Examination of the Cross-Sectional Association between Insulin Resistance (HOMAIR) and an Inflammatory Marker (CRP) in a Representative Canadian Non-Diabetic Population.

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By

Rabia Shahid

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ABSTRACT

Background: Insulin resistance (IR) can contribute to the development of type 2 diabetes. Asymptomatic individuals with high insulin resistance benefit from early interventions to prevent the progression to overt diabetes. Multiple causes of IR have been identified, many of which are reversible. It has been suggested that inflammation may contribute to IR. Our study aims to determine the association between insulin resistance and the inflammatory marker C - reactive protein (CRP) in the non-diabetic Canadian population and, furthermore, to examine potential differences in this association by gender, age, and at different serum levels of glucose and HbA1c.

Methods: We examined 2963 non-diabetic adults who participated in the Canadian Health Measures Survey, which is a national cross-sectional survey of the general Canadian population. Insulin resistance was calculated by HOMAIR. Individuals with an acute or chronic condition or those who were taking a platelet aggregation inhibitor or HMG-CoA reductase inhibitor were excluded because it can interfere with CRP levels. A cut off level of 3mg/L was used to define high and low CRP. Multiple linear regression was performed for statistical analysis.

Results: After adjusting for age, race, sex, smoking history, blood pressure, triglyceride, LDL, HDL, BMI, waist circumference and hip circumference, the insulin resistance, as reported by HOMAIR, was greater with high levels of CRP. HOMAIR for low and high CRP were 1.59 (95% CI: 1.51-1.61) and 2.76 (2.41-3.11) respectively in age group 18-30, 1.60 (1.55-1.65) and 2.58 (2.42-3.2.75) in age group 31-45 years, 1.68 (1.62-1.74) and 2.66 (2.47-2.86) in age group 46-60 years, and 1.82 (1.74-1.90) and 2.44 (2.26-2.62) in age group 61 and older. The results were statistically significant (P<0.01). Insulin resistance was also elevated with high CRP in both men and women. HOMAIR in men was 1.81 (1.77-1.86) and 2.88 (2.72-3.06) with low and high CRP respectively (p<0.05). Whereas in women it was 1.48 (1.44-1.51) and 2.43 (2.29-2.57) with low and high CRP respectively (p<0.05). Adjusted HOMAIR was also positively associated with CRP independent of the level of fasting glucose and HbA1c level.

Conclusion: Our study demonstrated a significant and positive association between insulin resistance and inflammatory markers in the Canadian population. Future studies are needed to confirm our findings and determine role of anti-inflammatory drugs in the prevention of diabetes.

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LIST OF ABBREVIATIONS

ADA – American Diabetic Association
ANOVA – Analysis of variance
BRAMS – Brazilian Metabolic Syndrome Study
BMI – Body Mass Index
CAPI – Computer-Assisted Personal Interviewing
CDA – Canadian Diabetes Association
CHMS – Canadian Health Measurement Survey
CRP – C-Reactive Protein
CV – Coefficient of Variation
CVD – Cardiovascular Disease
DECODA – Diabetes Epidemiology: Collaborative analysis Of Diagnostic Criteria in Asia
DECODE – Diabetes Epidemiology: Collaborative analysis Of Diagnostic Criteria in Europe
EGIR – European Group for the study of Insulin Resistance
EPRICE – Epidemiological Study of Renal Insufficiency in Spain
DM2 – Type 2 Diabetes
FPG – Fasting Plasma Glucose
HOMA – Homeostatic Model Assessment
HDL – High-density lipoproteins
hs-CRP – High Sensitive C-Reactive Protein
IFG – Impaired Fasting Glucose
IGT – Impaired Glucose Tolerance
IL – Interleukin
IR – Insulin Resistance
IRAS – Insulin Resistance Atherosclerosis Study
IRS – Insulin Resistance Syndrome
LFS – Labor Force Survey
MEC – Mobile Examination Center
METSIM – Metabolic Syndrome in Men
NAHANES – National Health and Nutrition Examination Survey
NDDG – National Diabetes Data Groups
NSAID – Non-steroidal anti-inflammatory drugs
OGTT – Oral Glucose Tolerance Test
OHS – Ontario Health Survey
PAI-1 – Plasminogen activator inhibitor-1
PIVUS – Prospective Investigation of the Vasculature in Uppsala Seniors
TNF – Tumor Necrosis Factor
TZD – Thiazolidinedione
WHO – World Health Organization
WOSCOPS - West of Scotland Coronary Prevention Study

CHAPTER ONE: INTRODUCTION

1.1 Rationale of the Study

Diabetes mellitus type 2 (DM2) is a metabolic syndrome manifested by the presence of high blood sugars due to insufficient action of insulin and/or defects in insulin secretion[1]. The global prevalence of diabetes (type 1 and 2) among adults over eighteen years of age was 4.7% in 1980 and it increased to 8.5% in 2014. As of 2016, 11 million Canadians have been diagnosed with diabetes or prediabetes, and this number is expected to increase to 13.9 million by 2026[2,3]. Moreover, the prevalence of diabetes is projected to rise to approximately 11.6% (4.9 million) from 9.2% (3.5 million) over this same period[2,3]. The complications associated with diabetes can cause premature death and are associated with significant comorbidities. Diabetes is responsible for 30% of strokes, 40% of heart attacks, 50% of kidney failures requiring dialysis, and 70% of non-traumatic lower limb amputations[3]. People with diabetes are twenty-five times more likely to become blind than those without diabetes [4]. Additionally, 15%–25% of people may develop serious foot infections associated with diabetes in their lifetime[5]. Between 2011 and 2012 one-third of the amputations in Canada were performed due to diabetic foot infections[6]. In 2016, the cost of diabetes in Canada was $3.4 billion, and this cost was estimated to increase to $5 billion by 2026[2].

Diabetes mellitus type 2 is the triad of insulin resistance, pancreatic beta cell dysfunction, and dysregulated hepatic glucose/glucagon production. IR is the main defect in DM2[7]. An initial change in the pathogenesis of DM2 is the development of IR[8,9]. Insulin resistance, even before the development of diabetes, is known to increase the risk of cardiovascular diseases (CVD)[10]. Patients at this phase may benefit from lifestyle modification and pharmacological intervention to reverse insulin resistance and prevent the progression of a disease[11].

Multiple causes of insulin resistance have been identified, many of which are reversible. Correction of IR can preclude overt hyperglycemia and DM2. Chronic low-grade inflammation is emerging as a new risk factor for the development of diabetes[12] with the assumption that correction of inflammation can help to offset insulin resistance. In low-grade inflammation,

classic clinical signs of inflammation are absent and only minor degrees of elevation in inflammatory markers are present when tested. This is different from acute inflammation and can occur in various chronic conditions and metabolic conditions such as coronary artery diseases, hypertension, and high cholesterol[13, 14]. Epidemiological studies show that minor degrees of elevation of multiple serum inflammatory markers are present in a high proportion of the general population and are associated with various lifestyle choices and common medical conditions such as atherosclerosis, osteoarthritis, and periodontis[15,16].

Correlation between inflammatory markers and insulin resistance have been explored in populations from Europe, Peru and USA[17-20]. Yet, data on the association of IR and inflammatory markers is relatively unexplored in the general Canadian population. To our knowledge, no population-based epidemiological study has been done that considers the association between insulin resistance and inflammatory markers in the Canadian population.

1.2 Research Questions

1. Is insulin resistance higher in the presence of low grade inflammation in the non-diabetic population?
2. Does the relationship between insulin resistance and inflammation vary by age, gender, and ethnicity?

1.3 Primary Objective

1. The objective of this thesis is to examine the cross-sectional association between insulin resistance (HOMAIR) and the inflammatory marker CRP, in a representative sample of the Canadian non-diabetic population.

1.4 Secondary Objectives

Through a study of a representative sample of the Canadian non-diabetic population, we will:

1. Compare the association of IR and CRP levels between men and women.

2. Examine the association between IR and CRP among different self-reported ethnic groups.

3. Examine the difference in IR and CRP at various glucose and HbA1c level in non-diabetic populations.

CHAPTER TWO: DIABETES AND INSULIN RESISTANCE

2.1 Definition and Type of Diabetes

Diabetes mellitus (type 1 and 2) is a metabolic disorder characterized by the presence of hyperglycemia due to defective insulin secretion, inadequate insulin action, or both[21]. The diagnostic criteria for diabetes promoted by Diabetes Canada is a fasting plasma glucose level of ≥7.0 mmol/L, a 2-hour plasma glucose value after a 75-g oral glucose load of ≥11.1 mmol/L, or a glycated hemoglobin (HbA1c) value of ≥6.5%[49]. Type 1 diabetes is characterized by the destruction of pancreatic beta cells leading to absolute insulin deficiency. This is usually due to the autoimmune destruction of pancreatic beta cells[21]. The definite cause of type 1 diabetes is not known, and the disease is currently not preventable even in those with known autoantibodies[22]. DM2 is more common than type 1 as it accounts for more than 80% of all cases. Type 2 is the combination of genetic susceptibility, environmental influence, sedentary lifestyle, obesity, and acquired insulin resistance. Gestational diabetes mellitus refers to hyperglycemia with onset, or first recognition, during pregnancy. Other types of diabetes/hyperglycemia include a wide variety of relatively uncommon conditions, primarily specific genetically defined forms of diabetes or diabetes associated with other diseases or drug use[22].

2.2 Natural History of Type 2 Diabetes

Diabetes mellitus type 2 accounts for 90-95% of diagnosed cases of diabetes, is caused by insulin resistance, and causes pancreatic beta cell dysfunction[22]. IR is the main defect in people with DM2[23]. As the sensitivity to insulin by the body decreases, there is an increase in the amount of insulin that is released by the pancreatic cells to compensate. At the early stages, this compensation is successful. The compensation by pancreatic cells can keep glucose levels normal for several years, but its effect diminishes due to failing beta cell capacity. Clinically, this failure can be detected through impaired glucose tolerance with mild post-prandial blood glucose elevations and, as IR becomes worse, the pancreatic beta cell function declines resulting in impaired regulation of hepatic glucose production. Together, these defects lead to an increase in blood glucose. Beta cell dysfunction and IR can cause hyperglycemia which, in turn, can lead to

overt DM2. It can progress from an asymptomatic stage in the beginning with normal blood glucose to high blood glucose needing pharmacological intervention.

A study of the natural history of diabetes is a key element in knowing the pathological differences between the early (insulin resistance) and late (insulinopenic) stages of the disease's development. Understanding the stages of diabetes is an important factor in choosing treatment targets and modifying treatment approaches. The progression of diabetes from the asymptomatic stage to overt diabetes can take years or even decades. Various lifestyle interventions, such as maintaining healthy body weight, can be effective in combating the progression of type 2 diabetes. Current thought includes the possibility that pharmacological interventions aimed at reversing chronic low grade inflammation may also be a viable treatment target.

2.3 Prediabetes

Prediabetes refers to cases where testing indicates high glucose levels that still fall within the normal range, such as identification through the standard 75-gram oral glucose tolerance test. Impaired glucose tolerance and prediabetes are terms that were first introduced by the World Health Organization (WHO) and the National Diabetes Data Groups (NDDG) to replace the terms borderline, chemical, and asymptomatic diabetes. Later, different definitions of impaired glucose tolerance (IGT) have been recommended by various organizations and committees. The diagnostic criteria of prediabetes, fasting glucose levels, and average glucose levels have changed over time and include several complementary measures such as serum glucose levels and HbA1c levels. There is no worldwide agreement on the definition of impaired fasting glucose (IFG) and prediabetes. Diabetes Canada and the World Health Organization define impaired fasting glucose as a fasting plasma glucose (FPG) value of 6.1 to 6.9 mmol/L while the American Diabetic Association (ADA) defines it as a value of 5.6 to 6.9 mmol/L[24,25]. The American Diabetes Association defines prediabetes as an HbA1c between 5.7% and 6.4%, and Diabetes Canada includes an HbA1c between 6.0-6.4% as one of the diagnostic criteria for prediabetes[24,25]. However, HbA1c levels below 6.0% have been associated with an increased risk for diabetes[26] and may be relevant to consider. In a systemic review of 44,203 individuals from sixteen cohort studies with a follow-up of 5.6 years, those with HbA1c between 5.5-6.0% had an

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increased risk of diabetes (five-year incidence from 9-25%), and this is reflected in the ADA cutoff values of 5.7% and higher. Those with an HbA1c range of 6.0-6.5% had a five-year risk of developing diabetes between 25-50%. The combination of an FPG of 6.1 to 6.9 mmol/L and an HbA1c of 6.0% to 6.4% is predictive of 100% progression to type 2 diabetes over a five-year period, without intervention[27].

Not all individuals with prediabetes will progress to diabetes. It has been shown in large clinical cohorts that approximately one-third of the individuals with impaired glucose tolerance will progress to DM2[23,28]. According to the American Diabetes Association, 70% of people with prediabetes will progress to diabetes. Globally, it is expected that there will be 398 million people with prediabetes by 2030[29].

It has been now recognized that even non-diabetic levels of hyperglycemia, including impaired fasting glucose, and impaired glucose tolerance are associated with an elevated risk of CVD and premature mortality[30-32]. In the Diabetes Epidemiology: Collaborative Analysis of Diagnostic criteria in Europe (DECODE), the all-cause mortality and CVD mortality was higher in individuals with impaired glucose tolerance, independent of impaired fasting glucose (HR 1.73 (1.45-2.06) for all causes, 1.40 (1.02-1.92) for cardiovascular disease, 1.56 (1.03-2.36) for coronary heart disease, and 1.29 (0.66-2.54) for stroke mortality)[30]. Coutinho et al. showed that IFG ($\geq$6.1 mmol/L) was associated with both fatal and non-fatal CVD events. Significantly, they reported that even a 1 mmol/L rise in fasting blood glucose was associated with an increased risk of cardiovascular outcomes (RR = 1.09)[32]. The significance of the relationship between elevated fasting blood glucose and incidence of cardiovascular diseases persisted, even after adjusting for diabetic status[33]. In a large population-based cohort study, both IGT and IFG have been shown to be a predictor of premature mortality. People with known diabetes (type 1 and 2), impaired fasting glucose, and impaired glucose tolerance have a greater five-year mortality rate than those with normal glucose tolerance[34].

