Systems engineering investigation into the effects of different lifestyle factors on chronic diseases

Johanna Maria Espach

Student number: 20501226

Dissertation submitted in partial fulfilment of the requirements for the Degree Magister in Chemical Engineering at the North-West University

Supervisor: Prof. L. Liebenberg

November 2012

PREFACE

This dissertation is presented in the form of four research articles (all under review for publication) with a preceding consolidating discussion. The co-authors have given their consent to use these articles for the purpose of this master's degree.

The title of the first paper (Appendix A) is: "The glycemic effect of several lifestyle factors on inflammation." Co-authors for the first article are Prof. E.H. Mathews and Prof. L. Liebenberg. This article discusses the effects of several lifestyle factors on the inflammatory response employing high sensitivity C-reactive protein (hs-CRP) as a biomarker for inflammation. It quantifies each lifestyle factor in terms of a state of the art model, namely equivalent teaspoons sugar (ets) and emphasises the importance of blood glucose in the development of inflammation.

The title for the second paper (Appendix B) is: "Blood glucose and coronary heart disease: Comparing lifestyle effects." Co-authors for this article are Prof. E.H. Mathews, Mr G. Mathews and Prof. L. Liebenberg. It investigates the role of blood glucose on coronary heart disease and employs a common unit in which lifestyle factors can be quantified in terms of their glycaemic effect.

The third paper (Appendix C), "The effect of cigarette smoking on blood glucose and coronary heart disease", shows the link between cigarette smoking, blood glucose and the adverse implications thereof on coronary heart disease. For this paper, the co-authors were Prof. E.H. Mathews and Prof. L. Liebenberg.

The title of the final paper is: "The effect of various lifestyle factors on blood glucose and breast cancer" (Appendix D). This paper presents the glycaemic effects of lifestyle factors, using the ets model for quantification purposes. The co-authors for this paper are Prof. E.H. Mathews and Prof. L. Liebenberg.

ABSTRACT

Background: Both coronary heart disease (CHD) and breast cancer (BC) are multifactorial diseases with complex aetiologies. Various research publications suggest that inflammation is the link between several chronic illnesses such as BC and CHD. Inflammation is influenced by several different lifestyle factors, such as excessive food intake, alcohol consumption, stress, smoking, exercise and fibre intake. The systemic effects of each of these lifestyles on CHD and BC have yet to be integrated. It also is unclear which of these factors has the largest impact on the different chronic diseases, as they are quantified in different units. However, it is known that blood glucose (BG) levels are directly linked to inflammation and, therefore, to CHD and BC.

Aim: To develop a comprehensive model to account for the variety of systemic influences on CHD and BC, with an emphasis on lifestyles and the inflammatory state. The interconnected nature of the lifestyle effects and of inflammatory pathways necessitates the development of a unifying system property, chosen to be BG.

Method: A common unit known as *ets* (equivalent teaspoons of sugar) was developed for each of the above lifestyle factors, quantifying each factor in terms of its BG (glycaemic) effect. Data were collected from various published meta-studies and transformed using the *ets* model. A systems engineering approach was followed to investigate the numerous cross-couplings that exist between the CHD and BC pathogenetic factors and lifestyle effects. This resulted in graphical representations illustrating the effects the different lifestyle factors have on inflammation, as well as the relative risk (RR) for BC and CHD.

Results: Stress, excessive food intake and smoking contribute to increased BG levels. High BG levels are associated with increased levels of inflammation, RR for CHD and RR for BC. Psychological stress is the largest contributor to inflammation and the risk for CHD and BC. It increased hs-CRP (an important biomarker for CHD) values four-fold, RR for CHD 4.4 fold and RR for BC 2.5 fold. Dietary fibre intake, low to moderate intensity exercise and

moderate alcohol consumption are inversely associated BG levels. Lower BG levels are related to a decrease in inflammation and risk for BC and CHD. Low to moderate exercise had the strongest anti-inflammatory effect and reduced BC risk approximately two-fold. Moderate alcohol consumption plays an important role in the reduction of RR for CHD.

Conclusion: A systems engineering-based analysis of CHD and BC reveals the interconnected, systemic nature of these diseases. Despite their complex aetiologies, both diseases show the pivotal role of BG in disease progression or proliferation. This highlights the importance of glucose controlled therapeutics and lifestyle interventions in managing CHD and BC.

Key words: Blood glucose (BG), chronic diseases, coronary heart disease (CHD), breast cancer (BC), inflammation, lifestyle factors, cigarette smoking, psychological stress, alcohol, dietary fibre, excessive food intake, physical exercise, equivalent teaspoons sugar (*ets*), relative risk (RR), C-reactive protein (CRP), grams (g) of fibre, grams (g) of ethanol , cigarettes per day, Metabolic Equivalent (METs), Glycaemic Load (GL), insulin sensitivity, blood pressure, blood viscosity and insulin resistance

ACKNOWLEDGEMENTS

First and foremost, I would like to thank TEMM International (Pty) Ltd and MCI (Pty) Ltd for sponsoring my studies. I am also extremely grateful to my supervisors, Prof. Edward Mathews and Prof. Leon Liebenberg. I would also like to thank Prof. Edward Mathews for his guidance, expertise, support and patience.

I am deeply grateful to Prof. Leon Liebenberg, if it was not for his encouragement, positive attitude and inspirational talks, this dissertation would not have come to realisation. I am so thankful for his endless support and guidance all the way from Switzerland.

I owe gratitude to all the experts in the field for their publications and data I used in developing my models in my dissertation. I also want to thank Mr Doug Velleman for his time and assistance in reviewing my work.

Many thanks to Karin Iten for proof reading my work. I appreciate her time and patience in checking and correcting language, spelling and grammar mistakes.

Lastly, I would like to thank Johnathan Harley for his love, patience and support throughout this year and my fellow employees who were happy to help me in any situation.

TABLE OF CONTENTS

LIST OF SYMBOLS

ets	**E**quivalent **t**easpoons **s**ugar (-)
ets_{CHO}	**E**quivalent **t**easpoons **s**ugar for carbohydrates ingested (-)
$ets_{Fib\ added}$	**E**quivalent **t**easpoons **s**ugar for dietary fibre added to a meal (-)
$ets_{Exercise}$	**E**quivalent teaspoons sugar consumed during physical exercise (-)
ets_{Stress}	**E**quivalent **t**easpoons **s**ugar produced during prolonged high-level psychological stress (-)
$ets_{Alcohol}$	**E**quivalent **t**easpoons **s**ugar due to alcohol consumption (-)
$ets_{Smoking}$	**E**quivalent **t**easpoons **s**ugar due to cigarette smoking (-)
Δets	Change in **e**quivalent **t**easpoons **s**ugar (-)
Δets**/day**	Change in **e**quivalent **t**easpoons **s**ugar daily (-)
η_{CHO}	Metabolic efficiency of the carbohydrate (-)

η_{Sugar}	Metabolic efficiency of the sugar (-)
GI_{CHO}	Glycaemic index of the carbohydrates ingested (-)
m_{CHO}	Mass of carbohydrates (g)
$m_{Fib\ added}$	Mass of fibre added to the meal (g)
ΔI	Change in insulin levels (mU/l)
ΔBG	Change in blood glucose levels (mmol/L)
$E_{\ Teaspoon\ sugar}$	Energy from a teaspoon of sugar (-)

ABBREVIATIONS

AGE	Advanced glycation end products
ANG-II	Angiotensin-II
BC	Breast cancer
BG	Blood glucose
CHD	Coronary heart disease
CHO	Carbohydrate
CI	Confidence interval
COX-2	Cyclo-oxygenase-2
DNA	Deoxyribonucleic acid
eNOS	Endothelial nitric oxide
GI	Glycaemic index
GL	Glycaemic load

HbA_{1C}	Glycated haemoglobin
HDL	High density lipoprotein
HR	Hazard ratio
hs-CRP	High sensitivity C-reactive protein
IDC	Invasive ductal carcinoma
IDC-NOS	Invasive ductal carcinoma nonspecific
IDC-NST	Invasive ductal carcinoma no special type
IGF-I	Insulin growth factor
IL-6	Interleukin-6
ILC	Invasive lobular carcinoma
LDL	Low density lipoprotein
METs	Metabolic equivalents
NO	Nitric oxide

OR	Odds ratio
PKC	Protein kinase C
RNS	Reactive nitrogen species
ROS	Reactive oxygen species
RR	Relative risk
TF	Tissue factor
TNF-α	Tumour necrosis factor alpha
UV	Ultraviolet
VCAM-1	Vascular cell adhesion molecule 1
VLDL	Very low density lipoprotein
WHO	World Health Organisation

GLOSSARY

Advanced glycation end products: Reducing sugars which react with proteins in a translational modification process. The products are made up of a heterogeneous group of irreversible adducts known as advanced glycation end products.[1]

Apoptosis: Single cell death, usually through shrinkage of the cell, condensation of chromatin and fragmentation of the cell into membrane bound bodies which are removed by phagocytosis.[2]

Atherogenesis: The process by which sub-intimal plaques are formed in the blood vessels.[3]

Blood glucose (BG): Glucose is the body's primary source of energy and is transported around the body via the blood. Blood glucose is produced through catabolising carbohydrates (CHOs) as well as proteins and fats.[4]

Breast cancer (BC): A type of cancer that originates most commonly from the inner lining of the milk ducts (ductal carcinomas) or lobules (lobular carcinomas) of the breast.[5]

Carcinogenesis: The process responsible for the formation and promotion of cancer.[3]

---

[1] Vlassara H, Li YM, Imani F, Wojciechowicz D, Yang Z, Liu FT, Cerami A. Identification of galectin-3 as a high-affinity binding protein for advanced glycation end products (AGE): A new member of the age-receptor complex. *Molecular Medicine*. 1995;1(6):634-646.

[2] Dorland's Medical Dictionary for Health Consumers. 1st ed. Huntington Valley: Elsevier Health Sciences; 2007.

[3] Mosby's Medical Dictionary. 8th ed. St. Louis: Elsevier Health Sciences; 2008.

[4] Concise Dictionary of Modern Medicine: McGraw-Hill Medical; 2005.

[5] Sariego J. Breast cancer in the young patient. *The American Surgeon*. 2010;76(12):1397-400.

Coronary heart disease (CHD): CHD comprises of the narrowing or obstruction of the coronary blood vessels, caused by atheromas forming inside the capillary walls, also known as hardening of the arteries (atherosclerosis).[6]

Cytokines: Regulatory proteins, such as lymphokines and interleukins that are produced by immune system cells and act as intercellular mediators in the modulation of immune response.[3]

Diapedesis: The passage of red or white blood cells and other biological corpuscles through the lining of the endothelium, without damage to the vessel.[3]

Dyslipidaemia: Abnormal levels of lipids and lipoproteins in the blood. Examples include high blood cholesterol, high triglyceride levels, high levels of low density cholesterol and low levels of high density cholesterol.[7]

Fibrinolysis: The continuous process in which fibrin is decomposed by fibrinolysin. It is the mechanism for the elimination of small fibrin clots. Usually initiated by anoxia (absence of oxygen) or the inflammatory response.[3]

Foam cells: Cells found in atheroma derived from macrophages, smooth muscle cells and lipids.[8]

Gluconeogenesis: The process by which glucose is synthesised from sources other than CHOs, such as amino and fatty acids.[2]

---

[6] Encyclopedia Medline Plus, June 22, 2012. http://www.nlm.nih.gov/medlineplus/ency/article/007115.htm. (Accessed October 04, 2012).

[7] Anon.Dyslipidaemia. *Exercise is Medicine*. 2011;1(1):1-2.

[8] Stary HC, Chandler AB, Glagov S, Guyton JR, Insull W, Rosenfeld ME, Schaffer SA, Schwartz CJ, Wagner WD, Wissler RW. A definition of initial, fatty streak, and intermediate lesions of atherosclerosis. *Circulation*. 1994;89(5):2462-2478.

Glycogenolysis: The process by which glycogen is converted into glucose.[3]

Hazard ratio (HR): It measures how often a certain event happens in one group compared to another group, over time. In clinical trials, it is often used, for example, to measure the survival of a particular group of people who are subjected to a specific treatment compared to a control group receiving no treatment or a placebo.[9]

Hypertension: It is a chronic medical condition referring to increased blood pressure.[3]

Leukocytes: A white blood cell with the primary function being to protect the body against microorganisms causing disease. Leukocytes can be classified in two groups: Granular and non-granular.[2]

Lipid rafts: Microdomains from the plasma membrane that consists of high levels of cholesterol and glycated lipids.[10]

Metalloproteinase: Metalloproteinase is an enzyme responsible for the breakdown of protein such as collagen. They require zinc or calcium atoms in order to function. These enzymes are often involved in tumour cell invasion and metastasis, wound healing and angiogenesis.[11]

Monocyte: A phagocytic white blood cell with a single nucleus and fine granules in the cytoplasm. 3-8% of the white blood cells in the human body are monocytes.[12]

Nuclear Pleomorphism: The changeability of the nucleus of a cell, its size as well as shape.[2]

---

[9] NCI Dictionary of Cancer Terms. *National Cancer Institute*. http://www.cancer.gov/dictionary? (Accessed October 31, 2012).

[10] Pike LJ. Lipid rafts. *Journal of Lipid Research*. 2003;44:655-667.

[11] Longe JL, Gale T. The Gale Encyclopaedia of cancer*: A guide to cancer and its treatments*. 2nd ed: Gale Group; 2005.

[12] The American Heritage Medical Dictionary: Houghton Mifflin Company; 2004.

Odds ratio (OR): A measure of the odds of an event occurring in a particular group compared to the same event occurring in another group. In clinical studies, odds ratios are used to find out if the exposure of a certain substance will increase the risk of developing a certain type of illness. The odds of exposure are determined in both groups and then compared.[9]

Relative risk (RR): It determines the risk of a specific event taking place in one group compared to the same event happening in another group. In clinical trials, relative risk is often used to compare the risk of contracting a certain disease or illness through for example the exposure to a certain substance. A comparison is made between a control group and the exposure group and the risk is compared. A relative risk of one suggests that there is no difference between the two groups in terms of their risk of contracting a disease.[9]

Serine proteinases: Enzymes that cleave peptide bonds in proteins. Serine acts as the nucleophillic amino acid at the active site of the enzyme. In the human body, serine proteinases co-ordinates digestion, the immune response, blood coagulation and reproduction.[13]

Stenosis: The narrowing of an opening or passage-way in the body. In arteries, stenosis is caused by a build-up of atherosclerotic plaque, disease or other disorder.[11]

Thrombosis: Involves the formation of a blood clot that obstructs the blood flow in blood vessels, either completely leading to infarction or partially causing tissue death.[11]

Triglycerides: Esters consisting of three fatty acids and a glycerol. The fatty acids can either be the same or different. Triglycerides are the primary lipids constituting fats and oils and their function is to store chemical energy in the human body.[12]

---

[13] Hedstrom L. Serine proteinase mechanism and specificity. *Chemical Reviews*. 2002;102(12):4501-4524.

LIST OF FIGURES

LIST OF TABLES

1. INTRODUCTION

The introduction provides the background information that illustrates the importance of doing research on the different topics considered in this study. It also gives an overview of the purpose, aim, scope and structure of the mini-dissertation.

1.1. Background

1.1.1. Chronic disease statistics

Chronic diseases such as cardiovascular disease, cancer and diabetes are leading causes of death globally [1]. In 2005, statistics showed that of all global deaths 60% were due to chronic diseases, primarily cardiovascular disease followed by diabetes and cancer, respectively [1].

Cardiovascular disease can be divided into several different components with the two predominant ones being coronary heart disease (CHD) and ischaemic stroke [1]. The American Heart Association completed a study on CHD and stroke death rates in 2007 and it was found that almost 50% of cardiovascular deaths in the United States (USA) are a consequence of CHD [2]. In Figure 1 the breakdown for cardiovascular deaths in the USA in 2007 is provided [2].

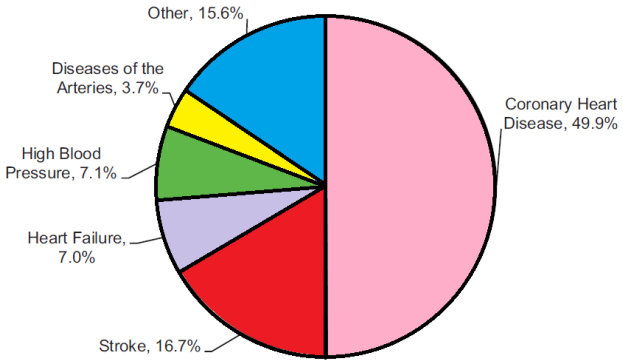


Figure 1: Breakdown of cardiovascular deaths in the USA (2007) [2]

When considering all the deaths in the USA in 2007, one in six deaths was caused by CHD. This means that an American dies approximately every minute from a coronary event [2]. CHD is not only responsible for deaths in the USA - worldwide approximately 3.8 million men and 3.4 million women die annually from CHD [3].

Another chronic disease known for its major death tolls is cancer. A study done on cancer death rates in 2011 illustrated that of all deaths one in four in the USA can be attributed to

cancer [4]. Breast cancer (BC) for females and prostate cancer for males are the cancers diagnosed most frequently in the USA. The rates at which females in the USA are diagnosed with different types of cancer are illustrated in Figure 2. It is apparent that BC for women is the most popular diagnosed cancer over the past 32 years [4].

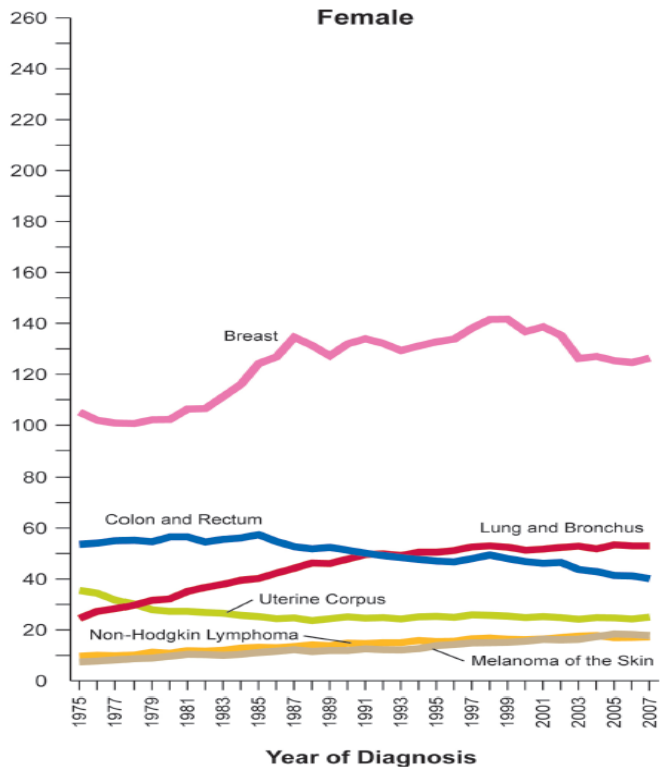


Figure 2: Yearly female cancer incidence rates adjusted for age [4]

Worldwide BC is also the most frequent cancer among women. Statistics from 2008 show that approximately 1.38 million people were diagnosed with BC [5]. While BC ranks as the fifth cause of death from cancer overall, it is still the most common cause of death in women worldwide [5].

From these statistics it is evident that both BC and CHD are major public health concerns in the USA and the world. It is therefore, becoming increasingly important to understand the

epidemiology of these diseases and to have sufficient knowledge of the underlying causes and the preventative measures that can be taken.

1.2. Problem statement

Blood glucose (BG) is known to play a vital role in the development of both CHD and BC [6], [7]. Research has shown that an increase in BG leads to an increase in risk of both of these diseases [6], [7]. It is believed that both these illnesses can be linked to inflammation which is also known to be fuelled by high BG levels [8], [9].

There are many research publications showing how different lifestyle factors impact inflammation and the risk for both BC and CHD. There are, however, no publications that integrate the effect which the lifestyle factors have on BG and then in turn its effect on inflammation, CHD and cancer.

The lifestyle factors that are often researched include: Excessive food intake, psychological stress, cigarette smoking, alcohol consumption, dietary fibre intake and physical exercise. These different lifestyle factors are quantified in different units making it difficult to understand the impact each of these have on the chronic diseases mentioned in comparison to one another. A common unit will be able to provide a way to illustrate which lifestyle factor is the largest contributor to these diseases and also which factor contributes the most to the prevention of inflammation, BC and CHD.

1.3. Aim

To develop a comprehensive model that accounts for the variety of systemic influences on CHD and BC, with an emphasis on lifestyle factors and the inflammatory state. The interconnected nature of the lifestyle effects and of the inflammatory pathways necessitates the development of a unifying system property, chosen to be BG.

A common energy term known as —ets (equivalent teaspoons sugar) will be used to quantify the different lifestyle factors in the same glycaemic unit. RR and CRP data from various publications will be analysed and combined to give illustrations of the effect of the different lifestyle factors through their glycaemic effect on inflammation, BC and CHD. In this way, the lifestyle effects on these diseases can be compared and the importance of BG in these chronic diseases will be proven.

1.4. Scope and structure of dissertation

This dissertation forms a consolidated discussion of four articles, all of which are under review for publication. Due to the nature of this dissertation, repetition of information from the articles is inevitable. The articles discuss the role of Blood Glucose (BG) in inflammation, Coronary Heart Disease (CHD) and Breast Cancer (BC) separately, using a state of the art quantification method (—ets). This consolidated discussion integrates the information from the different articles, providing an all-encompassing discussion as to the role of BG in chronic disease.

A systems engineering approach is followed to ensure the role of BG in each disease is emphasised. Because of the interconnected pathways associated with the development of both CHD and BC, a systems based methodology will illustrate the atherogenic and carcinogenic processes in a more simplified manner. This will enable the reader to see the effects of BG on the two chronic diseases at a micro- and macroscopic level.

The major factors that influence each disease will be investigated separately, followed by a look at the effect of BG on each factor. The lifestyle factors' effects on BG will also be investigated independently, after which, all the effects will be combined in a consolidated process diagram. The lifestyle effects on BG are then quantified in terms of—ets. This model, in combination with clinical data from published studies, enables comparisons to be drawn between lifestyle effects and the different chronic diseases. The consolidated diagram of effects and the results obtained accentuates the role of BG in the development of inflammation, CHD and BC. Figure 3 is a summary of the process followed in this dissertation.

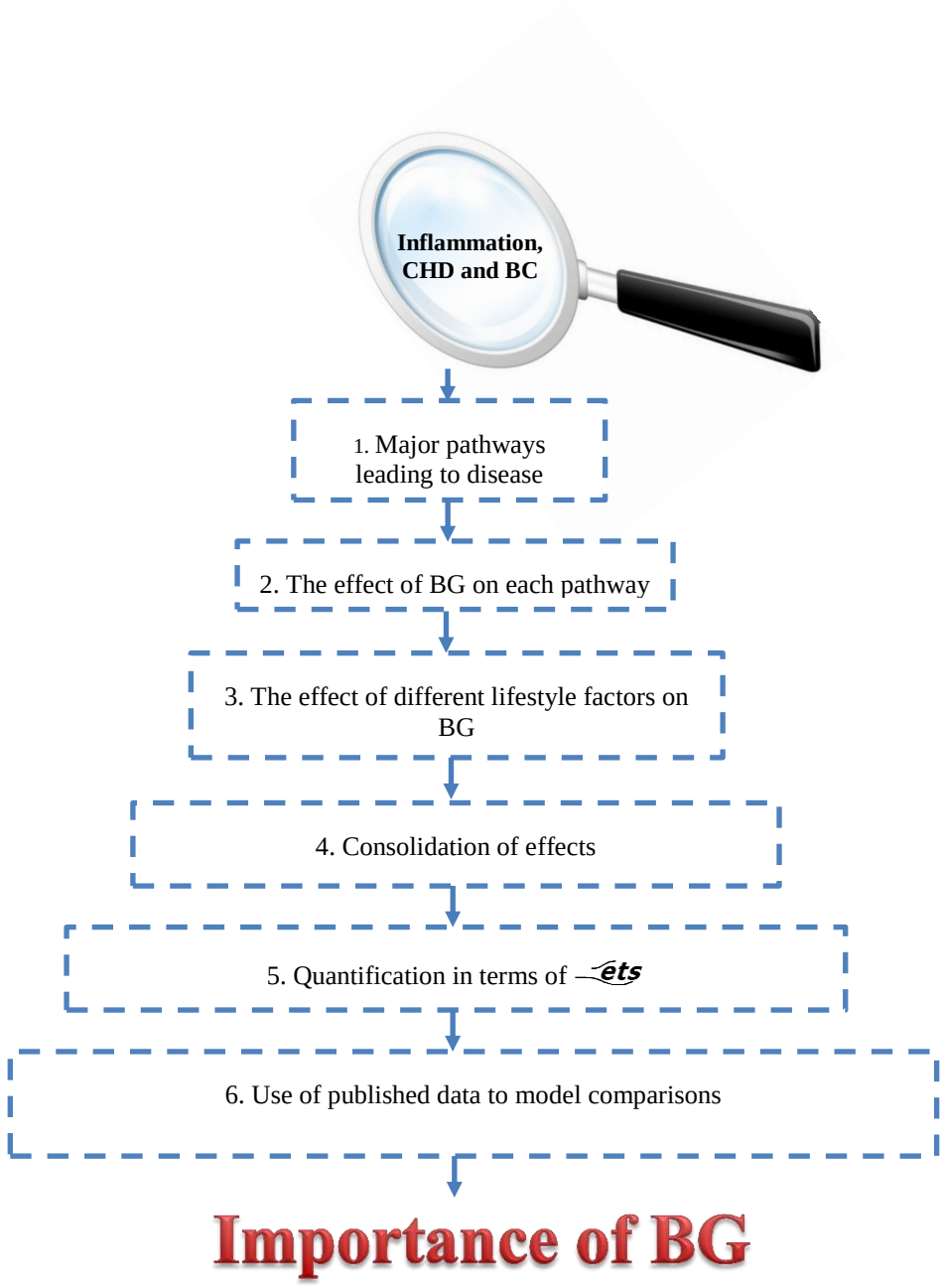


Figure 3: The systems engineering process followed in this dissertation

The structure of this dissertation can be found in Figure 4.

.

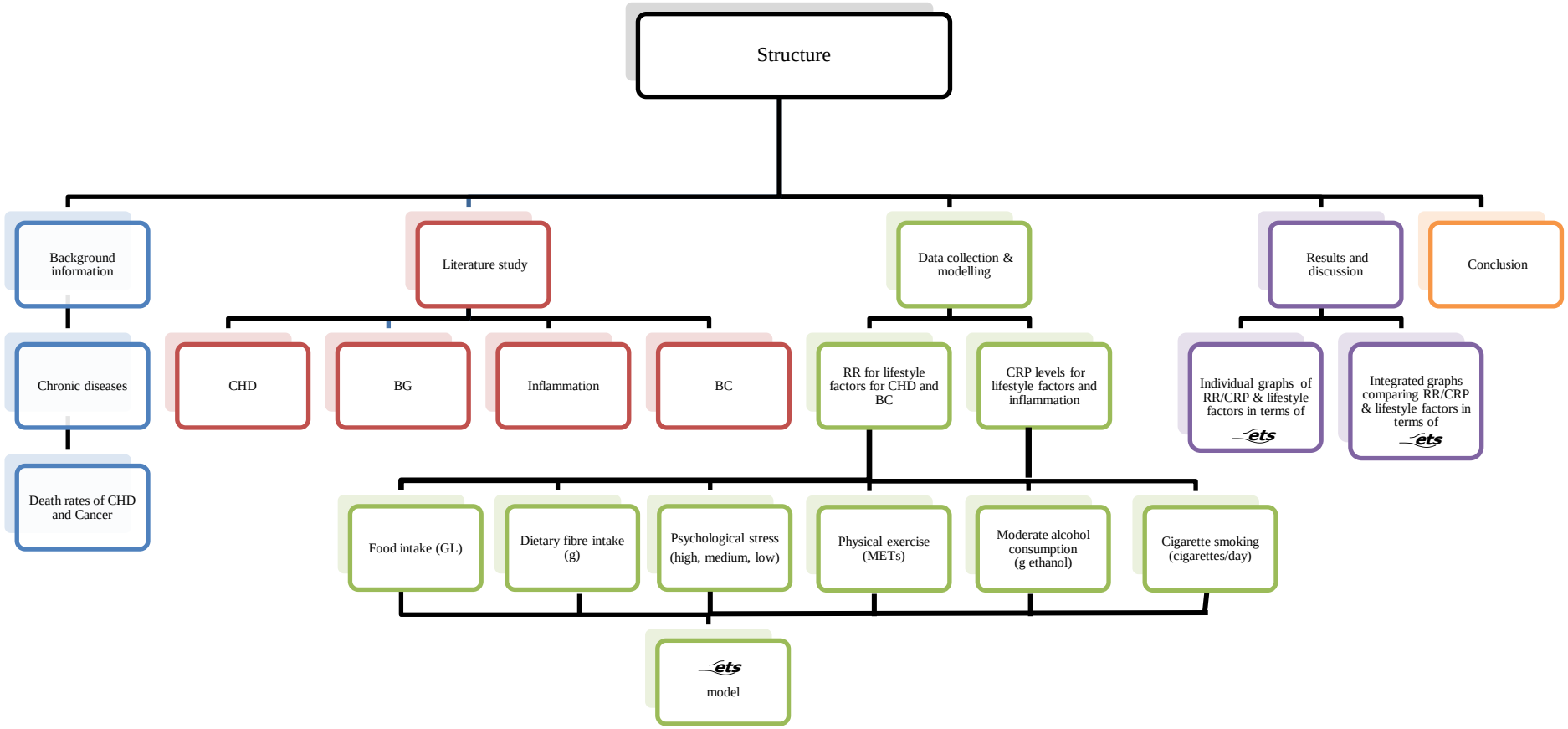


Figure 4: Structure of dissertation

REFERENCES

[1] Beaglehole R, Ebrahim S, Reddy S, Voute J, Leeder S. Prevention of chronic diseases: A call to action. *Lancet*. 2007;370:2152-2157.

[2] Véronique RL, Go AS, Lloyd-Jones DM, Adams RJ, Berry JD, Brown TM, Carnethon MR, Shifan D, de Simone G, Ford ES, Fox CS, Fullerton HJ, Gillespie C, Greenlund KJ, Hailpern SM, Heit JA, Ho MP, Howard VJ, Kissela BM, Kittner SJ, Lackland DT, Lichtman JH, Lisabeth LD, Makuc DM. Heart disease and stroke statistics 2011 update. *Circulation*. 2011;123:e18-e209.

[3] Bramkamp M, Radovanovic D, Erne P, Szucs TD. Determinants of costs and the length of stay in acute coronary syndromes: A real life analysis of more than 10 000 patients. *Cardiovascular Drugs and Therapy*. 2007;21(5):389-398.

[4] Siegel R, Ward E, Brawley O, Jemal A. The impact of eliminating socio-economic and racial disparities on premature cancer deaths. *A Cancer Journal for Clinicians*. 2011;61(4):212-236.

[5] Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. *International Journal of Cancer*.

2010;127(12):2893-2917.

[6] Aronson D, Rayfield EJ. How hyperglycemia promotes atherosclerosis: Molecular mechanisms. *Cardiovascular Diabetology*. 2002;1(1):1-10.

[7] Mjiyad NE, Caro-Maldonado A, Ramirez-Peinado S, Munoz-Pinedo C. Sugar-free approaches to cancer cell killing. *Oncogene*. 2011;30:253-264.

[8] Federico A, Morgillo F, Tuccillo C, Ciardiello F, Loguercio C. Chronic inflammation and oxidative stress in human carcinogenesis. *International Journal of Cancer*. 2007;121(11):2381-2386.

[9] Kucharz EJ. Chronic inflammation-enhanced atherosclerosis: Can we consider it as a new clinical syndrome? *Medical Hypothesis*. 2012;78(3):396-397.

2. STATE-OF-THE-ART: BLOOD GLUCOSE, INFLAMMATION, CORONARY HEART DISEASE, AND BREAST CANCER

The chapter provides relevant information from existing publications in the field to equip the reader with the knowledge to understand some of the more multifaceted details in the dissertation. The mechanisms that link BG, inflammation and the different chronic diseases are explained in a simplified manner.

2.1. Inflammation

2.1.1. Introduction

The inflammatory response mechanism is a complex one involving various intricate pathways and details. For the purpose of this dissertation, only the relevant mechanisms will be explained and discussed. This involves an overview of the acute and chronic inflammatory response mechanism, the role of BG in inflammation and C-reactive protein as a biomarker of the inflammatory state.

Inflammation is the body's complex immune defence mechanism that acts in response to tissue injury; it makes use of leucocytes from the circulatory system to destroy invasive foreign substances that could cause damage to tissues [10], [11]. Acute inflammation is a favourable response, the innate immune response acts within minutes and is supported, if necessary, by the adaptive immune system to reconstruct tissue and destroy unwanted agents within a couple of days [10].

If, however, it fails to destroy all the foreign substances or the termination of the process is inefficient, it can lead to chronic or systemic inflammation [10]. Systemic inflammation is linked to various chronic diseases such as CHD, diabetes mellitus, cancer and rheumatoid arthritis [12], [13].

2.1.2. Mechanism for inflammation

Damage is caused to cells through, for example, injury. The affected cells respond by up - regulating heat shock proteins, initiating macrophages to release cytokines (TNF-α, IL-6, IL-1), as well as highly reactive oxidants (which help in the elimination of pathogens) and reactive nitrogen species [14]. It also initiates lipid mediators, such as complement cleavage, (C5A) through enzymatic degradation of membrane phosphor lipids [14]. The increase in cytokines and lipid mediators activate and modify endothelial cells causing extravasion of neutrophils by diapedesis. The accumulation of neutrophils at the affected area creates a physical barrier that promotes blood coagulation and tissue repair (redness and heat) [14].

