Measurements
0747 Vocational

### LANGUAGE, LITERATURE, AND LINGUISTICS

Language
0679 General
0289 Ancient
0290 Linguistics
0291 Modern
0681 Rhetoric and Composition

Literature
0401 General
0294 Classical
0295 Comparative
0297 Medieval
0298 Modern
0316 African
0591 American
0305 Asian
0356 Australia, New Zealand, and Oceania
0352 Canadian (English)
0355 Canadian (French)
0360 Caribbean
0593 English
0311 Germanic
0312 Latin American
0315 Middle Eastern
0313 Romance
0362 Scandinavian and Icelandic
0314 Slavic and East European

### PHILOSOPHY, RELIGION, AND THEOLOGY

0422 Philosophy

Religion
0318 General
0321 Biblical Studies
0319 Clergy
0320 History of
0322 Philosophy of
0469 Theology

### SOCIAL SCIENCES

0323 American Studies

Anthropology
0324 Archaeology
0326 Cultural
0339 Medical and Forensic
0327 Physical
0304 Biography
0325 Black Studies

Business Administration
0310 General
0272 Accounting
0770 Banking
0454 Management
0338 Marketing
0385 Canadian Studies

Economics
0501 General
0503 Agricultural
0505 Commerce-Business
0508 Finance
0509 History
0510 Labor
0511 Theory
0358 Folklore
0366 Geography
0351 Gerontology
0733 Gender Studies
0737 Hispanic American Studies

History
0578 General
0579 Ancient
0581 Medieval
0582 Modern
0331 African
0332 Asia, Australia, and Oceania
0328 Black
0334 Canadian
0330 Church
0335 European
0336 Latin American
0333 Middle Eastern
0722 Military
0724 Russian and Soviet
0337 United States
0585 History of Science
0751 Jewish Studies
0398 Law
0750 Military Studies
0730 Museology
0740 Native American Studies

Political Science
0615 General
0616 International Law and Relations
0617 Public Administration
0814 Recreation
0452 Social Work

Sociology
0626 General
0627 Criminology and Penology
0938 Demography
0631 Ethnic and Racial Studies
0628 Individual and Family Studies
0629 Industrial and Labor Relations
0703 Organizational
0630 Public and Social Welfare
0700 Social Structure and Development
0344 Theory and Methods
0709 Transportation
0999 Urban and Regional Planning
0453 Women's Studies

## THE SCIENCES AND ENGINEERING

### BIOLOGICAL SCIENCES

#### Agriculture

0473 General
0285 Agronomy
0475 Animal Culture and Nutrition
0476 Animal Pathology
0792 Fisheries and Aquaculture
0359 Food Science and Technology
0478 Forestry and Wildlife
0471 Horticulture
0479 Plant Culture
0480 Plant Pathology
0777 Range Management
0481 Soil Science
0746 Wood Technology

#### Biology

0306 General
0287 Anatomy
0433 Animal Physiology
0715 Bioinformatics
0308 Biostatistics
0309 Botany
0379 Cell
0329 Ecology
0353 Entomology
0369 Genetics
0793 Limnology
0410 Microbiology
0307 Molecular
0317 Neuroscience
0416 Oceanography
0718 Parasitology
0719 Physiology
0817 Plant Physiology
0778 Veterinary Science
0720 Virology
0472 Zoology

#### Biophysics

0786 General
0760 Medical

### EARTH SCIENCES

0725 Atmospheric Sciences
0425 Biogeochemistry
0996 Geochemistry
0370 Geodesy
0372 Geology
0373 Geophysics
0388 Hydrology
0411 Mineralogy
0345 Paleobotany
0426 Paleoecology
0418 Paleontology
0985 Paleozoology
0427 Palynology
0368 Physical Geography
0415 Physical Oceanography
0799 Remote Sensing

### HEALTH AND ENVIRONMENTAL SCIENCES

0768 Environmental Sciences

#### Health Sciences

0566 General
0300 Audiology
0567 Dentistry
0350 Education
0766 Epidemiology
0769 Health Care Management
0758 Human Development
0982 Immunology
0564 Medicine and Surgery
0347 Mental Health
0569 Nursing
0570 Nutrition
0380 Obstetrics and Gynecology
0354 Occupational Health and Safety
0992 Oncology
0381 Ophthalmology
0571 Pathology
0419 Pharmacology
0572 Pharmacy
0573 Public Health
0574 Radiology
0575 Recreation
0382 Rehabilitation and Therapy
0460 Speech Pathology
0383 Toxicology
0386 Home Economics

### PHYSICAL SCIENCES

#### *Pure Sciences*

#### Chemistry

0485 General
0749 Agricultural
0486 Analytical
0487 Biochemistry
0488 Inorganic
0738 Nuclear
0490 Organic
0491 Pharmaceutical
0494 Physical
0495 Polymer
0754 Radiation
0405 Mathematics

#### Physics

0605 General
0986 Acoustics
0606 Astronomy and Astrophysics
0608 Atmospheric Science
0748 Atomic
0611 Condensed Matter
0607 Electricity and Magnetism
0798 Elementary Particles and High Energy
0759 Fluid and Plasma
0609 Molecular
0610 Nuclear
0752 Optics
0756 Radiation
0753 Theory
0463 Statistics

#### *Applied Sciences*

0346 Applied Mechanics
0800 Artificial Intelligence
0984 Computer Science
0791 Energy

#### Engineering

0537 General
0538 Aerospace
0539 Agricultural
0540 Automotive
0541 Biomedical
0542 Chemical
0543 Civil
0544 Electronics and Electrical
0775 Environmental
0546 Industrial
0547 Marine and Ocean
0794 Materials Science
0548 Mechanical
0743 Metallurgy
0551 Mining
0552 Nuclear
0549 Packaging
0765 Petroleum
0771 Robotics
0554 Sanitary and Municipal
0790 System Science
0428 Geotechnology
0796 Operations Research
0795 Plastics Technology
0994 Textile Technology

### PSYCHOLOGY

0621 General
0384 Behavioral
0622 Clinical
0633 Cognitive
0620 Developmental
0623 Experimental
0624 Industrial
0625 Personality
0989 Physiological
0349 Psychobiology
0632 Psychometrics
0451 Social