In the Whitehall study, London-based male civil servants between forty and sixty-four years of age were studied prospectively over thirty-three years to examine the relationship between high glucose after meals and mortality from coronary artery disease. Participants were given a 50-

gram oral glucose tolerance test. Those with 2-hour blood glucose levels ≥11.1 mmol/L were classified as a newly diagnosed diabetic group. Participants with a 2-hour blood glucose > 5.3–11.0 mmol/L were classified as glucose intolerant, and, those below this level were classified as normoglycemic. Median survival differed by ~four years between the normoglycemic and glucose intolerant groups, showing that even glucose intolerance before the development of diabetes can increase the risk of cardiovascular complications[35]. Prediabetes has also been associated with microvascular complications like retinopathy, microalbuminuria, and neuropathy[36-41].

Once DM2 is diagnosed, it is well known that people may already have complications due to its often-silent presentation and unsuspected sustained hyperglycemia. The asymptomatic stage (high insulin resistance) and the stage of mild postprandial hyperglycemia are significant markers for patients at risk of developing diabetes. It is important to identify those high-risk people from millions of prediabetic cases, and to determine who will benefit most from the pharmacological interventions to prevent DM2. Patients who have sub-clinical inflammation could be at highest risk of converting from IR to DM2 and may benefit from pharmacological intervention to prevent the progression of insulin resistance[42].

2.4 Pathogenesis of Insulin Resistance

Insulin is a peptide hormone. It is secreted by the β cells of the pancreatic islets of Langerhans. The major function of insulin is to maintain normal blood glucose levels. Insulin regulates the metabolism of carbohydrates, amino acids, and lipids[43]. Insulin exerts its effects predominately in the liver, muscle, and adipose tissue where it binds the cell surface insulin receptor. This triggers a signaling cascade that promotes anabolic metabolism and glucose uptake for cellular energy through the Kreb's cycle. In the liver, insulin inhibits the production of glucose by inhibiting gluconeogenesis and glycogenolysis, and instead promotes the storage of glycogen. In muscle and fat tissue, insulin is anabolic resulting in adipose tissue stores of energy and protein synthesis to maintain muscle bulk[44].

Insulin resistance is one of the acknowledged contributors in the pathogenesis of diabetes. It is defined as a subnormal biologic response to a given concentration of insulin[45,46]. IR can be measured indirectly by a ratio of fasting glucose and insulin levels. Higher ratios of insulin to glucose correspond to higher degrees of insulin resistance.

Insulin resistance at the levels of muscle and liver are characteristic features of glucose intolerance in individuals with DM2. Insulin is needed to transport glucose to muscle and adipose tissue. Lack of insulin signaling at the muscle prevents the expression of glucose transporters and uptake of insulin from the blood stream[47]. In the basal state, the liver represents a major site of insulin resistance and failure of insulin signaling to turn off gluconeogenesis results in inappropriate overproduction of glucose despite the presence of high fasting insulin and glucose. Thus, the higher rate of glucose production by the liver is the primary determinant of high-fasting plasma glucose concentration. After glucose ingestion, both decreased muscle glucose uptake and impaired suppression of hepatic glucose production contribute to insulin resistance[48].

2.5 Etiology of Insulin Resistance

Multiple causes of insulin resistance have been identified, many of which are reversible. The causes of the IR vary from lifestyle modification to the defect in genes important for insulin action. Specific hormonal or metabolic factors such as excess glucocorticoids (both exogenous and endogenous), excess growth hormone such as acromegaly, catecholamine excess, and excess glucagon can also cause IR. Other common reversible causes that are related to inflammation such as fever, sepsis, and infection are associated with IR.

Environmental factors have been emerging as contributing factors for insulin resistance as well. Interestingly, the prevalence of IR increases as ethnic groups migrate from a less-developed area of the world to more urban and westernized regions. The prevalence of DM2 is four times higher in Japanese Americans in Seattle than Japanese citizens in Tokyo. Japanese American men with DM2 had significantly higher level of plasma insulin for the same level of hyperglycemia during 75- gram oral glucose tolerance test. This effect persists even after adjusting for BMI, suggesting that there are more factors responsible for insulin resistance other than BMI and ethnicity[50,51].

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Currently, inflammation is emerging as one of the causes of IR, which will be discussed in more detail later in this chapter.

Insulin resistance, even before the development of diabetes, can increase the risk of cardiovascular diseases. Significant associations between insulin resistance (measured by HOMAIR) and subsequent risk of CVD outcomes have been demonstrated in a large population-based study. These associations remain even after adjustment for multiple potential confounding variables. Additionally, the study demonstrated that IR increased the risk of CVD independent of other risk factors and that waist circumference was not a significant variable in a multivariate analysis. This study also suggested that IR increased CVD risk independent of central adiposity and there was no significant evidence of effect modification by adiposity, glucose tolerance status, dyslipidemia, hypertension, ethnicity, or sex[52].

2.6 Methods to Measure Insulin Resistance

Mathews et al. described the Homeostatic Model Assessment (HOMA) of beta cell function and insulin resistance in 1985[47]. It is a computer-generated model of insulin/glucose interactions and used to plot an array of fasting plasma insulin and glucose concentrations that would be expected for varying degrees of beta cell deficiency and insulin resistance. These HOMA estimates have been compared with other estimates from other models like a euglycaemic hyperinsulinaemic clamp, hyperglycaemic clamp, and continuous infusion of glucose with model assessment (CIGMA)[53-55].

Although the hyperinsulinemic euglycemic clamp is referred to as the gold standard test for insulin sensitivity, the correlation between estimates of insulin resistance derived from HOMA and from the euglycemic clamp (R_s 0.88, p< 0.0001) is generally consistent[53-55]. When measured, the median insulin resistance in normal subjects was 1.21 by HOMA and 1.45 by euglycaemic clamp, while in diabetic subjects it was 2.89 by HOMA and 4.1 by euglycaemic clamp[53-55]. HOMA has shown a good correlation with various other models as well (Hyperglycemic clamp R_s 0.69, p < 0.01, CIGMA R_s = 0.87, p < 0.0001, Minimal Model R_s 0.7, p<0.001). (Appendix A).

Due to the invasiveness of the insulin clamp and the technical difficulty in performing the test, HOMAIR has been widely used in epidemiological studies to quantitate insulin resistance. It is calculated by dividing the product of fasting insulin and glucose (SI units) by 22.5[55]. HOMA analysis allows for the assessment of inherent beta cell function and insulin sensitivity and can characterize the pathophysiology in those with abnormal glucose tolerance. The use of HOMA to make comparisons across ethnic groups is valid, but the baseline HOMA from a normal glycemic population in each comparative group should be established first to determine whether a difference in insulin sensitivity between groups reflects a different baseline.

2.7 Thresholds for HOMAIR

HOMAIR is an effective tool to measure insulin resistance[53-55]. However, the threshold of how HOMAIR has been reported across different studies has been inconsistent. The difference in the threshold of HOMAIR levels can be explained by different clinical criteria used for insulin resistance and diversity in the specific population studied. Population-based studies have been conducted in different populations and in different world regions to define the threshold of HOMAIR. However, to our knowledge, no population-based study has defined the threshold of HOMAIR in the Canadian population.

2.8.1 Summary of Population Based Studies Defining the Threshold of HOMAIR

	Study Population	Definition of IR by HOMAIR
Enzo et al.[56]	Northeastern Italy Non-diabetic	90th percentile at 2.77
Jing et al. [57]	US population Non-diabetic	75th percentile at 2.86
Bruno et al. [58]	Brazilian population Non-diabetic	90th percentile at 2.71
Ascaso et al.[59]	Spanish population Non-diabetic	90th percentile at 3.8
Pilar et al.[60]	Spanish population Non-diabetic	75th percentile at 2.48
Hedblad et al.[61]	Malmo, Sweden Non-diabetic	75th percentile at 2.0
Marques et al. [62]	South-western France Both diabetic and non-diabetic	75th percentile at 3.8
Radikova et al. [63]	Rural Caucasian population Non-diabetic	75th percentile at 2.29
Chizumi et al. [64]	Japanese healthy population Non-diabetic	Using Clinical and Laboratory Standards Institute definition of reference interval – 2.5

Enzo Bonora, Stefan Kiechl, Johann Willeit, Friederich Oberhollenzer, Georg Egger, Giovanni Targher, Maria Alberiche, Riccardo C. Bonadonna, and Michele Muggeo,

Prevalence of Insulin Resistance in Metabolic Disorders, The Bruneck Study DIABETES, VOL. 47, OCTOBER 1998

In this study, subjects (n=225) who do not have a metabolic disorder and BMI ≤25 kg/m2 were included. Subjects were divided into the five quintiles were as follows: 0.19–1.11, 1.12–1.54, 1.55–2.03, 2.04–2.76, and 2.77–36.4. The presence of insulin resistance was defined as HOMAIR in the lower limit of the top quintile 90th percentile (i.e., 2.77)

Jing Chen, Rachel P. Wildman, L. Lee Hamm, Paul Muntner, Kristi Reynolds, Paul K. Whelton, Jiang He, Association Between Inflammation and Insulin Resistance in U.S. Nondiabetic Adults Results from the Third National Health and Nutrition Examination Survey Diabetes Care 27:2960 –2968, 2004

National Health and Nutrition Examination Survey (NHANES) III was conducted by the National Center for Health Statistics of the Centers for Disease Control and Prevention between 1988 and 1994. The top 25th percentile was compared with the bottom 75th percentile (2.86 vs. 2.86)

Summer AE, Cowie CC. Ethnic differences in the ability of triglyceride levels to identify insulin resistance. Atherosclerosis. 2008; 196:696-703

Summer et al. performed a study utilizing the National Health and Nutrition Examination Survey 1999–2002, to determine the prevalence of each of the metabolic syndromes and the ability of fasting triglycerides concentrations to identify insulin resistance by ethnicity. Participants were 2804 adults from NHANES 1999–2002. The cohort was divided into tertiles of homeostasis model assessment. Insulin resistance was defined as the upper tertile (≥2.73).

Bruno Geloneze, Ana Carolina Junqueira Vasques, Christiane França Camargo Stabe, José Carlos Pareja, Lina Enriqueta Frandsen Paez de Lima Rosado, Elaine Cristina de Queiroz, Marcos Antonio Tambascia, BRAMS Investigators HOMA1-IR and HOMA2-IR indexes in identifying insulin resistance and metabolic syndrome – Brazilian Metabolic

Syndrome Study (BRAMS) Arq Bras Endocrinol Metab. 2009;53/2

In this study, insulin sensitivity was assessed in normal subjects without any known risk factors for insulin resistance sampled from those of the Brazilian Metabolic Syndrome Study (BRAMS). BRAMS was a population-based survey of metabolic disorders, insulin resistance was measured in normal adults without any known risk factor. This study included 1317 subjects (976 women, 341 men), age: 40((±12 years), BMI: 34((±10 kg/m2). Insulin resistance (HOMAIR) was defined as at 90th percentile (2.71).

Ascaso JF, Romero P, Real JT, Priego A, Valdecabres C, Carmena R. Insulin resistance quantification by fasting insulin plasma values and HOMA index in a non-diabetic population Diabetes Care. 2000 Feb;23(2):171-5

Ascaso et al. studied 292 non-diabetic individuals, aged between twenty and sixty-five years. 97 subjects who lacked clinical and biological criteria of insulin resistance were selected. In this subgroup of ninety-seven subjects without clinical and biological criteria of IR, the diagnosis of IR was established when the HOMA index was >= 3.8 (cut off at 90th percentile). The prevalence of insulin resistance (HOMA >= 3.8) was 31.8%, with a higher frequency in men compared to women.

Pilar Gayoso-Diz, Alfonso Otero-Gonzalez, Marı́a Xose ́ Rodriguez-Alvarez, Francisco Gude, Carmen Cadarso-Suarez, Fernando Garcı́a, Angel De Francisco. Insulin resistance index (HOMAIR) levels in a general adult population: Curves percentile by gender and age. The EPIRCE study: Diabetes research and clinical practice 94 (2011) 146–155

The EPIRCE was an epidemiologic, cross-sectional population-based study that included a randomly selected sample of Spanish persons aged twenty years and older. 2246 individuals without diabetes were included for analysis. Mean Observed HOMAIR levels were higher in men than in women (2.06 vs. 1.93, respectively; P = 0.047). The distribution of HOMAIR was different in men and women in different decades of age. Observed HOMAIR at 75th percentile was 2.48 for the study population. For the population in this study, HOMAIR at 75th percentile for men was 2.88 and for women was 2.35. Women aged over fifty had significantly higher

HOMAIR levels (P for trend = 0.04). Whereas in men there was no association between age and HOMAIR.

Hedblad B, Nilsson P, Janzon L, Berglund G. Relation between insulin resistance and carotid intima-media thickness and stenosis in non-diabetic subjects. Results from a cross-sectional study in Malmo, Sweden. Diabet Med. 2000; 17:299-307

This was cross-sectional population-based study in Malmo, Sweden. Non-diabetic subjects were selected to assess the relationship between insulin resistance and carotid intima-media thickness. Insulin resistance (HOMAIR) defined at values exceeding 2.0 (75th percentile). Insulin resistance syndrome was defined by the presence of insulin resistance or fasting hyperinsulinemia in combination with at least two of the following conditions: hyperglycemia, hypertension, dyslipidemia, and/or central obesity. Age, sex and ethnicity were not taken into consideration to define the threshold of HOMAIR.

Marques-Vidal P, Mazoyer E, Bongard V, Gourdy P, Ruidavets JB, Drouet L, Ferrières J. Prevalence of insulin resistance syndrome in Southwestern France and its relationship with inflammatory and haemostatic markers. Diabetes Care. 2002; 25:1371-1377.

In a cross-sectional study done on a representative sample of the population in southwestern France aged thirty-five to sixty-four years, data was collected from 597 men and 556 women. Both diabetic and non-diabetic participants were included. Only subjects on insulin therapy were excluded. A HOMAIR cut off of 3.8 was used as one of the components of insulin resistance syndrome. The prevalence of insulin resistance syndrome was higher in men than women, but decreased with advancing age.

Radikova Z, Koska J, Huckova M, Ksinantova L, Imrich R, Vigas M, Trnovec T, Langer P, Sebokova E, Klimes I. Insulin sensitivity indices: A proposal of cut-off points for simple identification of insulin-resistant subjects. Exp Clin Endocrinol Diabetes. 2006; 114:249-256.

A study was done using 1156 subjects from a Caucasian rural population with no previous evidence of diabetes to define the cut off of insulin resistance. A 75-g oral glucose tolerance test was administered. HOMAIR of 2.29 (75th percentile) was used as the cut off point to define

insulin resistance

Esteghamati A, Ashraf H, Khalilzadeh O, Zandieh A, Nakhjavani M, Rashidi A, Haghazali M, Asgari F. Optimal cut-off of homeostasis model assessment of insulin resistance (HOMAIR) for the diagnosis of metabolic syndrome: Third national surveillance of risk factors of non-communicable diseases in Iran, Nutr Metab (Lond). 2010; 7:7-26.

