ETHNICITY AND THE DETERMINANTS OF CARDIOVASCULAR DISEASE AMONG SOUTH ASIANS, CHINESE, AND EUROPEAN CANADIANS

By

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A Thesis

Submitted to the School of Graduate Studies

in Partial Fulfillment of the Requirements

for the Degree

Doctorate of Health Research Methodology

McMaster University

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ETHNICITY AND CARDIOVASCULAR DISEASE

DOCTORATE OF HEALTH SCIENCES (2002) McMaster University
(Health Research Methodology) Hamilton, Ontario

TITLE: Ethnicity and the Determinants of Cardiovascular Disease among South Asians, Chinese and European Canadians

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NUMBER OF PAGES: xvii, 259

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ABBREVIATIONS

ACE	angiotensin converting enzyme
AHAS	Anger and Hostility Scale
AMI	acute myocardial infarction
ARIC	atherosclerosis risk in communities
ASMR	age standardized mortality rate
BMI	body mass index
CABG	coronary artery bypass graft surgery
CBVD	cerebrovascular disease
CHD	coronary heart disease
CUS	carotid ultrasound
CV	cardiovascular
CVD	cardiovascular disease
DALY	disability adjusted life years
ECG	electrocardiogram
FFQ's	Food Frequency Questionnaires
GWBS	General Well-being Schedule

GQ	General Questionnaire
ICC	intraclass correlation
IGT	impaired glucose tolerance
IMT	intimal medial thickness
Lp(a)	lipoprotein (a)
MONICA	MONItoring of trends and determinants in CArdiovascular disease
NaCl	Sodium chloride (salt)
PAI-1	plasminogen activator inhibitor-1
PTCA	percutaneous transluminal coronary angioplasty
SD	standard deviation
SES	socioeconomic status
SHARE	The Study of Health Assessment and Risk in Ethnic groups
SOLVD	Studies of Left Ventricular Dysfunction
WBQ	Well-Being Questionnaire
WHO	World Health Organisation
WOC	Ways of Coping

ABSTRACT

Significant differences in the cardiovascular mortality rate exist between Canadians of South Asian, Chinese and European origin. This thesis represents a six year effort to determine the prevalence of cardiovascular disease, the burden of atherosclerosis, and the prevalence of their major determinants among three ethnic groups in Canada. In addition to the study of the relationship of the "classical" cardiovascular risk factors to disease outcomes, the contribution to disease outcomes of selected "emerging" risk factors (e.g. markers of thrombosis, socio-economic, dietary, and psychosocial stress factors) was studied.

The major findings reported in this thesis include the confirmation that South Asians in Canada have the greatest prevalence, Europeans have an intermediate prevalence, and the Chinese have the lowest prevalence of cardiovascular disease. However, Europeans have significantly more atherosclerosis compared to the South Asians and Chinese. Yet, for any given amount of atherosclerosis, South Asians suffer more cardiovascular events. This may reflect an increased propensity of South Asians to develop arterial thrombosis.

Major differences in the daily calorie consumption, and in the sources of calories exist between the ethnic groups. Diet was measured using food frequency questionnaires developed for each ethnic group, which were found to reliably classify individuals into high or low consumers for a given macronutrient. This classification facilitates the study of diet-disease relationships.

Psychosocial stress was measured in a valid and reliable way using a single questionnaire created for use by all participants. Discrimination in the workplace is a challenge to measure, and while it was reported more often among South Asians and Chinese, its reproducibility was relatively low. Markers of social stability (e.g. income and employment) were associated with psychosocial stress factors, neurohormones, atherosclerosis and cardiovascular disease. This demonstrates the powerful influence that "social factors" have on the health of free-living Canadians.

ACKNOWLEDGEMENT

This thesis is the culmination of a six-year effort of the determinants and distribution of cardiovascular disease among three ethnic groups in Canada. I would like to thank all of the members of the SHARE team who worked long hours to complete this study. In particular, I would like to thank Patty Montague who coordinated this study, for her dedication to the project, and for her tireless efforts to make this study happen. I would like to thank my Thesis Committee members Dr. Mita Giacomini and Harry Shannon for their timely and careful review(s) and helpful critique(s) of my work. In particular, I would like to thank Dr. Salim Yusuf, who has spent countless hours with me on this project from its very beginnings, to its completion. He has been a wonderful role model and mentor, and his continual pursuit of excellence in research serves as a continual inspiration for me. I would also like to thank Kathy Antaya who has gone above and beyond the call of duty, and has shared with me many a late night at the office to complete this document. Finally, I dedicate this thesis to my husband, Myles, and my children, Anjali and Anand, who tolerate my unusual lifestyle, and support my quest to have the best of both worlds.

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2002

CHAPTER 1

GENERAL INTRODUCTION:

Introduction and goals of this thesis:

The rates of cardiovascular disease (CVD) vary substantially throughout the world. Differences in CVD occur between developed and developing countries, urban and rural communities, the wealthy and the poor, men and women, and among people of different ancestral origin. Given the multiple factors which influence the distribution of CVD, consideration of both hereditary and environmental factors and their unique interactions, is important to further our understanding of CVD causation.

Up to 20% of Canadians are immigrants {Census 1996} and the two fastest growing groups of immigrants in Canada are people of Indian origin (South Asians) and people of Chinese origin {Census 1996}. A recent analysis of the Canadian National Mortality Database demonstrated that among Canada's major ethnic groups, South Asians have the highest CVD mortality, Europeans have intermediate CVD mortality rates, and the Chinese have the lowest CVD mortality rates {Sheth 1999}. This observation is consistent with the observations of other investigators around the world {McKeigue 1995, Bhopal 1999}, and suggests that South Asians may possess risk factors that makes them susceptible to CVD, while people of Chinese origin may possess factors which protect them from CVD. This thesis is a summary of six years

of research directed at understanding the reasons for the differences in the burden of CVD between South Asians, Chinese, and Europeans living in Canada {Anand and Yusuf 1998}.

Preliminary Investigations:

In 1995, Anand and Yusuf reviewed the existing body of evidence which demonstrated that South Asians suffer a relative excess of CVD compared to the ancestral groups. These data were largely cross-sectional, yet some common observations emerged. First, the prevalence of type 2 diabetes and premature CVD is high among South Asian migrants to the United Kingdom, Fiji, Singapore, and South Africa {Enas 1996, Jha 1993}. Second, a change from a rural to an urban lifestyle is associated with weight gain {Reddy 1997, Bhatnagar 1995, Hughes 1990}. Third, Chinese people have lower age standardized mortality rate (ASMR) for coronary heart disease (CHD) and stroke compared to people in Western countries, and these rates increase when they migrate. Fourth, Europeans do not have the same increase in diabetes prevalence as do South Asians and possibly Chinese, despite having a similar or greater body weight.

Given the substantial numbers of South Asians and Chinese living in Canada, and the results of the Canadian National Mortality Database analysis, Anand and Yusuf developed a series of studies to address some of the outstanding questions regarding the increased susceptibility of South Asians to develop type 2 diabetes and CVD, and the lower susceptibility for CVD of Chinese migrants, compared to people of European

origin living in Canada. Their efforts began with the design and conduct of a small pilot study to generate preliminary data, test sampling methods, and pilot questionnaires as a feasibility test in preparation for a larger study of the determinants of atherosclerosis and CVD among South Asians, Chinese, and Europeans in Canada. The Study of Heart Assessment and Risk in Ethic groups (SHARE) pilot study was designed and conducted in 1995 in Hamilton {Anand and Yusuf 1997}. This preliminary study formed the basis of Anand's Master's thesis in Design, Measurement and Evaluation, which was completed in September 1996 {Anand 1996}. This was a cross-sectional study in which Canadians of South Asian and European origin were randomly sampled from Hamilton and invited to undergo a cardiovascular health assessment. An invitation letter was sent to all randomly selected households. This was followed by a series of telephone calls inviting the members with the earliest birth date between the ages of 35-75 years to participate in the study. During the 2 hour clinic visit, basic demographic, lifestyle, and nutrition data were collected. In addition, all participants provided fasting blood samples, 2 hour post glucose load blood samples, completed a dietary assessment, had a twelve lead electrocardiograph, and a carotid ultrasound. The main results of the pilot study have been published and the manuscript is found in Appendix A. Although the pilot study was designed to test the feasibility of the methods in preparation for a larger study, some interesting observations were made despite the small numbers of participants (Table 1).

Table 1: SHARE Pilot Study results

Variable	South Asian	Chinese	European
Number per group	31	26	20
Mean Age (years)	48	47	49
Years Lived in Canada	18	15	47
Ever Smoked (%)	21	17	62
University Educated (%)	57	17	43
Diabetes (%)	7	1	0
Serum Cholesterol (mmol/L)	5.10	4.79	4.99
HDL Cholesterol (mmol/L)	1.05	1.23	1.24
Lipoprotein (a) mg/dL	5.50	4.73	4.58
Body Mass Index (kg/m^2)	27.2	24.3	26.4
Waist to Hip ratio	0.91	0.86	0.95

Based on the experience of the pilot study, Anand and Yusuf designed a larger study called the Study of Health Assessment and Risk in Ethnic groups-SHARE.

The main questions of this thesis are:

1. What is the prevalence of CVD among Canadians of South Asian, Chinese and European origin? It is hypothesized that the prevalence of CVD will be highest among South Asians and lowest among the Chinese. The rationale for this hypothesis is taken from the observation that South Asians migrants to the United

Kingdom have an increased prevalence of coronary heart disease (CHD) compared to people of European origin in the United Kingdom {McKeigue 1991}. Further, the National Mortality Database analysis by Sheth and colleagues demonstrated that, within Canada, people of South Asian origin have the highest CVD mortality compared to the Europeans and Chinese {Sheth 1999}.

2. Does the average amount of carotid atherosclerosis as measured by quantitative B-mode ultrasonography differ between Canadians of South Asians, Chinese, and European origin? It is hypothesized that South Asians have the greatest degree of atherosclerosis, Europeans intermediate, and the Chinese the lowest amount of atherosclerosis. This hypothesis is based on the observation that South Asians have more CVD, and the main precursor to CVD is atherosclerosis.

3. Does the prevalence of conventional CVD risk factors (i.e. smoking, diabetes, elevated blood pressure, and elevated cholesterol) differ between the ethnic groups, and do these differences in the conventional risk factors correlate with the observed differences in the degree of atherosclerosis and CVD between the three groups? Prior studies indicate that South Asians have an increased prevalence of type 2 diabetes, increased triglycerides, and low HDL cholesterol compared to people of European origin.

4. Can dietary intake be measured in a valid and reliable way in a multiethnic cohort using self administered food frequency questionnaires? Do these instruments facilitate the study of diet-CVD associations among South Asians, Chinese, and European Canadians?

5. Can psychosocial stress be measured in a valid and reliable way among South Asians, Chinese, and European Canadians?

6. To what extent does the perceived inequality in employment and promotion, and future opportunities for children differ between Canadians of South Asian, European, and Chinese origin?

7. To what extent do reports of stress correlate with neurohormones which are known to be associated with stress? What is the relationship of stress and socioeconomic status, to neurohormones and disease outcomes such as atherosclerosis and CVD?

Outline of the contents:

Chapter 1 highlights the main questions addressed in this thesis, and provides the rationale for posing them.

Chapter 2 presents a discussion of the construct of ethnicity, outlines how this variable is used in health research, and discusses its usefulness. This chapter provides the context for the manuscript entitled *"Using ethnicity as a classification variable in health research: Perpetuating the myth of biological determinism, serving socio-political agendas, or making valuable contributions to medical sciences"* which was published in 1999 and is found in Appendix B.

Chapter 3 provides a literature review of ethnicity-based research as applied to CVD in the world and in Canada. This reviews the key highlights of work found in three appended publications, a book chapter *"Ethnicity and Vascular Disease"* published in Evidence-Based Cardiology in 1998, a review article entitled *"Cardiovascular Diseases in Ethnic Groups in Canada"* published in the Canadian Journal of Cardiology supplement in 1999, and *"Global Burden of Cardiovascular Disease"* a two part series published in Circulation 2001 (Appendix C).

Chapter 4 outlines the Objectives and the Design of SHARE, and reviews the challenges faced in the design of the study. This sets the context for the paper entitled *"The Study of Health Assessment and Risk in Ethnic groups (SHARE): Rationale and Design"*. Published in the Canadian Journal of Cardiology in 1998 (Appendix D).

In Chapter 5 the recruitment of participants and the main results of SHARE are discussed and described. The key highlights of this chapter are summarized in the paper entitled "*Differences in cardiovascular disease between ethnic groups are not explained by conventional risk factors or atherosclerosis. The Study of Health Assessment and Risk in Ethnic Groups (SHARE)*" which was published in the Lancet 2000 (Appendix E).

Chapter 6 reviews the study of diet-disease relationships in ethnicity studies, and the challenges of measuring diet. Key dietary analyses in SHARE are presented. The main validity and reliability analysis has been published in abstract form and submitted for publication (Appendix F).

Chapter 7 reviews the challenges of "measuring stress", sources of error, and presents the design of the psychosocial component of SHARE. Detailed analyses regarding the perceived inequalities in Canadian society experienced by SHARE participants are summarized and appear in detail in the paper entitled *"Perceived inequalities among ethnic groups in Canada"* which is currently being peer-reviewed. (Appendix G). In addition the relationship between neurohormones and stress to atherosclerosis and CVD are presented.

Chapter 8 is the conclusion chapter, which presents a general discussion, and the conclusions of the thesis, as well as recommendations for future research.

APPENDED PUBLICATIONS

Relevant Papers Published before entering the Doctoral Program:

Appendix A:

1. **Anand SS**, Yusuf S. Risk Factors for cardiovascular disease in Canadians of South Asian and European origin: A pilot study of the Study of Heart Assessment and Risk in Ethnic groups (SHARE). *Clinical and Investigative Medicine* 1997; 20(4): 204-210.

2. Sheth T, Nargundkar M, Chagani K, **Anand SS**, Nair C, Yusuf S. Classifying ethnicity utilizing the Canadian mortality database. *Ethnicity and Health* 1997; 2 (4):287-295.

3. Sheth T, Nair C, Nargundkar M, **Anand SS**, Yusuf S. Cardiovascular and cancer mortality among Canadians of European, South Asian and Chinese origin from 1979 to 1993: an analysis of 1.2 million deaths. *Can Med Assoc J* 1999 Jul 27; 161(2): 132-138.

Papers Published since entering the Doctoral Program:

Appendix B:

1. **Anand SS**. Using ethnicity as a classification variable in health research: Perpetuating the myth of biological determinism, serving socio-political agendas, or making valuable contributions to medical sciences? *Ethnicity and Health* 1999 Dec; 4(4): 241-244.

Appendix C:

1. **S. Anand**, S. Yusuf. Ethnicity and vascular disease. In *Evidence Based Cardiology* Salim Yusuf editor. London: BMJ, 1998: Chapter 22: 329-352.

Candidate's role: I collected and summarized the primary data for this review, and wrote the initial draft.

2. **Anand SS**, Yusuf S. Cardiovascular Diseases in Ethnic Groups. Canadian Cardiovascular Society Consensus Paper. *Can J Cardiol* 1999 Dec; 15 Suppl; G: 47G-50G

Candidate's Role: I collected and summarized the primary data for this review, and wrote the initial draft. This was one section of a consensus document of the Prevention of Cardiovascular Disease published in the Canadian Journal of Cardiology 1999 Dec; 15 Suppl G.

3. Yusuf S, Reddy S, Ounpuu S, **Anand S.** Global burden of cardiovascular disease published in Circulation 2001.

Candidate's Role: Much of the information contained in these manuscripts comes from the Ethnicity and CVD chapter written by Anand and Yusuf. In addition, the candidate provided editorial comments on drafts of the manuscripts when in preparation.

Appendix D:

1. **Anand SS**, Yusuf S, Vuksan V, Devanesen S, Montague P, Kelemen L, Sigouin C, Teo KK, Lonn E, Gerstein H, McQueen M, Hegele R for the SHARE Investigators. The Study of Health Assessment and Risk in Ethnic groups (SHARE): Rationale and Design. *Can J Cardiol* 1998 Vol 14 (11), November 1349-1357.

Candidate's role: I was involved in the design, collection, analysis and interpretation of the results, wrote the first draft of the manuscript, and coordinated all further statistical and editorial changes.

Appendix E:

1. **Anand SS**, Yusuf S, Vuksan V, Devanesen S, Teo KK, Montague PA, Kelemen E, Guo T, Lonn E, Gerstein H, Hegele RA, McQueen M. Differences in cardiovascular disease between ethnic groups are not explained by conventional risk factors or atherosclerosis. The Study of Health Assessment and Risk in Ethnic Groups (SHARE). *Lancet* 2000; 356: 279-84.

Candidate's role: I played a key role in the design, collection, analysis and interpretation of the results, wrote the first draft of the manuscript, and coordinated all further statistical and editorial changes.

Appendix F:

1. Kelemen L, Jain M, **Anand S**, Yusuf S. Dietary differences in ethnic groups in Canada. 4th International Conference on Preventive Cardiology, Montreal, June 29-July 3, 1997. *Canadian Journal of Cardiology* 1997;13 (Supp. B):241B.

2. Kelemen LE, **Anand SS**, Vuksan V, Yusuf S, Teo KK, Willett WC. Validity and reliability of a dietary questionnaire for South Asian Canadians. Accepted for presentation at the 4th annual International Conference on Dietary Assessment Methods, University of Arizona Prevention Center, Tucson, Arizona, Sept 17-20, 2000.

Candidate's role: I was involved in the study design, and in the analysis and interpretation of the results. I provided editorial comments in the first and subsequent drafts of this abstract.

3. Kelemen LE, **Anand SS**, Vuksan V, Yi Q, Devenesen S, Teo KK, Yusuf S. Validity and reliability of a dietary questionnaire for South Asian, Chinese and European Canadians. (in preparation).

Candidate's role: I was involved in the study design, and in the analysis and

interpretation of the results. I provided editorial comments in the first and subsequent drafts of this paper.

Appendix G:

1. **Anand SS,** Bosch J, Anand A, Yi C, Devanesen S, Teo K, Yusuf S. Perceived inequalities among ethnic groups in Canada *Ethnic and Racial Studies 2001* (Submitted)

Candidate's role: I conducted the qualitative substudy, which led to the development of the Well-Being Questionnaire, which was used to generate the data which appear in this manuscript. I was involved in the overall study design, and in the analysis and interpretation of the results, and coordinated all further statistical and editorial changes.

CHAPTER 2

ETHNICITY AS A CLASSIFICATION VARIABLE IN HEALTH RESEARCH

In Chapter 2, the construct of ethnicity as a variable for use in epidemiologic research is reviewed. Ethnicity is defined and differentiated from the concept of race and the potential value of this concept in health related research is discussed.

Classification of Human Beings:

Over the past 200 hundred years scientists have grouped the human species according to physical characteristics (e.g. skin colour), country of origin, cultural affiliations, and religious beliefs. This classification has been used to study human populations, for characteristics such as intelligence or physical capacity, and to study disease patterns {Gould 1995}. Historically, the concept of race was based on the belief that members of a race were homogenous with respect to biological inheritance {Senior 1994}. However, as racial classification was often based upon differences in skin colour and other physical features, it has become apparent that these distinguishing characteristics do not correlate with genetic heterogeneity. In fact, over the last 20 years, as the ability to unravel the genetic code has increased, there is little evidence to support that historical "racial" divisions actually reflect differences in genetic make-up {Jackson 1992}. Ethnicity, on the other hand, is used to describe a group of people whose lifestyles are characterized by distinctive social and cultural traditions, which are maintained within the group and passed on from generation to generation {Crews 1991, Bhopal 2002}. Therefore,

ethnicity has both sociocultural and biological components {Crews 1991}. However, "ethnicity" is a dynamic construct, and its definition is often unique to the context at hand {Senior 1994}. Therefore, when ethnicity is used as a classification variable in health research, its potential use must be well thought out and clearly defined at the outset of the investigation.

Defining Ethnic Groups:

Most evolutionary biologists believe that the human species is at most a few hundred thousand years old and three major subgroups of humans exist: African, Caucasian, and Mongoloid {Gould 1978}. This classification implies that people within each racial group have a similar genetic make up and that racial divisions reflect differences in genetic makeup {Goodman 1997}. This belief led to the widespread use of the term "race" to categorize groups of people who looked physically different from one another. Anthropologists have largely abandoned this biological concept of race {Littlefield 1982, Cooper 1986}, yet use of the term has persisted, and "RACE" is used widely to classify populations in epidemiologic studies. It appears now that the initial assumption that race designated important genetic differences between racial groups is false {Gould 1981, Lewontin 1984}. Scientists have now discovered that there is often more genetic heterogeneity within a so-called racial group than between racial groups (Lewontin 1984, Crews 1991). On the other hand, "ethnicity" refers to people who share common cultural characteristics such as language, diet, and social networks, and who may have an increased prevalence of specific genotypes {Aspinall 1997}. However, because the term

is vague, the interpretation of what ethnicity means is not always straight forward. Failure to clearly define the meaning of ethnic or ethnicity in a research context can lead to 'over' interpretation and 'mis' interpretation of the results.

The Impact of Social Variables on Ethnic Studies:

How human beings grow, develop, age, and die reflects an on-going interaction between our biological and social history. Abundant data support the notion that social conditions influence health. Differences in social factors produce inequalities in exposure to, susceptibility to, and resistance from pathogenic insults and processes across the life span {Krieger 1993, Ben-Schlomo 1999}. Therefore, studies of disease etiology should incorporate both social and biologic factors, and ethnic differences must be viewed as possibly being due to differences in biology, social factors, or both. Failure to address the social dimension of the ethnicity construct results in mis-interpretation of the research results. Given the complexity of the ethnicity construct, many reported ethnic differences, are in fact, due to differences in social factors such as income inequality, education, childhood socioeconomic status (SES) and other variables which are difficult to measure. For example, a recent paper by Exner and colleagues, which appeared in the leading medical journal the New England Journal of Medicine, reported that equivalent doses of angiotensin converting enzyme (ACE) inhibitors do not reduce blood pressure, and do not prevent cardiovascular events among blacks with left ventricular dysfunction to the same extent as they do, very effectively, among non-blacks {Exner 2001}. The authors adjusted their results for the limited socioeconomic data that were collected (e.g. financial

distress, and education level), and concluded that the lack of response of blacks to ACE inhibitors was due to "racial" (implying genetic) differences {Exner 2001}. Further, they cited several potential biologic mechanisms to explain their findings. It is very likely, however, that the absence of a drug effect in this post-hoc analysis was due to differences in other factors which likely differed between blacks and whites, such as adherence to the study medication, access to medical care and follow-up, and diet. This paper has very important implications given that it concludes ACE inhibitors may not be effective among Black people, and it was published in the medical journal which has the greatest impact on medical practice. The data from this analysis contrast the large volume of information which has demonstrated that ACE inhibitors reduce CVD, MI, and stroke among high risk individuals {Yusuf 2000, Flather 2000}, and may likely lead to many blacks being denied this important therapy.

Ethnic comparisons may be confounded by social factors, and this is an excellent example of how ethnic comparisons must explicitly address the issue of confounding by social factors. Failure to adjust for differences in income and employment status in ethnic comparisons, partial adjustment for socioeconomic disparities (given the measurement error associated with such measures), and residual confounding may lead to the misinterpretation that apparent ethnic differences reflect biologic differences between the groups {Kaufman 1997, Kreiger 1987}.

Is the Study of ethnic differences important?

The question of whether ethnicity-based research is important depends on who is asked. Ethnicity research provides information which is useful to ethnic communities, to health service providers, health planners, policy makers, and sometimes to the collective body of knowledge called 'science'. For members of a unique ethnic community, having information about their community's health and disease patterns, risk factors and treatment outcomes increases the acceptance and uptake of health information among their community members {Bhopal 1997}. From the societal perspective, ethnic-specific health information is used by health planners and policy makers to develop culturally acceptable health promotion programs, to justify the allocation of resources to ethnic specific projects, and to satisfy the demand of an ethnic group to have their own health information and health programs. From the perspective of advancing the collective knowledge of science, ethnicity-based research can provide insights into the pathogenesis of, and protection from, human disease. For example, the investigations of South Asians who suffer premature CHD has helped to characterize features of the "metabolic syndrome" (i.e. abdominal obesity, ↑ triglycerides, ↓ HDL cholesterol) which is observed among many migrant groups, (South Asians and Chinese) and is a risk state for CVD. These are some of the positive spin-offs of ethnicity-based research. However the 'negative spin-offs' of ethnicity research must also be considered. Emphasizing differences between groups of human beings which could perpetuate misunderstandings of the term "race", promote an "us versus them" mentality, and create the perception that health research must be replicated over and over again in every ethnic community, is

inefficient and costly. Further, others argue that researchers who highlight differences in risk states and health outcomes among ethnic minorities may deflect attention away from other health priorities {Bhopal 1997}. Even more importantly, spurious and underpowered subgroup results (especially of trials) based on race are potentially damaging as may happen in response to the use of ACE inhibitors.

Historically it has been attractive for epidemiologists to study populations who live in distinct environments and lead very different lifestyles {Marmot 1995}. Ancel Keys and colleagues studied comparative rates of CHD, serum cholesterol measurement and dietary fat intake across seven countries [Finland, Japan, United States, the Netherlands, Italy, Yugoslavia and Greece] {Keys 1986}. Intriguing differences in the CHD incidence, dietary fat, and serum cholesterol were observed between the countries. The age adjusted 10 year CHD mortality in Finland was 45.5 deaths per 10,000 population/year versus 6.0 deaths per 10,000 population/year in Japan. A significant difference in serum cholesterol (248 vs 167 mg/100 mL), was observed between these countries. These observations led to cholesterol and dietary intake of fat being intensively researched with the subsequent identification of these factors as among the major determinants of CVD. Critics of this type of research believe that such research is no more than "Black Box Epidemiology" meaning that, although associations between various factors and diseases are identified, the causal pathways are never determined {Skrabanek 1994}. In this case the Black Box of epidemiology refers to epidemiology where the exact causal mechanism behind an association remains hidden (Black) but the inference is that causal associations may be

found within the association (Box). However others argue that the Black Box approach serves a useful and important role in research, {Savitz 1994} as clues to the pathogenesis of disease may emerge when unexpected associations occur. Furthermore, it is usually not apparent to reviewers of such research that clues, which point to possible associations between risk factors and diseases, are easier to identify when comparing diverse communities who have extreme differences in lifestyle characteristics, rather than by studying associations among people who have similar lifestyle practices. For example, if a population with low rates of CVD that consumes large amounts of fish, is compared to a population with relatively high CVD rates that rarely consumes fish, the hypothesis that fish consumption is protective from CVD emerges.

Methodologic challenges of ethnicity based research:

An epidemiologist is primarily concerned with identifying the determinants and distribution of diseases {Last 1995}. Often, comparisons of disease rates between groups of varying ancestral origin yields interesting hypotheses about disease causation or protection. However, careful attention must be paid to how "ethnic status" was determined. Ethnicity classification may be direct, whereby individuals report their own ethnicity, or indirect, where ethnicity is presumed based on a surrogate characteristic such as country of birth, mother tongue, religion, or unique surname. Indirect classification of ethnicity is often performed by researchers who make ethnic comparisons in large databases and ethnicity is defined post-hoc. While this may be efficient, these results must be interpreted with caution. Error in classification of people by ethnicity can lead to

i) dilution of the true relationship between ethnicity and a health related outcome, or ii.) enhanced differences between groups, and iii) inaccurate conclusions if adjustment for potential confounding variables (e.g. socioeconomic status) cannot be adequately addressed. Therefore, at most, post-hoc classification of ethnicity is hypothesis-generating and not confirmatory about ethnic groups. An example of the potential for misclassification and misinterpretation of results comes from a Statistics Canada analysis of causes of death by ancestral groups. In 1990, Statistics Canada reported the CVD mortality across multiple ethnic groups, and classified people by ethnic group using the surrogate of country of birth {Nair 1990}. They reported that, overall lower CVD mortality rates were found for first generation Canadians from Latin America, China and South Asia (including India) and higher CVD mortality rates among people from Scandinavia and Africa. Between two five-year time periods (1969-73 and 1984-88), CVD mortality rates generally were found to decrease, except for immigrants from Africa (age 35+). Their data suggested that people who were born in Africa had the highest rate of CVD mortality, and one might infer from this that Black Africans in Canada have a high rate of CVD. However a large number of people who were born in Africa were of South Asian origin. By using a country of birth classification, they would be classified as "African". Given that South Asians suffer high rates of CVD, it is likely that the observed 'African excess' of CVD in Canada is due to the large proportion of people of South Asian origin who were born in Africa. Combining multiple surrogate measures of ethnicity can improve the accuracy of indirect classification. For example, by combining last name and country of birth to study mortality patterns of Canadians of South Asian

and Chinese the accuracy of ethnic classification can be dramatically improved {Sheth 1997}.

Direct classification of ethnic status is the most accurate classification method. The self-categorization of ethnicity appears to be the least biased and the most valid classification system {Howard-Hassrean 1999}. Individual level data collected in this manner facilitates hypothesis testing research. The limitations of such an approach are inherent in all individual level studies and include the challenges of recruitment (e.g. creation of a sampling frame and random recruitment by ethnic group), the effort and expense required to collect individual person data on a large scale, and, once completed, the limited generalizability of the results (e.g. results of South Asians in Canada may not be generalizable to South Asians in India). The Study of Health Assessment and Risk in Ethnic groups (SHARE), which is described in detail in this thesis, is an example of an in-depth study of ethnic differences of CVD and CVD risk factors in which "ethnic status" was initially determined by unique surname (public telephone directories), substantiated by self-report (over the telephone), and confirmed with a face to face interview {Anand 1998}.

Summary:

The concept of race continues to be widely used in health research, and it is based on the idea that the human species may be divided into genetically separate groups. However, the evidence does not support that genetically distinct groups within the human species exist. A more useful classification uses the construct of ethnicity which has both

biological and social dimensions. To avoid misinterpretation of results, researchers must clearly define their use of the ethnicity variable. Prior to embarking on an analysis of already collected data by ethnic or racial group, or prior to embarking upon an in-depth study of ethnic differences using primary data collection, researchers must i) carefully consider the threats to the validity of their findings and compensate for them if possible, ii) highlight their shortcomings if they are unable to adjust for them statistically, and iii) consider if the potential positive spin-offs of their research outweigh the potential negative spin-offs. With careful steps taken to minimize the bias, information regarding differences in risk factors, and disease rates between ethnic groups can be very informative for multiple users of health research information. In the following chapters, many of the issues raised here are addressed and their implications are discussed by using an example of ethnicity-based research designed to increase our understanding of the pathogenesis of CVD.

CHAPTER 3

Chapter 3 includes a brief overview of ethnicity-based research as it relates to CVD in multiple countries, including Canada. The rationale for conducting the Study of Health Assessment and Risk in Ethnic groups is also presented.

World-wide distribution of Cardiovascular Disease:

Globally, the major non-communicable diseases are CVD, cancer and diabetes {WHOIS 2001}. In most developed countries CVD rates are declining due to CVD risk factor modification, and improved secondary prevention strategies {McGovern 1996}. By contrast CVD rates are increasing in many developing countries. These increases are due to epidemiologic transitions resulting from a decrease in deaths due to acute infectious diseases and an increase in chronic diseases {World Heart Federation 1999}.

The Global Burden of Disease Study estimated that in 1990 the leading cause of death was CHD (6.3 million deaths) and stroke (4.4 million deaths) {Murray and Lopez 1997}. The World Heart Federation recently reported that CVD claims approximately 15 million lives in the world each year, with over 60% of these deaths occurring in developing countries {World Heart Federation 1999}. By the year 2020, CVD will

join infectious diseases as the leading cause of death and disability in these countries {World Heart Federation 1999}. The reasons for the increase in CVD related deaths in developing countries include increasing life expectancy secondary to declines in childhood and adult deaths from infections, and an increase in the prevalence of CVD risk factors associated with industrialisation and urbanisation {World Heart Federation 1999}.

Regional Differences:

The burden of CVD varies substantially between geographic regions. Apparent "ethnic variations" in CVD rates are closely tied to geographic patterns of disease {Marmot 1995}. Often the first clue that ethnic variations in disease burden exist comes from the observation of differences in disease prevalence between countries. These differences have provided many of the initial hypotheses about lifestyle factors and CVD. One of the first epidemiologic studies to highlight the variation in CHD rates between countries was the Seven Countries Study {Keys 1986}. In this major longitudinal study, a baseline assessment of blood pressure, dietary intake, and serum cholesterol was performed in 16 cohorts of men aged 49 to 59 years, and these cohorts were followed prospectively to ascertain CHD incidence. Large differences in CHD mortality between countries were observed, with low CHD rates in Japan and the Mediterranean countries, and high CHD rates in Finland and the United States (US) {Menotti 2001}. These differences were, in large part, explained by differences in diet, serum cholesterol, and blood pressure. The World Health Organisation (WHO) MONICA (MONItoring of trends and determinants

in CArdiovascular disease) is a CVD surveillance project which includes 117 reporting units in 40 centres from 26 countries {Bothing 1989}. These data indicate a greater than fourteen-fold difference in CHD mortality exists among men, and more than an eleven-fold difference in CHD mortality exists among women, across the countries. More recently the Global Burden of Disease Study estimated the deaths from CVD in eight regions of the world {Murray and Lopez 1997}. The absolute number of deaths from CVD is estimated to be greater in countries classified as "developing" compared to "developed" and developing countries account for approximately two-thirds of CVD death whereas developed countries account for approximately one-third.

Determinants of CVD Variations:

CVD variations by region can be attributed to multiple factors. These include i) differences in the prevalence of lifestyle factors such as dietary consumption, physical activity, psychosocial stressors, and cigarette smoking {Kannel 2000, Marmot 1989}. ii) unequal distributions of social factors such as the wealth of the economy, social capital, income disparity, and rates of employment {Marmot 2001}. iii) differences in the prevalence of genes associated with disease states known to be associated with CVD such as diabetes, obesity, and dyslipidemia {Hegele 1997}, and iv) differences in the access to health care, and type of health services offered in the primary prevention, secondary prevention and tertiary prevention settings. {Kreiger 1990, McGovern 2001} All of these factors influence the CVD rates within and between geographic regions.

Migrant Groups:

Migrant groups are ideal populations in which to study variations in CVD rates and risk factors because the effect of changing lifestyle on risk factor prevalence and CVD can be examined. Differences in disease rates observed among people of similar ancestral origin living in different environments (countries or regions) suggest that environmental influences strongly influence the occurrence of at-risk phenotypes such as abdominal obesity, sedentary lifestyles and CVD {Mckeigue 1991, Haffner 2000}. Observational studies reveal that when members from a given ethnic group move and live in a new environment (migration) their phenotypic characteristics change from those of the community they left to those of the community they adopt. Early on in the period after migration, the disease rates of migrants are usually similar to those of their native communities. However over time, migrants tend to adopt the CVD rates of their new community {Marmot 1995}. This occurs because migrants usually adopt the life-style practices of the host country. For example, the Ni-Hon-San Study tracked the rates of CHD and CHD risk factors among Japanese men living in Japan, Hawaii and San Francisco. They observed that with migration to Hawaii and San Francisco the rates of CHD, body weight, fat composition of the diet, and serum cholesterol increased while the rates of stroke and hypertension decreased {Kato 1973, Nichaman 1975}.

Below the global trends in CVD distribution, temporal trends of CVD and CVD risk factors, prevention strategies, and migrant patterns for white Caucasians, Chinese and South Asians are reviewed (Table 1).

People of European Origin:

People of European origin include those who originate from northern Europe including the Nordic countries, and Germany, western Europe including the United Kingdom and France, southern Europe including Spain and Italy, and eastern Europe including the Slavic countries.

Disease Burden:

Differences in the ASMR vary widely between European populations. Data from the WHO indicate that the CVD mortality rate is six-fold higher among men and women in the Russian Federation compared to people in France. In 1998, the ASMR for CHD among males in the Russian Federation was 639/100,000 compared to 85/100,000 among males in France {WHOSIS 2002}. The cerebrovascular disease (CBVD) ASMR was 361/100,000 among males in the Russian Federation compared to 41/100,000 in France {WHOSIS 2002}. Although the CVD mortality rates are much lower among women, large differences among women between countries also exist. Eastern European countries such as the Russian Federation, Hungary, and the Czech Republic have among the highest CVD rates in the world, which is in marked contrast to most economically stable European countries and North America in which significant declines in CVD mortality rates over the past 30 years have occurred.

Risk Factors:

CVD among European populations is mainly attributable to the major CVD risk factors, namely diets high in saturated fats, elevated serum cholesterol, elevated blood pressure, diabetes, and tobacco exposure. The epidemic of CVD in the eastern European countries appears to be related to high levels of smoking and excessive alcohol use along with diets high in saturated fat {Bobak, Marmot 1998}. However, CVD, like other epidemics, relates closely to social conditions, and its prevalence appears to be strongly related to the social and cultural conditions of a society. Research to explain why the Italian and French populations remain relatively "protected" from CHD has yielded numerous hypotheses. It is likely that dietary differences account for an important component of the differences in disease rates. It is believed that the high consumption of monounsaturated fats such as olive oil and antioxidants are responsible for the low rates of CHD in Italy. In France, the CHD mortality rate remains very low {Artaud-Wild 1993}. While this relative protection from CHD has been attributed to high consumption of alcohol, in particular wine, {Criqui and Ringel 1994} others believe the lower rate of CHD mortality maybe simply be due to a "time-lag" between increases in consumption of animal fat and serum cholesterol concentrations (which have occurred only recently) and the expected increase in mortality {Law 1994}. In the United States and Canada, among white Caucasians, the incidence of CVD has decreased by close to 30% over the past 40 years. This decline has been attributed to risk factor recognition and modification and improved treatments for patients with established CVD {McGovern 2001}.

Prevention:

It is clear that major lifestyle changes, and vigilant treatment of conventional risk factors results in declines in CVD rates. In Finland, an impressive 65% reduction in CHD mortality and stroke was observed between 1972 to 1995, and it is estimated that approximately 75% of this decline in CHD mortality can be explained by a lowering of serum cholesterol by 14% (0.93 mmol/L) in men and by 18% (1.19 mmol/L) in women, reduction in diastolic blood pressure by 9% (6.6 mm Hg) in men and by 13% (12.2 mm Hg) in women, and a significant reduction in smoking (by 30% in men) {Vartiainen et al. 1994}. In North America a 34% decline in CHD mortality occurred between 1980 and 1990 {AHA Statistical Facts 2002}. One-quarter of this decline is attributable to primary prevention efforts and about one-third is explained by secondary prevention efforts such as reduction in serum cholesterol, diastolic blood pressure, and smoking. Additionally, about 40% of this decline is attributed to improved medical and surgical management in patients with established coronary disease {McGovern 1996, AHA Statistical Facts}. More recently in Poland, during the 1990's, a rapid decrease (about 25%) in CHD deaths in early middle age was observed. This decline is attributed in a large part to marked dietary changes including an increased consumption of fruits and vegetables and a reduction in the consumption of animal fats {Zatonski 1998}.

People of Chinese Origin:

Disease Burden:

Death rates from CVD (particularly CHD) have been increasing in China in recent decades {Woo and Donnan 1989}. Although the CVD mortality rate in China is approximately the same as that in the United States, the CHD mortality rate is approximately 50% lower than the rates observed in most western countries, and the stroke rate is significantly higher. In 1999, in urban China, the ASMR for CHD for men and women aged 35-74 was 106/100 000 in men and was 71/100 000 in women {World Health Organization Website}. However, the ASMR for stroke in men and women aged 35-74 was 217/100,00 in men and 147/100,000 in women {Thorvaldsen 1995}. Comparison with five stroke registries from the west suggests that intracerebral haemorrhage occurs between two and three times more frequently in the Chinese than in white Caucasians {Hong 1994}. Only 6% to 12% of strokes in whites are reported as intracerebral haemorrhages compared to 25 to 30% of haemorrhagic strokes in Chinese {Thorvaldsen 1995}

Risk factors:

A case-control study from Hong Kong of acute myocardial infarction (AMI) sufferers indicates that conventional risk factors for CHD in Chinese remain important {Donnan 1994}. The odds ratio for AMI associated with cigarette smoking was 4.3, with hypertension 3.3, and 2.4 with diabetes. Although the mean serum cholesterol among Chinese is low by western standards, a prospective observational study of approximately

9,000 Chinese in urban Shanghai demonstrated that serum cholesterol was directly related (continuous relationship) to CHD mortality even at these low levels {Chen 1991}. Cigarette smoking is highly prevalent among Chinese males as over 60% of men smoke and there is evidence that these rates are increasing {Peto 1999}. In a recent cross-sectional study of 2,542 people aged 20-70 years in rural China, people with increased weight also tended to possess higher blood pressure, serum cholesterol, serum triglycerides, and lower HDL cholesterol; factors which tend to occur with weight gain and cluster together in people who eventually develop glucose intolerance {Hu F 2001}.

Geographic variations:

Trends in morbidity and mortality from CVD within China indicate that the mortality rate attributable to CVD is higher in north China (Beijing) than in south China (Guangzhou) {People's Republic of China-United States Cardiovascular and Cardiopulmonary Epidemiology Research Group 1992}. Furthermore, comparison of urban and rural areas in China indicate that CHD rates increase two-fold in urban areas compared to rural areas {People's Republic of China-United States Cardiovascular and Cardiopulmonary Epidemiology Research Group 1992}, yet surprisingly the stroke rates do not differ by region. The prevalence of hypertension, mean serum cholesterol, and mean body mass index (BMI) were all lower in the south compared to the north, and in rural compared to urban areas. However, the greatest differences in the prevalence of cigarette smoking exist between men and women (74% vs 20%) and this difference is observed in both urban and rural settings.

Migrant Patterns:

Data from Chinese migrants to Singapore and Mauritius provide evidence that the effects of exposure to urban environments lead to adverse risk factor profiles for CVD {Li 1992, Hughes 1990}. In a comparative study of Chinese migrants to Mauritius the prevalence of CHD by ECG was six times greater (24% versus 4%) than in Beijing, China. As well, the prevalence of diabetes was increased and the mean serum cholesterol was higher among Mauritius Chinese (5.5 mmol/L), than among Beijing Chinese (4.4 mmol/L), whereas the prevalence of hypertension and smoking was greater in Beijing {Li 1992}. In a study of Chinese migrants to the United Kingdom, 380 Chinese mean and women between ages 25-64 were recruited and compared to a cohort of United Kingdom residents of European origin. The prevalence of CHD was lower among Chinese men (4.9%) and women (7.3%) compared to European men (16.6%) and women (11.1%). Furthermore, they smoked less (23% vs 35%), and had lower serum cholesterol (5.1 vs 5.6) {Harland 1997}. Therefore, while Chinese migrants appear to be relatively lower risk when compared to people of European origin, when compared to their native rural Chinese counterparts, the prevalence of obesity, late onset diabetes, elevated serum cholesterol and CHD increases with migration.

Prevention:

Economic modernization in China is resulting in an increased prevalence of conventional CVD risk factors over time in urban populations {Zhai and McGarvey 1992}. This offers

a major challenge for prevention efforts among urban Chinese both in China and abroad, as the Chinese who have traditionally had a very low prevalence of CHD will likely not remain protected from developing CHD with the changes in lifestyle they are making. Important prevention strategies in this group include smoking cessation/prevention, and maintenance of a "traditional Chinese" diet (high vegetable, high tea, low fat consumption) to prevent increases in BMI, diabetes, serum cholesterol and hypertension.

People of South Asian Origin

South Asian refers to people who originate from India, Sri Lanka, Bangladesh, and Pakistan.

Disease Burden:

Studies of South Asian migrants demonstrate that they suffer a higher mortality from CHD when compared to other ethnic groups.

Within India:

There are relatively few mortality studies from India as there is no uniform completion of death certificates, and no centralized death registry for CVD {Reddy 1997}. However the WHO and the World Bank data indicate that death attributable to CVD has increased in parallel with the expanding population in India. As well, these data indicate CVD now accounts for a large proportion of disability adjusted life years (DALY). Of all deaths in 1990, approximately 25% were attributable to CVD, which is greater than the 10% due to

diarrhoeal diseases, the 13% due to respiratory infections, and the 8% due to tuberculosis {Murray and Lopez 1997}. Gupta and colleagues performed a meta-analysis {Gupta 1996} and reported that the prevalence of CHD in India ranged from between 7.6% to 12.1%. This is confirmed by a more recent population survey conducted among 1262 people living in south India in which the age standardized prevalence of CHD was 9% {Mohan 2001}

South Asian Migrants:

Studies of South Asian migrants to countries such as the United Kingdom, South Africa, Singapore, and North America indicate that South Asians suffer between 1.5 to 4.0 times higher CHD mortality compared to other ethnic groups {Enas 1992}.

