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Novel Epidemiologic and Mechanistic Aspects of The Metabolic Syndrome

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"Success is the ability to go from one failure to another without losing enthusiasm"
Sir Winston Churchill

To my family

Abstract

Introduction

The metabolic syndrome is a cluster of cardiometabolic risk factors that increase risk of developing cardiovascular disease. Its prevalence continues to rise worldwide and it is becoming a public health burden. The aim of my thesis was to help elucidate some of the epidemiologic and mechanistic aspects behind the metabolic syndrome.

Material and Methods

For paper I the National Health and Nutrition Examination Survey (NHANES) III was used. For paper II the NHANES III Mortality study was used with follow-up mortality on NHANES III subjects. For paper III, the 60 year old Stockholm county cohort, the Swedish Diet and metabolic syndrome (KOMET) study and the NHANES 2005-06 cohorts were used. For paper IV, the 65 year old Stockholm County physical activity intervention study was used.

Results

Paper I showed that the apolipoproteinB/apolipoproteinAI (apoB/apoAI) ratio is strongly associated with insulin resistance beyond the association explained by traditional risk factors, metabolic syndrome components, and inflammatory risk factors. Paper II showed that apolipoprotein measurements significantly predict coronary heart disease (CHD) death, independently of cardiovascular (CV) risk factors and that this predicting ability was better than any of the routine clinical lipid measurements. Paper III showed that gamma glutamyl transferase (GGT) is significantly associated with the metabolic syndrome in elderly asymptomatic subjects and that this association seems to be mediated, at least in part by C-reactive protein (CRP). Paper IV showed that change in adipose tissue gene expression is associated with changes in metabolic syndrome parameters. Furthermore, lifestyle modification can influence changes in adipose tissue gene expression, which may in turn modulate metabolic syndrome parameters.

Conclusions

ApoB/apoAI ratio is a marker of insulin resistance. Apolipoprotein B should be included in guidelines assessing cardiometabolic risk. GGT relationship to the metabolic syndrome seems to be mediated, at least in part, by changes in CRP. Changes in parameters of the metabolic syndrome seem to be mediated, at least in part, by changes in adipose tissue gene expression after increased physical activity.

LIST OF PUBLICATIONS

I. Sierra-Johnson J, Romero-Corral A, Somers VK, Lopez-Jimenez F, Wälldius G, Hamsten A, Hellénius ML, Fisher RM. ApoB/apoAI ratio: an independent predictor of insulin resistance in US non-diabetic subjects.
Eur Heart J. 2007; 28(21):2637-43
-Editorial: Sniderman AD. The apoB/apoAI ratio and insulin resistance: sorting out the metabolic syndrome. *Eur Heart J*. 2007; 28(21):2563-4

II. Sierra-Johnson J, Fisher RM, Romero-Corral A, Somers VK, Lopez-Jimenez F, Ohrvik J, Wälldius G, Hellenius ML, Hamsten A. Concentration of apolipoprotein B is comparable with the apolipoprotein B/apolipoprotein AI ratio and better than routine clinical lipid measurements in predicting coronary heart disease mortality: findings from a multi-ethnic US population. *Eur Heart J*. 2009; 30(6):710-7

III. Sierra-Johnson J, Sjögren P, Hamsten A, Rosell M, Basu S, DeFaire U, Hellenius ML, Fisher RM. Association between Increased Gamma Glutamyl Transferase Activity and Features of the Metabolic Syndrome is partially Mediated by CRP: Implications for Cardiometabolic Prevention. Manuscript, in process of submission

IV. Sierra-Johnson J, Kallings LV, Kolak M, Halldin M, Hamsten A, DeFaire U, Hellenius ML, Fisher RM. Modulation of Adipose Tissue Gene Expression in relation to changes in Metabolic Syndrome Parameters after Prescribing Physical Activity in a 6-month Randomized Controlled Intervention Study. Manuscript, in process of submission

CONTENTS

LIST OF ABBREVIATIONS

ApoB	Apolipoprotein B
ApoAI	Apolipoprotein AI
ApoB/apoAI	Apolipoprotein ratio
Apos	Apolipoproteins
ATP-III	Adult treatment panel III of the National Cholesterol Education Program
BMI	Body mass index
CCL2	Chemokine ligand 2
CHD	Coronary Heart Disease
CD36	Cluster of differentiation thirty six
CD68	Cluster of differentiation sixty eight
CRP	C-reactive protein
CV	Cardiovascular
GGT	Gamma glutamyl transferase
HDL-C	High density lipoprotein-cholesterol
HOMA	Homeostasis model assessment
HR	Hazards Ratio
IDF	International Diabetes Federation
IL-6	Interleukin six
LDL-C	Low density lipoprotein-cholesterol
LPL	Lipoprotein lipase
NHANES	National Health and Nutrition Examination Survey
PPARγ	Peroxisome proliferator activated receptor gamma
RPLP0	Ribosomal protein large P-zero (housekeeping gene)
TBP	TATA-box binding protein (housekeeping gene)
TNF-α	Tumor necrosis factor alpha
WHO	World Health Organization
11βHSD	Eleven-beta hydroxysteroid dehydrogenase

1 INTRODUCTION

1.1 WHAT IS THE METABOLIC SYNDROME?

The Metabolic Syndrome is a cluster of metabolic risk factors (namely: impaired fasting glucose and/or impaired glucose tolerance, hypertension, hyperlipidemia, central obesity or visceral adiposity, hypertension, and/or renal failure) which are connected to insulin resistance which is believed to be the shared pathophysiological disturbance.

All these risk factors appear to be influenced by both genetic and environmental factors. Having this cluster phenomenon increases cardiovascular risk leading eventually to cardiovascular death (See Figure 1).

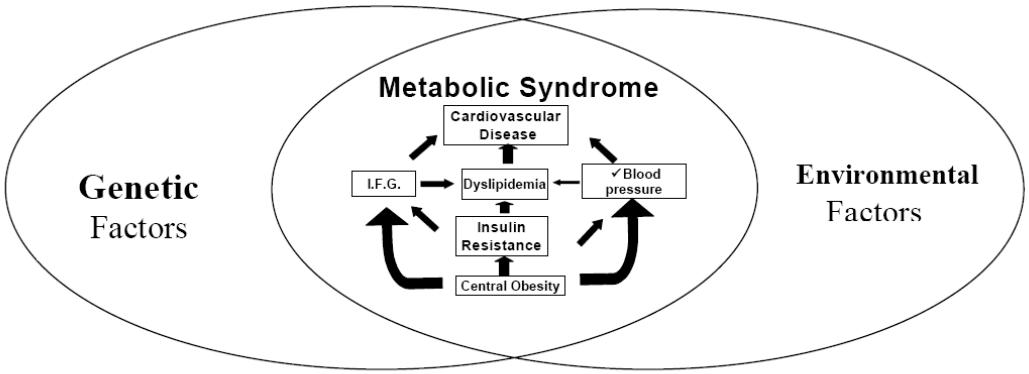


Figure 1. *Pathogenesis of the Metabolic Syndrome*

1.2 HISTORY

The Metabolic Syndrome concept has been around for many years, the first trace I could find, dates back to the 18th century.

Around 250 years ago a clever Italian anatomist called Giovanni Battista Morgagni [1] described the concept that general health was directly related to the well-functioning of many different organs. So if something disrupted total body harmony then pathologies would develop. Morgagni's anotomo-clinical records (Epistola anatomo clinica IV and XXI)[2] describe two different patients with accumulation of visceral adiposity. Morgagni with his anatomy dissections, uncovered the intra-abdominal fat related to the android obesity, and clearly described the association between visceral fat and hypertension, atherosclerosis, sleep, and hyperuricemia for the first time. I think it is fascinating that these observations made more than 250 years ago, perhaps describe one of the first subjects with the metabolic syndrome.

In the 1920's, right around the time when Frederick Banting and John Macleod[3] along with a young scientist named Charles Best (who was at the time doing his internship research) discovered insulin in Toronto (for which Banting and Macleod were later awarded the Nobel Prize in Physiology or Medicine in 1923), there were a couple of case-reports describing metabolic syndrome patients. In Vienna, Austria, Karl Hitzenberger and Martin Richter-Quitnner[4,5]showed relationships between hypertension and diabetes and almost simultaneously, a Swedish physician called Eskil Kylin[6] and a Spanish physician Gregorio Marañon[7] published a couple of papers independently on hypertension and diabetes. The Swedish physician Kylin later added hyperuricemia to his observations.[8]

In 1936, a landmark paper was published in "The Lancet" by British physician Harold P. Himsworth, describing for the first time the two different types of diabetes and introducing the concept of insulin sensitivity and insulin resistance.[9] Later, he went on to introduce the first insulin sensitivity measurement in-vivo using an oral glucose tolerance test with and without injecting insulin. Himsworth's contributions are notable for the later understanding of the pathophysiology of the metabolic syndrome.

In 1947, the French scientist Jean Vague from Marseille described sex differences in body fat distribution.[10] Professor Vague reported the importance of upper body obesity and its relationship with metabolic disturbances, called android obesity (popularly called 'apple shaped'), which compared to the gynecoid obesity (or pear-shaped), had different implications.[11-12]

Later, in 1970 Dr Phillips described the concept of metabolic risk factors for development of myocardial infarction, which included: hyperlipidemia, hypertension and hyperinsulinemia.[13] Later this concept was also posted by Dr Gerald Reaven at the famous 'Banting Lecture' in 1988.[14] There, Reaven proposed what he called 'Syndrome X' which included having insulin resistance as the main disturbance and described the cluster of other risk factors such as hyperlipidemia and hypertension, however, he failed to include abdominal obesity as part of the syndrome. A year later, Dr Norman Kaplan added abdominal obesity and called this the 'deadly quartet' which included: impaired glucose tolerance, hypertriglyceridemia, hypertension and central adiposity.[15]

For the last two decades, there has been a 'boom' in metabolic syndrome research, it will be impossible to acknowledge all the contributions from the past 15-20 years in this small section. The scientists mentioned above, are the most remarkable scientists in my view, who have influenced and contributed to the understanding of what we know today as the metabolic syndrome. I believe it is important to understand where we come from, and what other people have done that has helped us understand better this metabolic cluster phenomenon.

1.3 DEFINITIONS OF THE METABOLIC SYNDROME

There are many definitions of the metabolic syndrome. Even though the metabolic syndrome started as a concept, nowadays it is thought to be a useful tool for clinicians to detect subjects with the cluster phenomenon that would ultimately lead to cardiovascular disease. The World Health Organization (WHO) was one of the first definitions available of the metabolic syndrome in the early 1990's.[16] They defined the Metabolic syndrome as insulin sensitivity in the lowest quartile of the population or the presence of impaired glucose tolerance or type 2 diabetes and the presence of at least 2 of the following: abdominal obesity (waist-hip ratio>0.90 or body mass index ≥30 kg/m^2), dyslipidemia (serum triglycerides ≥150 mg/dl or HDL-cholesterol <50 mg/dl), hypertension (≥160/90 mmHg), or microalbuminuria. One of the disadvantages of using the WHO definition is that it requires a measure of insulin sensitivity, and this can hardly be something that can be applied on a routine basis for the general physician who is screening for metabolic disease.

On the other hand, the International Diabetes Federation (IDF)[17] definition requires a measure of central adiposity (gender and ethnic specific-waist circumference) as the cornerstone of the definition in addition to 2 or more of the following criteria: 1) triglycerides ≥150 mg/dl (1.7 mmol/L) or specific treatment for this lipid abnormality; 2) HDL<40 mg/dl (1.03 mmol/L) in men and <50 mg/dl (1.30 mmol/L) in women or specific treatment for this lipid abnormality; 3) systolic blood pressure ≥130 mmHg, diastolic blood pressure ≥85 mmHg, or treatment of previously diagnosed hypertension; and 4) fasting plasma glucose concentration ≥100 mg/dl (5.6 mmol/L) or previously diagnosed type 2 diabetes. And while it certainly has its advantages of using gender and ethnic specific waist cut-off points, a big disadvantage is that in some ethnic populations (such as the east Asian populations), the central obesity factor is not the major issue involving the metabolic syndrome, so by using waist as a defining factor you end up misclassifying subjects as healthy that may have metabolic alterations.

Alternatively, the National Cholesterol Education Program-Adult Treatment Panel III (ATP III)[18] has published an alternative clinical definition of the Metabolic syndrome given in Table 1 (which was recently updated)[19], which is the most current and widely used to identify the metabolic syndrome and it does not require a measure of insulin resistance, however this could be an important limitation for this definition.

Table 1. *Diagnosis of the Metabolic syndrome is established when >3 of these risk factors are present, as defined by the updated ATP-III.*[19]

Risk Factor	**Defining Level**
Waist circumference	
Men	≥102 cm (≥40 in)
Women	≥ 88 cm (≥ 35 in)
Triglycerides	≥150 mg/dl (1.7 mmol/L)
HDL-C	
Men	≤40 mg/dl (1.03 mmol/L)
Women	≤50 mg/dl (1.30 mmol/L)
Blood pressure	≥130/ 85 mmHg
Fasting Glucose	≥100 mg/dl (5.6 mmol/L)

Currently, there is not a perfect definition of the Metabolic syndrome, and the current definitions available are more like 'working definitions' of the Metabolic syndrome rather than dogmatic definitions. There is currently a controversy over whether the Metabolic syndrome is a practical definition and its relevance has been questioned, especially by the Endocrinologist groups.[20] Conversely, the Cardiology group support the concept of the metabolic syndrome and its clustering phenomenon.[19] Furthermore, there is evidence to suggest that the presence of the Metabolic syndrome alone predicts total and cardiovascular mortality[21]; nonetheless, there is skepticism as to whether the Metabolic syndrome adds information to current established cardiovascular algorithms such as the Framingham risk score. Moreover, the metabolic syndrome concept is more important and relevant than the current clinical definitions, which are sometimes arbitrary and imperfect. Hopefully, future research will help us implement better ways to detect patients with the metabolic syndrome and improve monitoring of disease progression.

1.4 PREVALENCE OF THE METABOLIC SYNDROME

The Metabolic syndrome is a dramatically increasing health problem in the Western world. The syndrome is comprised of a cluster or risk factors for coronary heart disease (CHD): central obesity, dyslipidemia, raised blood pressure and glucose intolerance. The metabolic syndrome is associated with significantly elevated risk for development of CHD, atherosclerosis, type 2 diabetes and some common cancers. Insulin resistance in skeletal muscle, adipose tissue and liver are of central importance for the development of the hyperinsulinemia and glucose intolerance associated with the syndrome. The mechanisms leading to the development of the clustering risk factor phenomenon are poorly understood. One of the latest estimates from the National Health Nutrition and Examination Survey (NHANES) 1999-2002 reported an increasing prevalence of 34.6% of the adult US population having the Metabolic syndrome using the updated ATP-III definition and 39.1% when using the IDF definition.[22] Furthermore the ongoing obesity epidemic, coupled with a rise in other metabolic risk factors, is rapidly affecting Metabolic syndrome prevalence.

1.5 IMPLICATIONS OF THE METABOLIC SYNDROME

The high prevalence of the metabolic syndrome is of significance for the occurrence of type 2 diabetes and coronary heart disease at the population level.[22] It is therefore of great importance to identify ways of reducing the occurrence of the Metabolic syndrome and improving insulin sensitivity in individuals with the syndrome. The metabolic syndrome is a problem that affects mostly developed countries, and its future projections are alarming, therefore being passive is not an option; we must act today to uncover the pathophysiology of the Metabolic syndrome, prevent it from occurring/developing and ultimately treat subjects at high cardiovascular risk to avoid unnecessary deaths and diminish the increasing burden that accompanies the Metabolic syndrome. The presence of the current metabolic syndrome definitions is not enough to predict cardiovascular disease, it is only when we take all the conventional risk markers into account (such as the Framingham risk score) and add the metabolic syndrome and/or its components into the equation that we can predict better global cardiometabolic risk.[23]

1.6 APOLIPOPROTEINS

Apolipoproteins (Apos) are proteins that bind to lipids and together they form lipoproteins which transport dietary fats through the bloodstream. Apos regulate the metabolism of lipopoproteins and their tissue uptake, thanks to their amphipathic properties that can solubilize the oily components of the lipoproteins that are not water soluble.[24] Apos also serve as enzyme co-factors and receptor ligands. There are currently known 6 major classes and various subclasses. In this thesis, we focused on apolipoprotein B (apoB) and apolipoprotein AI (apoAI).

1.7 APOLIPOPROTEIN B

ApoB is an essential structural part of lipoproteins, being part of large buoyant and small low density lipoproteins (LDL), very low density lipoporoteins (VLDL), intermediate low density lipoproteins (IDL) and chylomycrons. ApoB ease cholesterol delivery to the tissues, furthermore, apoB promotes cholesterol deposition or entrapment in the arterial wall. ApoB-100 is produced in the liver and it is the main ApoB protein in plasma. ApoB-48 is produced in the gut. Regularly, more than 90% of all apoB is found in LDL-cholesterol, but in cases where LDL-cholesterol is not elevated, apoB may indicate increased cardiovascular risk. Hence, total apoB represents the total number of potentially atherogenic particles, which includes the small LDL which are known to be atherogenic.[25] Thus, apoB is believed to represent the atherogenic process.

1.8 APOLIPOPROTEIN AI

Apolipoprotein AI (apoAI) is the structural component of high density lipoprotein (HDL) defining its size and shape. Its main function is to initiate the 'reverse cholesterol transport' by activating the lecithin-cholestesterol acyltransferase (LCAT), the key enzyme in the 'good cholesterol' process.[25,26] ApoAI will pick up the excess of

cholesterol from peripheral cells and transfer it back to the liver through the HDL particles. ApoAI has also some anti-inflammatory and antioxidant effects. Measure of apoAI is believed to reflect the anti-atherogenic process.

1.9 APOLIPOPROTEIN B/APOLIPOPROTEIN AI RATIO

Since apoB measures the atherogenic particles and apoAI measures the anthiatherogenic particles, a ratio between apoB and apoAI was created.[27] The apoB/ apoAI ratio may reflect cholesterol transport to and from the peripheral tissues, including the arterial wall. The measure of this ratio may represent the balance between the atherogenic and the anti-atherogenic process.[25,28]

1.10 APOLIPOPROTEINS AND CARDIOVASCULAR RISK

Research into apolipoproteins and cardiovascular risk go back at least a few decades.[24,27] There has been increasing evidence over the years that apolipoproteins predict cardiovascular risk. Recent reports from prospective risk studies, such as Apolipoprotein-related Mortality Risk (AMORIS)[28], the International Heart first myocardial infarction case-control study done in 52 countries across North and South America, Europe, Asia, Middle East, Australia and Africa (INTERHEART)[29], the European Prospective Investigation in Cancer study (EPIC-Norfolk)[30], Uppsala Longitudinal study of Adult Men (ULSAM)[31], and the Monitor of Trends and Determinants of Cardiovascular Disease (MONICA/KORA)[32] Augsburg study, indicate that the apoB/apoAI ratio is a useful predictor of risk of both non-fatal and fatal myocardial infarction. A recent meta-analysis by Thompson et al[33] on the apoB/apoAI ratio supports the use of apoB/apoAI ratio as a future risk marker of cardiovascular disease.

In a previous study done with by previous research group at the Mayo Clinic, the apoB/apoAI ratio was associated with the metabolic syndrome and its components in men and women.[34] The mean values of the apoB/apoAI ratio were associated with the presence and number of nonlipidic components of the metabolic syndrome, even after excluding patients with low HDL or high triglycerides. This important finding provided a novel perspective on the understanding of the metabolic syndrome and its pathophysiology. The association between the apoB/apoAI ratio and the metabolic syndrome was independent of lipid components, perhaps suggesting a shared underlying pathophysiology of this complex syndrome. Furthermore, the apoB/apoAI ratio was significantly associated with 2 definitions of the metabolic syndrome (ATP III and International Diabetes Federation) and with insulin resistance determined by homeostasis model assessment. [34,35] The relationship between the metabolic syndrome definitions and insulin resistance is less than perfect[36], therefore finding additional components of the metabolic syndrome that increase metabolic risk is paramount. Adding apolipoproteins to measure cardiovascular risk[37], adds and improves upon other risk factors such as traditional dyslipidemia[38], and or/ obesity.[39]

Recently, the Framingham study published a study reporting that apolipoproteins were not better at predicting cardiovascular risk than the total cholesterol and HDL-cholesterol.[40] However, we believe that this study had some limitations.[41,42] Just recently, apolipoproteins have been included in guidelines to assess cardiovascular risk in diabetic patients along with LDL concentrations.[43] Hopefully soon, we will see inclusion of apolipoproteins in general guidelines for cardiovascular risk.[44]

1.11 GAMMA GLUTAMYL TRANSFERASE

Gamma glutamyl transferase (GGT) is an enzyme found in the plasma originating from the liver that is involved in the transfer of amino acids across the cell membrane and in glutathione metabolism.[45] In the past it has been associated mostly with chronic alcohol abuse in the clinic. Recently, there has been an increased interest in the role of the liver in insulin resistance and its relationship to cardiovascular disease.[46]

1.12 GAMMAGLUTAMYL TRANSFERASE AND CARDIOVASCULAR RISK

Animal and human experimental studies have reported that GGT activity is present in coronary atherosclerotic plaques, in both animal and human experimental studies increased GGT activity has also been proposed as a marker of oxidative stress.[47,48] Moreover, the recently recognized functions of GGT in the generation of reactive oxygen species indicate that serum GGT may represent an important marker of atherosclerosis and cardiovascular disease (CVD).[49]

Recently, several prospective studies have reported GGT as an independent predictor of CVD and the metabolic syndrome.[50-54] However, the strengths of these associations have varied substantially. An important issue in using GGT in a clinical setting is how much additional cardiovascular risk information it provides beyond the traditional CVD risk factors, after controlling for alcohol ingestion. GGT is readily available in many primary care centers that do not have access to inflammatory markers such as C-reactive protein (CRP). Moreover, associations between inflammation and the metabolic syndrome have been reported[55] and since GGT is emerging as a cardiometabolic risk biomarker, its putative role in inflammatory pathways merits further consideration.