To establish the cut-off insulin resistance in the Iranian population with or without diabetes, a study was conducted based on the third National Surveillance of Risk Factors of Non-Communicable Diseases. The results for 3,071 adult Iranian individuals aged twenty-five to sixty-four years were analyzed. The threshold of HOMAIR for the diagnosis of metabolic syndrome was estimated to be 1.77 in non-diabetics and 4.00 in diabetic patients.

Chizumi Yamada, Toshitake Mitsuhashi, Noboru Hiratsuka, Fumiyo Inabe, Nami Araida, and Eiko Takahashi Optimal reference interval for homeostasis model assessment of insulin resistance in a Japanese population. J Diabetes Investigation. 2011 Oct 7; 2(5): 373–376.

A study was done to determine a threshold for homeostasis model assessment of insulin resistance (HOMAIR) in a Japanese population. Healthy subjects aged twenty to seventy-nine years with normal fasting plasma glucose and a body mass index < 25 kg/m^2 were selected. 2173 subjects were used as reference individuals, and 2153 subjects were used for analysis. It was determined that a HOMAIR of 2.5 should be considered a reasonable indicator of insulin resistance in Japanese population.

CHAPTER THREE: INFLAMMATION AND INSULIN RESISTANCE

3.1 Inflammation and Inflammatory Markers

The presence of low-grade inflammation in multiple chronic conditions is well documented. In cases of low-grade inflammation, classic clinical signs of inflammation are absent and only a minor degree of elevation in inflammatory markers are present when tested. This is different from acute inflammation and can occur in various chronic and metabolic conditions[65,66]. Epidemiological studies show that minor degrees of multiple serum inflammatory markers are elevated, are present in a high proportion of the population, and are associated with various lifestyle choices and medical conditions[67,68]. Multiple medical conditions, such as atrial fibrillation, hypertension, hypertriglyceridemia, and high blood pressure, that are not inflammatory, are associated with a minor elevation of C-reactive protein[68]. Smoking can cause mild elevation in CRP[69]. Exercise does not have anti-inflammatory effect immediately. However, it can have anti-inflammatory effects over the long term[70]. Moderate alcohol intake has been shown to reduce CRP[71].

Several bio-markers linked to inflammation have been identified and validated, and various other markers are being investigated. However, no one single inflammatory marker is a perfect measure. An increase in the concentration of these biomarkers, called acute phase reactants, correlates with tissue injury and inflammation. Although referred to as acute phase reactants, it represents inflammation in both acute and chronic conditions[72-74]. In current clinical practice, CRP is the most widely used inflammatory marker employed to monitor acute phase response and used to follow the activity of infections, inflammatory disorders, and tissue damage. It is also considered a valuable marker of low grade, chronic inflammation[75]. CRP is an acute phase reactant and a marker of systemic inflammation. It is regarded as an early indicator of infection or inflammation. A normal healthy subject has a median CRP level of 0.8mg/L. CRP is produced by hepatocytes, and its synthesis is regulated by pro-inflammatory cytokines, specifically,

interleukin-6. CRP shows little short-term fluctuation which makes it particularly useful to follow.

In recent studies, approximately 70–90% of samples from multiple reference populations had CRP concentrations less than 3 mg/L. This suggests that normal levels in the American population are less than 3 mg/L[76]. The plasma half-life of CRP is nineteen hours. When compared between normal healthy controls and people with disease, there was no difference in the turnover rate or body clearance of CRP. This indicates that there was no accumulation of CRP in people with cardiovascular disease to explain the higher levels of CRP correlated with CVD[77].

After the original reports noting that CRP elevation was associated with increased CVD, additional highly sensitive assays were developed to accurately quantitate the relatively low concentration of CRP found in healthy populations[78]. Traditionally, CRP levels were measured in the laboratories to detect concentrations up to 3mg/L. However, this did not have enough sensitivity to quantify low values in otherwise healthy men and women. Later, more-sensitive techniques were developed to measure low levels of CRP (high-sensitivity CRP; hs-CRP) to attain the desired quantification. Now, hs-CRP concentrations as low as 0.15 mg/L can be reliably measured[79]. CRP levels are unaffected by the gender and age of the patient[80].

We have included hs-CRP as a marker of inflammation as it is the most widely used inflammatory marker in current clinical practice due to it stability, availability, and low cost. We have divided CRP measurement into a dichotomous variable with the cut off of 3mg/L for the convenience of clinical interpretation.

3.2 Inflammation and Diabetes

More recently, chronic inflammation has emerged as an independent risk factor for the development of type 2 diabetes. Chronic subclinical inflammation is known to down-regulate major anabolic cascades by the release of cytokines involved in modulating insulin signaling and in turn promote insulin resistance in adipose, muscle, and hepatic tissues. This global insulin

resistance likely impairs the whole-body insulin sensitivity and causes IR[81]. Current evidence supports the idea that inflammation has an important role in the pathogenesis of DM2. The odds of developing diabetes are higher in people who have higher baseline inflammatory markers[82].

Chronic inflammation has long been associated with DM2, but it is unknown if it is a cause or an effect of this metabolic disturbance. A clue to the relationship between inflammation and diabetes dates back more than a century when high doses of salicylates (anti-inflammatory drugs) were seen to reduce glucose in the urine of diabetic patients. In 1876, Ebstein determined that sodium salicylate improved the symptoms of diabetes mellitus[83,84]. A similar effect was found later in 1901 by Williamson[85]. Later, Gross and Greenberg cited fifteen clinical reports on the beneficial effects of salicylates on lowering glucose levels[86].

In 1957, Reid and colleagues noticed that when insulin-dependent diabetic patients with rheumatic fever associated arthritis were given high doses of aspirin for their treatment, they no longer required insulin injections[87]. This effect persisted until the aspirin was discontinued. Salicylates are non-steroidal anti-inflammatory agents and can improve glucose control. Compared with placebo, salicylate have been shown to decrease fasting glucose by 13% ($P < 0.002$), CRP by 34% ($P < 0.05$) and glycated albumin by 17% ($P < 0.0003$) and can improve insulin sensitivity[88,89]. These early studies showed that salicylates not only improves blood glucose at higher doses, but also do not induce hypoglycemia. Unfortunately, high doses of salicylates are associated with several adverse side effects including: tinnitus, anorexia, nausea, and vomiting. Moreover, nausea and vomiting can cause starvation ketosis, which can be confused with diabetes ketosis, and might have led to discontinuing the use of salicylates[90,91].

3.2.1   C - reactive protein – Predictor of Diabetes and Cardiovascular Disease

High-sensitivity C-reactive protein and tumor necrosis factor alpha are present in individuals with prediabetes, and have been shown to predict the development of diabetes[92-94]. Pradhan et al. showed that CRP was an independent predictor of cardiovascular diseases after adjustment for body mass index (BMI), clinical risk factors, and fasting insulin levels in women. In this study, an association was found with interleukin-6, though of borderline statistical significance after

multivariate analysis. Baseline levels of IL-6 (p<0.001) and CRP (P< 0.001) were significantly higher among people who developed diabetes than those who did not develop diabetes. The relative risk of developing diabetes for women was 15.7 (95%CI, 6.5-37.9) for highest vs. lower quartile. The association persisted after adjusting for other contributors[94].

Baseline plasma C-reactive protein in a healthy individual can predict the risk of myocardial infarction, ischemic stroke, and diabetes[95-99]. CRP has been proven to have several advantages in the detection and monitoring of atherosclerosis and its complications. Use of CRP in several nested case-control studies in initially healthy subjects has shown an association between baseline CRP and cardiovascular outcomes[97, 100, 101]. The West of Scotland Coronary Prevention Study (WOSCOPS) found that C-reactive protein predicted the development of DM2 in middle-aged men independently of established risk factors[102].

CRP has proven to be a strong independent predictor of both incidents of diabetes and cardiovascular disease. It was found to have a linear increase in the incident of diabetes with increasing quartiles of CRP (6.9, 12.1, 16.2, and 19.9% in quartiles 1–4, respectively and was statistically significant (p= 0.001). The similar association was found for PAI-1. This relation was consistent in men and women, in lean and obese subjects, and across a different ethnic group[67, 94, 103].

Most hypoglycemic agents used to treat diabetes have an independent beneficial effect on inflammation. Extensive studies have been carried out with metformin, which demonstrated a moderate to strong anti-inflammatory response. Metformin is also known to lower fasting plasma glucose by decreasing hepatic glucose production and improving muscle insulin sensitivity[104]. Metformin can reduce the production of the pro-inflammatory cytokines interleukin IL-1, IL-6 and tumor necrosis factor (TNF)[74,105]. Evidence suggested that thiazolidinedione (TZD) therapy had an anti-inflammatory effect that can explain its favorable effect on inflammatory states in patients with DM2[106-110]. Other studies have shown the beneficial effect of other hypoglycemic agents, for example, dipeptidyl peptidase-4 inhibitors and Sulfonylureas, on inflammation[111-117].

3.2.2 *Previous Studies with Insulin Resistance and Inflammation in Selected Communities*

It has been hypothesized that chronic inflammation could be the trigger for insulin resistance and eventually DM2, as suggested by Pick and Crook in 1998[118].

Bizu Gelaye, Luis Revilla, Tania Lopez, Luis Suarez, Sixto E Sanchez, Karin Hevner, Annette L Fitzpatrick and Michelle a Williams, Association between insulin resistance and c-reactive protein among Peruvian adults, Diabetology & Metabolic Syndrome 2010, 2:30

Peruvian men and women who participated in the FRENT study, (Prevalence of Risk Factors for Non-Transmissible Diseases) were part of this large epidemiological study. There were 1,525 participants (569 men and 956 women). Here, subjects with no history of diabetes were included. As lipid lowering medications can reduce CRP, those medications were excluded. Insulin resistance was measured by HOMAIR. CRP values were divided into three defined tertiles: <0.81 mg/L, 0.81- 2.53 mg/L, and >2.53 mg/L. <0.81 mg/L, 0.81- 2.53 mg/L, and >2.53 mg/L. Age, BMI, and current smoking status were adjusted within a multivariate model. Insulin resistance was defined when HOMAIR was in the highest quartile (HOMAIR > 5.12). Men had higher rates of current smoker, mean waist circumference, triglycerides, and systolic and diastolic blood pressure. Women had higher mean age, high density lipoprotein, total cholesterol, and low density lipoprotein. Values of CRP were positively associated with HOMAIR (p<0.001). After adjusting for all the covariates, the odd ratio of insulin resistance in each tertiles of CRP was 1.35 and 2.18 in men and 2.67 and 2.58 in women. Limitations of the study were that it did not control for waist circumference, cholesterol profile, acute or chronic conditions, or blood pressure.

Pedro Marques-Vidal, Elizabeth Mazoyer, Vanina Bongard, Pierre Gourdy, Jean-Bernard Ruidavets, Ludovic Drouet, Jean Ferrie`Res, Prevalence of Insulin Resistance Syndrome in Southwestern France and Its Relationship with Inflammatory and Hemostatic Markers Diabetes Care, Volume 25, Number 8, August 2002

This was a cross-sectional study that included 597 men and 556 women. Subjects with HOMAIR

> 3.8 (lower level of the population upper quartile) were considered insulin resistant. Subjects on insulin therapy were excluded. Prevalence of IRS was higher in men than in women (23% vs. 12%, respectively; P < 0.001) and increased with age in both sexes

There was no difference in the age between men and women, however women had lower BMI, waist-hip ratio, blood pressure levels, total cholesterol and triglyceride levels, HOMA, insulin and higher HDL cholesterol, and fibrinogen than in men. After adjusting for age, alcohol consumption, smoking, and menopause, subjects with insulin resistance had significantly higher levels of CRP, white blood cell count, factor VII levels, coagulating factor VII levels. As the main objective of this study was to assess the prevalence of IRS in the general population of southwestern France, subjects with a history of hypertension, hypertriglyceridemia, or diabetes were not excluded from the analysis.

John S. Yudkin, C.D.A. Stehouwer, J.J. Emeis, S.W. Coppack C-Reactive Protein in Healthy Subjects: Associations with Obesity, Insulin Resistance, and Endothelial Dysfunction a Potential Role for Cytokines Originating from Adipose Tissue? Arterioscler Thromb Vasc Biol. 1999; 19:972-978.

Yudkin et al. looked at the association of C-reactive protein and interleukin-6 with the features of insulin resistance syndrome. They studied 107 non-diabetic adults aged forty to seventy-five years. Levels of C-reactive protein were significantly associated with interleukin-6 and tumor necrosis factor. C-reactive protein was associated with insulin resistance (HOMAIR), blood pressure, HDL, and triglyceride, markers of endothelial dysfunction (plasma levels of von Willebrand factor, tissue plasminogen activator, and cellular fibronectin).

E. Ingelsson, J. Hulthe, and L. Lind, Inflammatory markers in relation to insulin resistance and the metabolic syndrome Eur J Clin Invest 2008; 38

In the community of Uppsala, Sweden, between April 2001 and June 2004, all seventy-year-old (n=1016) individuals participated in the Prospective Investigation of the Vasculature in Uppsala Seniors (PIVUS) study. To account for acute or chronic infections and blood malignancies, participants with CRP > 10 mg L^{-1} or leukocyte count > 10 * 109 cells L^{-1} ($n = 73$) were excluded. The study sample of 943 participants (50% women) were included for the analysis.

Various circulatory interleukins, tumor necrosis factor, intercellular adhesion molecule-1, and markers of systemic inflammation (CRP and leukocyte count) were measured. The multivariate model was adjusted for sex, oral glucose lowering medications, statins, and antihypertensive to examine the association between these bio-markers of inflammation and HOMAIR. Among seventeen inflammatory bio-markers, E-selection and CRP demonstrated the strongest relationship between inflammation and insulin resistance in seniors over the age of seventy.

Andreas Festa, Ralph D'Agostino, Jr, George Howard, Leena Mykkänen, Russell P. Tracy and Steven M. Haffner Chronic Subclinical Inflammation as Part of the Insulin Resistance Syndrome: The Insulin Resistance Atherosclerosis Study (IRAS Circulation. 2000; 102:42-47

The Insulin Resistance Atherosclerosis Study (IRAS) was a multicenter, population-based epidemiological study that examined the association between insulin resistance, cardiovascular risk factors, and cardiovascular disease across different ethnic groups and various states of glucose tolerance. As part of the IRAS, 1088 non-diabetic individuals, ages forty to sixty-nine years participated. A standard 75-g oral glucose tolerance test was performed. Insulin sensitivity was assessed by a frequently sampled intravenous glucose tolerance test with minimal model analysis. 33% of participants had impaired glucose tolerance.