Temporal trends:

In India, CHD is rising in parallel with the increase in life expectancy due to an increase in per capita income, and a decline in infant mortality. The average life expectancy has increased from 47 years in 1960 to 58 years in 1990. This trend is expected to continue with life expectancy at birth reaching 72 years by 2030, leading to large increases in CVD prevalence {Lowy 1991}. Although the CHD mortality rate of South Asians compared to other populations remains high, a decline in CHD rates has been observed in most South Asian migrants over the past ten years. Still, this decline has been less than that observed in the general population in most countries {Balarajan 1991, Sheth 1999}.

Risk factors:

South Asians, despite having increased rates of CHD, do not display an excess of conventional cardiovascular risk factors such as smoking or hypertension, yet do possess an excess of type 2 diabetes {McKeigue 1991, McKeigue 1993}. Conventional CVD risk factors are strongly associated with the development of CHD in South Asians. Data from a case-control study in Bangalore, India {Pais 1996}, in which 300 cases of AMI were compared to 300 age and sex matched controls, revealed an increasing risk of MI as the number of conventional risk factors increased. The odds ratio for MI associated with smoking was 3.6, 2.6 for diabetes, and 2.7 for hypertension. In this study, serum cholesterol and lipid fractions did not differ between cases and controls, although the levels were similar to western values. Cross-sectional studies of CHD risk factors in South Asians have identified that this group suffers a high prevalence of impaired glucose tolerance (IGT), central obesity, elevated triglycerides, and low HDL cholesterol {McKeigue 1991}. The prevalence of IGT and type 2 diabetes is four to five times higher in South Asian migrants than in Europeans by the age of 55 (20% versus 4%) {McKeigue 1991, McKeigue 1993}. The prevalence of diabetes in South Asians in the UK was 10% to 19%, 21% in Trinidad, 25% in Fiji, 22% in South Africa, 25% in Singapore, and 20% in Mauritius {McKeigue 1991}. In rural India the prevalence of diabetes is 3%, and between 11% to 30% in urban India which is similar to the rates reported among Indians living abroad {Ramachandran 2001, Mohan 2001}. In addition, there is increasing evidence that elevation of blood glucose in the diabetic range is also a risk factor for CHD, a condition that is also frequently observed to exist in South Asians. There is also

evidence that South Asians have elevated levels of lipoprotein (a) [Lp(a)] a factor which is associated with both the development of atherosclerosis and thrombosis {Anand 1996}.

Geographic variations:

Striking differences in urban and rural CHD risk factor and CHD prevalence has been observed among South Asians living in India {Reddy 1997}. Data from India demonstrate at least a two-fold excess of CHD in urban compared to rural environments. A recent overview of prevalence surveys in India reported a nine-fold increase of CHD in urban centres, compared with a two-fold increase in CHD rates among rural populations over two decades {Gupta and Gupta 1994}. Associated with this increase in CHD rates in urban areas is an increase in the prevalence of lipid and glucose abnormalities. As well, an increased prevalence of IGT, and type 2 diabetes, lower HDL cholesterol and higher triglycerides, increased abdominal obesity, and BMI, and higher levels of hypertension are observed in the urban areas compared to the rural. By contrast, the rates of tobacco smoking are higher within rural environments.

Migration patterns:

A recent study which compared the risk profiles of urban South Asians living in the UK to their siblings living in India revealed that the UK cohort had a higher BMI (27 vs 23), higher systolic BP (144 mm Hg vs 137 mm Hg), higher total cholesterol (6.35 vs 5.0 mmol/L), lower HDL cholesterol (1.14 vs 1.27 mmol/L), and higher fasting glucose (5.4

vs 4.6 mmol/L) compared to their siblings {Bhatnagar 1995}. Lp(a), which is genetically determined, was similarly high in both groups. Therefore, adverse changes in CVD risk factors are observed when South Asians adopt an urban lifestyle, be it within India or abroad.

Variations in CVD Rates and risk factors between Ethnic groups in Canada:

Until recently there was little information regarding the rates of CVD and CVD risk factors among Canadians of varying ethnic origin {Anand and Yusuf 1999}. Ethnicity research is particularly relevant in a country such as Canada given that non-Canadian born individuals constitute 17.4% of the Canadian population {Census 1996}. The sources of immigration in Canada have changed markedly over the past 100 years and in 1996 people of European origin in Canada represented 47% of the total immigrant population. Currently, the fastest growing group of new immigrants in Canada comes from Asia (31% in 1996) and nearly 25% of all recent immigrants are from China and Indian sub continent. In the 1996 Census 921,600 people in Canada reported being of Chinese ancestry and 723,300 individuals reported being of South Asian ancestry {Census 1996}. These two groups make up the two largest non-white ethnic groups in Canada.

Health of Immigrants in Canada:

The overall health of immigrants in Canada appears to be better than that of the average Canadian. An analysis of Census data, vital statistics and data from the Health and

Activity Limitations Survey demonstrated that immigrants, especially those from non-European countries, have a longer life expectancy and more years of life free of disability and dependency than Canadian-born individuals {Chen 1996}. The belief is that this reflects the "healthy immigrant effect" whereby only the healthiest and wealthiest people to relocate to another country, excluding refugees.

Until recently, there were no Canadian data on the patterns of CVD morbidity and mortality by ethnic group. This is because the process of assigning the ethnicity to individuals is controversial, difficult, and requires detailed planning. Although now there is a self-defined ethnicity category on the Census form, the Canadian National Mortality database does not code ethnic origin on death certificates. Previous studies have tried to study the patterns of deaths among immigrants to Canada using only country of birth as the ethnicity classification system {Nair 1990}. However, classification by country of birth does not accurately reflect ancestral origin (for example, a person who originates from the Indian Sub continent who grows up in East Africa would be classified as "African").

To improve the accuracy of the country of birth classification of ethnicity, use of the ethnic group specific surnames for South Asians and Chinese can also be used. South Asian and Chinese surnames are highly specific for ancestral origin and have been used in many studies around the world previously {Harland 1997, Choi. 1993, Tjam 2001}. Using both country of birth and unique surnames, a recent analysis {Sheth 1999} of the

Canadian National Mortality Database since 1979 and 1993 suggested that the rates of chronic diseases such as CVD and cancer varied significantly among ethnic populations. Specifically Canadians of predominately European origin have high rates of cancer and CVD mortality, Canadians of South Asian origin (people who originate from India, Bangladesh, Pakistan and Sri Lanka) have high rates of CVD mortality but have relatively lower rates of cancer mortality, and Canadians of Chinese origin (people who originate from anywhere in China, Hong Kong and Taiwan) have low rates of CVD mortality but relatively high rates of cancer mortality. For CHD among South Asian Canadians, the ASMR per 100,000 was 320 among men and 144 among women. This was similar to the ASMR per 100,000 among European Canadians which was 320 among males and 110 among women. However the ASMR per 100,000 among Chinese males was 107, and among Chinese women was 40, which are significantly lower than the rates among South Asians and Europeans (Figure 1). Furthermore a significant decline in CHD death rates from 1979-1983 to 1989-1993 was observed in all groups with the greatest declines being apparent among South Asian men and women compared to European and Chinese Canadians respectively (decline in CHD deaths among males: 22%, 13%, and 5.4% and among females: 6%, 4%, and 2%) {Sheth 1999}. These intriguing variations in CVD mortality among Europeans, Chinese and South Asian people in Canada are consistent with the patterns observed in other countries such as the UK {Harland 1997} (Table 2). The difference in CVD burden observed between people of European, South Asian and Chinese Canadians provided the rationale for the Study of Health Assessment of Risk in Ethnic group (SHARE) - a Canadian-based study to determine the prevalence

of CVD, atherosclerosis and its determinants. SHARE was undertaken among three ethnic groups to determine the CVD prevalence, to determine the prevalence of conventional and emerging risk factors, to determine if the burden of atherosclerosis correlates with clinical events, and to study the relationship between diet and psychosocial stress with atherosclerosis and CVD.

Summary:

CVD accounts for the largest percentage of deaths world-wide. To date, recognition and modification of the major CVD risk factors have led to declines in CVD in most western countries, although these declines have lagged behind in most non-white populations. Socio-economic development, urbanization and increasing life-expectancy has led to a progressive rise in the CVD rates in developing countries such as India and China. It is clear that conventional CVD risk factors such as elevated serum cholesterol, elevated blood pressure, cigarette smoking and glucose intolerance are the major risk factors for CHD and stroke in most populations. However, other risk or protective factors (e.g. levels of endogenous fibrinolysis, dietary factors such as increased fish consumption) likely exist. Identification of these factors is important so that new approaches to prevention of CVD in these populations may be developed.

Figure 1: Variations in the Rates of Cardiovascular Disease (CHD) between Ethnic Groups in Canada {Sheth 1999}.

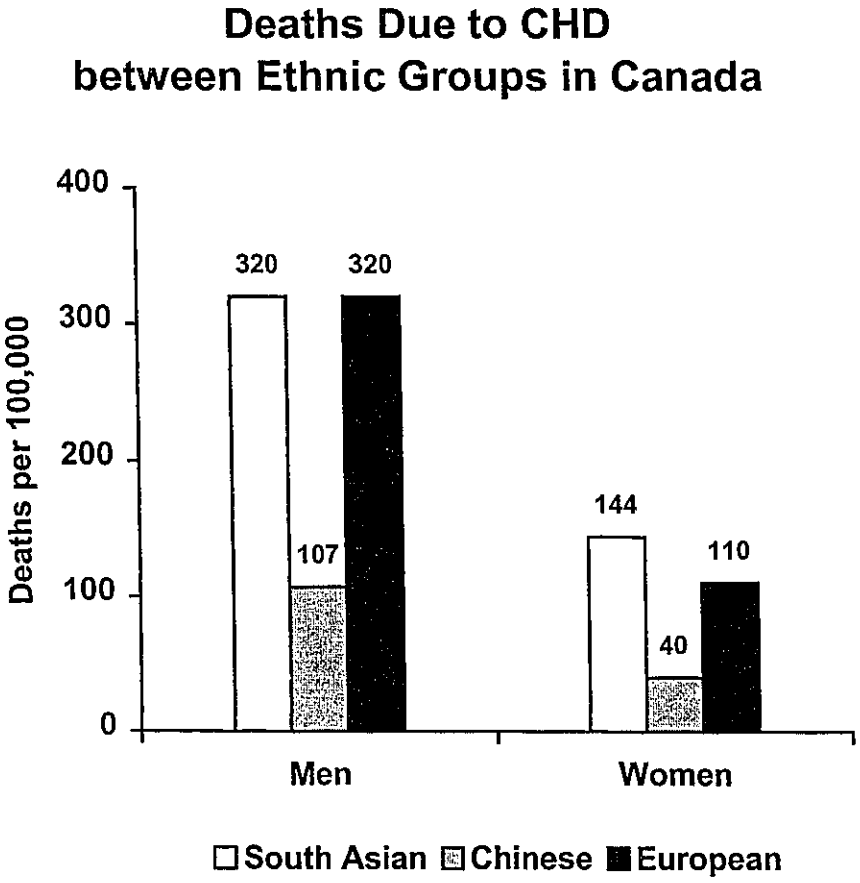


Table 2: Summary of the Key Differences between South Asians, Chinese and Europeans

	South Asians	Chinese	Europeans
Disease Burden* in Native Country	N/A	M: 100 F: 69	M: 60-390 F: 24-193[§]
Canada	M: 320 F: 144	M: 107 F: 40	M: 320 F: 110
Common Risk Factors	• Diabetes • Smoking • ↑Blood Pressure	• Smoking • ↑Blood Pressure • Diabetes	• Smoking • ↑Blood Pressure • ↑ Cholesterol

* Age Standardized Mortality Rates for CHD per 100,000; [§]: Range from France to Russia, N/A: Not Available

CHAPTER 4

OBJECTIVES AND DESIGN OF SHARE

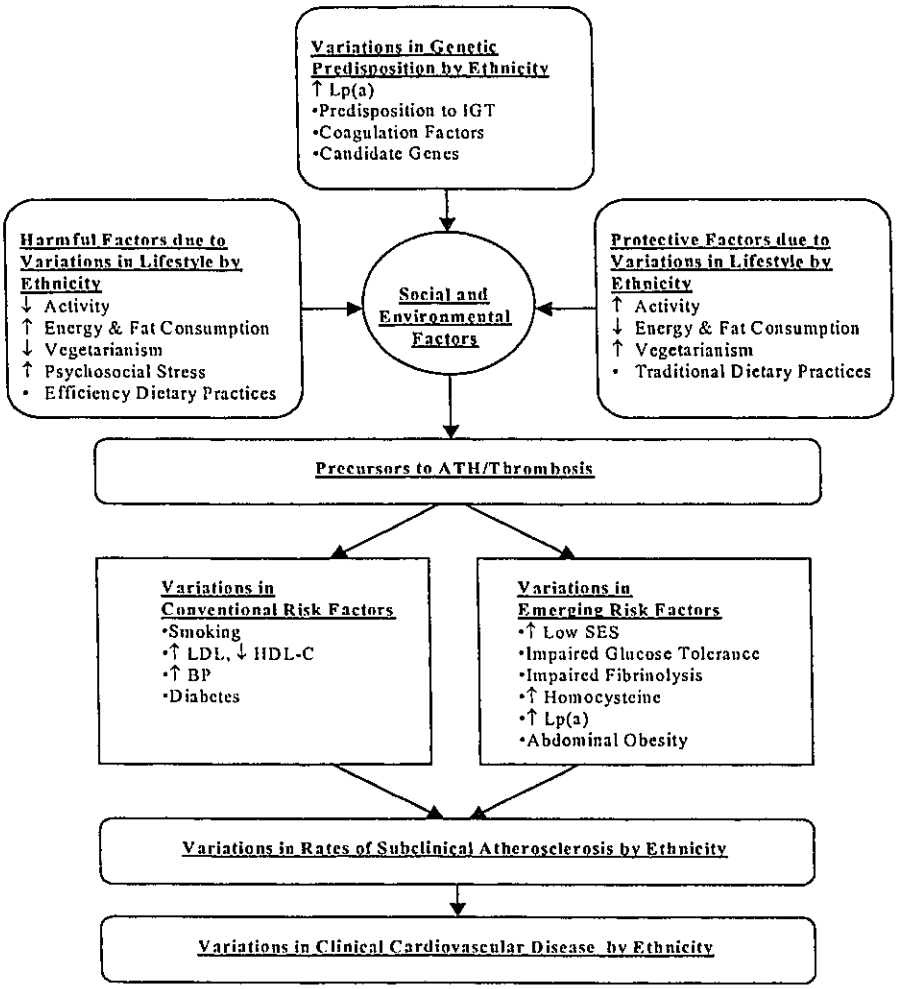
In this Chapter the objectives and the design of SHARE are presented. The rationale for various design features is also provided. The protocol details regarding the data collection process (e.g. laboratory methods, ultrasound protocol) are provided in the accompanying SHARE protocol manuscript which is found in Appendix D.

Introduction:

The Study of Health Assessment and Risk in Ethnic Groups (SHARE) was designed i) to determine the prevalence of conventional and emerging determinants of atherosclerosis and CVD and ii) to characterize the burden of atherosclerosis and determine the prevalence of CVD among three distinct populations: Canadians of South Asian origin, Chinese origin, and European origin. Given the potential influence of biomedical and social factors on the development of CVD, conventional (i.e. tobacco use, elevated blood pressure, glucose intolerance, abnormal lipid profile), emerging (i.e. prothrombotic factors, dietary factors), and social factors (income level, employment, marriage, and education) were measured in randomly selected individuals from three metropolitan centres in Canada: Hamilton, Toronto, and Edmonton. The conceptual framework of the relationship between established and emerging CVD determinants was developed a priori, and reflected the accumulated data supporting the key determinants of

atherosclerosis, thrombosis, and CVD derived from populations of white Caucasians, South Asian and Chinese origin.

Figure 2: Hypothesis Diagram in SHARE



Hypothesized model of development of cardiovascular disease among ethnic populations. ATH Atherosclerosis; BP Blood pressure; HDL-C High density lipoprotein cholesterol; IGT Impaired glucose tolerance; LDL low density lipoprotein; Lp(a) Lipoprotein-; SES Socioeconomic status. Efficient dietary practices include processed and fast foods. It is expected that there will be variations in genetic predisposition, and both conventional and emerging risk factors that could explain variations in disease across ethnic groups.

Note: In this hypothesis diagram the determinants are grouped into i) genetic factors, ii) harmful lifestyle factors (e.g. poor dietary intake), and iii) protective lifestyle factors (e.g. regular exercise) all of which are likely related to the development or prevention of atherosclerosis and possibly thrombosis.

Lifestyle factors:

The use of terms such as "lifestyle factors" has been criticized by some epidemiologists as being misleading given that "lifestyle factors" imply that individuals *freely* choose poor lifestyles without considering the social and economic circumstances that influences their lifestyle decisions {Kreiger 1993}. Proponents of eco-social theory emphasize the need to place health behaviours in their social context if they are to be understood or even altered in the future. They emphasize that social conditions are not "natural", but are constructed by people, and that the health observations of a population cannot always be reduced to individual attributes. This is known as the "individualistic fallacy" which is the assumption that individual data are sufficient to explain group-level phenomena, which is akin to the concept of "ecological fallacy" where the assumption is that population level data can be applied to individuals {Krieger 2000}. Integration of the macro and micro data is known as contextual, or multilevel, analysis which combines individual and group level data in a clearly specified and theoretically justified manner {Marmot 2000}. Both types of inquiry are needed, and SHARE represents a focused research investigation, the results of which can be used to formulate questions to be addressed at a population level, and demonstrates that both types of inquiry are important to fully understand the determinants of CVD.

Objectives:

In a random sample of Canadians of South Asian, Chinese and European origin the objectives of SHARE are to:

1) Identify the differences in the average intimal medial thickness, a measure of subclinical atherosclerosis, between age and sex matched ethnic populations.

2) Determine the relative prevalence of the established (e.g. cigarette smoking, lipids, blood pressure, glucose abnormalities) and some emerging risk factors (e.g. prothrombotic, dietary and social factors).

3) Determine the prevalence of CVD.

4) Determine the independent contributions of these factors and ethnicity to the presence and severity of carotid atherosclerosis and CVD.

Novel Features about SHARE:

While previous studies have been conducted among migrants of South Asian and Chinese origin in the United Kingdom {McKeigue 1985, Bhopal 1999}, by design SHARE has a number of novel design features. First, there has been no other study in Canada in which ethnic variations for atherosclerosis, CVD, and risk factors have been assessed. Second, SHARE is the first study among South Asians and Chinese migrants in which i) the carotid ultrasound has been used to measure subclinical atherosclerosis, ii) food frequency questionnaires have been developed to quantify macro-nutrient intake, and iii) an in-depth evaluation of psychosocial stressors and biologic markers has been conducted.

Investigators and Funding:

At the outset of SHARE, collaborations with investigators from Toronto and Edmonton were developed. Toronto was chosen because investigators at St. Michael's hospital expressed an interest in the objectives of our study, and it made sense to include them given that Toronto is the metropolitan centre which has the greatest number of South Asians and Chinese people living in it. Edmonton was chosen because of existing collaboration between Dr. Salim Yusuf and Dr. Koon Teo (a SHARE co-investigator). The coordinating centre was located in Hamilton and Dr.Yusuf was the Principal Investigator. All data were collected centrally in Hamilton. Questionnaires were transmitted into the database using Datafax technology in which optical character recognition facilitates the automatic transfer of data from the faxed case record form to the database. This obviated the need for manual data entry, and improved the efficiency and accuracy of data collection. Laboratory specimens were also collected and stored centrally in Hamilton. All analyses were performed in a central lab using standardized techniques. All electrocardiograms and carotid ultrasound tapes were collected and read centrally. Each centre had a study coordinator, and the lead study coordinator was located in Hamilton.

Study Design:

SHARE is a cross-sectional prevalence study of atherosclerosis, CVD, and its associated

risk factors in three randomly sampled ethnic populations of Canada. The following criteria were reviewed to determine eligibility in SHARE.

Ancestral origin:

People of South Asian origin were defined as individuals whose parents and grandparents originated from the Indian subcontinent specifically India, Pakistan, Bangladesh, and Sri Lanka. People of Chinese origin were defined as individuals whose parents and grandparents originated from mainland China, Hong Kong, or Taiwan, and Canadians of European origin were defined as individuals whose parents and grandparents originated from Canada, the United States or Europe. Aboriginal and people of African descent were excluded as they may have different CVD determinants than do people of European origin. These definitions were selected to provide a broad representation of people within each ancestral group which accurately reflected the make-up of immigrants in Canada. It is acknowledged that within each group there was a potential for a large degree of heterogeneity in language, religion, and lifestyle practices. For example, the South Asian group could include people who originated from North India or South India where the language, diet, and religion may differ substantially. In addition, the category of "European" includes people who originate from Italy or Germany, who also have very different lifestyle practices. The rationale for this decision was that the excess of CVD has been observed among all South Asian subgroups and is not restricted to just one or two sub-segments of the population, and second, most of the information regarding CVD

and risk factors has been derived from white Caucasians who are of European origin, and therefore this group was chosen as the reference group for the study.

***Age*:**

Only people between the ages of 35 to 75 years were eligible for the study. This age group was chosen because inclusion of young people who are relatively disease free would require us to recruit a larger sample of people to demonstrate significant differences in CVD prevalence and atherosclerosis, whereas inclusion of older people (> 75 years), may also blur the differences between groups given that the prevalence of CVD increases linearly with age. Furthermore, the risk factors and CVD relationship may be attenuated among older people compared to younger people {Howard 1997}, and the identification of the determinants of CVD in the group which stands to cost society the most if affected by CVD are the younger to middle aged members of society.

Length of Time in Canada:

Only people who had lived in Canada for more than 5 years were eligible (including first and second generation immigrants). This cut off was selected to avoid the inclusion of new immigrants or refugees whose lifestyle characteristics may reflect those of their native country, and not their adaptive lifestyle characteristics. Furthermore one objective of SHARE was to study differences in risk factors and social factors in all groups after a certain period of "exposure to a Canadian lifestyle" was studied.

Co-morbidity:

People with severe debilitating chronic illnesses such as terminal cancer or renal failure were excluded. Individuals with a history of CVD or diabetes were not excluded. Individuals with chronic diseases usually have abnormal risk factor profiles and other biologic markers. For example, a person with renal failure on dialysis may have extraordinarily high concentrations of homocysteine, and lower lipid measurements – states which are extreme and do not reflect the population average.

Sampling Methods:

i. Creation of the Sampling Frame: Given the high specificity of South Asian and Chinese surnames for ethnicity, separate sampling frames were created for the South Asian and Chinese cohorts based on surnames. South Asian surnames have been reported to be 95% specific for South Asian ethnicity, and Chinese surnames have been reported to be 80% specific {Sheth 1997}, and over 80% sensitive for Chinese ethnicity {Choi 1993}. These ethnic-specific lists of names were created by manual entry of comprehensive lists of South Asian or Chinese names from previously published lists, community telephone directories, and local community group membership lists. The lists of surnames were merged with a public telephone directory database developed by Pro Phone, Canada {ProPhone Canada 2002}. These lists were then shortened to include only people who lived in Hamilton, Toronto or Edmonton. These cities were chosen because they have substantial populations of South Asians and Chinese Canadians, and because the carotid ultrasound machine and trained technicians were available in these centres.

ii. Selection Method: Probability systematic random sampling was used to identify South Asian and Chinese households from their respective sampling frames. The European sampling frame was created using the postal codes of the South Asian and Chinese participants who were selected. These postal codes were entered into the CD program, and a list a people and their addresses who shared the same postal code was generated. From these lists surnames which were South Asian and Chinese were removed, and the Remaining households were randomly approached to identify an eligible and interested European origin participant. This system was used in order to sample European-origin Canadians from similar geographic regions as the South Asians and Chinese participants.

iii. Recruitment methods: A letter introducing the study was mailed to the selected households, and, beginning four days after mailing, up to twelve telephone calls were made from trained personnel of South Asian or Chinese origin who were based at the coordinating centre in Hamilton. South Asian and Chinese telephone recruiters were employed so that they could communicate with potential participants in their mother tongue. If more than 1 eligible subject lived within a household, the member with the earliest birth date in the year was targeted. The twelve calls were spread throughout the daytime, evenings, and weekends to ensure the largest number of people were at home.

iv. Non-Responders: Non-responders were defined as people who were eligible and allowed the telephone interview yet did not want to participate in the study. Basic

demographic, socioeconomic, and linguistic information was collected from all non-responders where possible in order to characterize this group and to assess non-responder bias by comparing these individuals to the responders. It is recognized that this somewhat underestimates the true non-responder characteristics given that no data were collected from people who refused to speak with the telephone recruiters. Responders were invited to attend one of three clinics: Hamilton General Hospital in Hamilton, Ontario, St. Michaels's Hospital in Toronto, Ontario, and the University of Alberta Hospitals, Edmonton, Alberta.

Clinic Visit:

Ethnic origin was further confirmed by the study coordinator at the time of the hospital visit on the basis of name, country of birth, and appearance. After written informed consent (including consent for DNA analysis and record linkage) the following was performed: i) Fasting blood samples (including neurohormones) and a random urine sample ii) Administration of oral glucose load: 75 grams (non-diabetics only), iii) Self administered general questionnaire, iv) Physical measurements: Weight, height, waist and hip circumference, blood pressure in the right arm and ankle, and heart rate recorded by standardized methods, v) B-mode carotid ultrasound, vi) Echocardiogram (2-D and M-Mode), vii) Resting 12-lead electrocardiogram, viii) Nutrition Assessment: Review of completed FFQ, and teaching for completion of 7 day food records to be taken home and completed prospectively, and mailed back to the Project Office, and ix) Psychosocial assessment: Completion of the Well-Being Questionnaire. All participants were informed

of their health assessment results approximately 6 months after completing their clinic visit.

Sample Size and Statistical Considerations:

One of the main objectives of SHARE was to identify the differences between ethnic populations, in the mean maximum intimal medial thickness (IMT) which is a measurement of subclinical atherosclerosis. Prior population studies have demonstrated that small differences, between 0.05 mm and 0.1 mm, in IMT represent substantial differences in the atherosclerotic burden {Burke 1995}. Using the mean maximal IMT among 30 European Canadians in the SHARE pilot study, 320 subjects per ethnic group provides over 90% power to detect at least a 0.05 mm difference in mmIMT between the groups {Anand 1998}. In addition, this sample size allows the detection of significant differences in risk factor prevalence among ethnic groups with significant power. Given that the standard deviation of mmIMT among men and women is similar, similar differences in mmIMT with high power can be detected between men and women overall, and high power to detect mmIMT differences of at least 0.08 mm between men and women within each ethnic group (115 per group) is possible. With this sample size, important differences in risk factor prevalence can also be detected. For example, the prevalence of diabetes and IGT is approximately 10% among European Canadians. With a sample size of 320 per group, SHARE has over 80% power to detect a 1.79 fold excess in diabetes and IGT, and over 90% power to detect two times this prevalence rate.

Analysis Plan:

In addition to comparing the burden of atherosclerosis, and prevalence values for conventional cardiovascular risk factors and CVD, an analysis of the relationship between i) the conventional and emerging risk factors and ii) atherosclerosis and CVD within the SHARE cohort was planned. Rather than studying the relationship between risk factors and disease outcomes separately in each ethnic group, the importance of various factors in the prediction of disease were tested using the conventional risk factors, the emerging risk factors, and the interaction between these factors. Given the multitude of data collected in SHARE, many exploratory analyses were also planned to determine the relationship of key risk factors such as dietary and social factors to atherosclerosis and CVD.

Examination and reporting of the data:

Prior to statistical analyses of the data, the distributions of variables were plotted to check the assumption of normality. If the variables were not normally distributed (e.g. triglycerides or Lp(a)), they were appropriately transformed (e.g. natural log) before conducting statistical analyses. Categorical variables were examined using logistic regression, and continuous variables were assessed using multiple linear regression controlling for age and gender.

The results are presented as prevalence rates of discrete variables in each ethnic group adjusted for age and sex using the direct method, whereby all participants in the study are

used as the standard population {Armitage and Berry 1998}. Continuous variables are shown as age and sex-adjusted means for each ethnic group with their standard deviations. Analysis of covariance is used to analyze continuous variables with adjustment for age and sex. Post-hoc comparisons were performed using Tukeys' approach to adjust for multiple comparisons. When comparing categorical variables between ethnic groups, logistic regression was used with age and sex as covariates.

The relationship of conventional and emerging risk factors to atherosclerosis:

We expect that several "emerging" (fasting glucose, Lp(a), waist/hip ratio, HDL-cholesterol) risk factors will predict atherosclerosis over "conventional" (hypertension, smoking, cholesterol) risk factors. A hierarchical linear regression model was fit predicting mmIMT on "conventional" and "emerging" risk factors and their interactions with ethnic group. Colinearity among these risk factors was tested before fitting this model. The order of testing in the model was *traditional risk factors (e.g. tobacco, blood pressure, cholesterol, and glucose)*, followed by *emerging risk factors (e.g. thrombotic markers, and social factors), and ethnicity.* A random effects model will be used given the random sampling of subjects. The methods of Gatsonis and Sampson {Cohen J and Cohen P 1983} uses a series expansion to determine the exact power required to identify independent predictors assuming a multivariate linear model to show a minimal desirable level of the partial multiple R^2. Using this method a total sample size of 990, will provide 90% power to detect a partial R of at least 0.16 (R^2 = 0.03) testing the independent

predictive value of the emerging risk factors and ethnic group while controlling for conventional risk factors.

The relationship of conventional and emerging risk factors to CVD:

A multiple logistic regression model was used to examine the relationship between conventional and novel risk factors, atherosclerosis, and ethnicity as predictors of prevalent CVD. The variables selected for entry into the model were based upon pre-existing hypotheses in the literature and results of the univariate testing. Interactions between ethnic status and conventional cardiovascular risk factors and atherosclerosis will be examined.

Data Collection and Outcome Measures:

Three questionnaires were created for use in SHARE. All questionnaires were self completed by participants and checked by the study coordinator at the end of the clinic visit. The General Questionnaire (GQ) was used to collect data on demographic characteristics and general lifestyle characteristics including conventional risk factors, socioeconomic factors, personal and family history of CVD. As no previously validated questionnaire was deemed to be appropriate for the multiethnic population of SHARE, a new questionnaire was designed. The GQ was compiled utilizing sections from previously validated questionnaires used in longitudinal studies of cardiovascular risk factors (Appendix G). Utilizing sections from existing instruments appears to be an acceptable approach in the creation of a new measurement instrument {McDowell 1996}.

The SHARE GQ included unique questions pertaining to ethnicity, religion and ethnic specific diet, and smoking habits and was initially tested in the SHARE pilot study (n=76) {Anand and Yusuf 1997} and was altered where necessary.

Translation:

Although the instruments used in the pilot study were only available in English, prior to the use of self-administered study instruments the final version of the GQ was translated and back translated by separate individuals into four languages including Punjabi, Tamil, Hindi, and Chinese. The translation process included translation of the individual items or questions into the other languages. This was performed by an individual who was fluent in both English and the specific language, who was knowledgeable about the content area, and aware of the intent of each item. The back translation was performed by another bilingual person who was not associated with the initial translation phase yet was also knowledgeable about the content area. If the meaning of a question was lost or altered, then that particular set of items were altered to ensure the original intent of the questions is conveyed. If participants were not able to read, an interpreter assisted them with the completion of the questionnaires.

Reliability of the General Questionnaire:

The reliability of the General Questionnaire was tested in a subset of SHARE participants (n=88) who completed the GQ a second time. The test-retest reliability of the GQ was excellent and the mean of the Kappa coefficients for 24 categorical variables was 0.75. In

addition, the responses to the General Questionnaire were cross-checked with responses to identical questions placed on other SHARE questionnaires. For example, we asked if a participant was employed on the General Questionnaire and on the Well-Being Questionnaire (WBQ). The level of agreement between responses to the same question on different questionnaires was excellent (kappa = 0.98, (95% CI: 0.97-0.99)). From this assessment it appears that the questionnaire is reliable (Table 3).

Table 3: Selected variables from General Questionnaire reliability

GQ Question	Agreement
Ethnic Status	0.85
Years in Canada	0.99
Employed	0.90
Smoke	0.88
Drink Alcohol	0.76

Reliability of Self- Classification of Ethnicity:

The agreement between Time 1 and Time 2 self described Ethnicity is 85%, and this indicates that an individual's perception of their ethnicity changes over time {Kreiger 2000}. As opposed to the variable such as gender, ethnicity is a subjective variable, which can change over time (Table 4).

Table 4:Reliability of Self-Classification of Ethnicity

	European$_2$	South Asian$_2$	Chinese$_2$	Other$_2$	Total
European$_1$	32			1	33
South Asian$_1$		17		4	21
Chinese$_1$			30		30
Other$_1$	2	2		1	5
	34	19	30	6	89

$_1$ Baseline responses on the General Questionnaires

$_2$ Repeat responses among 88 participants

Food Frequency Questionnaire:

Food frequency questionnaires (FFQs) are the instrument of choice for dietary assessments in large epidemiologic studies {Willett 1985}. Before the initiation of SHARE no representative FFQ's existed for South Asian and Chinese Canadians. Therefore, based on the SHARE pilot study data in which a 24 hour recall and food records were collected from all 76 participants, 3 FFQ's were created and based on the model provided by the Canadian Study of Diet Lifestyle and Health {Jain 1996}. Creating these questionnaires involved incorporating the commonly consumed foods and their typical portion sizes as reported in the pilot study. In addition, questions of dietary habits such as vegetarianism, visible fat consumed, types of fats used in frying, frequency of consuming fast-food and the degree of change in food intake that accompanied acculturation were incorporated. The validity of the FFQs was tested by comparing the FFQ's to 7 day food records which were collected in all participants at baseline. The

reliability was tested by re-administration of the FFQ approximately 6 months after the initial completion. The details of this assessment are provided in Chapter 6 of this thesis.

Well-Being Questionnaire:

The Well Being Questionnaire was made up of a series of questions designed to assess psychosocial factors experienced by participants. The specific subscales, the domains they assess, and the sources for these questions are found in the accompanying protocol manuscript in Appendix D. While some subscales were taken from previous surveys such as the National Population Health {NPHS 2000 Website}, and the US National Health and Nutrition Examination Survey {NHANES 2000 Website}, other questions were created based on a qualitative study we conducted among the SHARE pilot participants. In this substudy, three focus groups were conducted among Chinese, South Asian, and European Canadians, and qualitative methods were used to determine the most important life stressors for each ethnic group. These data were used to develop the Well Being Questionnaire which included questions associated with acculturation and perceived inequalities among ethnic migrants which are detailed in Chapter 7 of this thesis.

The validity of the WBQ was assessed using content criteria and reliability methods. After forming the WBQ, it was pre-tested among individuals of South Asian, Chinese, and European origin who were not study participants. The WBQ was translated and back translated and the original questions were compared with the translated questions by the study coordinator. Modifications to the questionnaire were made when necessary. The

questionnaire was reviewed by a small group of SHARE investigators, as well as some experts in the area for content validity. The General Well Being Schedule, which has been previously validated {Fario 1977} was incorporated into the questionnaire to perform criterion validity of the depression and self esteem questions found in other subscales in the WBQ. The reliability of the questionnaire was tested in 100 SHARE participants who were sent the questionnaire a second time approximately one month after the initial time of completion. The reliability co-efficient for the subscales are provided in detail in Chapter 7 of this thesis.

Physical Examination:

The physical assessment section of the study evaluated indicators of current health status and took approximately 10 minutes per participant to complete. Standard measurements were performed in duplicate by the same preceptor on each participant. The specific details of the physical measures are found in the protocol manuscript in Appendix D.

Carotid Ultrasound (CUS):

The CUS can be used to detect, non-invasively, the presence of both very early and advanced atherosclerosis. Pathological and epidemiological data support the use of CUS to detect early-stage carotid atherosclerosis. Several cross-sectional studies, including SHARE, have shown that an increased mmIMT of the carotids is a useful marker of atherosclerosis elsewhere in the arterial system, and five prospective studies have shown that increases in mmIMT predicts an increased risk of cardiovascular (CV) events

{Salonen 1991, Bots 1997, O'Leary 1996, Chambless 1997, Hodis 1996}. Furthermore, risk factors that predict clinical coronary heart disease also correlate with carotid atherosclerosis {Burke 1995}, and interventions that prevent coronary heart disease (e.g. lipid lowering), have also been shown to simultaneously reduce clinical events and carotid and coronary atherosclerosis {Byington 1999, Lonn 2001}.

Thus, mmIMT measured by the CUS is a valid surrogate for clinical events {Salonen 1991, Bots 1997, O'Leary 1996, Chambless 1997, Hodis 1996}. It identifies subclinical atherosclerosis, and it is useful in studying early disease changes thereby increasing the sensitivity of epidemiologic studies. In addition to being a useful measurement of atherosclerosis, utilizing B-mode CUS decreases sample size requirements to study risk factor- disease association, as it is a continuous variable that is available in all subjects. The scanning protocol used in SHARE was similar to that used and validated in several other large studies {Burke 1995, Lonn 2001}. The detailed scanning and reading protocol are found in the accompanying manuscript in Appendix D. Although studies were performed in 3 cities in Canada all studies were analyzed at the core-ultrasound lab in Hamilton, and the inter and intra-observer reliability was high {Anand 2000}.

Electrocardiograph:

A 12-lead electrocardiogram (ECG) was performed on all participants during their clinic visit. The ECG is of recognized value for the identification and prognosis of CVD in population-based epidemiologic studies {Crow 1997}. In SHARE the baseline ECG was

used to estimate the prevalence of previous myocardial damage and left ventricular hypertrophy.

Potential Threats to Validity:

Undercoverage Bias:

Undercoverage bias results when proportions of the target population from the sampling frame are missed. This can occur if a disproportionate number of individuals from an ethnic group does not have telephones or have unlisted numbers, or if the compact disk compilations of public telephone directories are out dated. In addition, the surname method also fails to include people of South Asian or Chinese origin who have married outside their ethnic group and changed their surname. However prior to initiation of this method, we reviewed the 1994 Household Survey by Statistics Canada which indicated that over 99% of Canadians had telephones and the majority of women of ethnic origin who have married outside their ethnic group and had changed their surname was approximately 1%. In addition, a supplementary mechanism was developed to identify unlisted South Asian and Chinese numbers with the addition of South Asian and Chinese community membership lists to the compact disc generated lists. Although, the compact disc software was updated as updates became available the compact disc software was usually 6 months to 1 year out of date by the time it was released. However, this is not expected to differentially affect one or another ethnic group.

Selection Bias:

In order to minimize selection bias, non-sampled volunteers were not accepted into SHARE. In order to characterize non-responders in this study we collected data where possible, from eligible participants who did not want to participate in the study. 44% of the people contacted would not complete a telephone interview and therefore the non-responder data which was collected only represent a sub-set of all non-responders. Questions regarding risk factors (e.g. smoking), disease prevalence (CHD and cancer) and socioeconomic status (e.g. employment) were asked of the non-responders. A comparison between non-responders and responders in SHARE is presented in Chapter 5.

Measurement Bias:

In the analyses of the carotid ultrasound and ECG readings, bias was minimized by blinding the readers to the last name of the participants, and other information which could reveal the ethnic origin of the participant to the reader.

Recall Bias:

Systematic error occurs due to differences in accuracy or completeness of recall to memory of past events or experience (e.g. dietary intake, or stressful events). In SHARE the reliability of responses was assessed in approximately 10% of participants for the GQ, and among a random sample of participants who completed the nutrition and well being questionnaires.

Regression to the Mean Phenomenon:

A random 10% from each ethnic group underwent repeat blood analyses, 6-12 months after their initial assessment to allow us to quantify and potentially adjust for the regression to the mean phenomenon (Table 5, Figure 3). If people are classified based on only one measurement then more people are classified as abnormal either because they are truly abnormal or because of random error (e.g. the observed value = the true value + random error). Therefore if two observed values per individual are used to classify them as abnormal or normal we diminish the effect of random error in producing an abnormal observed value is diminished {Streiner 2001}. A related concept known as regression dilution bias describes the dilution/attenuation in a regression coefficient that occurs when a single measured value of a covariate is used instead of the usual or average value over a period of time {Clarke 1999}. Analysis of the relationship between a covariate and outcome over time must be adjusted to account for measurement error or within person change overtime. Therefore, in the prospective follow-up of SHARE participants, repeat examinations (e.g. at 5 year intervals) are planned.

Table 5: Laboratory Measurement Reliability (n=89)

	Time 1	Time 2	Correlation
Fasting Glucose (mmol/L)	5.05 (0.56)	5.09 (0.56)	0.89
Fasting Cholesterol (mmol/L)	5.21 (0.89)	5.21 (0.84)	0.83
HDL (mmol/L)	1.18 (0.40)	1.21 (0.40)	0.94
Lp(a) (mmol/L)	268.29 (239.34)	286.94 (256.32)	0.97
Insulin (pmol/L)	75.99 (41.98)	78.62 (51.53)	0.54

Note: The numbers displayed at Time 1 and Time 2 are means and the numbers in parenthesis are standard deviations. No significant differences between ethnic groups were observed.