The endothelial cells also become more permeable, which allows plasma fluid and proteins to leak into tissues. The plasma fluid activates dendritic cells to migrate to the lymph nodes and cause drainage into lymph (swelling and pain) [14]. Chronic wounds fail to go through this usual sequence of tissue repair and, instead, remain in a chronic state of inflammation [15]. Pro-inflammatory cytokines, chemokines and adhesion molecules (such as VCAM-1) are continuously produced, creating a hostile micro environment inducing further tissue damage rather than tissue repair [15]. IL-6 is a major contributor to chronic inflammation as it is involved in the transition of neutrophil to monocyte recruitment [11]. Extended IL-6 presence causes neutrophillic apoptosis, phagocytosis and mononuclear cell recruitment at the site of injury [11]. To stop chronic inflammation, treatments such as anti-inflammatory drugs are used to inhibit the production of pro-inflammatory cytokines (responsible for inducing the inflammatory response) [11]. Down-regulation of pro-inflammatory cytokines breaks the chronic inflammatory loop [11]. The simplified mechanism for inflammation can be seen in Figure 5.

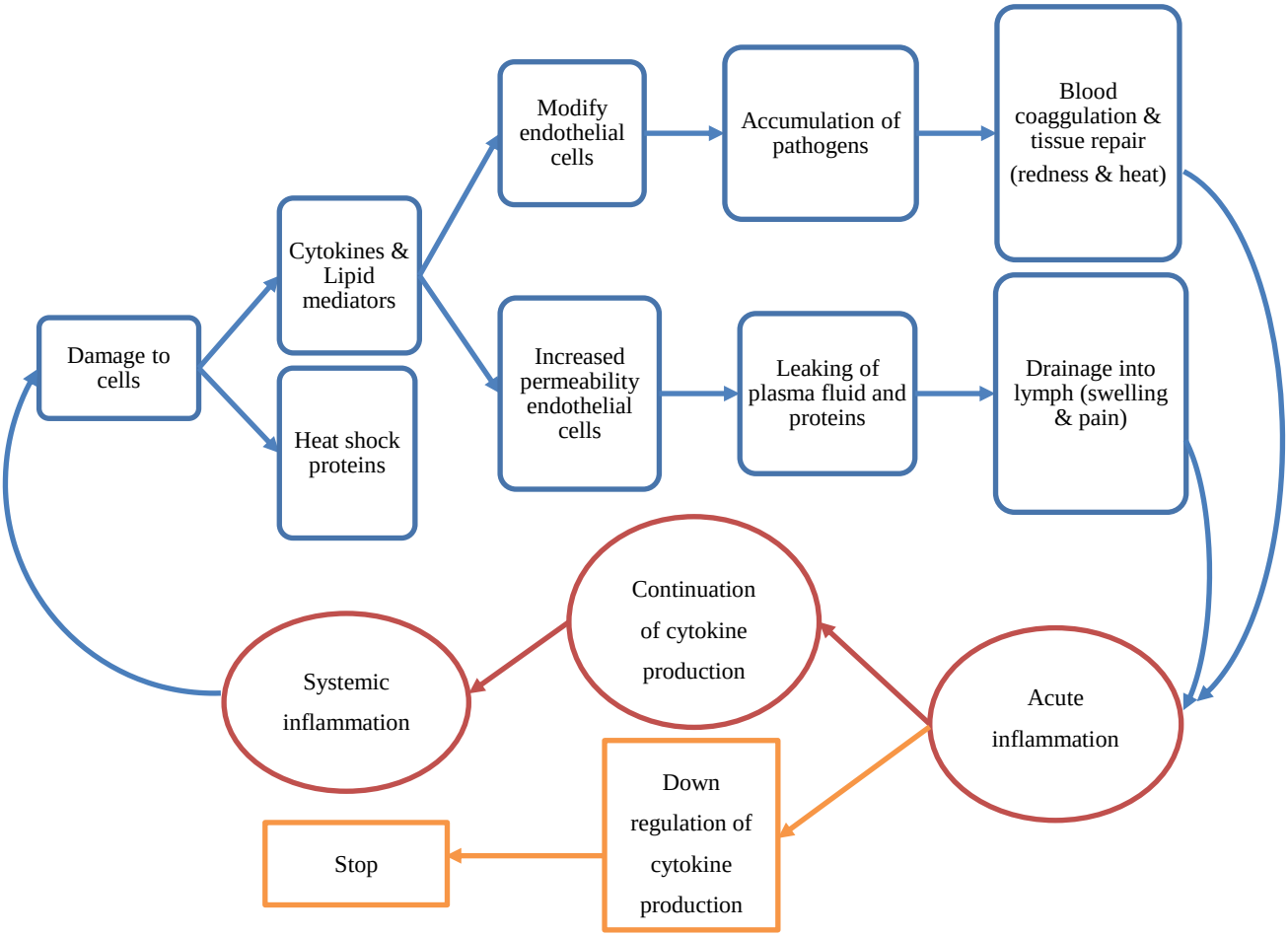


Figure 5: Summarised mechanism for inflammation, adapted from [14]

2.1.3. The role of BG in inflammation

Hyperglycaemia is a state where an excessive amount of glucose is present in the blood (i.e. higher than 6 mmol/L) [16]. High BG levels are known to fuel inflammation [17]. It has been suggested that the mechanism by which high BG fuels inflammation can be unified is through increased production of reactive oxygen species (ROS) by the mitochondria [17]. Increased ROS activate the following four biochemical processes: Increased flux through the hexosamine and polyol pathway, increased production of advanced glycation end products (AGEs) and the activation of protein kinase C [17].

The four pathways, in turn, lead to increased levels of inflammation each in its specific way. The pathways and their connection to inflammation are summarised in Figure 6.

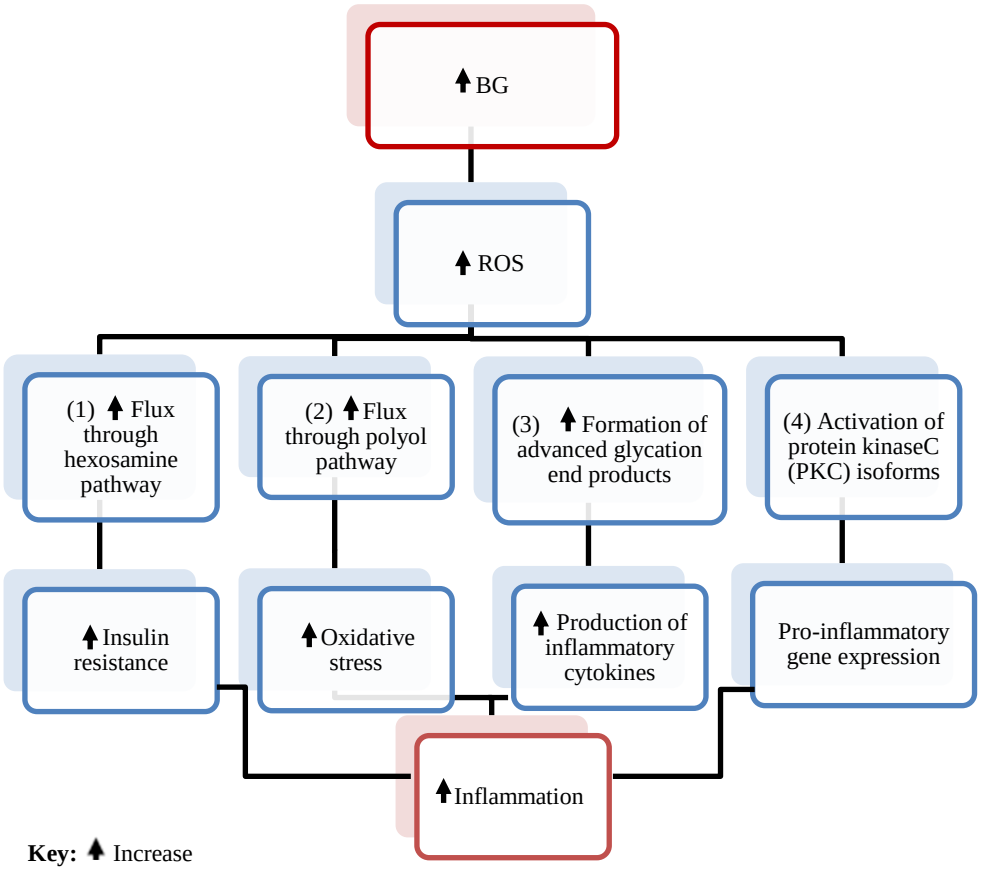


Figure 6: Hyperglycaemia and its contribution to inflammation, adapted from [17]

2.1.4. High sensitivity C-reactive protein (hs-CRP)

High sensitivity C-reactive protein (hs-CRP) is synthesised in the liver in response to IL-6, and has been identified as the first marker for low-grade inflammation [18], [19]. It has been widely studied and is currently one of the only trustworthy biomarkers for chronic inflammation [18]. hs-CRP is a part of the pentraxin family, and is found in the blood [20]. In chronic inflammation, cytokine levels are elevated which leads to raised levels of hs-CRP [21]. Levels of hs-CRP are measured with the high sensitivity test that measures low levels of hs-CRP in the blood. Levels lower than 1 mg/L are regarded as normal, levels between 1- 3 mg/L are considered to be slightly elevated and above 3 mg/L are known as high hs-CRP levels and associated with inflammation [21]. hs-CRP, in the past was known as only a biomarker for inflammation but is currently also used as a predictor for endothelial dysfunction and atherosclerosis [21].

2.2. Coronary heart disease (CHD)

2.2.1. Introduction

CHD comprises of the narrowing or obstruction of the coronary blood vessels, caused by atheromas forming inside the capillary walls. This is also known as hardening of the arteries (atherosclerosis) [22]. An atheroma is an atherosclerotic lesion caused by the accumulation of macrophages and debris containing cholesterol and fibrous tissue [23]. Atheromas exist in a stable and unstable state. Stable atheromas stay intact and cause stenosis, whereas unstable atheromas are prone to rupture and can cause occlusive thrombus formation [24]. Most myocardial infarctions are caused by thrombosis [25].

There are several factors that play a major role in the development of CHD. These factors are all influenced by BG [6] and will be discussed in terms of the effect BG has on each factor. The factors include: Insulin resistance, high blood viscosity [26], [27], blood coagulation [28], [29], hypertension [30], dyslipidaemia [31], endothelial dysfunction [32] and inflammation [33].

2.2.2. Insulin resistance

Insulin is an anabolic hormone secreted by the pancreas. While its primary responsibility is glucose homeostasis, it also plays a role in lipid metabolism [34]. Insulin ensures the uptake of glucose from the blood into the muscles and increases lipid synthesis in the liver [34].

Insulin resistance is a state where the cells no longer respond to insulin, causing BG and insulin levels to rise and the body to enter a state of hyperglycaemia and hyperinsulinaemia [34].

Insulin resistance is shown to be a risk factor for atherosclerosis and CHD [35]. It also contributes to other risk factors such as inflammation [36], hypertension [37], blood coagulation [38], dyslipidaemia [39] and endothelial dysfunction [40]. The role of insulin resistance and its effect on each of the risk factors mentioned will be discussed in the relevant sections of the chapter.

2.2.3. High blood viscosity

High blood viscosity is associated to increased risk of CHD [26], [27]. The following factors are shown to correspond to increased blood viscosity: Hyperglycaemia, water loss, lower blood temperature, fat ingestion and increased mass of leukocytes, blood and erythrocytes and low blood flow [41]. Blood with a higher viscosity is more abrasive and can cause areas of low wall shear stress in the arteries [42], [43]. Shear stress is proportional to the product of the blood viscosity and the spatial gradient blood velocity at the endothelium wall [44].

Low shear stress in the wall of the arteries leads to a variety of atherogenic complications. Firstly, it reduces nitric oxide (NO), which possesses anti-inflammatory, anti-apoptotic, anti-vasodilatory and anti-thrombotic properties [44]. In arterial regions with low shear stress, the bioavailability of NO is reduced (through ROS produced in these regions) [44]. The messenger RNA molecule (eNOS) and protein expression are reduced [44], [45]. Furthermore, in conjunction with up-regulating edothelin-1, known for its strong vaso-constrictive properties, it down-regulates prostacyclin, which is a vasodilatory mitogenic substance [44]. All of these factors act together and expose the arteries to atherogenesis [44], [45].

Secondly, low shear stress promotes the synthesis of LDL cholesterol, as well as its permeability and uptake [44]. It stimulates sterol regulatory binding proteins, which are responsible for the up-regulation of the LDL receptor and cholesterol and fatty acid synthesis [44]. Accumulation of cholesterol in the arteries is one of the leading causes for atherosclerosis and CHD [46] and will be discussed in more detail in paragraph 2.2.6.

When LDL cholesterol gets entrapped in the endothelial wall, it is prone to oxidative modification [44]. Low endothelial wall shear stress increases the secretion of ROS through enhancing gene expression and transcriptional activity of the primary oxidation enzymes [44]. It also decreases the ROS scavengers, increasing oxidative stress [44]. Oxidative stress enhances atherosclerosis through inflammation and NO reduction [44].

Lastly, low shear stress in the endothelium enhances inflammation. Entrapped LDL molecules and increased ROS concentrations stimulate the inflammatory response [44].

Inflammation promotes atherosclerosis and its mechanism in atherosclerosis will be discussed in paragraph 2.2.8. A summary of the effect of hyperglycaemia on blood viscosity and atherosclerosis is given in Figure 7.

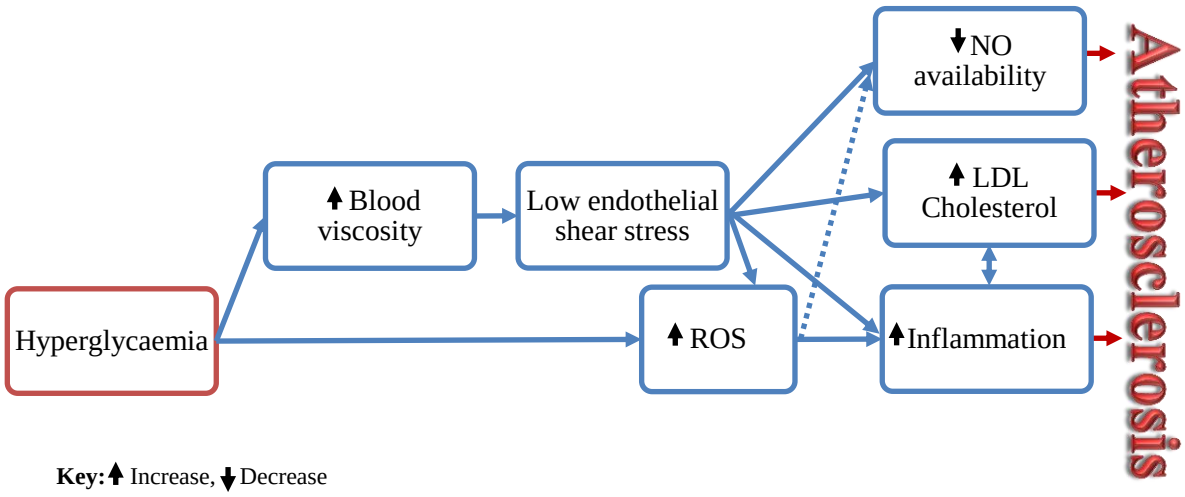


Figure 7: Summary of the effects of hyperglycaemia and high blood viscosity on atherosclerosis

2.2.4. Blood coagulation

Under normal physiological conditions, the coagulation system reacts in response to the rupture of the endothelium and ensures that blood is exposed to the extravascular tissue and forms a platelet plug that stops the bleeding [28]. Blood coagulation consists of platelet adhesion, activation and accumulation of fibrin and fibrinolysis. These three elements interact with one another [29].

In pathophysiological conditions, these three elements cause a blood clot (thrombosis) inside the vessels, which leads to atherosclerosis [29], [28]. The formation of a blood clot, requires an altered blood vessel endothelium (i.e. endothelial dysfunction or inflammation), changed blood pressure (i.e. hypertension) and altered blood composition (i.e. increased blood viscosity or coagulation) [29], [28].

The primary mechanism for the initiation of blood coagulation is the tissue factor (TF) pathway [29]. This pathway involves the formation of the tissue factor VII /factor VIII complex that promotes the intrinsic pathway of coagulation that forms thrombin and fibrin [29]. Platelet adhesion and activation, as well as interactions with leukocytes, expedite thrombin development through delivering catalytic surfaces. These catalytic surfaces express tissue factor and coagulation proteinases, which accelerate thrombin formation [29], [28].

Insulin resistance syndrome is often responsible for the body being in a state of hyperglycaemia and hyperinsulinaemia [47]. Hyperglycaemia and hyperinsulinaemia have been reported to activate the tissue factor pathway through increasing circulating tissue factor pro-coagulant levels, tissue factor VII,VIII activity levels, monocyte tissue factor expression and plasma thrombin generation [48]. Furthermore, the combination of hyperglycaemia and hyperinsulinaemia also increases platelet aggregation [48]. The combination of the activation of the tissue factor pathway with the platelet aggregation increases blood coagulation and create a pro-thrombotic and atherosclerotic environment [48].

Blood coagulation is also closely related (by also being a part of the host defense response) to inflammation which is another key factor in the development of atherosclerosis [49]. These factors are linked in three ways [49]. Firstly, through the endothelium, both respond with adhesive protein expression to damage caused to the endothelium. Secondly, through platelets, both are responsible for platelet activation which then secretes proteins with pro-inflammatory and pro-coagulant properties [49].

The third connection is serine proteinases which are responsible for activation of inflammation and coagulation cells [49]. Integration between these systems, whereby inflammation initiates and fuels coagulation but also that coagulation is responsible in part for activating inflammation, has been documented [49]. Combined inflammation and blood coagulation promotes atherosclerosis and CHD [49].

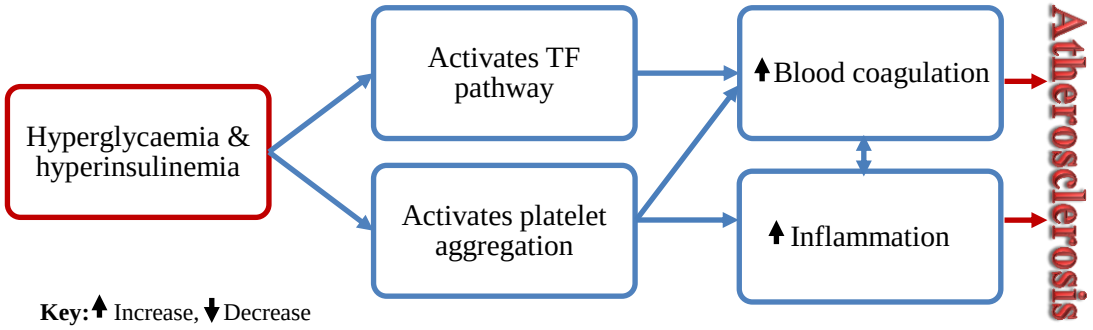


Figure 8: Summary of the effects of hyperglycaemia and hyperinsulinaemia on blood coagulation and atherosclerosis

2.2.5. Hypertension

Hypertension is a known risk factor for coronary heart disease [30]. Studies show that hyperglycaemia contributes to the physiology of hypertension through the generation of ROS [50]. ROS inactivates NO (vasodilator agent), which then contributes in the re-modelling process of the endothelial wall causing endothelial dysfunction [51]. This increases peripheral resistance, increases cardiac contractibility, baroreceptor sensitivity and adrenergic activity [51]. Together, this leads to increased blood pressure [51].

Lipid accumulation is one of the key features in hypertension [52]. Firstly, dyslipidaemia and the oxidation of LDL cholesterol contribute to endothelial dysfunction [52]. The accumulation of cholesterol also contributes to insulin resistance, as well as peripheral resistance in the arteries, which promotes hypertension [37]. Dyslipidaemia and hypertension almost always exist together. Blood viscosity is another important subject when considering hypertension. High BG levels increase the blood viscosity which, therefore, contributes to increased blood flow resistance and consequently hypertension [53].

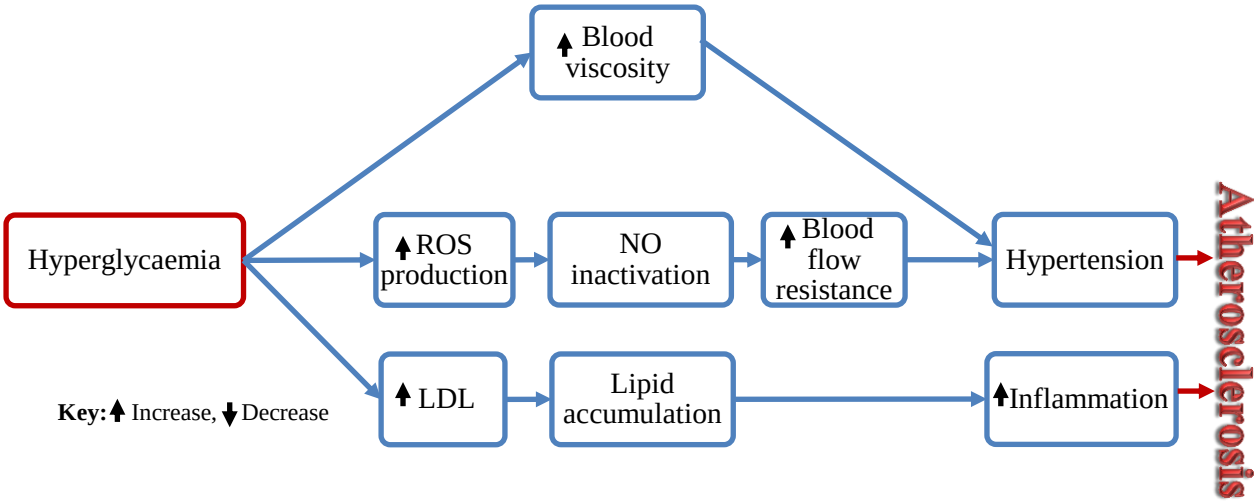


Figure 9: Summary of hyperglycaemia on hypertension and atherosclerosis

2.2.6. Dyslipidaemia

High density lipoprotein (HDL) is known as "good cholesterol" and low density lipoprotein (LDL) or very low density lipoprotein (VLDL) is considered "bad cholesterol" [54], [55]. Low levels of HDL, high levels of LDL/VLDL (i.e. dyslipidaemia), oxidised LDL/VLDL and glycated LDL/VLDL are associated with increased risk for coronary heart disease [54], [55].

Apolipoproteins (lipoproteins attached to proteins) undergo glycation in hyperglycaemic conditions [56]. Glycated lipoproteins are more susceptible to oxidation [56] [57]. Oxidised LDL induces inflammation through the expression of inflammatory cytokines such as IL-6, as well as CRP [56] [57]. Glycated LDL is regarded as more toxic as it suppresses NO production, alters the anti-thrombic properties of the endothelium, enhances the expression of adhesion molecules and inflammatory molecules and induces cell death [56].

Hyperglycaemia also reduces the uptake of LDL through the LDL receptor [56]. This is due to the glycation of apolipoproteins taking place near the receptor binding site, that alters the receptors affinity [56]. Due to the fact that the plasma concentration of LDL corresponds to blood sugar and glycated haemoglobin (HbA1C), hyperglycaemia directly adds to

hyperlipidaemia by postponing the clearance of LDL [56]. AGE proteins also attach to LDL initiating a further delay in LDL uptake [56].

Lipase activity is reduced under hyperglycaemic conditions, which leads to the glycation of VLDL and explains the increased levels of triglycerides [56]. Decreased HDL levels also contribute to the delay of LDL clearance [54]. HDL is responsible for the absorption of VLDL and LDL and if, therefore, HDL levels are lowered, less VLDL and LDL can be removed from the endothelium [54].

Insulin resistance is another major risk factor for dyslipidaemia; this can be attributed to increased levels of triglyceride rich apolipoproteins being produced at a much faster rate by the intestine in persons suffering from insulin resistance [39]. This increased triglyceride rich apolipoproteins is another factor that adds to the impaired clearance of LDL [39].

Increased LDL and VLDL cholesterol accumulates on the endothelium lining, stimulating the inflammatory response [58], [59] and contributing to endothelial dysfunction [52] and atherosclerosis [52].

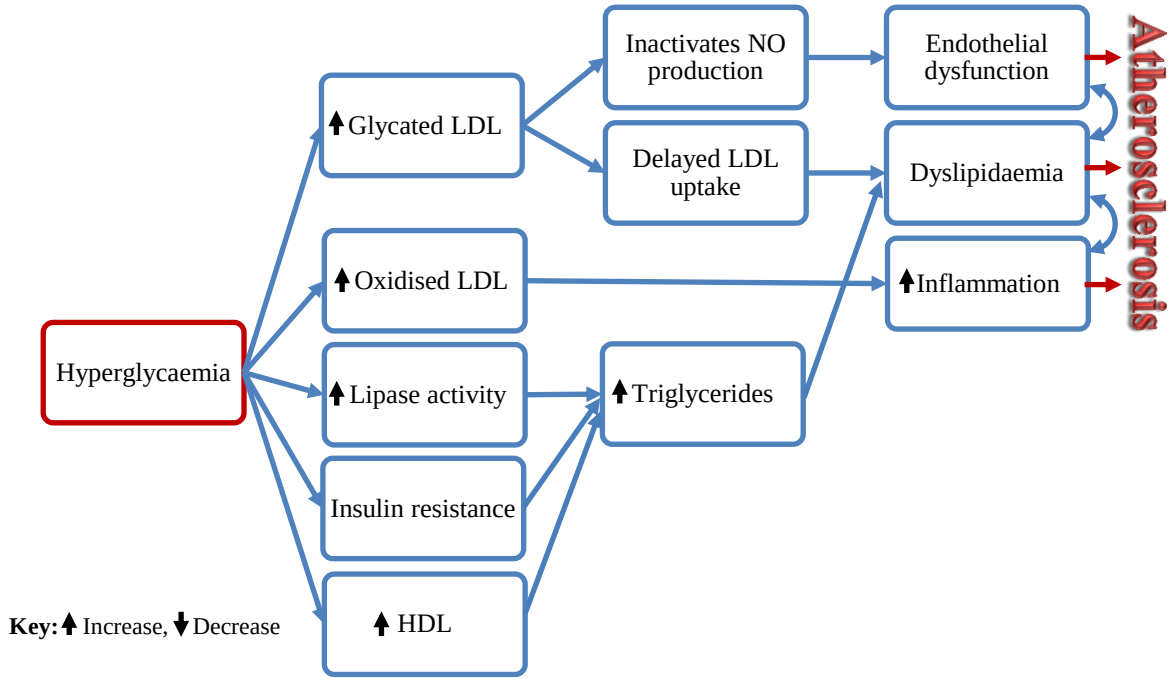


Figure 10: Summary of the effect of hyperglycaemia on dyslipidaemia and atherosclerosis

2.2.7. Endothelial dysfunction

The endothelium is responsible for the maintenance of vascular homeostasis [52]. It regulates the balance between vasodilation and vasoconstriction, the initiation and inhibition of muscular cell proliferation and migration, as well as atherogenesis and fibrinolysis [52]. As soon as this balance is disrupted, endothelial dysfunction is the outcome and causes impairment to the endothelium wall [52].

Endothelial dysfunction is usually caused by a loss of NO bioactivity in the wall of the artery [60], [61]. NO reacts with the ROS to form peroxynitrate in the endothelium and increases the production of angiotensin-II (ANG-II) (the peptide hormone responsible for vasoconstriction). The influx of ANG-II causes impairment of the endothelium's vaso-constricting/relaxing properties, leading to endothelial dysfunction and hypertension [60], [61]. As previously discussed, ROS production is often a cause of high BG levels [32].

Dyslipidaemia also plays a large role in endothelium dysfunction. Increased LDL cholesterol levels, allow more LDL to undergo oxidation by ROS [52]. Oxidised LDL increases the production of caveolin-1, which inhibits NO synthesis and further reductions in NO stimulate endothelium dysfunction [52].

Insulin resistance is also often associated with endothelial dysfunction, not only through inducing hyperglycaemic states but also by influencing the endothelium derived NO [40].

If, however, the endothelium is damaged it cannot function properly and these effects are disturbed. Consequently, the endothelium becomes unstable and unable to resist platelet adhesion, inflammation and cholesterol accumulation and an atherogenic environment exist [52].

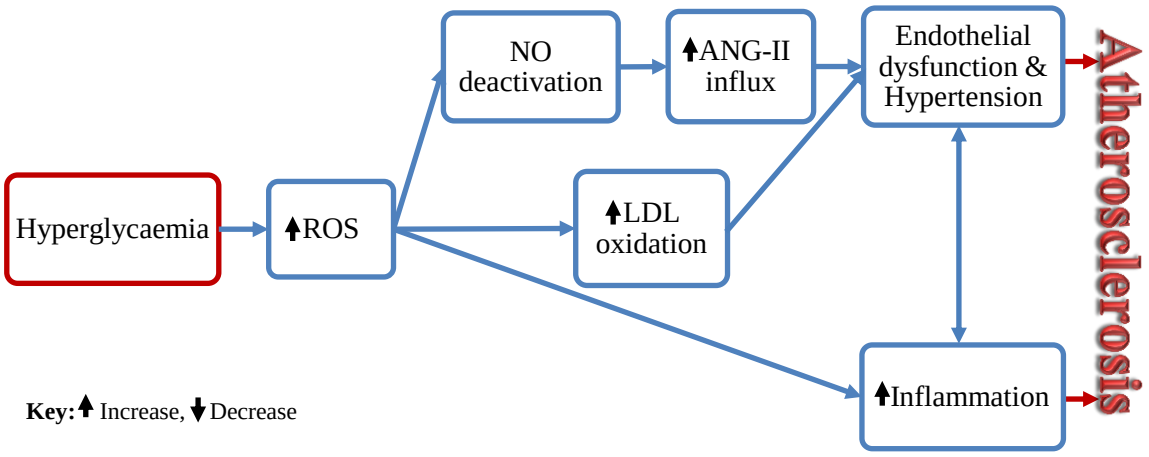


Figure 11: Summary of the effects of hyperglycaemia on endothelial dysfunction and atherosclerosis

2.2.8. Inflammation

CHD is known as an inflammatory disease and without inflammation, the development of atherosclerosis is unlikely [33]. Therefore, inflammation is considered the leading cause of CHD [33]. The inflammatory mechanism, together with metabolic risk factors, activate and proliferate lesions and drives the rupture of these atheromas in arteries [33], [59], [62]. High BG levels increase the potential for inflammation [63], as previously discussed. The role of inflammation in atherosclerosis and CHD will be discussed in more detail.

The role of inflammation in atherosclerosis:

Stage 1: Leukocyte adhesion

Under normal circumstances, leukocytes adhere poorly to the arterial endothelium, but if the endothelium is in a state of inflammation, adhesion molecules (such as VCAM-1) are expressed causing leukocytes to readily bind to the artery wall [58], [59]. Inflammatory cytokines are also expressed, which causes blood monocytes (most popular cells in inflammation) to attach to the leukocytes. These cells are dominant in plaque formation [58], [59]. The cytokines ensure the migration of the monocytes into the intima where they can be transformed into macrophages [58], [59]. The macrophages are augmented into expressing

scavenger receptors by inflammatory mediators, which engulf the lipid particles. These inflammatory mediators also cause replication of macrophages within the intima [58], [59].

Stage 2: Atheroma formation and proliferation

The cytoplasm becomes saturated with lipids and the formation of the foam cells typically found in atherosclerotic lesions exists [58], [59]. Proliferation of the macrophages within the intima occurs, causing enzymes to be released by the inflammatory response. These enzymes can cause destruction to the extra cellular matrix [58], [59]. Pro-inflammatory mediators contribute by inhibiting collagen synthesis, resulting in a thin fibrous cap of the atheroma, which is prone to rupture [58], [59]. These atheromas, present in the arteries, cause obstruction and narrowing of arteries making efficient blood flow to the heart difficult. This results in the heart having to work harder and contributes to CHD [58], [59].

Stage 3: Thrombus formation

If rupture occurs, tissue factor is initiated by inflammatory signalling and induces thrombus formation [58], [59]. Thrombus obstructs arterial blood flow to the heart and is the leading cause for myocardial infarction [58], [59].

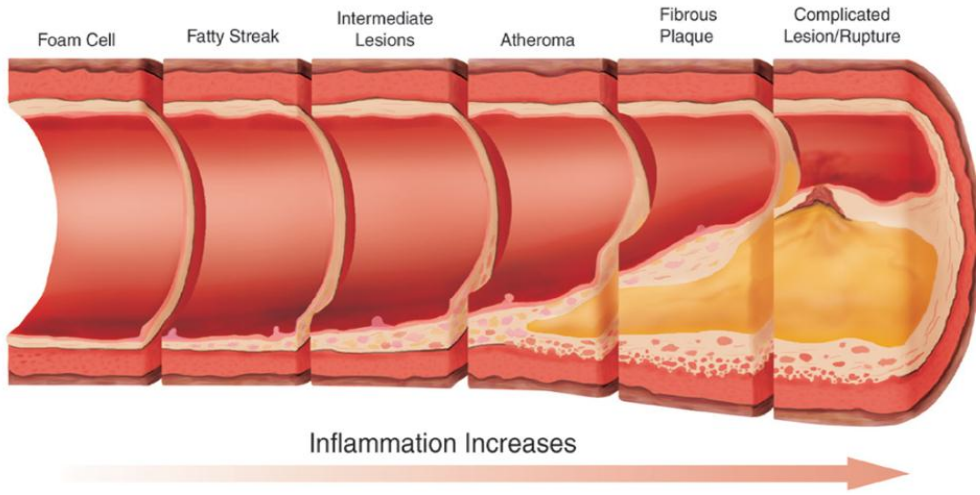


Figure 12: Inflammations role in atherosclerosis and CHD [64]

2.3. Cancer

2.3.1. Introduction

The average adult human is composed of nearly 10^{15} cells [65]. These cells develop all the tissues and organs in the human body through cell division and differentiation [65], [66]. Even though during cell division there are multiple regulatory systems that ensure that normal proliferation occurs, mutations resulting from damage to the genome do occur. When these mutations accumulate, it leads to cancer [65], [66]. The genome damage can be a result of a number of endogenous developments for example: errors in DNA replication, chemical instability of DNA bases or from free radical attack [65], [66].