Any participant with a current acute illness and clinically overt coronary artery disease were excluded. People with clinically overt coronary artery disease and history of myocardial infarction were also excluded. The relationship of three inflammatory markers (CRP, Fibrinogen, and white blood cells) were examined with components of the metabolic syndrome. The multivariate model was adjusted for age, sex, ethnicity, clinic, and smoking status. In the model, interaction was also tested for BMI, insulin, and pro-insulin. All three inflammatory markers were related to the metabolic syndrome. However, the association was strongest for CRP as it showed that CRP was independently associated with insulin sensitivity.

Andreas Festa; Anthony J.G. Hanley; Russell P. Tracy; Ralph D'Agostino; Steven M. Haffner, Inflammation in the Prediabetic State Is Related to Increased Insulin Resistance Rather Than Decreased Insulin Secretion,

An additional cohort of 906 non-diabetic subjects, non-diabetic at baseline, were followed for 5.2 years from the same population of IRAS. Subjects who developed diabetes during follow-up were defined as prediabetic, and those who remained non-diabetic were defined as non-converters. A standard 75-g oral glucose tolerance test was performed. Insulin sensitivity was assessed by a frequently sampled intravenous glucose tolerance test with minimal model analysis. Prediabetic people had higher inflammatory markers at baseline than non-converters. Prediabetic individuals who were insulin resistant had higher CRP (mean [95% CI], 2.88 mg/L [2.33 to 3.56] versus 1.68 mg/L [1.13 to 2.49] than prediabetic subjects with high insulin sensitivity. It was shown that increased inflammatory markers in prediabetics are predominately related to insulin resistance and not with primary defect in beta cell dysfunction.

Chen J, Wildman RP, Hamm LL, Muntner P, Reynolds K, Whelton PK, He J; Third National Health and Nutrition Examination Survey. Association between inflammation and insulin resistance in U.S. nondiabetic adults: results from the Third National Health and Nutrition Examination Survey. Diabetes Care. 2004 Dec; 27(12):2960-5

The National Health and Nutrition Examination Survey (NHANES III) was conducted by the National Center for Health Statistics of the Centers for Disease Control and Prevention between 1988 and 1994. A subsample of participants was randomly selected as a fasting morning sample. Participants with a history of diabetes, abnormal fasting blood glucose, or who were using diabetic medications at the time were excluded. 5959 participants were included for the main analysis. HOMAIR was used to assess the participants' insulin resistance. Elevated HOMAIR was defined as being in the upper 25th percentile ($\geq$2.86). Multivariable models were adjusted for age, sex, race, education, physical activity, current and former smoker, NSAID use in the past month, alcohol intake, systolic blood pressure, BMI, waist circumference, serum total cholesterol, and triglycerides. The odds ratios of insulin resistance were calculated between detectable C-reactive protein (0.22–0.99 mg/dl), clinically elevated C-reactive protein ($\geq$1.0 mg/dl equivalent to 10mg/L), and undetectable C-reactive protein. The clinically elevated CRP (>1mg/dl) was associated with 0.63 (0.23-1.04, P=0.003) higher insulin resistance (measured by

HOMAIR) after adjusting for potential confounder. The association was consistent in both men and women.

Maria Fizelova, Raimo Jauhiainen, Antti J. Kangas, Pasi Soininen, Mika Ala-Korpela, Johanna Kuusisto, Markku Laakso, and Alena Stanc̆aˊkova ; Differential Associations of Inflammatory Markers with Insulin Sensitivity and Secretion: The Prospective METSIM Study, J Clin Endocrinol Metab 102: 3600–3609, 2017

The Metabolic Syndrome in Men (METSIM) study included 10,197 Finnish middle-aged men The baseline study was performed from 2005 to 2010. A subset of 8749 men without type 2 diabetes at baseline were selected to examine the association between markers of inflammation (glycoprotein acetyls (GlycA), interleukin-1 receptor antagonist, and C-reactive protein) with insulin secretion, insulin sensitivity, and incident type 2 diabetes. Glucose tolerance was done using a 2-hour oral glucose tolerance test (OGTT) with 75- g of glucose. Men with history of diabetes were excluded. CRP levels were associated with insulin sensitivity (Hazard ratio, 1.13; 95% confidence interval, 1.07 to 1.20).

Martin K. Rutter; James B. Meigs; Lisa M. Sullivan; Ralph B. D'Agostino; Peter W.F. Wilson; C-Reactive Protein, the Metabolic Syndrome, and Prediction of Cardiovascular Events in the Framingham Offspring Study. Circulation. 2004; 110:380-385

The Framingham Offspring Study was a community-based observational study that examined the risk factors for cardiovascular disease. Participants from this study were selected from cycle five (January 1991 through 1995) to examine the association of inflammation with metabolic syndrome and cardiovascular disease. 3037 Participants who did not have history of diabetes or prevalent cardiovascular disease were included for analysis. Insulin resistance was assessed through the use of HOMAIR. The multivariable model was adjusted for age and sex. It was found that HOMAIR was higher in men than in women. Moreover, both C-reactive protein (HR, 1.8; 95% CI 1.4-2.5) and metabolic syndrome (HR, 1.9; 95% CI, 1.2-2.9) were independent risk factors for cardiovascular diseases, even after adjusting for age and sex.

CHAPTER FOUR: STUDY METHODOLOGY

4.1 Canadian Health Measure Survey (CHMS)

The Canadian Health Measure Survey has been developed by Statistics Canada to measure the indicators of health and wellness of Canadians. They began collecting data in 2007[119]. Originally, a representative sample of around 5000 Canadians, aged six to seventy-nine years was selected. The data from cycle one to four has been released to the Research Data Centre by Statistics Canada. At the time of this analysis, cycle one, two, and three were available and used as part of this study. (Appendix C).

Data collection for the CHMS takes place every two years[119]. The CHMS is conducted in two steps. First, an interviewer visits the respondents' home and administers a household questionnaire. Second, the respondents visit a mobile health clinic where trained medical staff take direct physical health measures. In the mobile health clinic, blood is drawn for laboratory investigations and a urine sample is collected for analysis[120].

The CHMS developed a conceptual framework to include all important measures that would allow for a comprehensive assessment of individual and group health. The conceptual framework diagram (Appendix B)[119] illustrates the importance of measuring non-individual level variables that may serve as important moderators of individual health indicators. One of the key component of the CHMS is a direct measure of physical health. Health information collected through self-reported surveys or administrative records may be incomplete or inaccurate as many variables cannot be determined in the absence of direct physical measures. The clinical team consists of a manager, a health measure specialist that administers most of the physical tests (blood pressure, anthropometry, fitness testing and spirometry, etc.), and a laboratory technician or technologist who performs the phlebotomy as well as processes the bio-specimens for storage and shipment to the reference laboratories. Staff are selected based on the level of education, experience, and certification(s) required for each position. In addition, a significant amount of survey-specific training is provided to all field staff, emphasizing quality control guidelines and the need for standardization of all survey procedures. The CHMS has four components: The

Household Component, the Mobile Examination Centre, the Laboratory Component, and the Biobank Component.

4.1.1   Household Component

The household component includes a detailed questionnaire which takes participants approximately seventy-five minutes to complete[121]. Interviewers ask participants a variety of questions about their health and living situation, including:

- Identifying any known acute or chronic conditions.
- Information on food and nutrition status.
- Environmental and socioeconomic information.
- General health-related questions.

The interviewer's questions are arranged to accommodate for computer-assisted personal interviewing (CAPI)[120]. The advantage to using CAPI in this extensive national study is that it provides interviewers with tools to exclude out of range values and helped limit flow errors by ensuring that questions that do not apply to the respondents are excluded and that inconsistent reporting by participants was identified.

4.1.2   Mobile Examination Center (MEC)

When the household interview is complete, the interviewer provides the respondent with guidelines and timelines for attending and participating in the physical examination component of the CHMS[121]. This step is in part based on the successful use of mobile examination centers in the NHANES in the US[121]. These guidelines are to ensure standardization, and it is essential to the accuracy and credibility of the study that the guidelines are followed as closely as possible. Each visit lasts for approximately two hours. At the beginning of the physical examination, examiners ensure that participants are following the pre-examination guidelines prior to continuing. During the examination, physical measurements that are taken may include: anthropometric, cardiovascular, and musculoskeletal fitness measures, physical activity, oral health (cycle one only), spirometry, and biological specimens.

4.1.3 Laboratory Component

Most biological samples collected at the mobile examination center are processed (e.g; centrifuged, aliquoted) before they are shipped to the reference laboratories, with the exception of DNA. The sole test completed on site is a complete blood count, all other blood and urine samples are sent to one of three laboratories for analysis. These laboratories include: Health Canada Laboratory, Bureau of Nutritional Sciences Nutrition Research Division, National Microbiology Laboratory, and L'Institut de Sante Publique du Quebec. Participants's blood samples are measured for diabetes, cardiovascular health, infectious disease markers, nutritional information, and other general information.

4.1.4 Biobank Component

For the purposes of record-keeping and future study, blood, urine and other bio-specimens which are collected during the CHMS from consenting participants were stored at the CHMS Biobank located at the National Microbiology Laboratory in Winnipeg.

4.1.5 Sampling Methodology

The sample methodology differs depending on the cycle. Generally, the CHMS targets individuals aged three to seventy-nine years that live in private homes. The study selects respondents equally by age group and sex. Collection sites are spread across five regions to ensure that all Canadian regions are represented. These regions include: British Columbia, the Prairies, Ontario, Quebec, and the Atlantic provinces. The amount of collection sites within each region differs depending on the cycle, as does the total number of respondents.

4.1.6 Estimation and Quality Control

Each person taking part in the final survey is assigned a survey weigh[122]. This weight is a proportional representation of that person to their corresponding members of the Canadian population. When inferring an estimate from this study, it is imperative that the survey weight is used in order for the estimate to be representative of the population. If it is not used, then it only represents the survey sample.

For the purposes of accuracy and quality assurance, interviewers received extensive training from Statistics Canada and were provided with comprehensive information manuals. Furthermore, interviews received regular oversight. This was to ensure strict adherence to protocol, and to protect the quality of data collection and interaction with participants. When needed, experts observed and evaluated staff to ensure rigorous levels of testing and record keeping. In cases where participants refused to answer questions, managers followed-up to encourage participation. If the participant maintained a position of non-response then the final weight of the household was modified to accommodate for that non-response[122].

Statistics Canada received Research Ethics Board approval for the CHMS. Participation is voluntary and participants are able to decline to answer any specific question or participate in any specific measure. They can also decline to receive lab results, participate in the measurement and reporting of reportable diseases, and in the storage of their DNA. The collection for the first cycle for CHMS began in 2007. Planning up to cycle eight is currently underway. Dissemination for a cycle usually begins ten months after the end of the cycle's collection period. CHMS cycles one, two, and three were available for this thesis.

Despite the efforts to maintain a high degree of accuracy, the estimates will be subject to a small degree of non-sampling error. This may occur because of non-response, population coverage, differences in the interpretations of questions, and errors in recording, and coding and processing data.

4.1.7   Fasted Sub-Sample

For the fasted subsample, each household is randomly identified as to whether a respondent should fast or not prior to their appointment. Those that are flagged for fasting need to do so for ten hours prior to their appointment. However, those households that are not flagged have less severe eating restrictions placed on them. In household where pregnant women, people with diabetes, children less than six years old, and where other special cases were present, fasting is not required, even if it has been identified a fasting household. This random identification of households is intended to prevent bias. For the final collection of survey results, rates are

adjusted so that 50% of respondents are from fasting households and 50% are from non-fasting households.

4.1.8   Cycle One (C1) (March 2007 to March 2009)

The target population for the first cycle of the CHMS included individuals between six and seventy-nine years of age. The sample was allocated over ten age/gender groups, and 500 units per group were required to produce usable national estimates. In total, there were 5,000 reporting units[123]. Data collection for this reference period took place from March 1st, 2007 through March 31st, 2009. 257 sites were created, including two sites in the Territories. These sites were spread across the five regions of Canada. It was decided that a sample of fifteen collection sites was required. These sites have been allocated by region in proportion to their populations: Atlantic (1), Quebec (4), Ontario (6), Prairies (2) and British Columbia (2). Approximately 350 reporting units per sites participated in all parts of the survey.

4.1.9   Cycle Two (C2) (August 2009 to November 2011)

During the second cycle, the CHMS included participants aged three to seventy-nine years. For this cycle, individuals living on reserves and other Aboriginal settlements, members of the Canadian Forces, the institutionalized population, and certain other residents were excluded. The data collection for this cycle was from August 8th, 2009 through to November 30th, 2011. The sample was allocated over eleven age/gender groups, with 500 to 600 units per group (5,700 total) required to produce usable national estimates[124]. 257 sites were created, including two sites in the Territories. These various sites were spread across the five Canadian regions. In this case, eighteen sites were created in these five regions. They were allocated as follows: Atlantic (2), Quebec (4), Ontario (6), Prairies (3) and British Columbia (3). Sites were randomly selected using a systematic sampling method with probability proportional to the size of each site's population. There were approximately 350 reporting units per site that participated in all parts of the survey. There was a total of 6,400 participants across all sites[124].

4.1.10 Cycle Three (C3) (January 2012 to December 2013)

The target population for the third cycle consisted of persons aged three to seventy-nine years. Data collection for this reference period began on September 1st, 2009 and ended on December 17th, 2013[125]. The sample was allocated over eleven age/gender groups. To produce national estimates, groups with between 500 to 600 units were required. It was estimated that sample size of 5,700 was needed to yield usable national results. Like previous cycles, sites were stratified based on the five Canadian regions. Sixteen sites were created within the five regions. The sites were allocated by region as follows: Atlantic (2), Quebec (4), Ontario (6), Prairies (2) and British Columbia (2).

4.4 Inclusion Criteria

1. Fasted subsample from three CHMS cycles.
2. Age eighteen and older.
3. Fasted insulin and glucose available (all three cycles).