Figure 3a: Correlation between Fasting Glucose Measurements

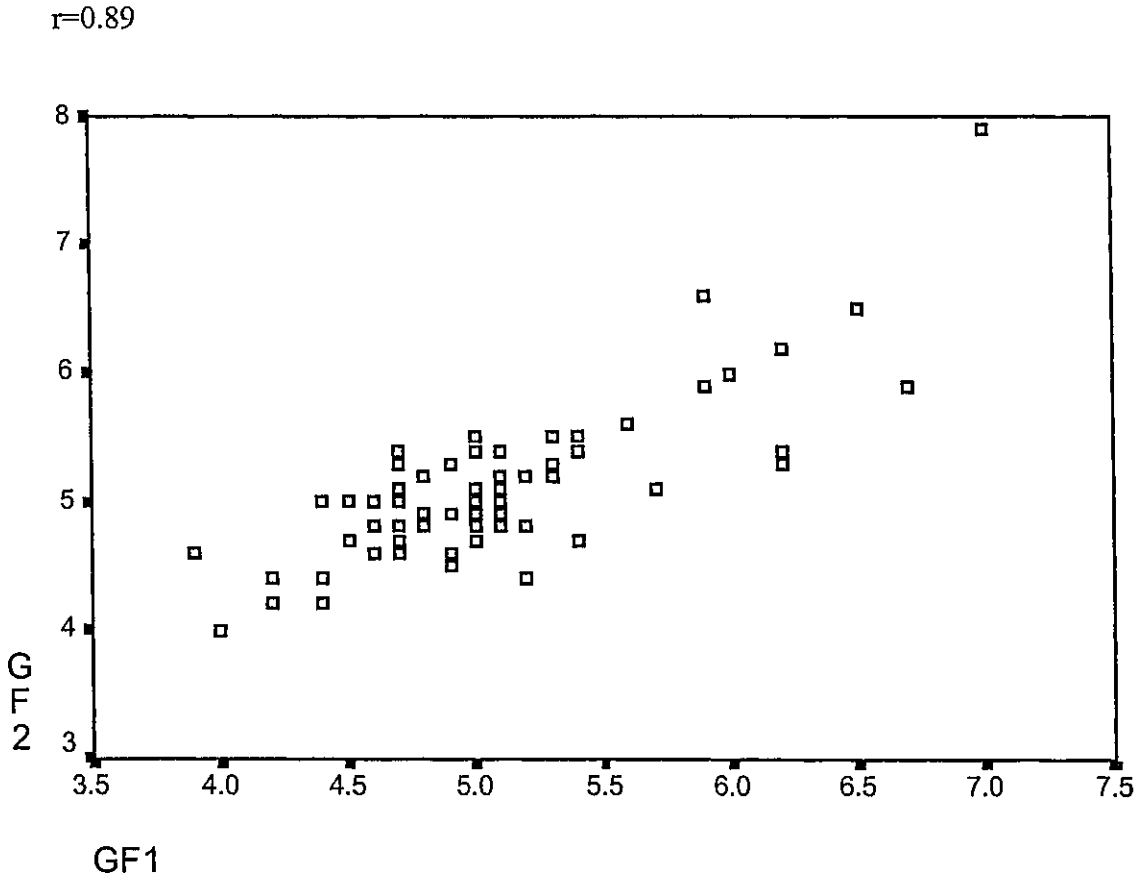


Figure 3b: Correlation between Lipoprotein(a) Measurements

r=0.97

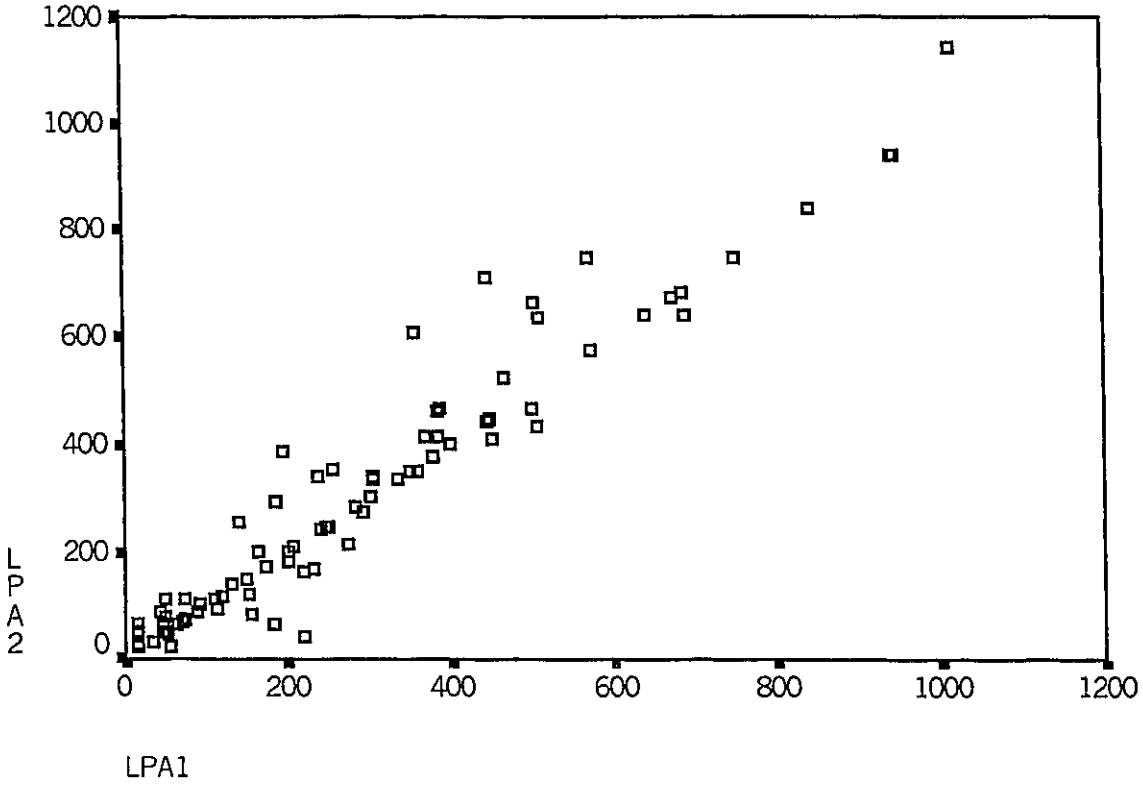
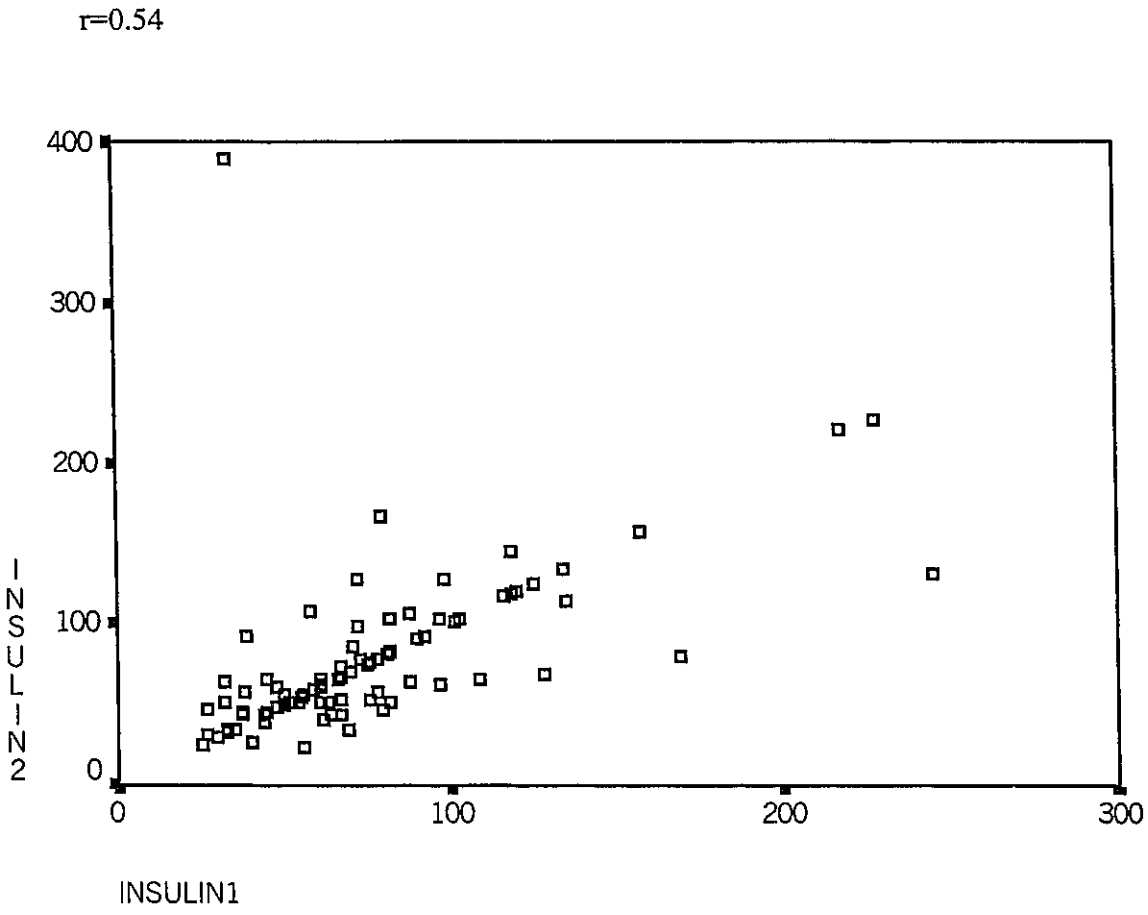


Figure 3c: Correlation between Fasting Insulin Measurements



Summary:

The SHARE protocol represents a broad-based approach to understanding the determinants of risk factor prevalence, atherosclerosis and CVD among a multi-ethnic cohort in Canada. The main challenges in the design of SHARE were developing a method to sample and recruit people of varying ethnic origin from three cities across Canada, and developing questionnaires (lifestyle, diet, and psychosocial) which could be

self-administered among a large proportion of people in whom English is their second language. Further, standardized protocols, to assess laboratory factors, ECG, and atherosclerosis were developed,

CHAPTER 5

SAMPLING ISSUES, RECRUITMENT, AND MAIN RESULTS:

In this Chapter the recruitment experience and the main results are presented and discussed.

Recruitment of Participants:

Recruitment of participants occurred in SHARE between October 1996 and October 1998, and 985 men and women (342 South Asians, 317 Chinese, 326 Europeans) completed all components of the clinic visit. Using the method of recruitment described in Chapter 4, three sampling frames were created. In total, 7,728 households were selected in a random manner from these sampling frames. Of these households, 5,752 (74%) of households were contacted by telephone; of those contacted by telephone 3,214 (56%) of people agreed to complete the screening telephone call; and 1,654/3,214 (51%) of these people were eligible. Of this group, 1175 (71%) agreed to participate, and 985 people (85%) completed the clinic visit.

Conservative and optimistic response proportions were calculated to assess the 'response rate' using two sets of assumptions. The conservative estimate represents the number people who completed the clinic visit out of the total number of household names

selected from the sampling frames (minus the number of people who were ineligible at the time of the telephone interview). The optimistic response proportion assumes that the people who allowed the telephone interview had the same eligibility percent as those who did not allow the interview, and also assumes that all of the people who were not contactable had invalid telephone numbers. It is likely that the true response proportion lies between the conservative (16%) and the optimistic proportions (34%). The response proportions were highest among people of European origin (range 19-36%), and slightly but not significantly lower among South Asians (16-30%) and Chinese (14-35%) (Table 6).

Table 6: Recruitment of SHARE Participants

Factor	South Asians	Chinese	Europeans	Total
# Letters Mailed out	2710	3058	1960	7728
# Contacted by phone	2087 (77%)	2293 (75%)	1372 (70%)	5752 (74%)
# Allowed interview	1189 (57%)	1216 (53%)	809 (59%)	3214 (56%)
# Eligible	642 (54%)	486 (40%)[ϕ]	526 (65%)	1654 (51%)
# Agree to participate	462 (72%)	345 (71%)	368 (70%)	1175 (71%)
# Completed clinic visit	342 (74%)	317 (92%)	326 (88%)	985 (85%)
Optimistic Response Proportion ^ (of those who allowed the interview)	(.74*.72*.57) = 30%	(.92*.71*.53) = 34.6%	(0.88*.70*.59) = 36.3%	33.8%
Conservative Response proportion [ϵ]	16%	14%	19%	16%

^: This proportion assumes that those people who allowed the interview had the same eligibility percent as those who did not allow the interview. This also assumes that all of the people who were not contacted had invalid telephone numbers i.e. they were no longer working numbers. [ϵ] Conservative Response proportion: The proportion of people who completed the clinic visit of all letters mailed out (minus the people who were found to be ineligible during the phone interview). This provides a lower limit of response proportion. [ϕ] Significantly fewer people of Chinese origin were eligible. This was primarily due to a greater number of people who were presumed to be of Chinese origin based on their surname but were not (i.e. surname such as Lee or Young)

Overall 342 South Asians, 317 Chinese and 326 Europeans completed the clinic visit. The number of people recruited from each city also varied significantly, as the majority of participants were recruited from Hamilton (38.5%), and Edmonton (35.9%), followed by Toronto (25.6%). (Table 7)

Table 7: Recruitment by Ethnicity and By City

	South Asian	Chinese	European	Total
Hamilton	115	111	153	379
Toronto	98	73	81	252
Edmonton	129	133	92	354
Total	342	317	326	985

Reasons for Ineligibility:

The main reasons for ineligibility were incorrect ethnicity (45%), age - too old or too young (39%), duration of time lived in Canada (13%), and co-existing medical conditions (2%). More people of Chinese origin were ineligible because of incorrect ethnicity compared to the South Asians or Europeans.

Non-responder and Responder Comparisons:

When the non-responders (n=1,527 of whom answered questions over the telephone) were compared to the participants (n=985), no differences in the rates of smoking (12% vs. 11%), heart disease (5% vs. 6%) or cancer (3% vs. 4%) were identified. However non-responders were less likely to be employed (61% vs. 70%, p=0.001) and more likely to have some post secondary education (53% vs. 39%, p=0.001) compared to participants. When these factors were examined by ethnic group, no significant differences were observed for smoking, heart disease, and cancer between responders and non-responders. However South Asian and European non-responders had received more post secondary education compared to responders (South Asians: 57.8% vs 44.4 %, P=

0.01), (Europeans: 62.8% vs 32.5%, P<0.0001), and fewer Chinese and European non-responders compared to responders were employed (Chinese 62.0% vs 71.6%, P= 0.07), (European: 53.2% vs 66.3%, P = 0.02). It is difficult to discern if these differences in education and employment proportions introduce any bias in the prevalence estimates determined in SHARE. One may surmise that because more responders were employed, they represent a healthier group and therefore the estimate of risk factors and disease prevalence among responders may be an underestimate of the true prevalence. Conversely, because responders were less educated than non-responders, one may surmise that they represent, a less healthy subgroup of the population, and the SHARE prevalence estimates generated may be overestimates (Table 8).

Table 8: Non-responder Characteristics in SHARE

	Non-Responders (n=1527)	Participants (n=985)	P Value
Smoking %	12	11	0.44
Heart Disease %	5	6	0.27
Cancer %	3	4	0.20
Employed %	61	70	0.001
Post-Secondary Education %	53	39	0.001

***Key Demographic Differences*:**

The detailed demographic characteristics of the three ethnic cohorts are presented in Table 9. Briefly the European sample was significantly older (51.2 years), the South

Asians were intermediate (49.4 years) and the Chinese the youngest (47.4 years). Approximately half of all participants were women. The majority of South Asians (71.3%) were born in the Indian subcontinent; 43.8% reported their mother tongue as Punjabi, 14.9% as Gujarati, 12.9% as Hindi and 7.3% as Tamil, and the commonest practiced religions were Hinduism (34.6%), Islam (26.7%), Sikhism (25.2%), and Christianity (9.1%). The majority of the Chinese participants originated from Mainland China (43.0%), Hong Kong (20.2%), Malaysia (5.7%), and 3.6% originated from Taiwan. The commonest practiced religion among the Chinese was Christianity (42.1%), followed by the traditional Chinese religion (17.4%), and Buddhism (14.5%). Of the European group, the majority reported their country of origin as Canada (72.6%) and the United Kingdom (8.0%), and the most common religion practiced was Christianity (91.4%). Only 21% of the European cohort were immigrants to Canada.

The South Asian and Chinese migrants sampled in SHARE represent a selected population. For example in the Indian subcontinent the majority of people are Hindus (> 60%), followed by Muslims (< 30%), Christians (< 5%), and Sikhs (< 2%). In SHARE, Hindus and Muslims are relatively under represented, and Sikhs and Christians being over represented. For the Chinese, a larger relative proportion of Chinese in SHARE came from Hong Kong compared to Mainland China. This likely reflects the selective migration of people to Canada based on historical migration patterns (e.g. Sikhs coming to work as labourers), relatives who already live in Canada, and wealth (e.g. people form Hong Kong are wealthier than people form Mainland China).

Table 9: Key demographic characteristics of the SHARE cohort

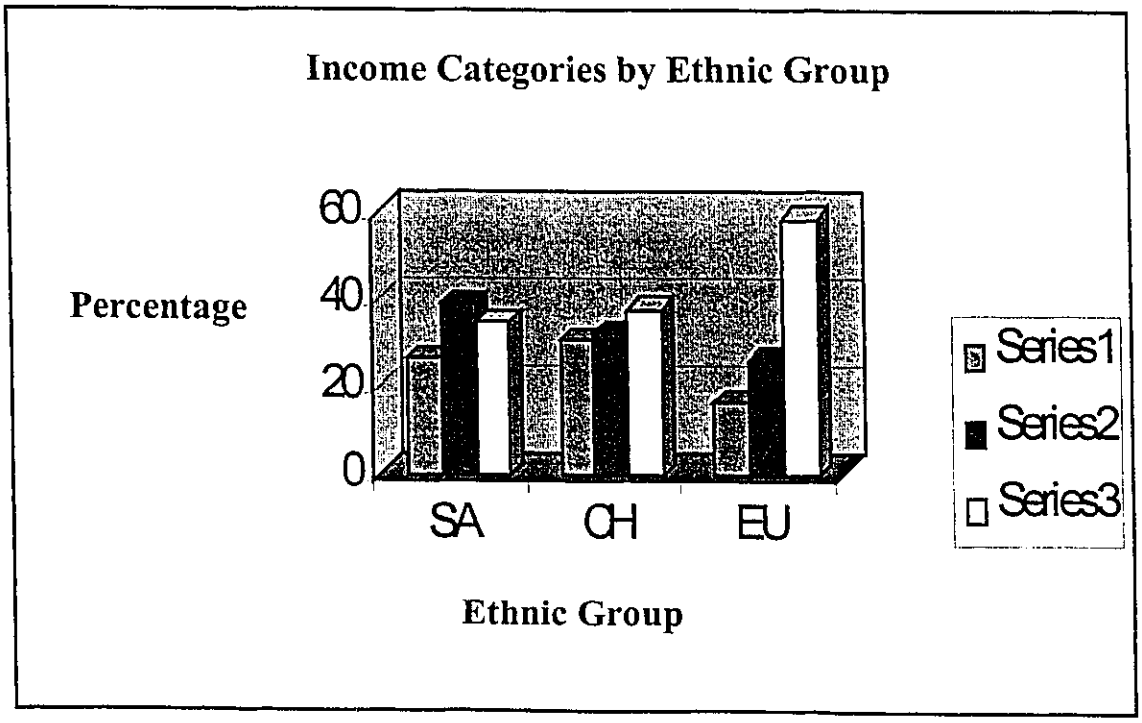
Factor	SA N=342	CH N=317	EU N=326	Overall Significance P <	Pair wise Comparisons SA vs. CH	Pair wise Comparisons CH vs. EU	Pair wise Comparisons SA vs. EU
Age (mean)	49.4 (9.8)	47.4 (9.8)	51.2 (9.8)	0.001	0.03	0.0001	0.04
Female %	45.3	48.9	51.8	0.21	-	-	-
Years in Canada	19.5 (10.5)	20.5 (10.6)	44.5 (10.6)	0.001	0.46	0.0001	0.0001
Hypertension on Tx (%)[¶]	13.7	15.9	11.0	0.07	0.32	0.02	0.16
Elevated Cholesterol on Tx (%)[¶]	6.3	6.0	5.0	0.67	-	-	-
Diabetes on Tx (%)[¶]	6.2	2.6	2.2	0.02	0.08	0.48	0.007
Current Smokers (%) [§]							
Males	16.6	9.7	19.5	0.016	0.03	0.005	0.43
Females	2.1	1.6	13.7	0.0001	0.94	0.0001	0.0001
Former Smokers (%)[§]							
Males	15.8	28.7	37.0	0.0001	0.016	0.069	0.0001
Females	0.0	6.1	30.6	0.0001	0.94	0.0001	0.0001

SA: South Asian, CH: Chinese, EU: European, Tx: treatment. Numbers in parentheses are standard deviations. [¶] Age and Sex Standardized. [§] Age Standardized

Socio-economic Variables:

35.1% of South Asians, 33.8% Chinese, and 34.8% of Europeans reported their job category as being "professional", although South Asians and Chinese were more likely to have received a university education (44.4% and 40.1% respectively) compared to their European counterparts (32.5%). Despite this, significantly more people of European origin reported having an annual household income greater than or equal to $60,000 (57.9% versus 37.5%) among the Chinese and 34.7% among the South Asians, P<0.001 (Figure 4).

Figure 4: Income Distribution by Ethnic Group



Note: Series 1 < 29,000, Series 2: 30,000-59,999; Series 3: ≥ 60,000; SA: South Asians, CH: Chinese, EU: European.

Objective 1: The Relative Prevalence of Conventional and Emerging Risk Factors:

Numerous differences in the prevalence of cardiovascular risk factors were observed between the groups. Comparisons between the ethnic groups for the major conventional risk factors (i.e. hypertension, elevated cholesterol, diabetes, and tobacco) revealed interesting differences (Table 9). Briefly, the Chinese group had the highest prevalence of hypertension, the South Asian group suffered the highest prevalence of diabetes, and the Europeans were more likely to be current or former smokers. No differences in the proportion of individuals with abnormal lipids who were taking drug therapy were identified.

Blood pressure:

No differences in the mean systolic blood pressure was identified between the groups, although South Asians had significantly higher diastolic blood pressures (Table 10). Subdividing participants into people with established hypertension and those without hypertension revealed that the mean systolic and diastolic blood pressures were significantly higher among those individuals with established hypertension even when on medical therapy.

Table 10: Mean Systolic and Diastolic Blood Pressure in SHARE*

	Overall		Established Hypertension n=143		No History of Hypertension n=842	
	Systolic^	Diastolic €	Systolic#	Diastolic§	Systolic×	Diastolic «
South Asian	119 (15.7)	76 (10.5)	136.4 (17.5)	83.8 (9.2)	115.3 (13.9)	74.1 (10.2)
Chinese	119 (15.8)	75 (10.6)	141.3 (18.3)	87.3 (8.9)	113.7 (13.5)	72.5 (9.6)
European	118 (15.8)	73 (10.6)	129.5 (17.6)	80.0 (8.8)	116.3 (13.6)	72.0 (9.8)

* Adjusted for age and sex; Numbers represent means, and numbers in parenthesis represent standard deviations. ^ Overall P comparing systolic blood pressure between the ethnic groups = 0.90. € Overall P for diastolic BP = 0.006; Post Hoc comparisons SA vs EU = 0.008, SA vs CH =0.71, CH vs EU = 0.01. # Overall P for systolic BP =0.003; Post Hoc comparisons SA vs EU =0.04 , SA vs CH =0.14 , CH vs EU =0.001. § Overall P for diastolic = 0.0001; Post Hoc Comparisons: SA vs CH =0.05, SA vs EU=0.03, CH vs EU =0.0001. × Overall P for systolic BP =0.08. " Overall P for diastolic = 0.04; Post Hoc Comparisons: SA vs CH = 0.06, SA vs EU = 0.01, CH vs EU: 0.57.

Comment:

People with established hypertension have significantly higher systolic and diastolic blood pressure compared to people without hypertension. The differences in the systolic blood pressures between the established hypertensives and those without a history of hypertension are greater among South Asians (Δ =21.1 mm Hg) and Chinese (Δ= 27.6 mm Hg), than among Europeans (Δ = 13.2 mm Hg). This may reflect that Europeans with established hypertension probably received different treatments, or that they are more compliant with prescribed treatments compared to the South Asians and Chinese. No differences in the prevalence of undetected hypertension (defined as a systolic BP > 140 or a diastolic BP > 90) were detected between the ethnic groups [SA = 12%, CH = 9.5%, EU=12.2%].

Lipids:

Among people who were not receiving lipid lowering therapy, South Asians had the highest total cholesterol, LDL cholesterol, and triglycerides, and the lowest HDL cholesterol compared to the Chinese and Europeans (Table 11). Further the South Asians had the greatest prevalence of dyslipidemia, defined as LDL > 3.40 or HDL <0.90 mmol/L compared to the other groups (63.1% vs 48.0% in Chinese and 49.5% among Europeans (Table 11).

Table 11: LDL and HDL Cholesterol Concentration overall and by treatment

	Overall		On Lipid Lowering Medication n=70		No Lipid Lowering Medication n=915		LDL > 3.40 or HDL <0.90** (%)
	LDL ^	HDL$^{\epsilon}$	LDL #	HDL§	LDL ×	HDL$^{\text{“}}$	
South Asian	3.30 (0.72)	1.04 (0.31)	3.54 (0.97)	1.07 (0.22)	3.28* (0.76)	1.04 (0.32)	63.1
Chinese	3.15 (0.70)	1.18 (0.32)	3.66 (0.99)	1.07 (0.24)	3.11 (0.76)	1.19 (0.33)	48.0
European	3.17 (0.71)	1.18 (0.32)	3.42 (1.01)	1.01 (0.24)	3.15 (0.76)	1.19 (0.33)	49.5

* Adjusted for age and sex; Numbers represent means, and numbers in parenthesis represent standard deviations. ^ Overall P = 0.03 between the ethnic groups, Post Hoc comparisons SA vs EU = 0.03, SA vs CH = 0.01, CH vs EU = 0.73. ϵ Overall P = 0.0001, Post Hoc comparisons SA vs EU = 0.0001, SA vs CH = 0.0001, CH vs EU = 0.98. # Overall P = 0.77 between the ethnic groups. § Overall P = 0.62 between the ethnic groups. × Overall P =0.02 between the ethnic groups, Post Hoc Comparisons: SA vs CH =0.008, SA vs EU=0.04, CH vs EU =0.54. “Overall P = 0.0001 between the ethnic groups, Post Hoc Comparisons: SA vs CH = 0.0001, SA vs EU = 0.0001, CH vs EU: 0.86. ** Chi Square =17.24. df=2; P<0.0001

Glucose:

Significantly more South Asians had established diabetes compared to the Chinese or Europeans (Table 9). Excluding people with diabetes, South Asians also had a significantly increased mean fasting glucose concentration (5.47 mmol/L), the Chinese intermediate (5.19 mmol/L), and the Europeans had the lowest (5.13 mmol/L) (Table 12). A 2-hour glucose test was performed in all non-diabetic participants. South Asians had more impaired glucose tolerance (19%), compared to the Chinese (15%) or Europeans (12.5%), P<0.03. In addition, 10% of South Asians, 5% of Chinese, and 6% of Europeans, P = 0.02 were diagnosed as having new diabetes, and 6.7% South Asians, 2.5% of Chinese, versus 5.5% had impaired fasting glucose (IFG), P=0.04. Therefore after exclusion of diabetics at entry, the prevalence of newly diagnosed glucose intolerance (impaired glucose tolerance plus new diabetes) was 28% among South Asians vs. 20% among Chinese and 18% among the Europeans.

Table 12: Fasting Glucose by Diabetes Status and Ethnic Group

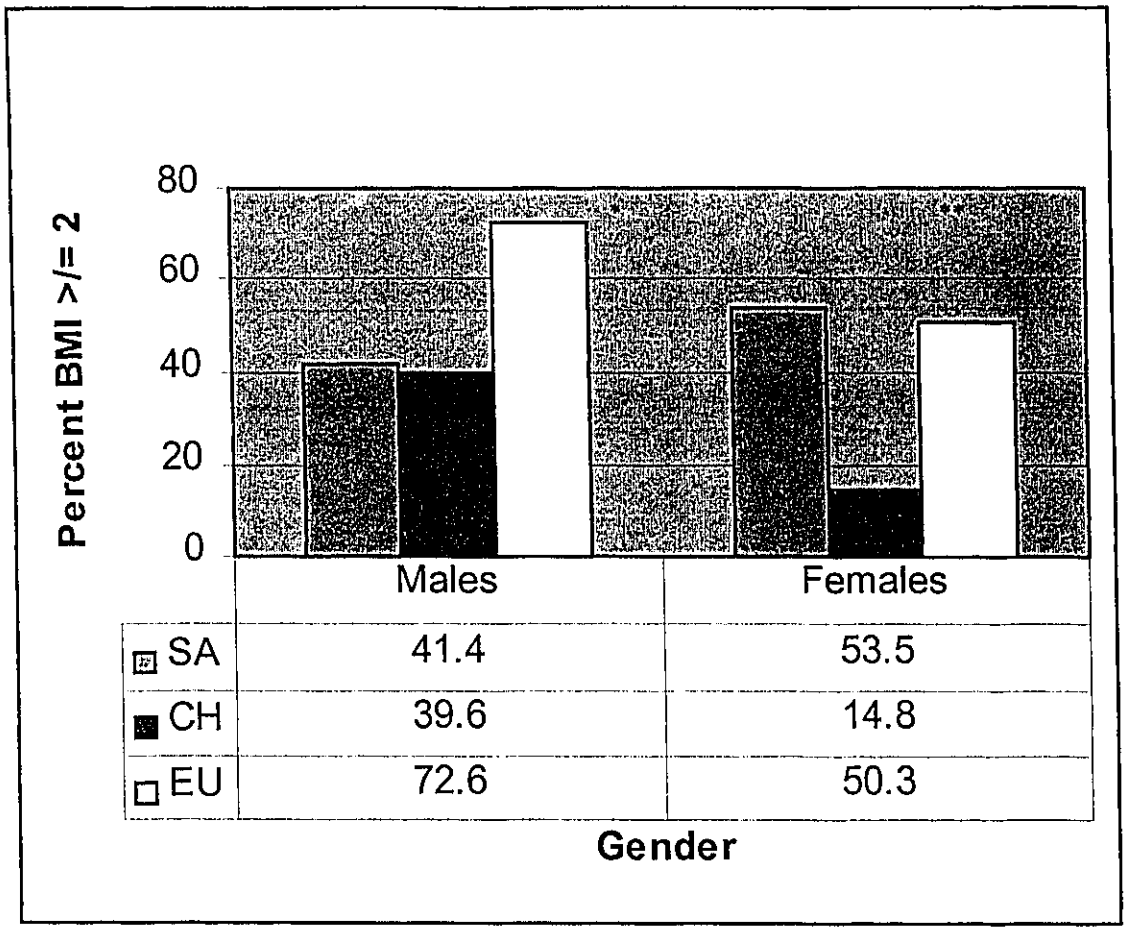
Established Diabetes			No History Diabetes		Undetected Diabetes **	
Glucose $^{\epsilon}$ (mmol/L)			Glucose§ (mmol/L)			
South Asian	9.78 (2.46)	N=20	5.72 (1.40)	N=321	5.47 (1.00)	32/320$^{\perp}$ (10.0%)
Chinese	6.76 (2.52)	N=8	5.26 (1.40)	N=308	5.19 (0.98)	14/307 (4.6%)
European	12.17 (2.52)	N=9	5.29 (1.41)	N=317	5.13 (0.99)	20/315 (6.3%)

^ Overall P = 0.0001, Post Hoc comparisons SA vs EU = 0.0001, SA vs CH = 0.0001, CH vs EU = 0.75
ϵ Overall P = 0.0001, Post Hoc comparisons SA vs EU = 0.0001, SA vs CH = 0.0001, CH vs EU = 0.49
§ Overall P = 0.001, Post Hoc comparisons SA vs CH = 0.007, SA vs EU = 0.03, CH vs EU = 0.0001.
** Chi Square=7.4, df=2, P=0.02
$^{\perp}$: Note 1 SA, 2, CH, and 2 EU did not complete the tests to determine diabetic status

Overweight and Abdominal Obesity:

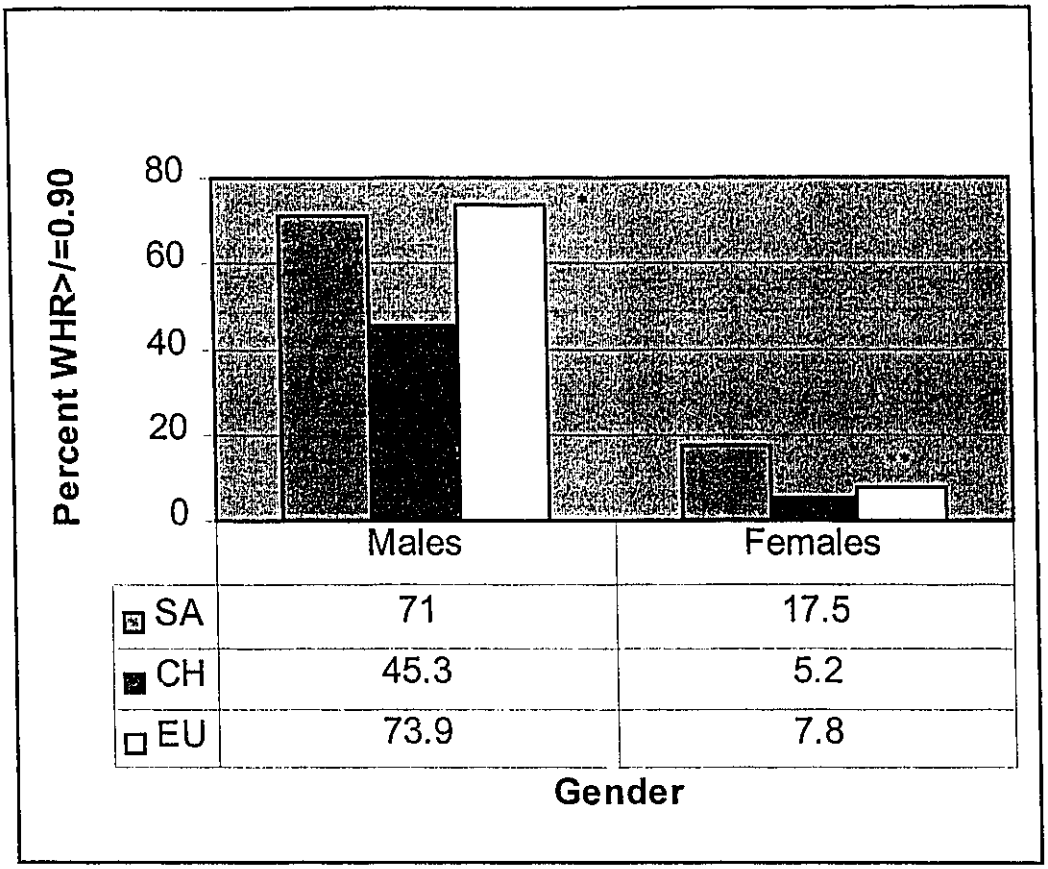
European men were the heaviest, South Asian men intermediate, and the Chinese men were the lightest (body mass index: European: 28.4 +/- 3.9, South Asian: 26.0 +/- 3.9, Chinese: 25.1 +/- 3.9, all P<0.0001). Among women, the Europeans and the South Asians were the heaviest compared to the Chinese, (BMI European: 26.6 +/-4.1, South Asian: 26.5 +/- 4.2 versus Chinese: 22.8 +/-4.2, all P<0.0001) (Figure 5). Similarly, European and South Asian men had the greatest amount of abdominal adiposity, as measured by the ratio of the waist to hip circumference compared to the Chinese men, and South Asian women had significantly more abdominal adiposity compared to the European and Chinese women (Figure 6).

Figure 5: Prevalence of Overweight



*Overall P =0.0001 EU>SA and CH ** Overall P =0.001 SA/EU > CH

Figure 6: Prevalence of Abdominal Obesity



*Overall P = 0.0001; **Overall P = 0.001 (SA > EU/CH)

Tobacco Use:

The rates of current and former smoking varied significantly between the ethnic groups with people of European origin having the greatest exposure to smoking. Parental smoking patterns revealed that 75% of European participants parents smoked compared to 59% of Chinese, and 33% of South Asians (Table 13).

Table 13: Prevalence of Current, Former and Never Smoking

	South Asians (n=339)	Chinese (n=317)	European (n=322)
Former Smoking	31 (9.1%)	50 (15.8%)	112 (34.8%)
Current Smoking	33 (9.7%)	17 (5.4%)	51 (15.8%)
Never Smoker	275 (81.1%)	249 (78.8%)	159 (49.4%)

Note: European Canadians had a significantly greater prevalence of Former and current smoking. More than 80% of the South Asians were never smokers.

Emerging Risk Factors:

A number of pro-thrombotic markers which are related to the excess CVD were measured in SHARE. The four markers included homocysteine, plasminogen activator inhibitor-1 (PAI-1), (Lp(a)) and fibrinogen. Prior studied have reported significant increases in Lp(a), and homocysteine among South Asians {Bhatnagar 1995, Chambers 1998, Chambers et al. 2000}. All four factors were significantly increased among South Asians (Table 14). It is difficult to discern whether these elevations of fibrinogen, PAI-1, Lp(a), homocysteine cause the increased cardiovascular events observed among South Asians, or if some factors (e.g. fibrinogen and PAI-1) are secondarily elevated in response to excessive stimulation of the clotting cascade {Schneidau 1989}.

Table 14: Prothrombotic Factors

	SA	CH	EU	Overall Significance P <	Pair wise Comparisons SA vs. CH	Pair wise Comparisons SA vs. EU	Pair wise Comparisons CH vs EU
Homocysteine (μmol/L)	11.22 (3.76)	9.21 (3.79)	10.00 (3.78)	0.0001	0.0001	0.0001	0.02
PAI-1 (units/mL)	17.1 (9.61)	15.7 (9.57)	15.1 (9.92)	0.02	0.13	0.02	0.71
Lp(a)-ln $^{\phi}$(mg/dL)	2.93 (1.18)	2.59 (1.19)	2.59 (1.19)	0.001	0.0006	0.0005	0.99
Fibrinogen (g/L)	3.07 (0.85)	2.89 (0.86)	2.93 (0.86)	0.001	0.02	0.10	0.81

SA: South Asian, CH: Chinese, EU: European. Lp(a): Lipoprotein (a), PAI-1: Plasminogen activator inhibitor-1. *Adjusted for age and gender. $^{\phi}$ ln: Natural Log. Numbers in parentheses are standard deviations.

Social Factors and Atherosclerosis:

A proxy variable for social stability, the socio-economic index was created using the variables of education, income, marriage, and employment {Lynch 1997}. The scale was constructed so that a higher score reflected greater social stability (Table 15,16).

Table 15: Creation of the Socio-economic Index

Factor	Score	Frequency	
Post Secondary Education	0 = No 1 =Yes	0 = 28.9% 1 = 71.1%	
Income Ranges (mean and SD)	1-7	5.16 (2.01)	
Marriage/Living with Some-one	0 = Not Married 1 = Married/Common Law	0 =18.1% 1 = 81.7%	
Employment	0 =Unemployed 1= Employed 2= Retired	0 = 14% 1 = 85.2% 2 = 0.7%	
Socio-Economic Index	Range 1-11	Mean = 7.56 (2.46)	Median = 8.00

Legend: *Income Ranges: 1:0-14,999; 2:15,000-19,999; 3:20,000-29,999; 4:30,000-39,999; 5:40,000-49,999; 6:50,000-59,999; 7: >60,000

Table 16: Variations in Social Stability by Ethnic Group

	SA	CH	EU	Overall P	SA vs CH	SA vs EU	CH vs EU
N	334	311	320				
Mean Socio-economic Index (SD)	7.40 (2.5)	7.27 (2.5)	8.02 (2.3)	0.001	0.79	0.003	0.0001
Post Secondary Education %	74.3%	68.7%	70.0%	0.25	NA	NA	NA
Mean Income Range	4.94 (2.00)	4.89 (2.08)	5.66 (1.88)	0.001	0.72	0.0001	0.0001
Married or Living with someone %	87.7%	75.1%	82.6%	0.001	0.06	0.0001	0.02
Employed %	80.7%	90.8%	84.5%	0.007	0.03	0.0001	0.08

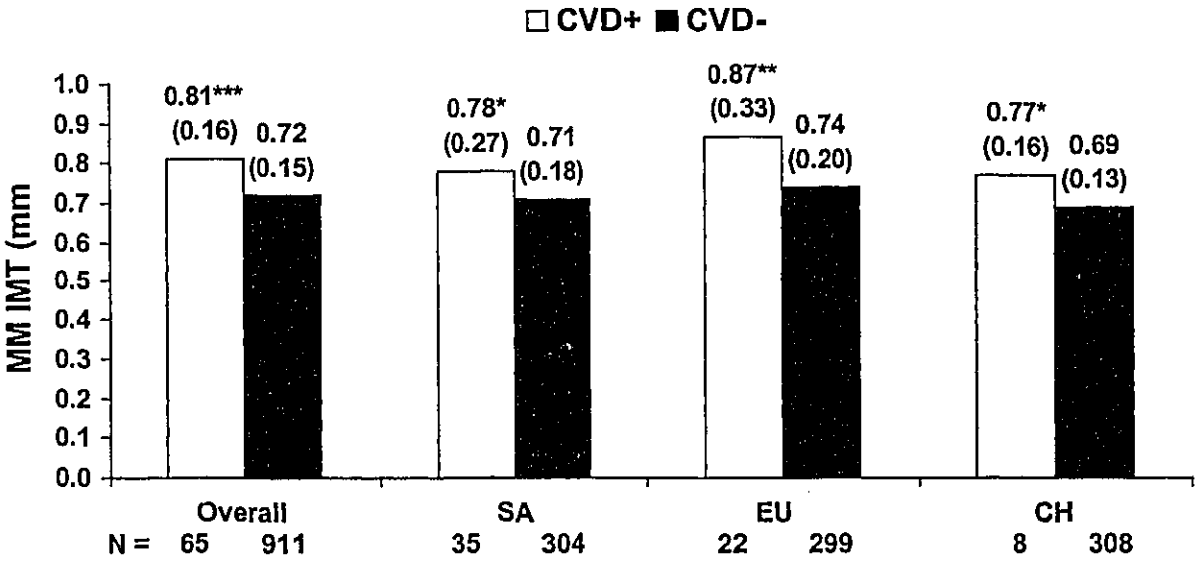
Legend: SA: South Asian, CH: Chinese, EU: European, SA vs EU < 0.003; SA vs CH = 0.79; EU vs CH < 0.0001

Note: The Europeans in SHARE have a higher social stability to the South Asians and Chinese.

Objective 2: To Quantify the amount of Subclinical atherosclerosis:

The mean of the maximal IMT values reflects the average amount of atherosclerosis observed in 6 well-defined carotid artery segments in each of the right and left carotid artery per person scanned. In each segment, the maximum IMT is identified and calculated, and these values are averaged per person. In SHARE, the European group had the greatest mean of the maximum IMT = 0.75 (0.16 mm), the Chinese had the lowest 0.69 (0.16 mm) and the South Asians had an intermediate amount 0.72 (0.15 mm); P for South Asian vs. European is 0.00098, P for South Asians vs. Chinese = 0.12, and P for European vs. Chinese = 0.0001, after adjustment for age and sex and recruiting centre. This pattern, whereby the Europeans had the most atherosclerosis, the South Asians intermediate, and Chinese the lowest was also observed when comparing the single maximal IMT measurements [EU =1.27 mm (SD =0.54); SA = 1.23 (0.55); CH= 1.15 (0.53); overall p=0.058]. This result contradicted our hypothesis that South Asians have a greater burden of atherosclerosis compared to the Europeans. We assessed the validity of the carotid atherosclerosis assessment overall and within each ethnic group by dividing people into those with established CVD and those without established CVD and then comparing the mmIMT's. The expectation of this comparison was that people with CVD would have greater mmIMT values compared to those without disease. Figure 7 demonstrates that the correlation between mmIMT and established CVD is present overall and within each ethnic group.

Figure 7. Validation of carotid thickness (mean max IMT) as a correlate of CVD



* P< 0.05, ** P<0.01, ***P < 0.0001

Note: Overall and within each ethnic group, mean of the maximum intimal medial thickness (mmIMT) is greater in those people with CVD compared to those without CVD.

Objective 3: Prevalence of Cardiovascular Disease:

The prevalence of CVD was highest among South Asians (10.7%) followed by the Europeans (5.4%), and the lowest among the Chinese (2.4%), overall P=0.001. The prevalence of cardiovascular events are provided in Table 17. South Asians had significantly increased history of myocardial infarction, were more likely to have undergone prior percutaneous transluminal angioplasty (PTCA) and coronary artery bypass graft surgery (CABG), and were more likely to have suffered from angina

compared to the other two groups. Overall, South Asians had the highest prevalence of CHD, and when standardized for age and gender this was 10.7% among South Asians, 4.6% among Europeans, and 1.7% among Chinese, overall P= 0.001. This is consistent with the pattern of cardiovascular mortality between these ethnic groups observed in the Statistics Canada National Mortality Database {Sheth et al. 1999}. The prevalence of stroke was the highest among the Europeans, although it was very low in all three groups.

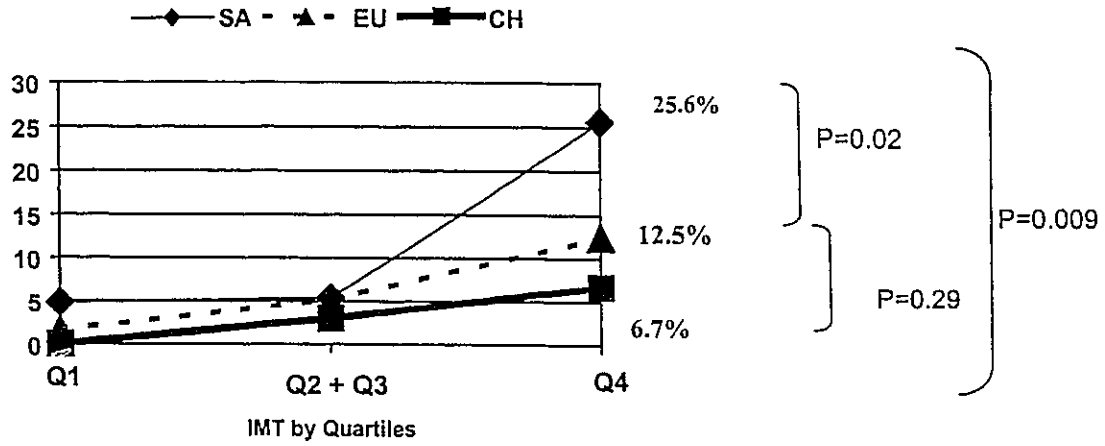
Table 17: Prevalence of Coronary Heart Disease and Cardiovascular Disease

Factor	SA N=342	CH N=317	EU N=326	Overall Significance P <	Pair wise Comparisons SA vs CH	Pair wise Comparisons SA vs EU	Pair wise Comparisons CH vs EU
History of MI	10 (2.9%)	0	4 (1.2%)	0.001	0.0006	0.03	0.06
Silent MI	8 (2.3%)	2 (0.6%)	2 (0.6%)	0.06	0.06	0.03	0.85
PTCA/ CABG	14 (4.1%)	0	6 (1.8%)	0.0001	0.0001	0.02	0.01
MI or PTCA/ CABG	26 (7.6%)	2 (0.6%)	9 (2.8%)	0.0001	0.0001	0.0003	0.14
Angina	20 (5.8%)	4 (1.3%)	14 (4.3%)	0.010	0.003	0.07	0.16
Any CHD*⊥	10.7%	1.7%	4.6%	0.001	0.0001	0.002	0.13
Stroke	1 (0.3%)	2 (0.6%)	6 (1.8%)	0.32	0.39	0.13	0.62
Any CVD**⊥	10.7%	2.4%	5.4%	0.001	0.0002	0.01	0.15

SA: South Asian, CH: Chinese, EU: European. * Any CHD = History of MI, Angina, Silent MI, PTCA, or CABG. ** CVD = History of MI, Angina, Silent MI: ECG evidence of MI without a prior history, PTCA, CABG, or Stroke. ⊥ Age and sex standardized

To try and understand why South Asians had significantly more CVD, yet did not have significantly more subclinical atherosclerosis, all individuals were divided into quartiles of carotid atherosclerosis. In each IMT quartile the South Asians had an excess of cardiovascular events compared to the Europeans and the Chinese. For example, the highest quartile of atherosclerosis, the prevalence of CVD was 26% among South Asians, 13% among Europeans and 7% among Chinese, overall p=0.001 (Figure 8).