1.13 C-REACTIVE PROTEIN

The process by which the body responds to injury is called ‘inflammation’. This process is highly relevant in the atherosclerotic pathway. CRP is an acute phase reactant protein that in presence of systemic inflammation elevates its levels. Its role in predicting cardiovascular disease is well established. [56] However, there is an ongoing controversy as to whether CRP is a causal factor of atherosclerosis or merely a marker that is elevated in response to the inflammatory process. This has significant implications since CRP could be used as a treatment goal in high cardiovascular risk patients. In a recent study published by Zacho and colleagues[57], a polymorphism study of the CRP gene in a heart disease population, CRP was reported not to be causally involved in atherosclerosis, suggesting that immediate targeting of CRP concentrations is unlikely to be beneficial in reducing the risk of cardiovascular disease. Nonetheless, in the recent American Heart Association meeting at New Orleans in late 2008, Ridker and colleagues[58] reported in the Justification for the Use of Statins in Primary Prevention (JUPITER) trial, that treating subjects with statins (rosuvastatin) that were otherwise healthy but had mildly elevated CRP was beneficial. The JUPITER trial included subjects with low LDL-cholesterols (less than 130 mg/dl) but with mildly levated CRP concentrations (more than 2.0 mg/L). The clinical trial was ended before two years due to benefit in hard cardiovascular events. These fascinating new results point to rethink the way we use CRP in clinical practice, as CRP could be a key player in elucidating the preventive atherosclerotic process.

1.14 GAMMA GLUTAMYL TRANSFERASE AND C-REACTIVE PROTEIN

There is compelling evidence for the importance of inflammation in the atherosclerotic process at both the basic and clinical level, particularly for CRP.[59,60] Elevated levels of CRP in otherwise healthy subjects have proven to have predictive value for future cardiovascular events.[61] Furthermore, CRP concentrations have correlated well with many cardiovascular risk factors. A recent study[62] in middle age Japanese men, reported that serum GGT concentrations were independently associated with systemic inflammation, even in subjects without the metabolic syndrome. This indicates that elevated serum GGT concentrations are independent markers of an activation of systemic inflammation. These previous results, in combination with our current results, might indicate that subjects who are at increased risk of cardiometabolic disease might be missed by only considering standard definitions of the metabolic syndrome that do not take into account the inflammatory component. Elevations of GGT may additively worsen the atherogenic state in subjects with the metabolic cluster phenomenon.

Our study suggests that elevation of serum GGT in the metabolic syndrome is mediated, at least in part by the inflammatory response, which appears to be present in an early stage of cardiovascular risk in otherwise healthy individuals. There have been previous reports[63,64] of a relationship between serum GGT and CRP levels.

1.15 ADIPOSE TISSUE

The idea that adipose tissue is an inactive tissue that serves only as fat repository is not longer accepted. There have been many advances in understanding the role of adipose tissue, the discovery of Leptin in 1995 was one of the landmark moments, which helped accept the view that adipose tissue was indeed an endocrine organ. Adipose tissue actively secretes many hormones (e.g., leptin, adiponectin, resistin) and adipokines (e.g., chemerines, visfatin, interleukin-6, plasminogen activator-1, tumor necrosis factor-alfa, retinol binding protein-4) with local and distant effects. These substances are believed to regulate the metabolic balance of the human body through very complex and different mechanisms.[65] These substances have the potential to modulate carbohydrate, lipid and insulin metabolism and/or inflammation. They have the ability to cross-talk and/or regulate with neuroendocrine systems.

Leptin is a protein-hormone that plays a key role in energy intake and energy expenditure. Its name comes from the Greek and it means ‘thin’. Leptin has receptors through out the body.[66,67] In the hypothalamus it is believed to affect the satiety signal, is believed to inhibit lipogenesis, stimulate lipolysis and improve insulin sensitivity.
In obese humans, leptin is elevated, thus presenting a type of leptin resistance similar to insulin resistance that affects cardiometabolic risk factors.[68] Increased levels of leptin have been related to cardiovascular disease[69] and to coronary heart disease.[70,71] Adiponectin (also termed, adipocyte complement-related protein -Acrp 30-) is a protein-hormone that regulates glucose regulation and fatty acid catabolism. It increases insulin sensitivity in the liver. Adiponectin levels are low in diabetics[72,73] and insulin resistance[74], and recently this has been tied to an increased cardiovascular risk.[75] Adiponectin is believed to inhibit monocyte adhesion to endothelial cells, facilitate macrophage transformation into foam cells and endothelial cell activation. Adiponectin

expression in the adipose tissue and serum concentrations are diminished in obesity and the metabolic syndrome.

1.16 ADIPOSE TISSUE AND INFLAMMATION

A pro-inflammatory state, as indicated by elevated circulating interleukin six (IL-6), tumor necrosis factor alpha (TNF-α) and CRP are usually present with the metabolic syndrome, and glucose tolerance and insulin sensitivity are reduced in individuals with elevated circulating inflammatory biomarkers.[76] Adipose tissue is an important endocrine organ that produces a variety of cytokines that are involved in inflammatory pathways. This low grade inflammation is believed to be a chronic effect that is paramount in the metabolic syndrome pathophysiology and it seems to be mediated by macrophage accumulation in different metabolic tissues.[77] However, there are different types of macrophages which seem to have benefit or a deleterious effect in insulin resistance and the metabolic syndrome. Obesity and insulin resistance have recently been shown to be associated with local inflammation and macrophage accumulation within adipose tissue.[76] While the underlying mechanism(s) for this inflammation remain(s) unknown, the consequences are clear: an increase in the production of inflammatory cytokines and a decrease in adiponectin. Thus, these "adipokines" may be important factors linking central obesity to the other components of the metabolic syndrome.

1.17 ADIPOSE TISSUE GENE EXPRESSION

The regulation of adipose tissue gene expression is still for the most part unknown. Changes in the levels of a few different mRNAs have been reported, but it is not clear what role it pays in the development of the metabolic syndrome. The following candidate genes of interest were quantified. Below is a brief description of each gene's pathophysiologic role:

ADIPONECTIN: Adiponectin is a protein-hormone expressed in adipocytes that regulates glucose regulation and fatty acid catabolism. Lower levels of this protein have been associated with the metabolic syndrome and with impaired glucose tolerance.[78-80]

LEPTIN: Leptin is a protein-hormone produced by adipose tissue that is related to a satiety signal in the hypothalamus. Leptin has pro-inflammatory properties and exerts its biological actions through binding with its receptors which are found in a variety of tissues. In humans, there appears to be leptin resistance in cardiometabolic disease.[81-82]

TNF-α: Tumor necrosis factor α (TNF-α) is a cytokine with multiple functions, originally was described in cachexia and acute ischemia. TNF- α is secreted by stromavascular cells and adipose tissue, and it correlates well with obesity and insulin resistance measures. [83]

11BHSD: Eleven-beta hydroxysteroid dehydrogenase (11BHSD) is an enzyme expressed in both macrophages and adipocytes that converts cortisone to cortisol and it is elevated in insulin resistant states. [84]

IL-6: Interleukin-6 (IL-6) acts as both a pro-inflammatory and anti-inflammatory cytokine that it is secreted by macrophages and T cells to stimulate immune response that leads to inflammation. [85]

CCL2: Chemokine ligand 2 (CCL2) belongs to the monocyte chemotactic protein-1 family (MCP-1). CCL2 is known for recruiting monocytes, memory T cells and dendritic cells to the injury site. [86-87]
CD68: Cluster of differentiation 68 (CD68) is a glycoprotein which binds to low density lipoprotein that it is expressed on monocytes/macrophages and it is a marker for macrophage accumulation. [88]
CD36: Cluster of differentiation 36 (CD36) is an integral membrane protein found on the surface of many cells that has been identified to have a key role in fatty acid and glucose metabolism. [89]
LPL: Lipoprotein lipase (LPL) is an enzyme that hydrolyzes lipids in lipoproteins. LPL is found in endothelial cells lining the capillaries.[90]
PPARγ: Peroxisome proliferator activated receptor gamma (PPARγ) is a master regulator of adipocyte differentiation and lipid metabolism that regulates fatty acid storage and glucose metabolism. Many insulin sensitizing drugs (like thiazolidinediones TZD's) used in the treatment of diabetes target PPARγ to lower serum glucose without increasing pancreatic insulin secretion. [91,92]

1.18 ADIPOSE TISSUE GENE EXPRESSION AND PHYSICAL ACTIVITY

Physical inactivity has long been recognized as risk factor for development of cardiovascular disease[93], and is now also part of the environmental factors that affect the metabolic syndrome.[94-97] However, to our knowledge, there is no research in the current literature that has examined the effects of increased physical activity on adipose tissue gene expression. Therefore, it is not clear to what extent changes in adipose tissue metabolism/function are associated with a concomitant modulation of metabolic syndrome parameters. Furthermore, physical activity on prescription[97-100], it is a novel and effective way to induce lifestyle modification in subjects with the metabolic syndrome. It only involves writing a prescription for physical activity by the treating physician, and it can make a big change in patient response.

2 AIMS

Understanding the pathophysiology of the metabolic syndrome will enable us to prevent and treat better the cluster risk phenomenon. Furthermore, a combination of detailed epidemiologic investigations and molecular biology techniques (to examine the effects of adipose tissue gene expression on the metabolic syndrome parameters) were employed in an integrated mechanistic approach. This thesis provides novel insights into the pathways underlying the metabolic syndrome and improves our understanding of the etiology of this disease, which may ultimately provide potential new sites for intervention.

The following project aimed to study novel epidemiological and mechanistic aspects of the metabolic syndrome taking advantage of already well characterized epidemiologic cohorts such as the National Health and Nutrition Examination Survey (NHANES) and the 60 year Stockholm County cohort. We proposed to identify novel epidemiologic and mechanistic aspects that might lead to the development of the metabolic syndrome. We addressed this by investigating the following specific aims.

AIM 1) To determine if there was an independent association between the apoB/apoAI ratio and insulin resistance beyond traditional cardiovascular risk factors, metabolic syndrome components, and inflammatory risk factors in a US non-diabetic multi-ethnic representative population (NHANES III).

AIM 2) To determine if there was a prospective association between the apoB/apoAI ratio and CHD mortality, independently of traditional cardiovascular risk factors and C-reactive protein (CRP) in a US multi-ethnic representative population.(NHANES III Mortality study).

AIM 3) To determine whether circulating gamma glutamyl transferase (GGT) concentrations are associated with the metabolic syndrome in a Swedish representative population based cohort of asymptomatic 60 year old men and women, and whether this relationship was mediated by CRP.

AIM 4) To determine if changes in metabolic syndrome parameters could be modulated by changes in adipose tissue gene expression in a clinical study of elderly subjects with abdominal obesity and a high prevalence of the metabolic syndrome after increased physical activity.

3 MATERIAL AND METHODS

3.1 STUDY SUBJECTS

For this project we took advantage of already well-characterized cohorts that we describe in detail below.

3.1.1 NHANES III (1988-1994)

The National Health and Nutrition Examination Survey (NHANES) is a periodic survey performed in the US to assess overall health.[101] It is a representative sample of the US-non-institutionalized civilian population. The sampling is not simple but rather a stratified complex that over-samples minorities in order to capture the representative nature of the US population. The age covers infants to elderly subjects, but for this thesis we have focused only in the adult population aged 20 to 89 years old. We chose a limit of 89, because all subjects aged 90 or more were captured as 90 years old and we wanted to avoid any bias regarding survival in older subjects. NHANES III covers the period from 1988 to 1994, and is a periodic survey conducted by the United States National Center for Health Statistics. The data are made publicly available, with strict guidelines for analysis. Subjects underwent institutional review board approval and included written informed consent. It is important to note that all data from NHANES are coded and it is not possible to track the personal information of any patient.

Out of a sample of 39,695 adults and children selected for the NHANES III, 33,994 were interviewed and 30,818 submitted to an examination by a physician at a mobile examination center, including extensive anthropometric, physiological, and laboratory testing. NHANES information on life-style characteristics, previous and current medical conditions and medication was obtained during an in-home interview followed by a medical evaluation and blood sample collection at the mobile examination center.

For paper I, the sample was restricted to adults aged 20 to 89 years (n=16,881). We excluded participants who were pregnant and those missing data for the apoB/apoAI ratio (n=9,285) and with missing follow-up (n=2). Measurement of apolipoproteins in NHANES III was done after collecting all the blood samples and it involved a complex randomization process done by NHANES protocol to avoid any selection bias. This resulted in a final analytic sample of 7,594 subjects (3,881 men and 3,713 women). We used this cohort for paper and paper II.

3.1.2 NHANES III Mortality Study

The NHANES III mortality study comprises all NHANES III participants linked to mortality data status. All subjects aged 20 to 89 years for whom data were available for matching to the National Death Index to determine mortality status were analyzed.

The National Death Index was searched up to December 31, 2000, for follow-up. NHANES III and the National Death Index are linked by probabilistic matching in the NHANES III mortality study. The National Center for Health Statistics conducted the

linkage and created scores for potential matches. For a selected sample of NHANES III records, the Center reviewed the death certificate record to verify correct matches. Overall, 20,024 adult NHANES III participants were eligible for mortality follow-up by linkage with the National Death Index, of whom 3,384 were identified as deceased. A complete description of the methodology used to link NHANES III records to the National Death Index can be found elsewhere.

For paper II, the sample was restricted to adults aged 20–89 years (n = 16 881). We excluded participants who were pregnant and those missing data for the apoB/apoAI ratio (n = 9285) and with missing follow-up (n = 2). Measurement of apolipoproteins in NHANES III was done after collecting all the blood samples and it involved a complex randomization process done by NHANES protocol to avoid any selection bias. This resulted in a final analytic sample of 7594 subjects (3881 men and 3713 women) that was weighted according to the NHANES III analytic guidelines to account for the complex stratified sample.

For death follow-up information, we used the underlying cause-of-death that had been recoded using a standard list of 113 causes of death from the NHANES public-use mortality file according to the corresponding International Classification of Diseases, Ninth Revision (ICD-9) and ICD-10 codes. We grouped deaths into cardiovascular disease (codes 53–75) and all other causes; we then subdivided deaths from cardiovascular disease into deaths from coronary heart disease (codes 58–63) and all cardiovascular deaths unrelated to coronary heart disease (codes 53–57, 64–75). Person-months of follow-up were calculated for each participant based on the end of follow-up (date of death for those assumed deceased or December 31, 2000, for those assumed alive) minus the date of the NHANES III examination. Total mortality at follow-up was ascertained for 99% of our sample. We used this cohort for paper II.

3.1.3 NHANES 2005-2006

This the latest periodic survey from NHANES released. We limited the present analysis to subjects who had serum measurements of both CRP and GGT aged ≥60 years and ≤75 years (to ensure comparability with our initial cohort), who attended a morning medical examination and who had fasted ≥8 hours, with a final analytic sample n=927. Subjects underwent institutional review board approval and included written informed consent. For the third part of paper III we used this cohort.

3.1.4 Stockholm County 60-year old cohort

From August 1997 to March 1999, every third man and woman living in Stockholm County who was born between 1 July 1937 and 31 June 1938 was invited to participate in a thorough health screening study.[95,102] The participants underwent a physical examination, fasting blood samples were taken and a comprehensive questionnaire was completed. The study was approved by the ethics committee at Karolinska Institutet. All the study participants gave their informed written consent. In total, 5460 subjects (2779 men and 2681 women) were invited to participate in the study, and a total of 4232 individuals (78% response rate) participated. For this study we excluded subjects

with known CVD (n=313), diabetes (n=297) and/or cancer (n=36). This resulted in a final analytic sample of 3605 subjects (1686 men and 1919 women). For paper III, we used this cohort in the first part of the analysis.

3.1.5 KOMET Study

The Diet and Metabolic Syndrome study (KOMET- KOst och det METabola Syndromet) was a subset study from the original Stockholm county 60-year old cohort.[103] Exclusion criteria were non-Swedish descent, BMI over 35 kg/m^2, previous history of cardiovascular disease, hypertension, dyslipidemia, diabetes, cancer and other chronic disease. From the original cohort, there were in total 2039 men, and 995 fulfilled the inclusion criteria and were divided into tertiles of fasting plasma insulin concentration. Approximately 100 men from each tertile (participation rate 71%) were included in the current study. These men represented a wide range of insulin sensitivities (by randomly recruiting ~100 men from each tertile of fasting plasma insulin concentrations). This gave a final subset of 301 healthy men (mean 63 ± 0.6 years of age) that was recruited from the larger population-based cohort (Stockholm County 60-year old Study) to be able to study in more detail disturbances associated with the metabolic syndrome. The Ethics Committee of Karolinska Institutet approved the study and all subjects gave informed consent to participate. For the second part of paper III we used this cohort.

3.1.6 Stockholm County Intervention Study

In 2005, an invitation and pre-screening questionnaire was sent to 407 individuals who met the inclusion criteria of being otherwise healthy, but overweight (BMI ≥25 kg/m^2 and <40 kg/m^2), centrally obese (waist circumference ≥102 cm in men and ≥88 in women) and physically inactive. Subjects with previous coronary heart disease, diabetes, hypertension, dyslipidemia, cancer and other chronic diseases were excluded.[97] One hundred and one subjects total subjects, fulfilled the inclusion criteria and were included in the present study in 2006, now aged 67-68 years old. They were randomized to either a control group (n=54, 23 men and 31 women) or to an exercise intervention group (n=47, 20 men and 27 women) with a baseline and a 6 month follow-up. Subcutaneous abdominal adipose tissue was collected at baseline and at 6 months under local anesthesia by needle biopsy for determination of gene expression. A total of 53 subjects (31 men, 22 women) completed the study with biopsies both at baseline and at 6 months. The Ethics Committee of Karolinska Institutet approved the study and all subjects gave informed consent to participate.

Due to ethical considerations, the control group received usual care, i.e. a low intensity intervention, with one page of written general information about the importance of physical activity for health. The intervention group received in addition patient centred counselling and individualized written prescription of physical activity. In brief, the main aim of the intervention was to achieve a daily physical activity level of at least 30 minutes as well as aerobic and strength exercise of moderate intensity for at least 30 minutes 2-3 times a week. Participants were also encouraged to reduce their time spent in sedentary behaviour. The prescription for physical activity included specified types of physical activities and intensity, frequency, duration of the different activities, as

well as the reason for the prescription. A seven consecutive day diary was used to measure total physical activity, and daily steps (over 7 consecutive days) were assessed with a pedometer. For paper IV, we used this cohort.

3.2 LABORATORY METHODS

Apolipoprotein analysis

For paper I and II, samples were thawed at room temperature and mixed thoroughly for 30 min on a blood-rotating device before analysis. ApoB and apoAI were measured by radial immunodiffusion in the first 8.2% (1055 specimens) of the specimens during the first 5 months of the study and by rate immunonephelometry for the remaining specimens during the last 31 months. At the beginning of the survey there were no standardized reference materials on which to base the measurements. Over the following years, the World Health Organization-International Federation of Clinical Chemistry (WHO-IFCC) First International Reference Materials for apoB and apoAI became available. The Northwest Lipid Research Laboratories, Seattle, WA, served as the coordinating laboratory for the development of these materials. The results were used to transform the immunonephelometry values to equivalent WHO-IFCC International Reference Materials-based values.

Biochemical measurements

For paper I and II, lipids were measured enzymatically with commercially available reagents (Cholesterol/HP, cat. no. 816302, and Triglycerides/GPO, cat. no. 816370, both from Boehringer Mannheim). HDL-C was measured in the clear supernatant after precipitating the other lipoproteins with heparin and $MnCl_2$ (1.3 g/L and 0.046 mol/L, respectively) and removing excess Mn^{2+} by precipitation with $NaHCO_3$. The biases (coefficients of variation) averaged –0.3% (1.7%), –2.1% (3.9%), and 0.3% (3.4%) for cholesterol, triglycerides, and HDL-C, respectively. C-reactive protein (CRP) concentrations were measured by latex-enhanced nephelometry on a Behring Nephelometer (Dade Behring Diagnostics Inc., Somerville, NJ, USA).