4.5 Exclusion Criteria

1. Known pregnancy, either on household questionnaire or clinic visit.
2. Any case with self-reported history of diabetes in household questionnaire.
3. According to the Canadian Diabetic Association, to diagnose diabetes, anyone with the fasting blood glucose greater than 7 mmol/L and HbA1c% greater than 6.5% and who do not have any symptoms of hyperglycemia, needs confirmatory test to diagnose diabetes. As we do not have any information on the symptoms or on confirmatory test, anyone with fasting blood glucose of greater than 7mmol/L and HbA1c% greater than and equal to 6.5% were excluded.
4. Chronic conditions were excluded, as CRP could be high in those conditions. This includes self-reported history of: asthma, rheumatoid arthritis, chronic bronchitis, emphysema, chronic obstructive pulmonary disease, heart disease, heart attack, history of stroke, kidney dysfunction or disease or on dialysis, organ transplant, or liver or gall bladder problems.

5. Anyone who received chemotherapy in the previous four weeks.

6. Anyone with an acute condition (cold, flue, trauma, acute infection) was also excluded as these conditions can also cause elevated CRP.

7. Certain medications can alter the response of the inflammatory markers. To account this effect people taking platelet aggregation inhibitors and HMG-CoA reductase inhibitors were excluded.

4.6 Dependent Variable

Dependent variable (HOMAIR) is a continuous variable. Insulin Resistance (HOMAIR) is calculated by:

$$\text{Fasting Glucose (mmol/L) x Fasting Insulin (uUnits/L) / 22.5}$$

4.7 Independent Variables

High Sensitive CRP (hs-CRP) was originally a continuous variable. Population studies have shown that people with hs-CRP greater than 3 mg/L are at highest risk of cardiovascular complications[126]. As such, for this study we categorized hs-CRP into two categories with the cut-off of 3mg/L.

Sex is used as the dichotomous variable, male and female. Standing height, waist and hip circumference, high density lipoproteins, low density lipoprotein, serum triglycerides, and systolic and diastolic blood pressure were taken continuous variables.

BMI was used a categorical variable with six categories, using the CHMS classification:
1. = < 18.5
2. = 18.5-24.99
3. = 25-29.99
4. = 35-34.99
5. = 35-39.99
6. = 40 and above

Respondents were asked to identify their cultural and racial origin. The categories of race were aggregated into six categories to allow for comparison with adequate numbers in each group which are as follows:

1. Whites
2. Korean, Chinese, Japanese, Filipino,
3. South East Asians, South Asians, Western Asians
4. Black
5. Aboriginal (North American Indian, Metis, or Inuit)
6. Others (Latin, Multiple origins, Arab, and others)

To maintain the confidentiality of the survey participants, the minimum number of subjects in a cell cannot be less than thirty. Later, for the analysis, to ensure the adequate number of subjects for each cell, race was further aggregated into three categories and are as follows:

1. Whites
2. Korean, Chinese, Japanese, Filipino, South East Asians, South Asians and Western Asians
3. Black, Aboriginal, Others, Latin American, Arabs and others

Age was initially a continuous variable in the survey, but based on description, it was divided into four categories. Respondents were categorized into:

1. = Age 18 and 31years
2. = Age 31 and 46 years
3. = Age 46 and 60 years
4. = Age 60 years and above

In the CHMS study, smoking was categorized as self-reported type of smoker (daily, occasional, former daily, former occasional and never smoked). We grouped the smoking status categories into three categories as follows:

1. = Current Smoker
2. = Former Smoker
3. = Never Smoker

Patients in the non-diabetic category were divided into three categories. Data was divided so one subject was counted in each category. The categories are as follows:

1. HbA1c % less than 5.6% and Fasting Glucose less than 5.5mmol/L

2. HbA1c% 5.6-6% or Fasting Glucose between 5.5 and 6.1mmol/L

3. HbA1c greater than 6% or less than 6.5% or Fasting Glucose greater than 6.1 mmol/L and less than mmol/L

Each independent variable was put into the model individually to determine its relationship with the outcome variable. Only the variables reaching the initial cut-off significance of $p \leq 0.25$ were placed in the multiple linear regression model. Once a model with only significant predictors was established, the variables were tested for possible interactions and confounding.

4.8 Methods

CHMS cycles one, two, and three were used for this study. The data in each cycle was cleaned separately to select the variable of interest. All data files from the three cycles were merged with the combined weight file as per the Statistics Canada Guidelines.

The total number of participants in CHMS cycle one, two, and three was 17,695. After selecting participants from the fasted subsample who were eighteen years and older and did not have any history of self-reported diabetes, and if HbA1c and fasting blood glucose was less than 6.5% and 7mmol/L respectively, we have a total sample size of 4828. 837 who have been identified with a chronic disease and 326 respondents with an acute condition were also excluded. 266 respondents were excluded who were taking either antiplatelet or HMG Co-reductase inhibitors. There was some missing data related to CRP, LDL, and HDL and those cases were removed from the study. 2963 cases were included in the final analysis. (Appendix D).

4.9 Statistical Analysis

CHMS is a complex survey design. All variables with statistical significance of $p<0.20$ in bivariable analysis were included in the multivariable analysis. The two-sample student t-test

was conducted to compare the means between groups[127,128]. One-way ANOVA was used to compare means of three or more groups[127,128].

To determine the quality of an estimate using the coefficient of variation (CV) or to calculate confidence intervals, the standard error of the estimate was calculated. The standard error is the square root of the sampling varianc[129]. Since the CHMS uses a multi-stage survey design, there is no simple formula that can be used to calculate sampling variance. Instead, the bootstrap re-sampling method is used to consider the sample design information and to easily obtain variance estimates. *This method selects in each stratum, a simple random sample of (n-1) of the n first stage sampling units selected with replacement to form a replicate. In each replicate, the survey weight for each record in the (n-1) selected first stage sampling units is recalculated. These weights are then post-stratified according to demographic information in the same way as the survey weights to obtain the final bootstrap weights. This process is repeated 500 times for the CHMS. Combined bootstrap weights for C1, C2 and C3 provided by Statistics Canada were used for variance and sample weights for point estimation were applied[129].*

As HOMAIR was not normally distributed, log transformation was done to satisfy the assumption of multiple linear regression. Bivariable linear regression was conducted using log HOMAIR as a dependent variable and including each independent variable at a time in simple regression model. All independent variables had $p < 0.2$ except smoking and age category 2 (31-45 years). As smoking can cause high CRP, it was kept in the multivariable model because of its biological significance. (Appendix E).

CHAPTER FIVE: RESULTS

5.1   Population Characteristics

The overall response rate of people who fasted was equivalent for both male and female
participants (male = 46.5% and female 46.5%). In the final analysis, there was a total of 2963
participants that represented 7,234,480 members of the Canadian population. There were 1426
males and 1537 females. Cases in age category 1 (18-30 years), category 2 (31-45 years),
category 3 (46-60 years), and category 4 (61 and older) were 667, 1031, 714 and 551
respectively. 2293 cases were present in the hs-CRP category that were less than and equal to
3mg/L, and 670 cases were present in hs-CRP category greater than 3mg/L. In the smoking
category, 574 cases were current smokers, 813 former smokers, and 1576 never smokers. The
population was predominately of White ethnicity (n=2373) followed by Korean, Japanese,
Filipino (n=189), South East, South and West Asian (n=142), Black (n=83), and Aboriginal
(n=56). There were 1799 cases if HbA1c % <5.6% and fasting glucose <5.5mmol/L; 947 cases if
HbA1c% in the range 5.6-6% and fasting glucose between 5.5 and 6.1mmol/L; and 217 cases if
HbA1c > 6% and <6.5% or fasting glucose >6.1 mmol/L and <mmol/L (Table 5.1). Mean
adjusted HOMAIR was calculated using one-way ANOVA. Mean unadjusted HOMAIR in males
was 2.30(($\pm$1.81) (mean(($\pm$ S.E.)) and in females was 1.93(($\pm$1.49). Mean unadjusted HOMAIR
was 2.30(($\pm$1.66), 2.05(($\pm$1.63), 2.14(($\pm$1.67), 2.26(($\pm$1.68) for age groups 18-30 years, 31-45
years, 46-60 years and older than 61 years respectively. Mean unadjusted HOMAIR was 1.86(($\pm$
1.37) and 2.94 $\pm$((2.21) for CRP < 3 and CRP > 3 respectively. For non-diabetics, unadjusted
HOMAIR was 1.86(($\pm$1.43), 2.29(($\pm$1.65), 3.34(($\pm$2.55) if HbA1c < 5.6% and FBG <
5.5mmol/L, HbA1c 5.6-5.9% or FBG 5.5-6 mmol/L, and HbA1c 6-6.4% or FBG 6.1-6.9mmol/L
respectively. In the current-smoker category, it was 2.01(($\pm$1.53), in the former-smoker
2.23(($\pm$1.83), and in the never-smoker 2.08(($\pm$1.66). The mean unadjusted HOMAIR was
2.08(($\pm$1.64) among study participants of White ethnicity; 1.76 (($\pm$1.15) in Korean, Japanese, and

Filipino; 2.45((±1.94) in South East, South and West Asian; 2.54 ((±1.88) in Black; 2.65((±2.03) in Aboriginal; and 2.33((±1.77) in Others. (Table 5.1)

Table 5. 1 Population Characteristics

	Unadjusted HOMAIR Mean((±SD)
Sex	
Male (n=1426)	2.30((±1.81)
Female (n=1537)	1.93((±1.49)
Age	
18-30 (n=667)	2.30((±1.66)
31-45 (n=1031)	2.05((±1.63)
46-60 (n=714)	2.14((±1.67)
Older than 61 (n=551)	2.26((±1.68)
C Reactive Protein	
Less than 3mg/L(n=2293)	1.86((±1.37)
More than 3mg/L (n=670)	2.94((±2.21)
Smoking Category	
Current Smoker (n=574)	2.01((±1.53)
Former Smoker (n=813)	2.23((±1.83)
Never Smoker (n=1576)	2.08((±1.66)
Race	
White (n=2372)	2.08((±1.64)
Korean, Japanese, Filipino (n=189)	1.76((±1.15)
South East, South and West Asian (n=142)	2.45((±1.94)
Black (n=83)	2.54((±1.88)
Aboriginal (n=56)	2.65((±2.03)
Others (n=120)	2.33((±1.77)

Non-Diabetic Category	
HbA1c < 5.6 and FBG < 5.5 (n=1799)	1.86((±1.43)
HbA1c 5.6-5.9 or FBG 5.5-6 (n=947)	2.29((±1.65)
HbA1c 6-6.4 or FBG 6.1-6.9 (n=217)	3.34((±2.55)

5.2 Mean of Independent Variable in the Total Population by Sex

Mean ((± S.E.) age at the time of clinic visits was 42.79((±15) years for males and 43((±15) years for females. Mean insulin (pmol/L) ((±S.E) was 65.5((±47.81), 70.17((±52.01), 61.46((±43.1) in the total population, males and females respectively. Mean insulin (used in the calculation of HOMAIR) was lower in females than males, which was consistent with the evidence that females have lower insulin resistance. Mean glucose (mmol/L) was 4.93((± 0.49), 5.05((±0.48), and 4.82((±0.49) in the total population, males and females respectively. Mean CRP (mg/L) was 2.18((±2.49) in the total population, 1.91((±2.19) in males, and 2.44((±2.70) in females. Mean CRP was slightly higher in females than males. In the multivariate model, CRP was used as a categorical variable with the cut-off of 3 mg/L and, therefore, would not affect the results. Mean HDL (mmol/L) was 1.41((± 0.39) in the total population, 1.25((±0.31) in males, and 1.54((±0.41) in females. Mean triglycerides (mmol/L) in the total population was 1.29((± 0.77), in males was 1.42((±0.89) and in females was 1.18((±0.62). Mean LDL (mmol/L) was 3.04((± 0.99), 3.19((±1.04), and 2.90((±0.92) in the total population, male, and female respectively. Mean BMI was 26.63 in the total population, 27((±4.59) in males and 26((±5.55) in females (Table 5.2).

Table 5. 2 Mean and Standard Deviation of Independent Variables in Male And Female

	Mean((±SD)	Mean((±SD) Male	Mean((±SD) Female	p- value
Insulin	65.5((±47.81)	70.17((±52.01)	61.46((±43.1)	<0.0001
Glucose	4.93((±0.49)	5.05((±0.48)	4.82((±0.49)	<0.0001
C-reactive protein	2.18((±2.49)	1.91((±2.19)	2.44((±2.70)	<0.0001
HOMAIR	2.10((±1.66)	2.30((±1.81)	1.92((±1.47)	<0.0001
HDL cholesterol	1.41((±0.39)	1.25((±0.31)	1.54((±0.41)	<0.0001
Triglycerides	1.29((±0.77)	1.42((±0.89)	1.18((±0.62)	<0.0001
LDL cholesterol	3.04((±0.99)	3.19((±1.04)	2.90((±0.92)	<0.0001
Total cholesterol	4.99((±1.004)	5.0((±1.01)	4.97((±0.99)	<0.0001
Hip Circumference	35.84((±5.93)	40.55((±3.32)	40.74((±4.71)	<0.0001
Waist Circumference	40.65((±4.10)	37.59((±5.32)	34.21((±6.01)	<0.0001
Body Mass Index	26((±5)	27((±4.59)	26((±5.55)	<0.0001
Average Systolic BP	110((±14)	112.18((±13)	108.15((±16)	<0.0001
Average Diastolic BP	70((±9)	73((±9)	68((±8)	<0.0001
Age at clinic visit	43((±15)	42.79((±15)	43((±15)	<0.0001

(Value of Insulin in pmol/L, Glucose in mmol/L, CRP in mg/L, HDL, Triglycerides, LDL, Total Cholesterol in mmol/L, Hip and Waist Circumference in inches, Blood pressure in mmHg)

5.3 Mean of Independent Variable in the Total Population by Race

Study participants of White ethnicity were slightly older [Mean ((±S.E.): 44((±15)] compared to Korean, Japanese, Filipinos, East, South and West Asian 39((±13) and Aboriginal, Black and Others 39((±14). Fasting insulin levels were the highest in Aboriginal, Black and Others 77.93(±54.79), followed by Whites 64.49((±47.05) and Korean, Japanese, Filipinos, East, South and West Asian 64.38((±46.12). Fasting glucose values were very close in all three categories of Race 4.95((±0.50), 4.90((±0.46), 4.87((±.48). Body mass index was highest in Aboriginal, Black and Others 27.36((±5.77), followed by Whites 26.84((±5.14) and Korean, Japanese, Filipinos, East, South and West Asian 24.59((±4.09). Waist circumference was highest in Aboriginal, Black and Others 36.57± ((8.13) and Whites 36.09((±5.75) followed by Korean, Japanese, Filipinos, East, South and West Asian 33.47((±4.46) (Table 5.3).