Figure 8: Prevalence of CVD for given levels of carotid atherosclerosis



	Q1	Q2+Q3	Q4	P for trend
SA	5/104 (4.8%)	8/149 (5.4%)	22/86 (25.6%)	0.0001
EU	1/63 (1.6%)	8/155 (5.2%)	13/104 (12.5%)	0.004
CH	0/102 (0%)	5/169 (3.0%)	3/45 (6.7%)	0.016

Note: Overall P value < 0.0001, comparing slopes of atherosclerosis vs CVD between SA, CH and EU. For a particular level of atherosclerosis, the rates of clinical events vary between the three ethnic groups. P for trend is within each ethnic group. These differences are maintained after adjustment for the presence of diabetes and IGT.

Objective 4a: Determinants of Atherosclerosis:

The univariate associations between selected conventional risk factors (e.g. blood pressure, lipids, tobacco use, and glucose) and atherosclerosis, as well as emerging determinants of atherosclerosis (e.g. body mass index, waist to hip ratio, lipoprotein (a), plasminogen activator inhibitor-1, fibrinogen and homocysteine, and the socio-economic index) are presented in Table 18.

Table 18: Univariate Analysis of Conventional and Emerging Risk factors with Atherosclerosis (mmIMT)

Variable	Beta[1]	SE[2]	Standardized Beta[3]	Significance[4]
Age	1.14×10^{-2}	0.001	0.58	0.0001
Gender	-6.5×10^{-2}	0.01	-0.17	0.0001
Systolic BP	4.55×10^{-3}	0.0001	0.41	0.0001
Diastolic BP	3.06×10^{-3}	0.001	0.18	0.0001
HDL-C	-2.64×10^{-2}	0.02	-0.05	0.13
APO-B	0.16	0.02	0.21	0.0001
Tchol/HDL	1.01×10^{-2}	0.003	0.12	0.0001
LDL-C	3.25×10^{-2}	0.01	0.13	0.0001
Current Smoking	6.6×10^{-2}	0.02	0.10	0.001
Former Smoking	7.7×10^{-2}	0.02	0.16	0.0001
HBA1c	5.79×10^{-2}	0.01	0.27	0.0001
BMI	5.5×10^{-3}	0.001	0.12	0.0001
WHR	0.50	0.07	0.23	0.0001
Lp(a)-ln	-2.37×10^{-3}	0.005	-0.01	0.65
PAI-1	-1.02×10^{-4}	0.001	-0.005	0.88
Fibrinogen	2.68×10^{-2}	0.01	0.12	0.0001
Homocysteine	8.00×10^{-3}	0.002	0.17	0.0001
Socio-economic Index	-8.53×10^{-3}	0.003	-.11	0.001

Legend: BP: Blood Pressure, HDL-C: High Density Lipoprotein Cholesterol, Tchol: Total Cholesterol, LDL: Low Density Lipoprotein Cholesterol, HbA1c: Hemoglobin A1c, BMI: Body Mass Index, WHR: Waist to Hip Ratio, Lp(a): Lipoprotein (a), PAI-1: Plasminogen activator inhibitor-1

Footnotes:
[1] Df: Degrees of Freedom, for each Sum of Squares
[2] Mean Square: Sum of Squares/df
[3] F Ratio: Ratio of Regression Mean Square and the Residual Mean Square of Error.
[4] The Significance value of the F test is given in the adjacent column.
[5] R Squared: Partial Correlation squared which reflects the amount of variance of the dependent variable (i.e. atherosclerosis) explained by the independent variables
[6] Adjusted R^2: Corrected R^2 to reflect the goodness of fit for the population
[7] Beta = The unstandardized coefficients are the coefficients of the estimated regression model
[8] SE: Standard error of the unstandardized coefficients. The SE of Beta measures how sensitive the estimate of the parameter is to changes in a few observations in a sample. Therefore a large SE casts doubt on the estimate.
[9] Sig: Significance Test of the beta coefficient

Legend: Systolic BP: Systolic Blood pressure; Tchol/HDL: Total cholesterol/HDL ratio; CFSMOKE: Current or former smoker; Ethnic: Ethnic group

Multivariate Prediction of Atherosclerosis:

A hierarchical linear regression model was fit with atherosclerosis (mmIMT) as the dependent variable. Based on the univariate analysis, the following factors were tested in the multivariate linear regression model. **Conventional factors which were entered into the model** included systolic blood pressure, HbA1c, and current and former smoking, and the total cholesterol to HDL cholesterol ratio. All of these factors have been shown in other studies to be significant determinants of atherosclerosis {Chambless 1997, Wilson 1987}. Of the conventional factors, the correlation between systolic and diastolic BP was 0.65 and between total cholesterol and HDL was -0.66 and between total cholesterol/HDL ratio and LDL it was 0.58, therefore diastolic BP, HDL-C, and LDL cholesterol were not included in the group of conventional factors assessed in the multiple regression model.

The **emerging determinants** which were tested included body mass index, waist to hip ratio, fibrinogen, homocysteine, and the socio-economic index. In **Step 1** the main effects of conventional factors, ethnicity, and the interactions of the conventional factors with ethnicity were computed. In **Step 2**, the main effects of the emerging factors, ethnicity, and the interactions of the emerging factors and ethnicity were computed. In **Step 3**, the significant factors identified in Step 1 and Step 2, were entered into the model with age and sex as covariates. This model was then refined to include only the significant

independent variables. The final model included systolic blood pressure, HbA1c, ethnic group, HbA1c x ethnic interaction, age and sex.

Step 1: Conventional Factors, Ethnic and their interactions (independent variables) on Atherosclerosis (as measured by the mmIMT)

Table 19a: Step 1: Analysis of Variance

Variable	Df[1]	Mean Square[2]	F[3]	Sig.[4]
Systolic BP	1	4.84	170.9	0.0001
HbA1c	1	1.60	55.4	0.0001
Tchol/HDL	1	0.00009	0.003	0.95
CF Smoke	1	0.23	8.14	0.004
Ethnic	2	0.12	4.13	0.02
Ethnic x Systolic BP	2	0.098	3,46	0.03
Ethnic x HbA1c	2	0.13	4.60	0.01
Ethnic x Tchol/HDL	2	0.06	2.13	0.12
Ethnic x CF Smoke	2	0.013	0.45	0.63
Error	958	0.028		

[5] R Squared = .27, [6]Adjusted R Squared = .26

Footnotes:
[1] DF: Degrees of Freedom, for each Sum of Squares
[2] Mean Square: Sum of Squares/df
[3] F Ratio: Ratio of Regression Mean Square and the Residual Mean Square of Error
[4] The Significance value of the F test is given in the adjacent column
[5] R Squared: Partial Correlation squared which reflects the amount of variance of the dependent variable (i.e. atherosclerosis) explained by the independent variable
[6] Adjusted R^2: Corrected $R^2$to reflect the goodness of fit for the population

Legend: Systolic BP: Systolic Blood pressure; Tchol/HDL: Total cholesterol/HDL ratio; CFSMOKE: Current or former smoker; Ethnic: Ethnic group, BMI: Body Mass Index, WHRATIO: Waist to Hip circumference ratio, HYCST: Homocysteine concentration, FIBRI: Fibrinogen, SEI: Socioeconomic Index

Comment:

Shaded areas rows represents significant factors which will be used in subsequent models.

Table 19b: Step 1: Linear Regression

Variables	Beta[7]	SE[8]	Significance[9]
Systolic BP	0.005	0.001	0.0001
HbA1c	0.076	0.01	0.0001
TChol/HDL	-0.006	0.01	0.28
CFSMOKE	0.040	0.02	0.03
South Asian	0.20	0.12	0.08
Chinese	0.35	0.12	0.004
European*	0		
South Asian x Systolic BP	-0.001	0.001	0.40
Chinese x Systolic BP	-0.002	0.001	0.01
South Asian x HbA1c	-0.043	0.01	0.004
Chinese x HbA1c	-0.040	0.02	0.02
Intercept	-0.24	0.09	0.006

* Reference Group

Footnotes:
[7]Beta = The unstandardized coefficients are the coefficients of the estimated regression model
[8]SE: Standard error of the unstandardized coefficients. The SE of Beta measures how sensitive the estimate of the parameter is to changes in a few observations in a sample. Therefore a large SE casts doubt on the estimate.
[9]Sig: Significance Test of the beta coefficient

Legend:
Systolic BP: Systolic Blood pressure; Tchol/HDL: Total cholesterol/HDL ratio; CFSMOKE: Current or former smoker; Ethnic: Ethnic group, BMI: Body Mass Index, WHRATIO: Waist to Hip circumference ratio, HYCST: Homocysteine concentration, FIBRI: Fibrinogen, SEI: Socioeconomic Index

Step 2: Emerging Factors and Atherosclerosis

Table 20a: Step 2: Analysis of Variance

Source	Df[1]	Mean Square [2]	F[3]	Sig.[4]
Intercept	1	.83	25.2	.000
BMI	1	0.05	1.7	.20
WHRATIO	1	1.08	32.9	.000
HCYST	1	0.55	16.9	.000
FIBRI	1	0.38	11.7	.001
SEI	1	0.63	19.3	.000
ETHNIC	2	0.07	2.0	.13
ETHNIC * BMI	2	0.01	0.4	.64
ETHNIC * WHRATIO	2	0.01	0.4	.65
ETHNIC * HCYST	2	0.07	2.2	.11
ETHNIC * FIBRI	2	0.06	1.7	.17
ETHNIC * SEI	2	0.25	7.7	.000
Error	923	0.03		
Total	941			

[5]R Squared = .15, [6] Adjusted R Squared = .13

Footnotes:
[1] DF: Degrees of Freedom, for each Sum of Squares
[2] Mean Square: Sum of Squares/df
[3] F Ratio: Ratio of Regression Mean Square and the Residual Mean Square of Error
[4] The Significance value of the F test is given in the adjacent column
[5] R Squared: Partial Correlation squared which reflects the amount of variance of the dependent variable (i.e. atherosclerosis) explained by the independent variable
[6] Adjusted R^2: Corrected $R^2$to reflect the goodness of fit for the population

Legend:
Systolic BP: Systolic Blood pressure; Tchol/HDL: Total cholesterol/HDL ratio; CFSMOKE: Current or former smoker; Ethnic: Ethnic group, BMI: Body Mass Index, WHRATIO: Waist to Hip circumference ratio, HYCST: Homocysteine concentration, FIBRI: Fibrinogen, SEI: Socioeconomic Index

Comment:

Waist to hip and BMI are correlated with one another and therefore BMI is dropped from the model.

Table 20b: Step 2: Linear Regression

	B[7]	Std. Error[8]	Sig.[9]	95% Confidence Interval	
				Lower Bound	Upper Bound
Intercept	.51	.10	.000	.31	.71
BMI	-0008.34	.002	.73	-5.64 x 10-03	3.97E-03
WHRATIO	.47	.11	.000	.24	.67
HCYST	0.0037	.003	.09	-7.18 x 10-04	9.45x10-03
FIBRI	0.012	.008	.16	-4.59 x10-03	2.79x10-02
SEI	-0.024	.004	.000	-3.31 x10-02	-1.56x10-02
South Asian	-.22	.16	.18	-.54	.10
Chinese	-.30	.16	.05	-.60	6.29x10-03
European	0	.	.	.	.
[South Asian] * SEI	0.02	.006	.005	5.15 x 10-03	2.89x10-02
[Chinese] * SEI	0.023	.006	.000	1.14x 10-02	3.56x10-02

*Reference group

Footnotes:
[7]Beta = The unstandardized coefficients are the coefficients of the estimated regression model
[8]SE: Standard error of the unstandardized coefficients. The SE of Beta measures how sensitive the estimate of the parameter is to changes in a few observations in a sample. Therefore a large SE casts doubt on the estimate.
[9]Sig: Significance Test of the beta coefficient

Legend:
Systolic BP: Systolic Blood pressure; Tchol/HDL: Total cholesterol/HDL ratio; CFSMOKE: Current or former smoker; Ethnic: Ethnic group, BMI: Body Mass Index, WHRATIO: Waist to Hip circumference ratio, HYCST: Homocysteine concentration, FIBRI: Fibrinogen, SEI: Socioeconomic Index

Step 3: Conventional and Emerging Factors and Ethnic Group

Table 21a: Step 3: Linear Regression: Main Effects

	B[7]	Std. Error[8]	Sig.[9]
Intercept	0.02	0.07	0.76
SYSBP	0.003	0.0001	0.000
HbA1c	0.04	0.01	0.000
CFSMOKE	0.03	0.01	0.01
WHRATIO	0.10	0.07	0.12
HCYST	0.003	0.001	0.01
FIBRI	0.006	001	0.31
SEI	-0.007	0.02	0.003
South Asian	-0.06	0.01	0.0001
Chinese	-0.08	0.01	0.0001
Europeans	0	.	.

Note: *Correlation between WHR and HBA1c = r =- 0.22, WHR with sys BP = -.249, Sys BP is not correlated with HBA1c. Waist to hip ratio and fibrinogen are non-significant an are dropped from the model.

Footnotes:
[7]Beta = The unstandardized coefficients are the coefficients of the estimated regression model
[8]SE: Standard error of the unstandardized coefficients. The SE of Beta measures how sensitive the estimate of the parameter is to changes in a few observations in a sample. Therefore a large SE casts doubt on the estimate.
[9]Sig: Significance Test of the beta coefficient

Legend:
Systolic BP: Systolic Blood pressure; Tchol/HDL: Total cholesterol/HDL ratio; CFSMOKE: Current or former smoker; Ethnic: Ethnic group, BMI: Body Mass Index, WHRATIO: Waist to Hip circumference ratio, HYCST: Homocysteine concentration, FIBRI: Fibrinogen, SEI: Socioeconomic Index

Table 21b: Step 3: Linear Regression: Main Effects with Age and Sex Adjustment

	B[7]	Std. Error[8]	Sig.[9]
Parameter			
Intercept	0.0082	.06	.89
SYSBP	0.00174	.000	.000
HbA1c	0.0307	.006	.000
CFSMOKE	0.0180	.01	.13
HCYST	-0.000132	.001	.92
SEI	-0.00217	.002	.31
South Asians	-0.043	.01	.001
Chinese	-0.0584	.01	.000
Europeans*	0	.	.
AGE	0.00883	.001	.000
SEX	-0.00373	.01	.001

* Reference group

Note: When Age and Sex are added to the model, Socio-economic index, CF smoke, and homocysteine become non-significant and therefore are dropped form the model

Footnotes:
[7]Beta = The unstandardized coefficients are the coefficients of the estimated regression model
[8]SE: Standard error of the unstandardized coefficients. The SE of Beta measures how sensitive the estimate of the parameter is to changes in a few observations in a sample. Therefore a large SE casts doubt on the estimate.
[9]Sig: Significance Test of the beta coefficient

Legend:
Systolic BP: Systolic Blood pressure; Tchol/HDL: Total cholesterol/HDL ratio; CFSMOKE: Current or former smoker; Ethnic: Ethnic group, BMI: Body Mass Index, WHRATIO: Waist to Hip circumference ratio, HYCST: Homocysteine concentration, FIBRI: Fibrinogen, SEI: Socioeconomic Index

Table 22a: Step 3: ANOVA: Main Effects and Interactions with Ethnic Group

Variable	Df[1]	Mean Square[2]	F[3]	Sig.[4]
Intercept	1	0.04	1.6	0.21
SYSBP	1	0.85	37.5	0.000
HbA1c	1	0.73	32.1	0.000
ETHNIC	2	0.05	2.3	0.10
ETHNIC * SYSBP	2	0.04	1.9	0.15
ETHNIC * HBA1C	2	0.08	3.4	0.03
AGE	1	5.52	243.7	0.000
SEX	1	.38	16.9	0.000
Error	961	0.02		
Total	972			

[5] R Squared = .41, [6]Adjusted R Squared = .41

Note: The ethnic and systolic BP interaction is not significant and therefore will not be tested in the final model

Footnotes:
[1] DF: Degrees of Freedom, for each Sum of Squares
[2] Mean Square: Sum of Squares/df
[3] F Ratio: Ratio of Regression Mean Square and the Residual Mean Square of Error
[4] The Significance value of the F test is given in the adjacent column
[5] R Squared: Partial Correlation squared which reflects the amount of variance of the dependent variable (i.e. atherosclerosis) explained by the independent variable
[6] Adjusted R^2: Corrected $R^2$to reflect the goodness of fit for the population

Legend:
Systolic BP: Systolic Blood pressure; Tchol/HDL: Total cholesterol/HDL ratio; CFSMOKE: Current or former smoker; Ethnic: Ethnic group, BMI: Body Mass Index, WHRATIO: Waist to Hip circumference ratio, HYCST: Homocysteine concentration, FIBRI: Fibrinogen, SEI: Socioeconomic Index

Table 22b: Step 3: Linear Regression: Main Effects and Determinants with Ethnic Group

	B[7]	Std. Error[8]	Sig.[9]
Parameter			
Intercept	-.19	.08	.02
SYSBP	0.00235	.001	.000
HbA1c	0.0533	.010	.000
South Asian	.16	.10	.12
Chinese	.22	.11	.04
European	0	.	.
South Asian * SYSBP	-0.000143	.001	.84
Chinese * SYSBP	-0.00117	.001	.08
European * SYSBP	0	.	.
South Asian * HBA1C	-0.034	.01	.01
Chinese * HBA1C	-0.0264	.01	.08
European * HBA1C	0	.	.
AGE	0.00876	.001	.000
SEX	-0.0410	.010	.000

[7]Beta = The unstandardized coefficients are the coefficients of the estimated regression model
[8]SE: Standard error of the unstandardized coefficients. The SE of Beta measures how sensitive the estimate of the parameter is to changes in a few observations in a sample. Therefore a large SE casts doubt on the estimate.
[9]Sig: Significance Test of the beta coefficient

Legend:
Systolic BP: Systolic Blood pressure; Tchol/HDL: Total cholesterol/HDL ratio; CFSMOKE: Current or former smoker; Ethnic: Ethnic group, BMI: Body Mass Index, WHRATIO: Waist to Hip circumference ratio, HYCST: Homocysteine concentration, FIBRI: Fibrinogen, SEI: Socioeconomic Index

Final Model:

Table 22c Linear Regression:

	B[7]	Std. Error[8]	Sig.[9]	95% Confidence Interval	
Parameter				Lower Bound	Upper Bound
Intercept	-.14	.07	.04	-.27	-0.007
SYSBP	0.002	.0001	.000	0.001	0.0023
HbA1c	0.05	.01	.000	0.03	0.07
South Asian	0.14	.07	.06	-0.003	.29
Chinese	0.11	.08	.21	-0.06	.27
European	0	.	.	.	.
South Asian * HbA1c	-0.03	.01	.01	-0.06	-0.008
Chinese * HbA1c	-0.03	.01	.05	-0.06	-0.0005
European * HbA1c	0	.	.	.	.
AGE	0.009	.001	.000	0.008	0.010
SEX	-0.04	.01	.000	-0.06	-0.02

*Reference Group

Footnotes:
[7]Beta = The unstandardized coefficients are the coefficients of the estimated regression model
[8]SE: Standard error of the unstandardized coefficients. The SE of Beta measures how sensitive the estimate of the parameter is to changes in a few observations in a sample. Therefore a large SE casts doubt on the estimate.
[9]Sig: Significance Test of the beta coefficient

Legend:
Systolic BP: Systolic Blood pressure; Tchol/HDL: Total cholesterol/HDL ratio; CFSMOKE: Current or former smoker; Ethnic: Ethnic group, BMI: Body Mass Index, WHRATIO: Waist to Hip circumference ratio, HYCST: Homocysteine concentration, FIBRI: Fibrinogen, SEI: Socioeconomic Index

Figure 9: Final Equations

South Asians: mmIMT = -.139 + .00184* (Sys BP) + 0.054* (HbA1c) + 0.142 - 0.0339*HbA1c + .00881 (Age) + (-.041) (Sex)

Chinese: mmIMT = -.139 + .00184* (Sys BP) + 0.054* (HbA1c) + 0.106* - 0.0301*HbA1c + .00881 (Age) + (-.041) (Sex)

European: mmIMT = -.139 + .00184* (Sys BP) + 0.054* (HbA1c) + .00881 (Age) + (-.041) (Sex)

Comment:

Systolic BP, HbA1c, ethnicity and the ethnic x HbA1c interaction, age and sex are the significant independent predictors of atherosclerosis.

Clinical Importance of the HbA1c interaction by ethnic group:

To demonstrate what impact the HbA1c x ethnic interaction will have on the prediction of atherosclerosis (mmIMT), 4 cases are presented below with corresponding mmIMT values, based on the set of risk factors identified to be significantly associated with mmIMT (i.e. age, sex, systolic blood pressure and HbA1c) in the multiple linear regression model (Table 13, Figure 10).

For each case below, the specific values for the major predictors of atherosclerosis are provided using the equations in Figure 9. The amount of atherosclerosis (mmIMT) is calculated. These results are also summarized in Table 23.

Case 1: The mmIMT for a 45 year old **male** with a systolic blood pressure of 140 mm Hg and a haemoglobin A1c of 5% is 0.71 mm if he is South Asian, 0.65 mm if he is Chinese, and 0.73 mm if he is of European origin.

Case 2: The mmIMT for a 45 year **woman** with a systolic blood pressure of 140 mm Hg and a haemoglobin A1c of 5% is 0.67 mm if she is South Asian, 0.61 mm if she is Chinese, and 0.70 mm if she is of European origin.

Case 3: The mmIMT for a 45 year old **male** with a systolic BP of 140 mm Hg and a raised HbA1c of 7.0% is 0.75 mm for a South Asian, 0.72 mm for a Chinese, and 0.80 mm for a European. This demonstrates that for a given change in HbA1c there is a greater change in mmIMT among Europeans compared to South Asians and Chinese.

Case 4: The mmIMT for a 45 year old **woman** with a systolic BP of 140 mm Hg and a raised HbA1c of 7.0% is 0.71 mm for a South Asian, 0.68 mm for a Chinese, and 0.76 mm for a European.

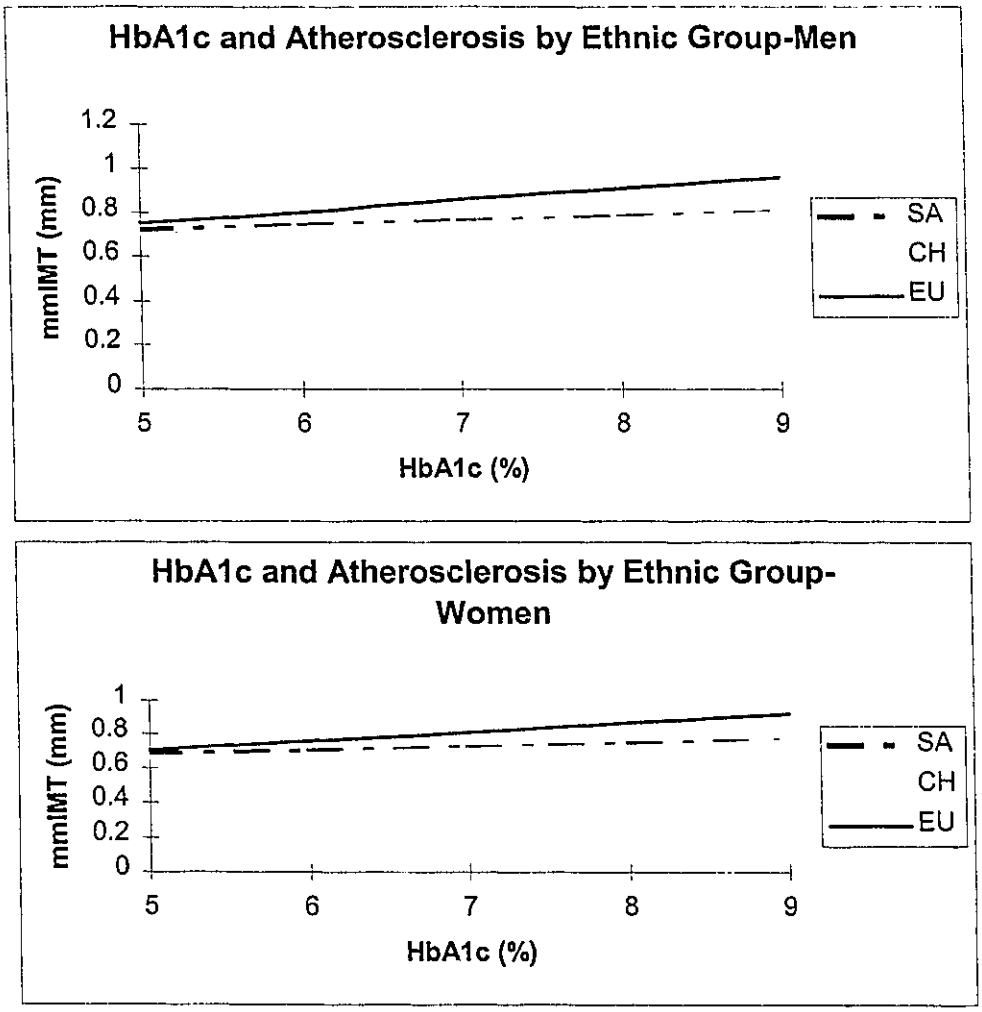
Table 23: Examples of risk Prediction by Ethnic group for Atherosclerosis

	Systolic BP	HbA1C	AGE	Sex: (Male or Female)	mmIMT South Asian (mm)	mmIMT Chinese (mm)	mmIMT European (mm)
Case 1	140	5	45	Male	0.72	0.70	0.75
Case 2	140	5	45	Female	0.69	0.66	0.71
Case 3	140	7	45	Male	0.76	0.75	0.85
Case 4	140	7	45	Female	0.72	0.71	0.81

Comment:

Given the standard deviation of mmIMT is approximately 0.16 mm, although the differences in mmIMT in millimetres may appear small, in each case the European mmIMT is significantly greater than the Chinese, and is also significantly increased in Cases 1, 3, and 4 when compared to South Asians. In Case 2, among women aged 45 who have a systolic blood pressure of 140 mm Hg, and a normal HbA1c, (i.e. 5%), no significant difference in mmIMT between Europeans and South Asians is observed. In addition, among women for a given set of parameters the mmIMT is not significantly different between the South Asians and the Chinese.

Figure 10: HbA1c and Atherosclerosis (mmIMT)



Conclusion:

The predictors of atherosclerosis are conventional factors including systolic blood pressure, HbA1c, age and gender. This relationship varies significantly by ethnic group. For a given increase in HbA1c, a greater change in atherosclerosis is observed among people of European origin.

Objective 4b: Determinants of CVD and the contribution of Ethnicity

To identify the predictors of cardiovascular events in all participants multiple logistic regression was used {Hosmer and Lemeshaw 1989}. Prevalent cardiovascular disease was the dependent variable and conventional factors such as age, sex, systolic, and diastolic blood pressure, HDL-C, total cholesterol, smoking, diabetes, and left ventricular hypertrophy were used to create a risk score in all participants {Wilson 1987}. Atherosclerosis as measured by the mmIMT and novel risk factors such as PAI-1, Lp(a), homocysteine, and fibrinogen as well as ethnicity were used in independent variables. The recruiting centre (Hamilton, Toronto, Edmonton), the number of years that each participant lived in Canada, as well as interaction terms were also entered. The results of this logistic regression are shown in Table 24.

Table 24: Univariate Analysis of Selected Risk Factors and CVD

Variable	B Coefficient[1]	Standard error[2]	Odds Ratio (95% CI)[3]	P Value
Framingham Risk Score				
Moderate vs low	1.50	0.64	4.49	0.02
High vs low	2.94	0.60	(1.27-15.89)	
			18.80	0.000
			(5.80-61.07)	
Atherosclerosis-mmIMT for a 0.1 mm increase	.328	0.48	1.46	0.0001
			(.52-2.72)	
PAI-1 for a 10 unit increase	0.35	0.1	1.40	0.009
			(1.22-1.61)	
Lp(a)	0.22	0.11	1.24	0.05
			(0.99-1.56)	
Homocysteine	0.060	0.02	1.06	0.008
			(1.01-1.11)	
Fibrinogen	0.20	0.11	1.23	0.06
			(0.99-1.52)	
Ethnicity:	0.41	0.28	1.5	0.47
SA vs EU	-1.07	0.42	(0.86-2.60)	
CH vs EU			0.34	0.01
			(0.15-0.77)	
Years in Canada	0.023	0.01	1.02	0.001
(Per year in Canada)			(1.01-1.04)	

Legend: PAI-1: Plasminogen Activator Inhibitor-1, Lp(a): Lipoprotein (a), SA: South Asian, CH: Chinese, EU: European

[1]: B Coefficient: Estimated coefficient from the logistic regression model

[2]: Standard Error: Standard Error of the B coefficient

[3]: Odds Ratio and 95% CI: The Exp (B) is the predicted change in odds for a unit increase in the predictor, and the 95% confidence intervals for the EXP (B)

Table 25: Predictors of CVD by multivariate logistic regression

Variable	Beta Coefficient[1]	Standard error[2]	Odds Ratio (95% CI)[3]	P Value
Framingham Risk Score				
Moderate vs low	0.93	0.67	2.49 (0.67-9.20)	0.18
High vs low	1.72	0.66	5.28 (1.45-19.16)	0.007
Atherosclerosis-mmIMT per 0.1 mm increase	2.14	0.60	1.24 (0.06-2.41)	0.0002
PAI-1 per 10 unit increase	0.04	0.015	1.49 (1.46-1.52)	0.006
Lp(a)	0.26	0.13	1.29 (1.01-1.08)	0.03
Homocysteine	-0.006	0.03	0.99 (0.94-1.06)	0.69
Fibrinogen	0.31	0.25	1.36 (0.84-2.21)	0.95
Ethnicity:				
SA vs EU	1.51	0.57	4.51 (1.46-13.89)	0.02
CH vs EU	0.05	0.63	1.05 (0.30-3.63)	0.91
Years in Canada (Per 10 years in Canada)	0.04	0.01	1.49 (1.47-1.51)	0.03
Centre				
TO vs Ham	0.43	0.39	1.53 (0.72-3.27)	0.27
Ed vs Ham	0.45	0.35	1.57 (0.80-3.11)	0.19

SA: South Asian, CH: Chinese, EU: European, TO: Toronto, Ham: Hamilton, ED: Edmonton.

[1] Beta Coefficient: Estimated coefficient from the logistic regression model

[2] Standard Error: Standard Error of the Beta coefficient

[3] Odds Ratio and 95% CI: The Exp(Beta) is the predicted change in odds for a unit increase in the predictor, and the 95% confidence intervals for the EXP (Beta)

Note: Shaded areas represent significant independent predictors of CVD. No significant interactions of ethnicity with the Framingham score and mmIMT, as well as sex, were identified.

Summary:

These results demonstrate that the conventional CVD factors remain important predictors of CVD, yet over and above this perhaps independent of those factors, atherosclerosis is a risk factor for cardiovascular disease. Furthermore, over and above conventional risk factors and atherosclerosis, emerging factors such as PAI-1 and Lp(a) appeared as independent risk factors for cardiovascular events. After all of these factors were entered, South Asian ethnicity was identified as an independent determinant of CVD with a significant odds ratio of 4.51 as compared to Europeans. No significant interactions between ethnicity and conventional factors and atherosclerosis were detected, therefore South Asian ethnicity on its own should be considered as a risk factor for CVD.

The main results of SHARE were published in the Lancet 2000; 356: 279-284, and the full manuscript is found in Appendix E. Like most evaluations, the study has added new pieces to the puzzle of why South Asians suffer high rates of CVD (Figure 11), and has raised new questions for future study.

Figure 11: New Observations in SHARE

- South Asians in Canada have a significantly elevated LDL cholesterol compared to Europeans and Chinese in Canada
- The prevalence of diabetes and impaired glucose tolerance is significantly greater among South Asians, intermediate among Chinese, and lowest among Europeans
- European Males had the greatest prevalence of overweight and obesity compared to the South Asians and Chinese
- South Asian and European women weighed significantly more than Chinese women
- European men had the greatest prevalence of abdominal obesity compared to the other males, South Asian women had the greatest prevalence of abdominal obesity compared to the other women
- South Asians had significant elevation in PAI-1, Lp(a), homocysteine, and fibrinogen
- Europeans had the greatest social stability as measured by the socio-economic index, and SEI exerts a protective effect on CVD
- South Asians had the highest prevalence of CVD, but did not have the most atherosclerosis.
- South Asian ethnicity is an independent marker of increased risk for CVD after accounting for conventional risk factors, novel risk factors, degree of atherosclerosis, SEI and duration of stay in Canada.
- Duration of stay in Canada increased the risk of CVD independent of all other risk factors.

CHAPTER 6

MEASURING DIET: THE DESIGN AND VALIDATION OF THE SHARE DIETARY QUESTIONNAIRES

Background:

Dietary factors have been implicated in the pathogenesis of CVD, and in the protection from CVD {Willett 1990, Blackburn 1973, Keys 1986, Pearson 2000}. The initial observation which sparked interest in the diet and cardiovascular area was that people who ate different diets (usually from different countries) had different rates of CHD {Keys 1986, Shaper 1996, Jenkins 1987}. This observation led to an extensive and ongoing exploration of the relationship between dietary factors and CVD. Currently the major components of diet which are believed to *cause or promote* CVD include increased consumption of saturated fats, increased consumption of trans-fatty acids, and increased consumption of high-glycemic carbohydrates {Jenkins 1987}. In addition, other dietary factors are implicated more proximally in the development of CVD risk factors such as salt consumption and its associated increase in blood pressure {Morris 1999, Stamler 1991}.

On the other hand, some dietary patterns have been observed among populations who have a low prevalence of CHD such as increased fish consumption, high consumption of

fresh fruits and vegetables, and diets which are high in polyunsaturated or monounsaturated fats. {Zhang 1999, Liu 2000, Kuller 1997} (Table 26). Apart from specific adverse or protective components of the diet which are associated with CHD, total caloric intake has a major influence on body weight. Increased body weight is associated with the development of CVD risk factors such as diabetes, increased blood pressure and abnormal serum lipids {Barrett-Connor 1996}. Therefore, accurate measurement of dietary intake in studies of CVD pathogenesis is essential and usually incorporates numerous objectives, such as the study of the macro-nutrient profile (e.g. fats, carbohydrates and protein), micro nutrient intakes (e.g. vitamins and minerals), daily caloric intake, specific dietary components (e.g. trans-fatty acids and fish), and cooking methods.

Table 26: Diet and Chronic Disease Associations {Shetty 1997}

Nutrient	Direction of Association with CHD	Association with Cancers	Risk factors
Total fats	• ↑ CHD	• Colon • Prostate • Breast	• Obesity
Saturated Fats	• ↑ CHD	• Colon • Prostate • Breast	• ↑ LDL • ↑ Tchol
PUFA Omega-3 Omega-6 Fish Oils	• ↓ CHD	• Unclear	• ↓ LDL • ↓ Tchol • ↓ HDL
Monounsaturated Fats	• ↓ CHD	• Unclear	• ↓ LDL • ↓ Tchol
Dietary Cholesterol	• ↑ CHD	• ↑ colon cancer	• ↑ LDL • ↑ Tchol
Trans fatty acids	• ↑ CHD	• ↑ colon cancer	• ↑ LDL
Plant Foods (Fruits, vegetables, legumes, whole grain cereals)	• ↓ CHD	• ↓ Cancer of lung, colon, esophagus, and stomach	• ↓ BP
Complete Vegetarians	↓ CHD	• ↓ Cancer	• ↓ LDL • ↓ Triglycerides
Folic Acid, Vit B12, Vit B6	• ↓ CHD	• ↓ Cancer of Colon	• ↓ Homocysteine
Alcohol	• Moderate = ↓ CHD • Heavy = ↑ CVA+CHF	• ↑ Cancer of mouth, pharynx, larynx	• Heavy ↑ BP
Salt	• ↑ CVA	• ↑ Gastric cancer	• ↑ BP (> 6 grams per day)

Legend: LDL: Low density lipoprotein, HDL: High density lipoprotein, BP: Blood Pressure, Tcholesterol: Total cholesterol ; CVA: Cerebrovascular Accident; CHF: Congestive Heart Failure; CHD: Coronary Heart Disease; PUFA: Polyunsaturated fatty acids

Studying Ethnic differences in dietary intake:

The variation in CVD burden across ethnic groups, as well as their extreme differences in dietary practices offers important opportunities to examine the role of dietary factors in relation to CVD. The variations in CVD and cancer mortality rates between South Asians, Chinese, and European Canadians within Canada {Sheth 1999} raise the issue of whether these differences are attributable to genetic factors, environmental factors (e.g. diet) or some interactions between genetic and environmental factors. One of the important environmental contributors to the development of CVD risk factors, atherosclerosis, and CVD is likely to be dietary intake.

Challenges of Epidemiologic Studies of Dietary factors and Disease:

Bradford Hill's criteria for causality include strength of association, consistency of an association across studies and populations, the presence of a dose response gradient, an appropriate temporal relationship, biologic plausibility, and coherence of data across studies {Hill 1962}. In studying diet-disease relationships, while associations may be found, there are also some exceptions to the Hill Criteria. For example, even apparently weak associations between dietary factors and disease could be very important in a population because dietary exposures are common, and because dietary measures are imperfect and may underestimate the association. Second, a given diet-disease association may not be observed consistently across populations with markedly different diets, even if a causal relationship exists, because the nutrient may not be consumed in enough quantity to be studied. Third, dose response relationships are most likely non-

linear as diseases associated with deficiencies of a nutrient are usually different from diseases associated with excesses of a nutrient. Finally, the finding of no relationship between a dietary factor and a disease must also be interpreted with caution. Possible explanations include low variability in diets of individuals *within* a population and therefore no association with disease is detected because everyone is eating the same diet. For example, if the intake of saturated fat is high in the population under study, demonstrating that increasing the intake of saturated fat is associated with excess atherosclerosis may be difficult. Further, the lack of precision in measuring diet, and inadequate number of events or people studied, leads to low statistical power. This situation is further affected by "negative confounding" which refers to the observed lack of association between two variables when, in fact, one exists but it is hidden because of a third unaccounted for, or unknown, variable {Stram 2002}. For example, if people who smoke consume fewer calories, yet suffer more clinical events, failure to account for smoking may explain the apparent lack of association between increasing calorie intake and clinical events.

Effects of Within Person variation on Measures of association:

Within-person variation, or random variability above and below a person's true long-term average nutrient intake, can have a profound effect on the measurement of diet. The effect of within-person variation is most prominent when one (e.g. 24 hour recall) or only a few days of dietary intake are measured. The effect of this variation usually leads to a misrepresentation of the individual's usual intake and results in an attenuated correlation

with another factor (i.e. another dietary measure or disease outcome). Within-person variation in one of two variables (e.g. X and Y) being correlated will cause the observed correlation between these variables to be attenuated or lower than their true correlation.

To estimate the true correlation from the observed correlation (e.g. taking into account the measurement error), Sempos and co-workers {Sempos 1985} have shown that, for most nutrients, many days of dietary intake are necessary to avoid a major attenuation in the correlation between a nutrient and another factor. Regression coefficients are also attenuated because of within-person variation in the independent variable (e.g. nutrient of interest). Conversely, random variation in the dependent variable (in this case atherosclerosis) does not systematically bias (or attenuate) the regression coefficient, as the variation in the dependent variable will decrease the precision of the regression coefficient (i.e. increase the standard error). Random within-person variability can be assessed using reliability or repeated measurement, whereas the measure of systematic error requires a validation study. In general, substantial between person differences for most dietary factors still exist once the within-person variability is removed (Table 27).

Table 27: Within and Between-Person Variations and Error

	Within Person Variation	Between Person Variation
Random Error	• Day to day variation due to changes in food intake	• One or Few replicates (↑ SD) • May balance out and generate true mean because it is high for some and low for others, but would tend to dilute any relationship with the disease to the null
Systematic Error (Bias)	• Social Desirability or reporting bias • Important food items for a person (but not necessarily all people) may have been omitted from the dietary questionnaire • Subjects misinterpret the Questions	• Omission of commonly eaten foods (e.g. for some but not all ethnic groups) • Incorrect Nutrient composition in the food database

Legend: SD = Standard deviation

Note: Errors which are random do not alter the nutrient mean substantially from the true value provided that a number of replicates have been completed. Systematic error produces a mean value which is different from the true value.

Objectives of the SHARE dietary component:

1. To develop and asses the validity of three self-administered dietary questionnaires in a multiethnic population in Canada.

2. To determine differences in the energy intake, selected macronutrients, and salt intake in a multiethnic population in Canada.

3. To assess how dietary patterns change among migrants from their host country to their adopted land.

4. To study the relationship between saturated fat intake and trans fatty acids and atherosclerosis in three ethnic groups.

Objective I: Measuring diet:

Although determining the role of dietary factors in the causation of CVD is important, the measurement of dietary factors is challenging. The FFQ is the most commonly used method to assess dietary intake in epidemiologic studies of diet and chronic diseases {Willett 1985}. The FFQ is an instrument which records a respondent's frequency of consumption of specific items per day, per week, or per month and provides an estimate of the "usual diet" over a specific period of time (e.g. one year). "Usual diet" is measured because long-term dietary habits are likely to be better predictors of chronic diseases than are short-term fluctuations in intake {Willett 1987}. In addition, FFQs are an efficient way of collecting a large amount of data and they are usually self-administered. For these reasons, the FFQ has become the principal dietary survey method in epidemiologic studies {Willett 1990, Hankin and Wilkins 1994, Feskanich 1993}. Other options to measure usual dietary intake include in-depth interviews, multiple 24-hour recalls, or collection of several days of food records at multiple time periods {Jain, Howe and Rohan 1996, Willett 1990}. However, these methods are not as feasible in large

epidemiologic surveys because they are more time consuming and require multiple contacts with participants (Table 28).

Table 28: Attributes of Various Instruments used to Measure Diet

Method	Definition	Pros	Cons
In-Depth Interviews	Performed by a nutritionist using models and pictures.	Allows for greater assessment of individual food items. More precise at determining nutrient intake.	Not feasible and expensive in population-based studies.
Single 24-Hour Recall	Subjects are asked to recall what they consumed over the preceding 24 hours.	Efficient Potential for recall bias is limited and likely reasonable.	Potential for extreme variability in diet as it reflects only one day.
Multiple 24-Hour Recalls	Subjects are asked to recall what they consumed over the preceding 24 hours on multiple occasions chosen at random	Multiple 24 hour recalls is considered to be the gold standard of nutrient intake if recalls are repeated over time. Two or 3 recalls per subject is sufficient for multiple recalls {Willett 1990}. Multiple recalls take into account variability due to season and day of the week.	The optimal number of recalls to perform is unknown, although 3-4 produce statistically similar results as 7 when compared to the gold standard of prospectively collected food records {Willett 1990}.
Food Records	Records of daily intake completed by subject at home prospectively for 4 or 7 days, and attempts to give accurate recording of volumes and portion size.	Gold Standard: If the population is highly literate and motivated. Does not rely on memory.	The assessment of an individual's "usual" intake is based on only 4 or 7 days of their food consumption Social desirability bias.

There are currently a number of FFQs which have been developed for use in Canada, the United States, and Europe {Willet 1985, Longnecker 1993, Lee 1994, Hernandez 1998, Wirfalt 1998, Hankin 2001}. FFQs have been used in more than 30 large cohort studies involving over 3 million men and women {Willett 1990}. Correlations between FFQs and more detailed dietary assessments for the major macronutrients generally run between 0.5 and 0.7 {Willett 1990, 2000}. In reviewing the existing FFQs at the outset of SHARE there were no FFQs which could measure the diets of people of South Asian or Chinese origin in Canada. Therefore using the model of a FFQ developed in Ontario, Canada for the Canadian Study of Diet Lifestyle and Health {Jain 1996} three ethnic specific FFQs for South Asians, Chinese and European Canadians were developed for use in SHARE (Appendix G).