For the first part of paper III, Serum glucose was measured with an enzymatic colorimetric test (Bayer Diagnostics, Tarrytown, USA). Serum insulin concentrations were determined using the ELISA technique (Boehringer Mannheim GmbH, Diagnostica, Germany). Cholesterol and triglycerides in serum were analyzed using enzymatic methods (Bayer diagnostics, Tarrytown, USA). HDL-cholesterol in serum was measured enzymatically after precipitation of LDL and VLDL (Boehringer Mannheim Gmbh, Germany) and LDL-cholesterol was estimated using the method of Friedewald.

GGT Activity

For paper III, GGT activity in serum (μkat/l) was determined using an enzymatic colorimetric test (Bayer Diagnostics, Tarrytown, USA). For purposes of comparison and standardization, GGT activity was converted to international units (U/L, 1μkat=60U).

CRP and Free 8-iso-$PGF_{2\alpha}$ Measurements
For paper III, the subset of 294 men, serum CRP was quantified by ELISA (Hemochrom Diagnostica GmbH, Essen, Germany) with coefficient of variation of 11%. Free 8-iso-$PGF_{2\alpha}$ was determined in 24-hour urine samples by radioimmunoassay (coefficient of variation of 13%) and corrected for glomerular filtration rate, assessed as equal to the clearance of creatinine per minute and calculated as (urinary creatinine x urinary volume)/(serum creatininex1440).

Gene expression in adipose tissue
For paper IV, following collection of subcutaneous adipose tissue sample the samples were rinsed immediately in 0.9% NaCl to remove excess blood and stored in RNAlater (Qiagen) at -70°C until they were later analyzed. RNA was extracted from approximately 150 mg tissue: homogenisation in phenol-containing TRIzol (Invitrogen), DNaseI treatment and spin column purification (RNeasy, Qiagen). RNA concentrations was determined spectrophotometrically and the quality analysed with an Agilent Bioanalyzer. 100 ng total RNA was used for cDNA synthesis using oligo-dT(15) primers. The mRNA expression of specific genes was quantified by real time PCR using an Applied Biosystems (TaqMan) system and gene-specific primer and probe mixtures (pre-developed TaqMan Gene Expression Assays). Samples were run in duplicate. Relative expression levels were determined using a standard curve of serially diluted human adipose tissue cDNA. Gene expression quantified in biopsies was taken at the start of the study and at the end of the intervention study (6 months). Relationships between gene expression and parameters related to the metabolic syndrome (e.g. plasma lipids, inflammatory markers, body composition, adipose tissue) were investigated. Changes in gene expression were related to changes in metabolic syndrome parameters.

Genes analyzed

Housekeeping genes: TATA box binding protein (TBP) and Ribosomal protein (RPLP0)
Basic characterization Genes: Lipoprotein lipase (LPL), CD36, PPARγ, 11βHSD1
Obesity genes: Leptin, Adiponectin
Inflammatory genes: CD68, TNF-α, IL-6 and CCL2

In summary, mRNA expression levels of Adiponectin, Leptin, PPARG, CD36, LPL, CCL2, IL-6, TNF-alpha, 11BHSD1, CD68, RPLP0 and TBP0 were quantified by real-time PCR using the ABI 7000 Sequence Detection System instrument and software (Applied Biosystems, Foster City, CA, USA). cDNA synthesized from 15 ng of total RNA was mixed with TaqMan Universal PCR Master Mix (Applied Biosystems) and a gene-specific primer and probe mixture (predeveloped TaqMan Gene Expression Assays, Applied Biosystems). We used the assays: Adiponectin, Hs00605917_m1; PPARG, Hs00194153_m1; CD36, Hs00169627_m1; LPL, Hs00173425_m1; Leptin, Hs00174877_m1; 11BHSD1, Hs00194153_m1; CD68, Hs00154355_m1; CCL2, Hs00234140_m1; TNF alpha, Hs00174128_m1; IL6, Hs00174131_m1.. Expression levels were expressed in arbitrary units and normalized relative to the housekeeping gene RPLP0 to compensate for differences in cDNA loading. The levels of RPLP0 and TBP0 were comparable between all subjects in the study.

3.3 STATISTICAL METHODS

Metabolic syndrome definition

The updated ATP-III definition of metabolic syndrome was met when three or more of the following criteria were present: waist circumference ≥102 cm (40 in) in men and ≥88 cm (35 in) in women; HDL <1.03 mmol/L (40 mg/dl) in men and <1.30 mmol/L (50 mg/dl) in women or specific treatment for this lipid abnormality; triglycerides ≥1.7 mmol/L (150 mg/dl) in men and women or specific treatment for this lipid abnormality; systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥85 mmHg in men and women or treatment of previously diagnosed hypertension; and fasting glucose ≥5.6 mmol/L (100 mg/dl) in men and women.[18,19]

Definition of cardiovascular risk factor variables

For papers I and II, subjects were considered to have dyslipidemia if they reported current usage of medications to lower blood cholesterol, had a self-reported diagnosis of hypercholesterolemia, and/or LDL-C ≥4.10 mmol/L (160 mg/dL), and/or HDL-C <1.036 mmol/L (40 mg/dL) in men and <1.30 mmol/L (50 mg/dL) in women, and/or triglycerides ≥1.7 mmol/L (150 mg/dL).[19] Subjects were considered to be hypertensive if they were taking antihypertensive medications, had a self-reported diagnosis of hypertension and/or if their systolic pressure was ≥140 mmHg or diastolic pressure was ≥90 mmHg.[104] Subjects were considered to be in the smoking group if they were current, former or ever smokers (>100 cigarettes in their life). Subjects were considered to have diabetes if they reported current usage of antidiabetic medications (insulin and oral medications), self-reported diagnosis of diabetes, and/or if their fasting plasma glucose was ≥7.0 mmol/L (126 mg/dL).[105] Obesity was defined as body mass index (BMI) ≥30 kg/m^2 and/or waist circumference ≥102 cm in men and ≥88 cm in women. We decided to combine measures of total and central obesity since BMI alone might not be the best measure of obesity and/or metabolic risk. [106, 107] We defined 'high CRP' as the sex-specific highest quartile of CRP (mg/l) (≥0.33 in men; ≥0.44 in women) when compared with the three lowest quartiles (used as reference).

NHANES Analysis

The analysis of the NHANES III data was conducted according to the guidelines in the 'Analytic and Reporting Guidelines: The Third National Health and Nutrition Examination Survey, NHANES III (1988 to 1994)'. Data were summarized by calculating means and standard deviations (SDs) for quantitative variables and percentages for qualitative variables. All analyses were adjusted (weighted) to the general US population using weights calculated for that purpose by the National Center for Health Statistics.

For paper I, we calculated HOMA2, and reduced its positive skewness by applying a log transformation. Insulin resistance was defined as the upper quartile of HOMA2.[108] We defined 'high apoB/apoAI ratio' as the highest sex-specific quartile of the apoB/apoAI ratio (⩾0.97 in men; ⩾0.86 in women) and we then compared it to the

lowest quartile. Data were summarized by calculating sex-specific means and standard deviation for quantitative variables and percentages for categorical variables by high apoB/apoAI ratio and low apoB/apoAI ratio. We compared the median and the interquartile ranges of the apoB/apoAI ratio for individual components of the metabolic syndrome, ATP-III definition of the metabolic syndrome, and insulin resistance, all considered as qualitative variables using the *t* test for unequal variances. We applied logistic regression models adjusted for age and sex to determine the association between apoB/apoAI ratio and insulin resistance adjusting for metabolic syndrome components, traditional and inflammatory risk factors. Because of the high correlation between glucose and HOMA2, we did not include glucose in the model.

To analyze the additional contribution of apoB/apoAI to insulin resistance, multiple linear regression modeling was used to assess the simple and joint associations of apoB/apoAI, metabolic syndrome components, traditional and inflammatory risk factors with HOMA2. Age and race were always included as covariates, and all analyses were stratified by sex. Initially traditional risk factors, metabolic syndrome components, inflammatory risk factors, and apoB/apoAI were considered one at a time. Selection of predictor variables was done using a forward stepwise fashion with strict variable entry and elimination criteria in each predictors group (traditional risk factors, metabolic syndrome components, and inflammatory risk factors group). Consequently, the final parsimonious models for each sex only included those measures that made independent contributions to the prediction of HOMA2. The predictive value of each predictor group was assessed by comparing R^2 values of the models obtained from each group. Incremental additive value was judged by the increase in R^2 obtained when apoB/apoAI was added to the most predictive cardiovascular risk factors.

For paper II, multiple Cox-proportional hazard regression was used to estimate adjusted relations between lipid and lipoprotein risk factors and CV mortality. Hazard ratios were calculated after adjusting for different variables per SD increment. Two-sided *P*-values of <0.05 were considered statistically significant. The assumption of proportional hazards was assessed by visual inspection of the log–log survival curves for the categorical variables. Continuous variables were categorized and a graphical approach was applied to verify the linearity assumption. We investigated apolipoproteins as potential predictors of risk, over and above total cholesterol (TC), HDL-C, and LDL-C, with continuous measurements. We controlled for age, race, and sex as possible confounders. Additional adjustments were used for dyslipidaemia, high blood pressure, smoking, diabetes, obesity and high CRP. Also multiple Cox models were created to evaluate the predictive ability of the apoB/apoAI ratio quartiles for CV mortality. To address whether the apoB/apoAI ratio had incremental predictive utility over the TC/HDL-C ratio, we performed multi-variable Cox-proportional hazards regression to investigate the relations of the apoB/apoAI ratio to CHD death adjusting for traditional risk factors and TC/HDL-C ratio. Crude Kaplan–Meier survival curves were created to evaluate the quartiles of apoB and the apoB/apoAI ratio using the Log-rank test. All analyses were performed using SAS windows version and SUDAAN 9.0.3 for papers I and II.

In paper III, data were summarized by calculating means and standard deviations for quantitative variables and percentages for GGT sex-specific quartiles. To reduce the positive skewness of HOMA-2, a log transformation was applied. Insulin resistance was defined as the upper quartile of HOMA-2. We defined “high GGT” as the highest sex-specific quartile (in men >51U/L; in women >33 U/L) and we then compared it to

the lowest quartile. Mean values or frequencies were calculated, and comparisons performed using ANOVA (analysis of variance) or chi-square analysis. We assessed the association between serum GGT activity and each of the metabolic syndrome components with Pearson correlation coefficients. We applied logistic regression models adjusted for sex, education, physical activity, smoking, cholesterol and alcohol intake to determine the association between GGT and metabolic syndrome components. The information utility of the additional measures was assessed by comparing R^2 values of a full model that included the controlled variables with a reduced model that did not. When analyzing the subset of 294 men, linear regression modeling was applied to assess the simple and joint associations of each of the metabolic syndrome components with GGT, 8-iso-$PGF_{2\alpha}$ and CRP and we compared the additional information by comparing R^2 values. Alcohol intake was always included as a covariate. All analyses were performed using the SAS windows version.

For paper IV, data were summarized by calculating means and standard deviations for quantitative variables. Relationships between gene expression and parameters related to the metabolic syndrome (e.g. plasma lipids, inflammatory markers, body composition) were investigated. To account for changes in metabolic syndrome parameters and adipose tissue gene expression after 6 months, we calculated delta changes (6 months – baseline). Comparisons between groups were performed using ANOVA (analysis of variance) analysis. Correlations between gene expression levels, delta changes in genes and delta changes in metabolic syndrome parameters were performed using Spearman rank analysis. All analyses were performed using the SAS windows version

4 RESULTS

4.1 THE APOB/APOAI RATIO IS ASSOCIATED WITH INSULIN RESISTANCE (PAPER I)

Table 1 from paper I shows the descriptive characteristics of the sample. After adjusting for age and race, high apoB/apoAI ratio was significantly associated with insulin resistance in both sexes (in men: OR, 5.15; 95% CI, 3.51–7.72; in women: OR, 4.44; 95% CI, 3.04–6.57). To further evaluate the predictive effects of the apoB/apoAI ratio, quantitative traits rather than dichotomized were considered. Age and race accounted for 1% of the observed interindividual variation in HOMA2 in men ($P < 0.001$) and 3% of the variation in women ($P < 0.001$). In both sexes after controlling for age and race, each risk factor considered one-at-a-time made a significant additional contribution to the prediction of HOMA2 ($P < 0.05$) (See table 2 from paper I).

Overall, for the traditional risk factors (dyslipidaemia, hypertension, and smoking), the additional percentage of variation in HOMA2 explained by each measure ranged from 1 to 6%, with dyslipidaemia being the strongest predictor. For metabolic syndrome components (waist circumference, triglycerides, HDL-C and blood pressure), the additional percentage of variation in HOMA2 explained by each measure ranged from 1 to 25%, with waist circumference being the strongest predictor. For the inflammatory risk factors (C-reactive protein and fibrinogen), the additional percentage of variation in HOMA2 explained by each measure ranged from less than 1 to 10%, with C-reactive protein being the strongest predictor. The additional percentage of variation in HOMA2 explained by apoB/apoAI ratio was 11% for men and 9% for women ($P < 0.001$). In a final parsimonious model adjusting for age, race, and the best predictors of HOMA2 from the metabolic syndrome components, traditional and inflammatory risk factors, apoB/apoAI ratio still made an additional independent contribution to the prediction of HOMA2 (in men: additional $R^2 = 0.09$, $P < 0.001$; in women: additional $R^2 = 0.05$, $P < 0.001$) (See Table 3 of Paper I).

Previous studies have shown that adverse effects of excess body fat on cardiovascular outcomes only become apparent in subjects with BMI ≥30 kg/m^2 and paradoxically subjects with a BMI ranging 25–29.9 kg/m^2 have better survival and fewer cardiovascular events than lean subjects (BMI≤25 kg/m^2).[80,81] Therefore, we investigated whether the relationship between HOMA2 and apoB/apoAI was found in both obese (BMI ≥30 kg/m^2 and/or high waist circumference according to the metabolic syndrome definition) and non-obese subjects and in both of these groups the apoB/apoAI ratio remained a significant predictor of HOMA2 ($P < 0.001$).

4.2 APOB IS A BETTER PREDICTOR OF CHD MORTALITY THAN ROUTINE CLINICAL LIPID MEASUREMENTS (PAPER II)

Table 1 from paper II shows the descriptive characteristics. There were 7594 subjects with apolipoprotein measurements and for whom cardiovascular mortality follow-up data were available. Mean age was 45 years and 50% of the subjects were females. There were 673 subjects with cardiovascular death of which 432 (64%) were from

CHD. The median follow-up for this sample was 124 person-months (inter-quartile range 75–25% 114–134 person-months).

Concentrations of apoB (Hazards ratio [HR] per standard deviation increment, 1.98, 95% CI 1.09–3.61), apoAI (HR 0.48, 95% CI 0.27–0.85) and TC (HR 1.17, 95% CI 1.02–1.34) were significantly related to CHD death, whereas the concentration of HDL-C (0.68, 95% CI 0.45–1.05) was of borderline significance (See Table 2 of paper II). Both the apoB/apoAI ratio (HR 2.14, 95% CI 1.11–4.10) and the total cholesterol/HDL-C ratio (HR 1.10, 95% CI 1.04–1.16) were related to CHD death. When we substituted LDL-C for TC in the total cholesterol/HDL-C ratio, the prediction of CHD death was not improved (HR 0.81, 95% CI 0.96–1.24). When adjustments were made for traditional cardiovascular risk factors that included CRP, the total cholesterol/HDL-C ratio was no longer significant in the model (HR 1.02, 95% CI 0.91–1.14), whereas only the apoB/apoAI ratio (HR 2.09, 95% CI 1.04–4.19) and apoB (HR 2.01, 95% CI 1.05–3.86) remained significant.

The apoB/apoAI ratio remained significantly associated with CHD death (HR 2.98, 95% CI 1.07–6.58), after adjusting for traditional cardiovascular risk factors and the total cholesterol/HDL-C ratio; in contrast, the total cholesterol/HDL-C ratio was not significant (HR 0.92, 95% CI 0.79–1.09), after adjustment for traditional cardiovascular risk factors and the apoB/apoAI ratio. Nonetheless, when we tested the superiority of the apoB/apoAI ratio vs. using apoB alone it was non-significant. Similarly, subjects in the highest quartile of the apoB (HR 1.92, 95% CI 1.18–3.13) and the apoB/apoAI ratio (HR 1.73, 95% CI 1.06–2.77) had significantly greater risk of cardiovascular mortality compared with those in the lowest quartile, whereas subjects in the highest quartile of the total cholesterol/HDL-C ratio did not (HR 1.35, 95% CI 0.77–2.36). Accordingly, the incidence of cardiovascular death in the highest quartile of apoB and the apoB/apoAI ratio was greater than that in the lowest quartile (8.3% and 2.0%, respectively for apoB $P < 0.001$; 7.4% and 2.9%, respectively for the apoB/apoAI ratio $P < 0.001$). The event-free rate for CV mortality according to quartiles of apoB and the TC/HDL-C ratio is shown in Figure 1 of paper II. Stratification of the subjects above and <75 years of age revealed that the apoB/apoAI ratio was a significant predictor of CHD death irrespective of age, whereas TC/HDL-C ratio was only significantly associated with CHD death in the subjects <75 years (see Table 3 in paper II).

4.3 THE RELATIONSHIP BETWEEN GGT AND THE METABOLIC SYNDROME IS PARTIALLY MEDIATED BY CRP (PAPER III)

Table 1 of paper III shows the descriptive characteristics according to GGT quartiles. Overall, there were 830 subjects with GGT measurements who had the metabolic syndrome (prevalence 23%). There were 377 subjects with high GGT (i.e. Q4) who had the metabolic syndrome (prevalence 42%); in contrast there were only 64 subjects with low GGT (i.e. Q1) who had the metabolic syndrome (prevalence 7%), $P<0.0001$. Subjects with high GGT were significantly heavier, more likely to be less educated, to be smokers, to drink more alcohol and to have a more unfavorable cardio-metabolic profile than those with low GGT.

We found a significant correlation between serum GGT activity and all metabolic syndrome components, including HOMA-2 index in both men and women. Overall,

waist circumference had the strongest correlation with serum GGT activity (r=0.38, P<0.001), while HDL-cholesterol had the weakest correlation (r =-0.18, P<0.001).

Table 2 from paper III shows the significant association of high GGT with all of the metabolic syndrome components (waist, triglycerides, HDL-cholesterol, fasting glucose and blood pressure) after controlling for sex, education, physical activity, smoking, cholesterol and alcohol intake. Furthermore, high GGT was also independently associated with the definition of metabolic syndrome (OR, 5.58 - 95% CI, 4.21-7.46) and with insulin resistance (OR, 4.88 - 95% CI, 3.80-6.30) after controlling for potential confounders in both men and women. To further evaluate the additional utility of quantitative levels of GGT rather than dichotomized, we conducted multiple variable linear regression analyses in which the outcome variable was the quantitative level of each of the metabolic syndrome components including insulin sensitivity (Table 3 of paper III). Overall, GGT still added information to each of the metabolic syndrome components after controlling for sex, education, physical activity, smoking, cholesterol and alcohol intake (P<0.0001).

To investigate whether associations between GGT and components of the metabolic syndrome could be explained, at least in part by inflammation or oxidative stress, we used the subset of 294 healthy men recruited from the original cohort. In these men inflammation was assessed by circulating CRP and oxidative stress by urinary 8-iso-$PGF_{2\alpha}$. Analysis revealed that 68% (n=201) had at least one component of the metabolic syndrome and 11% (n=31) had the full metabolic syndrome. In these men, mean values ± SD were 10.2 ± 9.1 U/L for serum GGT, 14.1 ± 6.3 nmol/L/GFR for urinary 8-iso-$PGF_{2\alpha}$, and 2.1 ± 2.5 mg/L for serum CRP. When we investigated in multivariable analyses the additional contribution of 8-iso-$PGF_{2\alpha}$ and CRP to each of the metabolic syndrome components once GGT was in the model, CRP explained a significant percentage of variation for all of the components, while 8-iso-$PGF_{2\alpha}$ explained a significant percent in the variation only for waist circumference and systolic blood pressure. For example, when we included both GGT and CRP in a model to account for the interindividual variation of waist circumference, the model explained a total of 14%. GGT alone explained 7%, while CRP explained 11% and they shared 4% of the information (See Figure 1 of paper III). When we used both GGT and 8-iso-$PGF_{2\alpha}$ in a model to explain the interindividual variation of waist circumference, together they explained a total of 8% sharing less than 1% of the information. To confirm these findings, we looked at the relationship between GGT and metabolic syndrome parameters in a larger population (NHANES 2005-06) and we confirmed the CRP-mediated relationship of GGT with the metabolic syndrome components in a subset of elderly NHANES subjects (n=927). Descriptive characteristics of these subjects are given in Table 4 of paper III. A model that included both GGT and CRP explained a total of 9% of the interindividual variation of waist circumference after controlling for age, race and sex; GGT and CRP shared 5% of this information. Similarly, both CRP and GGT were significant independent predictors of all the metabolic syndrome parameters (triglycerides, HDL-cholesterol, fasting glucose and blood pressure) in the NHANES 2005-06 subset, and also shared most of the predictive information

4.4 CHANGES IN METABOLIC SYNDROME PARAMETERS ARE MEDIATED BY ADIPOSE TISSUE GENE EXPRESSION (PAPER IV)

Of the 101 subjects that entered the study at baseline, 91 completed the intervention and attended the 6 month follow up (10% dropout rate). Adipose tissue biopsies were obtained from 53 individuals at both baseline and 6 month follow-up (30 controls, 23 interventions) and from which it was possible to extract RNA and quantify gene expression. The characteristics of these 53 individuals did not differ significantly from the cohort as a whole. Table 1 from Paper IV shows descriptive characteristics for these subjects at baseline and at 6 months. The expression levels of 10 genes with important roles in adipose tissue metabolism were quantified in subcutaneous adipose tissue biopsies and expressed in arbitrary units relative to the house keeping genes RPLP0 and TBP. Analysis of adipose tissue biopsies taken at 6 months revealed no significant differences in gene expression for any of the 10 genes analyzed (or for the house keeping genes RPLP0 and TBP) compared to baseline in either the control or intervention groups, Table 2 of Paper IV. Therefore, we pooled the results from the control and intervention groups in order to gain power for further analysis.