Exogenous factors such as UV and ionising radiation, as well as chemical carcinogens, can also cause genome damage [66]. Cells have evolved to repair these damages but mistakes can still occur and cause mutations [65]. It is important to understand that the genome damage is not the mutagenic event, but the cell division in response to the damage that causes a change in the DNA and this is known as the mutation [65], [66]. Proliferation is, therefore, the key in formation of mutations and malignancy of cancer cells. These malignant cells grow clonally to form tumours, which exhibit the potential to metastasise [66].

Malignant growth can be attributed to six essential alterations in cell physiology namely: Growth self-sufficiency, insensitivity to growth and growth inhibitory signals, evasion of apoptosis (cell death), limitless replicative properties, continuous angiogenesis (growth of blood vessels) and tissue invasion metastasis [67]. These physiological changes are developed during tumourigenesis and are shared by most, or perhaps all, types of human tumours [67].

In this paragraph, a brief discussion will be given on BC and the pathology of the two most popular types of invasive carcinomas. BG plays a central role in the development of BC and, therefore, the factors that influence BC through BG will be deliberated.

2.3.2. Breast cancer (BC)

As seen in the introduction, BC is the most commonly diagnosed cancer among women in the world and one of the leading causes of death [68]. BC is often known as an assortment of different diseases, which originate in the same anatomical organ with different risk factors, clinical and pathological features and even different responses to therapy [69], [70].

The mammary epithelium gives rise to a variety of carcinomas which, depending on how they are diagnosed, can amount to between 20 and 30. This is a remarkable phenomenon if you consider that the mammary epithelium is derived embryologically from a single ectodermal primordium [71]. Carcinoma cells are identified by their loss of organised cell patterns; they exhibit no cell to cell contact inhibition or basement membrane anchorage-dependent growth [71].

BC can be classified into subgroups through either its histological grade or type. Grade classification is an assessment of the differentiation and proliferation degree (i.e. tubule formation, nuclear pleomorphism and mitotic index) of a tumour [69]. Whereas type is more frequently used to describe a tumour to the ordinary person and refers to the growth of the tumour [69].

BC can either be non-invasive (in situ), which refers to the cancer being situated in the epithelial lining of the terminal duct lobular unit and is usually where the carcinoma originally originates, or it can be invasive, which refers to the cancerous cells growing through the ducts or lobules into the tissue of the breast [72]. These cells, especially ductal carcinomas, often continue to grow at a rapid pace and cause a lump or thickening and can metastasise through the blood or lymph nodes into other parts of the body [72].

Usually, invasive carcinoma presents itself as a breast mass; but sometimes it shows itself through nipple discharge or breast pain. If the invasive tumour is small it might only be identified through a mammography [72]. Invasive ductal carcinomas are the most common type of breast cancer. According to the World Health Organisation (WHO), 50-80% of breast cancer patients around the world have this type of carcinoma [69]. The second most popular carcinoma is the invasive lobular carcinoma, which accounts for 5-15% of the breast cancer

population [69]. These two types of invasive breast cancer will, therefore, be focussed on in this dissertation.

I. Invasive ductal carcinoma (IDC)

The IDC is not a homogenous group; the feature that defines these carcinomas is the lack of similar defining characteristics [69], [71]. IDCs are also often known as infiltrating ductal carcinoma, nonspecific (IDC-NOS) or no special type (IDC-NST) [69], [73]. Their cells range from being small and uniform to large and wildly pleomorphic [71]. Arrangement of these IDCs can either be in sheets, in nodules of varying sizes or in neoplastic grand like constructions [71]. The unrefined masses formed by IDCs are multi-nodular or stellate. Multi-nodular masses are composed of neoplastic cells with fibrotic centres and smooth embossed outlines, which are predominantly located in the periphery. Stellate masses have a central dense core from which long tentacle-like projections protrude [71]. These projections contain carcinogenic ducts and are surrounded by mixed elastic and collagen tissue [71].

Figure 13 is an illustration of a normal duct, an in situ ductal carcinoma and an IDC.

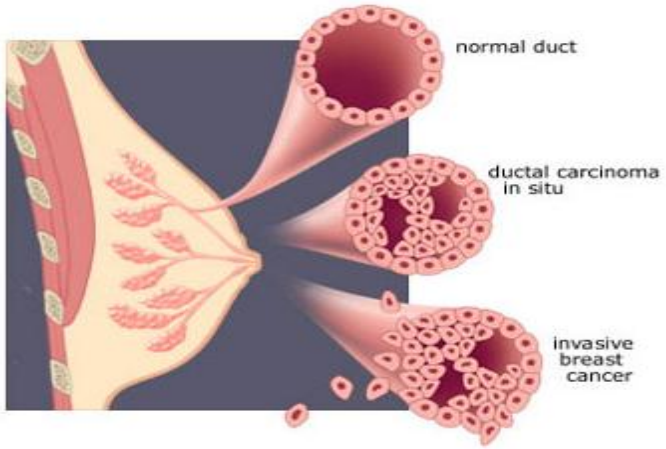


Figure 13: A representation of a normal duct, an in situ ductal carcinoma and an IDC [74]

II. Invasive lobular carcinoma (ILC)

ILCs morphological features are different from IDCs. They consist of single, or sometimes small clusters of, neoplastic cells dispersed about in an "Indian file" pattern around the non-neoplastic ducts [71]. ILC have slight cytoplasm and appear insipid. When they infiltrate, ILCs do not characteristically terminate anatomical structures [75]. Due to their unique growth pattern these carcinoma often fail to form cancerous masses, making ILCs difficult to diagnose with palpitation or mammography [75]. In Figure 14, an illustration of a typical ILC can be found. Notice the single tumour cells infiltrating the stoma in the targeted pattern around the uninvolved duct [75].

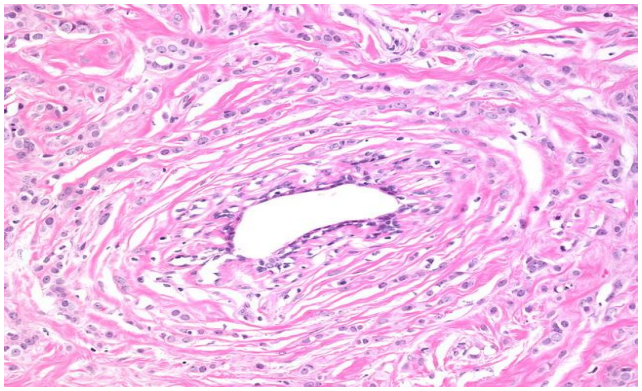


Figure 14: An illustration of a typical ILC [77]

2.3.3 Important factors influencing the development of BC

There are several key factors associated with the development of BC. The way in which these factors are linked to BC will be discussed as well as the BG contribution to each. The following risk factors will be considered: Insulin resistance [78], inflammation [79], [80], endogenous hormones (i.e. oestrogen) [81] and lipid profiles [82].

I. Insulin resistance

Hyperinsulinaemia either directly affects BC risk by stimulating the receptors in the breast tissue or indirectly by inducing the secretion of insulin growth factor (IGF-I). IGF-I is responsible for increased production of sex steroids, such as androgens, and the reduction of sex-hormone-binding-globulin [78]. Elevated levels of androgens increase cellular growth

and proliferation via the androgen receptor and also initiate tissue oestrogen levels to rise – this enhances BC development [78].

Hyperglycaemia directly influences BC risk [79]. Neoplastic cells are known to use glucose for proliferation. Increased BG levels ensure increased glucose metabolism toward the pentose pathways, which is one of the key metabolic features of malignant tissues [79].

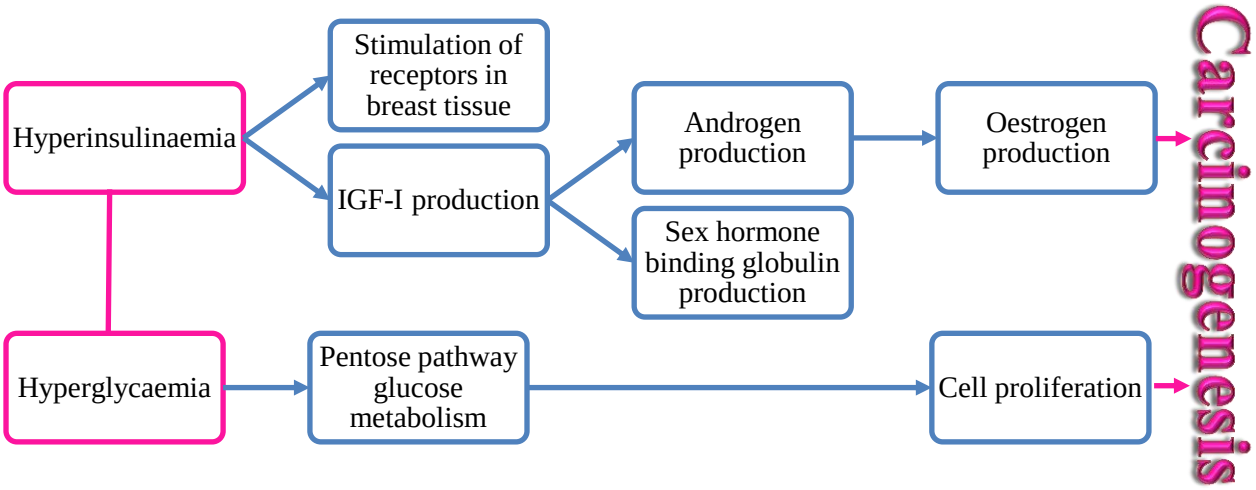


Figure 15: Summary of the effects of hyperglycaemia and hyperinsulinaemia on carcinogenesis

II. Lipid profiles

Total cholesterol and LDL/VLDL cholesterol have been shown to play a crucial role in the carcinogenesis of the breast [80]. Hyperglycaemia increases LDL/VLDL levels and reduces HDL cholesterol levels [80]. The role of HDL cholesterol in cancer development is still unclear. Many studies indicate that increased levels of HDL are associated with BC risk and, in other publications, the contradiction is true [81], [82]. Several studies, however, show that LDL/VLDL and total cholesterol influence the growth and the metastatic potential of breast carcinomas through numerous mechanisms [81], [82]. These mechanisms are responsible for the proliferation and migration of cancerous cells [82].

Cholesterol also plays a key role in the development of lipid rafts, which serve as platforms for various signalling pathways including the migration and invasion cascades [81]. If cholesterol levels are reduced, lipid raft formation is disturbed, that inhibits the cell signalling events involved in breast cancer development [81].

Cholesterol is also active in the regulation of oestrogens and high levels of oestrogen are associated with cellular signalling pathways, which cause breast cancer [81].

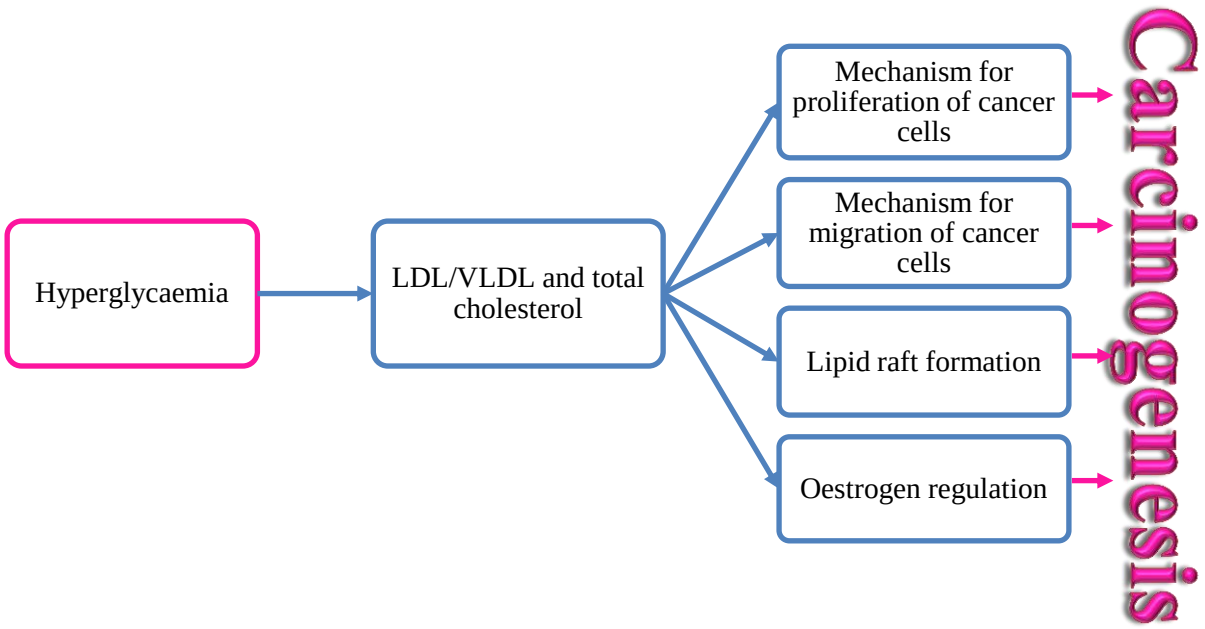


Figure 16: The effect of hyperglycaemia on cholesterol and carcinogenesis

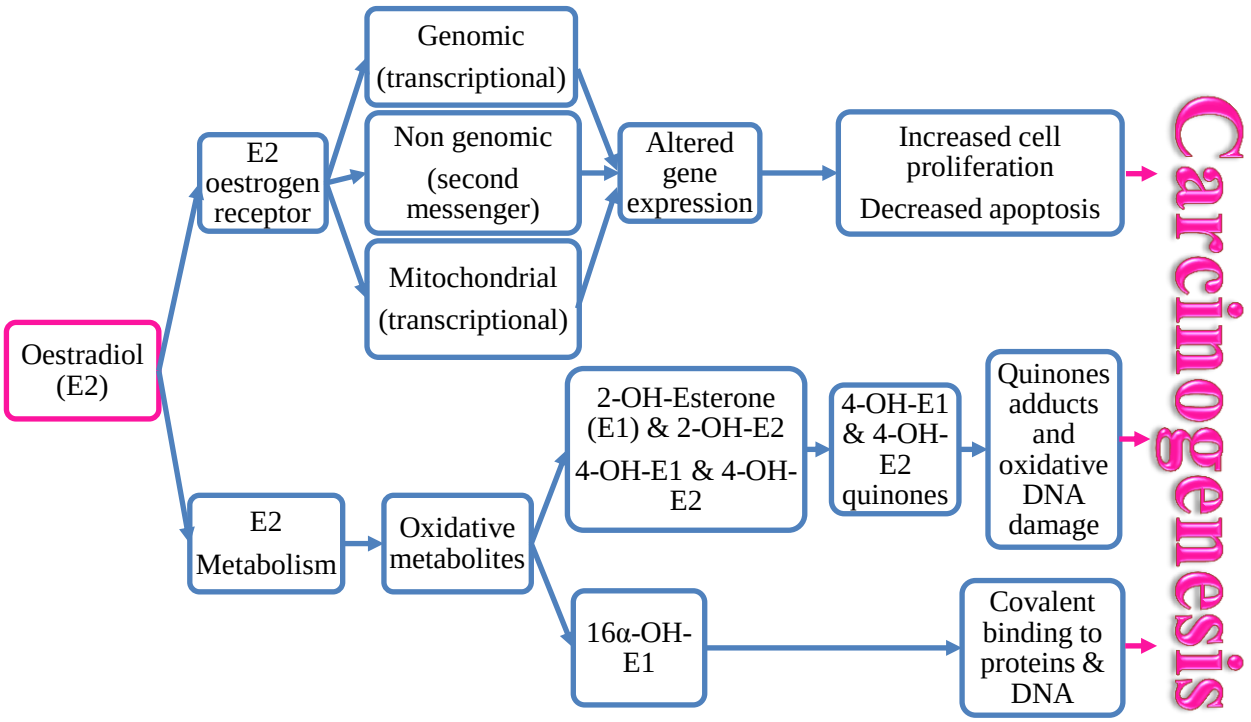
III. Endogenous hormones (i.e. oestrogen)

Sex hormones are produced throughout a woman's life and vary considerably with age. The three hormones of importance include androgens, oestrogen and progesterone. Oestrogens are the most significant hormone secreted by the ovaries in terms of their morphogenetic and mitogenetic abilities [83]. Androgens (testosterones and androstenedione) are a precursor of oestrogen and are secreted by the ovaries as well as the adrenals. Androgens are present in similar levels to oestradiol (type of oestrogen) in the pre-ovulation peak and rise to much higher concentrations during the menstrual cycle [83]. After menopause, the secretion of

oestrogen and progesterone fall, but androgen secretion prevails, making it the dominant sex hormone throughout a woman's life [83].

As previously discussed, hyperglycaemia is associated with insulin resistance, which causes the secretion of IGF-I that elevates androgen levels [78]. Androgens are responsible for breast carcinogenesis through aromatisation of androgens into oestrogen (oestradiol particularly) [84].

Oestradiol contributes to breast carcinogenesis through two pathways that can be found in Figure 17 [85]:



- 2-OH- 2hydroxy, 4-OH- 4hydroxy, 16α-OH- 16 alpha

Figure 17: Pathway in which oestrogen contributes to the initiation, promotion and progression of BC, adapted from [85]

It should be noted that postmenopausal women are more prone to BC. This can be illustrated by the cells adapting to the lower oestrogen concentrations by increasing number of cell cycles, therefore, increasing the probability of DNA replication errors and mutations [83].

IV. Inflammation

The link between carcinogenesis and inflammation has been thoroughly researched [86]. Chronic inflammation has been proven to increase apoptosis resistance and proliferation of cells which promote carcinogenesis [86]. The ROS and RNS produced in the inflammatory response act as chemical effectors in inflammation driven carcinogenesis [87]. In Figure 18 the role of inflammation through ROS and RNS production on carcinogenesis is illustrated.

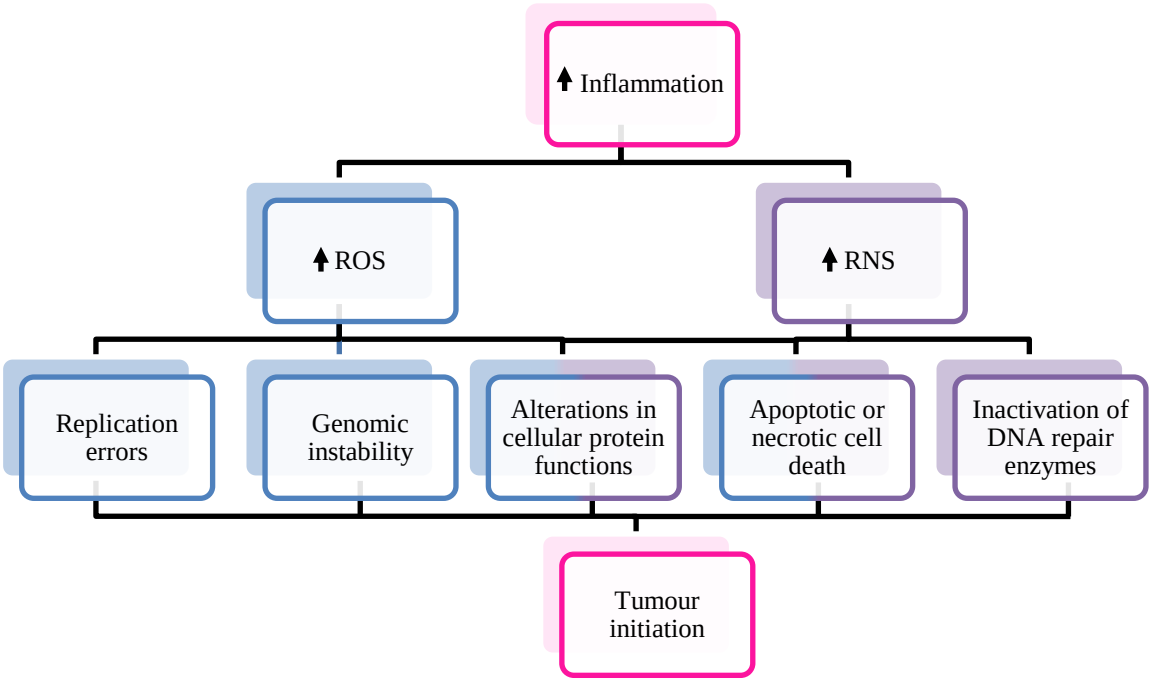


Figure 18: The role of inflammation in carcinogenesis through ROS and RNS, adapted from [87]

Over-expression of cytokines in the inflammatory response also promotes tumour initiation [86]. Pro-inflammatory cytokines up-regulate cyclo-oxygenase (COX-2), which is an enzyme responsible for the production of prostaglandins [88]. Increased prostaglandin levels ensure increased levels of growth factors and metalloproteinases, which decrease cell differentiation, inhibit apoptosis, induce vasodilation and carcinogenesis [88]. IL-6 is known as a pro-angiogenic cytokine [88]. It promotes the growth of new blood vessels required for breast tumour growth [88]. High BG levels increase ROS levels, as well as IL-6 levels, which are both involved in the promotion of BC [88].

2.4. Conclusion

BG plays a central role in inflammation and the development of CHD and BC. Hyperglycaemia is responsible for the production of increased ROS which activates four biochemical processes and leads to increased inflammation (increased flux through the hexosamine and polyol pathway, increased production of AGEs and the activation of PKC).

Important factors that promote atherosclerosis and CHD include: Insulin resistance, high blood viscosity, increased blood coagulation, hypertension, dyslipidaemia, endothelial dysfunction and inflammation. All these factors are interlinked and increased BG levels adversely affect all of them.

Insulin resistance, increased lipid accumulation, endogenous hormones and inflammation are the primary contributors to carcinogenesis and BC. These factors, once again are fuelled by increased BG levels.

2.5. References

[10] Kanterman J, Sade-Feldman M, Baniyash M. New insights into chronic inflammation-induced immunosuppression. *Seminars in Cancer Biology*. 2012; doi:10.1016/j.semcancer.

[11] Gabay C. Interleukin-6 and chronic inflammation. *Arthritis Research and Therapy*. 2006;8(2):1-6.

[12] Rodriguez-Vita J, Lawrence T. The resolution of inflammation and cancer. *Cytokine and Growth Factor Reviews*. 2010;21(1):61-65.

[13] Vodovotz Y, Constantine G, Rubin J, Csete M, Voit EO, An G. Mechanistic simulations of inflammation: Current state and future prospects. *Mathematical Biosciences*. 2009;217(1):1-10.

[14] Penguin Dictionary of Human Biology. London: Penguin global; 2009.

[15] Eming SA, Krieg T, Davidson JM. Inflammation in wound repair: Molecular and cellular mechanisms. *Journal of Investigative Dermatology*. 2007;127:514-525.

[16] Laakso M. Hyperglycemia and cardiovascular disease in type 2 diabetes. *Diabetes*. 1999;48:937-942.

[17] Brownlee M. The pathobiology of diabetic complications. *Diabetes*. 2005;54(6):1-11.

[18] Kluft C, de Maat MPM. Sensitive markers of inflammation make it possible to study the chronic process: The rise of interest in low levels of C-reactive protein. *Vascular*

Pharmacology. 2002;39(3):99-104.

[19] Hurlimann J, Thorbecke GJ, Hochwald GM. The liver as the site of C-reactive protein formation. *The Journal of Experimental Medicine*. 1966;123(2):365-378.

[20] Black S, Kushner I, Samols D. C-reactive protein. *The Journal of Biological Chemistry*. 2004;279(47):48487-48490.

[21] Verma S, Szmitko PE, Yeh ET. C-Reactive protein. *Circulation*. 2004;109:1914-1917.

[22] Encyclopedia Medline Plus. June 22, 2012. http://www.nlm.nih.gov/medlineplus/ency/article/007115.htm. (Accessed October 04, 2012.)

[23] Hansson GK. Inflammation, atherosclerosis, and coronary artery disease. *The New England Journal of Medicine*. 2005;352:1685-1695.

[24] Reiner E. Pathophysiology and classification of cardiovascular diseases caused by atherosclerosis. *The Journal of the International Federation of Clinical Chemistry and Laboratory Medicine*. 2002;13(2):1-4.

[25] Davies M. The pathophysiology of acute coronary syndromes. *Heart*. 2000;83:361-366.

[26] Stoll G, Bendszus M. Inflammation and atherosclerosis: Novel insights into plaque formation and destabilization. *Stroke*. 2006;37:1923-1932.

[27] Koenig W, Sund M, Birgit F, Doring A, Lowel H, Ernst E. Plasma viscosity and the risk of coronary heart disease. *Journal of the American Heart Association*. 1997;18:768-772.

[28] Dahlbäck B. Blood coagulation. *Lancet*. 2000;355:1627-1632.

[29] Spronk HMH, van der Voort D, ten Cate H. Blood coagulation and the risk of atherothrombosis: A complex relationship. *Thrombosis Journal*. 2004;2(12):1-12.

[30] Kaperonis EA, Liapis CD, Kakisis JD, Dimitroulis D, Papavassiliou VG. Inflammation and atherosclerosis. *European Journal of Vascular and Endovascular Surgery*. 2006;31(4):386-393.

[31] Vega GL, Sirtori C. Dyslipidemia and coronary heart disease. *Current Opinion in Lipidology*;1996;7(4):179-182.

[32] McGorisk M, Treasure CB. Endothelial dysfunction in coronary heart disease. *Current Opinion in Cardiology*. 1996 ;11:1-4.

[33] Hansson GK. Inflammation, atherosclerosis and coronary artery disease. *New England Journal of Medicine*. 2005;352:1685-1695.

[34] Sesti G. Pathophysiology of insulin resistance. *Best Practice and Research Clinical Endocrinology and Metabolism*. 2006;20(4):665-679.

[35] Semenkovich C. Insulin resistance and atherosclerosis. *The Journal of Clinical Investigation*. 2006;116:1813-1822.

[36] Bornfeldt KE, Tabas I. Insulin Resistance, hyperglycemia, and atherosclerosis. *Cell Metabolism Review*. 2011;14:575-585.

[37] Sowers J. Insulin resistance and hypertension. *American Journal of Physiology*. 2004;286(5):H1597-H1602.

[38] Abnormalities of coagulation, platelet function, and fibrinolysis associated with syndromes of insulin resistance. *Coronary Artery Disease*. 2005;16(8):473-476.

[39] Hsieh J, Hayashi AA, Webb J, Adeli K. Postprandial dyslipidemia in insulin resistance: Mechanisms and role of intestinal insulin sensitivity. *Atherosclerosis Supplements*. 2008;9(2):7-13.

[40] Steinberg HO, Chaker H, Leaming R, Johnson A, Brechtel G, Baron AD. Obesity/Insulin resistance is associated with endothelial dysfunction implications for the syndrome of insulin resistance. *The Journal of Clinical Investigation*. 1996;97(11):2601-2610.

[41] Cinar Y, Kosku N. Hypothesis: temperature stress and blood viscosity affects the leukocyte flexibility coagulation, intracranial hypertension, and hemodynamics. *International Conference on Life Science and Technology*. 2011;3:120-126.

[42] Reneman RS, Hoeks AP. Wall shear stress and plaque in subjects with asymmetrical carotid atherosclerosis. *Stroke*. 2008;46:499-507.

[43] Gnasso A, Irace C, Carallo C, De Franceschi MS, Motti C, Mattioli PL, Pujia A. In vivo association between low wall shear stress and plaque in subjects with

asymmetrical carotid atherosclerosis. *Stroke*. 1997;28:993-998.

[44] Chatzizisis YS, Coskun AU, Jonas M, Edelman ER, Feldman CL, Stone PH. Role of endothelial shear stress in the natural history of coronary atherosclerosis and vascular re-modelling. *Journal of American College of Cardiology*. 2007;49(25):2379-2393.

[45] Malek AM, Alper SL, Izumo S. Hemodynamic shear stress and its role in atherosclerosis. *Journal of the American Medical Association*. 1999;282(21):2035-2042.

[46] Grundy SM. Atherogenic dyslipidemia associated with metabolic syndrome and insulin resistance. *Clinical Cornerstone*. 2006;8(1):S21-S27.

[47] Stegenga ME, van der Crabben SN, Levi M, de Vos AF, Tanck MW, Sauerwein HP, van der Poll T. Hyperglycemia stimulates coagulation, whereas hyperinsulinemia impairs fibrinolysis in healthy humans. *Diabetes*. 2006;55(6):1807-1812.

[48] Boden G, Rao AK. Effects of hyperglycemia and hyperinsulinemia on the tissue factor pathway of blood coagulation. *Current Diabetes Reports*. 2007;7(3):223-227.

[49] Strukova S. Blood coagulation-dependent inflammation. *Frontiers in Bioscience*. 2006;11:59-80.

[50] Cerielo A, Motz E, Cavarape A, Lizzio S, Russo A, Quatraro A, Giugliano. Hyperglycemia counterbalances the anti-hypertensive effect of glutathione in diabetic patients: Evidence linking hypertension and glycemia through the oxidative stress in diabetes mellitus. *Journal of Diabetes and its Complications*. 1997;11(4):250-255.

[51] Sáez GT, Josep R. Oxidative stress in hypertension. *Revista Brasileira*. 2003;10(4):239-249.

[52] Davignon J, Ganz P. Role of endothelial dysfunction in atherosclerosis. *Circulation*. 2004;109:III27-III32.

[53] Rubegni P, Mondillo S, De Aloe G, Agricola E, Bardelli AM, Fimiani M. Possible role of increased blood viscosity in the hemodynamics of systemic hypertension. *The American Journal of Cardiology*. 2000;85:1265-1268.

[54] Manninen V, Tenkanen L, Koskinen P, Huttunen JK, Manttari M, Heinonen OP, Frick MH. Joint effects of serum triglyceride and LDL cholesterol and HDL cholesterol concentrations on coronary heart disease risk in The Helsinki Heart Study. Implications for treatment. *Circulation*. 1992;85:37-45.

[55] Willerson JT, Ridker PM. Inflammation as a cardiovascular risk factor. *Circulation*. 2004;109(II):II2-II10.

[56] Veiraiah A. Hyperglycemia, lipoprotein glycation, and vascular disease. *Angiology*. 2005;56(4):431-438.

[57] Hulthe J, Fagerberg B. Atherosclerosis and lipoproteins. *Arteriosclerosis, Thrombosis, and Vascular Biology*. 2002;22:1162-1167.

[58] Libby P, Ridker PM, Maseri A. Inflammation and atherosclerosis. *Circulation*. 2002;105:1135-1143.

[59] Libby P, Yoshihisa O, Rocha VZ, Folco E. Inflammation in atherosclerosis:Transition from theory to practice. *Circulation*. 2010;74:213-220.

[60] Mah E, Brunoa RS. Postprandial hyperglycemia on vascular endothelial function: mechanisms and consequences. *Nutrition Research*. 2012; doi:10.1016/j.nutres.

[61] Cai H, Harrison DG. Endothelial dysfunction in cardiovascular diseases: The role of oxidant stress. *Circulation*. 2000;87(1):840-844.

[62] Pedicino D, Giglio AF, Galiffa VA, Cialdella P, Trotta F, Graziani F, Liuzzo G. Infections, immunity and atherosclerosis: Pathogenic mechanisms and unsolved questions. *International Journal of Cardiology*. 2012; doi:10.1016/j.ijcard.

[63] Mazonne T, Chait A, Plutzky J. Cardiovascular disease risk in type 2 diabetes mellitus insights from mechanistic studies. *Lancet*. 2008;371:1800-1809.

[64] Tóth PP. An urgent matter identifying your patients' cardiovascular risk and improving their outcomes. *The Journal of Family Practice*. 2009;58(11):15-43.

[65] Lobo NA, Shimono Y, Dalong Q, Clarke MF. The biology of cancer. *Annual Review of Cell and Developmental Biology*. 2007;23:675-99.

[66] Bertram JS. The molecular biology of cancer. *Molecular Aspects of Medicine*. 2001;21(6):167-223.

[67] Hanahan D, Weinberg RA. The hallmarks of cancer. *Cell*. 2000;100:57-10.

[68] Akhtari M, Mansuri J, Newman KA, Guise TM, Seth P. Biology of breast cancer bone metastasis. *Cancer Biology and Therapy*. 2008;7(1):3-9.

[69] Weigelt B, Geyer FC, Reis-Filho JS. Histological types of breast cancer: How special are they? *Molecular oncology*. 2010;4(3):192-208.

[70] Hanby AM. The pathology of breast cancer and the role of the histopathology laboratory. *Clinical Oncology*. 2005;17(4):234-239.

[71] Gallager SH. Pathologic types of breast cancer: Their prognoses. *Cancer*. 1984;53(S3):623-629.

[72] Bateman AC. Pathology of the breast. *Surgery*. 2004;22(7):iii-vii.