Development of the Food Frequency Questionnaire:

The steps involved in the development of the FFQ are outlined in Figure 12. The first step was to identify commonly consumed food items in the population of interest. In 1995-1996, in the SHARE pilot study, such information was collected using multiple (i.e. 2 per subject) 24-hour recalls *or* 4 day food records from 21 people of European origin, 30 people of South Asian origin, and 26 people of Chinese origin living in the Hamilton area {Anand and Yusuf 1997}. All reported foods and beverages were ranked according to the frequency of their use. Foods and beverages consumed by more than two individuals within an ethnic group were incorporated into a preliminary food list generated for each ethnic group. The South Asian food list was comprised of 163 items,

the Chinese of 169 items, and the European food list had 157 items. Review of these food lists demonstrated that, although there were certain common foods consumed by all three ethnic groups (e.g. bread, cereal, milk, coffee, tea, and fruit), there was little overlap between the groups for the majority of foods consumed. Therefore, to avoid developing a single lengthy questionnaire with limited relevance to certain subgroups of the study participants, three separate FFQ's were created {Hankin and Wilkens 1994}. Using the FFQ of the Canadian Diet Lifestyle and Health as a model {Jain 1996}, the commonly reported food items collected in the pilot study were incorporated into three unique questionnaires, one for each ethnic group. Apart from food items, the frequency of consumption of the item (i.e. number of servings per day or per week or per month or per year) and the serving size were recorded. An average portion size of food was defined as that portion which was reported with the greatest frequency among pilot study participants. To assist participants in their choice of serving sizes, we included photographs of three portion sizes of commonly consumed foods into each FFQ (Appendix G). For example, for the item "boiled rice", participants had to first check off how often rice was consumed and indicate whether they had a small, medium or large serving. In addition to the specific items listed in the FFQ's, an open-ended section in the questionnaire was available to participants to add other commonly consumed items that did not appear on our list. Questions regarding vegetarianism, amount of fat in the meat that was eaten, the kind of fat used for cooking, the kind of fat used for frying, the kind of fat used for baking, and the types of oils used were also included. Questions to determine the frequency of consumption of fried foods and take-out foods were also added.

Respondents were asked how close their current diet was to their traditional diet in their country of ancestral origin. Finally, a section on consumption of vitamins and supplements and other health products was added (Figure 12).

After the questionnaires were created for each ethnic group they were tested among people of that ethnic origin for readability and responder-burden issues. Adjustments to the questionnaires were made where deemed necessary. A nutrient database was compiled in order to calculate a nutrient profile based on the FFQ information. The challenge in creating this database was that existing nutrient databases such as the ones available in North America do not include the majority of foods consumed by people of South Asian and Chinese origin. In order to ensure that the nutrient database in SHARE was comprehensive, and included the majority of food consumed by these groups, food composition tables for many of the ethnic specific food items were obtained from the National Institute of Nutrition in Hyderabad in India {Gopalan 1984}, the Chinese Academy of Medicine in China. The ESHA Food Processor Nutrient Analysis software {ESHA Website} was chosen as the main nutrient composition database, as it incorporates the US Department of Agricultural Food Bank and the Canadian Nutrient File in its system, and has very few missing values {ESHA Website}. This database was also modified to include the nutrient compositions of Canadian fast foods and ethnic-specific food items (e.g. chicken curry). The former was done in collaboration with researchers at University of Western of Ontario and Health Canada. For the latter, multiple recipes were entered for the same item listed in our food records, to create

"average" nutrient compositions. Development of this master data bank of nutrient compositions, to analyze our FFQs and food records, required an intensive effort which was essential to study the differences in macro and micro nutrient between the ethnic populations in SHARE. This database is the first of its kind in Canada and will provide future researchers in North America the opportunity to study dietary differences in selected ethnic groups.

Figure 12: Summary of the Development of the FFQ

- Identify commonly consumed foods by multiple 24 hour recalls and records from pilot study data (n=30 SA, n=26 CH, n=21 EU)
- Incorporate the most commonly considered foods into questionnaire format
- Decide on set-up of questionnaire i.e. frequency of consumption by day, week, year etc. and serving size options using the Canadian Study of Diet, Lifestyle and Health FFQ {Jain 1996} as a template
- Initial Test of the Questionnaire and modification where necessary.
- Incorporation of photographs of common foods as a visual aid
- FFQ formatted for a scanner using the DataFax system
- FFQ translated into 3 South Asian languages (Punjabi, Hindi, and Tamil), and Chinese script for use in the main study

Validity and Reliability Testing:

The next step after the FFQ was created was to test its validity and reliability. The first step of the validation process involving a reference standard. In SHARE, seven day food

records were chosen as the reference standard against which to validate the FFQs. Given that neither our FFQ nor the reference standard are perfect measures of dietary intake, it is important that the errors of both of these methods be independent to avoid spuriously high estimates of validity. The reasons food records were chosen are i) they are likely to have the least correlated error with the FFQs given that the food records are open ended, ii) they do not depend on memory (completed prospectively) and, iii) they allow direct assessment of portion size as compared to FFQs which impose a fixed food items, rely on memory and perception of portion size, and they rely on the correct interpretation of the questions by the participant (Figure 13). In food records, participants record exactly what they consume, the volume or the amount, and provide recipes when they make complex dishes (e.g. chicken curry). An example of the detail recorded on a food record is provided in Appendix G. Food records are believed to have greater face validity than a single 24 hour recall, and are considered the gold standard method of validation when the population is highly motivated and literate {Willett 1990}. Furthermore, it is more feasible to collect data once rather than using multiple 24 hour recalls, given the relatively high costs of administering multiple recalls in person or by telephone, which include the interviewers time to contact subjects via telephone days on random days and the potential language barriers which exist given the multi-ethnic nature of our population. In addition, the results of the SHARE pilot study in 1995-1996 demonstrated that the dietary data collected from 4 day food records was more complete than the dietary data collected from multiple 24 hour recalls {Linda Kelemen Personal communication}.

Figure 13: Potential Sources of Error with the Dietary instruments in SHARE

FFQ	Food Records
• Item is not present on FFQ	* Attention to detail
• Participant does not understand how to complete it	* Accurate reporting
• Recall of usual dietary history may be inaccurate	* Completeness of reporting
• Understanding of volume (i.e. ½ cup of rice)	* Coding and data entry
• Social desirability	
• Food preparation differences	
• Nutrient composition of item is accurate/available (e.g. brown rice vs. all rice)	

Sample Size Estimates for the Validation Study:

In dietary analyses, correlations for validity generally tend to be in the range of 0.5-0.7 {Willett 1990}. Correlations below 0.4 seriously tend to attenuate associations between dietary variables and outcomes in multiple regression {Willett 1990}. Willett and Rosner have observed that in general, validation studies of > 150-200 people add little to the precision of the correlation coefficient, whereas studies of < 30 subjects are associated with a major increase in the width of the confidence intervals around the correlation coefficient {Rosner 1996, 2001}. Before calculating the correlation coefficients, nutrient values were checked for normality. If they were not normally distributed they were corrected by log transformation. Alternatively, to assess the simple correlation between two non-normal variables, a Spearman coefficient was computed. For the reliability assessment of the FFQ at 2 time points, the intraclass correlation (ICC) was calculated.

Methods:

The process of validation of the three FFQs was attempted in a random sample of men and women of each ethnic group. The steps involved in the validation process included: i) correlation of the reported nutrient intake of selected nutrients from the FFQ with the reported intake of the same nutrients from a composite of Food Records, ii) correlation of the FFQ at baseline (FFQ1) and at 6 months later (FFQ2) (Figure 14). We aimed to have approximately one-third of the participants complete the food records and FFQ a second time, 6 months after their clinic visit. Although we had an excellent response rate for our initial dietary assessment, given the responder burden associated with completing dietary records and the FFQ, the number of people who completed the second set of dietary information was lower than expected (Table 29). However, in consultation with Dr. W. Willett from Harvard University it was agreed that the food records from time 1 and time 2 could be added up to create a composite food record value for participant who completed two sets of food records (i.e. 14 days of food records per person). This composite was then correlated with the baseline FFQ for the validation. The total number of participants in the validation substudy was 114 South Asians, 67 Chinese, and 88 Europeans, and 58 South Asians, 64 Chinese, and 86 Europeans completed a second FFQ for reliability testing (Table 29).

Figure 14: Time Sequence of Proposed Validity and Reliability Study

Time 1: FFQ1 administered. 7 day Food Record-1

Time 2: 6 months later FFQ2, 7 day Food Record-2

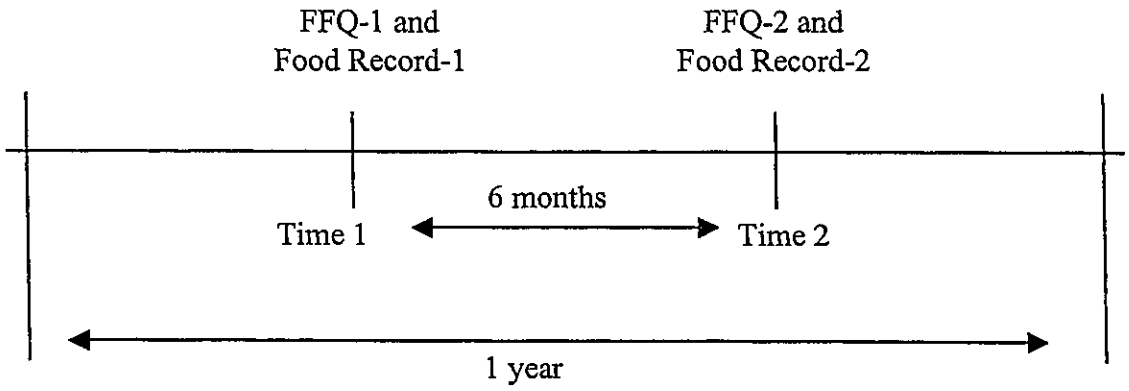


Table 29: Response rate for the diet record and FFQ among South Asian, Chinese and Europeans participating in the SHARE validity and reliability sub-study

	South Asian	Chinese	European
Total sample in cohort	**342**	**317**	**326**
Completed first FFQ n (%)	313	286	317
Completed first diet record n (%)Ψ	233	262	276
Participants in validity substudy n (%)	**114**	**67**	**88**
Returned second FFQ (%)	**61**	**71**	**88**
Participants in the Reliability Study*	**58**	**64**	**86**

Ψ: Randomly selected for repeat set of food records. * 3 FFQs of South Asian, 7 of Chinese, and 2 of Europeans were not properly completed to use in the reliability substudy

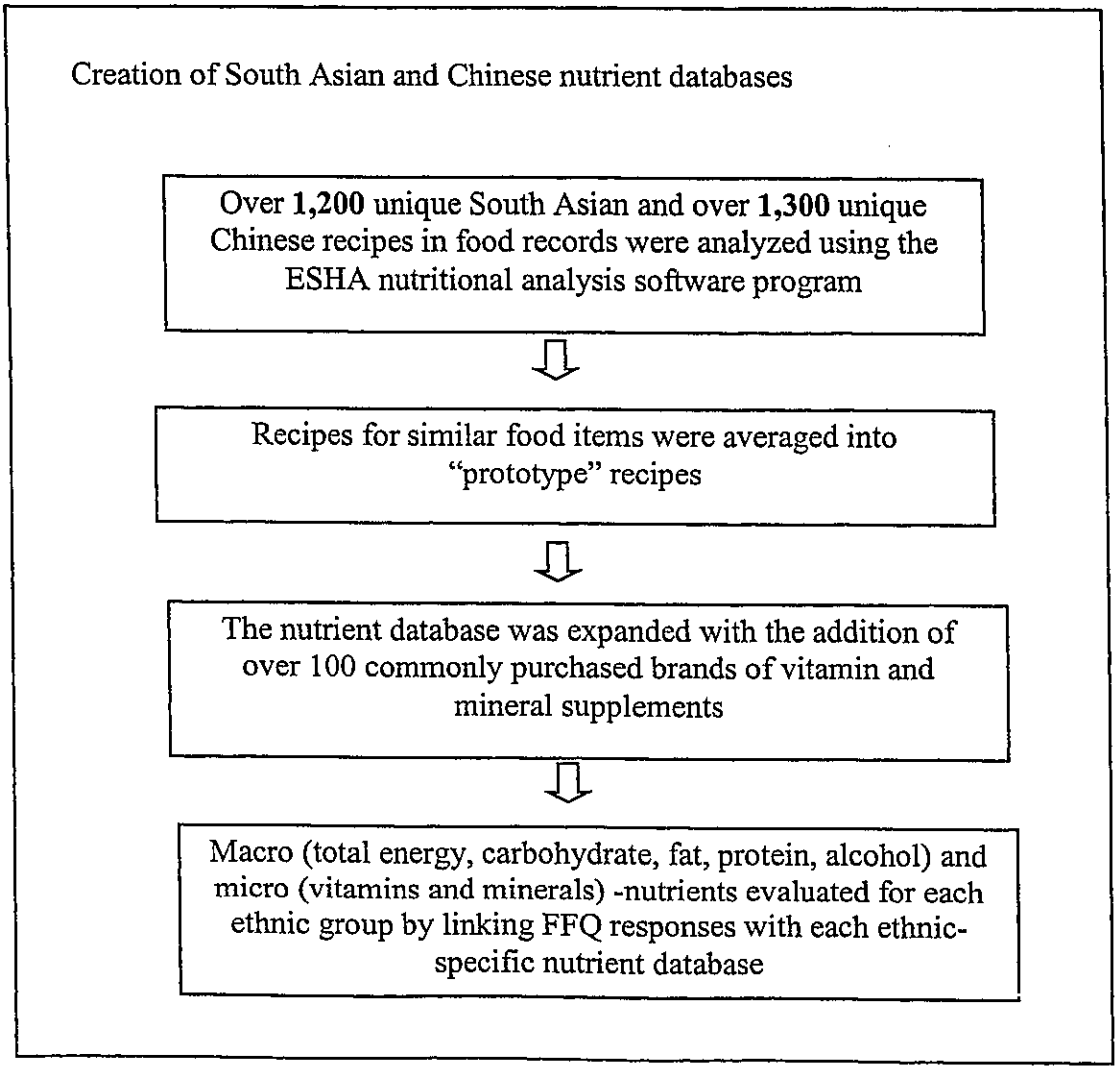
Food Record Analysis:

Collection of two sets of food records was attempted in the validation study in order to obtain a maximum of 14 days of dietary information per participant. These food records were coded and manually entered into a database by the study nutritionist. The composite of days of dietary records would be adequate to estimate individual intakes for most nutrients and would also capture seasonal variation. In completing dietary records, participants recorded the type, the frequency and the amount of the consumption of regularly eaten food for a given period of time (Appendix G). In SHARE, detailed instructions were provided by the nutritionist to all participants. They were instructed to record everything they ate or drank over a period of 7 consecutive days, as well as to record information on the method of cooking, the recipes, the type and brand names of various foods and supplements in a food record booklet provided to them at the clinic visit. Participants were not required to weigh foods, but were asked to record the volume of bowls and cups used. The food records were returned to the SHARE project office by mail and were checked for completion by the study nutritionist. Collection of missing information was attempted by follow-up telephone calls made by the study nutritionist. Non-English speaking participants were provided a translated food record booklet in their native language.

After the food and beverage items were coded and entered manually into a database by the study nutritionist, the average daily nutrient profile for each individual was calculated using the expanded ESHA. Furthermore the recipes for ethnic specific foods (e.g. chicken

curry) which were provided by the participants on the food records were entered into the ESHA nutritional software program to create an average nutrient profile for a given ethnic food. These prototype nutritional profiles were then used to calculate the nutrient profile for the participants who completed the food frequency questionnaires (Figure 15a)

Figure 15a: Creation of Nutrient Databases from Food Records



Food Frequency Questionnaire Analysis:

The FFQ's were created in Datafax format which enabled the forms to be faxed directly into the database {Datafax 2001}. An individual's daily nutrient intake was determined by merging the reported frequencies and volume of foods with nutrient values for these items in the expanded ESHA nutrient database (Example see Figure 15b). Average daily nutrient intakes for selected macro and micro nutrients were correlated with the average daily nutrient intake from the food records. The FFQ was administered on two occasions to all participants in the validation study at baseline and at 6 months later.

Figure 15b: Example of Calculating Energy & Nutrition Compositions Information from the Food Frequency Questionnaire

FOOD: Boiled Rice

Step 1: FFQ information completed by participant.

South Asian FFQ	CH FFQ	EU FFQ
Item 98 ☐ Rice, Boiled	Item 53 ☐ Rice, Boiled	Item 115 ☐ Rice, Boiled

Serving Frequency ☐☐ Per day ☐☐ Per Week ☐☐ Per Month ☐ Per year or Never

Average Serving Size* [S] [M] [L] photo A

Average servings/days

- 1 small serving = .5x medium serving, 1 Large serving = 1.5x medium serving

Step 2: Energy information from Nutrient database "Expanded ESHA" for one medium serving of boiled rice

	South Asian	Chinese	European
Calories *	227	244	229
Carbohydrate (g)	48	53	49.3
Protein(g)	4.4	4.7	4.9
Total Fat (g)	1.2	0.4	0.8
Sugar (g)	0	0	0
Fibre (g)	0.6	0	0.7

*Calories and food composition vary between the ethnic groups due to differences in the type of rice, and the way it is prepared.

Step 3: Calculation of Energy & Nutrient Composition for a Rice Serving

	South Asian	Chinese	European
Servings/day	0.5	1.0	0.2
Daily calories from Rice	102.3	237.1	44.7
Adjusted calories	87.9	208.9	38.1
Carbohydrate (g)	21.6	23.8	22.2
Protein(g)	2.0	2.1	2.2
Fat (g)	0.5	0.2	0.4

Correlation of two dietary sources:

The nutrient content for the selected nutrients from the FFQ and the food records were correlated using the Spearman correlation coefficient {Armitage 1998} (Table 28). The Spearman correlation reflects the extent of a linear relationship between two variables, and may be used when one or both of the variables are not normally distributed as was the case for many of the macronutrients tested in the validation substudy. In keeping with other validation studies, an acceptable level of correlation between the FFQ and the food records is between 0.5 and 0.7 {Willett 2000}. The nutrient intake of specific dietary factors was examined before and after adjustment for total caloric intake using the residual method: total calories were used as the independent variable in a regression model with the absolute nutrient intake as the dependent variable {Tseng 1999}. The residual of each individual was then added to the group mean to derive the energy adjusted mean for each individual {Tseng 1999}.

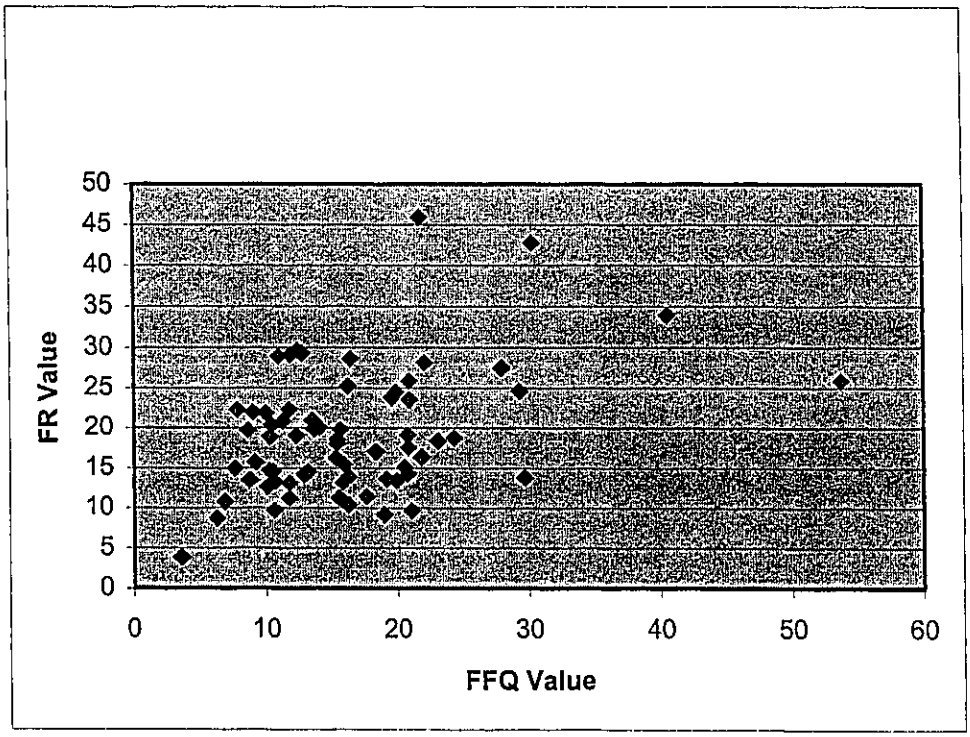
Table 28: Validity: FFQ_1 & Food Records

	South Asian				Chinese				European			
	FFQ1	FR*	Spearman	Energy Adjusted	FFQ1	FR*	Spearman	Energy Adjusted	FFQ1	FR*	Spearman	Energy Adjusted
N	114	114			67	67			88	88		
Total Calories	1822.23 (696.80)	1834.07 (475.6)	0.38	NA	1927.45 (738.33)	2030.71 (468.01)	0.32	NA	1956.72 (620.58)	2023.45 (522.67)	0.44	NA
CHO grams	276.51 (101.78)	264.45 (72.46)	0.46	0.44	244.09 (86.19)	263.11 (56.52)	0.22	0.33	276.28 (94.49)	264.12 (72.04)	0.37	0.42
Protein grams	62.3 (25.6)	71.30 (22.43)	0.35	0.40	91.09 (44.22)	90.56 (24.03)	0.34	0.26	76.13 (26.11)	80.62 (22.97)	0.41	0.44
Saturated fat	16.72 (8.70)	16.44 (22.43)	0.37	0.55	16.01 (8.00)	19.02 (7.63)	0.29	0.32	21.07 (9.43)	23.43 (10.46)	0.56	0.54
Polyunsat fat	10.53 (5.04)	11.83 (6.28)	0.24	0.29	15.8 (8.0)	14.83 (6.85)	0.33	0.14	8.62 (3.46)	10.90 (4.10)	0.28	0.29
Monounsat fat	20.31 (10.53)	21.58 (11.09)	0.36	0.43	26.13 (14.82)	25.88 (9.8)	0.24	-0.04	22.11 (9.2)	25.72 (9.9)	0.42	0.43

Note: There is greater variability for macronutrients as measured by the FFQ as compared to the food records
Note: Each macronutrient was checked for normality, if the distribution was non-normal,a non-parametric tests i.e. the Spearman's Rho was calculated instead of the Pearson correlation coefficient.

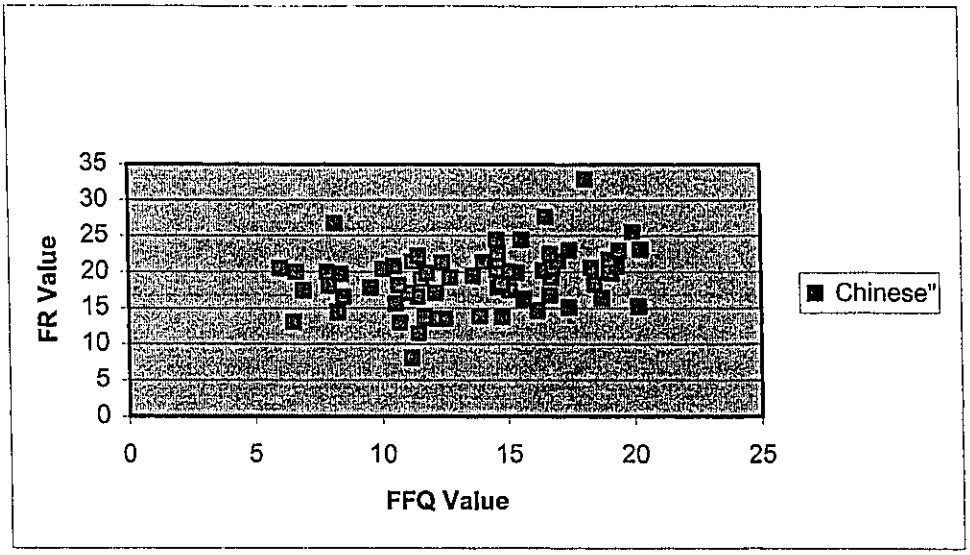
The energy adjusted correlation coefficients ranged between 0.40 to 0.55 for the major macronutrients (carbohydrates, protein, and fat) among the South Asians and the Europeans. The correlation coefficients were generally lower among the Chinese. The crude and energy adjusted relationship for saturated fat between the FFQ and FR is depicted among the Chinese participants Figures 16a-b.

Figure 16a: Crude Correlation between FR and FFQ for Saturated Fat among Chinese



r=0.29

Figure 16b: Energy Adjusted Correlation between FFQ and FR for Saturated Fat



r=0.32

Saturated Fat By FFQ Quartile:

While the conventional approach to testing validity is to determine the correlation between two independent measures of diet, other methods of demonstrating the validity of the new instrument, to discriminate between people's dietary consumption as measured by the gold standard, also exist. Many studies of diet and disease relationship compare disease rates between high consumers versus low consumers of a particular nutrient. For example, Willett and colleagues have used a semiquantitative FFQ, comparing the relative risks of cardiovascular events in the highest quintile of consumption for a particular macronutrient to the lowest quintile. Using this approach, they have reported associations with CVD and fat intake {Willett 2001}, trans fatty acids {Willett 1993, Hu 2000}, and an inverse association between CVD and alcohol

consumption {Rimm 1991}. To asses the ability of the SHARE FFQs to discriminate between high and low consumers of saturated fat (a known correlate of atherosclerosis), quartiles of saturated fat consumed, as determined by the FFQ, were created (1=Lowest, 4= highest), and the average saturated fat intake of people within each FFQ quartile, as determined by the food records, (gold standard measure) was examined (Table 30a-d, Figure 17a-d).

Table 30a: Overall Discrimination by FFQ

Quartile by FFQ	1	2	3	4
N/group	62	71	72	61
Mean Sfat intake by FR (SD) grams /day	14.9 (6.2)	16.9 (5.9)	20.3 (6.9)	25.6 (11.9)
95% CI	13.4-16.5	15.6-18.3	18.7-22.0	22.6-28.7

Figure 17a: Mean Saturated Fat Intake (FR) by FFQ Quartile Overall

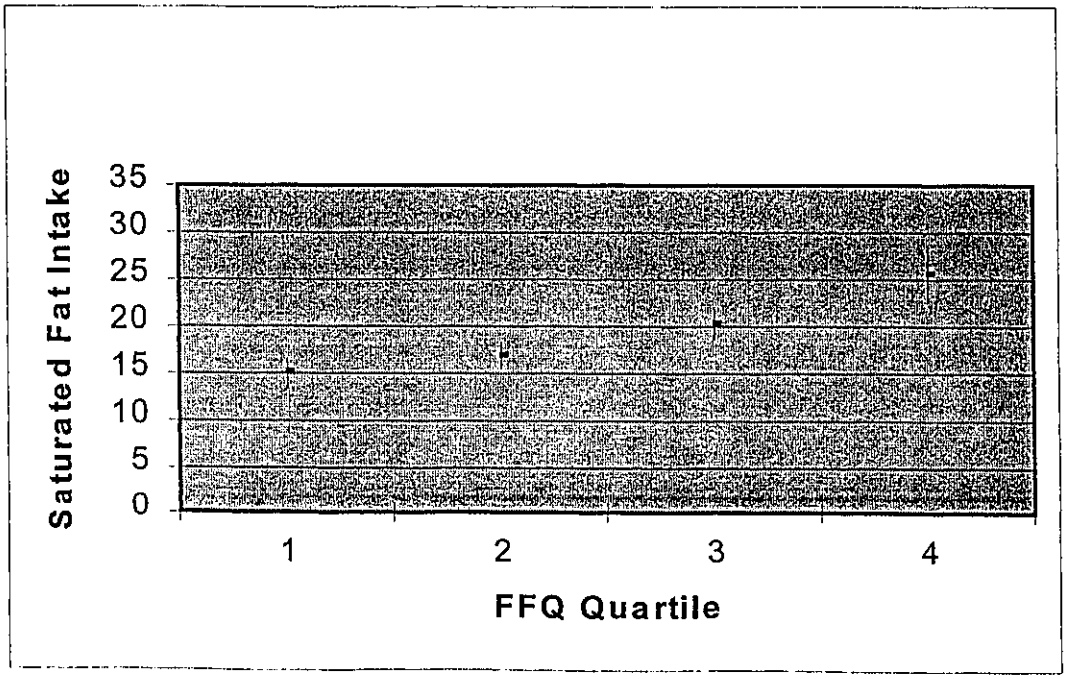


Table 30b: Discrimination by FFQ within ethnic group - South Asian

Quartile by FFQ	1	2	3	4
South Asians (N/group)	29	31	26	27
Mean Nutrient by Food record (SD) grams/day	14.4 (6.0)	13.7 (5.3)	19.0 (6.3)	19.5 (6.9)
95% CI	12.1-16.7	11.8-15.7	16.4-21.5	16.8-22.2

Quartile of Saturated Fat by FFQ: 1 = lowest, 4 = highest

Figure 17b: Mean Saturated Fat Intake (FR) by FFQ Quartile among South Asians

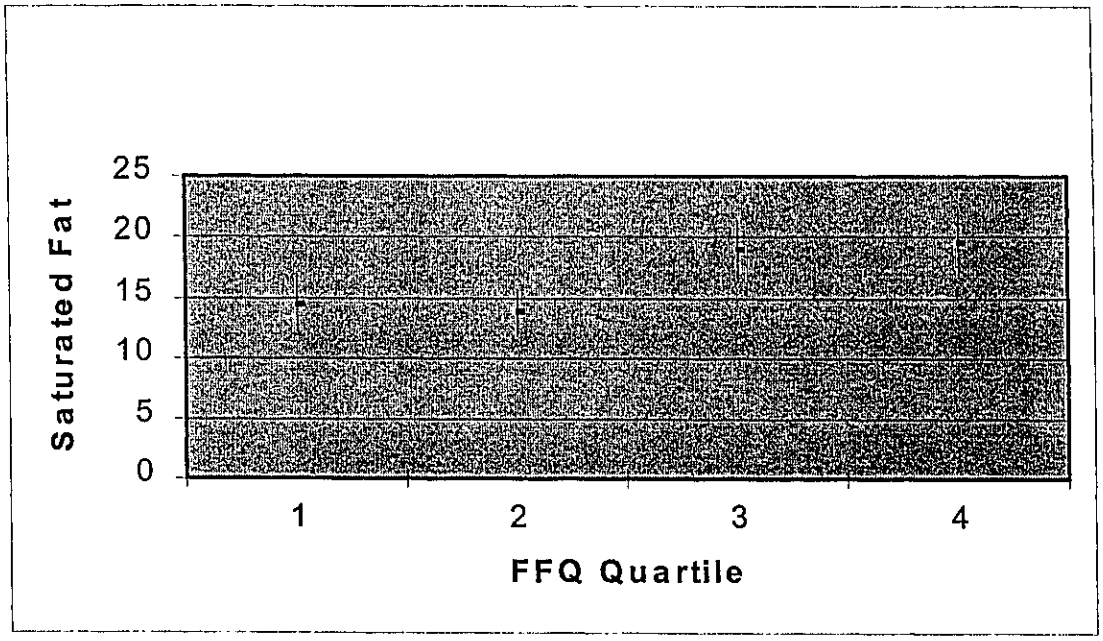


Table 30c: Chinese FFQ

FFQ Quartile	1	2	3	4
Chinese (N/group)	11	19	19	17
Mean Nutrient by Food record (SD) grams/day	15.1 (6.0)	19.4 (6.3)	17.3 (5.8)	23.2 (10.0)
95% CI:	11.0-19.1	16.4-22.5	14.5-20.1	18.1-28.4

Figure 17c: Mean Saturated Fat Intake (FR) by FFQ Quartile among Chinese

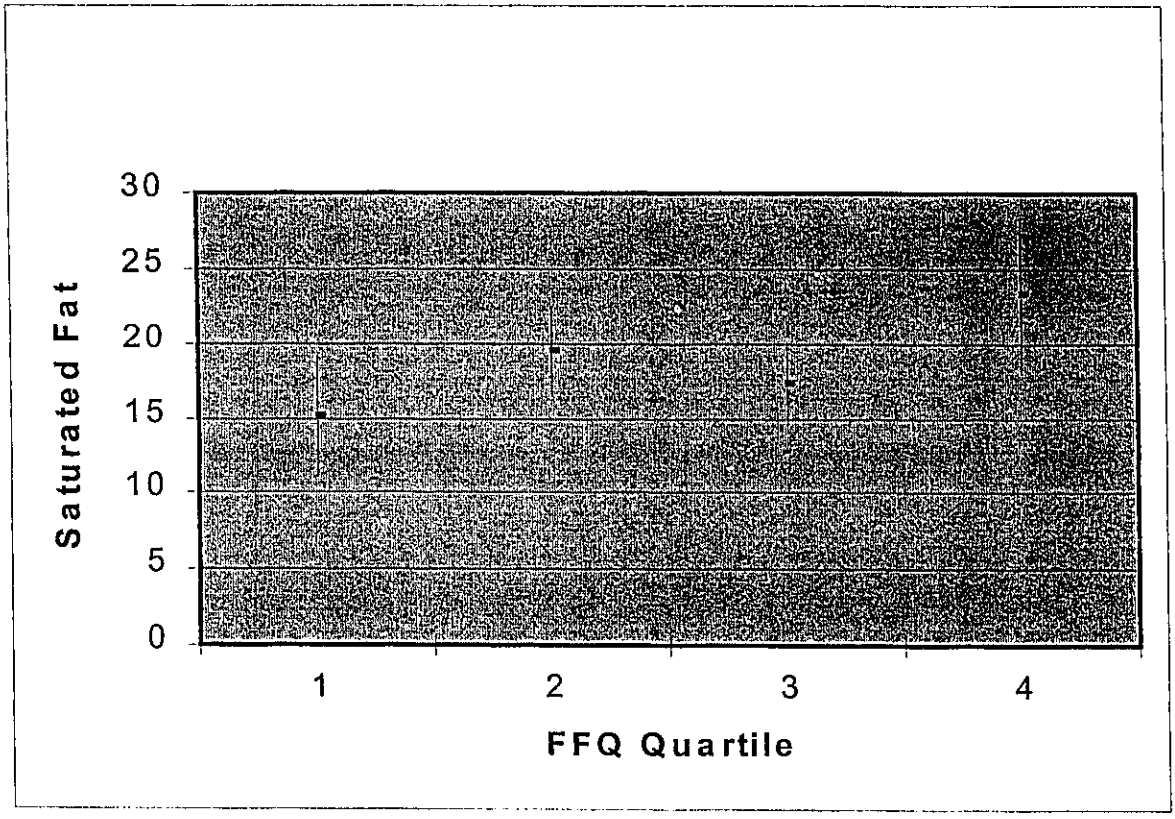
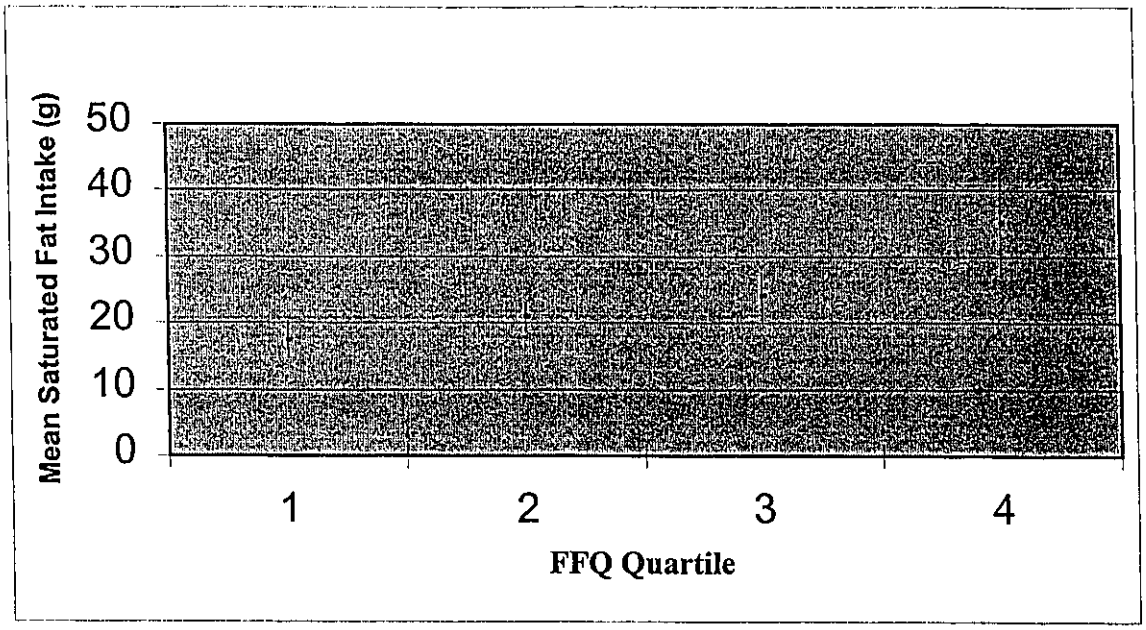


Table 30d: European FFQ

Quartile by FFQ	1	2	3	4
European (N/group)	24	21	24	16
Mean Nutrient by Food record (SD) grams/day	17.5 (6.6)	20.8 (4.7)	23.9 (8.7)	35.0 (14.9)
95% CI	14.7-20.2	18.7-22.9	20.4-27.5	27.0-42.9

Figure 17d: Mean Saturated Fat Intake (FR) by FFQ Quartile among Europeans



Comment:

The FFQ discriminates between people with the highest saturated fat intake and the lowest saturated fat intake, a categorization which is often used when exploring diet and disease relationship. The precision of the saturated fat intake by food records is maximized when the data is examined overall due to larger numbers of participants, yet the trend is present within each ethnic group.

Reliability Testing:

Reliability testing is the process by which the reproducibility of the FFQ is determined. The FFQ will only be deemed valid if it is reliable. Reliability testing is essential to uncover problems in a questionnaire's performance, and it allows the assessment of

dietary changes over time (i.e. seasonal variations). Unfortunately, it is difficult to interpret the reasons for low correlations. Accepted correlations range from 0.4 to 0.7. In SHARE, the FFQ was re-administered to those people who completed the first FFQ and returned the first 7 day food records (Table 32). The approximate time interval between administration of the FFQs was 6 months. The intraclass correlation coefficient (ICC) was used to assess the reproducibility of the FFQ. The ICC will yield a value of 1.0 only if all the observations on each subject are identical, which dictates a slope of 1.0 and intercept of 0. Another desirable feature of the ICC is that it can be used for more than two observations (e.g. if the FFQ was completed more than 2 times) {Bland and Altman 1994}.

Table 32: Reliability of the FFQ

	South Asians			Chinese			Europeans		
	T_1	T_2	*ICC*	T_1	T_2	*ICC*	T_1	T_2	*ICC*
N	58	58		64	64		86	86	
Total Calories	1836.96 (676.37)	1709.87 (614.74)	0.53 (0.22-0.72)	1907.80 (725.34)	1786.60 (839.61)	0.63 (0.41-0.77)	1956.72 (620.58)	1965.77 (928.93)	0.68 (0.51-0.79)
CHO grams	283.68 (103.2296)	265.67 (94.75)	0.52 (0.19-0.71)	241.58 (84.95)	226.09 (106.34)	0.63 (0.40-0.77)	276.28 (94.49)	278.76 (128.03)	0.67 (0.50-78)
Protein grams	63.72 (25.43)	59.59 (20.49)	0.56 (0.27-0.74)	91.31 (43.06)	85.35 (46.95)	0.59 (0.33-0.74)	76.13 (26.11)	75.73 (37.31)	0.64 (0.46-.77)
Sat fat	16.28 (8.05)	15.02 (7.56)	0.64 (0.40 (0.78)	16.35 (8.03)	15.46 (8.08)	0.55 (0.36-0.69)	21.07 (9.43)	20.46 (14.7)	0.70 (0.54-0.80)
Polyunsat fat	10.65 (5.37)	9.87 (4.13)	0.53 (0.21-0.717)	15.56 (7.7)	14.75 (7.96)	0.56 (0.30-0.728)	8.62 (3.46)	8.96 (5.54)	0.70 (0.54-0.80)
Monounsat fat	20.30 (10.15)	21.57 (11.09)	0.43 (0.17-0.60)	25.54 (10.47)	19.02 (7.63)	0.32 (0.10-0.58)	22.11 (9.2)	22.29 (15.87)	0.71 (0.56-0.81)

Legend: ICC: Intraclass correlation, CHO: Carbohydrate, Sat Fat: Saturated fat, Polyunsat fat: Polyunsaturated , Monounsat: Monounsaturated, Numbers in brackets represent standard deviations.

Comment:

The reliability of the FFQs for the major macronutrients carbohydrates, protein and fat are above 0.5 in each ethnic group.

Objective II: Dietary differences between ethnic groups:

The crude and energy adjusted nutrient values for selected items are presented. Depending on the hypothesis being tested, crude energy intake for a given macronutrient versus the energy adjusted nutrient is used. The level of energy may be a primary determinant of disease. Conversely, sometimes it is desirable to employ a measure of nutrient intake that is independent of total caloric intake {Willett 1994}. Most nutrient intake is correlated to total energy intake. This results from the tendency of larger, more active and less metabolically efficient people to consume more food in general. Most components of the diet such as fat, carbohydrates, and protein as well as vitamin and minerals (which do not contribute to energy intake) correlate with total energy intake. If higher absolute nutrient intakes were correlated with disease then those people who consume more food in general for various reasons, should be at higher risk of disease. However, no strong associations in this regard have been observed, which makes it less plausible that absolute nutrient intake is causative of disease. Therefore, adjustment for energy intake is important when studying the direct relationship between dietary components and disease {Willett 1990}.

Various methods exist to adjust nutrient intake for total calories. Two commonly used methods are presented below. First is the residual method, where adjustment for total energy intake is done using a method in which the total calories are regressed on the specific nutrient calories and then the group mean intake of that variable is added to the residuals of each person to produce an energy adjusted value (Figure 18).

Figure 18: Adjustment Method by total Calories

Calorie Adjusted Rice Cals = Residual + Mean Rice Calories of all participants

↓

Residual = Rice Calories - (regression slope x total daily calories + regression intercept)

Regression Line of total cals (x) vs. Rice cals (y)

$y = 0.0297 x + 66.14$

Example

South Asian individual eats 0.85 serving/day = 194 rice calories/day
Daily caloric intake = 810 calories
Mean Rice calories of all people = 124.37 calories/day

Rice Calories adjusted = [194 – (0.0297 x 810) + 66.14] + 124.37
for total calories = 228.17

Multivariate modeling can also be used to energy-adjust nutrients. In multivariate modeling, the absolute nutrient and total energy intake (calories) are both entered as independent variables in a linear regression model with the outcome of interest (in this case atherosclerosis) as the dependent variable. This provides a Beta coefficient for the association between the macronutrient and atherosclerosis, "adjusted" for energy intake (Figure 19).

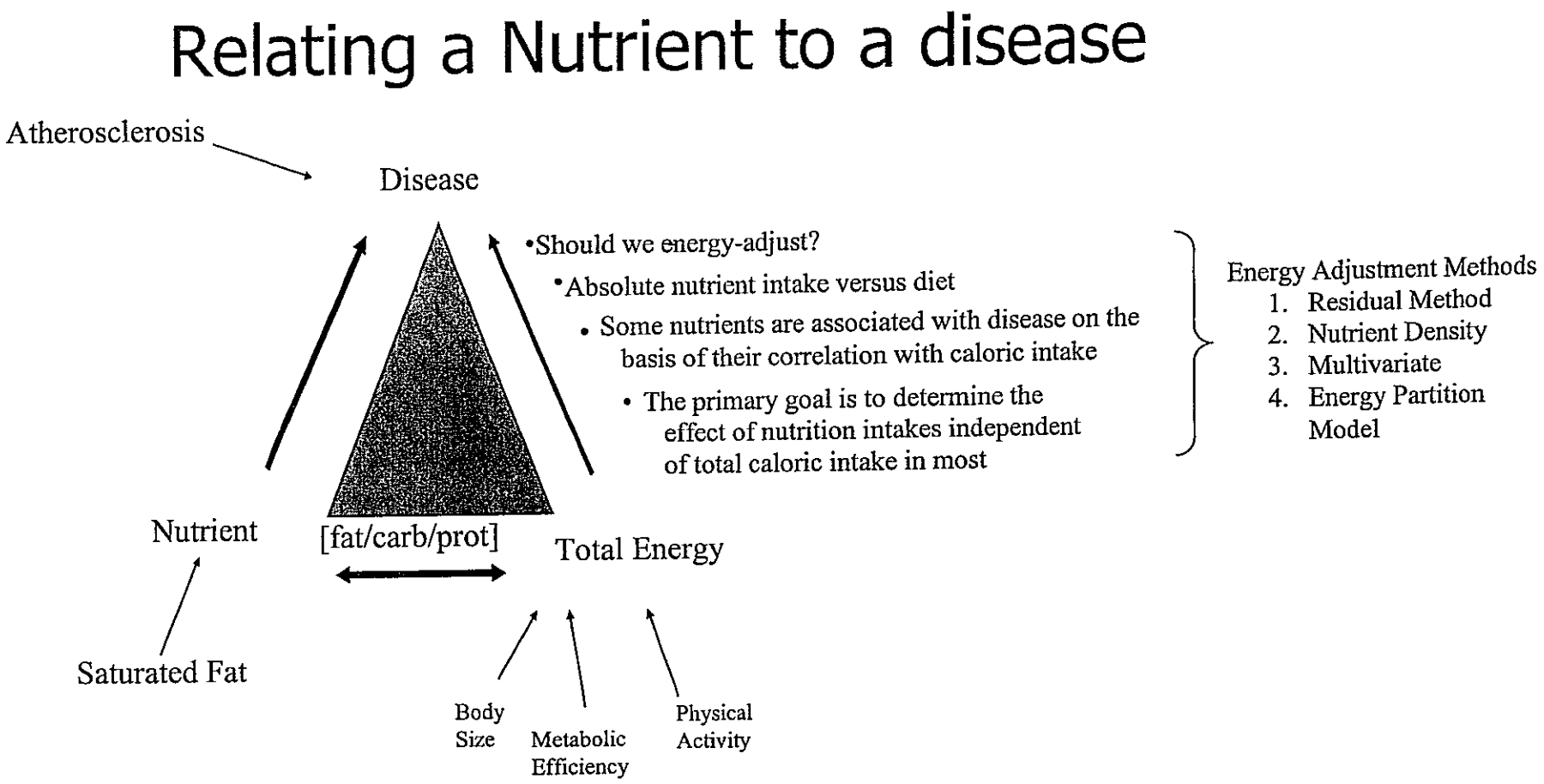
In Table 33, the crude and energy adjusted intakes for the major macronutrients for South Asians, Chinese, and Europeans are provided.