When we looked at Relationships between Adipose Tissue Expression Levels at Baseline we found that at baseline, analyzing all subjects, expression levels of the macrophage marker CD68 were positively associated with mRNA levels of CCL2 ($r=0.537$, $P<0.001$) (Figure 1a of Paper IV), TNFα ($r=0.276$, $P=0.04$) and IL6 ($r=0.302$, $P=0.02$). Expression of the anti-inflammatory adipokine adiponectin was positively associated with expression of LPL ($r=0.347$, $P=0.01$) and negatively with IL6 ($r=-0.423$, $P=0.001$) (Figure 1b of Paper IV). When analyzing relationships between baseline adipose tissue gene expression and circulating metabolic parameters, CD68 expression was found to be positively associated with circulating concentrations of CRP ($r=0.514$, $P<0.001$) (Figure 1c of Paper IV) and negatively with HDL-cholesterol ($r=-0.444$, $P=0.0009$). Adiponectin expression was negatively associated with waist circumference ($r=-0.360$, $P=0.008$). Waist circumference expression was positively associated with IL6 expression ($r=0.363$, $P=0.007$) (Figure 1d of Paper IV). Conversely, BMI was not significantly associated with expression levels of any of the genes analyzed.

When we looked at changes in Adipose Tissue Gene Expression Levels and Changes in Metabolic Variables we found that Δ-CD68 expression was positively associated with Δ-CCL2 ($r=0.558$ $P<0.001$) (Figure 1e of Paper IV) and with Δ-11BHSD ($r=0.517$, $P=0.0006$) and negatively with Δ-triglycerides ($r=-0.330$, $P=0.019$). Δ-adiponectin expression was not significantly associated with any other Δ-gene expression level. However, Δ-adiponectin expression was positively associated with Δ-systolic blood pressure ($r=0.285$, $P=0.044$), with Δ-triglycerides ($r=0.284$, $P=0.045$), and with Δ-GGT ($r=0.28$, $P=0.041$). Δ-Waist circumference was positively associated with Δ-PPARγ expression ($r=0.34$ $P=0.022$) (Figure 1f of Paper IV).

In the next pages, I have added the full analysis for all gene expression Pearson correlations.

4.5 FULL GENE EXPRESSION ANALYSIS (PAPER IV)

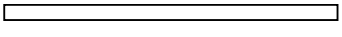
ALL SUBJECTS

CORRELATIONS BETWEEN BASELINE GENES & BASELINE METABOLIC SYNDROME PARAMETERS

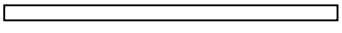
Nonparametric: Spearman's ρ

Variable	by Variable	Spearman ρ	Prob>|ρ|	Plot
CCL2 B	CD68 B	0.5371	<.0001	
TNF a B	CD68 B	0.2761	0.0499	
TNF a B	CCL2 B	0.1063	0.4577	
IL6 B	CD68 B	0.3021	0.0279	
IL6 B	CCL2 B	0.3959	0.0033	
IL6 B	TNF a B	0.1379	0.3345	
PPARY B	CD68 B	-0.2502	0.0797	
PPARY B	CCL2 B	-0.1854	0.1974	
PPARY B	TNF a B	-0.0994	0.4969	
PPARY B	IL6 B	-0.0607	0.6752	
ADIPO B	CD68 B	-0.1569	0.2618	
ADIPO B	CCL2 B	-0.2433	0.0791	
ADIPO B	TNF a B	-0.0691	0.6297	
ADIPO B	IL6 B	-0.4237	0.0016	
ADIPO B	PPARY B	0.0317	0.8268	
LPL B	CD68 B	-0.1497	0.2896	
LPL B	CCL2 B	-0.0965	0.4963	
LPL B	TNF a B	-0.0646	0.6524	
LPL B	IL6 B	-0.4169	0.0021	
LPL B	PPARY B	0.3882	0.0053	
LPL B	ADIPO B	0.3471	0.0117	
CD36 B	CD68 B	0.2281	0.1150	
CD36 B	CCL2 B	-0.0592	0.6863	
CD36 B	TNF a B	-0.0518	0.7267	
CD36 B	IL6 B	-0.1445	0.3219	
CD36 B	PPARY B	0.3732	0.0090	
CD36 B	ADIPO B	0.2153	0.1374	
CD36 B	LPL B	0.1750	0.2291	
LEPTIN B	CD68 B	0.1891	0.1883	
LEPTIN B	CCL2 B	0.1552	0.2817	
LEPTIN B	TNF a B	-0.0830	0.5747	
LEPTIN B	IL6 B	0.1687	0.2416	
LEPTIN B	PPARY B	0.2564	0.0753	
LEPTIN B	ADIPO B	-0.2036	0.1560	
LEPTIN B	LPL B	0.2304	0.1112	
LEPTIN B	CD36 B	0.2893	0.0486	
11BHSD B	CD68 B	0.2764	0.0572	
11BHSD B	CCL2 B	0.1232	0.4041	
11BHSD B	TNF a B	-0.2152	0.1463	
11BHSD B	IL6 B	0.1596	0.2786	

Variable	by Variable	Spearman ρ	Prob>|ρ|	Plot
11BHSD B	PPARY B	0.1184	0.4227	
11BHSD B	ADIPO B	-0.0249	0.8668	
11BHSD B	LPL B	-0.1372	0.3524	
11BHSD B	CD36 B	0.3037	0.0380	
11BHSD B	LEPTIN B	0.4473	0.0016	
SBP	CD68 B	0.1792	0.1992	
SBP	CCL2 B	0.1417	0.3113	
SBP	TNF a B	-0.0386	0.7881	
SBP	IL6 B	0.2970	0.0308	
SBP	PPARY B	0.1991	0.1657	
SBP	ADIPO B	-0.2665	0.0537	
SBP	LPL B	-0.0723	0.6104	
SBP	CD36 B	0.2683	0.0623	
SBP	LEPTIN B	0.0498	0.7314	
SBP	11BHSD B	0.3138	0.0298	
DBP	CD68 B	0.1223	0.3830	
DBP	CCL2 B	0.0345	0.8061	
DBP	TNF a B	0.1008	0.4814	
DBP	IL6 B	0.2802	0.0421	
DBP	PPARY B	0.0826	0.5685	
DBP	ADIPO B	-0.3201	0.0195	
DBP	LPL B	-0.2576	0.0652	
DBP	CD36 B	0.1347	0.3560	
DBP	LEPTIN B	0.0295	0.8388	
DBP	11BHSD B	0.3872	0.0066	
DBP	SBP	0.6525	<.0001	
BMI	CD68 B	0.0876	0.5330	
BMI	CCL2 B	0.2689	0.0515	
BMI	TNF a B	-0.1001	0.4847	
BMI	IL6 B	0.1820	0.1922	
BMI	PPARY B	-0.0396	0.7847	
BMI	ADIPO B	-0.0278	0.8433	
BMI	LPL B	0.0196	0.8906	
BMI	CD36 B	0.0221	0.8800	
BMI	LEPTIN B	0.0532	0.7139	
BMI	11BHSD B	0.2982	0.0395	
BMI	SBP	0.2789	0.0324	
BMI	DBP	0.2581	0.0484	
GGT	CD68 B	0.1616	0.2477	
GGT	CCL2 B	0.0780	0.5789	
GGT	TNF a B	0.0412	0.7740	
GGT	IL6 B	0.3094	0.0242	
GGT	PPARY B	-0.1925	0.1805	
GGT	ADIPO B	-0.2766	0.0449	
GGT	LPL B	-0.2512	0.0724	
GGT	CD36 B	-0.1844	0.2045	
GGT	LEPTIN B	-0.0291	0.8408	

Variable	by Variable	Spearman ρ	Prob>|ρ|	Plot
GGT	11BHSD B	0.1229	0.4052	
GGT	SBP	0.1351	0.3078	
GGT	DBP	0.3556	0.0057	
GGT	BMI	-0.0431	0.7460	
CRP	CD68 B	0.5149	<.0001	
CRP	CCL2 B	0.2666	0.0537	
CRP	TNF a B	0.2370	0.0941	
CRP	IL6 B	0.2275	0.1014	
CRP	PPARY B	-0.2982	0.0354	
CRP	ADIPO B	0.1189	0.3963	
CRP	LPL B	-0.0104	0.9415	
CRP	CD36 B	0.2137	0.1403	
CRP	LEPTIN B	0.1475	0.3068	
CRP	11BHSD B	0.1160	0.4325	
CRP	SBP	-0.0782	0.5562	
CRP	DBP	-0.0474	0.7212	
CRP	BMI	0.0817	0.5383	
CRP	GGT	0.1234	0.3519	
LDL	CD68 B	-0.1643	0.2397	
LDL	CCL2 B	-0.1646	0.2390	
LDL	TNF a B	-0.0806	0.5738	
LDL	IL6 B	-0.3596	0.0082	
LDL	PPARY B	-0.0542	0.7086	
LDL	ADIPO B	0.1803	0.1964	
LDL	LPL B	0.1561	0.2691	
LDL	CD36 B	0.0969	0.5078	
LDL	LEPTIN B	-0.0417	0.7736	
LDL	11BHSD B	0.0988	0.5040	
LDL	SBP	0.0020	0.9881	
LDL	DBP	0.0921	0.4877	
LDL	BMI	-0.0914	0.4909	
LDL	GGT	-0.0175	0.8955	
LDL	CRP	-0.1544	0.2429	
ApoAI	CD68 B	-0.3491	0.0104	
ApoAI	CCL2 B	-0.1941	0.1638	
ApoAI	TNF a B	0.0528	0.7131	
ApoAI	IL6 B	-0.2413	0.0817	
ApoAI	PPARY B	-0.1213	0.4015	
ApoAI	ADIPO B	0.1224	0.3825	
ApoAI	LPL B	0.1996	0.1560	
ApoAI	CD36 B	-0.3217	0.0242	
ApoAI	LEPTIN B	0.0348	0.8107	
ApoAI	11BHSD B	-0.2590	0.0755	
ApoAI	SBP	-0.0602	0.6506	
ApoAI	DBP	-0.0832	0.5310	
ApoAI	BMI	0.0354	0.7900	
ApoAI	GGT	-0.1596	0.2273	

Variable	by Variable	Spearman ρ	Prob>|ρ|	Plot
ApoAI	CRP	-0.2041	0.1211	
ApoAI	LDL	0.1657	0.2098	
ApoB	CD68 B	-0.0942	0.5023	
ApoB	CCL2 B	-0.1159	0.4086	
ApoB	TNF a B	-0.1195	0.4035	
ApoB	IL6 B	-0.2735	0.0475	
ApoB	PPARY B	-0.1542	0.2849	
ApoB	ADIPO B	0.1262	0.3678	
ApoB	LPL B	0.0458	0.7473	
ApoB	CD36 B	0.0319	0.8276	
ApoB	LEPTIN B	-0.0127	0.9301	
ApoB	11BHSD B	0.1840	0.2105	
ApoB	SBP	-0.0148	0.9116	
ApoB	DBP	0.1022	0.4411	
ApoB	BMI	0.0116	0.9305	
ApoB	GGT	0.1104	0.4050	
ApoB	CRP	-0.0886	0.5044	
ApoB	LDL	0.8914	<.0001	
ApoB	ApoAI	0.1023	0.4408	
HDL	CD68 B	-0.4440	0.0009	
HDL	CCL2 B	-0.2463	0.0754	
HDL	TNF a B	-0.0184	0.8980	
HDL	IL6 B	-0.2542	0.0662	
HDL	PPARY B	-0.0168	0.9076	
HDL	ADIPO B	0.1480	0.2903	
HDL	LPL B	0.3392	0.0139	
HDL	CD36 B	-0.2584	0.0730	
HDL	LEPTIN B	0.0289	0.8419	
HDL	11BHSD B	-0.3199	0.0267	
HDL	SBP	-0.1543	0.2433	
HDL	DBP	-0.2098	0.1108	
HDL	BMI	-0.0880	0.5074	
HDL	GGT	-0.2611	0.0458	
HDL	CRP	-0.2175	0.0979	
HDL	LDL	0.1450	0.2731	
HDL	ApoAI	0.8577	<.0001	
HDL	ApoB	0.0215	0.8713	
Glu	CD68 B	0.1895	0.1830	
Glu	CCL2 B	0.2824	0.0446	
Glu	TNF a B	-0.1690	0.2457	
Glu	IL6 B	0.4572	0.0007	
Glu	PPARY B	0.0903	0.5374	
Glu	ADIPO B	0.0344	0.8105	
Glu	LPL B	-0.1054	0.4665	
Glu	CD36 B	-0.0054	0.9710	
Glu	LEPTIN B	0.0827	0.5723	
Glu	11BHSD B	0.2577	0.0803	

Variable	by Variable	Spearman ρ	Prob>|ρ|	Plot
Glu	SBP	0.3700	0.0046	
Glu	DBP	0.2318	0.0827	
Glu	BMI	0.2974	0.0246	
Glu	GGT	0.3040	0.0215	
Glu	CRP	0.0149	0.9124	
Glu	LDL	-0.1449	0.2823	
Glu	ApoAI	-0.1873	0.1630	
Glu	ApoB	-0.0417	0.7581	
Glu	HDL	-0.2306	0.0845	
TRIG	CD68 B	0.1771	0.2047	
TRIG	CCL2 B	0.1002	0.4753	
TRIG	TNF a B	-0.0019	0.9896	
TRIG	IL6 B	0.1329	0.3429	
TRIG	PPARY B	-0.0639	0.6594	
TRIG	ADIPO B	-0.0826	0.5567	
TRIG	LPL B	-0.1277	0.3668	
TRIG	CD36 B	0.0105	0.9429	
TRIG	LEPTIN B	-0.0168	0.9079	
TRIG	11BHSD B	0.4229	0.0027	
TRIG	SBP	0.1936	0.1419	
TRIG	DBP	0.3086	0.0174	
TRIG	BMI	0.1720	0.1928	
TRIG	GGT	0.2772	0.0336	
TRIG	CRP	0.0405	0.7609	
TRIG	LDL	0.2695	0.0390	
TRIG	ApoAI	-0.2407	0.0663	
TRIG	ApoB	0.4569	0.0003	
TRIG	HDL	-0.3889	0.0023	
TRIG	Glu	0.2604	0.0504	
Waist	CD68 B	0.1401	0.3170	
Waist	CCL2 B	0.2400	0.0834	
Waist	TNF a B	-0.0912	0.5244	
Waist	IL6 B	0.3632	0.0075	
Waist	PPARY B	-0.0479	0.7410	
Waist	ADIPO B	-0.3604	0.0080	
Waist	LPL B	-0.1768	0.2098	
Waist	CD36 B	-0.1589	0.2754	
Waist	LEPTIN B	0.0604	0.6771	
Waist	11BHSD B	0.2988	0.0391	
Waist	SBP	0.2872	0.0274	
Waist	DBP	0.3437	0.0077	
Waist	BMI	0.5933	<.0001	
Waist	GGT	0.4875	<.0001	
Waist	CRP	0.1322	0.3182	
Waist	LDL	-0.1992	0.1304	
Waist	ApoAI	-0.0563	0.6721	
Waist	ApoB	-0.0801	0.5467	

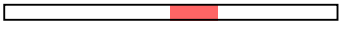
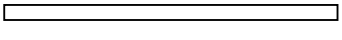
Variable	by Variable	Spearman ρ	Prob>|ρ|	Plot
Waist	HDL	-0.1643	0.2138	
Waist	Glu	0.4575	0.0003	
Waist	TRIG	0.2548	0.0515	

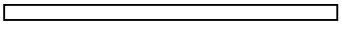
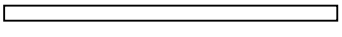
ALL SUBJECTS

CORRELATIONS BETWEEN DELTA DIFFERENCES IN GENES AND DELTA DIFFERENCES IN METABOLIC SYNDROME PARAMETERS

Nonparametric: Spearman's ρ

Variable	by Variable	Spearman ρ	Prob>|ρ|	Plot
CCL2 DIFF	CD68 DIFF	0.5581	<.0001	
TNF DIFF	CD68 DIFF	0.0984	0.5201	
TNF DIFF	CCL2 DIFF	0.0483	0.7553	
IL6 DIFF	CD68 DIFF	0.1722	0.2580	
IL6 DIFF	CCL2 DIFF	0.2775	0.0650	
IL6 DIFF	TNF DIFF	-0.1897	0.2289	
PPAR DIFF	CD68 DIFF	0.0767	0.6379	
PPAR DIFF	CCL2 DIFF	0.0914	0.5750	
PPAR DIFF	TNF DIFF	-0.1183	0.4794	
PPAR DIFF	IL6 DIFF	-0.0898	0.5917	
ADIPO DIFF	CD68 DIFF	-0.2353	0.0999	
ADIPO DIFF	CCL2 DIFF	-0.1379	0.3449	
ADIPO DIFF	TNF DIFF	0.1631	0.2844	
ADIPO DIFF	IL6 DIFF	-0.2693	0.0736	
ADIPO DIFF	PPAR DIFF	0.0593	0.7163	
LPL DIFF	CD68 DIFF	-0.1523	0.3124	
LPL DIFF	CCL2 DIFF	0.0615	0.6880	
LPL DIFF	TNF DIFF	-0.3088	0.0414	
LPL DIFF	IL6 DIFF	0.0145	0.9274	
LPL DIFF	PPAR DIFF	0.3657	0.0203	
LPL DIFF	ADIPO DIFF	0.0950	0.5298	
CD36 DIFF	CD68 DIFF	0.1387	0.3999	
CD36 DIFF	CCL2 DIFF	0.2209	0.1767	
CD36 DIFF	TNF DIFF	-0.1993	0.2304	
CD36 DIFF	IL6 DIFF	0.0121	0.9423	
CD36 DIFF	PPAR DIFF	0.3133	0.0555	
CD36 DIFF	ADIPO DIFF	0.1085	0.5109	
CD36 DIFF	LPL DIFF	0.6022	<.0001	
LEPTIN DIFF	CD68 DIFF	-0.0020	0.9898	
LEPTIN DIFF	CCL2 DIFF	0.1857	0.2450	
LEPTIN DIFF	TNF DIFF	-0.1319	0.4301	
LEPTIN DIFF	IL6 DIFF	0.2205	0.1897	
LEPTIN DIFF	PPAR DIFF	0.0636	0.7126	
LEPTIN DIFF	ADIPO DIFF	-0.2675	0.0868	
LEPTIN DIFF	LPL DIFF	0.1791	0.2752	
LEPTIN DIFF	CD36 DIFF	0.2831	0.1047	
11BHSD	CD68 DIFF	0.5174	0.0006	
11BHSD	CCL2 DIFF	0.2659	0.0973	