[73] Fischer ER, Gregorio RM, Fischer B. The pathology of invasive breast cancer. *Cancer*. 1975;36(1):1-85.

[74] Cosmetic surgery forums. 2008-2010. Available at: http://www.cosmeticsurgeryforums.com/breast_reconstruction_cancer_stages.htm. (Accessed October 07, 2012).

[75] Arpino G, Bardou VJ, Clark GM, Elledge RM. Infiltrating lobular carcinoma of the breast: Tumor characteristics and clinical outcome. *Breast Cancer Research*. 2004;6(3):R149-R156.

[76] Ramnani DM. Web Pathology: Breast. July 5, 2012. Available at: http://www.webpathology.com/image.asp?case=292&n=4. (Accessed October 07,

2012.)

[77] Ramnani DM. Web Pathology. *Infiltrating Lobular Carcinoma*. October 10, 2012. Available at: http://www.google.co.za/imgres?q=II.%09Invasive+lobular+carcinoma&start=287&hl=en&biw=1733&bih=807&tbm=isch&tbnid=XzuoTCmF5wg4-M:&imgrefurl=http://www.webpathology.com/image.asp%3Fcase%3D292%26n%3D1&docid=ZIvCKGOTu9J_4M&imgurl=http://www.webpathology. (Accessed October 25, 2012.)

[78] Larsson SC, Bergkvist L, Wolk A. Glycemic load, glycemic index and breast cancer risk in a prospective cohort of Swedish women. *International Journal of Cancer*. 2009;125(1):153-157.

[79] Patel SA, Heinrich C, Reddy Y, Srinivas B, Heidaran , Rameshwar. Breast cancer biology: The multifaceted roles of mesenchymal stem cells. *Journal of Oncology*. 2008; doi:10.1155/2008/425895.

[80] Kundu JK, Surh YJ. Inflammation: Gearing the journey to cancer. *Mutation Research*. 2008;659:15-30.

[81] Nicolas Dıaz-Chico B, German Rodrıguez F, Bilbao C, Gonzalez A, Ramırez R, Cabrera de Leon A, Aguirre Jaime A, Chirino R, Navarro D, Dıaz-Chico JC. Androgens and androgen receptors in breast cancer. *Journal of Steroid Biochemistry and Molecular Biology*. 2007;105(1-5):1-15.

[82] Danilo C, Frank PG. Cholesterol and breast cancer development. *Current Opinion in Pharmacology*. 2012; doi:10.1016/j.coph:1-6.

[83] Muti P, Quattrin T, Grant BJB, Krogh V, Micheli A, Schunemann HJ, Ram M, Freudenheim JL, Sieri S, Trevisan M, Berrino F. Fasting glucose is a risk factor for breast cancer: A Prospective Study. *Cancer Epidemiol Biomarkers and Prevention*. 2002;11:1361-1368.

[84] Avramoglu RK, Basciano H, Adeli K. Lipid and lipoprotein dysregulation in insulin resistant states. *International Journal of Clinical Chemistry*. 2006;368(1-2):1-19.

[85] Hasija K, Bagga HK. Alterations of serum cholesterol and serum lipoprotein in breast cancer of women. *Indian Journal of Clinical Biochemistry*. 2005;20(1):61-66.

[86] Kotsopoulos J, Narod SA. Androgens and breast cancer. *Steroids*. 2012;77(1-2):1-9.

[87] Yager JD, Davidson NE. Estrogen carcinogenesis in breast cancer. *New England Journal of Medicine*. 2006;354:270-82.

[88] Ness RB, Modugno F. Endometriosis as a model for inflammation-hormone interactions in ovarian and breast cancers. *European Journal of Cancer*. 2006;42(6):691-703.

3. STATE-OF-THE-ART: LIFESTYLE EFFECTS ON INFLAMMATION, CORONARY HEART DISEASE AND BREAST CANCER

In this chapter, the available literature on the effects of different lifestyle factors on inflammation, CHD and BC is summarised. The glycaemic effects of the lifestyle factors, as well as their contributions to inflammation and the two chronic diseases, are explained. The mechanisms consolidating the effects of the lifestyle factors (in terms of their effect on BG) on CHD and BC are presented.

3.1. Introduction

There are several factors that influence the initiation and development of chronic diseases, such as CHD and cancer. Fewer than 15% of the risk factors are genetic, with the balance being epigenetic factors such as lifestyle factors one can control. These lifestyle factors are, therefore, of particular interest and several articles have been published that investigate the effect of these different lifestyle factors on inflammation, CHD and BC. In this dissertation the following lifestyle factors are focussed on: Excessive food intake, psychological stress, cigarette smoking, dietary fibre intake, moderate alcohol consumption and physical exercise. The effect these lifestyle factors have on BG is of particular importance and will be discussed. The studies available on the effect of these lifestyle factors on inflammation, CHD and BC will also be presented.

3.2. Lifestyle factors that increase BG levels

I. Excessive food intake (GI and GL)

Carbohydrates (CHOs) are the primary source of energy in the average person's diet [89]. They are made up of sugar units. A simple CHO consists of one (monosaccharide) or two (disaccharide) sugar units, where complex CHOs are made up of many sugar units (polysaccharide) linked together [90]. When CHOs are ingested, they are catabolised, usually in the small intestine, into monosaccharides such as glucose and absorbed into the blood [90]. BG levels rise and insulin is secreted by the pancreas in response. This ensures that BG levels do not rise too high and induce hyperglycaemia, but instead are transported to the cells to provide energy for the body or to store for later use [91].

CHO intake is often quantified in terms of Glycaemic index (GI) and Glycaemic load (GL). The definition of GI is the incremental effect that the CHO in a food has on BG levels; it is expressed as a percentage of the effect of an equal amount of glucose [92]. To calculate the GL, the GI is multiplied by the amount of CHO consumed [93]. CHOs with high GI values are broken down into glucose quickly providing spikes in BG levels and increases short term satiety, whereas, low GI CHOs are broken down slowly resulting in sustained satiety in the long term [93], [94]. Excessive food intake leads to obesity, which is often responsible for

insulin resistance [95]. Obesity is associated with decreased adiponectin levels [95]. Adiponectin is a hormone found in the adipose tissue and is known for its anti-inflammatory and anti-atherosclerotic properties [96]. Adiponectin expression is initiated by insulin and inhibited by TNF-α [95]. Decreased adiponectin levels cause elevated TNF-α and IL-6 production. IL-6, as previously discussed, plays a large role in the initiation of the inflammatory response [97]. TNF-α, causes increased levels of tyrosine phosphatases [95]. They are responsible for the de-phosphorylation of the insulin receptor, contributing to insulin resistance [95]. Adiponectin also activates AMP kinase, which enhances glucose uptake in the muscles and increases fatty acid oxidation in the muscles, as well as the liver, to contribute to insulin resistance [98].

II. Psychological stress

Prolonged high-level psychological stress stimulates the hypothalamic adrenocortical axis, which initiates the production of cortisol [99], [100]. Cortisol is involved in hepatic gluconeogenesis and glycogenolysis. With increased psychological stress, cortisol levels increase which, in turn, elevates BG levels, glucagon, growth hormones and catecholamines [99].

Increased levels of catecholamines increase norepinephrine production, which is responsible for lipolysis and the release of free fatty acids into the blood stream [101]. Free fatty acids, in turn, serve as substrate for the synthesis of triglycerides and hepatic production of LDL and VLDL cholesterol [101].

Increased cholesterol levels can lead to obesity, which is again linked to decreased adiponectin levels, insulin resistance and inflammation [95], [98].

III. Cigarette smoking

Insulin resistance has been said to be the crucial link between cigarette smoking and chronic disease [102]. Adiponectin is an important anti-inflammatory protein known for its insulin sensitising abilities. Cigarette smoking reduces the adiponectin production and increases TNF- α and IL-6 levels leading to insulin resistance and inflammation [102].

3.3. Blood glucose lowering lifestyle factors

I. Dietary fibre intake

The majority of health benefits associated with fibre intake is due to its viscosity [103]. The viscosity of fibre is responsible for decreased digestion rates of nutrients and inhibition of bulk absorption of food in the small intestine [103]. Fibre is, therefore, known to have a low GI value and adding fibre to a meal will, in turn, lower the GI of the meal [103].

Slower absorption rates associated with fibre intake is also responsible for the reduction in glucose absorption in the small intestine, which ensures a lower rise in circulating insulin and lipids [103]. Lower postprandial insulin levels are responsible for the suppression of free fatty acids, causing an increase in insulin sensitivity [103]. Increased insulin sensitivity ensures that glucose is withdrawn from the blood at a faster rate, resulting in better BG control [103].

Another benefit of dietary fibre intake is the lowering of total cholesterol and LDL cholesterol [104]. Dietary fibre is said to act on the gastrointestinal tract decreasing absorption of cholesterol and fatty acids. It is also suggested that dietary fibre reduces cholesterol synthesis through alteration of hormones and fatty acids, which affect lipid metabolism [104].

The BG and cholesterol lowering effects, as well as its insulin sensitising properties, are responsible for dietary fibre intake being associated with a decrease in inflammation and RR for both CHD and BC [105], [106], [107].

II. Moderate alcohol consumption

The liver produces glucose from non-CHO substances, such as protein and fat. Moderate alcohol consumption suppresses the liver's ability to produce glucose via gluconeogenesis and glycogenolysis, lowering BG levels [108], [109], [110].

It also leads to increased hepatic production of HDL cholesterol. Increased HDL cholesterol removes cholesterol such as (VLDL and LDL) from arterial walls enhancing efflux of cholesterol back to the liver where it can be re-processed or excreted as bile salts [110]. Decreased VLDL and LDL cholesterol levels are associated with reduced inflammation, hypertension and atherosclerosis [54], [55].

Moderate alcohol consumption is associated with increased insulin sensitivity [96]. The link between moderate alcohol consumption and increased insulin sensitivity is thought to be through increased adiponectin levels [96]. This hormone reduces levels of TNF-α, which have long been implicated in decreased insulin sensitivity [112]. Several in vitro studies have shown that increased adiponectin reduces both TNF-α and its insulin desensitising effects [112].

III. Physical exercise

Physical exercise plays an important role in the prevention of chronic diseases [113]. When participating in physical exercise the muscles require additional energy and, therefore, utilises the glucose in the blood [114]. If the BG source is depleted, the muscles then depend on the liver to break down other substances, such as fat and protein, into glucose to supply the required energy [114]. Physical exercise is, therefore, associated with the lowering of BG [114].

Furthermore, physical activity has an anti-inflammatory effect. It supresses the production of inflammatory cytokines such as IL-6 and TNF- α, as well as other inflammatory markers such as hs-CRP [115]. It also enhances the production of anti-inflammatory indices such IL-4 and IL-10 [115].

Physical activity is associated with weight loss, which is accompanied by increased adiponectin levels and increased insulin sensitivity [114], [115]. Increased adiponectin levels also contribute to the anti-inflammatory effect [115]. In addition, adiponectin stimulates synthesis of eNOS, which is known to improve endothelial dysfunction [115].

3.4. Summary of effects

Psychological stress, cigarette smoking and excessive food intake are associated with increased BG levels and are associated with inflammation and insulin resistance in particular. Dietary fibre intake, moderate alcohol consumption and physical exercise are responsible for a decrease in BG levels and have insulin sensitising and anti-inflammatory properties. Increased BG levels are related to an increase in CHD and BC risk. Reduced BG levels are linked to a decrease in CHD and BC risk.

3.5. The effect of different lifestyle factors on inflammation, CHD and BC

In Table 1 the studies which investigated the effect of the different lifestyle factors on inflammation (hs-CRP levels), RR for CHD and RR for BC are presented with their outcome.

Table 1: Studies available in literature that investigated the effect of different lifestyle factors on inflammation, CHD and BC

Reference	*Cohort size (no. of subjects)*	*Type*	*Sex*	*Outcome*
LIFESTYLE FACTOR: Excessive food intake				
[116]	EPICOR study (32 578)	CHD	Women	Increased RR for CHD with increased GL. Comparing top and bottom quintiles: 2.24 (95% CI; 1.26-3.98).
[117]	HWCS study (5 830)	CHD	Men & women	Increased RR for CHD with increased GL. Comparing top and bottom quintiles: 2.64 (95% CI; 1.15-6.58).

Reference	*Cohort size (no. of subjects)*	*Type*	*Sex*	*Outcome*
[118]	Nurse's health study (75 521)	CHD	Women	Increased RR for CHD with increased GL. Comparing top and bottom quintiles: 1.98 (95% CI; 1.41-2.77).
[119]	EPIC-Morgen study (8 855)	CHD	Men	Increased RR for CHD with increased GI and GL. Comparing top and bottom quintiles: 1.17 (95%CI; 1.02-1.35).
[120]	WHS study (39 876)	Inflammation hs-CRP	Women	Increased GL increased hs-CRP levels. Comparing top and bottom quintiles: hs-CRP increase = 0.21 mg/L.
[121]	Prospective observational study (641)	Inflammation hs-CRP	Men & women	Increased GL increased hs-CRP levels. hs- CRP levels increased from a minimum of 0.03 mg/L to a maximum of 9.6 mg/L.

Reference	*Cohort size (no. of subjects)*	*Type*	*Sex*	*Outcome*
[122]	WHS (39 876)	Inflammation hs- CRP	Women	Increased GL increased hs-CRP levels. hs-CRP for the lowest quintile of dietary glycaemic load was 1.9 mg/L and 3.7 mg/L for the highest quintile.
[78]	Swedish Mammography Cohort (61 433)	BC	Women	Increased GL associated with increased RR for BC. Comparing extreme quintiles: 1.34(95% CI; 0.93-1.94).
[123]	ORDET study (10 786)	BC	Women	Increased GL is associated with increased RR for BC. Comparing extreme quintiles: 2.53(95% CI; 1.54-4.16).
[124]	EPIC Italy study (26 066)	BC	Women	Increased GL is associated with increased RR for BC. Comparing highest vs. lowest quintile: RR 1.45 (95% CI; 1.06-1.99).

Reference	*Cohort size (no. of subjects)*	*Type*	*Sex*	*Outcome*
[125]	SWHS study (75 221)	BC	Women	Increased GL associated with increased RR for BC. Increase of RR ranging from 1 (reference) to a maximum of 1.53 (95% CI; 0.96-2.45).
[126]	Case control study (2588)	BC	Women	Increased GL associated with increase RR for BC. Increase of RR ranging from 1 (reference) to a maximum of 1.34 (95% CI; 1.10-1.61).
[127]	Meta-analysis: 10 prospective cohort studies (577,538)	BC	Women	Increased GL associated with increased BC risk. Comparing highest and lowest quintiles: RR 1.04 (95% CI; 0.95-1.15).

Reference	*Cohort size (no. of subjects)*	*Type*	*Sex*	*Outcome*
LIFESTYLE FACTOR: Dietary fibre intake				
[106]	Japan public health centre COHORT (65 803)	CHD	Men	Increased fibre intake is associated with decreased RR for CHD. A decrease from RR of 1 (reference) to 0.71 (95% CI; 0.53-0.95) at the highest quintile.
[128]	EPIC-Norfolk study (25 639)	CHD	Men & women	Increased fibre intake is associated with decreased RR for CHD. Comparing highest to lowest quintiles: RR 0.84 (95% CI; 0.79-0.90).
[129]	NHS study (68 782)	CHD	Women	Increased fibre intake is associated with decreased RR for CHD. Comparing highest to lowest quintiles: RR 0.81

Reference	*Cohort size (no. of subjects)*	*Type*	*Sex*	*Outcome*
				(95% CI; 0.66-0.99).
[130]	Mixed pool COHORT	CHD	Men and Women	Increased fibre intake is associated with decreased RR for CHD. Overall fibre intake was associated with a 14% decrease in RR for CHD: 0.86 (95% CI; 0.78-0.96).
[105]	NHANES study (4 880)	Inflammation hs- CRP	Women	Increased fibre intake is associated with decreased hs-CRP levels. hs-CRP levels decreased with 2.4 mg/L from the lowest to the highest fibre quintile.
[131]	DASH diet study (35)	Inflammation hs- CRP	Men & women	Increased fibre intake is associated with decreased hs-CRP levels. Overall mean hs-CRP level changed from 4.4-3.8

Reference	*Cohort size (no. of subjects)*	*Type*	*Sex*	*Outcome*
				mg/L.
[107]	NIH–AARP study (185 598)	BC	Women	Increased fibre intake is associated with cancer prevention (postmenopausal women). Comparing highest to lowest quintile: RR 0.87 (95% CI; 0.77-0.98).
[132]	HEAL study (688)	BC	Women	Increased fibre intake is associated with cancer prevention. Comparing high fibre intake to low fibre intake: RR 0.53 (95% CI; 0.23-1.23).
[133]	UKWCS study (35 792)	BC	Women	Increased fibre intake is associated with cancer prevention. Highest to lowest quintile comparison: RR 0.48 (95% CI 0.24-0.96).

Reference	*Cohort size (no. of subjects)*	*Type*	*Sex*	*Outcome*
[134]	Mixed pool study	BC	Women	Increased fibre intake is associated with cancer prevention. Highest to lowest quintile comparison: RR 0.89 (95% CI; 0.83-0.96).

Reference	*Cohort size (no. of subjects)*	*Type*	*Sex*	*Outcome*
LIFESTYLE FACTOR: Moderate alcohol consumption				
[135]	Mixed pool study (266 986)	CHD	Men & women	Moderate alcohol consumption reduces the RR for CHD. For women moderate alcohol consumption reduces RR for CHD from 1(reference) to 0.68 (95% CI; 0.59-0.80). For men moderate alcohol consumption reduces RR for CHD from 1 (reference) to 0.83 (95% CI; 0.74-0.92).
[136]	Japan collaborative COHORT (83 682)	CHD	Men & women	Moderate alcohol consumption reduces the RR for CHD. For men moderate alcohol consumption reduces RR for CHD from 1(reference) to 0.94 (95% CI; 0.70-1.21). For women moderate alcohol consumption reduces RR for CHD from

Reference	*Cohort size (no. of subjects)*	*Type*	*Sex*	*Outcome*
				1 (reference) to 0.84 (95% CI; 0.54-1.33).
[137]	EPIC Spanish COHORT	CHD	Men & women	Moderate alcohol consumption reduces the RR for CHD. For women moderate alcohol consumption reduces RR for CHD from 1(reference) to 0.64 (95% CI; 0.37-1.11). For men moderate alcohol consumption reduces RR for CHD from 1 (reference) to 0.49 (95% CI; 0.32-0.75).
[138]	Mixed pool study	CHD	Men & women	All studies in the meta-analysis suggest inverse association between RR for CHD and moderate alcohol consumption.

Reference	*Cohort size (no. of subjects)*	*Type*	*Sex*	*Outcome*
[139]	General practice study (7 735)	CHD	Men	Moderate alcohol consumption reduces the RR for CHD. For moderate alcohol consumption the RR for CHD decreased from 1 (reference) to 0.78 (95% CI; 0.65-0.94).
[140]	National health and nutrition study in Germany (2 006)	Inflammation hs- CRP	Men & women	Moderate alcohol consumption reduces hs-CRP levels. hs-CRP levels reduce from 1.39 to 1.09 mg/L with moderate alcohol consumption.
[141]	Epidemiological study (72)	Inflammation hs- CRP	Men & women	Moderate alcohol consumption reduces hs-CRP levels for men by 0.66 mg/L and by 0.38 mg/L for women.

Reference	*Cohort size (no. of subjects)*	*Type*	*Sex*	*Outcome*
[142]	HPFS study (1 432)	Inflammation hs- CRP	Men & women	Moderate alcohol consumption reduces hs-CRP levels for men by 0.66 mg/L and for women by 0.38 mg/L.
[143]	Cross sectional study in Germany (7 887)	Inflammation hs- CRP	Men & women	Moderate alcohol consumption reduces hs-CRP levels from 1.63 to 1.26 mg/L.

Reference	*Cohort size (no. of subjects)*	*Type*	*Sex*	*Outcome*
LIFESTYLE FACTOR: Physical Exercise				
[144]	Health Professionals follow up study (44 452)	CHD	Men	Physical activity is associated with reduced RR for CHD. Half an hour of moderate exercise was associated with an 18% RR for CHD reduction: 0.82 (95% CI; 0.67-1).
[145]	WHIOS study (73 743)	CHD	Women	Physical activity is associated with reduced RR for CHD for postmenopausal women. For moderate exercise, the RR for CHD decreased from 1 (reference) to 0.72 (95% CI; 0.59-0.87).
[146]	JACC study	CHD	Men & Women	Physical activity is associated with reduced RR for CHD. For moderate

Reference	*Cohort size (no. of subjects)*	*Type*	*Sex*	*Outcome*
	(73 265)			exercise the RR for CHD decreased from 1 (reference) to 0.73 (95% CI; 0.56-0.95).
[147]	Harvard Alumni Study (12 516)	CHD	Men	Physical activity is associated with reduced RR for CHD. For moderate exercise the RR for CHD decreased from 1 (reference) to 0.81 (95% CI; 0.71-1.03).
[148]	Meta-analysis	CHD	Men & Women	Physical activity, for example a 30 minute walk per day is associated with a 19% reduced RR for CHD.
[149]	CHS cohort	Inflammation hs-CRP	Men & Women	Comparing the lowest quartile with the quartile of moderate physical activity there was a decrease of hs-CRP of

Reference	*Cohort size (no. of subjects)*	*Type*	*Sex*	*Outcome*
	(5 201)			between 3 and 4%.
[150]	ACLS study (722)	Inflammation hs-CRP	Men	Cardiorespiratory fitness is associated with lower hs-CRP levels. The highest adjusted hs-CRP value in the lowest fitness quintile: 1.64 mg/L. And the lowest adjusted hs-CRP value in the highest fitness quintile 0.70 mg/L.
[151]	Japanese women (227)	Inflammation hs-CRP	Women	Physical activity is associated with a reduction from 0.63 to 0.41 mg/L hs-CRP.
[152]	RCPM study (892)	Inflammation hs-CRP	Men & Women	hs-CRP levels decrease with increasing exercise. hs-CRP decreased by 0.061 mg/L for each 1 unit increase in

Reference	*Cohort size (no. of subjects)*	*Type*	*Sex*	*Outcome*
				metabolic equivalents (METs).
[153]	HPFS cohort (51 529)	Inflammation hs-CRP	Men& Women	Physical exercise is related to decreasing hs-CRP levels, for men from 2.04-1.45 mg/L and for women from 2.77-0.88 mg/L.
[154]	USRT cohort (45 631)	BC	Women	Physical exercise protects against BC. Comparing lowest to highest quartile: RR 0.57 (95% CI; 0.34-0.95).
[155]	Case control study (918)	BC	Women	Increased physical activity reduces RR for BC. Women taking part in physical activity between ages of 10 and 12 had reduced RR for BC: 0.68 (95% CI; 0.49-0.94). Women who had ever engaged in recreational physical activity had a

Reference	*Cohort size (no. of subjects)*	*Type*	*Sex*	*Outcome*
				reduced RR for BC compared with inactive women: 0.70 (95% CI; 0.56-0.88).
[156]	Case control study (400)	BC	Women	Physical exercise protects against BC. Risk reduction comparing lowest to highest quintile: 0.42 (95% CI; 0.26-0.73)
[157]	NHS study (121 700)	BC	Women	Physical activity reduces breast cancer risk (postmenopausal). Approximately 1 hour/day of brisk walking decreased risk: 0.85 (95% CI; 0.78-0.93).
[158]	Case control study	BC	Women	Physical activity reduces BC risk. RR associated with low to moderate physical activity were 1.00 (reference), 0.43 (95%

Reference	*Cohort size (no. of subjects)*	*Type*	*Sex*	*Outcome*
	(250)			CI; 0.25-0.75)
[159]	Prospective cohort study (74 171)	BC	Women	RR was reduced by 14 % for low to moderate intensity exercise. From RR 1(reference) to 0.86 (95% CI; 0.76-0.95)
[160]	Case control study (1 883 postmenopausal) and (1 628 premenopausal)	BC	Women	Physical exercise reduces RR for BC. RR reduction from 1(reference) RR 0.66 (95% CI; 0.48-0.90)

Reference	*Cohort size (no. of subjects)*	*Type*	*Sex*	*Outcome*
LIFESTYLE FACTOR: Cigarette smoking				
[161]	Smoking cessation clinic Taiwan (71)	CHD- Adiponcetin	Men & women	Cigarette smoking is associated with lower levels of adiponectin, contributing to CHD. A reduction in adiponectin levels from 11.47 mg/L in non-smokers to 8.35 mg/L in smokers was seen.
[162]	Aichi cohort (10 759)	CHD-Adiponectin	Men	Cigarette smoking is related to lower adiponectin levels, contributing to CHD. Adiponectin levels ranged from 6.40 mg/L in light smokers to 5.71 mg/L in heavy smokers.
[163]	Hygeias Melathron study	CHD-Adiponectin	Women	Cigarette smoking is related to lower adiponectin levels, contributing to CHD. Adiponectin levels varied from 7.2 mg/L

Reference	*Cohort size (no. of subjects)*	*Type*	*Sex*	*Outcome*
	(106)			in smokers to 9.2 mg/L in non-smokers.
LIFESTYLE FACTOR: Psychological stress				
[164]	NAS longitudinal study (2 280)	CHD	Men & women	Increasing levels of stress increases RR for CHD. RR for CHD varied from 1 (reference) to 1.48 (95% CI; 0.99-2.20).
[165]	HADS, PSDI &LSI cohort (655)	CHD	Men	Increasing levels of stress increases incidence for CHD. Comparing the highest and lowest tertiles: RR 2.8(95% CI; 1.2-6.8).
[166]	NESDA study	CHD	Men & women	RR for CHD is increased for subjects with anxiety disorders. With anxiety RR 2.70 (95%CI; 1.31-5.56), and comorbid

Reference	*Cohort size (no. of subjects)*	*Type*	*Sex*	*Outcome*
	(2 981)			anxiety: 3.54 (95% CI; 1.79-6.98).
[167]	Meta-analysis	CHD-	Men & women	RR for CHD increases with increasing stress levels. Studies showed increased RR: 1.26 (95% CI; 1.15-1.38).
[168]	Meta-analysis	CHD	Men & women	RR for CHD increased 2-2.5 fold with increasing stress levels.
[169]	PTSD study (NS)	CHD	Men & women	RR for CHD increases with increasing stress levels. Study showed increased RR: 1.26 (95% CI; 1.05-1.51).

Reference	*Cohort size (no. of subjects)*	*Type*	*Sex*	*Outcome*
[170]	Health, Aging, and Body Composition Study cohort, (2,191)	Inflammation hs- CRP	Men & women	Psychological stress increase inflammation. hs-CRP levels increased from 1 mg/L to 1.24 mg/L with increased stress levels.
[171]	Helsinki Heart Study (241)	Inflammation hs- CRP	Men & women	Psychological stress increase inflammation. hs-CRP levels were higher in persons experiencing high stress 4.4 mg/L versus 2.0 mg/L in other subjects.
[172]	MONICA Augsburg survey (936)	Inflammation hs- CRP	Men	Psychological stress increase inflammation. hs-CRP increased from 1.29 mg/L to 2.17 mg/L with increased stress levels.

Reference	*Cohort size (no. of subjects)*	*Type*	*Sex*	*Outcome*
[173]	Case control study (257)	BC	Women	Psychological stress is associated with increased RR for BC. Women with stress had 3.7 times higher risk for BC than women without stress.
[174]	A prospective study (991)	BC	Women	Psychological stress is associated with increased RR for BC. RR increased from 1 (reference) to 2.39 (95% CI; 1.12-5.16).
[175]	Prospective cohort study Finland (10 519)	BC	Women	Psychological stress is associated with increased RR for BC. RR increased from 1.00 (reference), 1.11 (95% CI;0.78-1.57).

3.6. Consolidation of pathways

The effects of the different lifestyle factors are combined into one process diagram for CHD and BC, respectively. It illustrates the inter-connectedness of the factors that influence the two chronic diseases. Furthermore it demonstrates the central role of BG in both CHD and BC, highlighting the importance of inflammation. In Figure 19 the lifestyle effects through BG on CHD is summarised. Figure 20 illustrates the lifestyle effects through BG on BC.

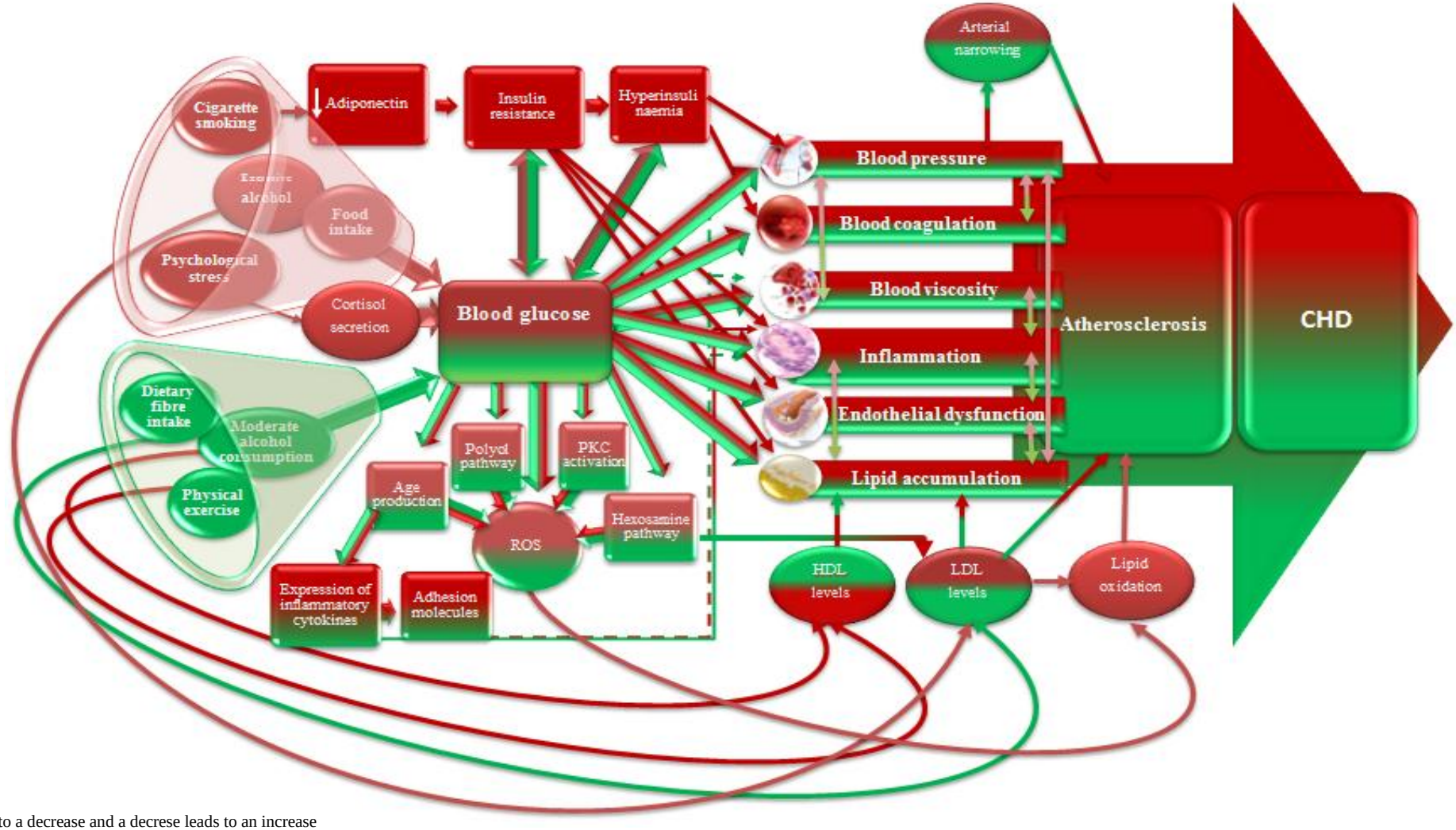


Figure 19: Consolidation of the different lifestyle effects on the development of CHD.