Table 33: Crude and Energy Adjusted Means for Macronutrients using the FFQ

	South Asian Crude	South Asian Adjusted	Chinese Crude	Chinese Adjusted	European Crude	European Adjusted	Overall P
N	313		286		319		
Total Calories/day	1872.3 (780.0)	NA	1904.6 (875.06)	NA	2048.20 (757.20)	NA	SA vs EU=0.02 CH vs EU=0.09
Carbohydrate g	281.9 (112.7)	290.7	234.6 (105.6)	239.4	280.2 (100.4)	267.2	SA vs CH=0.0001 SA vs EU=0.0001 CH vs EU=0.001
Protein g	64.9 (30.41)	68.1	96.3 (51.24)	98.1	81.1 (37.92)	77.00	SA vs CH=0.0001 SA vs EU=0.01 CH vs EU=0.0001
Saturated fat –g	17.8 (11.41)	18.6	15.8 (8.27)	16.2	22.5 (12.44)	21.4	SA vs CH =0.001 SA vs EU = 0.001 CH vs EU= 0.001
Polyunsaturated fat-g	11.1 (5.95)	11.6	16.2 (9.03)	16.4	9.5 (4.60)	8.7	SA vs CH=0.001 SA vs EU=0.0001 CH vs EU=0.0001
Monounsaturated fat-g	21.6 (12.62)	22.6	25.8 (13.95)	26.4	24.0 (12.10)	22.5	SA vs CH =0.001 SA vs EU=0.84 CH vs EU =0.001

G – grams * Adjusted for total calories in ANOVA model

Figure 19: Relating a Nutrient to a disease



Comment:

These data indicate that the macronutrient consumption varies significantly between the ethnic groups. Overall, the Europeans consume the most calories per day, and the South Asians consumed the least. Significantly more daily calories among South Asians and Europeans come from carbohydrates and saturated fat, and significantly lower amounts of calories come from protein compared to the Chinese. The Chinese appear to have the optimal dietary consumption as they consume the lowest amount of carbohydrate, the highest amount of protein, the lowest saturated fat, and the highest consumption of unsaturated fats. The difference in the nutrient densities or relative proportion of calories are from the macronutrients depicted in Figure 20 and Table 34. The food sources of the major macronutrients for each ethnic group are presented in Tables 35a-d.

Figure 20: Proportion of Calories by the major Macronutrients by ethnic group

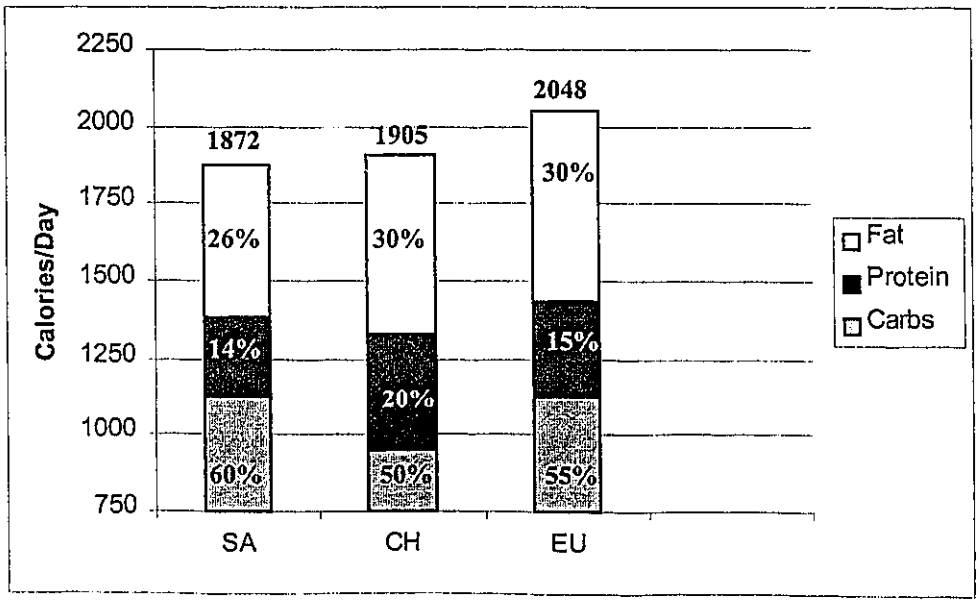


Table 34: Nutrient Densities

	South Asians	Chinese	Europeans
N	313	286	319
Carbohydrate (95% CI)	60% (55-65)	50% (43-55)	55% (48-59)
Protein (95% CI)	14% (10-18)	20% (15-25)	15% (11-19)
Fat (95% CI)	26% (21-31)	30% (25-35)	30% (25-35)
Total Calories/Day	1872	1905	2048

Table 35a: Common Sources of Carbohydrate by Ethnic Group*

	South Asians	Chinese	European
1	Roti, Chapati	Rice, Sticky Rice	Banana
2	Rice, boiled	Banana	Orange, Grapefruit Juice
3	Banana	Citrus Fruit	Bread Rolls
4	Apple, Pear	Colas, non dietetic	Rice, boiled
5	Colas, non dietetic	Apple, Pear	Apple, Pear
6	Orange, grapefruit Juice	Rice Congee	Colas, non dietetic
7	Sugar or Honey	White Bread, Man Tou	Red Wine
8	Lentil/Dal Curry	Orange, Grapefruit Juice	White Bread
9	White Bread	Fried Rice or Chow Fun	Whole Wheat Bread
10	2% milk	Bread Rolls, white flour	Potatoes, boiled

*Ranked by relative contribution to the total macronutrient for the ethnic group from most consumed to least. The amount is based on the frequency of the food, size and the serving, and amount of nutrient in each food item.

Table 35b: Common Sources of Protein for each ethnic group*

	South Asian	Chinese	European
1	Roti Chapati	Fish Soup	Chicken, Turkey
2	Yoghurt Curd	Chicken, only	Ground Beef
3	2% milk	Pork, only	2% milk
4	Lentil/Dal Curry	Rice, plain	Cheese, regular fat
5	Rice	Stir-fried Chicken	Skim Milk
6	Fried Chicken	Stir-Fried Pork	Steak
7	Whole Milk (homo)	Fresh Fish, Fish meat	Pasta with Cheese/meat
8	2% or 1% milk in Tea	Soup, no noodles	Roast Beef
9	Yoghurt	Beef, Veal or Lamb Mutton	Fish, steamed, baked
10	Roast, Tandoori Chicken	2% milk	Pork Chop

Table 35c: Common Sources of Protein By Vegetarian Status for South Asians

	Vegetarian n=58	Non-vegetarian n=255
1	Roti, Chapati	Roti, Chapati
2	Yoghurt, curd	2% milk
3	2% Milk	Yoghurt, curd
4	Lentil/Dal Curry	Fried Chicken
5	Yoghurt, buttermilk	Rice
6	Whole Milk (homo)	Ground Beef
7	Rice	Roast, Tandoori Chicken
8	2% or 1% milk in tea	Lentil/Dal Curry
9	Skim Milk	Other Beef
10	Whole-wheat Bread	Chicken Curry

Comment:

Even when divided by vegetarian and non-vegetarian status most South Asians' top three contributors of protein are Chapati (whole wheat flat bread), yoghurt and milk. There are too few vegetarians in the other groups to examine this relationship.

Table 35d: Common Sources of Total Fat (ranked by amount of nutrient consumption)

	South Asians	Chinese	European
1	Roti, Chapati	Fish Soup	Cheese, regular fat
2	2% Milk	Stir-fried Pork or beef	Ground Beef
3	Yoghurt Curd	Chicken	2% Milk
4	Nuts	Pork (67#)	Egg, fried
5	Whole Milk - homo	Stir Fried Chicken	Chicken Turkey
6	Butter on bread	Fresh-fish, Fish meat	Sausages
7	Fried Chicken	Egg, stir fried	Chocolate
8	Egg, fried	Soup, no noodles	Margarine on bread
9	Lentil/Dal Curry	Chinese mushrooms	Salad dressing

Apart from average macronutrient values computed from the FFQ, information regarding vegetarianism, and the frequency of consumption for specific beverages including alcohol, commonly consumed grains and fruits are provided below (Table 36).

Table 36: Food Frequency Questionnaire Results

	South Asians	Chinese	European	Significance
N	313	286	317	
Vegetarian (Vegan, lacto-veg, and lacto-ovo veg) (%)	58 (18.5)	1 (0.35)	2 (0.63)	0.001
Coffee (Cups/week)	4.53	6.07	20.00	SA vs CH =NS SA vs EU=0.0001 CH vs EU=0.0001
Tea (including green) Cups/week	11.69	0.36	5.49	SA vs CH=0.0001 SA vs EU=0.001 CH vs EU=0.001
White Wine (servings/week)	0.22	0.18	1.14	SA vs CH=NS SA vs EU=0.01 CH vs EU=0.01
Red Wine (servings/week)	0.19	0.23	1.27	SA vs CH=NS SA vs EU=0.01 CH vs EU=0.01
Spirits (servings/week)	0.89	0.11	1.08	SA vs CH=0.01 SA vs EU=NS CH vs EU=0.01
Eggs (servings/week)	1.70	1.97	2.05	0.21
Rice (servings/week)	3.15	6.80	1.37	SA vs CH = 0.01 SA vs EU=0.01 CH vs EU=0.01
Total servings fresh fruit/week	13.79	11.16	13.71	SA vs CH=0.01 SA vs EU=NS CH vs EU=0.01

Comment:

A significant proportion of South Asians are vegetarian, and this helps explain their reduced protein intake. Interesting cultural habits include the relatively high coffee

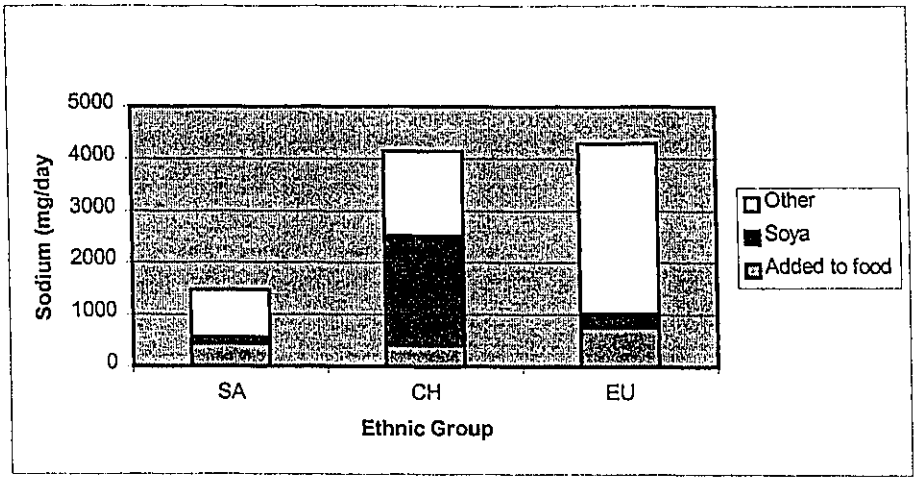
consumption among Europeans and high tea consumption of South Asians. The Europeans consume more alcoholic beverages than do the others, and this correlates well with their alcohol intake as self-reported on the General Questionnaire. The Chinese consume significantly more servings of rice compared to the South Asians and Europeans and significantly less fresh fruit servings per week.

Salt:

Salt (NaCl) is made up of sodium and chloride. One teaspoon of salt is approximately 5 grams of NaCl, and contains approximately 2 grams of sodium. Salt intake is associated with increased blood pressure, CHD, and some gastric cancers {Shetty 1997}. The INTERSALT project was an international co-operative study of electrolyte excretion and blood pressure, involving over 10,000 participants from 52 centres in 32 countries {Stamler 1997, Dyer 1996}. The systolic BP was significantly associated with sodium intake, and inversely with each of potassium intake, body mass, and high alcohol intake. An analysis of observational data of various communities indicated that a reduction in dietary intake of sodium of 100 mmol/24 h (or 3 g of salt – less than 1 teaspoon) lowers systolic blood pressure in subjects aged 50-65 years by 10 mm Hg on average. Much evidence corroborates this estimate, including data from a randomized controlled trial of reduction of intake of salt by older persons {Stamler 1997}. A reduction in blood pressure by 10 mm would reduce age-specific stroke mortality by an estimated 22% and mortality from CHD by 16% {Law 2000, Frost 1991}. In North America over the past twenty years, the increase in fast food consumption has led to an increase in sodium

intake, while the use of salt at the table has declined {French 1999}. Food preparation methods vary considerably between cultures {Hankin 1994}. Traditionally Chinese and Japanese cultures have a relatively high sodium intake given their food preparation methods with Soya and Oyster sauce, as well as fish curing. In SHARE, differences in the amount of Soya sauce and added salt were observed across the groups. The Chinese consumed substantially more Soya sauce compared to South Asians and Europeans, while the Europeans reported adding more salt to their meals compared to the Chinese and the South Asians. When the sodium content across a variety of foods was determined for each ethnic group, the European Canadians consumed the most sodium, followed closely by the Chinese, and the South Asians consumed substantially less sodium compared to either group. The main contributors to sodium intake among the Europeans included adding salt to meals at the table, and consumption of sausages and hotdogs. The largest contributors among the Chinese were Soya and Oyster sauce with cooking, followed by added salt at the table (Figure 21).

Figure 21: Daily Sodium Intake By Ethnic Group



Legend SA: South Asian, CH: Chinese, EU: European, * P<0.001 for CH/EU versus SA

Objective III: Changes with in Diet and Body Weight with Migration:

Changes in dietary intake and body weight have been observed among Japanese migrants from Japan to Hawaii to the United States {Wuetal 1996, Nichaman 1975}. In general, the dietary habits of the migrant group become closer to the diet of the adopted country. Among the Japanese migrants to the US saturated fat intake increased substantially as compared to their original diet. Second generation United Kingdom immigrants from the Caribbean, South Asia, East Africa tended to adopt British dietary patterns of increasing fat consumption and reducing vegetable and fruit, compared with first generation migrants {Landman and Cruickshank 2001}. Chinese women who migrate to western countries also consume more saturated fat, weigh more, and have higher incidence of breast cancer compared to their homeland counter parts {Boyd 1998}. In SHARE,

participants had to have lived in Canada for at least 5 years to be included into the study, so the diet of the new migrant cannot be compared to the well established migrants in the study. It is plausible however that the diet of migrants assimilates to that of the new country over time. In SHARE, this relationship between dietary change and years lived in Canada was assessed. On the FFQ, participants were asked 1. " If you were not born in Canada, can you show us by marking (X) in one of the boxes on this diagram, how you would describe your diet now?" Respondents were given a scale of options from 1 to 10, with 1 being " the usual diet in your country of birth" and 10 being " the type of diet that most people in this country eat". In addition, participants were asked, "What was your diet like during the past year compared to your diet before coming to this country?" [Possible responses included "About the same, a little different, or very different"] (Table 37).

Table 37: Change in Dietary Intake with Migration

Factor	South Asians	Chinese	Europeans
N= in people who were NOT born in Canada	N=308	N=262	N=70
Dietary Change with migration (mean and SD)*$^{\perp}$ (1=no,10=major)	4.82 (1.99)	4.32 (1.98)	5.81 (2.42)
Very different diet now %*	29.4	23.0	39.1
Dietary Change with Years in Canada$^{\perp}$	0.18 (P = 0.09)	0.09 (P=0.43)	-0.25 (NS)
Correlation between BMI and years lived in Canada	0.09 (P=0.09)	0.17 (P=0.003)	0.08 (P=0.13)
Correlation between Abdominal Fat and Years lived in Canada	0.02 (P=0.71)	0.15 (P=0.009)	0.15 (P=0.006)

*SA vs CH =0.01, SA vs EU=0.001, CH vs EU =0.0001; SD: Standard Deviation, $^{\perp}$Age Adjusted

Interestingly, immigrants from European countries reported that their diets had changed the most since coming to Canada, and 39% reported that they had changed their diets dramatically. Chinese reported the least change in their diet since migration, and only 23% expressed that their diets had changed dramatically. One-third of South Asians reported their diets had changed dramatically. The simple correlations, between the duration of time lived in Canada, and the amount of dietary change, were not strong, although significant among South Asians. This indicates that among South Asians their diet changes as they live in Canada longer which is not observed among people of Chinese origin (Table 36). No relationships, between the years in Canada, and the consumption of macronutrients (i.e. calories, fats, carbohydrates and protein), were identified. Increasing body mass index was weakly correlated with duration of years lived in Canada among South Asians and Europeans, although a stronger correlation coefficient was present in among the Chinese ($r=0.17$, $P=0.003$) compared to the other groups. Further, the correlation between increasing waist to hip ratio with increasing duration of time lived in Canada (after adjustment for age) among Chinese migrants was $r=0.15$, 0.009; and Europeans $r=0.15$, $P=0.006$. No relationship was observed among South Asians.

Objective IV: Diet-Disease relationship

One of the main objectives of this study was to examine the relationship between selected macronutrients and arteriosclerosis as measured by the B-Mode carotid ultrasound. In the

1950's a high intake of saturated fat was recognized to be a major risk factor for myocardial infarction and stroke {Keys 1967}. Increased saturated fat intake is associated with increased LDL cholesterol, which is a major contributor to atherosclerosis formation, and ultimately CHD {Ernest 1997}. Previous studies have demonstrated that a significant correlation between saturated fat intake and LDL cholesterol {Keys 1980}, and atherosclerosis {Chambless 1997} exists. More recently, trans-fatty acids have been demonstrated to be atherogenic {Ascherio 1994, Katz 2002}. Dietary trans fatty acids are formed when unsaturated fats are hardened by hydrogenation and when vegetable oils become hydrogenated during frying. They are found in fast foods, baked goods and salad dressings {Katz 2002}. There is relatively limited information regarding the relationship between trans fats among people of varying ethnic origin, and SHARE provides the ideal opportunity to examine this.

In SHARE, the relationship between saturated fat intake and atherosclerosis was examined in univariate and multivariate models. The SHARE FFQ collects information on the "usual diet" of participants and allows a quantitative estimation of saturated fat. The carotid ultrasound measures of the amount of atherosclerosis which has accumulated over time. Therefore neither the FFQ, completed at baseline (prior to the health assessment), nor the carotid ultrasound is subject to any lifestyles changes participants may make after their clinic assessment in SHARE. However participants in SHARE who had suffered a previous clinical cardiovascular event such as a myocardial infarction,

may have altered their diet and lifestyle, and, therefore, these participants will be excluded from the following analysis.

In **Step 1**, the simple correlation between saturated fat intake and atherosclerosis was calculated among SHARE participants who did not have a history of CVD (Table 38).

Table 38: Step 1: Simple Correlation between Saturated fats and Atherosclerosis

Group	Simple Correlation r
SHARE Cohort (n=985-66)	0.016
South Asian	0.02
Chinese	-0.01
European	-0.04

Comment:

The simple correlation between saturated fat and atherosclerosis is weak, and non-significant. Below the scatter plots between saturated fat and mmIMT are provided (Figure 22a-d). Note that there is very little spread in saturated fat grams ingested per day overall and among the ethnic groups.

Figure 22a: Simple Correlation between Atherosclerosis (mmIMT) and Saturated Fat among all participants

N=917, Pearson r =0.025

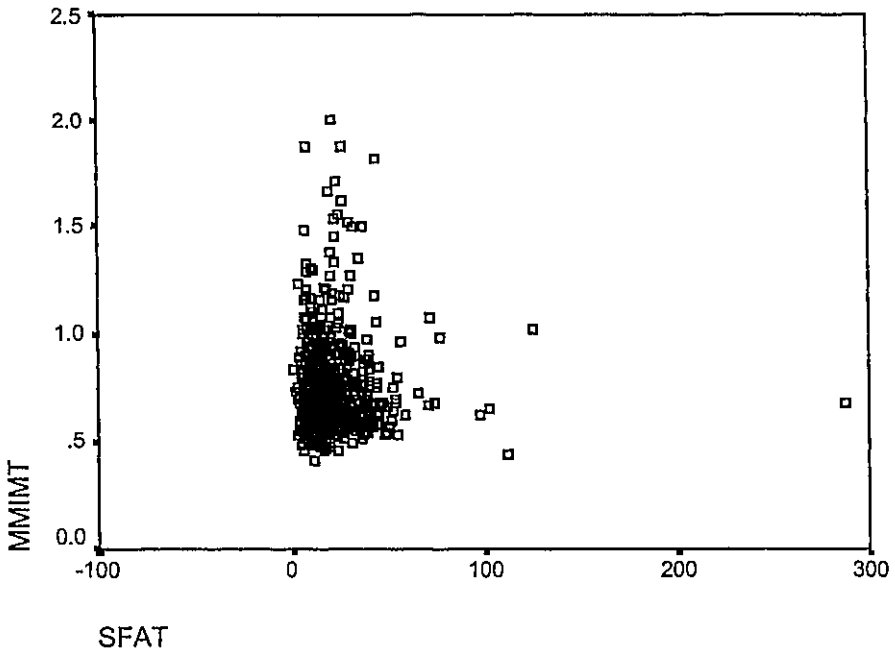


Figure 22b: Saturated Fat and Atherosclerosis (mmIMT) among South Asians

N=307, Pearson r =0.00

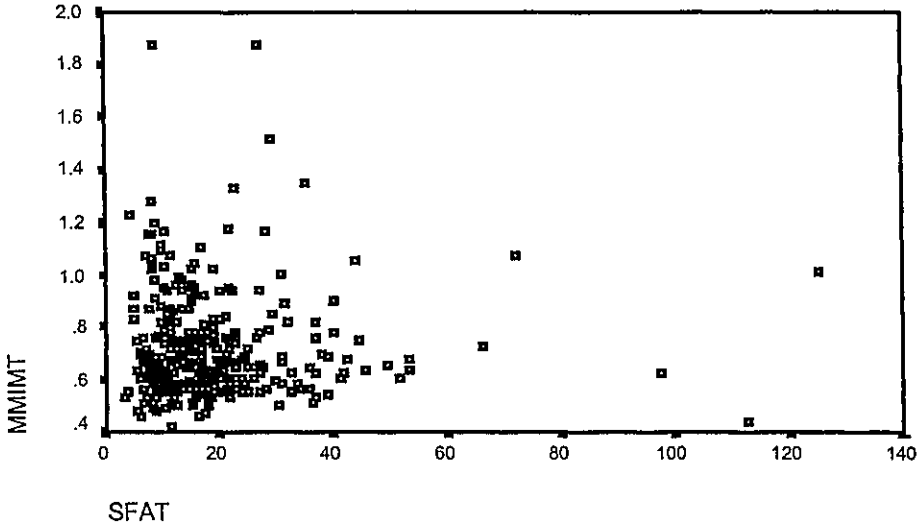


Figure 22c: Saturated Fat and Atherosclerosis (mmIMT) among Chinese

N=316, Pearson r =-0.017

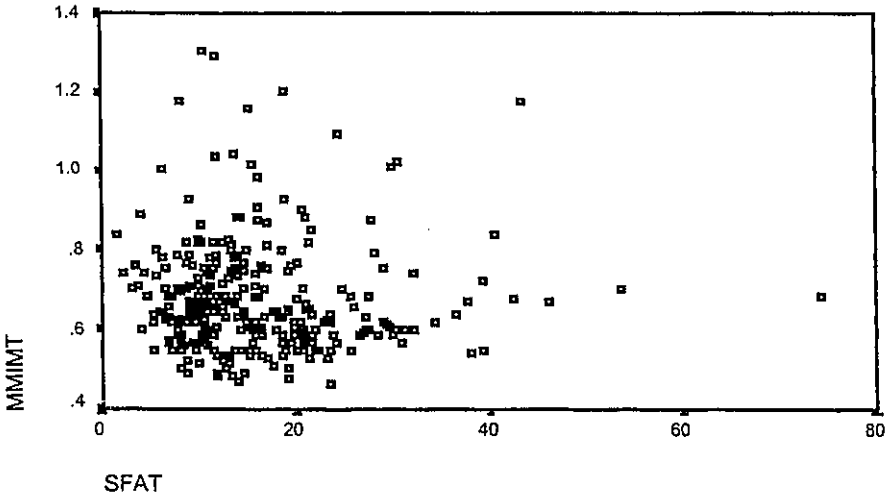
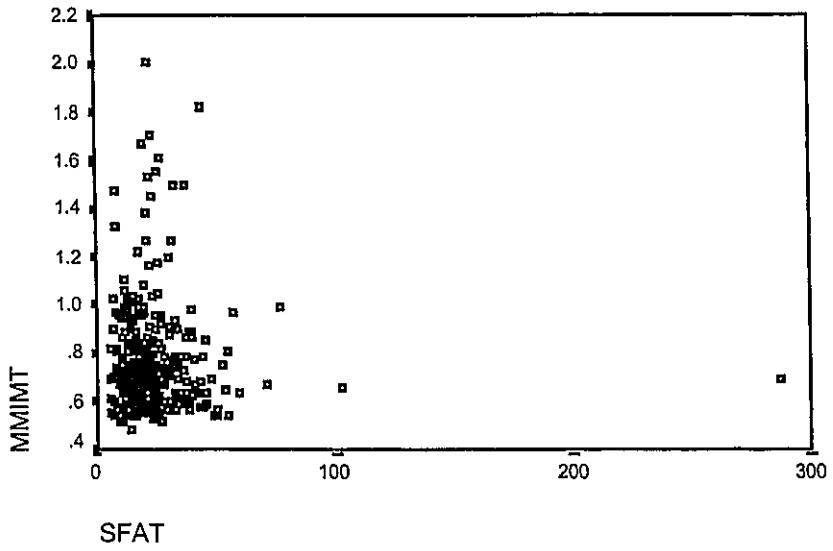


Figure 22d: Saturated Fat and Atherosclerosis (mmIMT) among Europeans

N=310, Pearson r=-0.018



Step 2: Adjustment for Total energy intake

A multiple linear regression model was fit with mmIMT as the dependent variable and saturated fat and energy intake as the independent variables. This provides the "energy adjusted" relationship between saturated fat and mmIMT.

Table 39: Step 2: Energy adjusted relationships of saturated fat and atherosclerosis

	B	Std. Error	Sig.	95% Confidence Interval	
Parameter				Lower Bound	Upper Bound
Intercept	.723	.014	.000	0.696	.751
Sat Fat	0.0013	.001	.142	-4.235E-04	2.944E-03
CALORIE	-0.000018	.000	.152	-4.214E-05	6.574E-06

$R^2 = 0.0028$

Step 3: Addition of age and sex as covariates into the model: With the addition of age and sex into the model saturated fat was a significant and independent predictor of mmIMT. The regression equation became:

[mmIMT = 0.00199 (satfat) + .011 (age) +0.048 (sex)-0.000022 (calorie) +0.115]

Table 40: Step 3: Energy adjusted relationships of saturated fat and atherosclerosis with age and sex adjustment

	B	Std. Error	Sig.	95% Confidence Interval	
Parameter				Lower Bound	Upper Bound
Intercept	.115	.031	.000	5.419E-02	0.176
Sat Fat	1.967E-03	.001	.005	6.101E-04	3.324E-03
CALORIE	-0.000022	.000	.028	-4.189E-05	-2.412E-06
AGE	0.01	.001	.000	9.794E-03	1.186E-02
SEX	0.048	.010	.000	2.824E-02	6.867E-02

R Squared = .356 (Adjusted R Squared = .353)

Step 4: Ethnic group was added to the model to determine if this improved the prediction of mmIMT, and was a significant predictor of atherosclerosis.

Table 41: Step 4: Ethnicity and saturated fat as a predictor of atherosclerosis

	Beta	Std. Error	Standardized Coefficients	Sig.
Intercept	0.29	.033		0.0001
SFAT	0.0018	.001	.152	0.009
CALORIE	-0.000021	.000	-.121	0.039
SEX	0.0499	.010	.136	0.000
AGE	0.0107	.001	.566	0.000
ETHNIC-South Asian	-0.024	0.01		0.06
Ethnic-Chinese	-0.04	0.01		0.001
European	0.0000			

$R^2 = 0.36$

Figure 23: The Regression equations for each Ethnic Group

South Asian: [mmIMT = 0.29+ 0.00181 (satfat) + .011 (age) +0.049 (sex)-0.000021 (calorie) -0.024]

Chinese: [mmIMT = 0.29+ 0.00181 (satfat) + .011 (age) +0.049 (sex)-0.000021 (calorie) -0.043]

European: [mmIMT = 0.29 + 0.00181 (satfat) + .011 (age) +0.049 (sex)-0.000021 (calorie)]

Step 5: Final Model The interaction between saturated fat and ethnic group was tested

No significant interaction between saturated fat and ethnic group was identified.

Therefore the model without the interaction term (Step 4) was the preferred model.

Table 42: Step 5:Testing the interaction between ethnicity and saturated fat on atherosclerosis

Source	df	Mean Square	F	Sig.	Beta	Std Error
Corrected Model	8	1.316	60.856	.000		
Intercept	1	.329	15.233	.000	0.15	0.03
Sat Fat	1	.110	5.064	.025	0.0014	0.001
Calorie	1	0.0702	3.244	.072	-1.96x10-5	0.000
AGE	1	8.664	400.625	.000	0.011	0.001
SEX	1	.505	23.341	.000	0.050	0.010
ETHNIC	2	.101	4.661	.010	SA:-0.025 CH: -0.069	0.02 0.022
ETHNIC * SFAT	2	0.0212	.979	.376		
Error	843	0.0216				
Total	852					

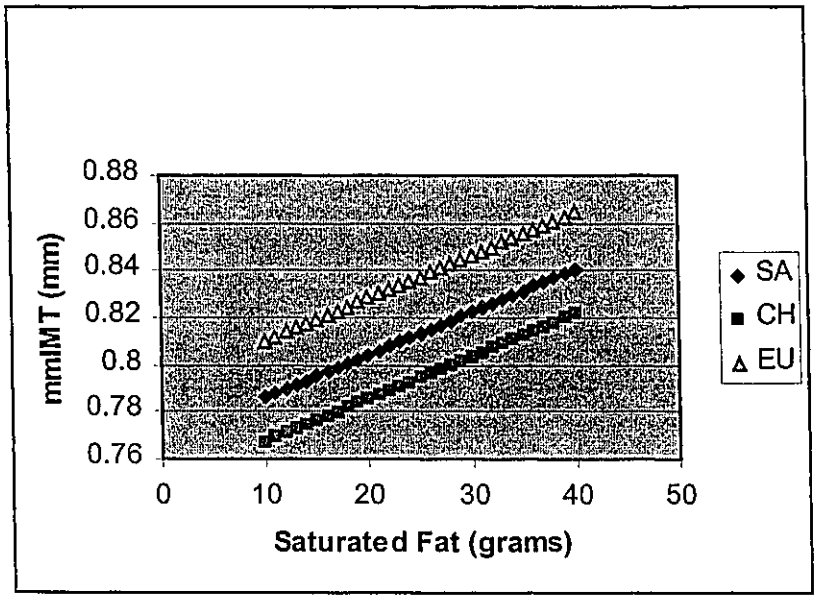
R Squared = .366 (Adjusted R Squared = .360)

Comment:

The simple unadjusted correlation between saturated fat and mmIMT is weak and non-significant. After adjustment for energy intake, age, sex the relationship becomes significant although still remain relatively weak. The relationship between these independent variables and atherosclerosis differ significantly between ethnic groups, and

no ethnic x saturated fat interaction is identified. Therefore, for a given saturated fat intake the increase in atherosclerosis was similar between the groups (Figure 24)

Figure 24: Saturated Fat and Atherosclerosis in 3 Ethnic Groups



Legend: SA = South Asians, CH = Chinese, EU=European
* Based on a 45 year old male who consumes 2000 calories per day.

Trans Fats:

Using the identical stepwise methods in the first example, the relationship between trans mmIMT were higher than the saturated fat correlations, although still relatively weak (Table 43). In the multiple regression model, trans fat did not share an independent relationship with mmIMT, and no significant interaction with ethnic group was identified (Table 44).

Table 43: Correlation between Trans Fatty Acids and Atherosclerosis (mmIMT)

Group	Simple Correlation r
SHARE Cohort (n=985-66)	0.08
South Asian	0.007
Chinese	0.10
European	0.07

Table 44: Multiple Linear Regression of Trans Fatty Acids and Atherosclerosis (mmIMT)

Step	Beta for Trans Fat	P	R^2
mmIMT on Trans Fat	beta=0.029	0.02	0.007
Adjusted by Calories	beta=0.03	0.009	0.008
Adjusted by Calories, Age and sex	beta=0.021	0.05	0.35
Adjusted by calories, Age, sex, Ethnic	beta=0.0085	0.45	0.36
Adjusted by calories, age, sex, ethnic, and testing ethnic x trans fats interaction	beta=0.018	0.96	0.36

Figure 25: Final Equations Trans Fatty Acids and Atherosclerosis

SA: mmimt=0.29 +0.008*trans FAT+0.00000082*calories
+0.010*age+.048*sex (female=1, male=2)-.025
CH: mmimt=0.29+0.008*trans FAT+0.00000082*calories
+0.010*age +.048*sex (female=1, male=2)-.05
EU: mmimt=0.29+0.008*trans FAT+0.00000082*calories
+0.010*age +.048*sex (female=1, male=2)

Discussion of findings:

Validity:

The validity of the three FFQs created in SHARE was assessed by correlation of the FFQ, taken at baseline, with the food records (either 7 or 14 days). The adjusted correlations ranged from 0.29-0.55 among South Asians, from 0.24-0.32 among Chinese and 0.34-0.54 among the Europeans for the major macronutrients. This is in keeping with the finding of other population dietary validation sub studies. Furthermore, the FFQ was able to reliably classify individual into quartiles of macronutrient consumption, which is the principle way the FFQ will be used in future diet and disease studies.

Reliability:

The reliability of the FFQ was tested by administering the FFQ on two occasions to the same people 6 months apart. Although it is possible people may have altered their dietary habits after their baseline clinic visit in SHARE, in general, the intraclass correlations range between 0.43-0.64 among South Asians, 0.32-0.63 among the Chinese and 0.67-0.71 among the Europeans.

Key Dietary Differences:

The major dietary differences between the groups included the Europeans higher consumption of calories compared to the Chinese who had the lowest, and the sources of calories. The South Asians and European consumed more saturated and trans fats than

did the Chinese, and relatively more carbohydrates, whereas the Chinese consumed more protein and unsaturated fats. More South Asians were vegetarian. Europeans consumed more alcohol and sodium.

Migration:

While a large proportion of the South Asian (308/331) and Chinese (262/326) populations were immigrants to Canada, relatively few of the Europeans were (68/342) immigrants. Of the migrants, the Europeans reported changing their dietary habits the most, whereas the Chinese changed the least. Approximately 40% of the European migrants reported dramatic changes in their diets compared to approximately 25% of the immigrant South Asian and Chinese. Therefore, despite 20 years in Canada, over two-thirds of South Asians and Chinese maintained a diet similar to that of their homeland.

Saturated Fat and Atherosclerosis:

The relationship between saturated fat intake (measured by the FFQ) and atherosclerosis (mmIMT) was examined. Although the crude correlations were weak and non-significant, after adjustment for calories, age and gender, saturated fat was an independent predictor of atherosclerosis. No significant saturated fat x ethnic group interaction was detected. Trans fats also showed a weak and non-significant correlation with atherosclerosis, even after adjustment. The atherogenic effect of trans fats may not only increase the amount of arterial atherosclerosis, but may be pathogenic by making the lipid contents plaques soft and, therefore, more prone to rupture {Katz 2002, Ascherio 1994}.

Conclusions:

In summary, while daily food intake is likely to have a profound influence on the development of hypertension, elevated cholesterol, atherosclerosis, and CVD, it is one of the most difficult aspects of "health" to measure precisely. Dietary measurements are challenged by within-person variability in dietary intake (e.g. weekday to weekend day, seasonal change) and between person variability (age, gender, ethnic group, socioeconomic strata). Due to these challenges no perfect dietary measurement tool exists. To study diet-disease relationships, a measurement tool, which can discriminate between high consumers of a macronutrient from low consumers reliably, is desirable. The SHARE FFQ correlates reasonably well with the imperfect, gold-standard food records, and it can classify people by consumption (e.g. high vs low). There are intriguing differences in the dietary intake between people of different cultures who live in the same country. Although some of these differences in macronutrient intake may seem subtle, when applied to a population they may result in substantial differences in disease burden. For example, a 1% reduction in saturated fat intake in a population significantly reduces the number of people who suffer CVD events {Pearson 2001}. The saturated fat intake in SHARE correlates directly with the CVD burden. Therefore although diet-disease investigations require an intensive effort, the information they yield can play a large role in public health and CVD prevention.

CHAPTER 7

MEASURING PSYCHOLOGICAL WELL-BEING

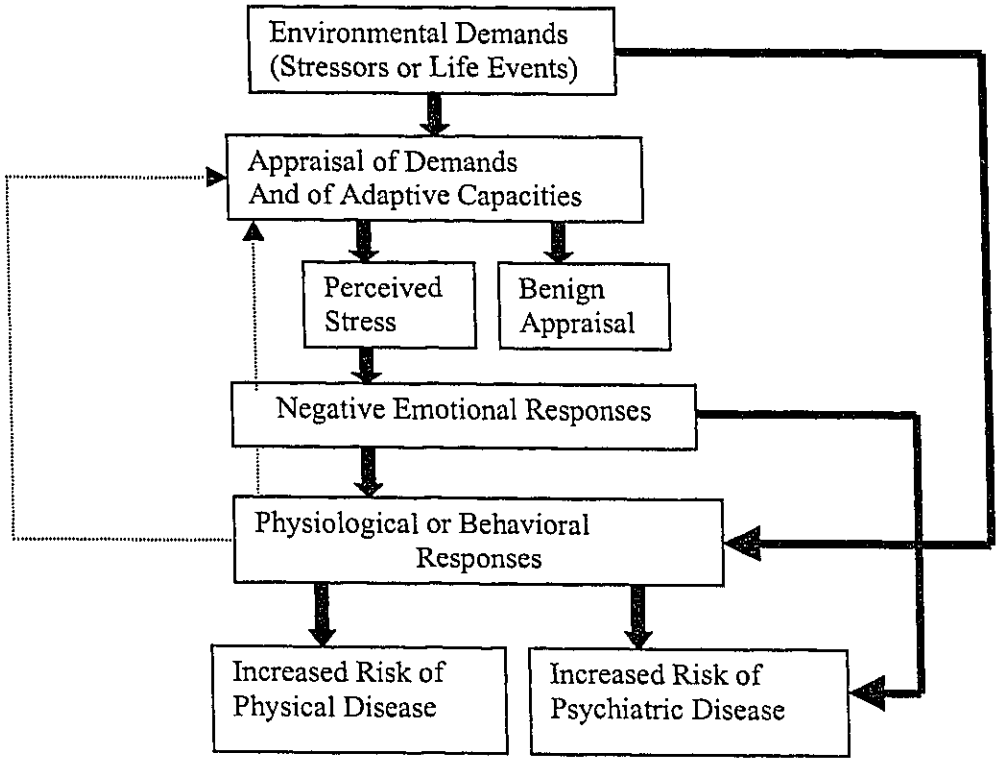
Background:

There is substantial evidence to suggest that cardiovascular disease (CVD) is associated with psychosocial stress factors such as depression, anxiety, poor coping responses, lack of social networks, and hostility {Jenkins 1971 Sesso 1998}. There are many putative explanations for these associations. Some of the biological explanations which have received the most attention include stress-induced increases in i. platelet activity, causing thrombosis {von Kanel, Roland, Mills 2001}, ii. circulating catecholamines, causing cardiac arrhythmias or left ventricular dysfunction {Benedict 1996}, and iii. atherosclerosis as a precursor to clinical vascular disease {Ross 1986, Ross 1999}. However, the results of studies of the association between stress factors and CVD have been inconsistent. These mixed results are due to a combination of factors, including methodologic limitations of the studies (i.e. small studies) and errors associated with measuring psychological stress factors. Both of these factors tend to underestimate the potential association between stress and CVD {O'Malley 2000, Julkunen 1994, Matthews 1998}

A hypothetical model of the patho-biological sequence of events from psychological stress to disease states is shown below. This model, developed by Cohen and colleagues, depicts scenarios in which environmental demands exceed the adaptive capacity of an

organism, resulting in psychological and biological changes that may place a person at risk for disease {Cohen 1983}. The key factors of this process include environmental factors [stressors], which place substantial demands on an individual (objectively), the individual's subjective abilities to cope with these demands [perceptions of stress], and the biological consequences which are influenced by the psychologically demanding conditions [stress responses] – Figure 26.

Figure 26: How Psychological Stress is Associated with Disease



A heuristic model of the stress process designed to illustrate the potential integration of the environmental, psychological, and biological approaches to stress measurement {Cohen, Kessler, Gordon and 1997}.

Objectives:

In SHARE, in order to explore the relationship between psychological stress factors and vascular disease a questionnaire to quantify key stress factors was created. In addition, biomarkers of stress in the circulation were measured. The main objectives of these investigations were:

1) To develop and validate a questionnaire to evaluate psychosocial factors among people of South Asian, Chinese, and European origin living in Canada.

2) To characterize ethnic differences in psychosocial stress factors, and ethnicity-related stress associated with being an immigrant.

3) To determine if psychosocial health is correlated with circulating levels of biomarkers associated with stress (e.g. neurohormones).

4) To explore the association between psychosocial stress factors, circulating biomarkers, and disease outcomes (i.e. atherosclerosis and CVD).

Objective 1: Development and Validation of a Psychosocial Questionnaire:

Measuring Stress:

For the purposes of this investigation, **stress is defined as negative adaptive responses to life events** {Cohen 1983}. In order to efficiently collect information about stress, in a systematic way in a large number of people, a self-administered stress questionnaire was developed. Qualitative data collected in the SHARE pilot study {Anand 1997}, were used to design a questionnaire to evaluate perceptions of job stress, depression, self esteem, inequality in Canadian society, social support, ways of coping and hostility among three ethnic groups within Canada.

Qualitative Data Collection in the SHARE Pilot Study:

Three focus groups were conducted among South Asian, Chinese, and European Canadians (10 per group). Specific probe questions were asked of each group and the discussions which ensued were tape-recorded and transcribed. The probe questions used to guide the discussions are found in Figure 27. These questions were designed to elucidate the reasons for migration to Canada, the differences in their current lifestyle compared to their lifestyle in their home country, the positive and negative attributes of life in Canada compared to their original country, issues around self identity and social support, interactions with local ethnic cultural groups, discrimination in the workplace, job stress, family dynamics, and concerns about the acculturation of their chiidren.

Three reviewers, two study investigators, and one external expert in qualitative research reviewed and coded the transcripts.

Figure 27: Probe Questions in Focus groups

- Factors which lead individuals to immigrate to Canada.
- Perception of South Asian and Chinese as equal members of Canadian society
- Uptake of the host country's cultural practices and change in lifestyle
- Explore the major social support structures of South Asian and Chinese immigrants for both parents and children in Canada (e.g. involvement with local cultural groups, and extended family and friends)
- Personal experiences of discrimination in general and in the workplace

The investigators independently reviewed the transcripts and met on two occasions to code and interpret the text. The major exploratory themes which dealt with acculturation and stressors associated with life in Canada were extracted. The following recurrent themes emerged i) stress at the workplace, ii) loss of social networks with migration, iii) on-going financial stress, and iv) concern about the future prospects of their children. The work-related stressors included on the job relationships with colleagues, stress around balancing work and family demands, and lack of fairness around job promotion. For social networks, many immigrants felt that they had diminished social supports to call upon in times of crisis compared to their social networks in their homelands. For example, some South Asian women recounted that while living in India their extended family including sisters and grandmothers would assist them with child-care, while they

attended university or went to work. However, once in Canada, child-care became more difficult for women. In addition, most immigrants, particularly South Asians and Chinese, expressed their concern about their children's loss of traditional cultural practices and adoption of Canadian characteristics. Despite voicing some of these stressors associated with life in Canada, what emerged from the focus groups from all ethnic groups was the sentiment that the quality of life in Canada was excellent. Further, immigrants felt life in Canada was better for them, and their families compared to life in their homeland.