Variable	by Variable	Spearman ρ	Prob>|ρ|	Plot
11BHSD	TNF DIFF	-0.3051	0.0590	
11BHSD	IL6 DIFF	0.2126	0.2000	
11BHSD	PPAR DIFF	0.1579	0.3438	
11BHSD	ADIPO DIFF	0.2347	0.1449	
11BHSD	LPL DIFF	0.2503	0.1193	
11BHSD	CD36 DIFF	0.4303	0.0079	
11BHSD	LEPTIN DIFF	-0.2230	0.1979	
SBP Diff	CD68 DIFF	-0.1308	0.3653	
SBP Diff	CCL2 DIFF	-0.2059	0.1558	
SBP Diff	TNF DIFF	-0.1759	0.2477	
SBP Diff	IL6 DIFF	-0.1021	0.5046	
SBP Diff	PPAR DIFF	0.0311	0.8491	
SBP Diff	ADIPO DIFF	0.2859	0.0441	
SBP Diff	LPL DIFF	0.0385	0.7996	
SBP Diff	CD36 DIFF	0.2429	0.1362	
SBP Diff	LEPTIN DIFF	-0.1201	0.4486	
SBP Diff	11BHSD	-0.0873	0.5923	
DBP Diff	CD68 DIFF	0.0469	0.7466	
DBP Diff	CCL2 DIFF	-0.0445	0.7616	
DBP Diff	TNF DIFF	-0.0307	0.8415	
DBP Diff	IL6 DIFF	-0.0479	0.7545	
DBP Diff	PPAR DIFF	-0.2511	0.1180	
DBP Diff	ADIPO DIFF	0.2700	0.0579	
DBP Diff	LPL DIFF	-0.1065	0.4814	
DBP Diff	CD36 DIFF	0.0208	0.9001	
DBP Diff	LEPTIN DIFF	-0.2165	0.1686	
DBP Diff	11BHSD	0.2421	0.1322	
DBP Diff	SBP Diff	0.2351	0.0730	
GGT Diff	CD68 DIFF	-0.2115	0.1403	
GGT Diff	CCL2 DIFF	-0.1381	0.3439	
GGT Diff	TNF DIFF	-0.2463	0.1028	
GGT Diff	IL6 DIFF	-0.0595	0.6979	
GGT Diff	PPAR DIFF	-0.0855	0.6001	
GGT Diff	ADIPO DIFF	0.2889	0.0419	
GGT Diff	LPL DIFF	0.2353	0.1154	
GGT Diff	CD36 DIFF	0.0563	0.7337	
GGT Diff	LEPTIN DIFF	0.0064	0.9679	
GGT Diff	11BHSD	-0.0015	0.9926	
GGT Diff	SBP Diff	0.0499	0.7072	
GGT Diff	DBP Diff	0.2503	0.0559	
BMI Diff	CD68 DIFF	-0.1559	0.2797	
BMI Diff	CCL2 DIFF	0.0399	0.7855	
BMI Diff	TNF DIFF	0.1302	0.3941	
BMI Diff	IL6 DIFF	-0.0969	0.5266	
BMI Diff	PPAR DIFF	0.2565	0.1102	
BMI Diff	ADIPO DIFF	0.1583	0.2723	
BMI Diff	LPL DIFF	0.0339	0.8232	

Variable	by Variable	Spearman ρ	Prob>|ρ|	Plot
BMI Diff	CD36 DIFF	0.1717	0.2961	
BMI Diff	LEPTIN DIFF	0.0564	0.7228	
BMI Diff	11BHSD	-0.2833	0.0765	
BMI Diff	SBP Diff	0.2093	0.1115	
BMI Diff	DBP Diff	0.1899	0.1496	
BMI Diff	GGT Diff	0.1263	0.3407	
CRP Diff	CD68 DIFF	0.1040	0.4724	
CRP Diff	CCL2 DIFF	-0.0948	0.5170	
CRP Diff	TNF DIFF	0.0800	0.6012	
CRP Diff	IL6 DIFF	0.1110	0.4678	
CRP Diff	PPAR DIFF	-0.1758	0.2778	
CRP Diff	ADIPO DIFF	0.0371	0.7980	
CRP Diff	LPL DIFF	-0.0392	0.7961	
CRP Diff	CD36 DIFF	0.0817	0.6210	
CRP Diff	LEPTIN DIFF	0.0910	0.5665	
CRP Diff	11BHSD	0.0945	0.5620	
CRP Diff	SBP Diff	-0.0122	0.9270	
CRP Diff	DBP Diff	0.0108	0.9353	
CRP Diff	GGT Diff	0.0763	0.5658	
CRP Diff	BMI Diff	0.2633	0.0439	
LDL Diff	CD68 DIFF	-0.0598	0.6801	
LDL Diff	CCL2 DIFF	0.0729	0.6188	
LDL Diff	TNF DIFF	-0.0656	0.6685	
LDL Diff	IL6 DIFF	0.0602	0.6945	
LDL Diff	PPAR DIFF	-0.1710	0.2913	
LDL Diff	ADIPO DIFF	-0.2850	0.0448	
LDL Diff	LPL DIFF	0.0074	0.9613	
LDL Diff	CD36 DIFF	0.0269	0.8710	
LDL Diff	LEPTIN DIFF	0.3423	0.0265	
LDL Diff	11BHSD	-0.0867	0.5946	
LDL Diff	SBP Diff	-0.1142	0.3892	
LDL Diff	DBP Diff	-0.2570	0.0494	
LDL Diff	GGT Diff	-0.1125	0.3963	
LDL Diff	BMI Diff	-0.0904	0.4959	
LDL Diff	CRP Diff	0.0378	0.7763	
ApoAI Diff	CD68 DIFF	-0.1021	0.4806	
ApoAI Diff	CCL2 DIFF	0.0479	0.7439	
ApoAI Diff	TNF DIFF	-0.0490	0.7491	
ApoAI Diff	IL6 DIFF	0.0442	0.7733	
ApoAI Diff	PPAR DIFF	-0.0125	0.9390	
ApoAI Diff	ADIPO DIFF	-0.0046	0.9749	
ApoAI Diff	LPL DIFF	-0.0733	0.6282	
ApoAI Diff	CD36 DIFF	0.0575	0.7280	
ApoAI Diff	LEPTIN DIFF	0.1332	0.4003	
ApoAI Diff	11BHSD	-0.1625	0.3163	
ApoAI Diff	SBP Diff	-0.0904	0.4958	
ApoAI Diff	DBP Diff	-0.2548	0.0515	

Variable	by Variable	Spearman ρ	Prob>|ρ|	Plot
ApoAI Diff	GGT Diff	0.2087	0.1127	
ApoAI Diff	BMI Diff	-0.0667	0.6159	
ApoAI Diff	CRP Diff	-0.2193	0.0951	
ApoAI Diff	LDL Diff	0.1282	0.3332	
ApoB Diff	CD68 DIFF	-0.0425	0.7697	
ApoB Diff	CCL2 DIFF	0.0235	0.8729	
ApoB Diff	TNF DIFF	0.1117	0.4649	
ApoB Diff	IL6 DIFF	-0.1196	0.4340	
ApoB Diff	PPAR DIFF	-0.2909	0.0685	
ApoB Diff	ADIPO DIFF	-0.0692	0.6330	
ApoB Diff	LPL DIFF	0.0744	0.6230	
ApoB Diff	CD36 DIFF	-0.1228	0.4564	
ApoB Diff	LEPTIN DIFF	0.1262	0.4260	
ApoB Diff	11BHSD	-0.1370	0.3991	
ApoB Diff	SBP Diff	-0.3335	0.0098	
ApoB Diff	DBP Diff	-0.2418	0.0650	
ApoB Diff	GGT Diff	0.0545	0.6819	
ApoB Diff	BMI Diff	-0.0971	0.4646	
ApoB Diff	CRP Diff	0.0887	0.5042	
ApoB Diff	LDL Diff	0.6259	<.0001	
ApoB Diff	ApoAI Diff	0.0595	0.6547	
HDL Diff	CD68 DIFF	-0.1842	0.2004	
HDL Diff	CCL2 DIFF	-0.0657	0.6537	
HDL Diff	TNF DIFF	-0.2272	0.1333	
HDL Diff	IL6 DIFF	0.0893	0.5597	
HDL Diff	PPAR DIFF	-0.0933	0.5668	
HDL Diff	ADIPO DIFF	-0.0697	0.6305	
HDL Diff	LPL DIFF	0.1220	0.4192	
HDL Diff	CD36 DIFF	0.0053	0.9745	
HDL Diff	LEPTIN DIFF	0.1010	0.5247	
HDL Diff	11BHSD	-0.2308	0.1518	
HDL Diff	SBP Diff	0.0706	0.5952	
HDL Diff	DBP Diff	-0.3105	0.0167	
HDL Diff	GGT Diff	0.1844	0.1620	
HDL Diff	BMI Diff	-0.1226	0.3548	
HDL Diff	CRP Diff	-0.1542	0.2435	
HDL Diff	LDL Diff	0.1859	0.1586	
HDL Diff	ApoAI Diff	0.7585	<.0001	
HDL Diff	ApoB Diff	0.1747	0.1856	
GLU Diff	CD68 DIFF	-0.0560	0.7056	
GLU Diff	CCL2 DIFF	0.1218	0.4095	
GLU Diff	TNF DIFF	0.0855	0.5858	
GLU Diff	IL6 DIFF	0.2112	0.1687	
GLU Diff	PPAR DIFF	0.2007	0.2143	
GLU Diff	ADIPO DIFF	0.2100	0.1519	
GLU Diff	LPL DIFF	0.3431	0.0226	
GLU Diff	CD36 DIFF	0.2531	0.1201	

Variable	by Variable	Spearman ρ	Prob>|ρ|	Plot
GLU Diff	LEPTIN DIFF	0.0449	0.7805	
GLU Diff	11BHSD	-0.0665	0.6837	
GLU Diff	SBP Diff	0.1023	0.4490	
GLU Diff	DBP Diff	-0.1771	0.1877	
GLU Diff	GGT Diff	0.1133	0.4012	
GLU Diff	BMI Diff	0.1467	0.2763	
GLU Diff	CRP Diff	-0.0469	0.7291	
GLU Diff	LDL Diff	0.2154	0.1076	
GLU Diff	ApoAI Diff	0.1400	0.2991	
GLU Diff	ApoB Diff	0.2279	0.0882	
GLU Diff	HDL Diff	0.0754	0.5772	
Trig Diff	CD68 DIFF	-0.3300	0.0192	
Trig Diff	CCL2 DIFF	-0.2574	0.0742	
Trig Diff	TNF DIFF	0.1909	0.2091	
Trig Diff	IL6 DIFF	-0.2208	0.1449	
Trig Diff	PPAR DIFF	0.0746	0.6475	
Trig Diff	ADIPO DIFF	0.2840	0.0456	
Trig Diff	LPL DIFF	-0.0374	0.8050	
Trig Diff	CD36 DIFF	0.0811	0.6235	
Trig Diff	LEPTIN DIFF	-0.1377	0.3844	
Trig Diff	11BHSD	-0.0183	0.9107	
Trig Diff	SBP Diff	-0.1340	0.3116	
Trig Diff	DBP Diff	0.1756	0.1833	
Trig Diff	GGT Diff	0.2242	0.0878	
Trig Diff	BMI Diff	0.2266	0.0844	
Trig Diff	CRP Diff	-0.0752	0.5715	
Trig Diff	LDL Diff	-0.2163	0.0999	
Trig Diff	ApoAI Diff	0.1043	0.4319	
Trig Diff	ApoB Diff	-0.0499	0.7075	
Trig Diff	HDL Diff	-0.1642	0.2139	
Trig Diff	GLU Diff	0.0960	0.4773	
Waist Diff	CD68 DIFF	-0.0434	0.7646	
Waist Diff	CCL2 DIFF	0.0846	0.5632	
Waist Diff	TNF DIFF	0.0236	0.8779	
Waist Diff	IL6 DIFF	-0.0686	0.6545	
Waist Diff	PPAR DIFF	0.3698	0.0188	
Waist Diff	ADIPO DIFF	0.0665	0.6465	
Waist Diff	LPL DIFF	0.2297	0.1247	
Waist Diff	CD36 DIFF	0.2131	0.1927	
Waist Diff	LEPTIN DIFF	0.0324	0.8384	
Waist Diff	11BHSD	-0.1877	0.2462	
Waist Diff	SBP Diff	0.2700	0.0387	
Waist Diff	DBP Diff	0.0098	0.9412	
Waist Diff	GGT Diff	0.1211	0.3609	
Waist Diff	BMI Diff	0.4282	0.0007	
Waist Diff	CRP Diff	0.1323	0.3177	
Waist Diff	LDL Diff	-0.1820	0.1676	

Variable	by Variable	Spearman ρ	Prob>|ρ|	Plot
Waist Diff	ApoAI Diff	0.0417	0.7538	
Waist Diff	ApoB Diff	-0.2304	0.0792	
Waist Diff	HDL Diff	0.0922	0.4874	
Waist Diff	GLU Diff	0.1396	0.3003	
Waist Diff	Trig Diff	-0.0232	0.8614	

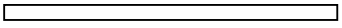
RANDOMIZED INTERVENTION CORRELATIONS

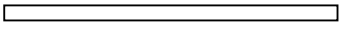
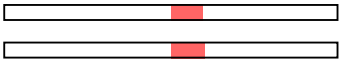
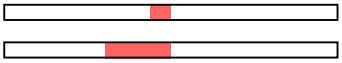
CONTROL GROUP

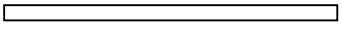
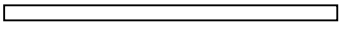
CORRELATIONS BETWEEN BASELINE GENES AND BASELINE METABOLIC SYNDROME PARAMETERS

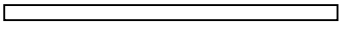
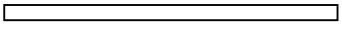
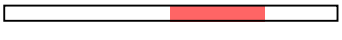
Nonparametric: Spearman's ρ

Variable	by Variable	Spearman ρ	Prob>|ρ|	Plot
CCL2 B	CD68 B	0.3989	0.0290	
TNF a B	CD68 B	0.0606	0.7549	
TNF a B	CCL2 B	-0.0276	0.8870	
IL6 B	CD68 B	0.3459	0.0611	
IL6 B	CCL2 B	0.1564	0.4092	
IL6 B	TNF a B	0.0222	0.9091	
PPARY B	CD68 B	-0.2277	0.2439	
PPARY B	CCL2 B	-0.2644	0.1740	
PPARY B	TNF a B	0.0164	0.9339	
PPARY B	IL6 B	-0.0120	0.9515	
ADIPO B	CD68 B	-0.3415	0.0648	
ADIPO B	CCL2 B	-0.3580	0.0521	
ADIPO B	TNF a B	-0.0724	0.7089	
ADIPO B	IL6 B	-0.4723	0.0084	
ADIPO B	PPARY B	0.0099	0.9603	
LPL B	CD68 B	-0.2571	0.1781	
LPL B	CCL2 B	-0.0990	0.6093	
LPL B	TNF a B	-0.1330	0.4916	
LPL B	IL6 B	-0.3315	0.0789	
LPL B	PPARY B	0.2649	0.1731	
LPL B	ADIPO B	0.4222	0.0225	
CD36 B	CD68 B	0.2451	0.2274	
CD36 B	CCL2 B	-0.1508	0.4622	
CD36 B	TNF a B	0.1077	0.6005	
CD36 B	IL6 B	-0.0366	0.8592	
CD36 B	PPARY B	0.3395	0.0897	
CD36 B	ADIPO B	0.1234	0.5481	
CD36 B	LPL B	0.1699	0.4066	
LEPTIN B	CD68 B	0.1954	0.3190	
LEPTIN B	CCL2 B	0.0274	0.8901	
LEPTIN B	TNF a B	-0.0611	0.7623	
LEPTIN B	IL6 B	0.1385	0.4822	

Variable	by Variable	Spearman ρ	Prob>|ρ|	Plot
LEPTIN B	PPARY B	0.1874	0.3492	
LEPTIN B	ADIPO B	-0.1171	0.5528	
LEPTIN B	LPL B	0.2479	0.2126	
LEPTIN B	CD36 B	0.2469	0.2341	
11BHSD B	CD68 B	0.2718	0.1792	
11BHSD B	CCL2 B	-0.2116	0.2994	
11BHSD B	TNF a B	-0.2130	0.2962	
11BHSD B	IL6 B	-0.0844	0.6817	
11BHSD B	PPARY B	0.2130	0.2962	
11BHSD B	ADIPO B	-0.1234	0.5481	
11BHSD B	LPL B	-0.1002	0.6263	
11BHSD B	CD36 B	0.2285	0.2720	
11BHSD B	LEPTIN B	0.4731	0.0169	
SBP	CD68 B	0.2841	0.1281	
SBP	CCL2 B	-0.0660	0.7288	
SBP	TNF a B	0.0263	0.8924	
SBP	IL6 B	0.1715	0.3649	
SBP	PPARY B	0.0033	0.9867	
SBP	ADIPO B	-0.1901	0.3144	
SBP	LPL B	-0.1433	0.4583	
SBP	CD36 B	0.2526	0.2131	
SBP	LEPTIN B	-0.2585	0.1841	
SBP	11BHSD B	0.1691	0.4090	
DBP	CD68 B	0.3016	0.1053	
DBP	CCL2 B	-0.0826	0.6644	
DBP	TNF a B	0.3139	0.0973	
DBP	IL6 B	0.1360	0.4738	
DBP	PPARY B	0.1117	0.5713	
DBP	ADIPO B	-0.1458	0.4421	
DBP	LPL B	-0.2446	0.2010	
DBP	CD36 B	0.0769	0.7090	
DBP	LEPTIN B	-0.2218	0.2566	
DBP	11BHSD B	0.2737	0.1761	
DBP	SBP	0.6156	<.0001	
GGT	CD68 B	0.4509	0.0124	
GGT	CCL2 B	-0.0769	0.6862	
GGT	TNF a B	-0.0741	0.7025	
GGT	IL6 B	0.2511	0.1808	
GGT	PPARY B	-0.1224	0.5351	
GGT	ADIPO B	-0.1164	0.5402	
GGT	LPL B	-0.1136	0.5574	
GGT	CD36 B	0.0357	0.8627	
GGT	LEPTIN B	-0.0480	0.8085	
GGT	11BHSD B	0.0888	0.6662	
GGT	SBP	0.2077	0.2313	
GGT	DBP	0.3343	0.0497	
BMI	CD68 B	0.1764	0.3510	

Variable	by Variable	Spearman ρ	Prob>|ρ|	Plot
BMI	CCL2 B	0.3927	0.0318	
BMI	TNF a B	0.1182	0.5413	
BMI	IL6 B	0.2392	0.2031	
BMI	PPARY B	-0.1565	0.4263	
BMI	ADIPO B	-0.1030	0.5881	
BMI	LPL B	0.0251	0.8971	
BMI	CD36 B	-0.0133	0.9485	
BMI	LEPTIN B	0.1631	0.4069	
BMI	11BHSD B	0.0215	0.9168	
BMI	SBP	0.2199	0.2043	
BMI	DBP	0.1296	0.4581	
BMI	GGT	-0.1138	0.5151	
CRP	CD68 B	0.6235	0.0002	
CRP	CCL2 B	0.1848	0.3284	
CRP	TNF a B	0.3659	0.0510	
CRP	IL6 B	0.3931	0.0316	
CRP	PPARY B	-0.3945	0.0378	
CRP	ADIPO B	-0.2193	0.2444	
CRP	LPL B	-0.2858	0.1329	
CRP	CD36 B	0.1754	0.3913	
CRP	LEPTIN B	0.2158	0.2701	
CRP	11BHSD B	-0.0144	0.9445	
CRP	SBP	-0.0768	0.6611	
CRP	DBP	0.1850	0.2874	
CRP	GGT	0.3913	0.0201	
CRP	BMI	0.1326	0.4477	
LDL	CD68 B	-0.1707	0.3672	
LDL	CCL2 B	-0.0958	0.6146	
LDL	TNF a B	-0.0705	0.7161	
LDL	IL6 B	-0.2720	0.1459	
LDL	PPARY B	0.1132	0.5662	
LDL	ADIPO B	0.0695	0.7151	
LDL	LPL B	0.0044	0.9818	
LDL	CD36 B	0.1096	0.5941	
LDL	LEPTIN B	0.0137	0.9448	
LDL	11BHSD B	0.3901	0.0488	
LDL	SBP	0.1973	0.2560	
LDL	DBP	0.2033	0.2414	
LDL	GGT	-0.1395	0.4243	
LDL	BMI	-0.1145	0.5125	
LDL	CRP	-0.3890	0.0209	
ApoAI	CD68 B	-0.2340	0.2133	
ApoAI	CCL2 B	0.0591	0.7566	
ApoAI	TNF a B	0.1027	0.5961	
ApoAI	IL6 B	-0.2037	0.2803	
ApoAI	PPARY B	-0.3923	0.0389	
ApoAI	ADIPO B	0.3606	0.0503	