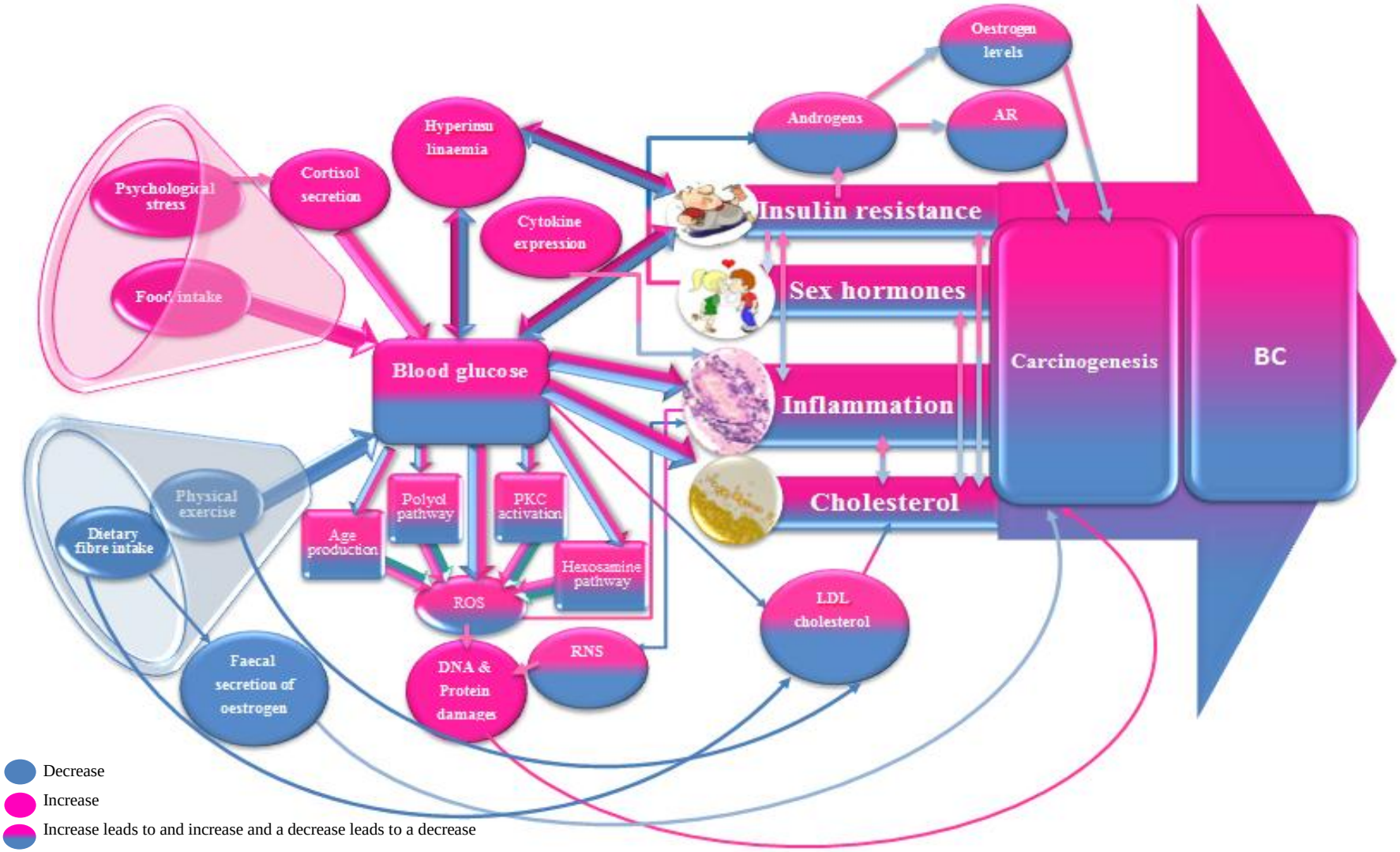


Figure 20: Consolidation of the different lifestyle effects on the development of BC.

3.7. Conclusion

The lifestyle factors that have an impact on inflammation, CHD and BC that have been thoroughly investigated include excessive food intake, cigarette smoking, psychological stress, moderate alcohol consumption, physical exercise and dietary fibre intake. These lifestyle factors are each expressed in a different unit and, therefore, the one that has the most significant effect on the different chronic diseases cannot be established. It has, however, been recognised that BG plays a major role in the development of chronic disease and each lifestyle factor has an effect on BG.

From the available literature, it has been shown that excessive food intake, psychological stress and cigarette smoking increases BG levels, whereas dietary fibre intake, moderate alcohol consumption and physical exercise have a BG lowering effect.

Increased BG levels are associated with atherosclerosis and CHD and also with carcinogenesis and BC. BG influences different risk factors such as inflammation, hypertension, dyslipidaemia, blood coagulation, blood viscosity and endothelial dysfunction, which are crucial for CHD development. It also fuels BC risk factors such as insulin resistance, lipid accumulation, endogenous hormones and inflammation. These risk factors are interlinked and influence one another.

BG, therefore, plays a central role in the development in chronic disease and by expressing the lifestyle factors in terms of their glycaemic effect could be beneficial for quantitative comparisons.

3.8. References

[54] Manninen V, Tenkanen L, Koskinen P, Huttunen JK, Manttari M, Heinonen OP, Frick MH. Joint effects of serum triglyceride and LDL cholesterol and HDL cholesterol concentrations on coronary heart disease risk in the Helsinki Heart Study. Implications for treatment. *Circulation*. 1992;85:37-45.

[55] Willerson JT, Ridker PM. Inflammation as a cardiovascular risk factor. *Circulation.* 2004;109(II):II2-II10.

[89] Anderson HG, Catherine L A N, Woodend DM, Wolever TMS. Inverse association between the effect of carbohydrates on blood glucose and subsequent short-term food intake in young men. *The American Journal of Medical Nutrition.* 2002;76(5):1023-1030.

[90] Miller D, Crane RK. The digestion of carbohydrates in the small intestine. *The American Journal of Clinical Nutrition*. 1963;12(3):220-227.

[91] Bessesen DH. The role of carbohydrates in insulin resistance. *Journal of Nutrition.* 2001;131(10):2782S-2786S.

[92] Monro JA. Glycaemic glucose equivalent: combining carbohydrate content, quantity and glycaemic index of foods for precision in glycaemia management. *Asia Pacific*

Journal of Clinical Nutrition. 2002;11(3):217-225.

[93] Ebbeling CB, Leidig MM, Sinclair KB, Hangen JP, Ludwig DS. A reduced glycemic load diet in the treatment of adolescent obesity. *Arch pediatricians adolescent medicine*. 2003;157(8):773-779.

[94] Mathews EH, Pelzer R. A new model to estimate bolus insulin need. *Diabetes Technology and Therapeutics*. 2009;11(12):813-817.

[95] Kahn BB, Flier JS. Obesity and insulin resistance. *Journal of Clinical Investigation.* 2000;106(4):479-481.

[96] Joosten MM, Beulens J, Kersten S, Hendriks HF. Moderate alcohol consumption increases insulin sensitivity and ADIPOQ expression in postmenopausal women: A randomised, crossover trial. *Diabetologia*. 2008;51:1375-1381.

[97] Ouchi N, Walsh K. Adiponectin as an anti-inflammatory factor. *Clinica Chimica Acta*. 2007;380:24-30.

[98] Gil-Campos M, Canete R, Gil A. Adiponectin, the missing link in insulin resistance and obesity. *Clinical Nutrition*. 2004;23:963-974.

[99] Mathews H, Liebenberg L. A Practical quantification of blood glucose production due to high-level chronic stress. *Stress Health*. 2012; doi:10.1002/smi.2415.

[100] Hucklebridge FH, Clow A, Abeyguneratne T, Huezo-Diaz P, Evans P. The awakening cortisol response and blood glucose levels. *Life Sciences*. 1999;64(11):931-9371.

[101] Wirtza PH, Ehlerta U, Bärtschi C, Redwine LS, von Känel R. Changes in plasma lipids with psychosocial stress are related to hypertension status and the norepinephrine stress response. *Metabolism Clinical and Experimental*. 2009;58:30-37.

[102] Reaven G, Tsao PS. Insulin resistance and compensatory hyperinsulemia: The key player between cigarette smoking and cardiovascular disease. *Journal of the American College of Cardiology*. 2003:1044-1047.

[103] Kendall CW, Esfahani A, Jenkins J. The link between dietary fibre and human health. *Food Hydrocolloids*. 2010;24:42-48.

[104] Marlett JA, Hosig KB, Vollendorf NW, Shinnick FL, Haack VS, Story JA. Mechanism of serum cholesterol reduction by oat bran. *Hepatology*. 1994;20(6).

[105] Ajani UA, Ford ES, Mokdad AH. Dietary fiber and C-reactive protein: Findings from national health and nutrition examination survey data. *Nutritional Epidemiology*. 2004;134:1181-1185.

[106] Kokubo Y, Iso H, Saito I, Yamagishi K, Ishihara J, Inoue M, Tsugane S. Dietary fiber intake and risk of cardiovascular disease in the Japanese population: The Japan Public Health Center-based study cohort. *European Journal of Clinical Nutrition*. 2011;65:1233-1241.

[107] Park Y, Brinton LA, Subar FA, Hollenbeck A, Schatzkin A. Dietary fibre intake and risk of breast cancer in postmenopausal women: The National Institutes of Health-AARP diet and health study. *American Journal of Clinical Nutrition*. 2009;90(3):664-671.

[108] Krebs HA, Freedland RA, Hems R, Stubbs M. Inhibition of hepatic gluconeogenesis by ethanol. *Biochemical Journal*. 1969;112(1):117-124.

[109] Siler SQ, Neese RA, Christiansen MP, Hellerstein MK. The inhibition of gluconeogenesis following alcohol in humans. *Endocrinology and Metabolism*. 1998;276(5):E897-E907.

[110] Bollen M, Keppens S, Stalmans W. Specific features of glycogen metabolism in the liver. *Biochemical Journal*. 1998;336(1):19-31.

[111] Spieker LE, Sudano I, Hürlimann D, Lerch PG, Lang MG, Binggeli C, Corti R, Ruschitzka F, Lüscher TF, Noll G. High-density lipoprotein restores endothelial function in hypercholesterolemic men. *Circulation*. 2002;105:1399-1402.

[112] Sierksma A, Patel H, Ouchi N, Kihara S, Funahashi T, Heine RJ, Grobbee DE, Kluft C, Hendriks HF. Effect of moderate alcohol consumption on adiponectin, tumor necrosis factor-α, and insulin sensitivity. *Diabetes Care*. 2004;27(1):184-189.

[113] McGuire KA, Janssen I, Ross R. Ability of physical activity to predict cardiovascular disease beyond commonly evaluated cardiometabolic risk factors. *The American Journal of Cardiology*. 2009;104(11):1522-1526.

[114] Hostmark AT, Ekeland GS, Beckstrom AC, Meen HD. Postprandial light physical activity blunts the blood glucose increase. *Preventive Medicine*. 2006;42(5):369-371.

[115] Das UN. Anti-inflammatory nature of exercise. *Nutrition*. 2004;20(3):323-326.

[116] Sieri S, Krogh V, Berrino F, Evangelista A, Agnoli C, Brighenti F, Pellegrini N, Palli D, Masala G, Sacerdote C, Veglia F, Tumino R, Frasca , Grioni S, Pala V, Mattiello A, Chiodini P, Panico S. Dietary glycemic load and index and risk of coronary heart disease in a large Italian cohort. *Archives of Internal Medicine*. 2010;170(7):640-647.

[117] Gutierrez ED, Huitron-Bravo G, Talavera JO, Castanon S, Gallegos-Carrillo K, Flores Y, Salmeron J. Dietary glycemic index, dietary glycemic load, blood lipids, and coronary heart disease. *Journal of Nutrition and Metabolism*. 2010;1:1-8.

[118] Liu S, Willett WC, Stampfer MJ, Hu FB, Franz M, Sampson L, Hennekens CH, Manson J. A prospective study of dietary glycemic load, carbohydrate intake, and risk of coronary heart disease in US women. *American Journal of Nutrition*. 2000;71(6):1455-1461.

[119] Burger KN, Beulens JW, Boer JM, Spijkerman AM, van der A DL. Dietary glycemic load and glycemic index and risk for coronary heart disease in Dutch men and women: The EPIC-MORGEN study. *PLoS one*. 2011;6(10).

[120] Levitan EB, Cook NR, Stampfer MJ, Ridker PR, Rexrode KM, Buring JE, Manson JE, Liu S. Dietary glycemic index, dietary glycemic load, blood lipids, and C-reactive protein. *Metabolism Clinical and Experimental*. 2008;57:437-443.

[121] Griffith JA, Ma Y, Chasan-Taber L, Olendzki BC, Chiriboga DE, Stanek III EJ, Merriam PA, Ockene IS. Association between dietary glycemic index, glycemic load, and high-sensitivity C-reactive protein. *Nutrition*. 2008; 24 :401-406.

[122] Liu S, Manson JE, Buring JE, Stampfer MJ, Willett WC, Ridker PM. Relation between a diet with a high glycemic load and plasma concentrations of high-

sensitivity C-reactive protein in middle-aged women. *The American Journal of Clinical Nutrition*. 2001;75:92-8.

[123] Sieri S, Pala V, Brighenti F, Pellegrini N, Muti P, Micheli A, Evangelista A, Grioni S, Contiero P, Berrino F, Krogh V. Dietary glycemic index, glycemic load, and the risk of breast cancer in an Italian prospective cohort study. *American Journal of Clinical Nutrition.* 2007;86:1160-1166.

[124] Sieri S, Pala V, Brighenti F, Agnoli C, Grioni S, Berrino F, Scazzina F, Palli D, Masala G, Vineis P, Sacerdote C, Tumino R, Giurdanella M, Mattiello A, Panico S, Krogh V. cohort, High glycemic diet and breast cancer occurrence in the Italian EPIC. *Nutrition, Metabolism & Cardiovascular Diseases*. 2012; doi:10.1016/j.numecd.

[125] Wen W, Shu XO, Li H, Yang G, Ji BT, Cai H, Gao YT, Zheng W. Dietary carbohydrates, fiber, and breast cancer risk in Chinese women. *Clinical Nutrition*. 2009;89:283-289.

[126] Augustin LS, Maso LD, LaVecchia C, Parpinel M, Negri E, Vaccarell S, Kendall CW, Jenkins DJ, Franceschi S. Dietary glycemic index and glycemic load, and breast cancer risk: A case-control study. *Annals of Oncology*. 2001;12 (11):1533-1538.

[127] Dong JY, Qin LQ. Dietary glycemic index, glycemic load, and risk of breast cancer: meta-analysis of prospective cohort studies. *Breast Cancer Research and Treatment*. 2011;126(2):287-294.

[128] Ward H, Keogh , Lentjes M, Luben R, Wareham N, Khaw K. Fibre intake in relation to serum total cholesterol levels and coronary heart disease risk: A comparison of dietary assessment methods. *European Journal of Clinical Nutrition*. 2011;66:296-304.

[129] Wolk A, Manson JE, Stampfer MJ, Colditz GA, Hu FB, Speizer FE, Hennekens CH, Willett WC. Long-term intake of dietary fiber and decreased risk of coronary heart disease among women. *Journal of American Medical Association*. 1999;281(21):1998-2004.

[130] Pereira MA, O'Reilly E, Augustsson K, Fraser GE, Goldbourt U, Heitmann BL, Hallmans G, Knekt P, Liu S, Pietinen P, Spiegelman D, Stevens J, Virtamo J, Willett WC, Ascherio A. Dietary fiber and risk of coronary heart disease. *Archives of Internal Medicine*. 2004;164(4):370-376.

[131] King DE, Egan BM, Woolson RF, Mainous III AG, Al-Solaiman Y, Jesri A. Effect of a high-fibre diet vs a fibre-supplemented diet on C-reactive protein level. *Archives of Internal Medicine*. 2007;167(5):502-506.

[132] Belle FN, Kampman , Mc Tiernan A, Bernstein L, Baumgartner K, Baumgartner R, Ambs A, Ballard-Barbash R, Neuhouser ML. Dietary fibre, carbohydrates, glycemic index, and glycemic load in relation to breast cancer prognosis in the HEAL Cohort. *Cancer Epidemiol Biomarkers and Prevention*. 2011;20:890-899.

[133] Cade JE, Burley VJ, Greenwood DC. Dietary fibre and risk of breast cancer in the UK Women's Cohort Study. *International Journal of Epidemiology*. 2007;36(2):431-438.

[134] Dong JY, He K, Wang P, Qin LQ. Dietary fiber intake and risk of breast cancer: A meta-analysis of prospective cohort studies. *American Journal of Clinical Nutrition*. 2011;94(3):900-905.

[135] Hvidtfeldt UA, Tolstrup JS, Jakobsen MU. Alcohol intake and risk of coronary heart disease in younger, middle-aged, and older adults. *Circulation*. 2010;121:1589-1597.

[136] Ikehara S, Iso H, Toyoshima H, Date C, Yamamoto A, Kikuchi S, Kondo T, Watanabe Y, Akio K, Wada , Inaba Y, Tamakoshi A. Alcohol consumption and the mortality from stroke and coronary heart disease among Japanese men and women: The Japan Cohort Study. *Stroke*. 2008;39:2936-2942.

[137] Arriola L, Martinez-Camblor P, Larranage N, Basterretxea M, Amiano P, Moreno-

Iribas C, Carracedo R, Agudo A, Ardanaz E, Barricarte A, Buckland G, Cirera L, Chirlaque MD, Martinez C, Molina E, Navarro C, Quiro's JR, Rodriguez L, Sanchez MJ, Tormo MJ, Gonzalez CA, Dorronsoro M. Alcohol intake and the risk of coronary heart disease in the Spanish EPIC Cohort Study. *Heart*. 2010;96:124-130.

[138] Rimm EB. Review of moderate alcohol consumption and reduced risk of coronary heart disease: is the effect due to beer, wine, or spirits? *British Medical Journal*. 1996;312:731-736.

[139] Wannamethee SG, Shaper AG. Type of alcoholic drink and risk of major coronary heart disease events and all-cause mortality. *American Journal of Public Health*. 1999;89(5):685-690.

[140] Imhof A, Froehlich M, Brenner H, Boeing H, Pepys MB, Koenig W. Effect of alcohol consumption on systemic markers of inflammation. *Lancet*. 2001;357:763-767.

[141] Raum E, Gebhardt K, Buchner M, Schiltenwolf M, Brenner H. Long-term and short-term alcohol consumption and levels of C-reactive protein. *International Journal of Cardiology*. 2007;121:224-226.

[142] Pai JK, Hankinson SE, Thadhani R, Rifai N, Pischon T, Rimm EB. Moderate alcohol consumption and lower levels of inflammatory markers in US men and

women. *Atherosclerosis*. 2006;186 :113-120.

[143] Imhof A, Woodward M, Doering A, Helbecque N, Loewel H, Amouyel P, Lowe GD, Koenig W. Overall alcohol intake, beer, wine, and systemic markers of inflammation in western Europe: results from three MONICA samples (Ausburg, Glasgow, Lille). *European heart journal*. 2004;25:2092-2100.

[144] Tanasescu M, Leitzmann MF, Rimm EB, Willet WC, Stampfer MJ, Hu FB. Exercise type and intensity in relation to coronary heart disease in men. *Journal of the American Medical Association*. 2002;288:1994-2000.

[145] Manson JA, Hu FB, Rich-Edwards JW, Colditz GA, Stampfer MJ, Willet WC. A prospective study of walking as compared with vigorous exercise in the prevention of coronary heart disease in women. *New England Journal of Medicine*. 1999;341:650-658.

[146] Noda H, Iso H, Toyoshima H, Date C, Yamamoto A, Kikuchi S, Koizumi A, Kondo T, Watanabe Y, Wada Y, Inaba Y, Tamakoshi A. Walking and sports participation and mortality from coronary heart disease and stroke. *Journal of the American College of Cardiology*. 2005;46(9):1761-1767.

[147] Sesso HD, Paffenbarger RS. Physical activity and coronary heart disease in men: The Harvard Alumni Health Study. *Circulation*. 2000;102:975-980.

[148] Zheng H, Orsini N, Amin J, Wolk A, Nguyen VTT, Ehrlich F. Quantifying the dose-response of walking in reducing coronary heart disease risk: Meta-analysis. *European Journal of Epidemiology*. 2009;24(4):181-192.

[149] Geffken DF, Cushman M, Burke GL, Polak JF, Sakkinen PA, Tracy RP. Association between physical activity and markers of inflammation in a healthy elderly population. *American Journal of Epidemiology*. 2001;153(3):242-250.

[150] Church TS, Barlow CE, Earnest CP, Kampert JB, Priest EL, Blair SN. Associations between cardiorespiratory fitness and C-Reactive protein in men. *Arteriosclerosis Thrombosis and Vascular Biology*. 2002;22:1869-1876.

[151] Okita K, Nishijima H, Murakami T, Nagai T, Morita N, Yonezawa K, Iizuka K, Kawaguchi H, Kitabatake A. Can exercise training with weight loss lower serum C-reactive protein levels? *Arteriosclerosis Thrombosis and Vascular Biology*. 2004;24:1868-1873.

[152] Aronson D, Sheikh-Ahmad M, Avizohar O, Kerner A, Sella R, Bartha P, Markiewicz W, Levy Y, Brook GJ. C-Reactive protein is inversely related to physical fitness in middle-aged subjects. *Atherosclerosis*. 2004;176:173-179.

[153] Pischon T, Hankinson SE, Hotamisligil GS, Rifai N, Rimm EB. Leisure-time physical activity and reduced plasma levels of obesity-related inflammatory

markers. *Obesity Research*. 2003;11(9):1055-1064.

[154] Howard RA, Leitzmann MF, Linet MS, Freedman DM. Physical activity and breast cancer risk among pre and postmenopausal women in the U.S. radiologic technologists cohort. *Cancer Causes Control*. 2009;20(3):323-333.

[155] Verloop J, Rookus MA, van der Kooy K, van Leeuwen FE. Physical activity and breast cancer risk in women aged 20-54 years. *Journal of the National Cancer Institute*. 2000;92(2):128-135.

[156] Awatef M, Olfa G, Rim C, Asma K, Kacem M, Makram H, Leila BF, Amel L, Slim AB. Physical activity reduces breast cancer risk: A case control study in Tunisia. *Cancer Epidemiology*. 2011;35:540-544.

[157] Eliassen AH, Hankinson SE, Rosner B, Holmes MD, Willett WC. Physical activity and risk of breast cancer among postmenopausal women. *Archives of Internal Medicine*. 2010;170(19):1758-1764.

[158] Kruk J. Lifetime physical activity and the risk of breast cancer: A case control study. *Cancer Detection and Prevention*. 2007;31:18-28.

[159] Mc Tiernan A, Kooperberg C, White E, Wilcox S, Coates R, Adams-Campbell LL, Woods N, Ockene J. Recreational physical activity and risk for breast cancer in

postmenopausal women. *Journal of the American Medical Association*. 2003;290:1331-1336.

[160] Carpenter CL, Ross RK, Paganini-Hill A, Bernstein L. Effect of family history, obesity and exercise on breast cancer risk among postmenopausal women. *International Journal of Cancer*. 2003;106:96-102.

[161] Tsai JS, Guo FR, Chen SC, Chiu TY, Chen CY, Hung SH, Chuang LM. Smokers show reduced circulating adiponectin levels and adiponectin mRNA expression in peripheral blood mononuclear cells. *Atherosclerosis*. 2011;218(1):168-173.

[162] Takefuji S, Yatsuya H, Tamakoshi K, Otsuka R, Wada K, Kunihiro M, Sugiura K, Hottaa Y, Mitsuhashi H, Oiso Y, Toyoshima H. Smoking status and adiponectin in healthy Japanese men and women. *Preventitive medicine*. 2007;45(6):471-475.

[163] Estathiou SP, Skeva II, Dimas C, Dimas C, Panagiotou A, Parisi K, Tzanoumis L, Kafouri A, Bakratsas K, Mountokalakis TD. Smoking cessation increases serum adiponectin levels in apparently healthy Greek population. *Atherosclerosis*. 2009;205(2):632-636.

[164] Kubzanski LD, Kawachi I, Spiro III A, Weiss ST, Vokonas PS, Sparrow D. Is worrying bad for your heart? A prospective study of worry and coronary heart disease in the Normative Aging Study. *Circulation*. 1997;95:818-824.

[165] Einvik G, Ekeberg O, Klemsdal TO, Sandvik L, Hjerkinn EM. Physical distress is associated with cardiovascular events in a high risk population of elderly men. *BMC Cardiovascular Disorders*. 2009;9:14-20.

[166] Vogelzangs N, Seldenrijk A, Beekman ATF, van Hout HPJ, de Jonge P, Penninx BWJH. Cardiovascular disease in persons with depressive and anxiety disorders. *Journal of Affective Disorders*. 2010;125(1-3):241-248.

[167] Roest AM, Martens EJ, De Jonge P, Denollet J. Anxiety and risk of incident coronary heart disease, a meta-analysis. *Journal of the American College of Cardiology*. 2010;76(2):38-46.

[168] Versteeg H, Pedersen SS, Denollet J, Spek V. Type D personality and health status in cardiovascular disease populations: A meta-analysis of prospective studies. *European Journal of Cardiovascular Prevention and Rehabilitation*. 2011: doi: 10.1177/1741826711425338.

[169] Kubzanski LD, Koenen KC. Is posttraumatic stress disorder related to development of heart disease? An update. *Cleveland Clinical Journal of Medicine*. 2009;76(2):S60-S65.

[170] Rodondi N, Marques-Vidal P, Butler J, Sutton-Tyrrell K, Cornuz J, Satterfield S, Harris T, Bauer D, Ferrucci L, Vittinghoff E, Newman AB. Markers of

atherosclerosis and inflammation for prediction of coronary heart disease in older adults. *American Journal of Epidemiology*. 2010;171(5):540-549.

[171] Roivainen M, Viik-Kajander M, Palosuo T, Toivanen P, Leinonen M, Saikku P, Tenkanen L, Manninen V, Hovi T, Manttari M. Infections, inflammation, and the risk of coronary heart disease. *Circulation*. 2000;101:252-257.

[172] Koenig W. Inflammation and coronary heart disease: An overview. *Cardiology*. 2001;9(1):31-35.

[173] Kruk J, Aboul-Enein HY. Psychological stress and the risk of breast cancer a case control study. *Cancer Detection and Prevention*. 2004;28:399-408.

[174] Metcalfe C, Smith GD, Macleod J, Hart C. The role of self-reported stress in the development of breast cancer and prostate cancer: A prospective cohort study of employed males and females with 30 years of follow-up. *European Journal of Cancer*. 2007;43:1060-1065.

[175] Lillberg K, Verkasalo PK, Kaprio J, Teppo , Helenius H, Koslenvuo M. Stress of daily activities and risk of breast cancer: A prospective cohort study in Finland. *International Journal of Cancer*. 2001;91:888-893.

4. DATA PROCESSING

This chapter explains the research methodology; giving details of the literature search strategy and provides the set of criteria with which the data was chosen and discarded. It also illustrates the full derivations of the different lifestyle factors' models.

4.1. Literature search strategy

Literature searches were done using databases such as ScienceDirect, Scopus, EBSCO, Google Scholar and IEEE Xplore. Subject headings related to the lifestyle factors (i.e. excessive food intake, dietary fibre intake; alcohol consumption, psychological stress, cigarette smoking and physical exercise) and chronic diseases (i.e. inflammation, BC and CHD) were used. The search was limited to English-language publications. Advanced searches were also conducted making use of the "AND" function. The reference lists from articles of interest were also checked to find the maximum number of related publications. After the articles were collected, they were analysed to confirm if they could be included into the meta-analysis.

4.2. Inclusion criteria for meta-analysis

Data inclusion and exclusion had to be done following certain criteria, as not all publications assess and define lifestyle factors in the same way. All of the data were selected according to the following criteria:

Data that were quantified in the following units (or that can be transformed into these units) were considered:

1. Excessive food intake GL;
2. Dietary fibre intake grams;
3. Alcohol consumption grams of ethanol;
4. Psychological stress high, medium and low;
5. Cigarette smoking number of cigarettes;
6. Physical exercise METs.

These measurements were decided on due to them being the most popular quantifications employed for each lifestyle factor in the publications investigated.

Statistically significant data were chosen, but this only includes trends with p-values ≤ 0.05. If multiple trends in one study were statistically significant, the trend adjusted for multiple variables was chosen (i.e. adjusted for sex, age, gender, etc). In terms of risk, data with odds ratios (OR), hazards ratios (HR) and relative risk (RR) were evaluated. OR and HR are classified as estimates of RR. The RR data for all lifestyle factor categories had to have 95% confidence intervals (CIs). Prospective cohort studies, as well as case controlled studies, were used to examine the effect of the different lifestyle factors on inflammation, BC and CHD. If multiple published reports from the same study cohort were available, only the data with the most recent updated and detailed information were included. It is recognised that some large significant studies could have been excluded as a result of the implementation of the above criteria.

4.3. Data modelling

4.3.1. Introduction

As previously discussed, each lifestyle factor is expressed in a different unit. To compare the effect the different lifestyle factors have on chronic disease, they will be quantified in terms of their effects on BG. A single, easy to understand and visualise unit will be employed for the quantification known as –ets. The modelling from each lifestyle factors' original unit into –ets will now be discussed. Note that for excessive food intake, dietary fibre intake and physical exercise, the –ets model is the same for inflammation, CHD and BC. For psychological stress, moderate alcohol consumption and cigarette smoking, the –ets model is more complex and involves interlinking relationships from various studies.

All the effects of the different lifestyle factors could not always be established as a result of inconsistent data, insignificant data, or lack of data. Therefore, the lifestyle factors used for inflammation were excessive food intake, psychological stress, dietary fibre intake, moderate alcohol consumption and physical exercise. There were insufficient data available for cigarette smoking and inflammation. With BC, there were inconsistencies with the moderate alcohol consumption data. The data for the effect of cigarette smoking on BC was insignificantly small and, therefore, excluded. For CHD, all the different lifestyle factors were investigated.

The derivations of the –ets models are also part of the various articles which can be found in Appendix A, Appendix B, Appendix C and Appendix D. The relevant appendix to consult for each model will be stated at the end of each derivation.

4.3.2. Inflammation

IV. Excessive food intake

Due to CHOs being the most popular source of energy, it makes sense to quantify it in terms of $\text{—}\overset{ets}{}$. The association between the BG energy metabolised from CHOs can be expressed in terms of $\text{—}\overset{ets}{}$ as [94]:

$$\text{—}\overset{ets}{}_{CHO} = \frac{\eta_{CHO}}{\eta_{Sugar}} \times \frac{m_{CHO}}{5} = \frac{GI_{CHO} m_{CHO}}{325} \quad (1)$$

All the *GI* values are referenced to the glucose standard.

η_{CHO} and η_{Sugar} are the metabolic efficiencies of the CHO and the sugar, respectively.

GI_{CHO} is the glycaemic index and m_{CHO} is the mass of the CHO.

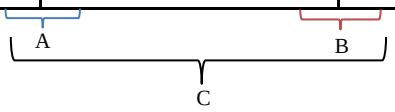
(*cf.* Appendix A, Appendix B and Appendix D)

V. Psychological stress

Research publications link hs-CRP levels to the relative risk of CHD, as illustrated in Table 2 by relationship A [99]. The relationship between psychological stress in terms of $\text{—}\overset{ets}{}$ also exist, and is shown by relationship B in Table 2 (discussed in further detail in paragraph 4.3.3 section I). With this information present, an association between psychological stress in terms of $\text{—}\overset{ets}{}$ on hs-CRP levels could be drawn, consult Table 2 link C.

Table 2: The relationship between psychological stress, hs-CRP levels and ets [164], [167], [169], [165], [166], [168], [176], [171], [172], [170]

hs-CRP (mg/L)	RR for CHD	ets Stress/day
0.6	1.2	3.0
1	1.17	2.6
1.1	1.8	12.1
2	1.7	10.6
2.2	2	15.2
3	1.31	4.7
3.8	3.56	38.8
4.5	2.6	24.3



Link A: $hs - CRP = f_1 CHD$ (2)

Link B: $CHD = f_2 ets_{Stress}$ (3)

Substituting Equation (3) into Equation (2):

Link C: $hs - CRP = f_3 ets_{Stress}$ (4)

Where f is the proportionality contant and CHD represents the RR for CHD. (*cf.* Appendix A)

VI. Dietary fibre intake

In order to establish a relationship between fibre intake and BG, fibre was added to different foods and the corresponding glucose response was measured by Jenkins [177]. Consequently it was found that when one gram of fibre is added to 50 grams of CHOs, the GI of the food was reduced by four units. This reduction is the equivalent of 0.6 —ets per gram of extra fibre added to a meal. Fibre's BG effect can now be expressed in terms of —ets $_{Fib\ added}$:

$$—ets_{Fib\ added} = 0.6 \times m_{Fib\ added} \tag{5}$$

Where $m_{Fib\ added}$ is the mass of the fibre added in grams. (*cf.* Appendix A, Appendix B and Appendix D)

VII. Physical exercise

Physical activity is often measured in metabolic equivalents (METs), which can be expressed in *kcal* ($1\ MET = 1\ \frac{kcal}{kg \times hr}$). When participating in physical exercise, approximately 20% of the energy comes from BG ($0.2 \times kcal_{Exercise}$) [178]. The energy expended during exercise ($kcal_{Exercise}$), can be translated into the BG energy expended in —ets $_{Exercise}$. There exists an established relationship between *kcal* and —ets (taken from equation (11) in [94]):

$$1—ets = E_{Teaspoon\ Sugar} = 0.65 \times 5g \times 4kcal/g = 13kcal \tag{6}$$

Resulting in:

$$—ets_{Exercise} = 0.2 \times kcal_{Exercise} \times (—ets/kcal) = 0.2 \times kcal_{Exercise} \times \frac{1}{13} = \frac{kcal_{Exercise}}{65} \tag{7}$$

$kcal_{Exercise}$ accounts for the type, duration and intensity of the exercise, and it also takes into consideration the body mass of the test subject [179]. (*cf.* Appendix A, Appendix B and Appendix D)

VIII. Moderate alcohol consumption

A number of publications investigated the effect of alcohol consumption in ethanol (g/day) and hs-CRP levels (mg/L). The results are illustrated in Table 3.

Table 3: Alcohol consumption in ethanol (g/day) and hs-CRP levels in (mg/L)

References	[143]		[140]		[140]		
Ethanol (g/day)	0	20	0	20	40	0	20
hs-CRP (mg/L)	1.63	1.25	1.39	1.3	1.09	1.29	1.25

A linear relationship is assumed between alcohol intake (*Alcohol)* and hs-CRP levels (*hs-CRP*). This is a valid assumption as only low to moderate alcohol consumption was considered. The relationship between alcohol consumption and hs-CRP levels is defined as:

$$hs - CRP = f_4 Alcohol \tag{8}$$

Now that there is a relationship between hs-CRP and alcohol, the expression of alcohol in terms of *ets* can commence. Firstly, alcohol is associated with the lowering of BG. The reduction of BG can be related to less insulin secretion. The following relationship exists between BG and insulin [94]:

$$\Delta I = f_5 \Delta BG \tag{9}$$

ΔI is the change in insulin.