***Subscales of the Well-Being Questionnaire*:**

In addition to the data obtained from the focus groups, scales measuring depression, coping responses, and hostility were incorporated into the questionnaire given the prior research relating these traits to cardiovascular health {McDowell 1996}. All of the scales (and their various domains) which make up the WBQ are summarized in Table 45.

Job Strain:

Previous research has studied the association between job strain and clinical CVD but the results are not consistent across studies {Johnson 1996, Hlatky 1995, Reed 1989}. Increased job strain has been previously associated with diminished health-related quality of life, including poorer physical functioning (e.g. back strain), social functioning, and mental health. Job strain is also correlated with poor health. {Lerner 1994}. The Job Stress questions were adapted from those used in the National

Table 45: Scales incorporated into the SHARE Well-Being Questionnaire

	Job Stress (NPHS) {Statistics Canada 2002}	General Well Being Schedule {Dupey 1977}	Interpersonal Support Evaluation List (ISEL) {Cohen et al 1985}	Ways of Coping {Folkman, Lazarus 1988}	Anger and Hostility Assessment Scale (AHAS) {Arthur 1999}	Equality Questions (SHARE)
Questions and response scale	13 questions 5 point response scale	12 questions 6 point response scale	20 questions True or False	40 questions 4 point response scale	20 questions 7 point response scale	13 questions Yes/No
Possible Score Range	13-65	12-72	20-40	40-160	20-140	13-26
	Overall Satisfaction	Anxiety	Appraisal	Confrontive	Hostility	Equal Opportunity
	Job Stress	Depression	Belonging	Distancing		Job promotion
		Positive Well Being	Tangible	Self Controlling		Children's Opportunities
		Self Control	Self Esteem	Seeking Social Support		Work Stress
		Vitality		Accepting Responsibility		Language
		General Health		Escape Avoidance		Physical Appearance
				Planful Problem Solving		
				Positive reappraisal		

Population Health Survey (NPHS Website) {Statistics Canada NPHS Website}. These data, and the concern about job stress raised in the focus groups, suggest that psychosocial stress in the workplace may have a significant impact on cardiovascular health.

General Well-Being:

The General Well-Being Schedule (GWBS) was chosen to measure the attributes of depression, self-esteem and well-being. The GWBS has been previously validated in large population-based studies such as the US Health and Nutrition Examination Survey 1 (NHANES 1). Created by Dupey in 1977, the GWBS is a brief, valid, and reliable indicator of feelings of psychological well-being and it incorporates traits such as anxiety, depression, general health, well being, and self control by vitality {Dupey 1977}. The GWBS consists of 18 items, and uses a time frame of the last month. It has been reported to be an excellent general population indicator of subjective well-being because it incorporates questions of depression and self esteem. For these reasons, the GWBS was selected to be the criterion standard against which other subscales could be correlated in the WBQ.

Social Support:

Social support is defined as "a process through which help is provided to, or exchanged with, others in an attempt to facilitate one or more adaptational goals" {Sarason 1991}.

The importance of assessing social support comes from research that has linked high levels of social support to positive health outcomes {Cohen and Syme 1985}. Health outcomes associated with social support include decreased susceptibility to disease, lower cardiovascular reactivity, {Kamarck 1990} enhanced immune function, {Jemmott 1988} better adjustment to and recovery from illness, {Mumford 1982, Trelawny-Ross 1987} lower rates of mortality, {Berkman 1979, Blazer 1982, House 1982} and increased psychological well-being. The "protective" effects of social support may be mediated a) by stress-buffering or b) as a main effect. In the stress-buffering model, social support buffers individuals from the negative effects of stressful events, meaning that, for individuals with high levels of social support, the negative effects of stress are reduced. In the main effect model, social support is viewed as having a beneficial effect on health outcomes whether or not an individual is under stress. The Interpersonal Support Evaluation List (ISEL) has been utilized to measure social support {Cohen, Mermelstein, Kamarck, and Hoberman 1985}. It is a 40-item assessment which measures four main areas of social support. These include tangible support, belonging support, appraisal support, and self-esteem support. Given this information, and the loss of social networks voiced to us in the focus groups, the ISEL was included in the WBQ.

Coping:

Coping definitions share the basic notion that coping is a struggle with demands, conflicts and emotions. Cohen and Lazarus (Cohen and Lazarus 1979) defined coping as the action-orientated efforts to manage environments and internal demands, and conflicts

among them, which tax or exceed a person's resources {Cohen and Lazarus 1979}. They later revised this definition to be the constantly changing cognitive and behavioural efforts to manage specific external and/or internal demands that are appraised as taxing or exceeding the resources of the person {Lazarus and Folkman 1984}. The Ways of Coping (WOC) scale was developed by Folkman and Lazarus in 1988, and incorporates various methods individuals used to deal with stressful situations {Folkman and Lazarus 1988}. There are eight varieties of coping in the WOC questionnaire. These include Confrontive Coping, Distancing, Self Controlling, Seeking social support, Accepting responsibility, Escape avoidance, Planful problem solving, and Positive reappraisal. There is also some evidence that coping responses, to stressful situations, and expression of emotions differ between culturally divergent populations. In some "neutral" cultures such as the Chinese, individuals do not readily show their feelings, while in "affect" cultures (e.g. Italians) individuals are more likely to express their emotions. It is plausible that ethnic groups who are "neutral" have higher anxiety and stress levels because they keep their emotions inside {Kazarian and Evans 2001}. Further, repression of emotions has been associated with increased mortality among men {Kauhenen et al. 1996}. Given this small but intriguing literature, and the lack of information regarding ethnic differences in coping responses, and the relationship of variations in coping responses to health outcomes, the Ways of Coping scale was incorporated into the SHARE WBQ.

Hostility:

Hostility is a negative stress response which has been postulated to be associated with an increase in CVD {Barefoot 1983}. Hostility is a personality and character trait with attitudinal (cynicism and mistrust of others), emotional (anger), and behavioural (overt and repressed aggression) components. {Shekelle 1983} In epidemiological studies, hostility has been frequently measured with the Cook-Medley questionnaire, an empirical scale originally designed to characterize mistrustful attitudes. High levels of expressed anger and hostility are correlated to increased essential hypertension, atherosclerosis progression, coronary artery calcification, coronary artery disease (CAD) morbidity and mortality {Angerer 2000}, {Iribarreb 2000}. However 3 studies have shown no relationship between hostility and CAD outcomes {Leon 1988, Hearn 1989, Helmer 1991}. We used the Anger and Hostility Scale (AHAS) to determine if differences in hostility were identifiable between ethnic groups {Arthur 1999}.

Inequality in Canadian Society:

From the focus group discussions, both the South Asians and the Chinese indicated that although discrimination on the basis of ethnic origin in the workplace and in their daily social interactions was not overt, they perceived it occurred in subtle ways such as denial of job promotion, and job acquisition. To "quantify" these perceptions, questions regarding perceived discrimination in the workplace, and perceived discrimination experienced by themselves and their children were added to the WBQ. The challenge of creating these questions was to ask the same questions of all three groups. Therefore the

questions had to be posed in such a way that people of European origin would also find the questions appropriate.

Methods:

Prior to finalization, the WBQ was pre-tested for content validity by focus group members and a convenience sample of local community members. Based on their comments, minor changes were made to improve the flow and readability of the questionnaire. From February 1997 until October 1998, 762 people completed the WBQ (211 South Asians, 269 Chinese, 282 Europeans) which this represents 762/985 (77%) of the total SHARE population. All WBQ's were self-administered and checked for completion by a study coordinator. Questionnaires were faxed in to the database using the Datafax software. The reliability of the WBQ was assessed in a subset of 100 participants who completed a mailed version of the questionnaire a second time, one month after the initial completion.

Validity Assessment:

Determining if a questionnaire is valid is challenging given that no reference standard exists {Norman and Streiner 1986}. The conventional approach to assess such an instrument is to use indirect methods to determine its validity (i.e. face validity, internal consistency, criterion validity and construct validity) {Norman and Streiner 1986}. A questionnaire is deemed to be of acceptable validity when a plausible and consistent set of data emerges, which provide enough evidence that the questions asked actually tapped

into the intended trait, or traits. The primary intent of the instrument in a population-based study is to be able to discriminate between people who possess various levels of a given attribute, reliably, and if so, the instrument is potentially useful.

Face Validity:

The first level of validity is content or face validity. This is defined as a judgment as to whether the questions included in the questionnaire sample most of the relevant and important content or domains {Norman and Streiner 1995}. This general statement boils down to a judgment that the questions asked look reasonable in the context of the study {Streiner and Norman 1995}. In this regard, the WBQ was pre-tested by focus group participants (5/ethnic group), by the investigators who created the questionnaire, by external people, some of whom were experts in the area {Arthur 1999}, and by community members who were representative of the people who would ultimately be completing the questionnaire.

Internal Consistency:

The second validation method is the assessment of a scales internal consistency. This method evaluates if the responses to questions within a scale are consistent with each other, and evaluates the average correlation among all items in a subscale. For example if an item in the job stress scale asks "Do you enjoy your colleagues at your office?", and another asks "Do you enjoy going to work every day?" one would expect responses to these questions, on a 5 point scale, would be highly correlated. If all items on a subscale

ask the same type of questions, then one would assess the correlation between an item and the overall average score of the scale. There are various ways to calculate such a correlation. The most commonly used is the **Cronbach's Alpha** {Cronbach 1951}. The value of Alpha which is considered acceptable is somewhat arbitrary. However, in general, items should correlate with the total score of a scale with a correlation coefficient of greater than 0.2, and items with lower correlations are usually discarded {Boyle 1991, Nunnally 1978}. The overall Cronbach's Alpha is dependent on the magnitude of the correlation among the items and on the numbers of items in the scale (see formula below). This presents a problem because a scale can be made to look very internally consistent by simply increasing the number of items of the scale. Furthermore, an Alpha which is very high, suggests that some items may be redundant. Therefore it is usually accepted that Cronbach's Alpha should be above 0.7 but probably not higher than 0.9 {Norman and Streiner 1995}.

$$\text{Alpha} = \frac{n}{n-1}\left[1-\sum (SD_{item})^2/(SD_{Total\ Score})^2\right]$$

n = number of items in the scale
SD = Standard deviation

For each WBQ scale, the internal consistency was assessed and the Cronbach's Alphas are shown in Table 2. For each scale, the item-total correlation (ITC) was computed. A small number of items have item-total correlations less than 0.20 and in future

administrations of the questionnaire these items can be discarded. The effect of leaving the item out, on the internal consistency is also shown in Table 46.

Table 46: Internal Consistency of WBQ Scales

	Cronbach's Alpha (95% CI)	Items with low ITC	Adjusted Cronbach's Alpha when item removed
Job Stress	0.61 (0.55-0.65)	Statement E $^{\Psi}$ ITC=0.06	0.65
GWBS	0.87 (0.86-0.89)		
Equality	0.48 (0.40-0.55)		
ISEL	0.73 (0.71-0.74)	Statement M$^{\phi}$ ITC=0.11	0.73
WOC	0.90 (0.89-0.91)		
AHAS	0.72 (0.68-0.74)	Statement 9k$^{\theta}$ ITC = -0.29	0.78

Legend: GWBS: General Well Being Schedule, ISEL: Interpersonal Support Evaluation List , WOC: Ways of Coping, AHAS: Anger and Hostility Scale, ITC: Item-Total Correlation, CI: Confidence Interval, $^{\Psi}$: Statement E: Your job is very hectic , $^{\phi}$ Statement M: If a family crisis arose a few of my friends would be able to give me good advise about handling it, $^{\theta}$: Statement 9K: I am always entitled to give my opinion on things

Comment:

Overall the internal consistency of the scales used was acceptable. When an item had a low ITC, the adjusted alpha when the item is removed is provided.

Criterion Validity:

Another level of validation is known as criterion validity. This refers to the correlation of a scale with some other previously validated scale, which measures the same trait {Norman and Streiner 1995}. In a sense, this previously validated measure is being used as a measuring tool of the true trait and the new scale is being correlated with this accepted standard. Usually the new scale is administered at the same time as the criterion scale, and the criterion validity is assessed by calculation of a Pearson correlation coefficient between the scales (Table 47). For the SHARE WBQ, given that the SHARE population was a random sample from the community as opposed to a hospitalized group, a scale, which did not make continual reference to physical symptoms or emotional stress as they relate to a medical condition, was incorporated. The criterion standard used in the WBQ was the GWBS. This scale has been used previously in the National Health and Nutrition Survey (NHANES) {NHANES Website 2002}. From this survey, the GWBS had acceptable internal consistency and test-re-test reliability. The internal consistency was reported as being 0.93 in 6,900 subjects {Monk 1981}, and the reliability coefficients after a 3 month interval were reported as being between 0.68 and 0.85 for two different groups {Fazio 1977}. The average correlation between the GWBS and other depression scales was 0.69 and the average correlation between the GWBS and 3 anxiety scales was 0.64 {Fazio 1977, Dupuy 1978}.

Table 47: SHARE WBQ: Criterion Validity

Item 1	Item 2	N	$Mean_1$ (SD)	$Mean_2$ (SD)	r	P
GWBS-Positive Well being Questions	ISEL-4 Self Esteem	771	11.98 (2.77)	7.63 (0.72)	0.43	0.01
Work 1 – Job Satisfaction	Work 2-Job stress	539	3.29 (0.65)	44.07 (5.41)	0.43	0.0001

Comment:

Taking into account measurement error associated with assessing the trait of self esteem and job stress, which would tend to attenuate the correlation, the criterion validity correlations are acceptable.

Construct Validity:

Perhaps the most abstract and subjective form of validation of an instrument is construct validity. This approach is used when there is no criterion standard to assess the validity of a new scale. In an assessment of construct validity, responses from the scale in question are related to another scale based on a hypothesized association {Norman and Streiner 1985}. However, if an expected correlation is not observed it is difficult to know if the problem lies with the hypothesis or with the way the particular construct was measured. Thus, this approach is an indirect form of validation. Failure to find a hypothesized association does not disprove the hypothetical association, and may reflect measurement error of a given trait.

Test of Construct Validity in SHARE:

There is evidence in the published literature that people who report greater job stress and have more sick days are more hostile than employees who report lower job stress and fewer sick days. {Levey 2001, Vahtera 2000, Vahtera 2000}. Therefore, it is reasonable to hypothesize apriori that *people who are more hostile will report more job stress* {Vahtera 2000}. In SHARE the correlation between hostility and job stress among 552 people who were actively employed was 0.16, P<0.01. This relationship was significantly stronger among the Chinese compared to the South Asians and Europeans (Table 48a, 48b, Figure 28).

Table 48a: Work Stress and Hostility

	Mean	Std. Deviation	N
Work (NPHS)	46.6	7.75	552
AHAS	84.93	14.3	551

r=0.16, P<0.01

Table 48b: Work Stress and Hostility by Ethnic group

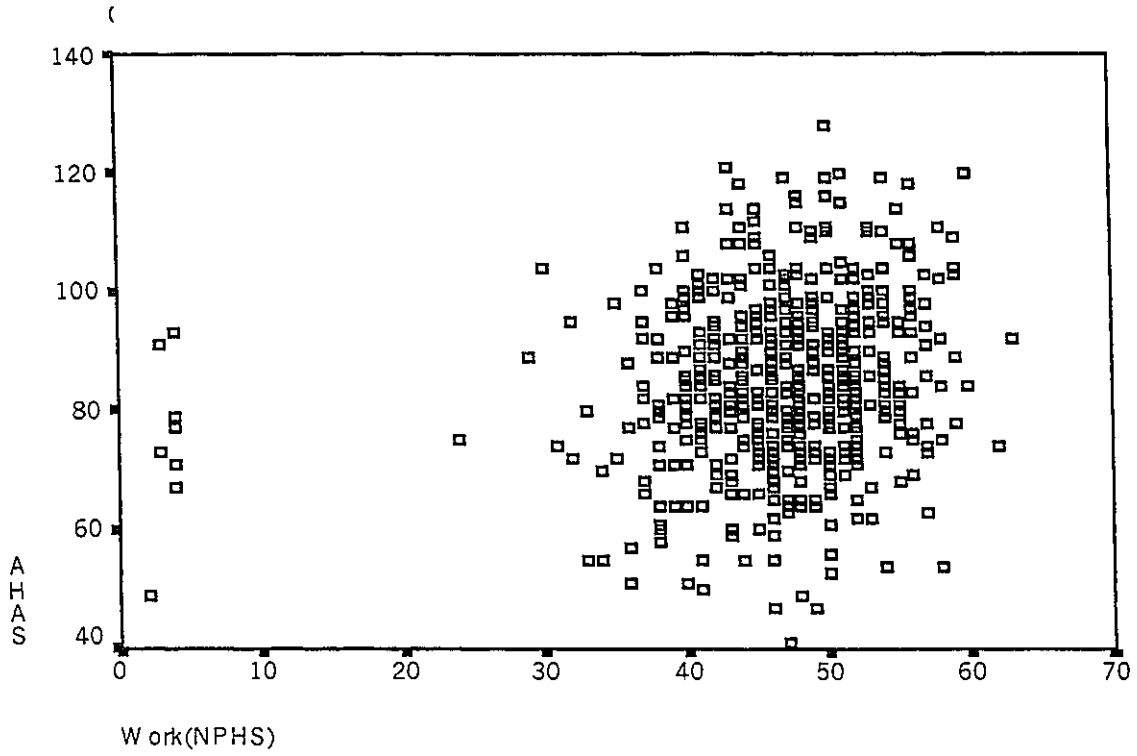
Ethnic	Pearson Correlation	P Value
Overall$^{\Delta}$	0.16	0.01
South Asian	0.11	0.18
Chinese	0.27	0.0001
European	0.16	0.02

$^{\Delta}$Significance Tests for the Post-Hoc Comparisons are corrected using the Bonferonni correction factor

Comment:

The overall correlation is weak (yet significant) at 0.16. This relationship appears to be significantly stronger among people of Chinese origin and weakest among the South Asians.

Figure 28: Correlation between Work Stress and Hostility



Legend: AHAS: Anger and Hostility Scale; NPHS: National Population Health Survey questions about work stress which were incorporated into the SHARE-WBQ

Comment:

Overall, the magnitude of the correlation is weak r=0.16, despite being statistically significant. It is reasonable to conclude, on the basis of the hypothesis that people who report more job stress are more hostile, that construct validity is demonstrated. This analysis may be of limited value given that there is little spread of responses on the work stress scale.

Reliability:

Reliability refers to reproducibility of responses. That is, it describes the agreement between responses given by an individual at one point in time and the responses of the same individual at a later point in time. If the agreement is high, the instrument is deemed reproducible or reliable. If the agreement is poor two possibilities exist. The first is that the instrument itself not reproducible (i.e. misses the target) and the second is that the attribute which is being measured varies naturally over a period of time (i.e. moving target) {Krieger 2000}.

Test/Retest Reliability:

The test re-test reliability was assessed among 100 people approximately 1 month from the time of the initial completion of the WBQ. The results are summarized for each subscale (Table 49).

Table 49: Test Re-Test Reliability for SHARE WBQ

Sub-Scale	N	Time 1	Average Score	Time 2	Average Score	Correlation	P
NPHS Work – sum 5 point scale, higher is better (13 items –max score =65)	69	43.76	3.37	43.61	3.35	0.77	0.0001
Work Satisfaction 4 response options to one question 4=very satisfied, 1 is not at all satisfied	68	N/A	3.23	N/A	3.16	0.75	0.0001
General Well Being Schedule (12 questions, max score=72) 6 point scale 6=good, 1=poor)	102	53.41	4.45	53.44	4.45	0.76	0.0001
ISEL (Social Support (True/False) 20 Questions, max score=40 (2=true, False=1)	103	36.14		36.86		0.87	0.0001
SHARE Equality Questions 3 questions,2=good, 1=bad, max score=6	102	4.71	1.57	4.95	1.65	0.43	0.0001
Ways of Coping (Problem Solving) 4 point scale-7 scales, max score=28	96	25.67	2.14	26.07	2.17	0.61	0.0001
Anger and Hostility 7 point scale, 20 questions, max score = 140	102	86.9	4.35	86.35	4.32	0.68	0.0001

Note: The Test-Retest Reliability of the Equality questions is relatively low. Further when the test-retest reliability of these questions was examined by ethnic group, the low reliability appears to be driven by the low agreement rates among the Chinese (Table 6).

Table 50: Test-Retest Reliability by Ethnic group

Scale	South Asian	Chinese	European
Work	0.84	0.72	0.72
Work Satisfaction	0.82	0.76	0.56
GWBS	0.81	0.65	0.79
ISEL	0.87	0.82	0.42
Equality	0.64	0.16	0.68
WOC	0.58	0.67	0.64
AHAS	0.71	0.56	0.73

Legend: GWBS: General Well Being Schedule, ISEL: Interpersonal Support Evaluation List, WOC: Ways of Coping, AHAS: Anger and Hostility Scale

Note: The reason for the low test–retest reliability for the Equality questions is not clear but may reflect a change in the respondents perception of inequality. For example, the low reliability among Chinese was driven by changes to answers to the questions, "Do you feel you have equal job opportunities compared to all other Canadians?" (Kappa 0.51), and "Do you feel you have equal opportunity for job opportunities or job promotion compared to other Canadians?" (Kappa = 0.59). Both questions offered dichotomous, Yes or No, response options. Previous investigations of self-reported discrimination and health have demonstrated that people who initially stated that they had not experienced ethno-racial discrimination on a questionnaire later said in in-depth interviews that they had experienced such discrimination but found it too hard, too frightening, or too pointless to discuss {Parker 1995}. In addition, asking the question the first time may lead individuals to reflect on the meaning of the question, which influences their response at the second time. Therefore, alternative approaches to assessing inequality which are more sensitive are needed.

Summary on Validity and Reliability of the SHARE WBQ:

In summary, the validity of the WBQ is acceptable based on its face validity, high internal consistency, and criterion validity. The WBQ is generally reliable, with the exception of the comparatively low reliability of the perceived inequality questions, particularly among people of Chinese origin. Given that this is a dynamic construct, increasing the response options to the equality questions from yes/no to multiple responses may improve reliability {Krieger 2000}.

II. Objective 2: Ethnic Differences in Psychosocial Health:

SHARE provides a unique opportunity to examine differences in psychosocial traits between randomly selected groups who are culturally diverse. The psychosocial data collected from participants were extensive and each psychological trait merits in-depth analysis which is beyond the scope of this thesis. For the purpose of this thesis, the main comparisons between group results are presented for each trait and an in-depth analysis is presented for the perceived inequality questions as this represents a new set of questions created for use in SHARE.

In Table 51, selected demographic differences between the ethnic groups are presented. Briefly, the Europeans were older and had lived in Canada significantly longer than the Chinese and South Asians. While fewer Europeans were employed, a greater proportion were retired. As presented in Chapter 5, the South Asians and Chinese had received significantly more university education, yet had lower household incomes compared to the Europeans. The socio-economic index, described in Chapter 5, is a reasonable surrogate for social stability and indicates that, on average, people of European origin had greater social stability compared to the South Asians or Chinese.

Table 51: Demographic Characteristics of the WBQ Respondents

Characteristics	South Asian	Chinese	European	Overall Test of Significance
Age	49.4 (9.8)	47.4 (9.8)	51.2 (9.8)	0.001
Years in Canada	19.5 (10.5)	20.5 (10.6)	44.5 (10.6)	0.001
Female (%)	45.3	48.9	51.8	0.001
Employed or Retired (%)	81.6	85.2	91.4	0.001
University Education (%)	44.4	40.1	32.5	0.006
Professional (%)	34.8	33.8	34.7	0.95
Household income ≥ 60,000 per year (%)	34.7	37.5	57.9	0.0001
Socio-economic Index *	7.4 (2.5)	7.3 (2.5)	8.0 (2.3)	0.0001

Legend: Numbers in parenthesis are standard deviations, * A composite of education, income, marital status, and employment

Job Stress:

On average no differences between ethnic groups in job stress were identified. Yet, for individual questions some significant differences are present and may be informative when explored in future analyses. For example, South Asians and Chinese report they are less likely to learn new things at work, have less decision latitude, and experience more job discrimination than do Europeans (Table 52).

Table 52: Responses to Questions regarding Job Stress by Ethnic Group

	South Asian	Chinese	European	Significance
Overall Score†	46.42 (0.63)	46.17 (0.57)	47.04 (0.56)	0.21
Learn new things?	3.94 (0.07)	4.04 (0.06)	4.24 (0.06)	0.01
Freedom to decide?	3.73 (0.07)	3.77 (0.07)	4.00 (0.07)	0.02
Discrimination?*	3.50	3.55	4.16	0.0001

† Higher score reflects "more" of the trait; * Note this corroborates the responses about discrimination elicited in the Equality section.

General Well-Being:

On average no significant differences in the GWBS were present between the ethnic groups.

Table 53: General Well Being Schedule Results by Ethnic Group

	Mean	Std. Error	95% Confidence Interval	
Ethnic Group			Lower Bound	Upper Bound
South Asians	53.72	.61	52.52	54.92
Chinese	53.32	.54	52.25	54.39
Europeans	53.33	.52	52.31	54.35

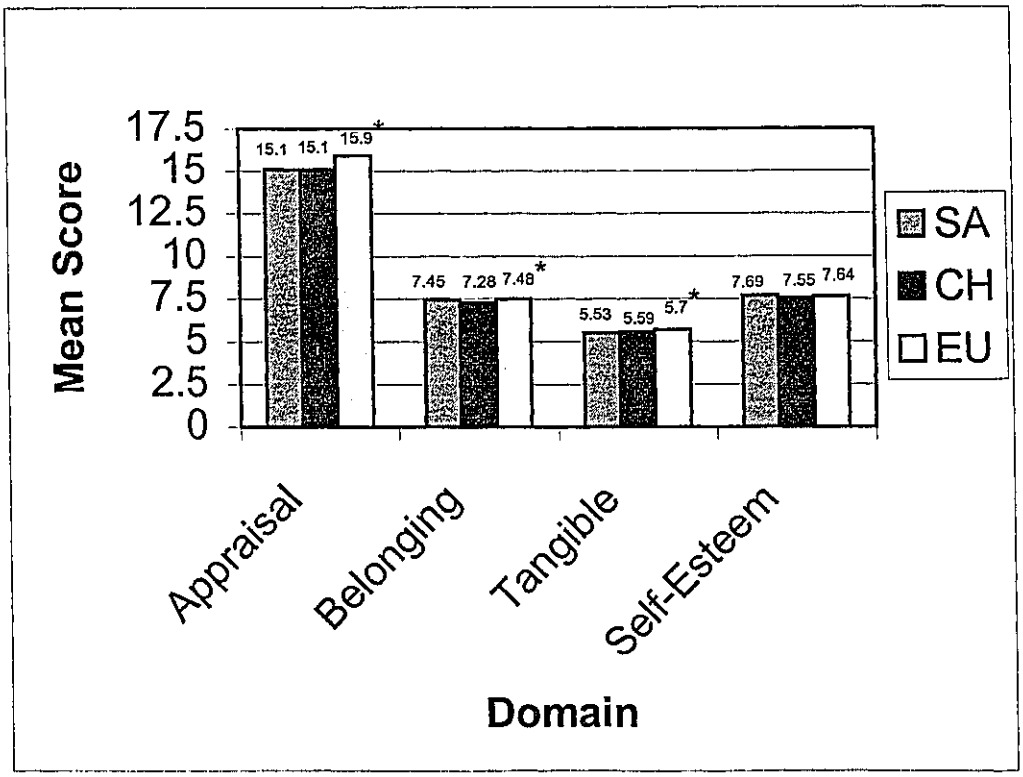
Comment:

No difference in the average score between ethnic groups is present. Overall P=0.86

Social Support:

On average, the Europeans had greater social support for the domains of appraisal (e.g. someone to talk to about one's problems), sense of belonging (e.g. people one can do things with), tangible social support (e.g. social networks), and a trend toward more self-esteem social support (e.g. a positive comparison when comparing oneself to others) (Figure 29). This is not unexpected, given that Europeans and their families have lived in Canada longer than South Asians and Chinese and so should have a greater extended family, and sense of belonging in Canada compared to the South Asians and Chinese.

Figure 29: Social Support By Ethnic Group

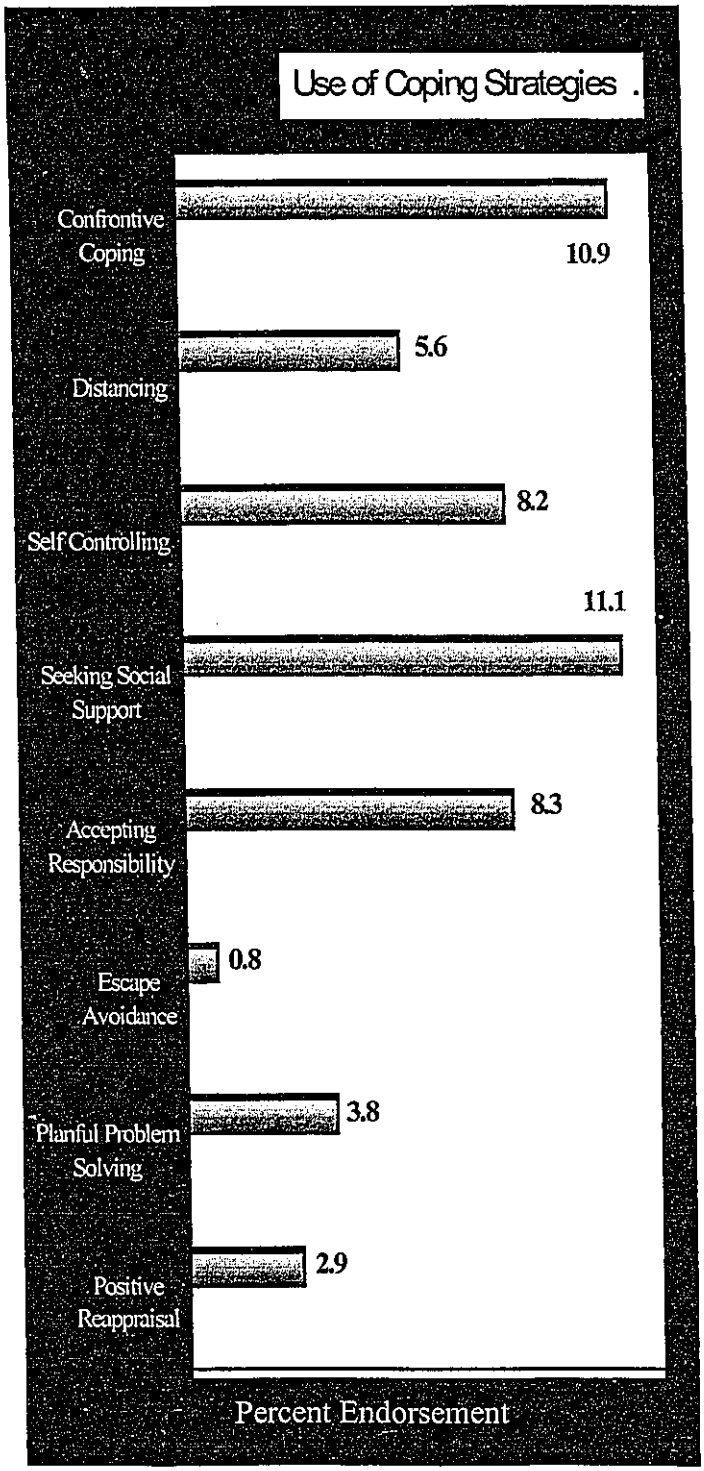


Legend: Appraisal: Someone to talk to about problems, Belonging: People to do things with, Tangible: Social Networks, Self Esteem: Positive self-assessment compared to others
* EU > CH/SA. P<0.05

Ways of Coping:

In the Ways of Coping Questions, respondents were asked to think of an on-going, specific stressful situation or a stressful situation that occurred in the past 1 month. Therefore, the coping traits are elicited as "episodic" because they elicit strategies that people actually use to deal with a particular stressful situation. The most commonly endorsed coping strategies, overall, were confrontive coping, self-controlling, seeking social support, and accepting responsibility (Figure 30). South Asians endorsed these significantly more often than the Chinese or Europeans. For each coping domain (confrontive, distancing, self-controlling, seeking social support, accepting responsibility, escape avoidance, planful problem solving, positive reappraisal) the European group scored lower than did the South Asians and the Chinese. It should not be interpreted that Europeans did not cope with stress, but rather that they were less likely to endorse the 8 potential coping strategies when under stress.

Figure 30: Use of Coping Strategies



Legend:

Scale 1: *Confrontive Coping* - Describes aggressive efforts to alter the situation and suggests some degree of hostility and risk taking.

Scale 2: *Distancing* - Describes cognitive efforts to detach oneself and minimize the significance of the situation.

Scale 3: *Self-Controlling:* Describes cognitive efforts to regulate one's own feelings.

Scale 4: *Seeking Social Support:* Describes efforts to seek informational support, tangible support, and emotional support.

Scale 5: *Accepting Responsibility* – Acknowledges one's own role in the problem with a concomitant theme of trying to put things right.

Scale 6: *Escape-Avoidance* – Describes wishful thinking and behavioural efforts to escape or avoid the problem.

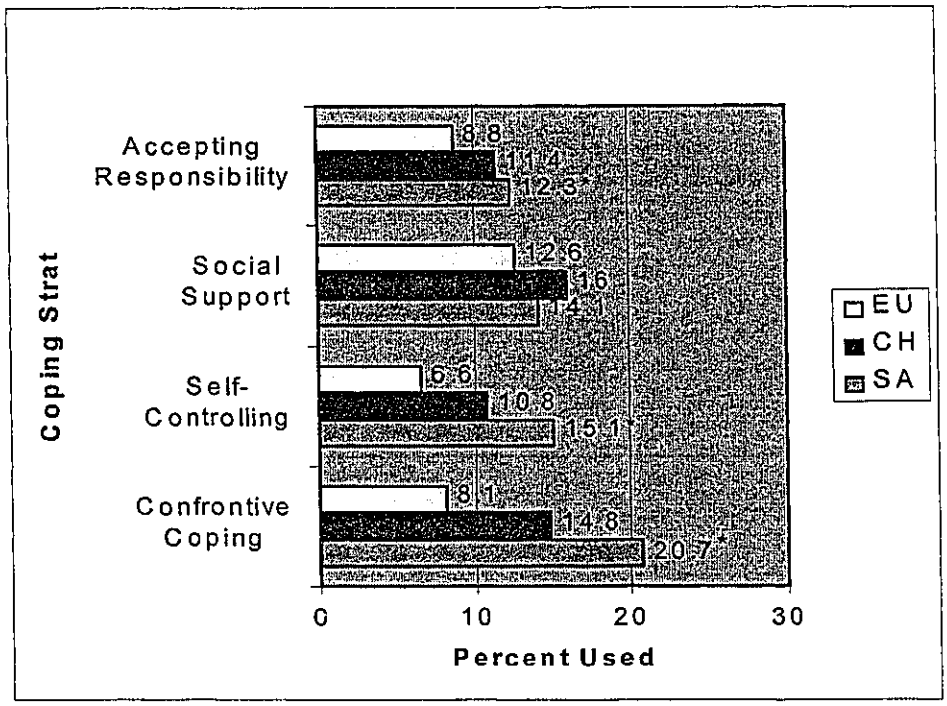
Scale 7: *Planful Problem Solving* – Describes deliberate problem focused efforts to alter the situation, coupled with an analytic approach to solving the problem.

Scale 8: *Positive reappraisal* – Describes efforts to create positive meaning by focusing on personal growth, and also has a religious dimension.

Comment:

Overall, the endorsement of the Ways of Coping strategies is low, with percentages ranging from 0.8 to 11.1%. This may reflect that participants use coping strategies which were not covered in this questionnaire, or that respondents were too sensitive to tell their true feelings. Hence, the social desirability bias may be operational. The ethnic differences for the most commonly used coping strategies are shown below in Figure 31. South Asians used accepting responsibility, self-controlling, and confrontive coping significantly more than the Chinese and Europeans.

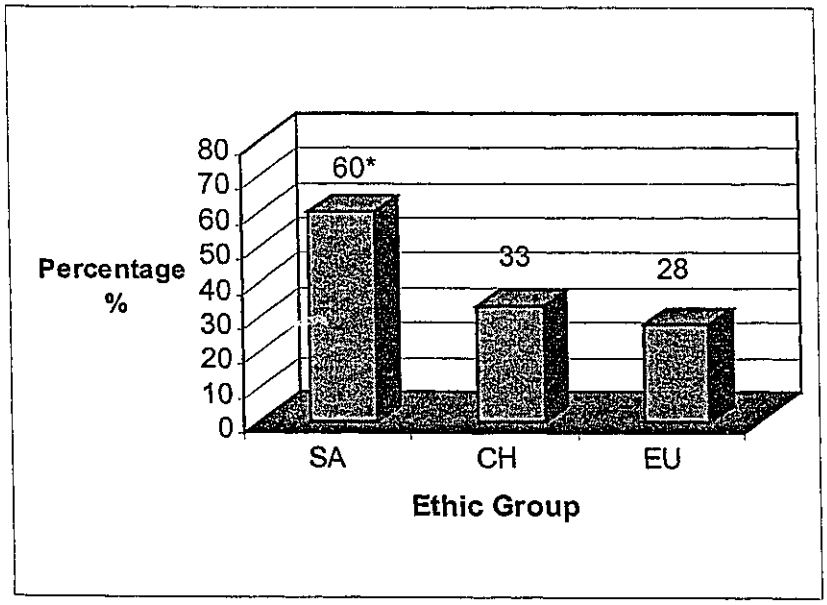
Figure 31: Coping Strategies by Ethnic Group



Legend: Accepting Responsibility: Acknowledges one's own role in the problem with a concomitant theme of trying to put things right, Seeking Social Support: Efforts to seek informational support, tangible support, and emotional support, Self-Controlling: Describes cognitive efforts to regulate ones own feelings, Confrontive Coping: Aggressive efforts to alter the situation and suggests some degrees of hostility and risk taking. * Overall $P < 0.05$

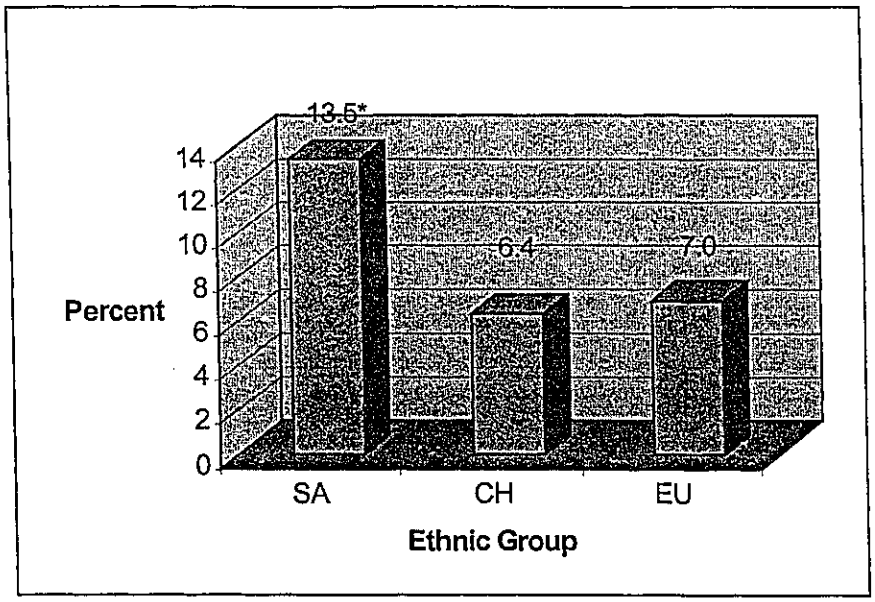
Notable differences were apparent between ethnic groups in terms of coping mechanisms which were used. A large proportion of South Asians (men and women) reported using prayer in response to stressful situations compared to the Chinese and Europeans (Figure 31). As well, a slightly greater proportion of South Asians (mostly men) turned to eating, drinking, smoking, drug or medication use to deal with stressful situations (Figure 32a, 32b).

Figure 32a: Use of Prayer in Stressful Situations



*Overall P=0.001

Figure 32b: Coping using Addictions



Addictions: Eating, drinking, smoking, using drugs, or medications
* P=0.01, SA: South Asian, CH; Chinese, EU: European

Hostility:

It is plausible that increased hostility might contribute to the development of coronary atherosclerosis through associated poor health habits (i.e. greater alcohol intake and tobacco use) which may be used by hostile people, or alternatively via other physiological mechanisms. For example, a number of recent investigations have found relationships between hostility and cardiovascular reactivity, blood pressure morning surge, {Pasic 1998}, increased platelet activation {Markovitz 1998}, and reduced beta - adrenergic receptor responsiveness {Suarez 1998}. Epinephrine is a recognized platelet activator {Larsson 1989, Douma 1992}, and hostile individuals show a marked increase of catecholamine levels during psychological stress {Suarez 1998}. In addition, previous

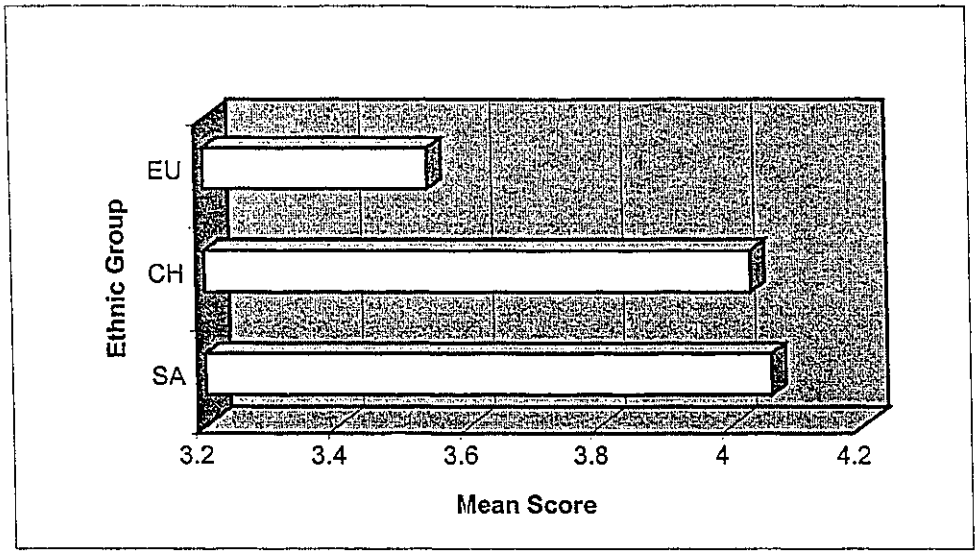
studies have shown that hostile persons have a propensity toward prolonged neuroendocrine responses to either psychological stressors or chronic stress associated with frequent and prolonged bouts of anger {Suarez 1997}. Among the 772 individuals sampled in SHARE, the South Asians and Chinese were more hostile compared to people of European origin (Table 54). This may reflect i) the true variation in hostility, ii) have occurred by chance, or iii) reflect an "ethnic-bias" in the set of questions used to measure hostility, given that the AHAS was developed for use among white Caucasians {Arthur 1999}. It is possible that the way in which the questions were framed elicited different scores {Kaheman and Tversky 1984} among the immigrant groups compared to the European group. For example, the statement, "When I play, I play to win" may be interpreted by some people as being a factual statement rather than having the tone of competitiveness (Figure 33). This possibility may be best explored by conducting in-depth interviews with representative members of each group to develop an understanding of how they interpret this statement.

Table 54: Hostility Score by Ethnic Group

Overall	South Asians	Chinese	European
N=772	210	268	294
85.68 (14.41)	84.02 (15.62)	84.40 (14.35)	88.02 (13.25)

**Overall P=0.002, Post-Hoc comparisons with Bonferroni correction SA vs EU = 0.006, CH vs EU, P=0.008. Note: The lower the score the greater the hostility

Figure 33: Hostility Example Questions



Overall P = 0.001, SA vs EU = 0.004, CH vs EU=0.003, SA vs CH=1.0

Perceived Inequality:

Public health methodology presently lacks a standardized methodology to measure self-reported experiences of discrimination {Krieger 2000}. There are relatively few studies (20 studies) in the public health literature in which instruments are used to measure self-reported experiences of discrimination. As a proxy to evaluate differences between ethnic groups and health, researchers have used indirect measures such as health care utilization data subdivided by ethnic groups. {Kreiger 2000} However, such analyses are potentially confounded and are not an adequate proxy for perceptions of discrimination, and the psychological stress associated with such perceptions. Prior direct measures of perceptions of discrimination have been associated with the adverse health outcomes of depression and psychological distress {Kreiger 2000}. Unfortunately, there has been very

little validation of these questions, which limits their use in large scale epidemiologic studies {Krieger N 2000, Schuman 1985, Jackman 1994}.