Table 5. 3: Mean and Standard Deviation of Independent Variables by RACE

	Mean((± SD)	Mean((±SD) White	Mean((±SD) Korean, Japanese, Filipinos, East, South and West Asian	Mean((±SD) Aboriginal, Black And Others
Insulin	65.5((±47.81)	64.49((±47.05)	64.38((±46.12)	77.93((±54.79)
Glucose	4.93((±0.49)	4.95((±0.50)	4.90((±0.46)	4.87((±.48)
C-reactive protein	2.18((±2.49)	2.23((±2.51)	1.78((±2.13)	2.31±((2.65)
HDL cholesterol	1.41((±0.39)	1.42((±0.41)	1.34((±0.34)	1.36±((0.37)
Triglycerides	1.29((±0.77)	1.29((±0.75)	1.37((±0.77)	1.29((±0.95)
LDL cholesterol	3.04((±0.99)	3.06((0.98)	2.93((±1.02)	2.99((±1.022)
Total cholesterol	4.99((±1.004)	5.02((±1.01)	4.85((±0.97)	4.89((±0.98)
Waist Circumference	40.65((±4.10)	36.09((±5.75)	33.47((±4.46)	36.57((±8.13)
Hip Circumference	35.84((±5.93)	36.09((±3.9)	38.53((±3.29)	41.35((±5.69)
Body Mass Index	26.63((±5.14)	26.84((±5.14)	24.59((±4.09)	27.36((±5.77)
Systolic BP	110((±14)	110((±15)	107((±13)	108((±14)
Diastolic BP	70((±9)	70((±9)	70((±9)	70((±10)
Age at clinic visit	43((±15)	44((±15)	39((±13)	39((±14)

Table 5. 4: Mean and Standard Deviation of Independent by Various Levels of Glucose and HbA1c

	Mean ((±SD)	Mean((±SD) HbA1c < 5.6 and FBG < 5.5	Mean((±SD) HbA1c 5.6-5.9 or FBG 5.5-6	Mean((±SD) HbA1c 6-6.4 or FBG 6.1-6.9
Insulin	65.5((±47.81)	60.7((±45.2)	69.22((±46.39)	91.10((±63.10)
Glucose	4.93((± 0.49)	4.76((±0.34)	5.09((±0.49)	5.62((±0.68)
C-reactive protein	2.18 ((± 2.49)	1.99((±2.36)	2.38((±2.62)	2.91((±2.69)
HDL cholesterol	1.41((± 0.39)	1.42((±0.39)	1.4((±0.40)	1.32((±0.36)
Triglycerides	1.29((± 0.77)	1.20((±0.67)	1.38((±0.83)	1.68((±1.07)
LDL cholesterol	3.04((± 0.99)	4.83((±0.96)	3.23((±1.02)	3.36((±1.14)
Total cholesterol	4.99((± 1.004)	4.84((±0.96)	5.20((±1.02)	5.32((±1.08)
Waist Circumference	35.84((± 5.93)	35.08((±5.88)	36.74((±5.75)	38.21((±5.97)
Hip Circumference	40.65((±4.10)	40.33((±4.04)	41.034((±4.08)	41.69((±4.37)
Body Mass Index	26.63((± 5.14)	26.02((±4.93)	27.34((±5.24)	28((±5.55)
Systolic BP	110.1((±14.88)	107((±13.38)	113((±16.29)	117((±15.49)
Diastolic BP	70.72((± 9.31)	69.57((±9.02)	72.18((±9.53)	73.92((±9.00)

(Value of Insulin in pmol/L, Glucose in mmol/L, CRP in mg/L, HDL, Triglycerides, LDL, Total Cholesterol in mmol/L, Hip and Waist Circumference in inches, Blood pressure in mmHg)

5.4 Observed (Unadjusted) HOMAIR

When we analyzed the threshold of HOMAIR between male and females, the cut-off of Observed HOMAIR was 2.88 for males and 2.33 for females at the 75th percentile. (Table 5.5.1).

Table 5.5: Percentile of Observed HOMAIR in Male and Female

Observed HOMAIR in Males: **Mean 2.30((±1.81)**   **75th Percentile at 2.88**
Observed HOMAIR in Females: **Mean 1.93((±1.47)**   **75th Percentile at 2.35**

		Males	Females
N		N= 1426	N = 1537
Percentiles	10	.7999	.7066
	20	1.0174	.9294
	25	1.1340	1.0000
	30	1.2560	1.0889
	40	1.5110	1.2910
	50	1.7825	1.5048
	60	2.0978	1.7733
	70	2.5689	2.1255
	75	2.8819	2.3497
	80	3.3023	2.6514
	90	4.4202	3.5540

The association of insulin resistance (HOMAIR) with C-reactive protein was significant after controlling for sex, HDL, triglyceride, blood pressure, waist and hip circumference, BMI, race, and age. As association was significant for Sex and CRP. Predicted values for logHOMAIR was calculated and the predicted mean (adjusted HOMAIR mean) was reported after taking the antilog.

5.5 Association between Adjusted HOMAIR and CRP by Age from a Multivariable Model:

Adjusted insulin resistance was higher in all age categories with high CRP for the adjusted model for BMI and waist circumference. HOMAIR from the adjusted model in different age groups was: Age category 1 (18-30 years) 1.56(($\pm$0.59) and 2.76(($\pm$2) for low and high CRP and was statistically significant; Age category 2 (31-45 years) was 1.60(($\pm$0.77) and 2.58(($\pm$1.28) for low and high CRP; Age category 3 (46-60 years) was 1.68(($\pm$0.7) and 2.66(($\pm$1.3) for low and high CRP, and; Age Category 4 (61 and older) was 1.82(($\pm$0.78) and 2.44(($\pm$1.09_ for low and high CRP (Table 5.7).

Table 5. 6 Adjusted HOMAIR with High and Low CRP by Age (Adjusted for sex, race, smoking, blood pressure, systolic and diastolic blood pressure, BMI, waist circumference, HDL, LDL, serum total cholesterol)

Adjusted HOMAIR Mean (95% CI)	Age (yrs)	CRP < 3mg/L	CRP>3mg/L	P-value
	18-30	1.56(($\pm$0.59)	2.76(($\pm$2.00)	<0.0001
	31-45	1.60(($\pm$0.77)	2.58(($\pm$1.28)	<0.0001
	46-60	1.68(($\pm$0.70)	2.66(($\pm$1.30)	<0.0001
	Older than 61	1.82(($\pm$0.78)	2.44(($\pm$1.09)	<0.0001
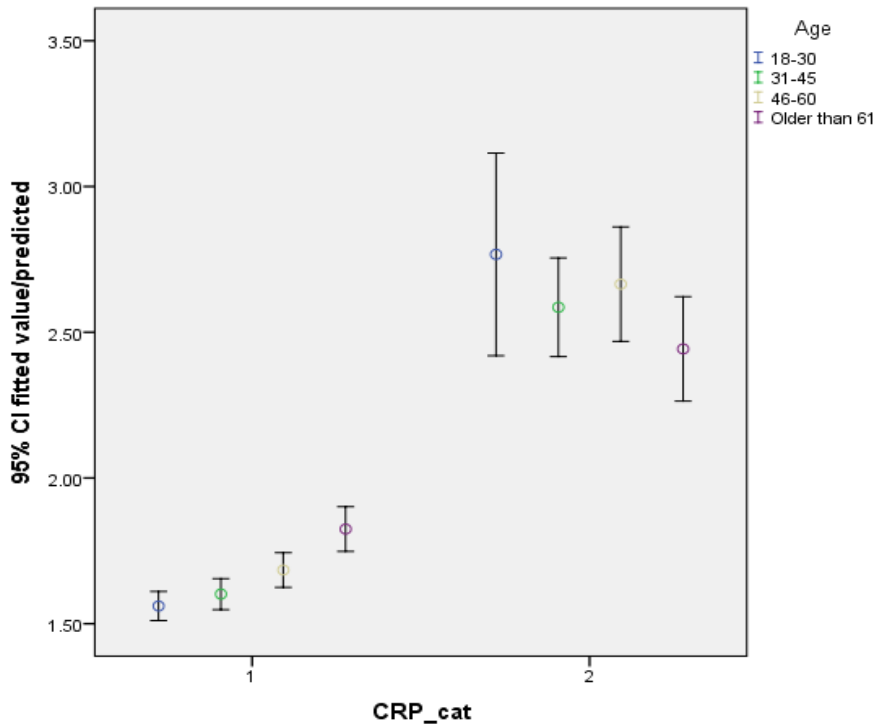
Figure 5. 1 Error Bar Plot: Association between CRP and HOMAIR by Age

5.6 Adjusted HOMAIR with CRP by Sex

Insulin resistance was higher in males than females. Adjusted HOMAIR((±SD) in males was 1.81((± .79) and 2.88((±1.39) with low and high CRP respectively. However, in females adjusted HOMAIR is 1.48((±.59) and 2.43((±1.412) with low and high CRP respectively. (Table 5.7). When stratified by age, in men HOMAIR was 1.63((±0.61) in age category 18-30 years with low CRP, and 3.11((±1.71) for high CRP, 1.83((±0.89) in age category 31-45 years with low CRP and 2.82((±1.13) with high CRP, 1.86((±0.76) in age category 46-60 years with low CRP and 2.95((±1.62) with high CRP and 1.99((±0.84) in age category over 61 years with low CRP and 2.75((±1.28) with high CRP.

In females, adjusted HOMAIR was: 1.49((±0.56) in age category 18-30 years with low and CRP 2.61((±2.11) for high CRP, 1.36((±0.52) in age category 31-45 years with low CRP and 2.39((±1.37) with high CRP, 1.48((±0.59) in age category 46-60 years with low CRP and

2.48((±1.01) with high CRP and 1.68((±0.69) in age category over 61 years with low CRP and 2.26((±0.93) with high CRP (Table 5.8).
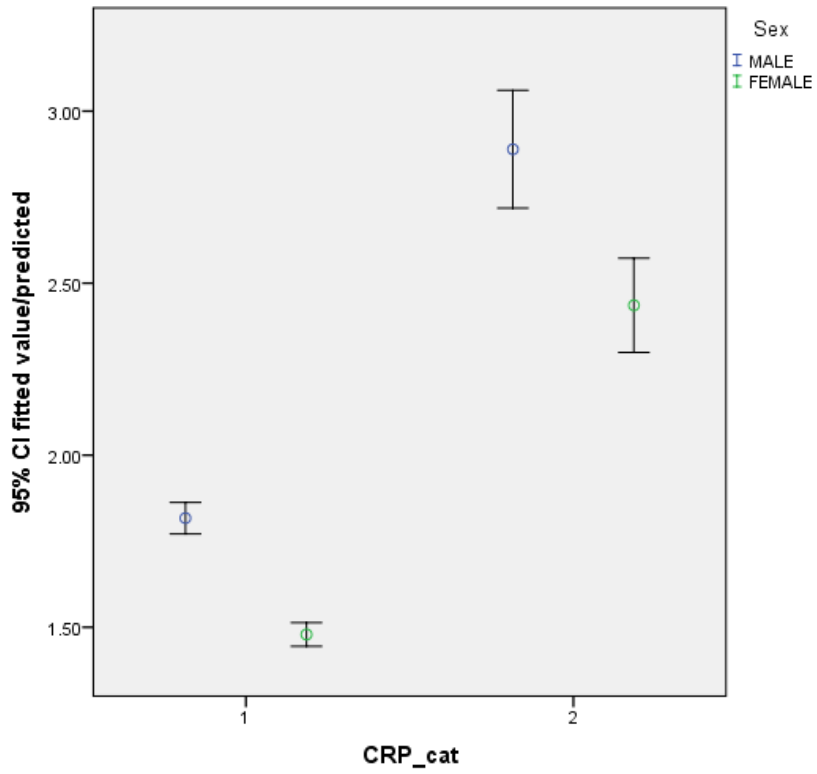
Figure 5. 2 Error Bar Plot: Association between CRP and HOMAIR by Sex:

Table 5. 7: **Difference in Insulin Resistance with High and Low CRP in Male and Female**

		CRP < 3mg/L	CRP>3mg/L	p-value
Adjusted HOMAIR Mean((±SD)	Male	1.81((± 0.79)	2.88((±1.39)	<0.0001
	Female	1.48((±0.59)	2.43((±1.412)	<0.0001

Table 5. 8: **Difference in Insulin Resistance with High and Low CRP in Male and Female by Age**

		CRP < 3mg/L		CRP>3mg/L		p-value
	AGE (yrs)	**Male**	**Female**	**Male**	**Female**	
Adjusted HOMAIR Mean ((±SD)	18-30	1.63((±0.61)	1.49((±0.56)	3.11((±1.71)	2.61((±2.11)	<0.0001
	31-45	1.83((±0.89)	1.36((±0.52)	2.82((±1.130)	2.39((±1.37)	<0.0001
	46-60	1.86((±0.76)	1.48((±0.59)	2.95((±1.62)	2.48((±1.01)	<0.0001
	Older than 61	1.99((±0.84)	1.68((±0.69)	2.75((±1.28)	2.26((±0.93)	<0.0001

5.7 Adjusted HOMAIR with CRP by Ethnicity

Mean adjusted HOMAIR in Whites was 1.63((±0.69)(1.59-1.66) with CRP < 3 mg/L and higher with high CRP at 2.57((±1.44)(2.44-2.69) with CRP > 3mg/L. In Korean, Chinese, Japanese and Filipino, South East Asian, South and West Asian mean adjusted HOMAIR was 1.62((±0.56)(1.55-1.68) and 2.51((±1.13)(2.22-2.81) with low and high CRP respectively. Mean adjusted HOMAIR in Black, Aboriginal and Others when CRP was low was 1.91((±1.08)(1.76-2.06) and when CRP was high was 3.07((±1.36)(2.72-3.41) (Table 5.9).