ΔBG is the change in BG levels.

It is also known that that there is a direct relation between change in BG level (ΔBG) and change in $\dot{Q}_{ets}$ ($\Delta \dot{Q}_{ets}$) [180]:

$$\Delta BG = f_6 \Delta \dot{Q}_{ets} \tag{10}$$

Substituting Equation (10) into Equation (9):

$$\Delta I = f_7 \Delta \dot{Q}_{ets} \tag{11}$$

The insulin sensitivity factor f_7, has to be determined in order to link insulin to $\dot{Q}_{ets}$. To determine the insulin sensitivity factor, glucose monitors were used on eleven test subjects. After three days, measurements were obtained which could be used to determine the average insulin sensitivity. In Table 4, an indication of how the insulin sensitivity factor was calculated is given.

Table 4: Calculation of the average insulin sensitivity factor f_7

Subject	$\Delta I / \Delta$ ets
1	0.77
2	0.83
3	0.67
4	0.53
5	0.77
6	0.30
7	1.43
8	0.56
9	0.43
10	0.77
11	0.56
Average = f_7	**0.69**

The average insulin sensitivity f_7 is 0.69.

Now that there is an established relationship between insulin and ets, a correlation between alcohol consumption and insulin can be investigated. Several research publications show the effect of alcohol consumption on insulin secretion. The change in insulin secretion due to alcohol consumption is illustrated in Table 5.

Table 5: Change in insulin secretion due to alcohol consumption

References	[181]		[182]	
Ethanol (g/day)	15.0	35.0	11.4	22.9
ΔI, Reduction in insulin secretion per day (mU/l)	3.89	4.32	5.9	5.6

The relationship between alcohol consumption and change in insulin levels can therefore be expressed as:

$$\Delta I = f_8 Alcohol \tag{12}$$

The reduction in insulin secretion corresponds to an increase in BG. This can be expressed in Δ–ets by using Equation (11).

Now that these associations have been recognised, Equations (11) & (12) can be substituted into Equation (8) to give the relationship between alcohol consumption expressed in terms of –ets and hs-CRP levels:

$$hs - CRP = f_9 \text{–ets}_{Alcohol} \tag{13}$$

f_4, f_5,f_6, f_8 and f_9 refer to the proportionality constant. (*cf.* Appendix A)

4.3.3. CHD and BC

As mentioned before, the –ets model for excessive food intake, dietary fibre intake and psychological stress is the same as for inflammation. For excessive food intake, consult paragraph 4.3.2 section I, for dietary fibre intake consult paragraph 4.3.2 section VI. The model for psychological stress on CHD and BC will now be discussed as well as the moderate alcohol consumption and cigarette smoking model for CHD.

I. Psychological stress

CHD:

Several publications researched the effect of food consumption (which could be transformed into—ets) on the RR for CHD as seen in paragraph 4.3.2 section V . From this relationship, an association between chronic stress and BG can be developed. This relationship could be linearly scaled for low and medium stress to find the relationship between psychological stress in terms of —ets and the RR for CHD [99]. The relationship between psychological stress,—ets and RR for CHD can be found in Table 6. (*cf.* Appendix B)

Table 6: Relationship between psychological stress, —ets and RR for CHD

Reference	Stress level	RR for CHD	—ets /day
[164]	low	1.48	7.2
	medium	2.41	21.6
	high	4.13	50.4
[169]	high	3.21	28.7
[165]	medium	2.8	25.1
[166]	medium	2.7	24.2
[167]	low	1.26	6.1
[168]	medium	1.94	17.4
[176]	medium	2.31	20.7

BC:

A number of studies investigated the effect of psychological stress and BC, as can be seen in Table 7 . This relationship could now be linked to the relationship already established for psychological stress and the RR for CHD where stress levels are already expressed in terms

of $\overline{ets}$ (*cf.* Table 6). Utilising the $\overline{ets}$ values assigned to the different stress levels, the effect of psychological stress on BC could be established. (*cf.* Appendix D)

Table 7: The effect of stress on the RR of BC from various research publications

Reference	Stress level	RR for BC
Lillberg *et al*. 2001	Low	1.09
	High	1.25
Metcalfe *et al*. 2007	Low	1
	Medium	2.04
	High	2.14
Kruk *et al*. 2004	Low	1.24
	Medium	2
	High	3.83

II. Moderate alcohol consumption

CHD:

Published data links moderate alcohol consumption (measured in grams of ethanol per day) with a lower relative risk (*RR*) of CHD [135], [137], [136]. This is shown in Table 8, or by the following equation:

$$RR_{CHD} = f_{10}Alcohol \tag{14}$$

Table 8: Publications showing the relationship between ethanol consumption in g/day and the RR for CHD

References	[136]		[135]				[137]		
Ethanol g/d	0	22.9	0	4.9	19.9	29.9	0	5	30
RR for CHD	1	0.84	1	0.78	0.68	0.52	1	0.72	0.58

Using Equations (9), (10), (11) and (12), ethanol consumption can be related to BG through insulin secretion as discussed in paragraph 4.3.2 section VIII. Combining these equations with Equation 14, results in the following:

$$RR_{CHD} = f_{11} \cancel{ets}_{Alcohol} \tag{15}$$

Where f is the proportionality constant. (*cf.* Appendix B)

III. Cigarette smoking

CHD:

Published data indicates that there is an accurate correlation between the number of cigarettes smoked and the relative risk (RR) of CHD. A linear relationship ($R^2 = 0.75$) was assumed to facilitate easy interpretation.

Using this data, a mathematical equation describing the RR as a function of the number of cigarettes smoked per day is suggested:

$$RR_{CHD} = f_{12} Cigarettes \tag{16}$$

As adiponectin plays such a definitive role in insulin resistance, published data are also available that depict the relationship between cigarette smoking and plasma adiponectin levels, consult Table 9. This relationship can be described by the following equation:

$$\Delta Adiponectin = f_{13} Cigarettes \tag{17}$$

Table 9: Published data showing the relationship between the number of cigarettes smoked and adiponectin levels

References	[161]		[162]		[163]		
Number of cigarettes	0	25	7.5	19.5	16.5	27.1	37.7
Adiponectin (µg/ml)	11.47	8.35	8.65	8.05	8.7	7.2	5.7

The link between plasma adiponectin and fasting insulin levels can also be found from published literature and is shown in Table 10.

Table 10: Relationship between fasting insulin and adiponectin

References	[183]			[184]			[185]		
Adiponectin (µg/ml)	7.79	24.77	16.98	15	17.5	20	4.4	7.1	9.8
Insulin (µU/ml)	8.89	18.19	27.49	3.3	6.6	10	8.4	11.3	14.2

$$\Delta Adiponectin = f_{14} \Delta I \tag{18}$$

By substituting equation (17) into (18):

$$Cigarettes = f_{15}\Delta I \tag{19}$$

A linear relationship is assumed between BG production and insulin secretion as previously discussed [94].There is also a direct correlation between change in BG level and the change in—ets, [180]. And the combination of these equations provide the relationship between change in insulin and change in—ets.

Combining Equations (19) and (14):

$$Cigarettes = f_{16}\Delta\text{—ets} \tag{20}$$

Finally substituting Equation (20) into Equation (16) the following relationship is established:

$$RR_{CHD} = f_{17}\Delta\text{—ets}_{\,Cigarettes} \tag{21}$$

The data from the different publications can now be interpreted and processed by the mathematical equations derived to establish the risk of smoking on CHD through—ets.

4.4. Conclusion

The lifestyle factors are quantified in terms of their glycaemic effect using one common unit namely —ets. Quantifying lifestyle factors in terms of —ets, enables the comparison of the risk posed by each lifestyle factor. The —ets concept is state of the art, easy to understand and to visualise, especially for the non-technical person. The effect that each lifestyle factor has on inflammation, CHD and BC can now be evaluated. The data can be inserted into the corresponding —ets model and plotted against either hs-CRP, RR for CHD or RR for BC.

4.5. References

[94] Mathews EH, Pelzer R. A new model to estimate bolus insulin need. *Diabetes Technology and Therapeutics.* 2009;11(12):813-817.

[99] Mathews H, Liebenberg L. A practical quantification of blood glucose production due to high-level chronic stress. *Stress and Health*. 2012; doi:10.1002/smi.2415.

[135] Hvidtfeldt UA, Tolstrup JS, Jakobsen MU. Alcohol intake and risk of coronary heart disease in younger, middle-aged, and older adults. *Circulation*. 2010;121:1589-1597.

[136] Ikehara S, Iso H, Toyoshima H, Date C, Yamamoto A, Kikuchi S, Kondo T, Watanabe Y, Akio K, Wada , Inaba Y, Tamakoshi A. Alcohol consumption and the mortality from stroke and coronary heart disease among Japanese men and women: The Japan Cohort Study. *Stroke*. 2008;39:2936-2942.

[137] Arriola L, Martinez-Camblor P, Larranage N, Basterretxea M, Amiano P, Moreno-Iribas C, Carracedo R, Agudo A, Ardanaz E, Barricarte A, Buckland G, Cirera L, Chirlaque MD, Martinez C, Molina E, Navarro C, Quiro's JR, Rodriguez L, Sanchez MJ, Tormo MJ, Gonzalez CA, Dorronsoro M. Alcohol intake and the risk of coronary heart disease in the Spanish EPIC Cohort Study. *Heart.* 2010;96:124-130.

[140] Imhof A, Froehlich M, Brenner H, Boeing H, Pepys MB, Koenig W. Effect of alcohol consumption on systemic markers of inflammation. *Lancet*. 2001;357:763-767.

[143] Imhof A, Woodward M, Doering A, Helbecque N, Loewel H, Amouyel P, Lowe GD, Koenig W. Overall alcohol intake, beer, wine, and systemic markers of inflammation in western Europe: Results from three MONICA samples (Ausburg, Glasgow, Lille).

European Heart Journal. 2004;25:2092-2100.

[161] Tsai JS, Guo FR, Chen SC, Chiu TY, Chen CY, Hung SH, Chuang LM. Smokers show reduced circulating adiponectin levels and adiponectin mRNA expression in peripheral blood mononuclear cells. *Atherosclerosis.* 2011;218(1):168-173.

[162] Takefuji S, Yatsuya H, Tamakoshi K, Otsuka R, Wada K, Kunihiro M, Sugiura K, Hottaa Y, Mitsuhashi H, Oiso Y, Toyoshima H. Smoking status and adiponectin in healthy Japanese men and women. *Preventitive Medicine.* 2007;45(6):471-475.

[163] Estathiou SP, Skeva II, Dimas C, Dimas C, Panagiotou A, Parisi K, Tzanoumis L, Kafouri A, Bakratsas K, Mountokalakis TD. Smoking cessation increases serum adiponectin levels in apparently healthy Greek population. *Atherosclerosis*. 2009;205(2):632-636.

[164] Kubzanski LD, Kawachi I, Spiro III A, Weiss ST, Vokonas PS, Sparrow D. Is worrying bad for your heart? A prospective study of worry and coronary heart disease in the Normative Aging Study. *Circulation.* 1997;95:818-824.

[165] Einvik G, Ekeberg O, Klemsdal TO, Sandvik L, Hjerkinn EM. Physical distress is associated with cardiovascular events in a high risk population of elderly men. *BMC Cardiovascular Disorders.* 2009;9:14-20.

[166] Vogelzangs N, Seldenrijk A, Beekman ATF, van Hout HPJ, de Jonge P, Penninx BWJH. Cardiovascular disease in persons with depressive and anxiety disorders. *Journal of Affective Disorders*. 2010;125(1-3):241-248.

[167] Roest AM, Martens EJ, De Jonge P, Denollet J. Anxiety and risk of incident coronary heart disease, a meta-analysis. *Journal of the American College of Cardiology*.

2010;76(2):38-46.

[168] Versteeg H, Pedersen SS, Denollet J, Spek V. Type D personality and health status in cardiovascular disease populations: A meta-analysis of prospective studies. *European Journal of Cardiovascular Prevention and Rehabilitation.* 2011: doi:10.1177/1741826711425338.

[169] Kubzanski LD, Koenen KC. Is posttraumatic stress disorder related to development of heart disease? An update. *Cleveland Clinical Journal of Medicine*. 2009;76(2):S60-S65.

[170] Rodondi N, Marques-Vidal P, Butler J, Sutton-Tyrrell K, Cornuz J, Satterfield S, Harris T, Bauer D, Ferrucci L, Vittinghoff E, Newman AB. Markers of atherosclerosis and inflammation for prediction of coronary heart disease in older adults. *American Journal of Epidemiology*. 2010;171(5):540-549.

[171] Roivainen M, Viik-Kajander M, Palosuo T, Toivanen P, Leinonen M, Saikku P, Tenkanen L, Manninen V, Hovi T, Manttari M. Infections, inflammation, and the risk of coronary heart disease. *Circulation*. 2000;101:252-257.

[172] Koenig W. Inflammation and Coronary heart disease: An Overview. *Cardiology*. 2001;9(1):31-35.

[176] Phillips AC, Batty D, Gale CR, Deary IJ, Osborn D, MacIntyre K, Carroll D. Generalised anxiety disorder, major depressive disorder, and their comorbidity as predictors of all-cause mortality: The Vietnam experience. *Psycosomatic Medicine.* 2009;71(4):395-403.

[177] Jenkins AL, Zdravkovic U, Wursch P, Vuksan V. Depression of the glycaemic index by high levels of β-glucan Fibre in two functional foods tested in type 2 diabetes. *European Journal of Clinical Nutrition*. 2002;56(7):622-628.

[178] Noakes TD. Lore of Running. Oxford, UK: Oxford University Press; 2001.

[180] Pelzer R, Mathews EH, Liebenberg L. Preliminary application of a new bolus insulin model for type 1 diabetes. *Diabetes Technology and Therapeutics.* 2011;13(5):527-535.

[181] Kroenke CH, Chu NF, Rifai N, Spiegelman D, Hankinson SE. A cross sectional study of alcohol consumption patterns and biological markers of glycaemic control among 459 women. *Diabetes Care*. 2003;26(7):1978-1978.

[182] Greenfield JR, Samras K, Jenkins AB, Kelly P, Spector TD. Moderate alcohol consumption, estrogen replacement therapy, and physical activity are associated with increased insulin sensitivity: Is abdominal adiposity the mediator? *Diabetes Care.* 2003;26(10):2734-2740.

[183] Nayak S, Ramsingh D, Gooding S, Bissram S, Mohammed A, Raychaudhuri A, Sahadeo B, Pandohie V, Figaro K. Plasma adiponectin levels are related to obesity, inflammation and insulin in type 2 diabetic and non-diabetic Trinidadians. *Primary Care Diabetes.* 2010;4(3):187-192.

[184] Engeli S, Feldpausch M, Gorzelniak K. Association between adiponectin and mediators of inflammation in obese women. *Diabetes.* 2003;52(4):942-947.

[185] Polak J, Kobacova Z, Holst C, Verdich C, Astrup A, Blaak E. Total adiponectin and adiponectin multimeric complexes in relation to weight-loss induced improvements in insulin sensitivity in obese women: The NUGENOB Study. *European Journal of Endocrinology*. 2008;158:533-541.

5. RESULTS AND DISCUSSION

Chapter 5 provides the results and the discussion from the meta-analysis with the incorporation of the literature search strategy, the inclusion criteria as well as the derived ets models.

5.1. Introduction

The —ets models derived in Chapter 4 are now used in combination with the data from the different publications chosen using the inclusion criteria described in paragraph 4.2 to produce graphical presentations of the lifestyle effects in terms of —ets on inflammation, CHD and BC. The results are divided each time into the lifestyle factors that have a negative effect and the lifestyle factors that have a positive effect. The results are consolidated into one graph to ensure that a comparison between the effects can be drawn and that the lifestyle factor that makes the largest impact can be recognised.

A linear regression model was employed for all the data. The reason for this was to simplify the implementation and interpretation of the results. Consequently, the R^2 values obtained are relatively low, and if a second order polynomial fit was done, the R^2 values would have been better. The second order fit would, however, complicate interpretation and the effect of the lifestyle factors would not be so apparent.

It should be taken into consideration that the degree of accuracy of the results depends on the accuracy of results of the clinical studies investigated. Furthermore, the —ets model is not a perfect model. It gives an estimate of the lifestyles in terms only of their glycaemic effect. Other contributing influences are not accounted for. If the —ets model was a perfect model the BG increasing effects would be perfect mirror images of the BG lowering effects.

The results discussed in this chapter can also be found in the relevant articles which are found in Appendix A, Appendix B, Appendix C and Appendix D. The corresponding appendix will be referred to throughout Chapter 5.

5.2. Inflammation

5.2.1. Lifestyle factors that fuel inflammation

I. Excessive food intake

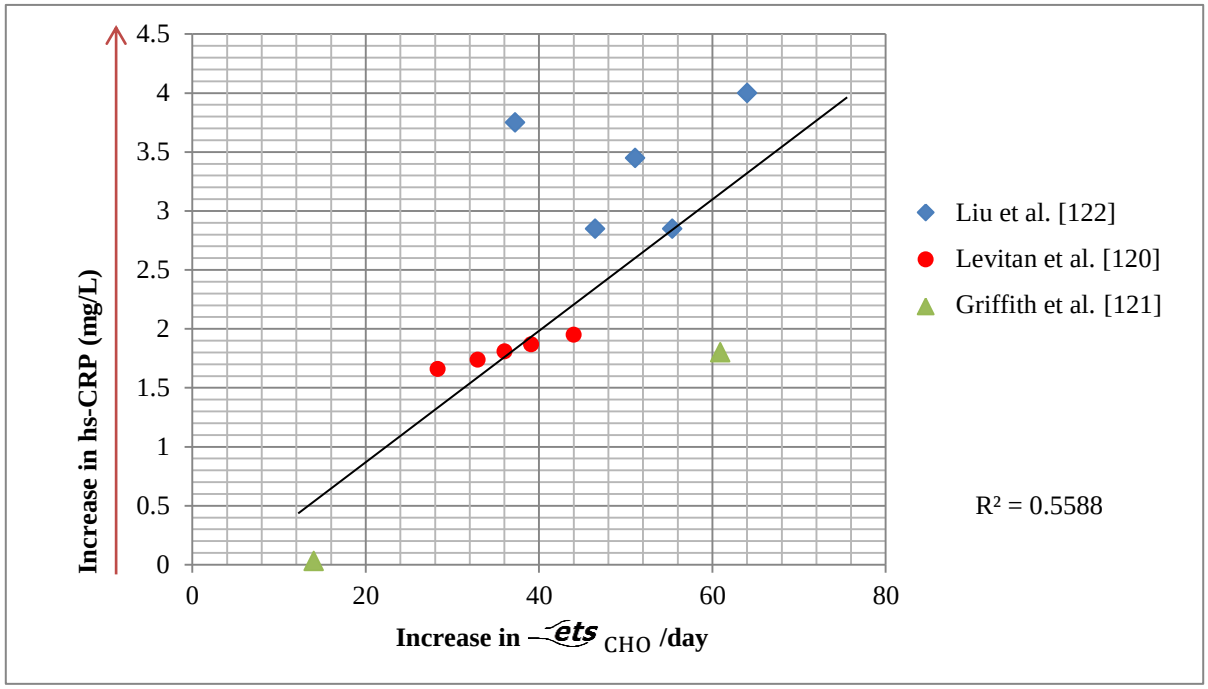


Figure 21: The linearised relationship between daily CHO consumption in terms of ETS $_{CHO}$ and hs-CRP levels from published clinical data.

The CHO ingested was transformed into ETS $_{CHO}$ and plotted against the corresponding hs-CRP levels (R^2=0.56). From Figure 21 it can be seen that hs-CRP levels increase proportionally with increasing energy (ETS $_{CHO}$) metabolised from CHO after around 28 ETS $_{CHO}$. It has been previously shown that a person's daily basal energy requirement is between 23 and 28 ETS [99], [192]. Adjusting Figure 21 for this basal energy requirement of approximately 23 ETS Figure 22 could be compiled. (*cf.* Appendix A)

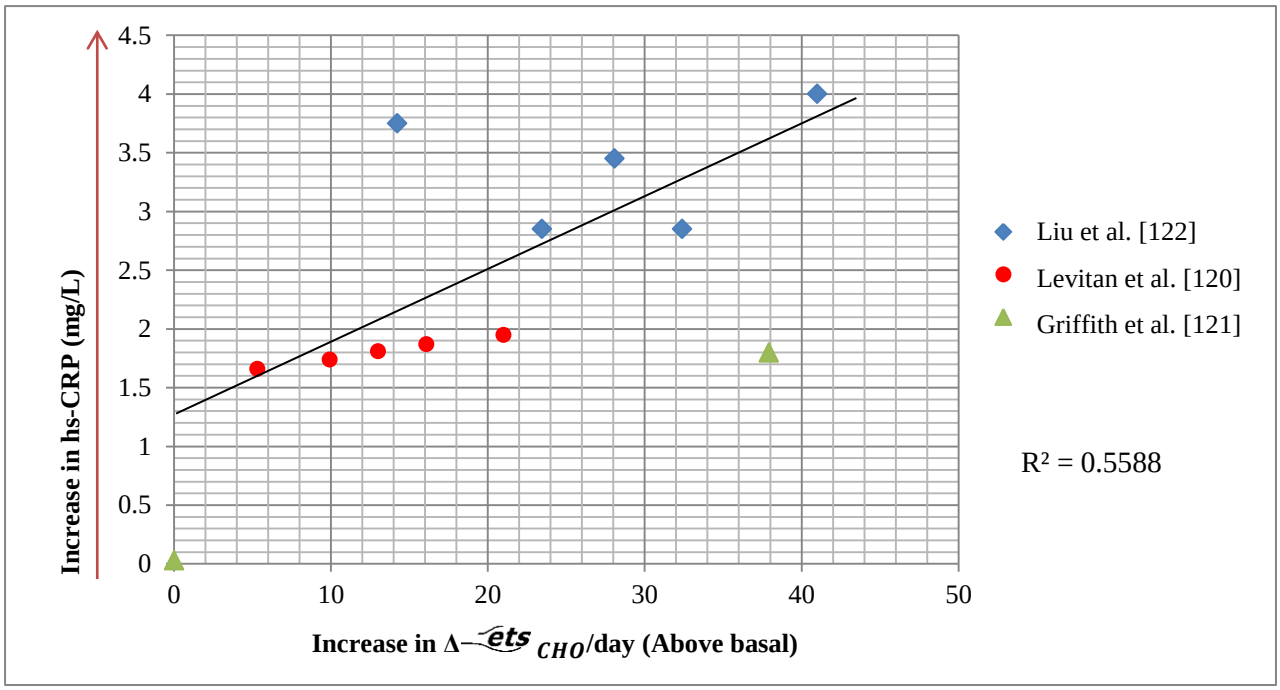


Figure 22: The relationship between excessive food intake (after adjusting for basal energy requirements) in terms of $-ets_{CHO}$ and the hs-CRP levels.

The body is considered to be in a chronic state of inflammation if the hs-CRP levels are above 3 mg/L [21]. Figure 22 shows that when consuming approximately 36 $-ets_{CHO}$ above basal requirements, which accounts for eating a medium sized fast food burger meal, a person will be in danger of entering a highly inflammatory state (hs-CRP = 3.5 mg/L). (*cf.* Appendix A)

II. Psychological stress

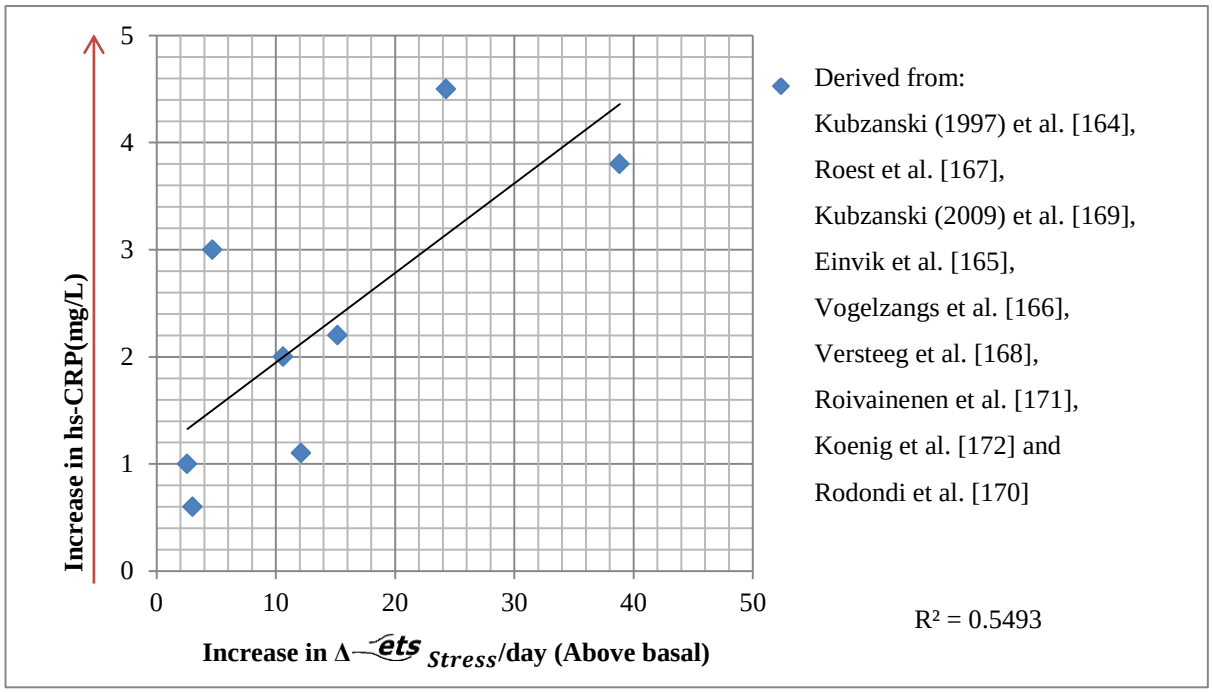


Figure 23: The effect of stress quantified in ets_{Stress} on hs-CRP levels

Plotting the values in Table 2 corresponding to the hs-CRP levels and the psychological stress in terms of ets_{Stress}, Figure 23 could be compiled ($R^2 = 0.55$).

Figure 23 suggests that with increasing levels of stress the level of hs-CRP is also increased. This suggests that stress, as suspected, fuels inflammation. Chronic inflammation hs-CRP levels is reached at a much lower ets (approximately 22 ets_{Stress}) value for stress than for excessive food intake. This indicates that psychological stress has a larger impact on inflammation than excessive food intake, and that even low to moderate levels of psychological stress (20 ets_{Stress}) can induce high levels of chronic inflammation. (*cf.* Appendix A)

5.2.2. Anti-inflammatory lifestyle factors

I. Dietary fibre intake

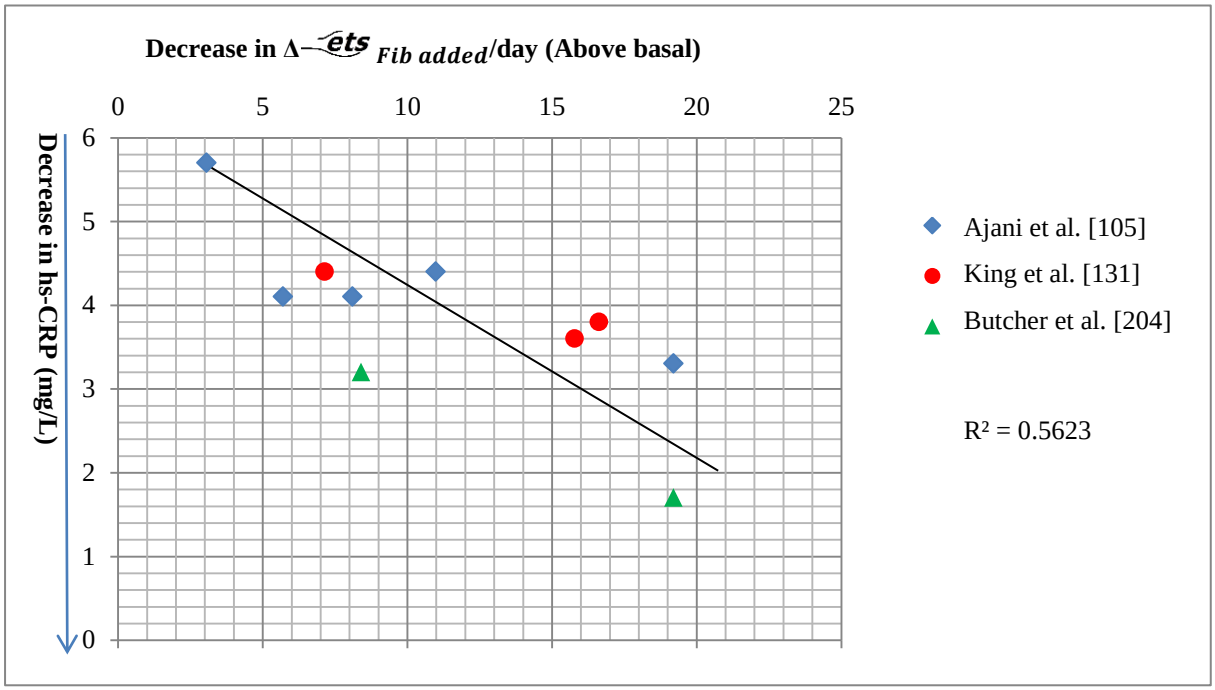


Figure 24: The linearised relationship between fibre intake in terms of $\overset{\frown}{ets}_{Fib\ added}$ and hs-CRP levels, taken from a number of published studies.

Figure 24 shows that hs-CRP levels are reduced with the increased fibre intake (expressed in terms of $\overset{\frown}{ets}_{Fib\ added}$), suggesting that dietary fibre intake can be an anti-inflammatory agent.

Note that the test subjects in these studies have initial hs-CRP levels that correspond to chronic inflammation. Even though the levels were not brought down to the normal hs-CRP level range for all of the studies, there is a clear reduction in hs-CRP levels and, therefore, inflammation. In terms of energy ($\overset{\frown}{ets}_{Fib\ added}$), it shows that by ingesting only 8.5 grams of fibre with a meal three times daily ($3 \times 8.5g \times 0.6 = 15.3 \approx 15\ \overset{\frown}{ets}_{Fib\ added}$) hs-CRP levels are reduced two-fold (hs-CRP from 5mg/L to 3mg/L). (*cf.* Appendix A)

II. Physical exercise

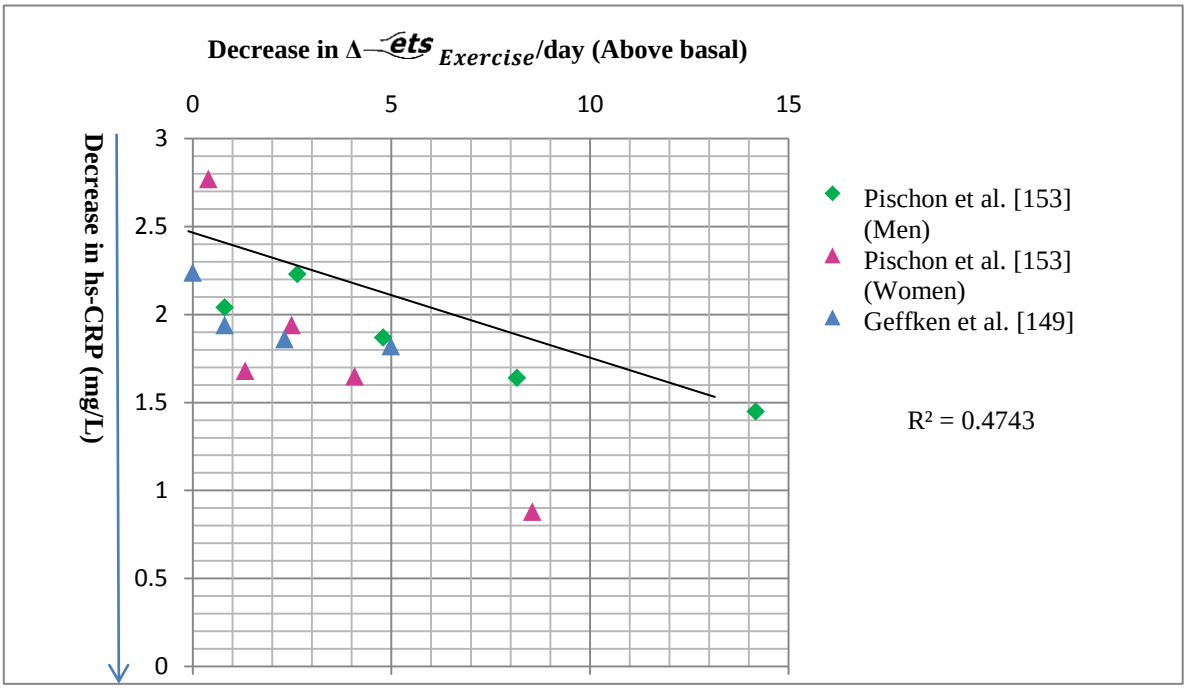


Figure 25: The linearised relationship between low to moderate intensity exercises expressed in $ets_{Exercise}$ and levels of hs-CRP for a number of published studies

Firstly it should be recognised that low to moderate intensity exercise was focussed on. This was due to the fact that this level of exercise is more practical to achieve for the ordinary person, rather than vigorous exercise. $ets_{Exercise}$ values for typical low to moderate physical activities are defined in Table 11. (*cf.* Appendix A)

Table 11: Typical $\overset{\sim}{ets}_{Exercise}$ values for low to moderate intensity of physical activities

Activity, (for a duration of 60 min)	Equivalent teaspoons sugar $\overset{\sim}{ets}_{Exercise}$ energy expended by an 70-kg male
Walking at 3 km/h	4
Cycling at 9 km/h, level road	6
Swimming (crawl)	6
Tennis	9
Walking at 6 km/h	8
Running at 11 km/h	17

In Figure 25 a linearised curve fit was once again implemented ($R^2 = 0.47$). From Figure 25 it follows that an increase in energy expended through low to moderate intensity exercise ($\overset{\sim}{ets}_{Exercise}$) induces a decrease in hs-CRP levels and inflammation. Figure 25 also suggests that by expending approximately 6 $\overset{\sim}{ets}_{Exercise}$ daily, which corresponds to around 60 minutes of swimming or cycling (at a pace of 9 km/h), hs-CRP levels can be reduced by 0.5 mg/L.