The SHARE Equality questions were designed to ask questions regarding perceived inequalities in Canadian society, in a standardized manner across 3 ethnic groups. The questions address perceived discrimination in the work place, for participants' children, and about perceived discrimination of physical appearance and language. The specific questions asked of all respondents are shown in Figure 34.

Figure 34: SHARE Equality Questions

- Do you feel you have equal job opportunities compared to other Canadians?
  Yes __, No__, If no: Better ___, Worse__
- Do you feel you have equal opportunities for job promotion compared to all other Canadians?
  Yes __, No__, If no: Better ___, Worse__
- Do you feel your children have the same opportunities as other Canadian Children in the areas of
  - Education? Yes ___ No___
  - Participation in after school activities? Yes ___ No___
  - Interaction with other children? Yes ___ No___
  - Future employment? Yes ___ No___
- Would you prefer your children to marry someone from your own cultural community? Yes ___ No___ Does Not Matter ___
- Do you expect your children to marry someone from your own cultural community?
  Yes ___ No___
- Do you feel comfortable bringing your traditional food to the workplace for lunch?
  Yes ___ No___ N/A ___
- Do your children object to bringing traditional food to school for lunch?
  Yes ___ No___ N/A ___
- My English embarrasses me when I talk to people
  Yes ___ No___ N/A ___
- My English embarrasses my children
  Yes ___ No___ N/A ___
- People treat me differently because I speak with an accent
  Yes ___ No___ N/A ___
- People treat me differently because I look different
  Yes ___ No___

Results - Employment Inequality:

Participants were asked two questions regarding their employment opportunities in Canada (Figure 34). Overall, 22% (172/775) of respondents perceived they had inferior

employment opportunities, and 25.9% (201/775) felt they had unequal opportunities for job promotion. Significantly more South Asians (28.2%) and Chinese (29.1%) Canadians perceived this more often than did European Canadians (11.6%), overall P<0.0001. A similar pattern was observed for opportunities for job promotion: South Asian (28.2%) and Chinese (35.8%) more often felt they had less opportunity for promotion compared to European Canadians (15.3%), overall P<0.0001. These perceptions of inequality may also be influenced by other factors such as education level, income and employment, and the local environment (i.e. city of residence). The influence of these factors on the association between ethnicity and negative employment perceptions was examined using multiple logistic regression. For job opportunities, the significant independent determinants of a negative perception of job opportunity included Chinese ethnicity, city of residence (Hamilton and Toronto being worse than Edmonton), a yearly household income of less than $60,000, and a shorter duration of residence in Canada (Table 55). For job promotion, Chinese ethnicity, city (Hamilton and Toronto), and household income of less than $60,000 per year remained significant predictors (Table 56). Gender was not associated with these perceptions. Therefore, while the association between Chinese ethnicity and inequalities in job acquisition and promotion remained significant, the association between South Asian ethnicity and these perceived inequalities weakened after addition of other inter-related factors (Table 55, 56).

Table 55: Unequal Job Opportunities

Variable	Odds Ratio	95% CI	P
Chinese vs. European	1.99	1.08 - 3.64	.03
South Asian vs. European	1.75	.94 - 3.28	.08
Hamilton vs. Edmonton	1.75	1.12 - 2.72	.01
Toronto vs. Edmonton	1.80	1.15 - 2.81	.01
Income Less than $60,000/year vs. > 60,000/year	1.94	1.29 - 2.92	.01
Years in Canada (per year)	.98	.96 - .99	.04
Employed vs. Unemployed	1.25	.79 - 1.98	.34
University Education vs. non University Education	.95	.62 - 1.46	.81
Professional vs. non professional	1.23	.78-1.91	.37
Gender: Females vs. males	.99	.68-1.44	.97

Legend: CI: Confidence Interval

Table 56: Unequal Job Promotion

Variable	Odds Ratio	95% CI	P
Chinese vs. European	2.74	1.37-3.35	.001
South Asian vs. European	1.30	.87-4.21	.09
Hamilton vs. Edmonton	2.23	1.47-3.38	.0001
Toronto vs. Edmonton	1.75	1.14-2.70	.01
Income Less than 60,000 vs. > 60,000/year	1.64	1.12-2.39	.04
Years in Canada (Years)	.993	.97-1.00	.17
Employed vs. Unemployed	1.00	.64-1.56	.99
University Education vs. No University Education	1.03	.69-1.55	.88
Professional vs. Non-Professional	1.05	.69-1.59	.81
Gender: Females vs. Males	1.09	.77-1.55	.63

Legend: CI: Confidence Interval

Inequality Based in Ethnic Characteristics:

Overall, 11% (108/744) of Canadians reported being treated differently because of their physical appearance. This was reported more frequently by Chinese Canadians (22%), intermediate among South Asians (18%) and significantly less often by European Canadians (3.7%), overall P<0.001. Eleven percent (109/762) of people perceived they were treated differently because of their accent when speaking English. This was felt most often by Chinese (26.4%) and South Asians (15.6%) compared to the Europeans (1.8%), overall P<0.001. Consistent with this, more Chinese Canadians reported that their children were embarrassed by their parents' accents (11.5% Chinese vs. 5.7% South Asian vs. 0.7% Europeans, overall P<0.001). Further, 15.7% of South Asians, 8.2% Chinese and only 1.8% of European responded that they were uncomfortable (P=0.001) bringing their traditional food to the work place. Interestingly, South Asian and Chinese parents reported their children were sometimes uncomfortable bringing their traditional foods to school, 35.1% of South Asians, and 19.5% of Chinese compared to only 3.6% of Europeans (P=0.001)

Expectations and Challenges for the Children:

Almost all participants, irrespective of ethnic origin, felt their children had equal opportunities for education, extra school activities, and future employment (97% South Asian, 97% Chinese, 98% European). Overall, 40% of parents (311/733) stated they would prefer their children to marry someone within their own cultural community, and 46% (329/715) expected that their children would marry someone from a similar ethnic

origin. South Asians held this belief most strongly 64% (121/190) compared to Chinese (45%) and Europeans (33%), overall P<0.001. Similarly, 66% (122/185) of South Asians reported they expected that their children would marry within their own cultural community compared to 45% (106/235) of Chinese, and 43% (101/235) of Europeans, overall P<0.001.

Summary:

There are significant differences in perceived opportunities for employment and promotion between Canadians of varying ethnic origin, particularly among Chinese Canadians. This is influenced by the city of residence, income, and the length of time immigrants have lived in Canada. In addition, South Asian and Chinese Canadians perceive they are treated differently on the basis of their physical appearance and, in the case of Chinese Canadians, on the basis of their accent when speaking English. South Asians are more likely to feel uncomfortable bringing their traditional foods to the workplace, as are their children. On the positive side, all participants irrespective of ethnic origin, are optimistic about the future opportunities for their children in Canada.

Objective 3: Correlations between Stress and Physiologic Markers of Stress:

The relationship between stress (subjective) and biologic parameters (objective) was examined. The hypothesis was that people who report more negative responses, such as depression, hostility, anxiety, low self esteem, and job stress would have higher

concentrations of nor-epinephrine, a catecholamine released by activation of the sympathetic nervous system which is believed to be turned on by acute triggers (i.e. fight or flight response) but may be chronically stimulated in response to negative stress responses {Suarez 1998}. This chronic elevation of nor-epinephrine may be associated with physiological changes such as increased heart rate, increased ventricular arrhythmias, increased left ventricular mass, and increased atherosclerosis {Schachinger 2001, Ueno 1997, Zhang 2001}. Second, cortisol is secreted from the adrenal cortex in response to activation by the pituitary hormone corticotropin (ACTH), which is also elevated in times of stress {Turner 2002}. It is plausible, therefore, that people with increased levels of stress have higher levels of cortisol. In SHARE, variations in neurohormones were examined overall and by ethnic group.

In Tables 57 and 58, the relationship between stress factors and neurohormones is presented. All of the subscales were scored so that the higher the summary score the lower the negative stressor. This was done to simplify the interpretation of responses in the analysis, although on the questionnaire, questions are formatted in a random fashion (see WBQ in Appendix) to reduce the chance of "acquiescence bias" {Couch and Keniston 1960}. This bias is also known as the "yea-saying" or "nay-saying" bias and occurs when people respond to a series of questions in a similar way irrespective of the content of the item, to the point that contradictory statements are endorsed. Below are the results of the correlation between the average score for a given trait and nor-epinephrine level. Inverse correlations depict the relationship of interest. No strong and significant

correlations between stress response variables and nor-epinephrine levels were identified overall or within a particular ethnic group. A weak correlation (r=-0.19) was observed between work satisfaction and norepinephrine concentration among between of European origin.

Table 57: Simple Correlations between Subscales and Nor-epinephrine Concentration

	Overall N=444	South Asians	Chinese	European
Work Stress	-0.03	-0.01	-0.01	-0.11*
Work Satisfaction	-0.05	0.02	0.03	-0.19
GWBS	-0.004	-0.04	0.11	0.01
ISEL	-0.02	0.01	-0.09	0.02
WOC	-0.03	0.08	-0.03	-0.07
AHAS	0.04	0.05	0.04	-0.003

Legend: GWBS: General Well Being Schedule, ISEL: Interpersonal Support Evaluation List, WOC: Ways of Coping, AHAS: Anger and Hostility Scale, *P<0.05

Overall there were no strong correlations between urine cortisol concentration and stress factors.

Table 58: Simple Correlations between Subscales and Urine Cortisol

	Overall N=772	South Asian	Chinese	European
Work Stress	.01	-0.14	.08	.03
GWBS	.04	.06	.07	-.006
ISEL	.005	.09	-.05	-.01
WOC	.02	.06	.004	.002
AHAS	.002	.10	.04	-.10

Legend: GWBS: General Well Being Schedule, ISEL: Interpersonal Support Evaluation List, WOC: Ways of Coping, AHAS: Anger and Hostility Scale

Differences in Neurohormones by Ethnic group:

The concentration of nor-epinephrine was significantly higher among South Asians and Europeans compared to the Chinese, after adjustment for age. (Table 59) No differences in the urine cortisol concentration were observed between the groups. (Table 60)

Table 59: Nor-Epinephrine [reference range: 1.27-2.81 nmol/L]

	Overall	South Asian	Chinese	European	Significance
N	806	158	239	237	
Mean (SD)	1.82 (1.03)	1.93 (1.05)	1.62 (0.93)	1.82 (0.96)	0.004
Ln (SD)	0.46 (0.53)	0.53 (0.50)	0.34 (0.55)	0.47 (0.52)	0.001

Legend : Ln : Natural log; Post Hoc Comparisons: SA vs CH: P=0.001, SA vs EU: P=0.85, CH vs EU: P=0.02

Table 60: Cortisol [reference range: 30-300 nmol/day]

	Overall	South Asian	Chinese	European	Significance
N	964	201	269	293	
Mean (SD)	191.7 (166.7)	199.3 (185.2)	185.2 (142.4)	189.4 (181.5)	0.77
Ln (SD)	5.0 (0.7)	5.0 (0.7)	5.0 (0.7)	5.0 (0.7)	0.84

Legend : Ln : Natural log

Comment:

South Asians and Europeans have a significantly higher concentration of nor-epinephrine compared to the Chinese, while there was no difference in the urinary concentration of cortisol.

Objective 4: The relationship between stress, atherosclerosis and CVD

Stress and Atherosclerosis:

One of the hypotheses at the outset of SHARE was that increased negative stress such as work-related stress, low social support, and hostility, would be positively correlated with atherosclerosis.

The Atherosclerosis Risk In Communities (ARIC) was a large cohort study of 10,801 men and women, in which the relationship between occupational stress and atherosclerosis (measured by B-mode carotid ultrasound) was examined {Muntaner 1998}. Negative associations between the complexity of work and skill discretion and atherosclerosis (as measured by the mean IMT of the carotid artery wall) were reported. However, after adjustment for conventional cardiovascular risk factors, the magnitude of these associations was substantially reduced {Muntaner 1998}. Work- related stress has also been correlated with atherosclerosis (measured by mmIMT) among men but not women in a randomly selected cohort of 573 employees of a utility company in the United States {Nordstrom 2001}.

The correlations between stress and atherosclerosis in SHARE are presented. All of the subscales were scored so that a high summary score represented the positive aspect of the trait. For example, a high score on the hostility index indicates low hostility, while a high score in the General Well Being Schedule represents high general well being. Therefore,

inverse correlations depict the relationship of interest. No significant inverse correlations between stress and atherosclerosis were observed overall or within ethnic groups, yet some trends were observed (Table 61). Surprisingly, some positive and significant correlations were observed, indicating that in some scenarios people with greater psychological well-being had more atherosclerosis.

Table 61: Correlations between mmIMT and Adaptive Responses

Subscale	Overall	South Asian	Chinese	European
	N=733	N=200	N=263	N=270
Work Stress	0.03	0.04	0.10*	-0.01
Work Satisfaction	0.10	0.13	0.07	0.05
GWBS	0.15*	-0.01	0.19*	0.15*
ISEL	0.04	-0.03	-0.09	0.07
Equality	0.10	-0.12	0.03	-0.04
WOC	-0.03	-0.10	-0.04	-0.09
AHAS	0.08	-0.02	0.08	0.03

Legend: GWBS: General Well Being Schedule, ISEL: Interpersonal Support Evaluation List , WOC: Ways of Coping, AHAS: Anger and Hostility Scale *P<0.05

Nor-epinephrine and disease outcomes:

Increased plasma nor-epinephrine concentrations are associated with increased mortality in patients with heart failure. In the Studies of Left Ventricular Dysfunction (SOLVD) trial, neurohormonal levels were elevated in patients with asymptomatic left ventricular

dysfunction, and this suggested that neurohormonal activation preceded the development of symptoms {Benedict 1996}. Nor-epinephrine was measured in 514 patients enrolled in the SOLVD prevention trial who had low left ventricular ejection fractions and who did not require treatment for congestive heart failure. Norepinephrine levels above the median of 393 pg/mL were associated with a relative risk of 2.59 (P = 0.002) for all-cause mortality, 2.55 (P = 0.003) for cardiovascular mortality, 2.55 (P = .005) for hospitalization for heart failure, 1.88 (P = 0.002) for development of heart failure, 1.92 (P = 0.001) for ischemic events, and 2.59 (P = 0.005) for myocardial infarction {Benedict 1996}. Further, there is evidence from animal and human studies that adrenergic hormones have a trophic effect on arterial intimal cells {Zhang 2001}, that patients who have suffered a myocardial infarction or stroke have elevated levels of adrenergic hormones as late as one-year after the event {Hauss 1990}, and the rate of recurrent MI is decreased in patients who have suffered an acute MI who are treated with beta-blockers {Yusuf 1985}. Therefore, it is possible that nor-epinephrine may contribute to the development of atherosclerosis.

Nor-epinephrine and Atherosclerosis:

The association between norepinephrine and atherosclerosis was explored in SHARE. No significant association between nor-epinephrine levels and atherosclerosis (P=0.22) (Table 62), and no significant interaction between ethnicity and norepinephrine levels with atherosclerosis were observed (P=0.53) (Table 63). Furthermore, atherosclerosis does not increase with increasing nor-epinephrine concentration by quartile (Figure 35).

Table 62: Neurohormones and Atherosclerosis

	Beta	Std. Error	Sig.	95% Confidence Interval	
Parameter				Lower Bound	Upper Bound
Intercept	0.73	.05	.000	.6	.82
NOREPI	8.299E-03	.01	.30	-7.572E-03	2.4E-02
AGE	1.188E-03	.001	.13	-3.664E-04	2.7E-03
SEX	-5.389E-02	.02	.000	-8.402E-02	-2.4E-02

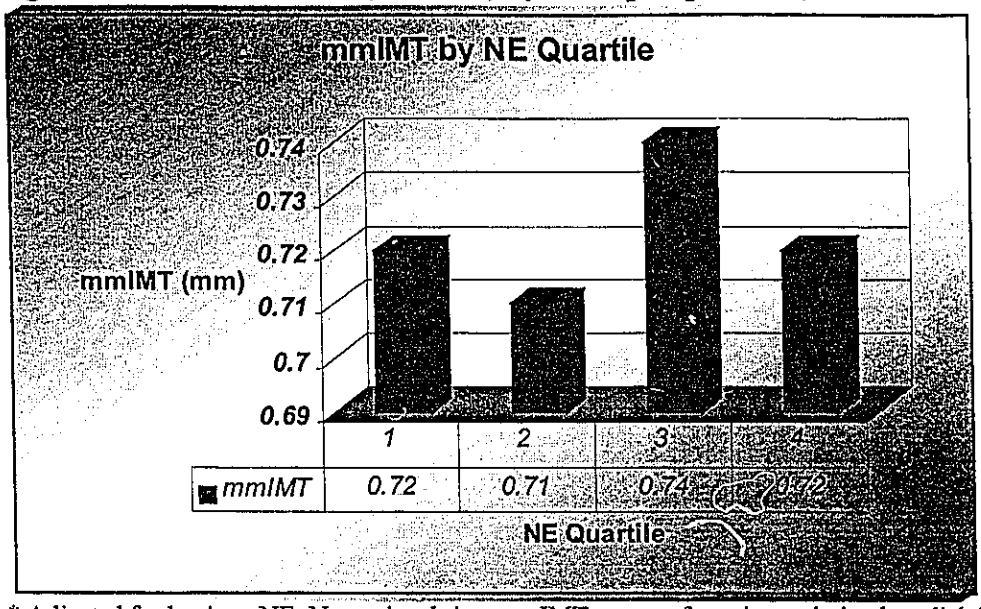
R Squared = .026 (Adjusted R Squared = .021)

Table 63: With Ethnic, and Ethnic x Nor-epinephrine interaction

Source	Sum of Squares	df	Mean Square	F	Sig.
Corrected Model	1.5	7	.22	6.3	.000
Intercept	9.1	1	9.1	257.8	.000
NOREPI	1.4E-02	1	1.4E-02	.40	.53
AGE	.11	1	.13	3.2	.07
SEX	.45	1	.45	12.7	.000
ETHNIC	.40	2	.20	5.7	.003
ETHNIC * NOREPI	4.4E-02	2	2.2E-02	.63	.53
Error	21.8	617	3.6E-02		
Total	348.4	625			

R Squared = .066 (Adjusted R Squared = .056)

Figure 35: Atherosclerosis (mmIMT) by Nor-epinephrine Quartile



* Adjusted for by Age; NE: Nor-epinephrine, mmIMT: mean of maximum intimal medial thickness

Nor-epinephrine and CVD:

The nor-epinephrine concentration in participants in SHARE who had suffered a previous CV event was compared to nor-epinephrine concentration among people with no established CVD. Nor-epinephrine was significantly increased (0.66 nmol/L) in those people with established CVD compared to those people who had not suffered a prior CV event (0.45 nmol/L), P = 0.007. When examined using logistic regression, after adjustment for age and sex, nor-epinephrine concentration was a significant predictor of CVD. For every 1 unit increase in nor-epinephrine, the odds of CVD increase by 2.64 times (Table 64).

Table 64: Relationship between Nor-epinephrine and Cardiovascular events

	B	S.E.	df	Sig.	Exp(B)	95.0% C.I.for EXP(B)	
						Lower	Upper
SEX(1)	.028	.352	1	.936	1.028	.516	2.049
AGE	.003	.017	1	.862	1.003	.970	1.037
NOREPI	.973	.347	1	.005	2.646	1.342	5.219
Constant	-3.539	.899	1	.000	.029		

Legend: CVD: Cardiovascular Disease – Prior diagnosis of myocardial infarction, stroke, angioplasty, coronary artery bypass graft surgery, or silent MI

Ethnic Variation in Nor-Epinephrine:

Given that nor-epinephrine concentration is increased among people with CVD, and among South Asians, the concentration of nor-epinephrine by ethnic group was examined after removing those individuals who had suffered cardiovascular events. Even after removing people with CVD, South Asians (0.53, 95% CI: 0.44-0.61) had significantly higher norepinephrine concentration compared to Chinese (0.33, 95% CI: 0.27-0.40) (P=0.007), and South Asians trended toward being higher compared to the Europeans (0.46, 95% CI: 0.39-0.53) (p=0.27). The Chinese had significantly lower nor-epinephrine compared to Europeans, P=0.01

Given the difference in norepinephrine concentration between the groups, and its association with CVD, the interaction between norepinephrine and ethnic group with CVD was explored. A significant interaction between norepinephrine and ethnic group was observed, specifically among the Chinese (Table 65a, b). Therefore, for a given nor-

epinephrine concentration the Chinese have a significantly lower (80% reduction) probability of having a cardiovascular event compared to people of European origin (Table 66).

Table 65a: Main Effects of Nor-epinephrine and Ethnicity and CVD

	Beta	S.E.	df	Sig.	EXP(B)	95.0% C.I. for EXP(B)	
						Lower	Upper
NOREPI	.37	.21	1	.182	1.46	.84	2.53
ETHNIC			2	.00			
South Asian	.69	.32	1	.03	2.00	1.07	3.72
Chinese	-.64	.44	1	.15	.53	.22	1.26
AGE	.10	.01	1	.000	1.10	1.07	1.13
SEX	.05	.28	1	.86	1.05	.60	1.83
Constant	-8.305	.99	1	.000	.000		

Table 65b: Interaction between Nor-epinephrine and Ethnic group on CVD

	Beta	S.E.	df	Sig.	EXP(B)	95.0% C.I. for EXP(B)	
						Lower	Upper
NOREPI	.48	.53	1	.36	1.62	.58	4.54
ETHNIC[⊥]			2	.55			
ETHNIC (South Asian)	.50	.48	1	.30	1.65	.64	4.26
ETHNIC (Chinese)	.11	.54	1	.83	1.12	.40	3.22
AGE	.10	.01	1	.000	1.10	1.07	1.14
SEX	.04	.28	1	.88	1.04	.60	1.82
ETHNIC * NOREPILN			2	.03			
South Asian * NOREPILN	.28	.64	1	.66	1.32	.38	4.64
Chinese * NOREPILN	-1.52	.79	1	.05	.22	.05	1.03
Constant	-8.53	1.04	1	.000	.000		

⊥ European is the reference group

Socio-economic index as a marker of social stability:

The relationship of the socio-economic index with stress factors, neurohormones, atherosclerosis and CVD was examined. The socio-economic index is a composite of the factors education, marital status, income, and employment. The higher the index, the greater the social stability of the individual. Higher socio-economic index, and hence social stability, was associated with lower reported work stress, greater general well being, and greater social support. Further, increased social stability was associated with ***lower norepinephrine concentrations*** (Beta=-2.4 x 10^{-2}, P=0.003), and ***less atherosclerosis*** (Beta =-1.08 x 10^{-2} P=0.001), after adjustment for age and gender. There was a ***significant association between increased social stability and CVD*** (odds ratio = 0.80, P=0.001).

Table 66: Relationship between Social Stability and Psychosocial Stress Factors

Trait	Pearson Correlation	P Value
Work Stress	0.26	0.0001
Social Support	0.18	0.0001
General Well Being	0.10	0.007
Hostility	0.08	0.03

Social Stability and Norepinephrine:

The simple correlation between the socio-economic index and norepinephrine is -0.09, P=0.009. When nor-epinephrine is regressed on socio-economic index, and adjusted for age and sex, the beta coefficient is -0.024, P=0.008 which demonstrates a significant

inverse relationship between social stability and nor-epinephrine levels. The greater the social stability, which is associated with lower work stress, general well being, and decreased social support, the lower the nor-epinephrine concentration.

Social Stability with Atherosclerosis:

The relationship between social stability and atherosclerosis was examined. The simple correlation is -0.10, P=0.006. When atherosclerosis is regressed on social stability, and adjusted for age and sex, the beta coefficient is -1.08×10^{-2}, P=0.008. This demonstrates an inverse relationship, meaning that greater social stability is associated with less atherosclerosis burden.

Social Stability and CVD:

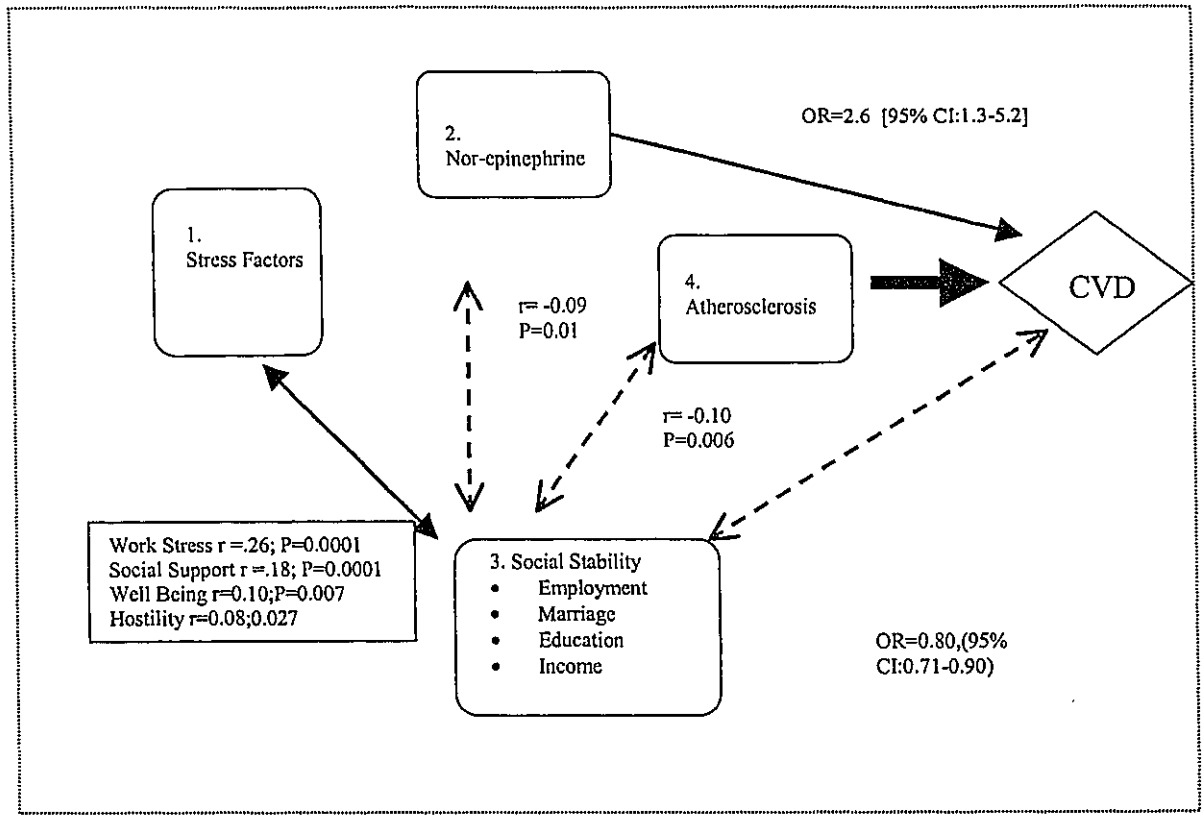
The relationship between social stability and CVD was examined in a logistic regression model with CVD as the dependent variable. The beta coefficient of socio-economic index is -0.221, P=0.001 meaning that the greater one's social stability the less probability one has of suffering a CV event. The odds ratio for a 1 point increase in the social stability index is 0.80 (95% CI: 0.71-0.90), equating to a reduction in CVD of 20%.

Summary Analysis:

The following observations have been made using the SHARE data. Psychosocial factors are not correlated with atherosclerosis or neurohormones. Furthermore, norepinephrine is a significant predictor of CVD, but is not correlated with atherosclerosis. Atherosclerosis

is a significant predictor of CVD. By examining the role of social stability in relation to these factors, the following path diagram can be constructed. It is plausible, based on these data, that decreased social stability is associated with increased negative stressors, higher levels of norepinephrine, and more atherosclerosis, all factors which increase the probability that an individual will suffer a cardiovascular event (Figure 36). In Table 65 the multivariate logistic regression is presented with CVD as the dependent variable, and social stability, atherosclerosis, nor-epinephrine, age, and sex as the independent variables. Increased social stability reduces the risk of CVD and atherosclerosis increases the risk of CVD.

Figure 36: Relationship of Social Stability to the Determinants of CVD



Notes:
1: Weak and non-significant associations between stress factors and nor-epinephrine, atherosclerosis and CVD.
2: Nor-epinephrine was a significant determinant of CVD (after adjusting for age, sex and gender). No significant relationship between nor-epinephrine and atherosclerosis was identified.
3: Social Stability was associated with less work stress, greater general well being, higher social support and less hostility
4. Social Stability was associated with lower nor-epinephrine concentrations, less atherosclerosis and was protective of CVD.

Table 67: Multivariate Logistic Regression relating Socio-economic index, Norepinephrine and Atherosclerosis to CVD

	Beta	S.E.	df	Sig.	EXP(B)	95.0% C.I. for EXP(B)	
						Lower	Upper
Social Stability	-.20	.08	1	.01	.82	.70	.96
mmIMT (for a 0.2 mm increase)	0.78	.14	1	.000	2.19	1.92	2.45
NOREPI	.18	.41	1	.65	1.20	.54	2.68
AGE	.01	.02	1	.52	1.01	.97	1.05
SEX (Females)	-.31	.43	1	.48	.74	.32	1.71
Constant	-5.23	1.26	1	.000	.005		

Methodologic issues to consider in interpreting these results:

Multiple Comparisons:

In making multiple comparisons between the ethnic groups, for these scales and subscales, the chance of committing a Type 1 error increases. To minimize the chances of finding spurious results, due to multiple comparisons between 3 groups the following approach was taken. First, the overall group means were compared in an ANOVA model. Then, if the global F-test was statistically significant, between group comparisons were made. In these cases, Tukey's test for multiple comparisons was used.

Implications of Low sample variability:

In the ideal scenario, in which there are a large number of outcome events (e.g. CV events), having a homogenous population for a given trait makes it difficult to show an association between the trait and the adverse health outcome. In a sense, the analysis is

"constrained" in its capacity to examine the disease risk associated with "extreme" stress levels. For example, trying to show that depression is associated with CVD in a population in which the prevalence of depression is very low is difficult. The ideal study population is one in which there are large number of outcome events and in which there are large variations in the responses to the trait of interest. For example in the GWBS we asked: "How often are you sad or discouraged?" Only 2.1% responded, "Very much so" or "Extremely so" versus 62% who responded, "Only a little bit" to "Not at all".

Implications of Low power:

If, in fact there is some variability in the responses for a given trait, for example social support, having a relatively low number of outcome events (e.g. CVD) limits the ability to demonstrate a statistically significant difference between those people with high social support and those people with low social support. However, in this study, there was ample power to study the association between psychological stress factors and determinants of CVD, such as atherosclerosis and norepinephrine.

Conclusions:

Interpretation of results:

In the WBQ, six scales were developed and completed by 762 participants from 3 ethnic groups. The main findings of this analysis were:

1. The SHARE WBQ has acceptable validity and reliability to evaluate work stress, general well being, social support, hostility, and selected coping strategies across three culturally heterogeneous groups. 2. The Equality Scale generally displayed lower reliability. This may reflect not the instrument used, but rather, the volatile nature of perceptions of discrimination. Increasing the response options, from Yes/No to a scaled response, may help capture a range of reactions to discrimination questions {Kreiger 2000}.

2. On average, there were no significant differences in reported job stress or general well being between the ethnic groups. Social support was greater among the well-settled people of European origin compared to Chinese or South Asians. The overall endorsement of the suggested coping responses was low. The most commonly reported coping strategies included confrontive coping, self controlling, seeking social support, and accepting responsibility. Prayer was reported, as a coping strategy for stressful situations, significantly more among South Asians compared to Chinese and Europeans. Interestingly, the South Asians and Chinese reported more hostility compared to the Europeans. The possibility that this set of questions introduced a systematic bias among the South Asians and Chinese is possible, and can only be explored in key informant interviews to elucidate if the interpretation of the hostility statements differed significantly between the ethnic groups. An in-depth analysis of the perceived inequalities demonstrated that South Asians and Chinese perceive inequality in the work place, more than do Canadians of European origin. As well, South Asians and Chinese

report discrimination on the basis of their physical appearance and accents when speaking English, yet they are optimistic about the future of their children in Canada.

3. No significant associations between negative psychological stress and increased "stress hormones" or disease outcomes (atherosclerosis and CV events) were observed overall or between ethnic groups. The stress hormone, nor-epinephrine was significantly elevated among South Asians and among people with established CV disease. The Chinese were relatively protected from CV events, for a given level of nor-epinephrine, compared to Europeans Canadians.

4. To examine the influence of social factors, such as education level, income, employment and marriage on psychosocial stress factors, norepinephrine, atherosclerosis, and CVD, a socio-economic index was created as a proxy for social stability. Higher social stability was associated with greater psychological well-being, lower concentrations of nor-epinephrine, less atherosclerosis, and fewer CV events. It presents a plausible biological pathway mechanism of how these factors interact.

CHAPTER 8

EPILOGUE AND CONCLUSIONS:

The conclusion chapter will review the main findings and discuss the implications and limitations of SHARE, and it will also comment on the potential value of ethnicity-based research.

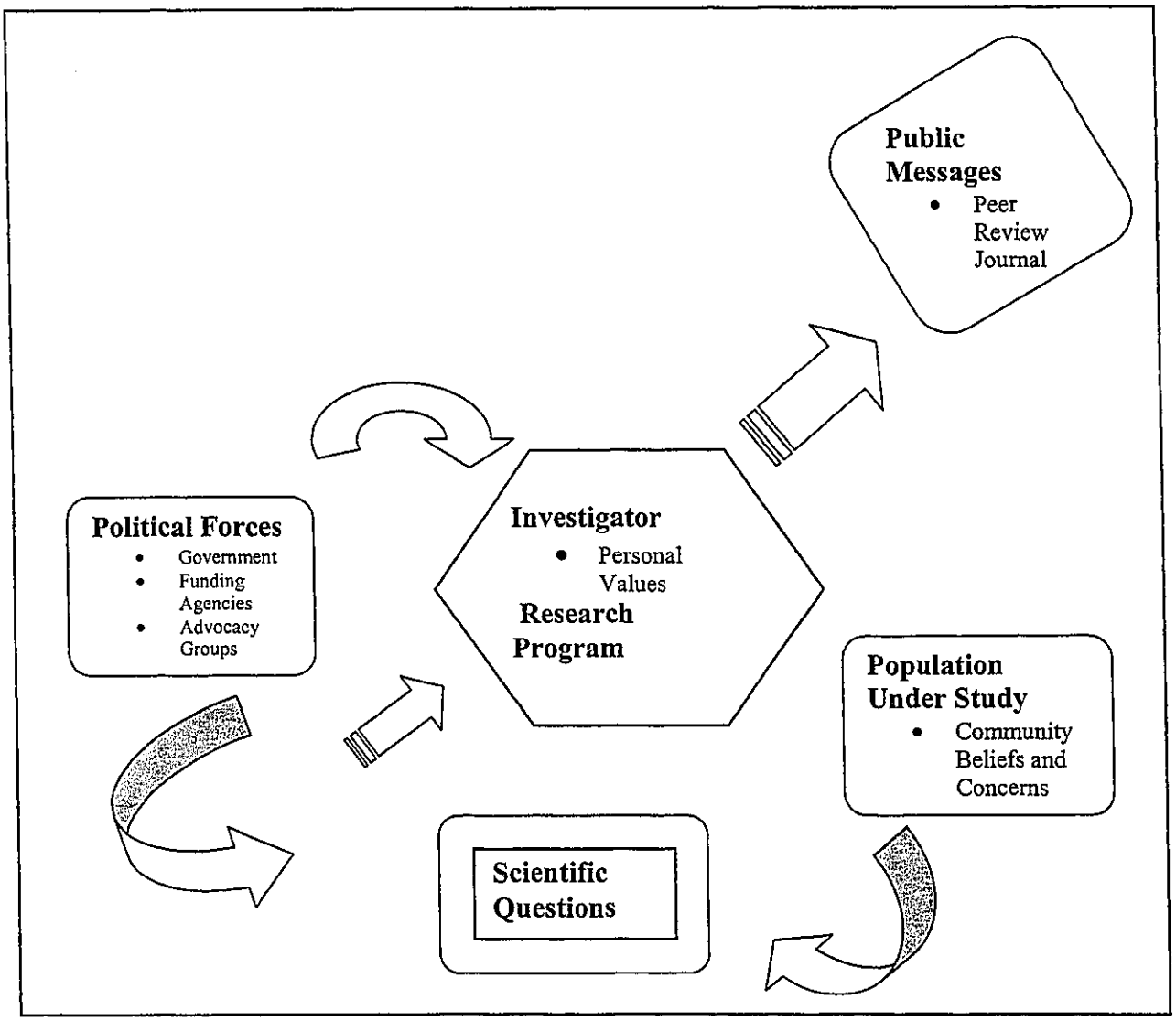
Introduction:

The concept of race continues to be widely used in health research, and it is based on the belief that human species can be divided into genetically separate groups {Crews and Bindon 1991}. To illustrate how common "race-based" research continues to be, over a one-year period beginning in January 1, 2001 there were 178 citations listed on PubMed in which the term "RACE" was used in the title. However, the wealth of evidence does not support the belief that genetically distinct groups within the human species exist. A more useful classification of human populations who have different cultural practices is ethnicity. Ethnicity is a dynamic construct, which has both biological and social dimensions. The dynamic nature of ethnicity is apparent given the less than perfect reproducibility of self-classification of ethnicity. When ethnicity is used as a variable in epidemiologic studies, some considerations are still necessary. To avoid *mis* or *over* interpretation of study results, researchers must clearly define the definition of ethnicity at the outset of their investigation. Researchers, who are analyzing data by ethno-racial

category which has already been collected (usually for another purpose), must carefully consider the threats to the validity of their findings, compensate for them if possible, or highlight the shortcomings of their analyses if they are unable to adjust for them statistically. All investigators must consider if the potential positive spin-offs of their research outweigh the potential negative consequences, and direct (and not be directed by) how their results are presented and publicized. The way in which the results of ethnicity based research are presented is influenced by multiple forces, including the investigators beliefs and values, the scientific questions being posed, the beliefs and concerns of the population under study, and political forces such as government agencies, funding bodies, and advocacy groups (Figure 37) {Anand 1999}. While it may be argued that these forces influence most scientific investigations, ethnicity and gender research appears to be particularly prone to public controversy. For example, some investigators such as Philip Rushton from the University of Western Ontario {Rushton 1992} promote the idea of genetic differences between blacks, whites and Orientals by stating that differences in brain and genital size between African, Oriental, and white Caucasians are due to genetic differences {Rushton 1996}. On the other hand, critics of his beliefs, such as Harvard Professor Stephen J Gould, vigorously challenge Rushton's statements, writing volumes on how such research is flawed and conducted only to fuel a political agenda {Gould 1981, Gould 1998}. Despite this ongoing debate, with careful steps taken to minimize bias, and an ability to maintain objectivity, ethnicity research can be useful, informative, and can yield very important information for multiple users of health research. For example, ethnicity-related research has led to important discoveries

including i) the knowledge that changing diet and physical activity increases migrants chance of developing chronic disease such as cancer and CVD, ii) that migrants who adopt a new lifestyle in a new country (or region) develop disease rates similar to those of the host country over time, iii) that some CV risk factors are more prevalent among certain subgroups (e.g. type 2 diabetes in South Asians), and iv) that CVD rates change rapidly in response to environmental changes such as socioeconomic status (e.g. decreased CVD in Japan, and increased CVD in Russia) {Marmot 1995, Bobak 1999}.

Figure 36: Influences on the Research Questions, Findings, and Messages of Ethnicity-Based Research



Note: This figure depicts the various factors which shape the public messages which are generated from medical research

This thesis represents an in-depth study of three culturally distinct groups who live in Canada. Canada is an ideal country to study the consequences of migration because there is less income inequality among its citizens compared to other countries (e.g. United Kingdom) {Ross 2000}. This allows exploration of the biological "responses" to migration, without constantly being concerned as to whether the results reflect socioeconomic differences which influence lifestyle. For example studies of risk factor and disease among South Asian migrants to the United Kingdom have recruited very poor working class migrants and compared them to European Caucasians of higher social position {Nazroo 2001}. Even without considering ethnic differences, one would expect to find more adverse risk behaviours and higher disease prevalence among the socially disadvantaged group. In SHARE, the major proxies of socioeconomic status were collected and studied in relation to the biological factors. This allowed for a balanced exploration of risk factors, both biologic and social, and disease outcomes.

Major findings of SHARE:

Key Demographic Features of the SHARE study cohort:

The average age of the participants was 50 years and approximately half were women. The majority of South Asians (71.3%) were born in the Indian subcontinent, most Chinese originated from Mainland China (43%) and Hong Kong (20.2%), and the majority of Europeans were born in Canada. Approximately one-third of participants in each group were "professional", although the migrant South Asian and Chinese were

more likely to have received a university education compared to their European counterparts. Despite this, the European Canadians were wealthier.

CVD Risk Factor Prevalence:

The South Asians had significant abnormalities in their lipids, glucose parameters, and prothrombotic factors. The Europeans, particularly men, had the greatest exposure to tobacco and were the most overweight. The Chinese had the most desirable risk factor profile of the three groups, yet suffered a higher prevalence of hypertension and had an intermediate prevalence of glucose intolerance.

Atherosclerosis and its determinants:

South Asians had the highest prevalence of CVD, but not atherosclerosis, compared to European and Chinese Canadians. While unexpected, this appears to be true, as the measurement of atherosclerosis seems to be valid as it correlated well with the prevalence of CVD events in each ethnic group. For any given amount of atherosclerosis, South Asians had more CV events compared to the other groups. This may be caused by an increased propensity to develop thrombosis among South Asians. This hypothesis is raised because, in SHARE, the levels of factors associated with thrombosis (Lp(a), homocysteine, PAI-1, and fibrinogen) were significantly higher among South Asians compared to the other groups. Yet even after adjusting for all of these risk factors, South Asian ethnicity emerged as an independent risk factor for CVD.

Atherosclerosis and its Determinants:

The primary determinants of atherosclerosis, in the entire study cohort, included systolic blood pressure, HbA1c, age and sex. A significant interaction between HbA1c and ethnicity with atherosclerosis was observed, with Europeans having a greater increase in atherosclerosis for a given increase in HbA1c.

CVD and its Determinants:

South Asians had the greatest prevalence of CVD, Europeans intermediate and the Chinese the lowest. The conventional risk factors (summarized by the Framingham Score), atherosclerosis, PAI-1, Lp(a), and South Asian ethnicity were independent determinants of CVD.

Dietary Profile:

The three FFQs developed for use in SHARE have acceptable validity, are efficient, reliable, and allow classification of individuals as high consumers versus low consumers. Europeans reported the higher consumption of calories per day and the Chinese the lowest. The South Asians and European consumed more saturated fats, trans fats and carbohydrates, whereas the Chinese consumed more protein. More South Asians were vegetarian. The Europeans and Chinese consumed relatively high amounts of sodium, a known correlate of blood pressure. Two-thirds of Chinese and South Asians reported they changed their diet very little since migration, despite living in Canada on average for 20

years. Although they represent a proportion of the European cohort (n=68), European migrants to Canada reported changing their diets to that of the host country more often than did the Chinese and South Asians. Saturated fat was a significant determinant of atherosclerosis, and this relationship was consistently observed across all ethnic groups.

***Psychological Stress*:**

The SHARE WBQ has acceptable validity and reliability for use in population-based epidemiologic studies. The Equality Scale had lower reliability scores and this may reflect the volatile nature of perceptions of discrimination, or the limitation of the dual response option in the equality questions. Interesting differences in psychological stress factors exist between the ethnic groups, and they are influenced by factors such as education level, employment, income, and marital status, markers of social stability. Low social stability was associated with more atherosclerosis, higher concentrations of nor-epinephrine, and was strongly associated with the presence of CVD.

Stress Associated with Migration:

South Asians and Chinese perceive inequality in the work place, more so than Canadians of European origin. As well, they perceive they are discriminated against on the basis of their physical appearance and accent when speaking English. Despite their own feelings of discrimination, they are optimistic about the future of their children's lives in Canada.

Conclusions:

Ethnicity-based research is useful and informative, and the SHARE investigation has led to an increased understanding of the risk patterns and pathogenesis of atherosclerosis and CVD among migrant South Asians and Chinese. Furthermore, SHARE represents one of the most comprehensive analyses of diet and psychosocial stress factors among South Asian and Chinese migrants. While this investigation has met the primary objectives of the study, additional questions have been raised which should lead to future investigations (Figure 38).

Figure 38: Future studies should address questions raised in SHARE

- South Asians may have an increased propensity to develop thrombosis
- Is high dietary glycemic load a risk factor for glucose intolerance and CVD among South Asians and Chinese or is it genetically mediated?
- What is the relationship between vegetarianism, B12 intake, B6 intake and plasma homocysteine levels?
- What is the relationship between folate intake, cooking method, folate levels, and plasma homocysteine?
- What is the association between gene frequencies and at-risk phenotypes overall and how do these relationships vary by ethnic group?
- What is the relationship between social factors, neurohormones, and LV mass?

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