Variable	by Variable	Spearman ρ	Prob>|ρ|	Plot
ApoAI	LPL B	0.0760	0.6951	
ApoAI	CD36 B	-0.3543	0.0758	
ApoAI	LEPTIN B	0.0378	0.8485	
ApoAI	11BHSD B	-0.0370	0.8576	
ApoAI	SBP	-0.1870	0.2821	
ApoAI	DBP	-0.1287	0.4614	
ApoAI	GGT	-0.2366	0.1712	
ApoAI	BMI	0.2364	0.1716	
ApoAI	CRP	0.0032	0.9856	
ApoAI	LDL	0.2413	0.1626	
ApoB	CD68 B	-0.1410	0.4575	
ApoB	CCL2 B	-0.0963	0.6128	
ApoB	TNF a B	-0.1269	0.5117	
ApoB	IL6 B	-0.2837	0.1287	
ApoB	PPARY B	0.0347	0.8610	
ApoB	ADIPO B	0.0947	0.6186	
ApoB	LPL B	0.0059	0.9756	
ApoB	CD36 B	-0.0127	0.9508	
ApoB	LEPTIN B	0.0704	0.7219	
ApoB	11BHSD B	0.4414	0.0240	
ApoB	SBP	0.1275	0.4656	
ApoB	DBP	0.1674	0.3364	
ApoB	GGT	-0.0118	0.9462	
ApoB	BMI	-0.0046	0.9789	
ApoB	CRP	-0.3034	0.0764	
ApoB	LDL	0.8794	<.0001	
ApoB	ApoAI	0.2871	0.0945	
HDL	CD68 B	-0.3323	0.0728	
HDL	CCL2 B	-0.0364	0.8484	
HDL	TNF a B	-0.0482	0.8038	
HDL	IL6 B	-0.1021	0.5912	
HDL	PPARY B	-0.1924	0.3266	
HDL	ADIPO B	0.2995	0.1079	
HDL	LPL B	0.2568	0.1787	
HDL	CD36 B	-0.2399	0.2377	
HDL	LEPTIN B	0.1220	0.5361	
HDL	11BHSD B	-0.0347	0.8664	
HDL	SBP	-0.3111	0.0689	
HDL	DBP	-0.3043	0.0756	
HDL	GGT	-0.3385	0.0467	
HDL	BMI	0.1504	0.3884	
HDL	CRP	-0.0494	0.7779	
HDL	LDL	0.1459	0.4030	
HDL	ApoAI	0.7912	<.0001	
HDL	ApoB	0.1001	0.5670	
Glu	CD68 B	0.3300	0.0805	
Glu	CCL2 B	0.1900	0.3236	

Variable	by Variable	Spearman ρ	Prob>|ρ|	Plot
Glu	TNF a B	-0.2215	0.2573	
Glu	IL6 B	0.4672	0.0106	
Glu	PPARY B	0.0264	0.8940	
Glu	ADIPO B	0.1224	0.5269	
Glu	LPL B	-0.0022	0.9911	
Glu	CD36 B	0.0189	0.9270	
Glu	LEPTIN B	0.0462	0.8154	
Glu	11BHSD B	0.1602	0.4343	
Glu	SBP	0.2476	0.1580	
Glu	DBP	0.2321	0.1865	
Glu	GGT	0.3221	0.0632	
Glu	BMI	0.3924	0.0217	
Glu	CRP	-0.0724	0.6841	
Glu	LDL	-0.0286	0.8725	
Glu	ApoAI	-0.1400	0.4295	
Glu	ApoB	0.0200	0.9105	
Glu	HDL	-0.2103	0.2326	
TRIG	CD68 B	-0.0479	0.8014	
TRIG	CCL2 B	-0.2045	0.2784	
TRIG	TNF a B	-0.0674	0.7282	
TRIG	IL6 B	-0.0894	0.6384	
TRIG	PPARY B	0.1411	0.4740	
TRIG	ADIPO B	0.0020	0.9916	
TRIG	LPL B	-0.1168	0.5462	
TRIG	CD36 B	-0.0148	0.9430	
TRIG	LEPTIN B	-0.1768	0.3682	
TRIG	11BHSD B	0.4144	0.0353	
TRIG	SBP	0.1966	0.2576	
TRIG	DBP	0.3276	0.0547	
TRIG	GGT	0.3337	0.0501	
TRIG	BMI	0.0640	0.7148	
TRIG	CRP	-0.1686	0.3330	
TRIG	LDL	0.4014	0.0168	
TRIG	ApoAI	0.0069	0.9686	
TRIG	ApoB	0.5637	0.0004	
TRIG	HDL	-0.2574	0.1355	
TRIG	Glu	0.2817	0.1065	
Waist	CD68 B	0.4816	0.0071	
Waist	CCL2 B	0.2766	0.1389	
Waist	TNF a B	-0.0673	0.7286	
Waist	IL6 B	0.3608	0.0501	
Waist	PPARY B	-0.0861	0.6632	
Waist	ADIPO B	-0.2328	0.2158	
Waist	LPL B	-0.1618	0.4017	
Waist	CD36 B	0.1260	0.5396	
Waist	LEPTIN B	0.1705	0.3858	
Waist	11BHSD B	0.2989	0.1380	

Variable	by Variable	Spearman ρ	Prob>|ρ|	Plot
Waist	SBP	0.1675	0.3363	
Waist	DBP	0.2755	0.1091	
Waist	GGT	0.4007	0.0171	
Waist	BMI	0.5827	0.0002	
Waist	CRP	0.3528	0.0376	
Waist	LDL	-0.1410	0.4191	
Waist	ApoAI	-0.0996	0.5691	
Waist	ApoB	-0.0357	0.8388	
Waist	HDL	-0.1941	0.2639	
Waist	Glu	0.4929	0.0031	
Waist	TRIG	0.2587	0.1335	

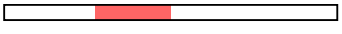
PRESCRIPTION ON PHYSICAL ACTIVITY GROUP

CORRELATIONS BETWEEN DELTA DIFFERENCES IN GENES AND DELTA DIFFERENCES IN METABOLIC SYNDROME PARAMETERS

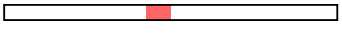
Nonparametric: Spearman's ρ

Variable	by Variable	Spearman ρ	Prob>|ρ|	Plot
CCL2 B	CD68 B	0.6611	0.0006	
TNF a B	CD68 B	0.4173	0.0533	
TNF a B	CCL2 B	0.1925	0.3906	
IL6 B	CD68 B	0.1561	0.4768	
IL6 B	CCL2 B	0.5840	0.0034	
IL6 B	TNF a B	0.1338	0.5527	
PPARY B	CD68 B	-0.2637	0.2357	
PPARY B	CCL2 B	-0.1203	0.5939	
PPARY B	TNF a B	-0.2273	0.3218	
PPARY B	IL6 B	-0.0186	0.9344	
ADIPO B	CD68 B	0.0632	0.7744	
ADIPO B	CCL2 B	-0.2460	0.2578	
ADIPO B	TNF a B	-0.0378	0.8673	
ADIPO B	IL6 B	-0.4279	0.0417	
ADIPO B	PPARY B	0.0661	0.7702	
LPL B	CD68 B	-0.0445	0.8403	
LPL B	CCL2 B	-0.0474	0.8298	
LPL B	TNF a B	0.0559	0.8048	
LPL B	IL6 B	-0.3794	0.0741	
LPL B	PPARY B	0.5099	0.0153	
LPL B	ADIPO B	0.3854	0.0694	
CD36 B	CD68 B	0.2184	0.3168	
CD36 B	CCL2 B	0.0049	0.9822	
CD36 B	TNF a B	-0.2377	0.2867	
CD36 B	IL6 B	-0.2678	0.2167	
CD36 B	PPARY B	0.4161	0.0541	
CD36 B	ADIPO B	0.2777	0.1996	
CD36 B	LPL B	0.1828	0.4038	
LEPTIN B	CD68 B	0.1688	0.4526	
LEPTIN B	CCL2 B	0.2953	0.1821	

Variable	by Variable	Spearman ρ	Prob>|ρ|	Plot
LEPTIN B	TNF a B	0.0195	0.9332	
LEPTIN B	IL6 B	0.3608	0.0990	
LEPTIN B	PPARY B	0.3665	0.0935	
LEPTIN B	ADIPO B	-0.4353	0.0429	
LEPTIN B	LPL B	0.2174	0.3311	
LEPTIN B	CD36 B	0.3676	0.0924	
11BHSD B	CD68 B	0.2614	0.2399	
11BHSD B	CCL2 B	0.2908	0.1892	
11BHSD B	TNF a B	-0.1896	0.4104	
11BHSD B	IL6 B	0.3800	0.0811	
11BHSD B	PPARY B	0.1259	0.5766	
11BHSD B	ADIPO B	-0.1383	0.5392	
11BHSD B	LPL B	-0.1779	0.4284	
11BHSD B	CD36 B	0.4116	0.0570	
11BHSD B	LEPTIN B	0.5291	0.0113	
SBP	CD68 B	-0.0285	0.8973	
SBP	CCL2 B	0.3498	0.1017	
SBP	TNF a B	-0.1645	0.4645	
SBP	IL6 B	0.4038	0.0560	
SBP	PPARY B	0.5277	0.0116	
SBP	ADIPO B	-0.4123	0.0506	
SBP	LPL B	-0.0060	0.9783	
SBP	CD36 B	0.2809	0.1942	
SBP	LEPTIN B	0.4820	0.0231	
SBP	11BHSD B	0.4015	0.0640	
DBP	CD68 B	-0.0755	0.7321	
DBP	CCL2 B	0.1515	0.4902	
DBP	TNF a B	-0.1543	0.4930	
DBP	IL6 B	0.3060	0.1557	
DBP	PPARY B	0.0953	0.6731	
DBP	ADIPO B	-0.5747	0.0041	
DBP	LPL B	-0.2249	0.3021	
DBP	CD36 B	0.1379	0.5304	
DBP	LEPTIN B	0.4679	0.0281	
DBP	11BHSD B	0.4340	0.0436	
DBP	SBP	0.6304	0.0010	
GGT	CD68 B	-0.0584	0.7912	
GGT	CCL2 B	0.0307	0.8894	
GGT	TNF a B	0.1454	0.5184	
GGT	IL6 B	0.2965	0.1695	
GGT	PPARY B	-0.2462	0.2694	
GGT	ADIPO B	-0.4554	0.0290	
GGT	LPL B	-0.3084	0.1522	
GGT	CD36 B	-0.4257	0.0428	
GGT	LEPTIN B	0.0419	0.8532	
GGT	11BHSD B	-0.0158	0.9442	
GGT	SBP	0.0194	0.9282	

Variable	by Variable	Spearman ρ	Prob>|ρ|	Plot
GGT	DBP	0.2924	0.1656	
BMI	CD68 B	0.0514	0.8159	
BMI	CCL2 B	0.0958	0.6635	
BMI	TNF a B	-0.2219	0.3209	
BMI	IL6 B	0.0198	0.9287	
BMI	PPARY B	0.1361	0.5459	
BMI	ADIPO B	0.1038	0.6376	
BMI	LPL B	0.1314	0.5500	
BMI	CD36 B	0.0395	0.8579	
BMI	LEPTIN B	-0.0548	0.8087	
BMI	11BHSD B	0.1993	0.3738	
BMI	SBP	0.2618	0.2166	
BMI	DBP	0.2469	0.2447	
BMI	GGT	-0.0732	0.7339	
CRP	CD68 B	0.3721	0.0804	
CRP	CCL2 B	0.2370	0.2762	
CRP	TNF a B	-0.0164	0.9422	
CRP	IL6 B	-0.0346	0.8753	
CRP	PPARY B	-0.1046	0.6432	
CRP	ADIPO B	0.4240	0.0437	
CRP	LPL B	0.3157	0.1423	
CRP	CD36 B	0.2830	0.1907	
CRP	LEPTIN B	0.0916	0.6852	
CRP	11BHSD B	0.1747	0.4367	
CRP	SBP	-0.1814	0.3963	
CRP	DBP	-0.4440	0.0297	
CRP	GGT	-0.2034	0.3404	
CRP	BMI	0.1585	0.4595	
LDL	CD68 B	-0.1543	0.4822	
LDL	CCL2 B	-0.2732	0.2072	
LDL	TNF a B	-0.0346	0.8784	
LDL	IL6 B	-0.5021	0.0146	
LDL	PPARY B	-0.3040	0.1690	
LDL	ADIPO B	0.3085	0.1520	
LDL	LPL B	0.3523	0.0992	
LDL	CD36 B	0.1269	0.5639	
LDL	LEPTIN B	-0.1537	0.4946	
LDL	11BHSD B	-0.2107	0.3467	
LDL	SBP	-0.3286	0.1169	
LDL	DBP	-0.0313	0.8844	
LDL	GGT	0.0981	0.6483	
LDL	BMI	-0.0935	0.6639	
LDL	CRP	0.2442	0.2501	
ApoAI	CD68 B	-0.4307	0.0402	
ApoAI	CCL2 B	-0.3649	0.0869	
ApoAI	TNF a B	0.0894	0.6924	
ApoAI	IL6 B	-0.1861	0.3951	

Variable	by Variable	Spearman ρ	Prob>|ρ|	Plot
ApoAI	PPARY B	0.1374	0.5420	
ApoAI	ADIPO B	-0.1099	0.6176	
ApoAI	LPL B	0.2777	0.1995	
ApoAI	CD36 B	-0.3114	0.1481	
ApoAI	LEPTIN B	0.0226	0.9204	
ApoAI	11BHSD B	-0.4987	0.0181	
ApoAI	SBP	0.0729	0.7351	
ApoAI	DBP	0.0426	0.8432	
ApoAI	GGT	-0.0397	0.8537	
ApoAI	BMI	-0.1782	0.4049	
ApoAI	CRP	-0.4887	0.0154	
ApoAI	LDL	0.0282	0.8961	
ApoB	CD68 B	-0.0124	0.9552	
ApoB	CCL2 B	-0.1265	0.5653	
ApoB	TNF a B	-0.0198	0.9303	
ApoB	IL6 B	-0.2961	0.1702	
ApoB	PPARY B	-0.5359	0.0102	
ApoB	ADIPO B	0.1508	0.4923	
ApoB	LPL B	0.0898	0.6838	
ApoB	CD36 B	0.0149	0.9463	
ApoB	LEPTIN B	-0.2064	0.3567	
ApoB	11BHSD B	-0.0278	0.9023	
ApoB	SBP	-0.2998	0.1547	
ApoB	DBP	0.0443	0.8373	
ApoB	GGT	0.3126	0.1369	
ApoB	BMI	0.0659	0.7598	
ApoB	CRP	0.3213	0.1258	
ApoB	LDL	0.8670	<.0001	
ApoB	ApoAI	-0.1945	0.3625	
HDL	CD68 B	-0.5430	0.0074	
HDL	CCL2 B	-0.4132	0.0500	
HDL	TNF a B	0.0779	0.7304	
HDL	IL6 B	-0.2725	0.2084	
HDL	PPARY B	0.1721	0.4439	
HDL	ADIPO B	0.0184	0.9336	
HDL	LPL B	0.3700	0.0823	
HDL	CD36 B	-0.2760	0.2024	
HDL	LEPTIN B	-0.1664	0.4593	
HDL	11BHSD B	-0.5474	0.0084	
HDL	SBP	0.0388	0.8572	
HDL	DBP	-0.0147	0.9456	
HDL	GGT	-0.1000	0.6421	
HDL	BMI	-0.2401	0.2584	
HDL	CRP	-0.4468	0.0286	
HDL	LDL	0.1817	0.3954	
HDL	ApoAI	0.9097	<.0001	
HDL	ApoB	-0.0864	0.6880	

Variable	by Variable	Spearman ρ	Prob>|ρ|	Plot
Glu	CD68 B	0.0290	0.8981	
Glu	CCL2 B	0.3782	0.0827	
Glu	TNF a B	-0.0975	0.6740	
Glu	IL6 B	0.4999	0.0178	
Glu	PPARY B	0.1689	0.4642	
Glu	ADIPO B	-0.0631	0.7802	
Glu	LPL B	-0.2172	0.3315	
Glu	CD36 B	-0.0392	0.8624	
Glu	LEPTIN B	0.0845	0.7159	
Glu	11BHSD B	0.3778	0.0914	
Glu	SBP	0.5803	0.0037	
Glu	DBP	0.1209	0.5826	
Glu	GGT	0.2572	0.2361	
Glu	BMI	0.1268	0.5642	
Glu	CRP	0.1277	0.5615	
Glu	LDL	-0.3049	0.1571	
Glu	ApoAI	-0.2928	0.1751	
Glu	ApoB	-0.1576	0.4726	
Glu	HDL	-0.2775	0.1998	
TRIG	CD68 B	0.4307	0.0402	
TRIG	CCL2 B	0.5298	0.0093	
TRIG	TNF a B	0.0269	0.9053	
TRIG	IL6 B	0.3537	0.0978	
TRIG	PPARY B	-0.3382	0.1237	
TRIG	ADIPO B	-0.1606	0.4642	
TRIG	LPL B	-0.1451	0.5089	
TRIG	CD36 B	0.0570	0.7960	
TRIG	LEPTIN B	0.1979	0.3773	
TRIG	11BHSD B	0.5823	0.0045	
TRIG	SBP	0.1457	0.4969	
TRIG	DBP	0.3324	0.1125	
TRIG	GGT	0.2336	0.2720	
TRIG	BMI	0.3768	0.0695	
TRIG	CRP	0.4062	0.0489	
TRIG	LDL	0.0384	0.8586	
TRIG	ApoAI	-0.6364	0.0008	
TRIG	ApoB	0.3284	0.1172	
TRIG	HDL	-0.5975	0.0020	
TRIG	Glu	0.3145	0.1438	
Waist	CD68 B	-0.1950	0.3726	
Waist	CCL2 B	0.0693	0.7534	
Waist	TNF a B	-0.1392	0.5368	
Waist	IL6 B	0.2876	0.1834	
Waist	PPARY B	0.0837	0.7110	
Waist	ADIPO B	-0.5499	0.0066	
Waist	LPL B	-0.2059	0.3459	
Waist	CD36 B	-0.4647	0.0255	

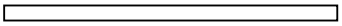
Variable	by Variable	Spearman ρ	Prob>|ρ|	Plot
Waist	LEPTIN B	0.0215	0.9243	
Waist	11BHSD B	0.0962	0.6703	
Waist	SBP	0.4091	0.0471	
Waist	DBP	0.3903	0.0594	
Waist	GGT	0.5827	0.0028	
Waist	BMI	0.4568	0.0248	
Waist	CRP	-0.1836	0.3905	
Waist	LDL	-0.3130	0.1364	
Waist	ApoAI	0.0100	0.9629	
Waist	ApoB	-0.0529	0.8062	
Waist	HDL	-0.0815	0.7051	
Waist	Glu	0.4638	0.0258	
Waist	TRIG	0.2933	0.1643	

CONTROL GROUP

CORRELATIONS BETWEEN DELTA DIFFERENCES IN GENES AND DELTA DIFFERENCES IN METABOLIC SYNDROME PARAMETERS

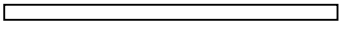
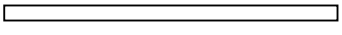
Nonparametric: Spearman's ρ

Variable	by Variable	Spearman ρ	Prob>|ρ|	Plot
CCL2 DIFF	CD68 DIFF	0.4773	0.0102	
TNF DIFF	CD68 DIFF	-0.1439	0.4830	
TNF DIFF	CCL2 DIFF	-0.1344	0.5129	
IL6 DIFF	CD68 DIFF	0.3846	0.0576	
IL6 DIFF	CCL2 DIFF	0.2554	0.2179	
IL6 DIFF	TNF DIFF	-0.2000	0.3488	
PPAR DIFF	CD68 DIFF	0.2174	0.3075	
PPAR DIFF	CCL2 DIFF	0.0165	0.9389	
PPAR DIFF	TNF DIFF	-0.0198	0.9287	
PPAR DIFF	IL6 DIFF	-0.2388	0.2844	
ADIPO DIFF	CD68 DIFF	-0.4023	0.0338	
ADIPO DIFF	CCL2 DIFF	-0.1363	0.4892	
ADIPO DIFF	TNF DIFF	0.2547	0.2092	
ADIPO DIFF	IL6 DIFF	-0.3615	0.0758	
ADIPO DIFF	PPAR DIFF	-0.1930	0.3661	
LPL DIFF	CD68 DIFF	0.0250	0.9014	
LPL DIFF	CCL2 DIFF	0.0824	0.6828	
LPL DIFF	TNF DIFF	-0.3764	0.0581	
LPL DIFF	IL6 DIFF	-0.0278	0.8973	
LPL DIFF	PPAR DIFF	0.2852	0.1767	
LPL DIFF	ADIPO DIFF	0.1862	0.3524	
CD36 DIFF	CD68 DIFF	0.2513	0.2593	
CD36 DIFF	CCL2 DIFF	0.1880	0.4020	
CD36 DIFF	TNF DIFF	-0.2242	0.3159	
CD36 DIFF	IL6 DIFF	0.1792	0.4370	
CD36 DIFF	PPAR DIFF	0.1169	0.6045	
CD36 DIFF	ADIPO DIFF	0.1022	0.6509	