It also suggests that by participating in minimal exercise, for instance walking at a pace of 3 km/h for 60 minutes daily, a difference in hs-CRP levels and inflammation will be experienced. (*cf.* Appendix A)

III. Moderate alcohol consumption

Note that *moderate* alcohol consumption in this paper is defined as having an alcohol blood concentration of below 0.05 g /100 ml. This is the legal limit for driving in South Africa and several other countries [186]. It is assumed that one unit of alcohol will give an alcohol blood concentration of approximately 0.02 g/100 ml for an average person with a mass of 68 kg. This suggests that moderate alcohol consumption correlates to approximately two units of alcohol [187].

Table 12 shows the volume of the different beverages that corresponds to drinking two units of alcohol. Using the ets model derived in Chapter 4, the consumption of two units of alcohol in terms of $ets_{Alcohol}$ could be determined as $4\ ets_{Alcohol}$.

Table 12: Consumption of two units of alcohol, and the corresponding volumes for the different beverages [187]

Beverage	**Two units of alcohol**
Wine (12% ethanol/volume)	180 ml
Beer (5% ethanol/volume)	425 ml
Spirits (40% ethanol/volume)	50 ml

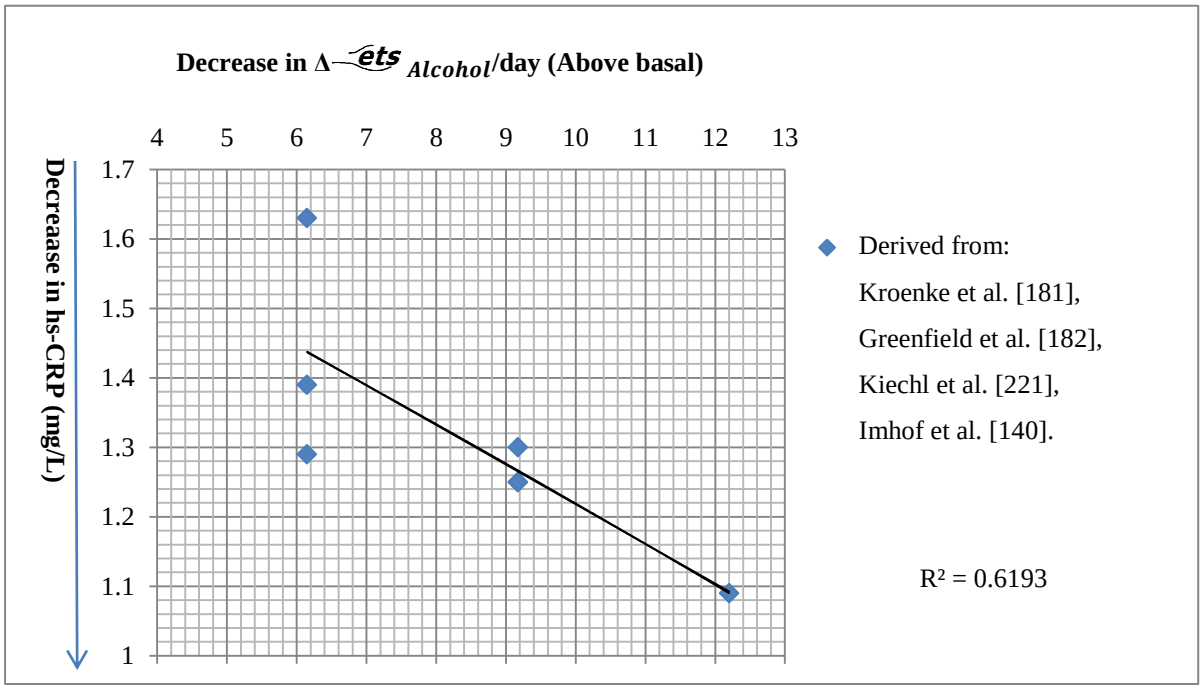


Figure 26: The effect of moderate alcohol consumption in terms of $ets_{Alcohol}$ on inflammation in terms of hs-CRP levels

Now that moderate alcohol consumption has been defined, from Figure 26 it can be deduced that moderate alcohol consumption lowers hs-CRP levels and inflammation. The practical inference from Figure 26 is that by drinking approximately one small glass of wine (125 ml) that consists of 12% alcohol (30 g ethanol = 6 $ets_{Alcohol}$), a person's hs-CRP levels can be reduced by approximately 0.32 mg/L.

As previously discussed high levels of ethanol consumption will have a negative effect on inflammation. These results however are not presented graphically, but they do suggests that when consuming 40 g of ethanol per day, (12 $ets_{Alcohol}$ or 330 ml of wine with 12% alcohol), an individual's CRP levels will start to rise [140]. (*cf.* Appendix A)

5.2.3. Consolidation of results

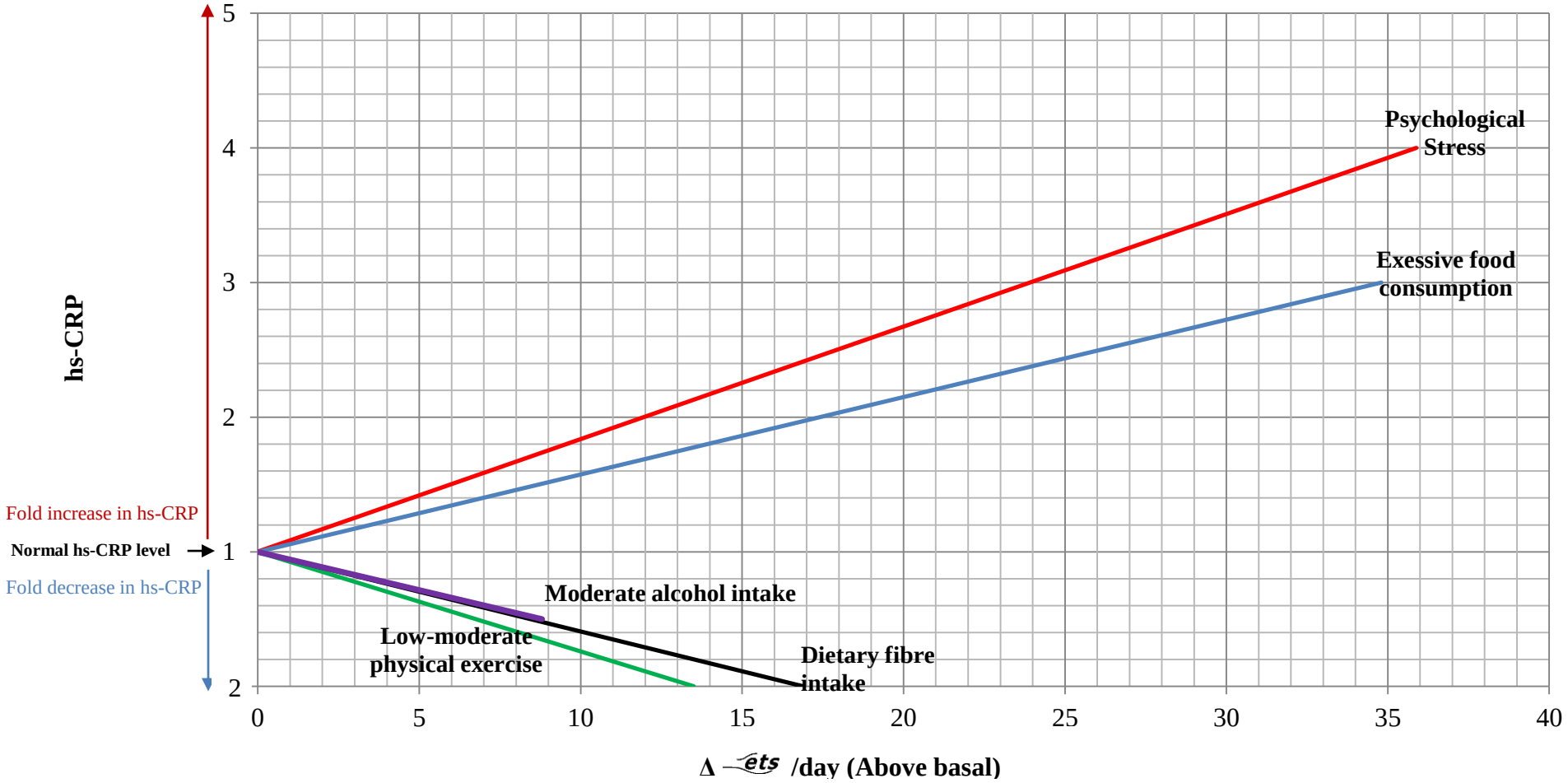


Figure 27: Consolidation of the effects of the different lifestyle factors on inflammation (hs-CRP) (*cf.* Appendix A)

Figures 20 to 25 were combined, resulting in Figure 27. The graph has been normalised to 1 on the y-axis, where 1 represents normal hs-CRP levels. To make an accurate comparison, the food graph had to be adjusted to take into consideration a person's basal energy requirements (the other lifestyle factors are already above basal energy needs). The lifestyle factors in the top half of the graph increase BG levels by the corresponding —ets value, whereas the lifestyle factors on the bottom half of the graph is responsible for reduction in BG levels by the correspondent —ets value.

From Figure 27, the five lifestyle factors can now be quantitatively compared. Stress and excessive food intake increase hs-CRP levels, which correspond to a pro-inflammatory effect. Psychological stress has a greater impact on inflammation, as well as a slightly greater glycaemic effect secreting up to 36 —ets and increasing hs-CRP levels and inflammation four-fold. Whereas excessive food intake, induces similar —ets values but increases hs-CRP levels three-fold instead of four.

Moderate alcohol consumption, dietary fibre intake and low to moderate intensity exercise decrease hs-CRP levels corresponding to a decrease in inflammation. The graphs for moderate alcohol consumption and dietary fibre intake almost have identical gradients, suggesting a similar anti-inflammatory effect. Dietary fibre, however, has a greater glycaemic effect and is responsible for lowering BG levels almost twice as much as moderate alcohol consumption, which corresponds to greater reduction in hs-CRP and inflammation.

Low to moderate intensity exercise is responsible for the largest anti-inflammatory impact, lowering hs-CRP levels rapidly. Its glycaemic effect, however, is slightly lower than that of dietary fibre intake. This suggests that exercise has other important properties, apart from its BG lowering ability, such as its aptitude to suppress the secretion of inflammatory cytokines [115] that contribute to its anti-inflammatory nature.

Due to psychological stress having the largest inflammatory impact, stress treatments should be investigated more extensively for the reduction of inflammation. With physical exercise having such an important anti-inflammatory effect, it should be more readily considered as a treatment for inflammation. Overall, the —ets model is accurate in predicting the lifestyle effects on inflammation, with BG lowering effects almost mirroring BG increasing effects.

5.3. CHD

5.3.1. Lifestyle factors which increase the risk for CHD

I. Food intake

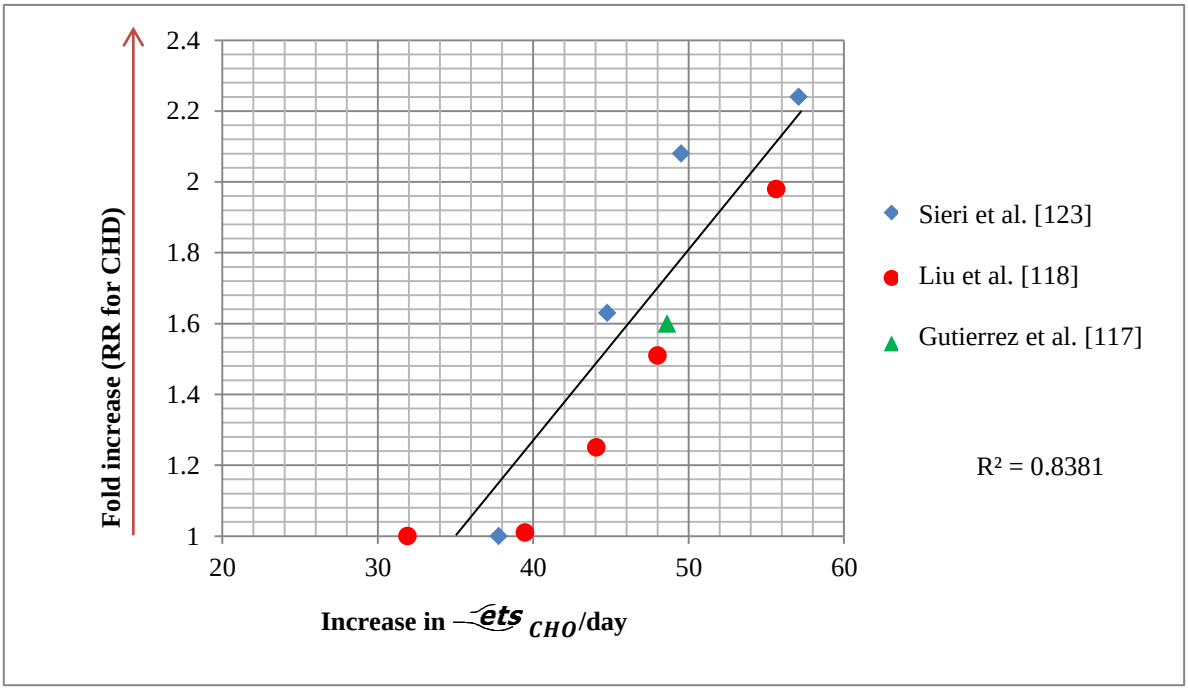


Figure 28: The effect of excessive food intake in terms of ets_{CHO} on the RR for CHD

Figure 28 (with $R^2 = 0.84$) suggests that the RR of coronary heart disease increases with BG energy metabolised from CHO as expressed in ets_{CHO}. The CHD risk starts to increase from consumption of about 36 ets_{CHO} per day. Figure 29 shows the adjustment for basal energy requirements. (*cf.* Appendix B)

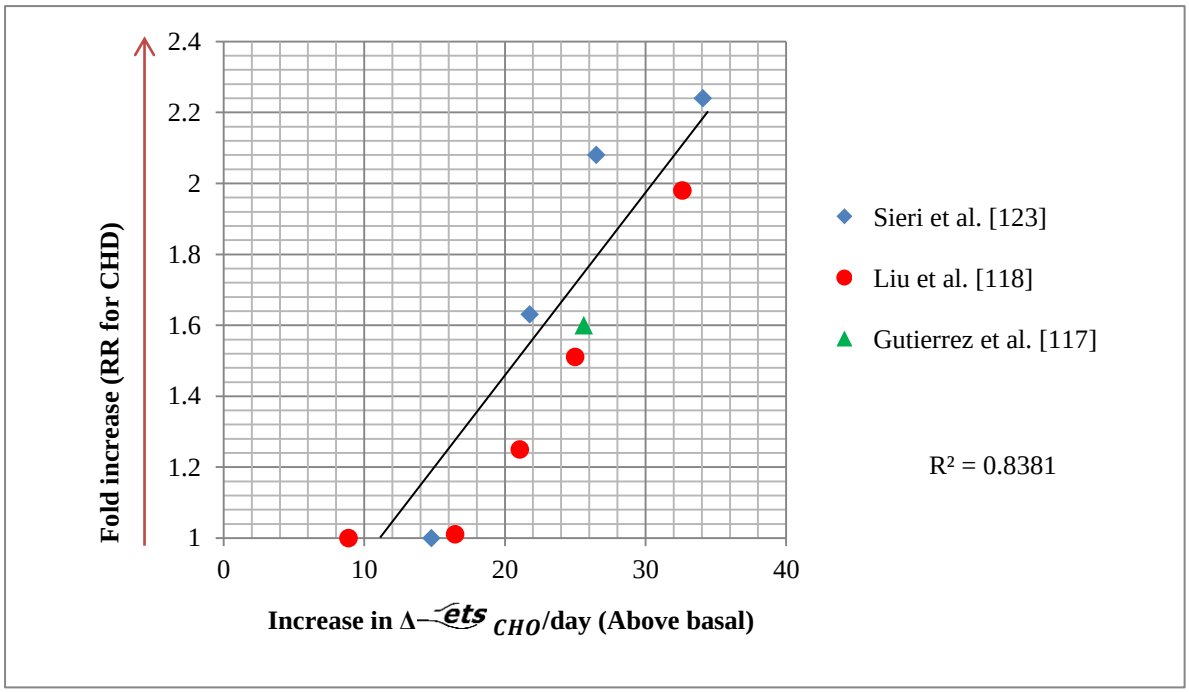


Figure 29: The relationship between the RR for CHD and the food consumed above basal requirements in terms of —ets $_{CHO}$.

From Figure 29 it is apparent that with the consumption of approximately 34 —ets $_{CHO}$ over and above basal needs, the RR for CHD more than doubles. This means that when consuming an extra medium sized burger meal (approximately 36 —ets $_{CHO}$) per day above basal needs, RR for CHD will increase more than two-fold. (*cf.* Appendix B)

II. Psychological stress

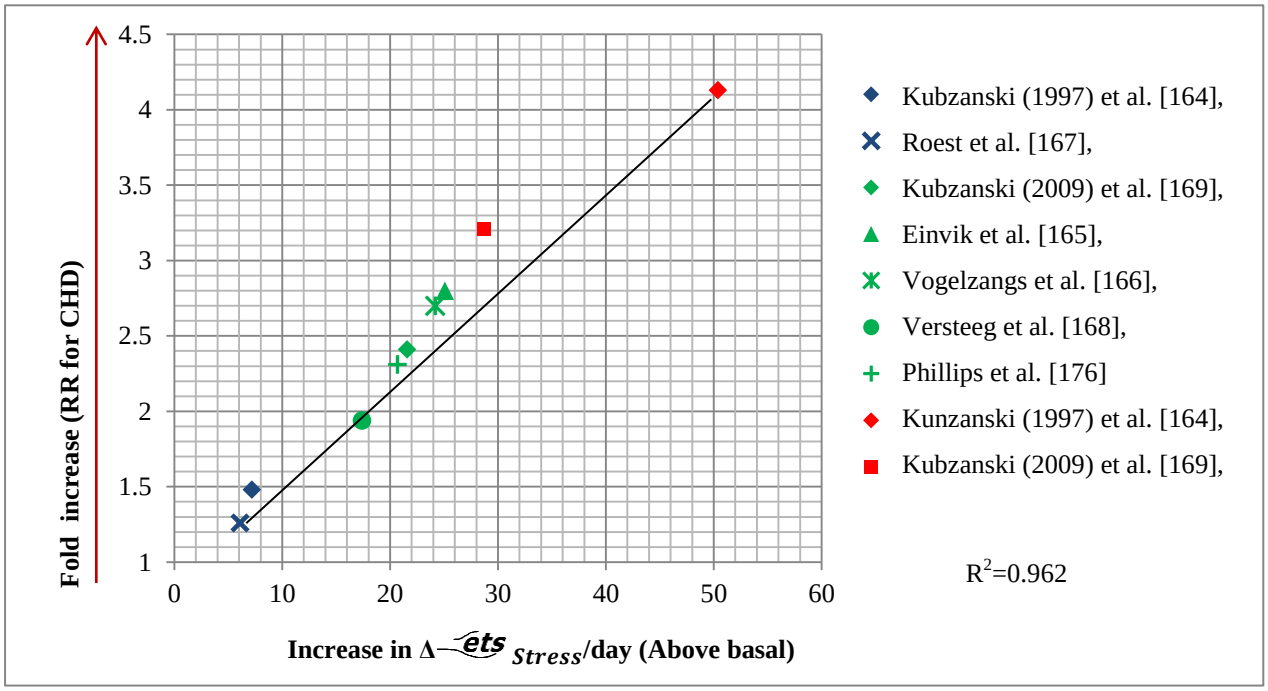


Figure 30: The effect of psychological stress in terms of ets_{Stress} on the RR for CHD

Figure 30 represents the ets_{Stress} secretion through low, moderate and high levels of psychological stress (R^2 = 0.96). The blue markers indicate low stress levels, the green markers represent moderate stress and the red markers high levels of stress. This linearised relationship suggest that with low levels of psychological stress the RR for CHD is increased by a factor of 1.5 (≈ 11 ets_{Stress}) , with medium levels (≈ 31 ets_{Stress}) of stress the RR for CHD increase almost three-fold and with high stress levels (≈ 50 ets_{Stress}) the RR for CHD are more than quadrupled.

It can be seen that psychological stress has a large impact on BG as high levels of chronic stress is responsible for the secretion of up to 50 ets_{Stress}. The ability of high psychological stress levels to increase the RR for CHD four times also shows the important role it plays in the development of CHD. Treatments for stress are, therefore, important when considering the prevention of CHD. (*cf.* Appendix B)

III. Cigarette smoking

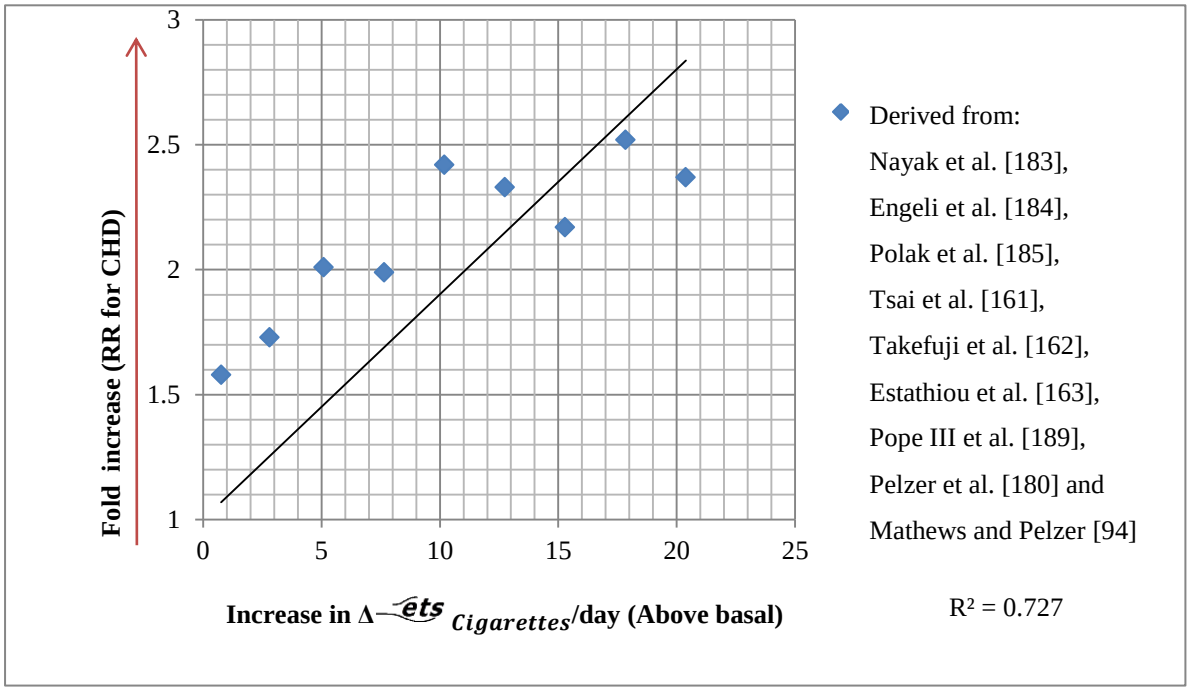


Figure 31: The effect of cigarette smoking in terms of its glycaemic effect ($\overset{ets}{}_{Cigarettes}$) on the RR for CHD

From Figure 31 it can be seen that with increasing $\overset{ets}{}_{Cigarettes}$ due to smoking cigarettes, the RR for CHD also increases as expected. It is, however, expected that smoking should have an even larger impact on the RR for CHD than the graph suggests. This shows that all the effects of smoking cannot be quantified just in terms of its BG effect. Cigarette smoking has other atherosclerotic effects, such as vasomotor dysfunction and modification of the lipid profile which are not taken into consideration in Figure 31 [188]. Figure 31, gives a good indication of the effect of smoking on BG and how elevated BG levels contribute to the development of CHD.

The practical implication of Figure 31 is that smoking 20 cigarettes a day (1 pack ≈ 12 $\overset{ets}{}_{Cigarettes}$) may cause BG levels to rise significantly, resulting in a two-fold increase in the RR for CHD. If the other atherosclerotic effects of smoking are also taken into consideration, the effects of smoking on RR for CHD would prove to be even more devastating. Cigarette smoking should be avoided at all costs, especially if a person is already at risk for developing CHD. (*cf.* Appendix C)

5.3.2. Lifestyle factors which protect against CHD

I. Dietary fibre intake

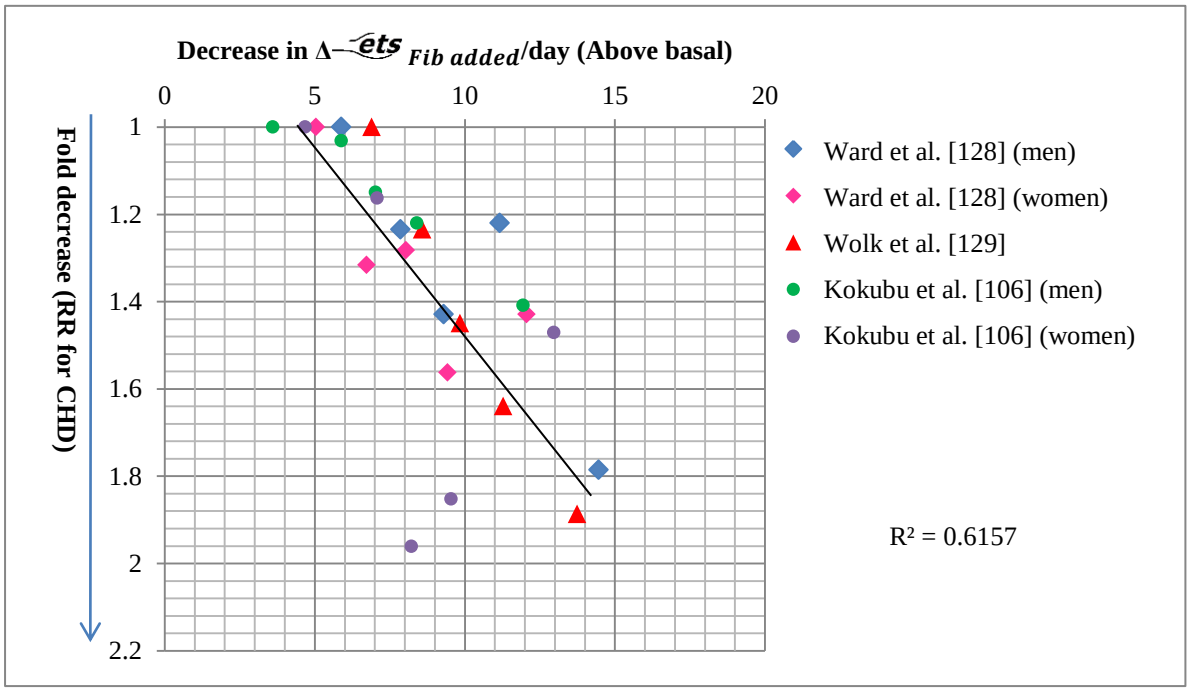


Figure 32: The effect of dietary fibre intake in terms of $\overset{ets}{\frown}_{Fib\ added}$ on the RR for CHD

The R^2 for the correlation between dietary fibre intake and relative risk for CHD is 0.62. There is an inverse association between the RR for CHD and fibre intake in terms of $\overset{ets}{\frown}_{Fib\ added}$. Practically, if one adds 8g of fibre to three meals a day ($3 \times 8g \times 0.6 = 14\ \overset{ets}{\frown}_{Fib\ added}$), the RR for CHD reduces by a factor of 1.8 (decrease in RR = 1.8). From Figure 32, it is also clear that extra fibre, equivalent to values less than 3 $\overset{ets}{\frown}_{Fib\ added}$, does not influence the RR for CHD. (*cf.* Appendix B)

II. Physical exercise

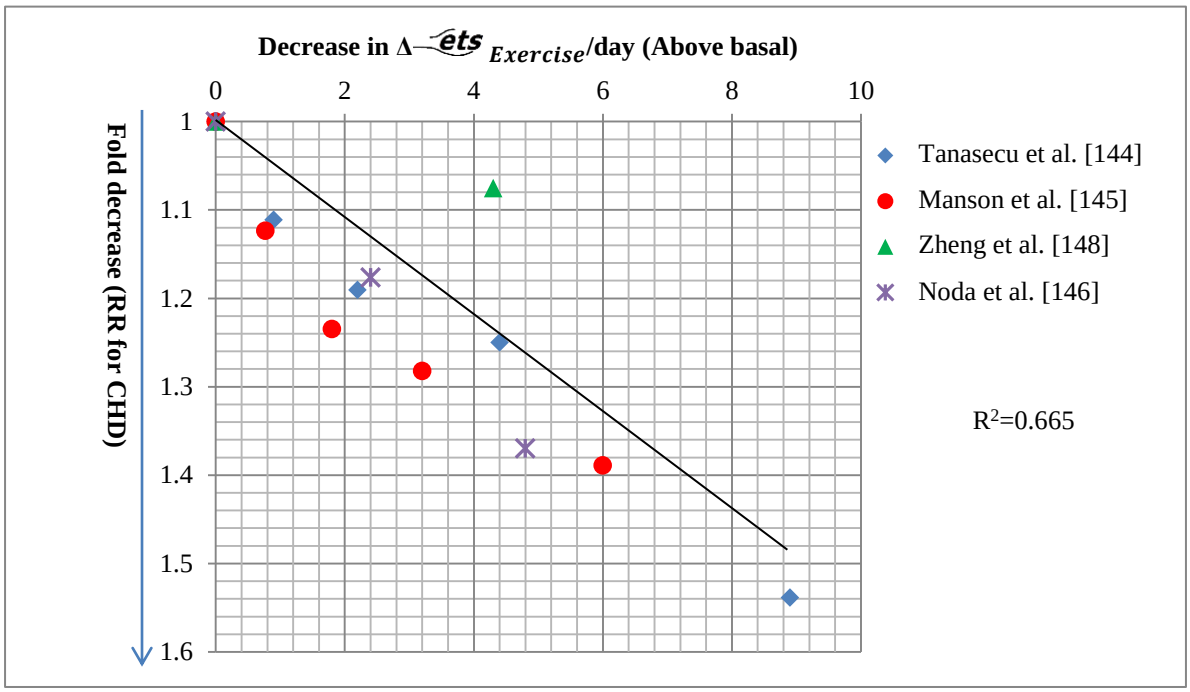


Figure 33: The effect of low to moderate physical exercise in terms of $ets_{Exercise}$ on the RR for CHD

The results from low to moderate intensity exercise studies are given in Figure 33 (R^2=0.67). From Figure 33, it can be seen that moderate intensity exercise lowers the RR for CHD. It suggests that daily moderate intensity exercise of approximately 7 $ets_{Exercise}$ reduces the risk for CHD by a factor of 1.4 (decrease in RR = 1.4). This is equivalent to approximately 60 minutes of walking at 6 km/h per day for the average person.

Physical exercise has an almost immediate RR reducing effect, unlike dietary fibre intake which only started to have an effect on the RR after the consumption of 3 $ets_{Fib\ added}$. Similar to the results of physical exercise and inflammation, Figure 33 shows that even minimal physical exercise makes a difference and reduces the RR for CHD significantly. (*cf.* Appendix B)

III. Moderate alcohol consumption

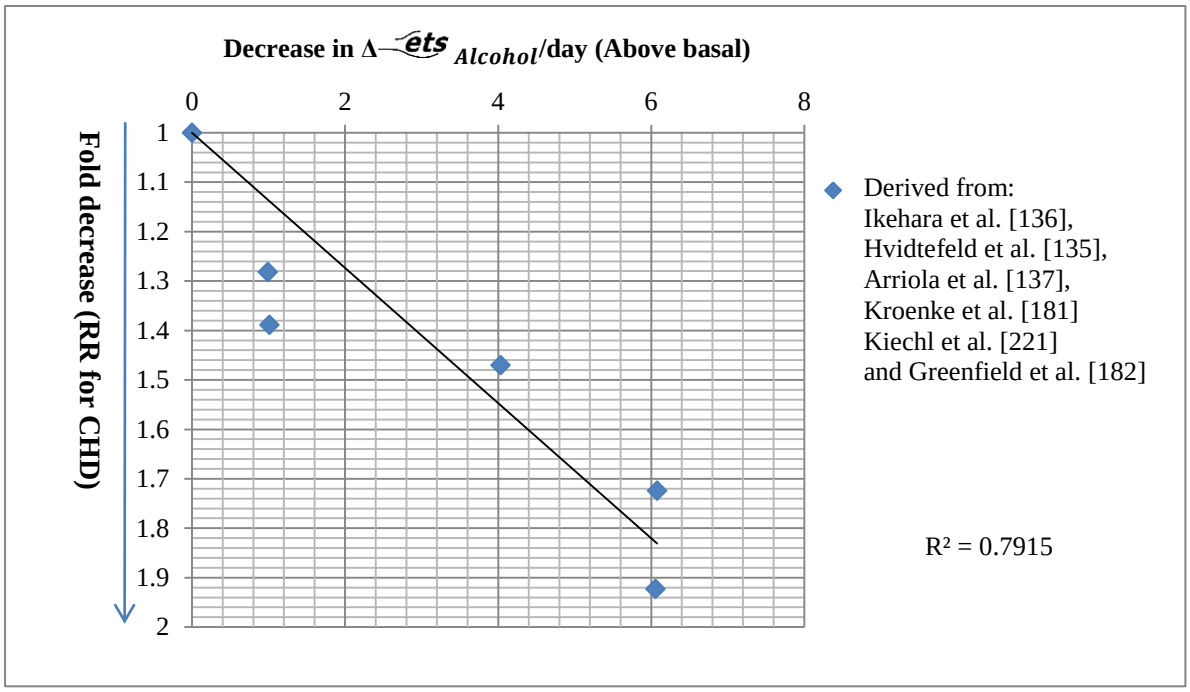


Figure 34: The effect of moderate alcohol consumption in terms of its glycaemic effect ($-ets_{Alcohol}$) on the RR for CHD

Figure 34 (with R^2 = 0.55) represents the effect of moderate alcohol intake in terms of $-ets_{Alcohol}$ on the RR for CHD. The data points which considered higher alcohol intake were discarded.