Table 5. 9: Difference in Insulin Resistance with High and Low CRP by Ethnicity

		CRP < 3mg/L	CRP>3mg/L	p-value
Adjusted HOMAIR Mean ((±SD)	**White**	1.63((±0.69)	2.57((±1.44)	<0.0001
	Korean, Chinese, Japanese and Filipino, South East, South and West Asian	1.62((±0.56)	2.51((±1.13)	<0.0001
	Black, Aboriginal, Others (Arabs and Latin American)	1.91((±1.08)	3.7((±1.36)	<0.0001

5.8 Adjusted HOMAIR with CRP by Various Levels of Glucose and HbA1c

Mean adjusted HOMAIR for HbA1c < 5.6% and FBG < 5.5 mmol/L was 1.57((±0.64) (1.54-1.60) and 2.44((±1.37) (2.31-2.59) with low and high CRP respectively. If HbA1c was between 5.6-5.9% and fasting blood glucose was between 5.5-6 mmol/L, mean adjusted HOMAIR was 1.74((±0.81) (1.68-1.80) with low CRP and 2.73((± 1.51) (2.54-2.93) with high CRP. If HbA1c was between 6-6.4% and fasting blood glucose between 6.1-6.9 mmol/L, it was 2.01((±0.88) (1.86-2.15) and 3.01((±1.28) (2.71-3.30) with high and low CRP respectively.

Table 5. 10 Difference in Insulin Resistance with High and Low CRP by Various Levels of Glucose and HbA1c: (Adjusted for BMI and WC)

		CRP< 3mg/L	CRP>3mg/L	p-value
Adjusted HOMAIR Mean ((±SD)	HbA1c < 5.6 and FBG < 5.5	1.57((±0.64)	2.44((±1.37)	<0.0001
	HbA1c 5.6-5.9 or FBG 5.5-6	1.74((±0.81)	2.73((±1.51)	<0.0001
	HbA1c 6-6.4 or FBG 6.1-6.9	2.01((±0.88)	3.01((± 1.28)	<0.0001

5.9 Confounding Factors to Consider

To be a confounder[130]:

1. The variable must be independently associated with the outcome (i.e. be a risk factor).
2. The variable must be also associated with the exposure under study in the source population.
3. It should not lie on the causal pathway between exposure and disease.

Confounding is present if the relationship between HOMAIR and CRP has meaningfully different (difference of > 10%) interpretations when extraneous variables are present. LDL, blood pressure, smoking can cause high CRP. BMI, waist circumference and hip circumference could be related to insulin resistance. Therefore, LDL, blood pressure, smoking, BMI, hip and waist circumference were checked for confounding[131].

The coefficient for CRP category did not change meaningfully when LDL was removed from the model to check for confounding.

The crude estimate for CRP was 0.067 (Standard error of estimate of 0.015, p<0.0001) when blood pressure was not included in the model, and the adjusted the CRP estimate was 0.068 (Standard error of 0.015, p<0.0001) when blood pressure was included in the model. This suggests blood pressure was not a confounder. Our crude estimate when smoking was not included in the model was 0.670074 (Standard error of estimate of 0.015, p< 0.0001) and adjusted estimate when smoking was in the model was 0.068 (Standard error of estimate 0.015, p<0.0001), which suggested that smoking is not a confounder.

Age did not appear to be a confounder when two models were fitted by including age in the model and by excluding it. The crude estimate for CRP when waist circumference was excluded from the model was 0.077 (Standard Error of estimate of 0.015 and p<0.000). The crude estimate for CRP when BMI was not in the model was 0.076 (Standard error of estimate 0.015 and p < 0.000). This was 10.5% higher than the adjusted estimate. Hip circumference was not a confounder with a crude estimate of 0.069 (Standard error of estimate is 0.015 and p<0.00) and an adjusted estimate of 0.068 (Standard error of estimate 0.015, p<0.000).

5.10 Accounting for Possible Interactions

Interaction is present when the relationship between HOMAIR and CRP is different at different levels of extraneous variable (smoking, age, sex)[130].

As smoking has been associated with high CRP, interaction between CRP and smoking was checked and was not statistically significant (p-value 0.666 for former smoker and 0.932 for former and never smoker with current smoker as a reference).

Interactions for CRP and age was not significant in our results as well (p value of 0.70, 0.44 and 0.564 for age 31-45, 46-60 and 61 and older with 18-30 as a reference category)

There was no interaction between BMI and CRP in our population. Interaction for CRP and sex was significant (p value of less than 0.008) and was included in the model.

5.11 Sub-Group Analysis

Physical activity has been shown to be inversely related to insulin resistance. The Physical Activity Index in cycles one and two was classified into active, moderate, or inactive based on the reported energy expenditure. The Physical Activity Index follows the same criteria used to categorize individuals in the Ontario Health Survey (OHS) and in the Campbell's Survey on Well Being[132]. In cycles one and two, the household questionnaire asked about the frequency and duration of physical activity in the last three months. However, in cycle three more detailed and specific questions were asked about the frequency and duration of the activity over the previous seven days. As the physical activity data was reported differently in C3 from C1 and C2, subgroup analysis was conducted by merging C1 and C2 to assess the association of level of physical activity and HOMAIR. The total sample size was 1949 after merging C1 and C2. There were 470 people in the active group, 522 in the moderate active group, and 957 in the inactive group. We acknowledge the obvious limitations of self-reported physical activity scores to make correlations with measures of insulin resistance.

One-way ANOVA was conducted to compare the means among all three groups with high and low CRP. Mean adjusted HOMAIR was highest in the inactive group and lowest in the active group. However, regardless of the physical activity index, adjusted HOMAIR was higher with high CRP. This shows that even in people who are physically active, HOMAIR is high with high CRP.

Table 5.11 Difference in Insulin Resistance with High and Low CRP by Physical Activity Index

Adjusted HOMAIR Mean((±SD)	Physical Activity Index	CRP < 3mg/L	CRP>3mg/L	P-value
	Inactive	1.69((±0.81)	2.64((±1.53)	<0.0001
	Moderate Active	1.67((±0.72)	2.47((±1.27)	<0.0001
	Active	1.55((± 0.62)	2.45((±1.65)	<0.0001

CHAPTER SIX: DISCUSSION

6.1   Insulin Resistance and Age

In the literature, the effect of age on insulin resistance is controversial. Some authors believe that age is a powerful indicator for insulin resistance and suggested that increasing insulin resistance with advancing age could be attributed to an increase in body fat composition and a decrease physical activity[133, 134]. Defronzo et al. demonstrated that insulin resistance increases with age by using the euglycemic clamp method in eighty-four healthy volunteers[133-136]. On the contrary, in a retrospective analysis of EGIR (European Group for the study of Insulin Resistance) study, when the euglycemic clamp method was used to determine insulin resistance, there was no increasing trend with age and insulin resistance[137]. Boden et al. concluded that insulin resistance appears to be more related to body fat than to the effect of age based on the uptake of glucose using the gold-standard euglycemic hyperinsulinemic clamp in healthy men of any age. They determined that body fat percentage correlated negatively with glucose uptake regardless of age[138]. Similarly, Basu et al. measured IR and insulin secretion with both meal and intravenous glucose minimal models and concluded that the defect in insulin action is mainly due to the degree of obesity rather than age in healthy adults[133].

We used calculated HOMAIR instead of a euglycemic clamp to determine insulin resistance, as discussed in Chapter 2. HOMAIR is less invasive and has a positive correlation with euglycemic clamp methods. In our study, after adjusting for all covariates (age, sex, race, smoking, blood pressure, systolic and diastolic blood pressure, BMI, waist circumference, HDL, LDL, serum total cholesterol) HOMAIR did not show any trend with increasing age (Table 5.6). Defronzo et al. in a retrospective analysis of EGIR did not adjust for sex when reporting IR with age, however in our study, when sex was taken into consideration, adjusted HOMAIR showed a positive trend with increasing age in males but not in females (Table 5.8). The Epidemiological Study of Renal Insufficiency in Spain (EPRICE) also used calculated HOMAIR for IR and did not show any association between increasing age and HOMAIR. Moreover, the EPRICE study, even when sex was taken into consideration, did not show any trend with age in males but did show a positive trend in females of fifty years and older[139].

We have reported mean adjusted HOMAIR stratified by age and sex when CRP was low and high (cut-off of 3mg/L), which deviates from the current literature. In this study, adjusted HOMAIR increased with age in males when CRP is low, however this trend was not seen when CRP was high in males (Table 5.8). In females, there was no trend observed with high or low CRP but HOMAIR was highest in the oldest age category (older than 61 years) when CRP was low. Women typically begin to experience menopausal symptoms between forty and fifty-eight years of age[140]. It has also been postulated that estrogen has a protective role for IR in females, which presumably would correlate with a lower calculated HOMAIR in premenopausal populations. This was consistent with the observation that increases in insulin resistance after menopause can be decreased through hormone replacement therapy[141]. Further to the role of estrogen in insulin sensitivity, when estradiol was given to the male rodents in animal studies, diabetes was reversed[142-144]. The highest HOMAIR was in the oldest age category (older than 61 years) when CRP was low is consistent with the literature that IR is highest in menopause[139]. However, we did not see this effect when CRP was high. It was difficult to compare these findings with the existing literature as, to the best of our knowledge, no study has considered the association of HOMAIR with CRP stratified by age and sex.

We had extensive data available on acute and chronic conditions in CHMS. Subjects with acute or chronic conditions were excluded from the analysis. Few, but not all, studies have adjusted for acute and chronic medical conditions. As the prevalence of chronic diseases keeps increasing with age, it is important to account for chronic diseases to assess the association of insulin resistance with inflammation. It is also crucial to see the effect on age in different sexes. In this study, age influenced insulin resistance in men but not in women.

6.2 Insulin Resistance and Sex

In our study, insulin resistance was higher in males than females after excluding any acute or chronic conditions and adjusting for all other covariates such as age, sex, race, smoking, blood pressure, systolic and diastolic blood pressure, BMI, waist circumference, HDL, LDL, and serum total cholesterol. The effect was persistent in all age categories with high or low CRP (Table 5.8). However, when CRP was high association was strongest in the youngest age category. In

age group 18-30 years in males the risk of high HOMAIR was seven-times higher with high CRP than with low CRP and almost three-times higher in women with high CRP than low CRP.

Females have a lower baseline mean HOMAIR then males[139]. We found lower HOMAIR in females than males with both low and high CRP. The greater amounts of visceral and hepatic fat, along with the lack of the protective effect of estrogens, may be related to higher insulin resistance in men than in women[145-148]. This indicates that gender hormones may have an influence on insulin resistance. The increase in insulin resistance with menopause suggests that estrogens may play a role in promoting the insulin sensitivity observed in women. Some of this risk is also hereditary. The risk of developing overt diabetes in much higher in women whose mother also is diabetic. However, for men the risk is equal if either parent is diabetic.

In our study inflammation (CRP) showed significant association with IR (HOMAIR) both in males and females in all age categories, as described in the previous section. It is consistent with findings found in the Peruvian adult population and the Japanese population where Bizu et al. and Nakanishi et al. demonstrated that high CRP is positively associated with insulin resistance (as measured by HOMAIR) in both males and females[149,150].

6.3 Insulin Resistance and Ethnicity

In our study, insulin resistance showed a significant association with inflammation (CRP) in all race categories. In most cases, Asians have statistically smaller height and weight averages with a higher percentage of body fat than whites. This observation was consistent in our results (Table 5.9). In the population we studied, Asians had the lowest BMI and waist circumference. Gao et al. examined the association of insulin resistance between adult Chinese, Malays, and Asian Indians residing in Singapore, postulating that as the incidence of type 2 diabetes was different between ethnic groups within Asia, insulin resistance was also different[151]. In that study, IR was measured using HOMAIR. HOMAIR was found to be highest in Asian Indians. The association between ethnicity and insulin resistance was mediated by BMI, BMI adjusted waist circumference, unidentified risk factors, and, to a small extent, C-reactive protein. These findings suggested that excess weight may play an important role in ethnic disparities of insulin

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resistance. C-reactive protein was also independently associated with insulin resistance after adjusting for intra-abdominal adipose tissue in whites but not in African Americans[152]. Unlike these other observation studies which reported that Asians have greater insulin resistance than Whites[153-154], we did not see higher HOMAIR in Asians as compared to Whites (Table 5.9). Due to the limited sample size, Asians were not analyzed separately in sub-groups. When more cycles of CHMS are available in future, separate analysis can be done to examine the association between IR and inflammation (CRP) in different Asians subgroups.

Adjusted HOMAIR was higher in Blacks, Aboriginal, Arabs, and Latin American than in Whites and Asians. Due to our subgroup sample size limitations, analysis was not done separately in Black, Aboriginal, Arab, and Latin American sub-groups. Data from the First Nation Bone Health Study in Canada suggested that Aboriginal women have higher insulin resistance than White women. However, there were only weak correlations between HOMAIR and inflammation markers (Tumor necrosis factor alpha, interleukin-6, and C-reactive protein) and the association was not significant after adjustment for body fat[155]. When more cycles of CHMS are available, data can be combined to assess any association between IR and CRP in Aboriginals and Black sub-groups separately.

Some studies have examined the association of inflammation and IR in different ethnicities individually, but to our knowledge there is no significant data available as they relate to the Canadian population. Our study is one of the first to consider the effects of inflammation in different ethnicities. A possible next step would be to include additional cycles of the CHMS when they become available in order to increase the sample size to better assess the association between IR and inflammation in each ethnicity. Certain ethnicities might have stronger associations between IR and inflammation and may require focused interventions to treat insulin resistance.

6.4 Insulin Resistance at Various Levels of Glycaemia

HOMAIR has a linear relationship with HbA1c and fasting blood glucose. In our study, we found a positive association between IR (HOMAIR) and inflammation (CRP) at any level of

glycemia (Table 5.10) after adjusting for age, sex, race, smoking, blood pressure, systolic and diastolic blood pressure, BMI, waist circumference, HDL, LDL, and serum total cholesterol. Even in subgroups that do not meet any definition of prediabetes, HOMAIR was higher with high CRP. It may be possible that inflammation triggers insulin resistance even before any change is noticed in fasting glucose and HbA1c. This means that interventions can be focused on this stage to prevent insulin resistance and the loss of pancreatic beta cells. Future prospective studies are needed to determine the incidence of CVD in diabetes in a sub-group who have normal fasting blood glucose and HbA1c but high CRP.

6.5 Limitations and Strengths of the Study

There are several limitations to this study. A cross-sectional design of this study did not allow us to definitively identify a causal relationship between insulin resistance and inflammation (CRP). Rather, prospective studies are needed to cleanly evaluate if high CRP is a causative factor for insulin resistance. Another limitation was related to our ability to assess physical activity. As data on physical activity in CHMS cycles one and cycle two was reported differently than cycle three, the model was not adjusted for physical activity. Another limitation of our study was that in some ethnic categories, sample size was small and separate analyses for individual ethnicities was not possible. In the future, when more cycles of CHMS are available, this type of analysis would be possible through an increased sample size. Finally, we did not adjust the multivariable model with alcohol consumption. Heavy alcohol consumption could have negative association with HOMAIR[139, 156,157]. In other studies, alcohol consumption was reported as grams per day or drinks per day. However, in our data it was reported as number of drinks per week or per month. Due to the discrepancy in how alcohol consumption was reported and in order to include only important covariates to keep the multivariable model small, we did not include alcohol consumption in our analysis.