Variable	by Variable	Spearman ρ	Prob>|ρ|	Plot
CD36 DIFF	LPL DIFF	0.5449	0.0087	
LEPTIN DIFF	CD68 DIFF	0.3115	0.1295	
LEPTIN DIFF	CCL2 DIFF	0.2123	0.3083	
LEPTIN DIFF	TNF DIFF	-0.0257	0.9074	
LEPTIN DIFF	IL6 DIFF	0.1846	0.4107	
LEPTIN DIFF	PPAR DIFF	0.2264	0.3109	
LEPTIN DIFF	ADIPO DIFF	-0.3769	0.0633	
LEPTIN DIFF	LPL DIFF	0.0817	0.7042	
LEPTIN DIFF	CD36 DIFF	0.2797	0.2323	
11BHSD	CD68 DIFF	0.6018	0.0024	
11BHSD	CCL2 DIFF	0.3360	0.1170	
11BHSD	TNF DIFF	-0.4249	0.0433	
11BHSD	IL6 DIFF	0.5403	0.0115	
11BHSD	PPAR DIFF	0.0446	0.8437	
11BHSD	ADIPO DIFF	0.0543	0.8055	
11BHSD	LPL DIFF	0.4496	0.0314	
11BHSD	CD36 DIFF	0.3649	0.1038	
11BHSD	LEPTIN DIFF	-0.0779	0.7371	
SBP Diff	CD68 DIFF	-0.3067	0.1124	
SBP Diff	CCL2 DIFF	-0.3857	0.0427	
SBP Diff	TNF DIFF	-0.4742	0.0144	
SBP Diff	IL6 DIFF	0.0050	0.9809	
SBP Diff	PPAR DIFF	-0.1257	0.5582	
SBP Diff	ADIPO DIFF	0.0311	0.8752	
SBP Diff	LPL DIFF	0.1937	0.3329	
SBP Diff	CD36 DIFF	0.2812	0.2050	
SBP Diff	LEPTIN DIFF	-0.3632	0.0743	
SBP Diff	11BHSD	0.0309	0.8888	
DBP Diff	CD68 DIFF	-0.0107	0.9568	
DBP Diff	CCL2 DIFF	0.1782	0.3642	
DBP Diff	TNF DIFF	0.0502	0.8078	
DBP Diff	IL6 DIFF	0.0565	0.7886	
DBP Diff	PPAR DIFF	-0.3138	0.1354	
DBP Diff	ADIPO DIFF	0.2228	0.2544	
DBP Diff	LPL DIFF	0.1224	0.5429	
DBP Diff	CD36 DIFF	0.1055	0.6402	
DBP Diff	LEPTIN DIFF	-0.3650	0.0728	
DBP Diff	11BHSD	0.3403	0.1121	
DBP Diff	SBP Diff	-0.0834	0.6337	
GGT Diff	CD68 DIFF	-0.1532	0.4365	
GGT Diff	CCL2 DIFF	0.0085	0.9657	
GGT Diff	TNF DIFF	-0.2764	0.1717	
GGT Diff	IL6 DIFF	-0.1738	0.4060	
GGT Diff	PPAR DIFF	-0.1930	0.3661	
GGT Diff	ADIPO DIFF	0.2805	0.1482	
GGT Diff	LPL DIFF	0.0660	0.7437	
GGT Diff	CD36 DIFF	0.0862	0.7029	

Variable	by Variable	Spearman ρ	Prob>|ρ|	Plot
GGT Diff	LEPTIN DIFF	-0.0602	0.7750	
GGT Diff	11BHSD	0.0318	0.8855	
GGT Diff	SBP Diff	-0.0856	0.6249	
GGT Diff	DBP Diff	0.3202	0.0608	
BMI Diff	CD68 DIFF	-0.1932	0.3246	
BMI Diff	CCL2 DIFF	-0.0109	0.9559	
BMI Diff	TNF DIFF	0.4332	0.0271	
BMI Diff	IL6 DIFF	-0.4692	0.0180	
BMI Diff	PPAR DIFF	0.1235	0.5654	
BMI Diff	ADIPO DIFF	0.2206	0.2593	
BMI Diff	LPL DIFF	-0.0250	0.9014	
BMI Diff	CD36 DIFF	0.1677	0.4557	
BMI Diff	LEPTIN DIFF	0.0738	0.7257	
BMI Diff	11BHSD	-0.3281	0.1264	
BMI Diff	SBP Diff	0.0200	0.9092	
BMI Diff	DBP Diff	0.1333	0.4451	
BMI Diff	GGT Diff	0.2339	0.1762	
CRP Diff	CD68 DIFF	0.3328	0.0835	
CRP Diff	CCL2 DIFF	-0.0506	0.7980	
CRP Diff	TNF DIFF	0.1474	0.4725	
CRP Diff	IL6 DIFF	0.1281	0.5417	
CRP Diff	PPAR DIFF	-0.3301	0.1152	
CRP Diff	ADIPO DIFF	-0.1713	0.3833	
CRP Diff	LPL DIFF	-0.0779	0.6995	
CRP Diff	CD36 DIFF	0.1214	0.5903	
CRP Diff	LEPTIN DIFF	0.2073	0.3200	
CRP Diff	11BHSD	0.1976	0.3660	
CRP Diff	SBP Diff	-0.1066	0.5422	
CRP Diff	DBP Diff	-0.1031	0.5557	
CRP Diff	GGT Diff	-0.0438	0.8025	
CRP Diff	BMI Diff	0.1871	0.2817	
LDL Diff	CD68 DIFF	-0.1306	0.5077	
LDL Diff	CCL2 DIFF	-0.1556	0.4292	
LDL Diff	TNF DIFF	0.0209	0.9192	
LDL Diff	IL6 DIFF	0.0062	0.9766	
LDL Diff	PPAR DIFF	-0.1081	0.6152	
LDL Diff	ADIPO DIFF	-0.0395	0.8418	
LDL Diff	LPL DIFF	0.0098	0.9613	
LDL Diff	CD36 DIFF	0.2382	0.2858	
LDL Diff	LEPTIN DIFF	0.4843	0.0142	
LDL Diff	11BHSD	-0.0342	0.8770	
LDL Diff	SBP Diff	0.1828	0.2931	
LDL Diff	DBP Diff	-0.0869	0.6196	
LDL Diff	GGT Diff	-0.1925	0.2680	
LDL Diff	BMI Diff	-0.0426	0.8081	
LDL Diff	CRP Diff	0.2149	0.2151	
ApoAI Diff	CD68 DIFF	0.0159	0.9360	

Variable	by Variable	Spearman ρ	Prob>|ρ|	Plot
ApoAI Diff	CCL2 DIFF	0.3068	0.1123	
ApoAI Diff	TNF DIFF	0.0404	0.8447	
ApoAI Diff	IL6 DIFF	-0.0277	0.8953	
ApoAI Diff	PPAR DIFF	-0.0544	0.8006	
ApoAI Diff	ADIPO DIFF	0.2213	0.2577	
ApoAI Diff	LPL DIFF	-0.2377	0.2324	
ApoAI Diff	CD36 DIFF	0.2738	0.2175	
ApoAI Diff	LEPTIN DIFF	0.2382	0.2515	
ApoAI Diff	11BHSD	-0.0752	0.7331	
ApoAI Diff	SBP Diff	-0.1310	0.4534	
ApoAI Diff	DBP Diff	-0.3587	0.0344	
ApoAI Diff	GGT Diff	0.1297	0.4578	
ApoAI Diff	BMI Diff	0.0852	0.6264	
ApoAI Diff	CRP Diff	-0.0930	0.5953	
ApoAI Diff	LDL Diff	0.0853	0.6263	
ApoB Diff	CD68 DIFF	-0.0241	0.9031	
ApoB Diff	CCL2 DIFF	0.0682	0.7301	
ApoB Diff	TNF DIFF	0.1524	0.4574	
ApoB Diff	IL6 DIFF	-0.0801	0.7034	
ApoB Diff	PPAR DIFF	-0.2709	0.2004	
ApoB Diff	ADIPO DIFF	0.2219	0.2563	
ApoB Diff	LPL DIFF	0.1317	0.5124	
ApoB Diff	CD36 DIFF	0.1205	0.5931	
ApoB Diff	LEPTIN DIFF	0.4927	0.0123	
ApoB Diff	11BHSD	-0.2117	0.3321	
ApoB Diff	SBP Diff	-0.1806	0.2993	
ApoB Diff	DBP Diff	-0.0922	0.5984	
ApoB Diff	GGT Diff	-0.0283	0.8719	
ApoB Diff	BMI Diff	0.1360	0.4360	
ApoB Diff	CRP Diff	0.1811	0.2978	
ApoB Diff	LDL Diff	0.5328	0.0010	
ApoB Diff	ApoAI Diff	0.1130	0.5181	
HDL Diff	CD68 DIFF	-0.1974	0.3139	
HDL Diff	CCL2 DIFF	0.0494	0.8030	
HDL Diff	TNF DIFF	-0.3125	0.1201	
HDL Diff	IL6 DIFF	0.1941	0.3526	
HDL Diff	PPAR DIFF	-0.0658	0.7601	
HDL Diff	ADIPO DIFF	0.1401	0.4771	
HDL Diff	LPL DIFF	0.1265	0.5295	
HDL Diff	CD36 DIFF	0.3251	0.1399	
HDL Diff	LEPTIN DIFF	0.3057	0.1372	
HDL Diff	11BHSD	-0.0884	0.6882	
HDL Diff	SBP Diff	0.0887	0.6123	
HDL Diff	DBP Diff	-0.5422	0.0008	
HDL Diff	GGT Diff	0.0447	0.7988	
HDL Diff	BMI Diff	-0.1542	0.3765	
HDL Diff	CRP Diff	-0.0596	0.7338	

Variable	by Variable	Spearman ρ	Prob>|ρ|	Plot
HDL Diff	LDL Diff	0.1043	0.5510	
HDL Diff	ApoAI Diff	0.6605	<.0001	
HDL Diff	ApoB Diff	0.1848	0.2878	
GLU Diff	CD68 DIFF	-0.0211	0.9167	
GLU Diff	CCL2 DIFF	-0.1886	0.3463	
GLU Diff	TNF DIFF	0.1257	0.5493	
GLU Diff	IL6 DIFF	-0.0432	0.8412	
GLU Diff	PPAR DIFF	-0.0144	0.9468	
GLU Diff	ADIPO DIFF	0.4787	0.0115	
GLU Diff	LPL DIFF	0.3458	0.0835	
GLU Diff	CD36 DIFF	0.4105	0.0577	
GLU Diff	LEPTIN DIFF	0.0139	0.9475	
GLU Diff	11BHSD	0.0084	0.9696	
GLU Diff	SBP Diff	0.2521	0.1503	
GLU Diff	DBP Diff	0.1381	0.4360	
GLU Diff	GGT Diff	-0.0098	0.9560	
GLU Diff	BMI Diff	0.2920	0.0938	
GLU Diff	CRP Diff	-0.2118	0.2292	
GLU Diff	LDL Diff	0.1179	0.5066	
GLU Diff	ApoAI Diff	0.0335	0.8508	
GLU Diff	ApoB Diff	0.3238	0.0617	
GLU Diff	HDL Diff	0.0049	0.9782	
Trig Diff	CD68 DIFF	-0.2343	0.2302	
Trig Diff	CCL2 DIFF	-0.1102	0.5768	
Trig Diff	TNF DIFF	0.3965	0.0449	
Trig Diff	IL6 DIFF	-0.2812	0.1733	
Trig Diff	PPAR DIFF	0.1058	0.6227	
Trig Diff	ADIPO DIFF	0.4532	0.0154	
Trig Diff	LPL DIFF	-0.2036	0.3085	
Trig Diff	CD36 DIFF	-0.0814	0.7186	
Trig Diff	LEPTIN DIFF	-0.3269	0.1108	
Trig Diff	11BHSD	-0.0005	0.9982	
Trig Diff	SBP Diff	-0.1785	0.3050	
Trig Diff	DBP Diff	0.2009	0.2472	
Trig Diff	GGT Diff	0.2289	0.1859	
Trig Diff	BMI Diff	0.3541	0.0369	
Trig Diff	CRP Diff	-0.2139	0.2173	
Trig Diff	LDL Diff	-0.2615	0.1292	
Trig Diff	ApoAI Diff	0.0911	0.6028	
Trig Diff	ApoB Diff	-0.1408	0.4199	
Trig Diff	HDL Diff	-0.2591	0.1329	
Trig Diff	GLU Diff	0.2136	0.2251	
Waist Diff	CD68 DIFF	-0.0082	0.9668	
Waist Diff	CCL2 DIFF	0.0780	0.6932	
Waist Diff	TNF DIFF	0.0992	0.6298	
Waist Diff	IL6 DIFF	-0.3468	0.0894	
Waist Diff	PPAR DIFF	0.4286	0.0366	

Variable	by Variable	Spearman ρ	Prob>|ρ|	Plot
Waist Diff	ADIPO DIFF	0.0168	0.9326	
Waist Diff	LPL DIFF	0.1522	0.4485	
Waist Diff	CD36 DIFF	-0.0471	0.8351	
Waist Diff	LEPTIN DIFF	-0.0189	0.9286	
Waist Diff	11BHSD	-0.3777	0.0756	
Waist Diff	SBP Diff	0.0705	0.6872	
Waist Diff	DBP Diff	-0.0849	0.6276	
Waist Diff	GGT Diff	0.0349	0.8425	
Waist Diff	BMI Diff	0.4313	0.0097	
Waist Diff	CRP Diff	0.0844	0.6296	
Waist Diff	LDL Diff	-0.1290	0.4601	
Waist Diff	ApoAI Diff	-0.0411	0.8147	
Waist Diff	ApoB Diff	-0.1432	0.4119	
Waist Diff	HDL Diff	-0.0021	0.9903	
Waist Diff	GLU Diff	0.1406	0.4277	
Waist Diff	Trig Diff	-0.0627	0.7206	

INTERVENTION GROUP

CORRELATIONS BETWEEN DELTA DIFFERENCES IN GENES AND DELTA DIFFERENCES IN METABOLIC SYNDROME PARAMETERS

Nonparametric: Spearman's ρ

Variable	by Variable	Spearman ρ	Prob>|ρ|	Plot
CCL2 DIFF	CD68 DIFF	0.6610	0.0011	
TNF DIFF	CD68 DIFF	0.5263	0.0206	
TNF DIFF	CCL2 DIFF	0.3209	0.1941	
IL6 DIFF	CD68 DIFF	0.0421	0.8601	
IL6 DIFF	CCL2 DIFF	0.3353	0.1484	
IL6 DIFF	TNF DIFF	-0.1269	0.6157	
PPAR DIFF	CD68 DIFF	-0.2882	0.2790	
PPAR DIFF	CCL2 DIFF	0.1441	0.5944	
PPAR DIFF	TNF DIFF	-0.2821	0.3083	
PPAR DIFF	IL6 DIFF	0.1471	0.5868	
ADIPO DIFF	CD68 DIFF	0.0887	0.6948	
ADIPO DIFF	CCL2 DIFF	-0.1195	0.6060	
ADIPO DIFF	TNF DIFF	0.0474	0.8473	
ADIPO DIFF	IL6 DIFF	-0.2000	0.3979	
ADIPO DIFF	PPAR DIFF	0.3559	0.1761	
LPL DIFF	CD68 DIFF	-0.5000	0.0293	
LPL DIFF	CCL2 DIFF	-0.0423	0.8676	
LPL DIFF	TNF DIFF	-0.2776	0.2647	
LPL DIFF	IL6 DIFF	0.0382	0.8804	
LPL DIFF	PPAR DIFF	0.6059	0.0129	
LPL DIFF	ADIPO DIFF	0.0632	0.7973	
CD36 DIFF	CD68 DIFF	-0.1324	0.6126	
CD36 DIFF	CCL2 DIFF	0.2083	0.4223	
CD36 DIFF	TNF DIFF	-0.1324	0.6251	
CD36 DIFF	IL6 DIFF	-0.2598	0.3139	

Variable	by Variable	Spearman ρ	Prob>|ρ|	Plot
CD36 DIFF	PPAR DIFF	0.6088	0.0123	
CD36 DIFF	ADIPO DIFF	0.2574	0.3187	
CD36 DIFF	LPL DIFF	0.6127	0.0089	
LEPTIN DIFF	CD68 DIFF	-0.3897	0.1220	
LEPTIN DIFF	CCL2 DIFF	0.1471	0.5868	
LEPTIN DIFF	TNF DIFF	-0.3643	0.1819	
LEPTIN DIFF	IL6 DIFF	0.2000	0.4748	
LEPTIN DIFF	PPAR DIFF	-0.0505	0.8637	
LEPTIN DIFF	ADIPO DIFF	-0.2402	0.3531	
LEPTIN DIFF	LPL DIFF	0.3321	0.2265	
LEPTIN DIFF	CD36 DIFF	0.2791	0.3338	
11BHSD	CD68 DIFF	0.4485	0.0709	
11BHSD	CCL2 DIFF	0.1324	0.6126	
11BHSD	TNF DIFF	-0.1353	0.6174	
11BHSD	IL6 DIFF	-0.0833	0.7505	
11BHSD	PPAR DIFF	0.3059	0.2493	
11BHSD	ADIPO DIFF	0.5172	0.0335	
11BHSD	LPL DIFF	0.0490	0.8518	
11BHSD	CD36 DIFF	0.4853	0.0567	
11BHSD	LEPTIN DIFF	-0.4286	0.1263	
SBP Diff	CD68 DIFF	0.0125	0.9561	
SBP Diff	CCL2 DIFF	0.0332	0.8863	
SBP Diff	TNF DIFF	0.0475	0.8468	
SBP Diff	IL6 DIFF	-0.2535	0.2809	
SBP Diff	PPAR DIFF	0.2293	0.3930	
SBP Diff	ADIPO DIFF	0.5967	0.0034	
SBP Diff	LPL DIFF	-0.0643	0.7938	
SBP Diff	CD36 DIFF	0.2451	0.3431	
SBP Diff	LEPTIN DIFF	-0.0074	0.9776	
SBP Diff	11BHSD	-0.0665	0.7998	
DBP Diff	CD68 DIFF	0.1854	0.4087	
DBP Diff	CCL2 DIFF	-0.2960	0.1926	
DBP Diff	TNF DIFF	-0.1246	0.6114	
DBP Diff	IL6 DIFF	-0.2561	0.2758	
DBP Diff	PPAR DIFF	-0.1663	0.5382	
DBP Diff	ADIPO DIFF	0.4147	0.0550	
DBP Diff	LPL DIFF	-0.3990	0.0906	
DBP Diff	CD36 DIFF	-0.0568	0.8285	
DBP Diff	LEPTIN DIFF	-0.2170	0.4028	
DBP Diff	11BHSD	0.1128	0.6663	
DBP Diff	SBP Diff	0.5713	0.0035	
GGT Diff	CD68 DIFF	-0.2963	0.1806	
GGT Diff	CCL2 DIFF	-0.3706	0.0982	
GGT Diff	TNF DIFF	-0.1890	0.4384	
GGT Diff	IL6 DIFF	-0.0331	0.8897	
GGT Diff	PPAR DIFF	0.0310	0.9094	
GGT Diff	ADIPO DIFF	0.3206	0.1457	

Variable	by Variable	Spearman ρ	Prob>|ρ|	Plot
GGT Diff	LPL DIFF	0.4156	0.0768	
GGT Diff	CD36 DIFF	-0.0344	0.8958	
GGT Diff	LEPTIN DIFF	-0.2297	0.3751	
GGT Diff	11BHSD	-0.0786	0.7644	
GGT Diff	SBP Diff	0.2094	0.3261	
GGT Diff	DBP Diff	0.2092	0.3265	
BMI Diff	CD68 DIFF	-0.2072	0.3548	
BMI Diff	CCL2 DIFF	0.1143	0.6218	
BMI Diff	TNF DIFF	-0.1596	0.5138	
BMI Diff	IL6 DIFF	0.1489	0.5310	
BMI Diff	PPAR DIFF	0.5853	0.0172	
BMI Diff	ADIPO DIFF	0.2298	0.3035	
BMI Diff	LPL DIFF	-0.0035	0.9886	
BMI Diff	CD36 DIFF	0.3039	0.2356	
BMI Diff	LEPTIN DIFF	0.1348	0.6060	
BMI Diff	11BHSD	-0.1446	0.5798	
BMI Diff	SBP Diff	0.5693	0.0037	
BMI Diff	DBP Diff	0.3166	0.1318	
BMI Diff	GGT Diff	0.0527	0.8068	
CRP Diff	CD68 DIFF	-0.2671	0.2295	
CRP Diff	CCL2 DIFF	-0.2403	0.2942	
CRP Diff	TNF DIFF	-0.0719	0.7698	
CRP Diff	IL6 DIFF	0.0842	0.7241	
CRP Diff	PPAR DIFF	0.2059	0.4443	
CRP Diff	ADIPO DIFF	0.2366	0.2891	
CRP Diff	LPL DIFF	0.0965	0.6943	
CRP Diff	CD36 DIFF	-0.0735	0.7791	
CRP Diff	LEPTIN DIFF	-0.0319	0.9034	
CRP Diff	11BHSD	-0.0074	0.9777	
CRP Diff	SBP Diff	0.1587	0.4590	
CRP Diff	DBP Diff	0.1966	0.3572	
CRP Diff	GGT Diff	0.3911	0.0588	
CRP Diff	BMI Diff	0.3530	0.0906	
LDL Diff	CD68 DIFF	0.0735	0.7451	
LDL Diff	CCL2 DIFF	0.2998	0.1867	
LDL Diff	TNF DIFF	-0.1195	0.6262	
LDL Diff	IL6 DIFF	0.2214	0.3482	
LDL Diff	PPAR DIFF	-0.2887	0.2782	
LDL Diff	ADIPO DIFF	-0.6446	0.0012	
LDL Diff	LPL DIFF	-0.0343	0.8893	
LDL Diff	CD36 DIFF	-0.2429	0.3474	
LDL Diff	LEPTIN DIFF	0.2110	0.4162	
LDL Diff	11BHSD	-0.1498	0.5661	
LDL Diff	SBP Diff	-0.4612	0.0233	
LDL Diff	DBP Diff	-0.4543	0.0257	
LDL Diff	GGT Diff	-0.0203	0.9250	
LDL Diff	BMI Diff	-0.2644	0.2118	

Variable	by Variable	Spearman ρ	Prob>|ρ|	Plot
LDL Diff	CRP Diff	-0.2906	0.1684	
ApoAI Diff	CD68 DIFF	-0.3806	0.0805	
ApoAI Diff	CCL2 DIFF	-0.3255	0.1499	
ApoAI Diff	TNF DIFF	-0.0853	0.7285	
ApoAI Diff	IL6 DIFF	0.0777	0.7448	
ApoAI Diff	PPAR DIFF	-0.0604	0.8241	
ApoAI Diff	ADIPO DIFF	-0.1818	0.4180	
ApoAI Diff	LPL DIFF	0.0889	0.7175	
ApoAI Diff	CD36 DIFF	-0.2543	0.3246	
ApoAI Diff	LEPTIN DIFF	-0.1634	0.5309	
ApoAI Diff	11BHSD	-0.3082	0.2288	
ApoAI Diff	SBP Diff	-0.0660	0.7594	
ApoAI Diff	DBP Diff	-0.1132	0.5983	
ApoAI Diff	GGT Diff	0.2456	0.2474	
ApoAI Diff	BMI Diff	-0.2724	0.1978	
ApoAI Diff	CRP Diff	-0.3604	0.0836	
ApoAI Diff	LDL Diff	0.1434	0.5037	
ApoB Diff	CD68 DIFF	0.0311	0.8907	
ApoB Diff	CCL2 DIFF	-0.0234	0.9198	
ApoB Diff	TNF DIFF	0.0676	0.7833	
ApoB Diff	IL6 DIFF	-0.1040	0.6627	
ApoB Diff	PPAR DIFF	-0.3108	0.2414	
ApoB Diff	ADIPO DIFF	-0.4450	0.0380	
ApoB Diff	LPL DIFF	0.0440	0.8582	
ApoB Diff	CD36 DIFF	-0.3337	0.1905	
ApoB Diff	LEPTIN DIFF	-0.1202	0.6459	
ApoB Diff	11BHSD	-0.0504	0.8477	
ApoB Diff	SBP Diff	-0.5229	0.0087	
ApoB Diff	DBP Diff	-0.4367	0.0329	
ApoB Diff	GGT Diff	0.1086	0.6135	
ApoB Diff	BMI Diff	-0.4532	0.0261	
ApoB Diff	CRP Diff	-0.0697	0.7464	
ApoB Diff	LDL Diff	0.7119	<.0001	
ApoB Diff	ApoAI Diff	-0.0124	0.9540	
HDL Diff	CD68 DIFF	-0.2315	0.3000	
HDL Diff	CCL2 DIFF	-0.2376	0.2997	
HDL Diff	TNF DIFF	-0.1609	0.5104	
HDL Diff	IL6 DIFF	0.0257	0.9142	
HDL Diff	PPAR DIFF	-0.1544	0.5680	
HDL Diff	ADIPO DIFF	-0.2303	0.3025	
HDL Diff	LPL DIFF	0.0663	0.7876	
HDL Diff	CD36 DIFF	-0.2855	0.2666	
HDL Diff	LEPTIN DIFF	-0.1646	0.5278	
HDL Diff	11BHSD	-0.2720	0.2910	
HDL Diff	SBP Diff	0.0469	0.8277	
HDL Diff	DBP Diff	0.0475	0.8254	
HDL Diff	GGT Diff	0.3714	0.0740	

Variable	by Variable	Spearman ρ	Prob>|ρ|	Plot
HDL Diff	BMI Diff	-0.1543	0.4715	
HDL Diff	CRP Diff	-0.2955	0.1609	
HDL Diff	LDL Diff	0.2812	0.1831	
HDL Diff	ApoAI Diff	0.8869	<.0001	
HDL Diff	ApoB Diff	0.0784	0.7159	
GLU Diff	CD68 DIFF	-0.0495	0.8312	
GLU Diff	CCL2 DIFF	0.4417	0.0450	
GLU Diff	TNF DIFF	0.0135	0.9577	
GLU Diff	IL6 DIFF	0.4921	0.0275	
GLU Diff	PPAR DIFF	0.5022	0.0474	
GLU Diff	ADIPO DIFF	-0.0788	0.7341	
GLU Diff	LPL DIFF	0.4790	0.0443	
GLU Diff	CD36 DIFF	0.0677	0.7964	
GLU Diff	LEPTIN DIFF	-0.0916	0.7357	
GLU Diff	11BHSD	-0.0530	0.8399	
GLU Diff	SBP Diff	-0.1384	0.5290	
GLU Diff	DBP Diff	-0.5562	0.0059	
GLU Diff	GGT Diff	0.2467	0.2564	
GLU Diff	BMI Diff	0.0203	0.9267	
GLU Diff	CRP Diff	0.2254	0.3012	
GLU Diff	LDL Diff	0.3053	0.1566	
GLU Diff	ApoAI Diff	0.2002	0.3596	
GLU Diff	ApoB Diff	0.1510	0.4915	
GLU Diff	HDL Diff	0.1440	0.5121	
Trig Diff	CD68 DIFF	-0.5136	0.0145	
Trig Diff	CCL2 DIFF	-0.5133	0.0173	
Trig Diff	TNF DIFF	-0.0967	0.6937	
Trig Diff	IL6 DIFF	-0.1590	0.5031	
Trig Diff	PPAR DIFF	-0.0545	0.8413	
Trig Diff	ADIPO DIFF	0.0730	0.7469	
Trig Diff	LPL DIFF	0.2019	0.4071	
Trig Diff	CD36 DIFF	0.1288	0.6222	
Trig Diff	LEPTIN DIFF	0.0135	0.9590	
Trig Diff	11BHSD	-0.2256	0.3839	
Trig Diff	SBP Diff	-0.0637	0.7673	
Trig Diff	DBP Diff	0.1894	0.3753	
Trig Diff	GGT Diff	0.1795	0.4013	
Trig Diff	BMI Diff	0.0266	0.9019	
Trig Diff	CRP Diff	0.2221	0.2970	
Trig Diff	LDL Diff	-0.2011	0.3460	
Trig Diff	ApoAI Diff	0.1002	0.6414	
Trig Diff	ApoB Diff	-0.0046	0.9831	
Trig Diff	HDL Diff	-0.0276	0.8982	
Trig Diff	GLU Diff	-0.1091	0.6201	
Waist Diff	CD68 DIFF	-0.2213	0.3223	
Waist Diff	CCL2 DIFF	0.0195	0.9330	
Waist Diff	TNF DIFF	-0.1072	0.6622	

Variable	by Variable	Spearman ρ	Prob>|ρ|	Plot
Waist Diff	IL6 DIFF	0.0889	0.7094	
Waist Diff	PPAR DIFF	0.4000	0.1248	
Waist Diff	ADIPO DIFF	0.1998	0.3727	
Waist Diff	LPL DIFF	0.3005	0.2112	
Waist Diff	CD36 DIFF	0.3544	0.1628	
Waist Diff	LEPTIN DIFF	0.0895	0.7326	
Waist Diff	11BHSD	-0.0098	0.9702	
Waist Diff	SBP Diff	0.5102	0.0109	
Waist Diff	DBP Diff	0.1739	0.4163	
Waist Diff	GGT Diff	0.1975	0.3550	
Waist Diff	BMI Diff	0.4923	0.0145	
Waist Diff	CRP Diff	0.1960	0.3586	
Waist Diff	LDL Diff	-0.2652	0.2105	
Waist Diff	ApoAI Diff	0.1201	0.5762	
Waist Diff	ApoB Diff	-0.3450	0.0987	
Waist Diff	HDL Diff	0.1689	0.4303	
Waist Diff	GLU Diff	0.1340	0.5421	
Waist Diff	Trig Diff	0.0301	0.8889	

5 DISCUSSION AND CONCLUSIONS

5.1 GENERAL

In paper I, we show in a representative sample of the US non-institutionalized civilian population, that the apoB/apoAI ratio is associated with insulin resistance in both men and women. Our findings indicate that the apoB/apoAI ratio predicts HOMA index independently of the traditional risk factors, metabolic syndrome components, and inflammatory risk factors; thus, adding independent information for the prediction of insulin resistance. Our results extend upon the findings in previous studies suggesting that apoB/apoAI is related to the metabolic syndrome, and go further by adding important information on its pathophysiologic link with cardiometabolic disorders. The fact that the association between the apoB/apoAI ratio and insulin resistance is independent of traditional risk factors, metabolic syndrome components, and inflammatory risk factors suggests the importance of including apoB/apoAI ratio in future guidelines. Recently, we published an association between the apoB/apoAI ratio and the metabolic syndrome definition in a similar representative sample of the US population that included diabetics[34]; moreover, none of the metabolic syndrome definitions used take into account insulin resistance as a cofactor and it was not clear if the association between the apoB/apoAI ratio and insulin resistance was in fact mediated by the other risk factors such as traditional risk factors, metabolic syndrome components, and/or inflammatory risk factors. It is this issue that we address in the present study of US non-diabetics subjects. Furthermore, these conclusions are strongly supported by the major findings of the INTERHEART study,[29] a case–control study, which showed that in all 52 countries investigated, the apoB/apoAI ratio was not only the strongest factor in explaining risk of acute MI, but that the ratio was also the most prevalent risk factor of all the nine conventional risk factors investigated irrespective of age, sex, race, and other lipids or lipid ratios. Furthermore, a recent post-hoc analysis from INTERHEART[109]showed that the apoB/apoA1 ratio was superior to any of the cholesterol ratios for estimation of the risk of acute myocardial infarction in all ethnic groups, in both sexes, and at all ages, making again the case for the use of apolipoproteins. Also, the AMORIS[110] study recently published that the use of the apoB/apoAI ratio as a marker of dyslipidemia was at least as efficient as conventional lipids, for the identification of subjects at increased risk of stroke (especially ischaemic stroke) but with the advantages that apolipoprotein measurement does not have be fasting. Other studies have tested the association between different apolipoproteins and cardiovascular risk factors, however none have explored its relationship with insulin sensitivity and insulin resistance further to determine the independence of the association.

In paper II, we show a prospective analysis of a representative multi-ethnic sample of the US civilian general population. The main findings are three-fold. First, the apoB/apoAI ratio was significantly associated with CHD death, independently of several established cardiovascular risk factors including CRP in the US population. Secondly, the predictive ability of apoB to detect CHD death was comparable with that of the apoB/apoAI ratio. Thirdly, both the apoB/apoAI ratio and apoB were better predictors of CHD death than the total cholesterol/HDL-C ratio and other traditional

cardiovascular risk factors. This suggests that the measurement of apolipoproteins has superior clinical utility over traditional risk markers such as the total cholesterol/HDL-C ratio in identifying subjects at risk for fatal cardiovascular disease.

Our results are strongly supported by the major findings of the INTERHEART[29] study. Moreover, recent reports from prospective risk studies, such as AMORIS[30], the European Prospective Investigation of Cancer-Norfolk study[31], ULSAM[32], the MONICA/KORA[33] as well as from other studies on diseases related to atherosclerosis indicate that the apoB/apoAI ratio is a useful predictor of risk of both non-fatal and fatal MI. A meta-analysis of the apoB/apoAI ratio also supports its use as a risk marker of future CV disease. Furthermore, in a cross-sectional analysis of the US population, LDL-C was not significantly correlated with history of atherosclerotic disease, suggesting that LDL-C is not the best target for lipid-lowering treatment strategies.

In paper III, we show a cross-sectional analysis of a representative elderly sample of the Swedish Stockholm County population. The main findings are 3-fold. First, GGT activity is significantly associated with the metabolic syndrome and each of its components in asymptomatic elderly men and women, independently of traditional risk factors. Second, adding GGT measurements to insulin resistance appeared to provide greater overall diagnostic accuracy than insulin resistance alone for identifying the metabolic syndrome, which is important given the imperfect relationship between insulin resistance and the metabolic syndrome. Third, CRP explained a statistically significant portion of the association between GGT and the metabolic syndrome; conversely, 8-iso-$PGF_{2\alpha}$ explained only a very small portion. Overall, our results suggest that GGT plays an important role in the development of the metabolic syndrome, which may be primarily mediated by inflammation, claiming further exploration into the inflammatory pathway and the complex relationship between GGT and CRP. There are previous studies looking at the relationship between metabolic syndrome and GGT; however, none of these studies have investigated the diagnostic accuracy of GGT to detect the metabolic syndrome (given that diagnosis of the metabolic syndrome requires a multi-factor definition, and that the correlation between insulin resistance and the metabolic syndrome is less than perfect) or the relationship of GGT with oxidative stress and inflammation markers in the elderly population.

In paper IV, we show that change in adipose tissue gene expression is associated with changes in metabolic syndrome parameters and that lifestyle modification can influence changes in adipose tissue gene expression, which may in turn modulate metabolic syndrome parameters. Our data highlight the ability of lifestyle changes to have effects at the molecular level, irrespective of the age of the subjects. Overall, our results suggest that lifestyle changes are crucial and a cornerstone in the treatment of cardiometabolic disease, claiming further exploration into the inflammatory pathway and the complex relationship between adipose tissue and the metabolic syndrome parameters. The original intervention study from which this study sample was taken, reported that an individualized prescription of physical activity decreases weight, abdominal obesity and cardiometabolic risk factors in elderly subjects, unfortunately due to the smaller sample size in our study we did not see any differences between control and intervention. Furthermore, within-group analysis of the whole cohort showed a significantly increased physical activity level in the intervention group regardless of the method of assessment, which lead us to conclude that individualized physical activity prescription improves body composition and cardiometabolic risk

factors in sedentary older overweight individuals. The present study is a follow-up that sheds some light into the pathophysiology behind the clustering of the metabolic syndrome phenomenon.

Low grade inflammation is believed to be a chronic effect that is paramount in the metabolic syndrome pathophysiology and seems to be mediated by macrophage accumulation in different metabolic tissues. However, different types of macrophages may have opposite effects on insulin resistance and the metabolic syndrome. In paper IV we quantified macrophage accumulation in adipose tissue by measuring gene expression of the macrophage-specific marker CD68, and evaluated inflammation through quantification of the expression of the inflammatory cytokines CCL2, IL6 and TNFα. Our results confirm that macrophage accumulation in adipose tissue (CD68 expression) is associated with an increased local production of pro-inflammatory cytokines (CCL2, IL6 and TNFα). Furthermore we show that local inflammation and macrophage accumulation in adipose tissue is related to systemic inflammation (circulating concentrations of CRP). Modulation of macrophage number (Δ-CD68 expression) in adipose tissue was related to corresponding changes in CCL2 and 11BHSD1 expression. The enzyme 11BHSD1, which is expressed in both adipocytes and macrophages, converts inactive cortisone to active cortisol and it has been shown to be increased in insulin-resistant obese subjects and lead to insulin resistance and hyperlipidemia in mice. Therefore our data indicate that reducing macrophage infiltration of adipose tissue leads to simultaneous reductions in local inflammatory cytokine and cortisol production, thereby improving insulin sensitivity of adipose tissue.

Adipose tissue adiponectin expression was inversely related to IL6 expression and positively to LPL expression, in line with the anti-inflammatory and insulin-sensitizing role assigned to this adipokine. However, changes in adiponectin expression were positively associated with Δ-systolic blood pressure, Δ-triglyceride and Δ-GGT concentrations, showing that in these elderly individuals, decreases in adiponectin were related to decreases in blood pressure, triglyceride and GGT. Given the beneficial metabolic effects usually ascribed to adiponectin, the interpretation of these somewhat surprising results remains unclear. Finally, in this study, we observed that changes in waist circumference were related to Δ-PPARγ adipose tissue expression. Since PPARγ is a master regulator of adipocyte differentiation and lipid metabolism, changes in expression of this transcription factor can be expected to have profound effects on metabolic pathways within adipose tissue.

Based on our results, we could hypothesize that changes taking place in adipose tissue, presumably as a result of a change in physical activity, could underlie changes in metabolic syndrome parameters, therefore taking an 'adipocentric' view. Changes in BMI and/or waist circumference are likely to reflect changes in adipose tissue mass and/or distribution. Such modulation of adipose tissue can be expected to lead to changes in its gene expression and subsequent metabolism, which may in turn underlie changes in metabolic parameters. The fact that our results come from an intervention study (as opposed to a cross-sectional study) strengthens our hypothesis.

5.2 PRACTICAL IMPLICATIONS

Paper I and paper II bring to light important clinical implications for cardiovascular risk assessment by indicating that apoB is equally predictive as the apoB/apoAI ratio for CHD death and better than routine clinical lipid measurements, thus showing an advantage of using apolipoproteins as cardiovascular risk predictors in parallel with the metabolic cluster risk-phenomenon.

ApoB can adequately measure the number of apoB-containing pro-atherogenic lipoprotein particles, including the small dense LDL particles, which is an advantage in patients with the metabolic syndrome, furthermore it might detect subjects at high cardiovascular risk that have low LDL-cholesterol levels. Moreover, the methods can easily be automated, analyses are cheap, can be performed on previously frozen sera, and importantly, non-fasted samples can be used. Apolipoprotein measurements were recently published in guidelines for diabetic subjects in the US. As this thesis goes to print, there still seems to be a controversy as to whether the apolipoproteins should be implemented in cardiovascular clinical guidelines, especially in the US. To me it seems clear that apolipoproteins provide risk information that other lipid markers like LDL-cholesterol miss, so its inclusion in future guidelines should happen in the near future. Perhaps economic studies should be implemented to determine if there will be a cost-benefit implementing apolipoproteins in clinical practice.

For paper III, serum GGT is a low-cost, readily available, steady (without circadian variation) laboratory test that should be considered in clinical practice as a cardiovascular risk marker. Its addition as a recognized risk factor for cardiometabolic disease may aid in detecting subjects at high risk that would otherwise be missed, especially in primary care practice where markers of inflammation might not be available. Epidemiologic studies have reported the usefulness of GGT in predicting the clinical evolution of cardiovascular disease, independently of hepatic disease, alcohol intake and traditional risk factors. Important clinical risk information provided by GGT should be recognized and may be considered in future clinical guidelines for primary prevention. Furthermore, its relationship with CRP should be recognized and explored further. The recent results from the JUPITER[58] trial have stirred many thoughts, and at this point we don't know the final implications on clinical practice of this trial. Further research is needed in this area, to identify those patients who are at high cardiovascular risk and move silently towards a cardiovascular event without getting noticed.

For paper IV, Modulation of adipose tissue inflammation may be of clinical relevance, in particular with respect to cardiovascular risk. Since all changes in gene expression in this study were achieved with only relatively modest changes in lifestyle in elderly subjects, our data support the concept from more intensive interventions that modulation of physical activity, however modest, can have beneficial effects on adipose tissue inflammation and metabolism, with subsequent effects on metabolism at the whole body level.

5.3 MAIN CONCLUSIONS

Paper I
The apoB/apoAI ratio is strongly associated with insulin resistance beyond the association explained by traditional risk factors, metabolic syndrome components, and inflammatory risk factors. These data suggest an additional mechanism that may help to explain the increased cardiovascular disease risk associated with insulin resistance.

Paper II
In the US population, apolipoprotein measurements significantly predict CHD death, independently of CV risk factors. Furthermore, the predictive ability of apoB alone to detect CHD death was comparable with that of the apoB/apoAI ratio and better than any of the routine clinical lipid measurements. Thus, apolipoprotein measurements are important for assessing CV risk in a multi-ethnic representative US population and their inclusion in future clinical guidelines should not be discarded.

Paper III
GGT is significantly associated with the metabolic syndrome in elderly asymptomatic subjects. This association seems to be mediated, at least in part by CRP. GGT should be recognized as a risk factor for cardiometabolic disease. And its relationship with CRP merits further exploration.

Paper IV
Changes in metabolic syndrome parameters after prescribing physical activity in elderly subjects at high cardiometabolic risk may be mediated, at least in part, by modulation of adipose tissue gene expression and subsequent metabolism.

Together, this thesis research hopes to bring some light into the complex epidemiologic and mechanistic aspects behind the metabolic syndrome concept. Further research is needed in the area, as the metabolic syndrome prevalence keep rising; thus, having numerous and important implications on our society.

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