The major strength of this study was the use of a large population-based sample (Table 5.1). The CHMS is an extensive survey with comprehensive information. CHMS is the first large population-based study that has collected information on multiple co-morbidities and clinical markers such as fasting insulin and glucose blood tests. It provided extensive information on

acute and chronic diseases, which were excluded from our analysis to avoid confounding. Also, to our knowledge, no studies have reported the associated between IR (inferred from HOMAIR calculations) and inflammation (CRP) by age and sex in a Canadian population.

CHAPTER SEVEN: SUMMARY AND FUTURE DIRECTIONS

7.1 Summary

Insulin resistance is one of the acknowledged contributors in the pathogenesis of DM2. The asymptomatic stage with high insulin resistance and the stage of mild postprandial hyperglycemia are significant markers for patients at risk of developing diabetes. Patients at this phase may benefit from lifestyle modification and pharmacological intervention to prevent the progression of a disease. Inflammation is emerging as one of the factors of inflammation. In this study, we examined the association between insulin resistance (HOMAIR) and inflammatory marker (CRP) using data from Canadian Health Measure Survey in a non-diabetic sample population of Canadians. We examined differences by gender, age, ethnicity, and at different levels of glucose and HbA1c. To our knowledge, this is the first population-based study to examine the relationship between insulin resistance and inflammation by age, gender, and ethnicity in Canadian non-diabetic population. We demonstrated that the association between insulin resistance and inflammation is positive and that further prospective studies and interventions are needed to show that inflammation may be a causative factor of insulin resistance.

7.2 Future Directions

More prospective studies are needed to evaluate the effect of anti-inflammatory medications in the prevention of diabetes in the subgroup of people even with normal glucose but with high CRP and insulin resistance (HOMAIR). Further studies can be done on available Canadian statistical information to determine if people with high CRP and high IR but normal glucose levels are more prone to have cardiovascular complications than people with low IR and low CRP. This study would help to define optimal cut off values for HOMAIR in the population with the limitation as described above.

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Correlation of HOMAIR With Other Methods to Measure Insulin Resistance:

Homeostasis model assessment: insulin resistance and cell function from fasting plasma glucose and insulin concentrations in man

D. R. Matthews, J. R Hosker, A. S. Rudenski, B. A. Naylor, D. F. Treacher and R. C. Turner Diabetes Research Laboratories, Radcliffe Infirmary,Oxford,UK
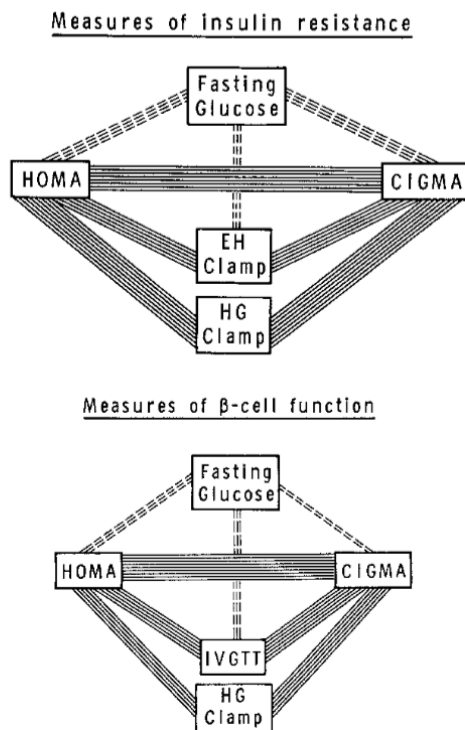
Diabetologia (1985)28:412-419

Fig. 4. A graphical summary of the correlations between the tests used to estimate β-cell function (upper panel) and insulin resistance (lower panel) from the six normal and six diabetic subjects studied on three occasions. HOMA=homeostasis model assessment; CIGMA=continuous infusion of glucose with model assessment; EH Clamp=euglycaemic hyperinsulinaemic clamp; HG clamp=hyperglycaemic clamp; IVGTT=intravenous glucose tolerance test. The hyperglycaemic clamp data are from 10 normal and 11 diabetic subjects. Each line represents a Spearman rank correlation coefficient of 0.1 units (thus 5 lines indicate $R_s=0.5$); —— $=p<0.05$, ----- $=p>0.05$

Conceptual Framework of The Canadian Health Measure Survey:

Conceptual framework for the CHMS

Shaded circles indicate interactions among the arrows.

Examples of non-modifiable population health determinants include: age, sex, ethnicity, genotype; examples of modifiable population health determinants include: income, education, social environment, physical environment, health care system; examples of health behaviours include: physical activity, nutrition, alcohol and substance abuse, smoking status, medication use, sex behaviours, stress exposures; examples of health characteristics include functional status, immunization status, stress reactivity, body weight, cardiovascular fitness, musculoskeletal fitness, metabolic fitness; examples of health outcomes include detectable disease, health care system contact, disability.
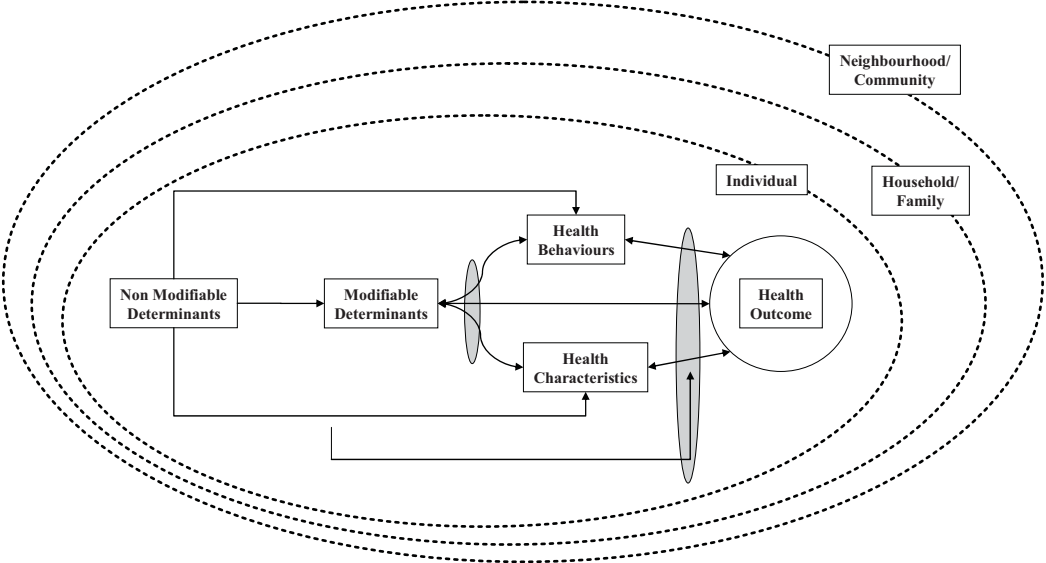
Adopted from Mark S. Tremblay, Sarah Connor Gorber, Canadian Health Measures Survey, Brief Overview; CANADIAN JOURNAL OF PUBLIC HEALTH: NOVEMBER – DECEMBER 2007

APPENDIX C

Summary of The Cycles of Canadian Health Measure Survey:

CHMS			
Cycle 1	2007-2009	New Brunswick, Quebec, Ontario, Alberta and British Columbia.	n = 5600 (6-79)
Cycle 2	2009-2011	Newfoundland and Labrador, Nova Scotia, Quebec, Ontario, Manitoba, Alberta and British Columbia.	n= 6,395 people (aged 3 to 79)
Cycle 3	2012-2013	Ten provinces across Canada	n = 5700 (aged 3 to 79)

APPENDIX D

Flow Chart Summarizing Inclusion and Exclusion Criteria:
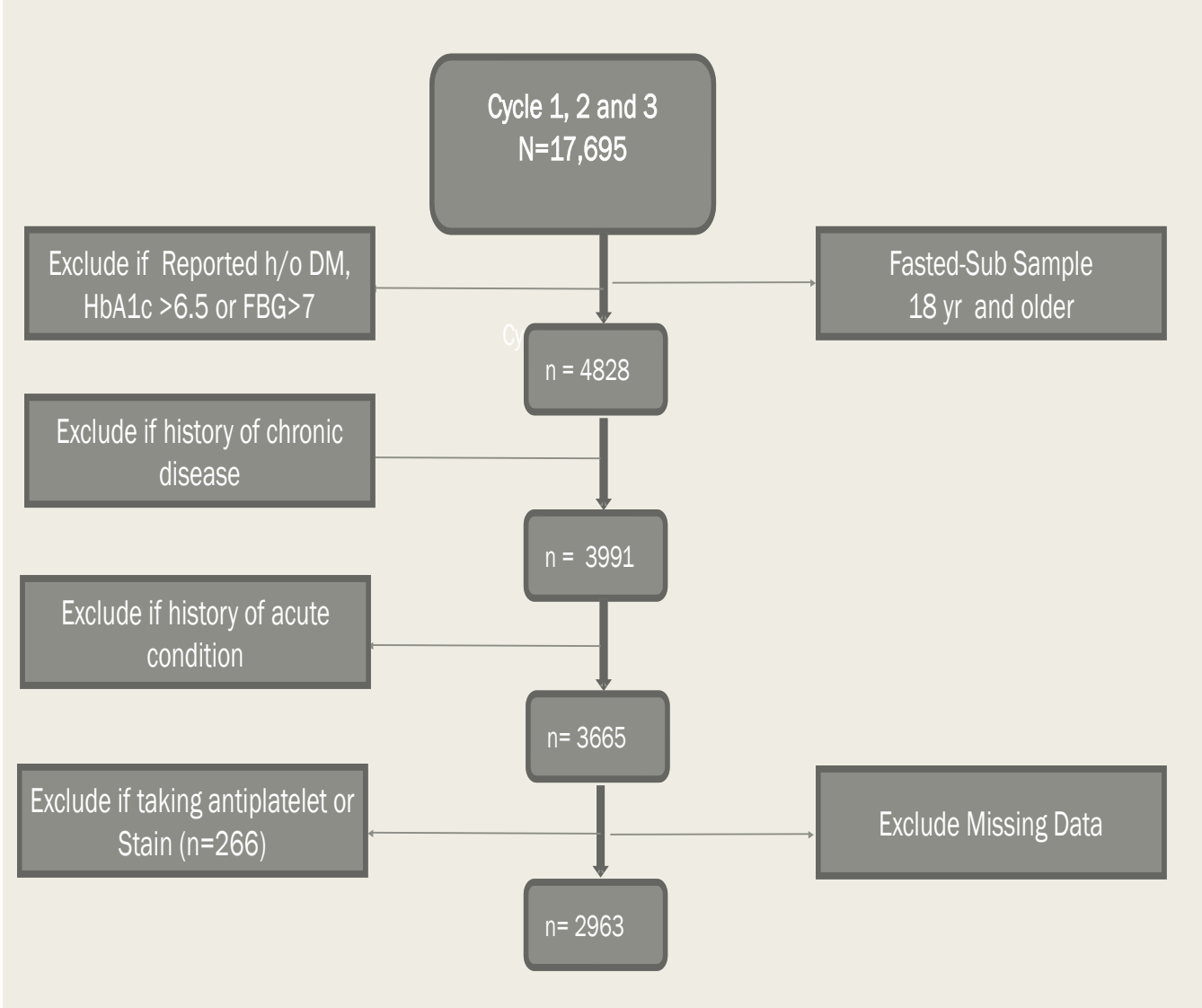
APPENDIX E

Final Multivariate Model:

```
. regress logHOMAIR i.Age i.CLC_SEX LAB_HDL LAB_TRIG LAB_LDL i.CRP_cat i.smoker HWMD14IN_Waist HWMD15IN_Hip HWMDBMI i.
> RACE  BPMDPBPS BPMDPBPD i.CRP_cat#i.CLC_SEX
```

Source	SS	df	MS			
Model	99.5126941	21	4.73869972			
Residual	133.760796	2941	.0454814			
Total	233.27349	2962	.078755399			

Number of obs = 2963
F(21, 2941) = 104.19
Prob > F   = 0.0000
R-squared   = 0.4266
Adj R-squared = 0.4225
Root MSE   = .21326

logHOMAIR	Coef.	Std. Err.	t	P>|t|	[95% Conf. Interval]	
Age						
2	-.0589348	.0111149	-5.30	0.000	-.0807286	-.037141
3	-.0610892	.0128467	-4.76	0.000	-.0862787	-.0358998
4	-.0281488	.0151409	-1.86	0.063	-.0578366	.001539
2.CLC_SEX	.0487658	.0104666	4.66	0.000	.0282433	.0692883
LAB_HDL	-.1048868	.011922	-8.80	0.000	-.1282631	-.0815105
LAB_TRIG	.0729087	.0059886	12.17	0.000	.0611665	.0846509
LAB_LDL	-.0030173	.0044527	-0.68	0.498	-.011748	.0057134
2.CRP_cat	.0682881	.0150905	4.53	0.000	.038699	.0978771
smoker						
2	.0097752	.0120002	0.81	0.415	-.0137543	.0333048
3	.0140761	.0106959	1.32	0.188	-.0068962	.0350484
HWMD14IN_Waist	.0102082	.0013944	7.32	0.000	.0074741	.0129422
HWMD15IN_Hip	-.0042397	.0021113	-2.01	0.045	-.0083795	-.0000999
HWMDBMI	.0174591	.0018073	9.66	0.000	.0139154	.0210028
RACE						
2	.0194658	.0166327	1.17	0.242	-.0131471	.0520787
3	.0594761	.0188679	3.15	0.002	.0224805	.0964716
4	.0674231	.0241703	2.79	0.005	.0200306	.1148156
5	.0257118	.0290733	0.88	0.377	-.0312943	.0827179
6	.0344283	.0201103	1.71	0.087	-.0050034	.0738599
BPMDPBPS	.0001217	.0004751	0.26	0.798	-.0008098	.0010532
BPMDPBPD	.0015579	.0007023	2.22	0.027	.0001808	.002935
CRP_cat#CLC_SEX						
2 2	-.051329	.0193147	-2.66	0.008	-.0892008	-.0134572
_cons	-.5032696	.0627016	-8.03	0.000	-.6262131	-.3803262