Moderate alcohol intake, defined as two units of alcohol, reduces the *RR* for CHD. If a person consumes one glass (approx. 180 ml) of dry white wine (12% ethanol per volume), it will be equivalent to 22 g of ethanol or approximately 4 $-ets_{Alcohol}$. From Figure 34, it can be seen that the RR for CHD then reduces by approximately a factor 1.55 (reduced RR = 1.55).

It is important to recognise that the BG lowering effect as well as the RR reducing effect of alcohol only accounts for *moderate* alcohol consumption and not excessive alcohol consumption. (*cf.* Appendix B)

5.3.3. Consolidated results

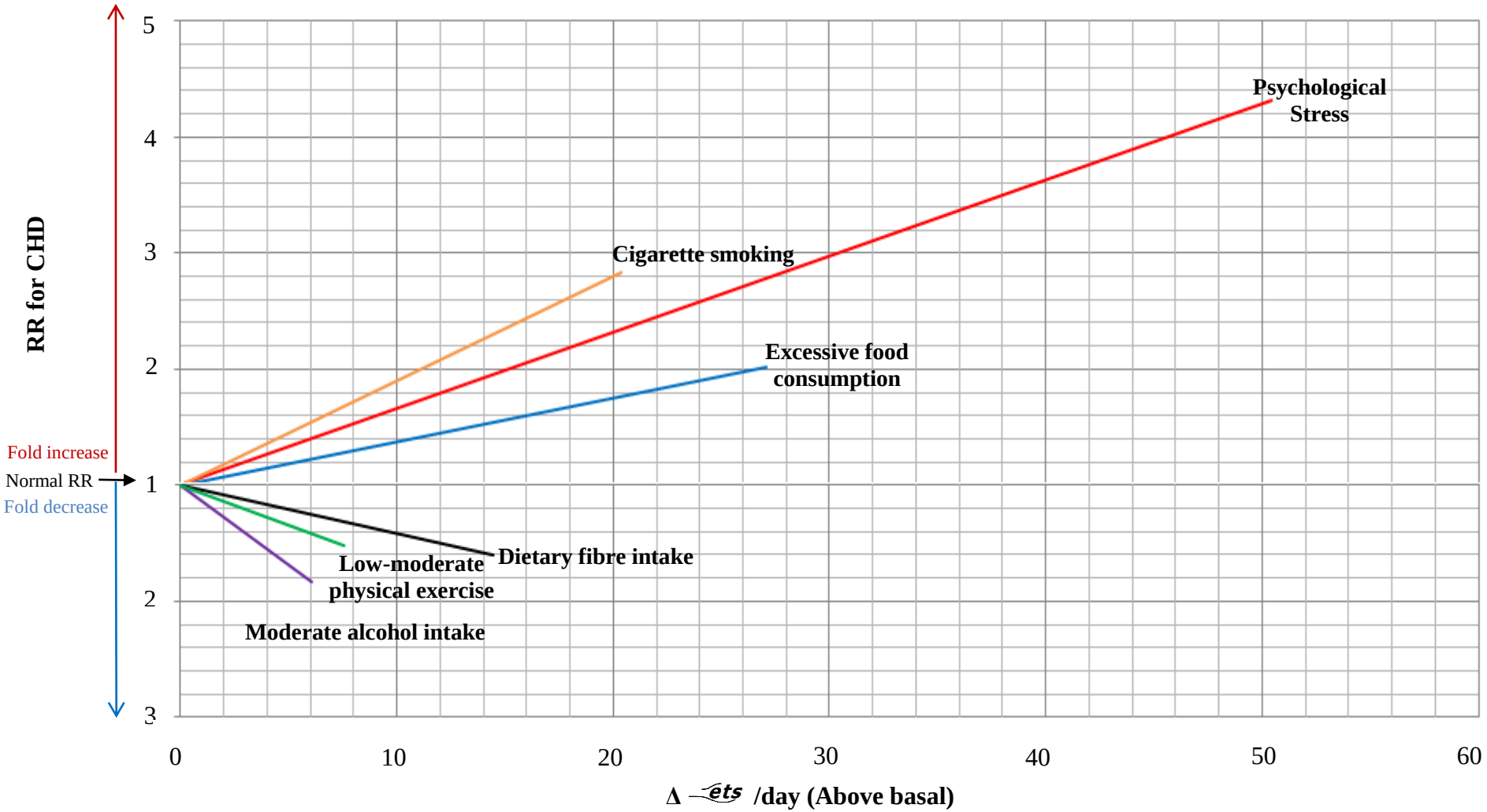


Figure 35: The consolidation of the glycaemic effect (in terms of ets) of the different lifestyle factors on the RR of CHD (*cf.* Appendix B)

Using the data from Figures 27 to 33, Figure 35 could be constructed. The graphs start at a normal relative risk (RR = 1) and show the fold increase and decrease of the relevant contributors. The food graph was, once again, adjusted for basal energy requirements.

From of Figure 35 it can be seen that psychological stress, cigarette smoking and excessive food intake is linked to an increase in RR for CHD. Psychological stress is associated with a substantial glycaemic and RR increasing effect of over four-fold, making it the greatest contributor to CHD development.

The graph for cigarette smoking has a greater gradient than that of stress and excessive food intake, suggesting that cigarette smoking has other atherosclerotic properties [188] apart from its glycaemic effect, contributing to this rapid three-fold increase in RR for CHD.

The BG lowering lifestyle factors, including dietary fibre intake, moderate alcohol consumption and low to moderate intensity exercise are associated with a reduction in RR for CHD. Moderate alcohol consumption shows the largest RR reduction (approximately two-fold), as well as the lowest glycaemic effect (lowering BG by less than 10 —ets). It, therefore, shows that moderate alcohol consumption has other anti-atherosclerotic effects such as its LDL and VLDL cholesterol lowering ability [111].

As CHD is known to be an inflammatory disease, it is interesting to compare the results from Figure 27 with that of Figure 35. A number of similarities can be observed. The general appearances of the graphs are similar with the same lifestyle factors inducing similar effects, suggesting that RR for CHD is related to inflammation.

The comparison further shows that psychological stress has the largest inflammatory and atherosclerotic effect. There are some differences comparing the bottom parts of the graphs, with the most significant difference being that moderate alcohol consumption has a larger impact than physical exercise on the RR for CHD graph. This difference can be because of two things: (1.) Inaccurate results from the clinical data used, (2.) lipid accumulation plays a key role in the development of atherosclerosis [57]. Even though lipid accumulation is important in inflammation, it is suggested to be to a lesser extent.

Physical exercise, which is associated more with anti-inflammatory properties, therefore has a larger impact on inflammation and moderate alcohol consumption with its lipid lowering abilities a larger impact on the RR for CHD.

Psychological stress treatments as well as moderate alcohol consumption should be strongly considered and further investigated for the prevention of CHD.

The *ets* model for CHD is fairly accurate with the graph gradients of the BG lowering lifestyle factors being similar to the gradients of the BG increasing gradients. It does, however, suggest that other atherosclerotic properties (apart from BG) play a role in the development of CHD.

5.4. BC

5.4.1. Lifestyle factors which increase BC risk

I. Excessive food intake

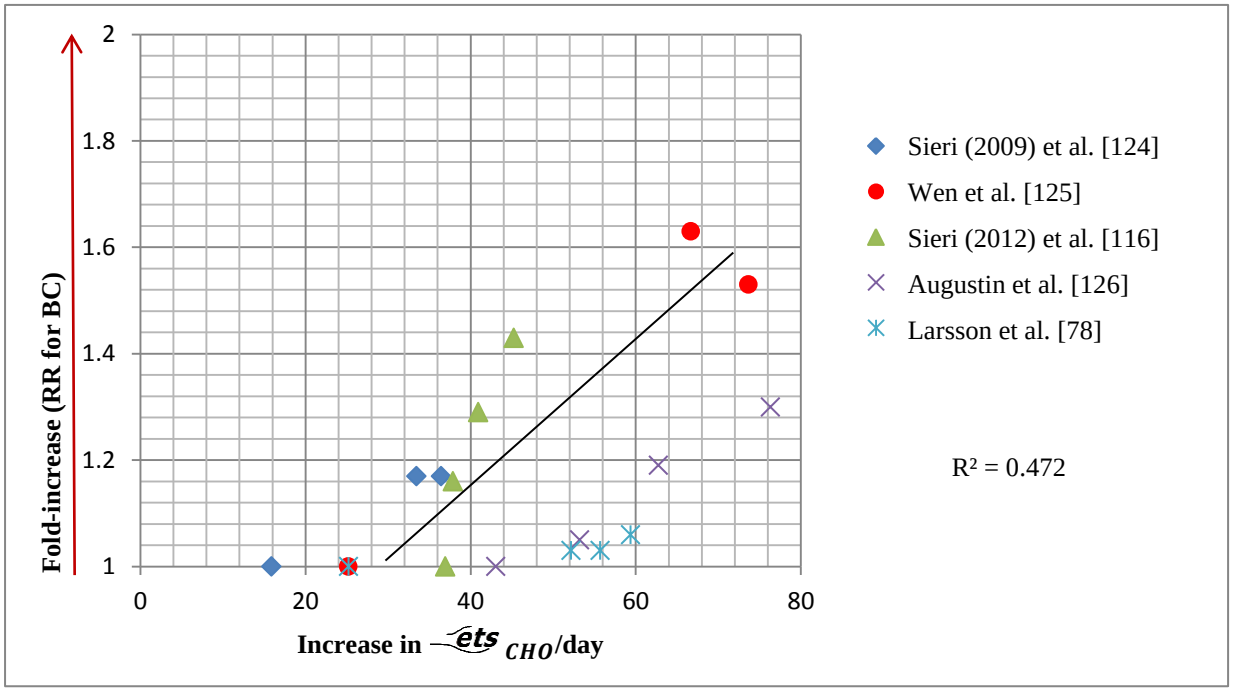


Figure 36: The effect of excessive food intake in terms of ets_{CHO} on the RR for BC.

Figure 36 implicates that with increased food intake, the RR for BC increases (R^2=0.47). The RR for BC starts to increase at around 23 ets_{CHO}, which is accurate with the assumption that a person requires approximately 23 ets_{CHO} as basal energy requirements. In Figure 37, the relationship between the above basal ets_{CHO} consumption and the RR for CHD is presented.

(*cf.* Appendix D)

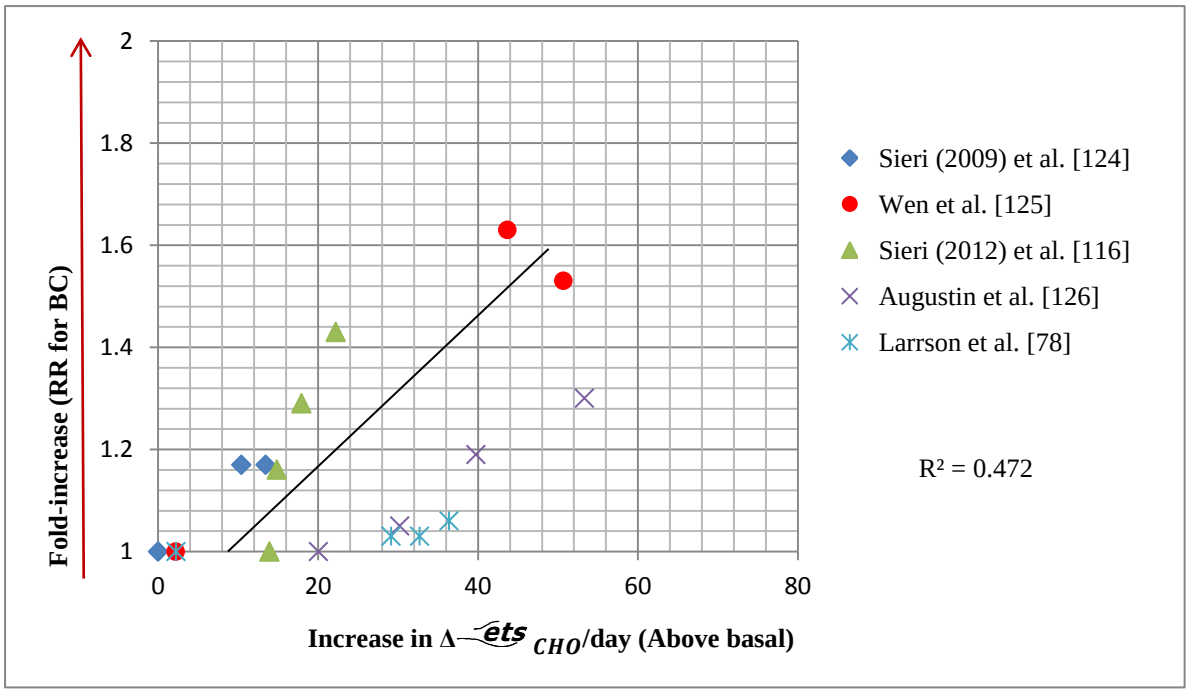


Figure 37: The linearized relationship between excessive food consumption above basal requirements in terms of $\overset{ets}{\frown}_{CHO}$ and the RR for BC

Practically, Figure 37 suggests that with consumption of an additional fast food burger meal corresponding to approximately 36 $\overset{ets}{\frown}_{CHO}$, the RR for BC increases with a factor of 1.4 (increase in RR = 1.4). Excessive food intake should be monitored especially in women who already have a family history of breast cancer. (*cf.* Appendix D)

II. Psychological stress

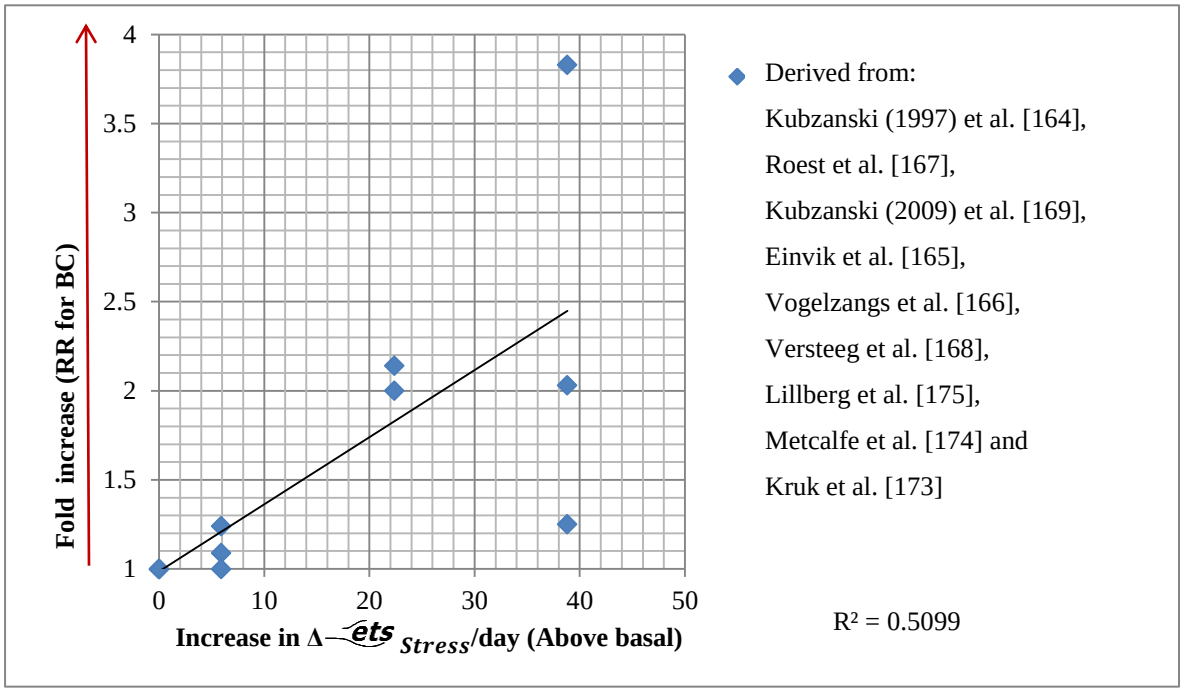


Figure 38: The impact of psychological stress in terms of —ets $_{Stress}$ on the RR for developing BC.

Psychological stress is responsible for an increase in RR for BC, as can be seen from Figure 38 (R^2 = 0.51). The glycaemic effect of psychological stress is substantial inducing —ets $_{Stress}$ values of almost 40 and a correspondent RR increase of 2.5 fold. The practical implication of Figure 38 is that low stress (≈ 11—ets $_{Stress}$) increase RR for BC by a factor of 1.5; medium levels (≈ 31—ets $_{Stress}$) are related to approximately a two-fold increase in the RR for BC, and chronic stress a 2.5 fold increase.

It is, therefore, important to keep stress levels under control and to avoid situations which induce unnecessary psychological stress, when considering the prevention of BC. (*cf.* Appendix D)

5.4.2. BC risk reducing lifestyle factors

I. Dietary fibre intake

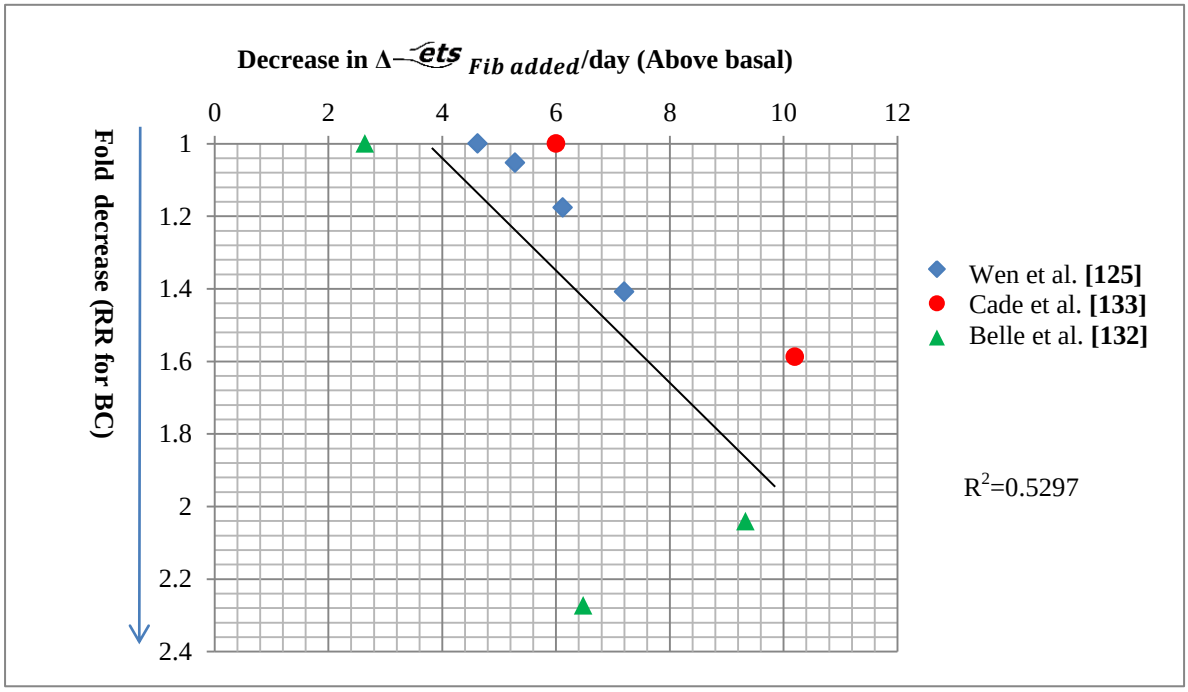


Figure 39: The glycaemic effect in terms of $ets_{Fib\ added}$ of dietary fibre intake on the RR for BC.

From Figure 39 it can be deduced that fibre intake is inversely associated with the RR for BC, (R^2 = 0.53). Fibre intake only has an impact on the RR of BC after the consumption of the equivalent of 4 $ets_{Fib\ added}$. The consumption of 10 $ets_{Fib\ added}$, which is equivalent to 5.5 g of fibre added to three meals daily, induces a two-fold reduction in RR for BC. (*cf.* Appendix D)

II. Physical exercise

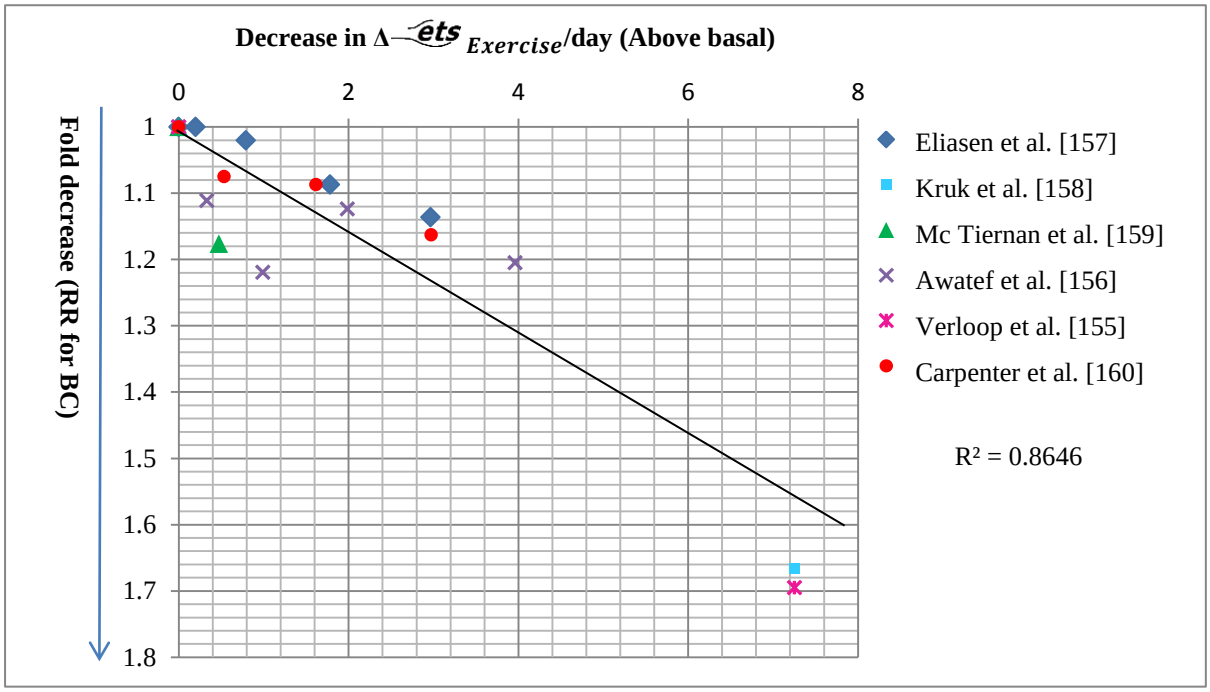


Figure 40: The effect of low to moderate physical exercise in terms of —ets $_{Exercise}$ on the RR for BC.

From Figure 40 it can be seen that there is an inverse relationship between low to moderate exercise and the RR for BC (R^2 = 0.86). Physical activity corresponding to approximately 7—ets $_{Exercise}$ (swimming or cycling at 9 km/hr for 60 minutes) reduces BC risk by factor of 1.6 (decrease in RR = 1.6). (*cf.* Appendix D)

5.4.3. Consolidated results

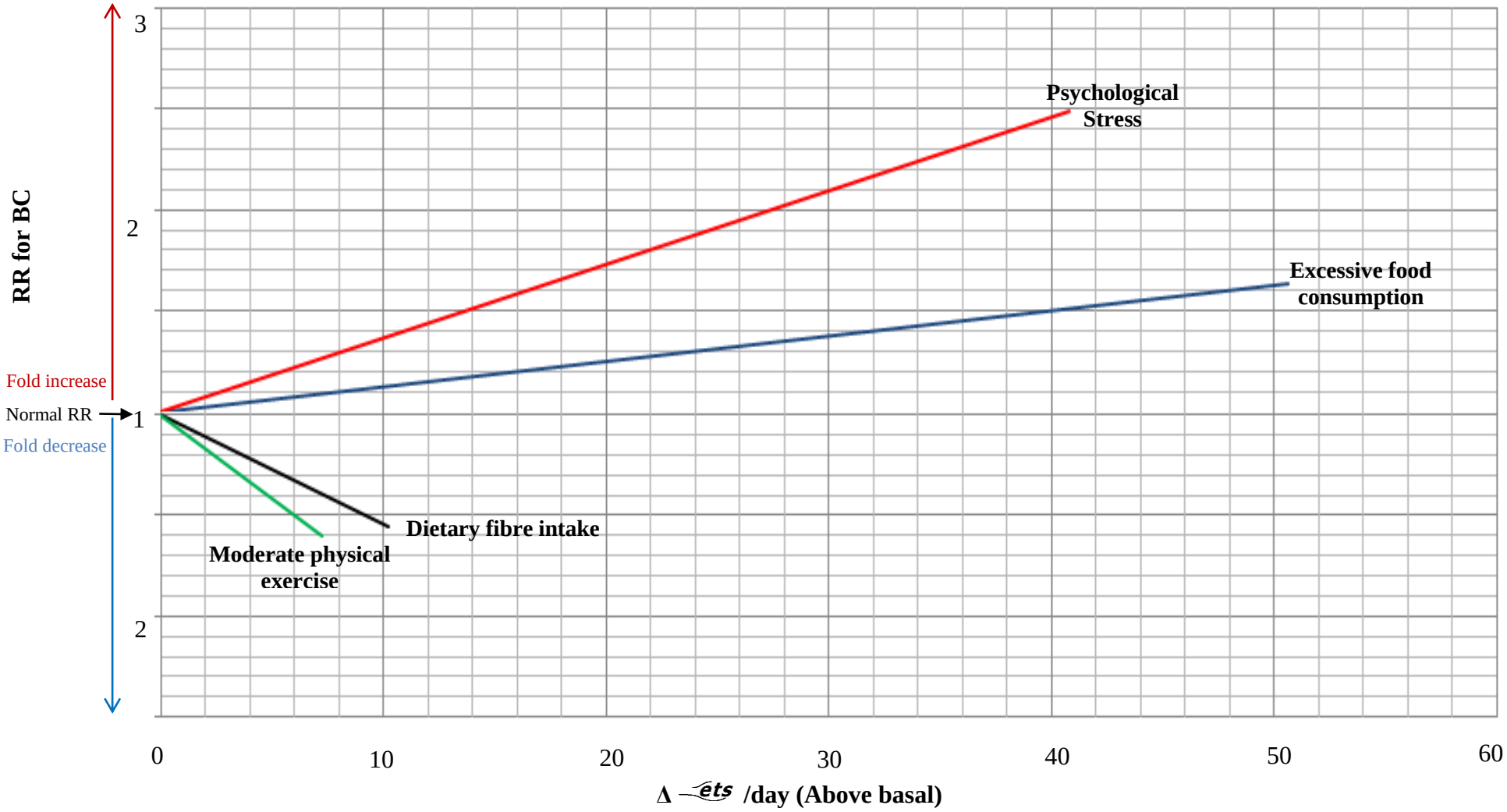


Figure 41: Consolidated effects of the different lifestyle factors on the RR for BC in terms of ets. (*cf.* Appendix D)

Consolidation of Figure 36 to Figure 40 enabled the construction of Figure 41. Psychological stress and excessive food intake increase the RR for BC and dietary fibre intake and moderate physical exercise reduce BC risk.

Psychological stress has the largest impact on carcinogenesis and the development of BC. It more than doubles the risk for BC while inducing significantly large ε_{ets} values. Excessive food consumption has a great glycaemic effect, but a lower BC risk increase than stress. This could be attributed to inconsistencies in the clinical data investigated.

Low to moderate physical exercise is related to the largest preventative effect against BC, closely followed by dietary fibre intake. Dietary fibre intake is associated with a slightly larger BG lowering effect, which suggests that low to moderate intensity exercise has other properties that contribute to its rapid reducing effect on BC risk. Both dietary fibre intake and exercise have insulin sensitising properties [103] [114]. The difference between the BC risk reductions can be attributed to the additional large anti-inflammatory effect of exercise.

Comparing the consolidated results for inflammation and the consolidated graph for BC, there are a number of similarities. This suggests that inflammation plays an important role in the development of BC, as suspected. Both graphs suggest that psychological stress is the primary negative contributor. The graphs also suggest that low to moderate intensity exercise is important in the reducing of inflammation and BC. The graphs are not identical, suggesting that inflammation is not the only contributor to BC.

Controlling stress in combination with some low moderate physical activity is suggested for pro-active prevention of BC.

The graph reflects the importance of BG in BC, but it is not a perfect model and BG is not the only contributing factor to consider in carcinogenesis and BC.

5.5. Conclusion

Lifestyle factors, such as excessive food intake, psychological stress and cigarette smoking, induce high levels of BG in terms of $\overline{ets}$. Increased BG is associated with increased levels of inflammation, RR for CHD and BC. Psychological stress has the largest pro-inflammatory effect, increasing hs-CRP levels four-fold. It is also responsible for increasing the RR for CHD and BC by the most significant amount (4.4 fold and 2.5 fold respectively).

Lifestyle factors that decrease BG levels include dietary fibre intake, moderate alcohol consumption and low to moderate intensity exercise. Lower BG levels are related to a decrease in inflammation and the risk for CHD and BC. Low intensity exercise was responsible for lowering inflammation and RR for BC (two-fold) to the greatest extent. Moderate alcohol consumption showed the greatest RR reducing effect on CHD.

The $\overline{ets}$ model proved to be the most accurate for predicting the lifestyle effects on inflammation, with the BG lowering factors almost mirroring the factors that increase BG. For CHD, the $\overline{ets}$ model was less accurate with some similarities in the opposing graph gradients, but other atherogenic properties still play a role. The $\overline{ets}$ model for BC, indicates that BG plays the least significant role out of the three models investigated. Other carcinogenic properties should be taken into consideration in the development of BC.

5.6. References

[21] Verma S, Szmitko PE, Yeh ET. C-reactive protein. *Circulation*. 2004;109:1914-1917.

[57] Hulthe J, Fagerberg B. Atherosclerosis and lipoproteins. *Arteriosclerosis, Thrombosis, and Vascular Biology*. 2002;22:1162-1167.

[78] Larsson SC, Bergkvist L, Wolk A. Glycemic load, glycemic index and breast cancer risk in a prospective cohort of Swedish women. *International Journal of Cancer.* 2009;125(1):153-157.

[94] Mathews EH, Pelzer R. A new model to estimate bolus insulin need. *Diabetes Technology and Therapeutics.* 2009;11(12):813-817.

[99] Mathews H, Liebenberg L. A practical quantification of blood glucose production due to high-level chronic stress. *Stress and Health*. 2012;doi:10.1002/smi.2415.

[103] Kendall CW, Esfahani A, Jenkins J. The link between dietary fibre and human health. *Food Hydrocolloids*. 2010;24:42-48.

[105] Ajani UA, Ford ES, Mokdad AH. Dietary fiber and C-reactive protein: Findings from National Health and Nutrition Examination Survey data. *Nutritional Epidemiology*. 2004;134:1181-1185.

[106] Kokubo Y, Iso H, Saito I, Yamagishi K, Ishihara J, Inoue M, Tsugane S. Dietary fiber intake and risk of cardiovascular disease in the Japanese population: The Japan Public Health Center-based study cohort. *European Journal of Clinical*

Nutrition. 2011;65:1233-1241.

[111] Spieker LE, Sudano I, Hürlimann D, Lerch PG, Lang MG, Binggeli C, Corti R, Ruschitzka F, Lüscher TF, Noll G. High-density lipoprotein restores endothelial function in hypercholesterolemic men. *Circulation*. 2002;105:1399-1402.

[115] Das UN. Anti-inflammatory nature of exercise. *Nutrition*. 2004;20(3):323-326.

[116] Sieri S, Krogh V, Berrino F, Evangelista A, Agnoli C, Brighenti F, Pellegrini N, Palli D, Masala G, Sacerdote C, Veglia F, Tumino R, Frasca , Grioni S, Pala V, Mattiello A, Chiodini P, Panico S. Dietary glycemic load and index and risk of coronary heart disease in a large Italian cohort. *Archives of Internal Medicine*. 2010;170(7):640-647.

[117] Gutierrez ED, Huitron-Bravo G, Talavera JO, Castanon S, Gallegos-Carrillo K, Flores Y, Salmeron J. Dietary glycemic index, dietary glycemic load, blood lipids, and coronary heart disease. *Journal of Nutrition and Metabolism*. 2010;1:1-8.

[118] Liu S, Willett WC, Stampfer MJ, Hu FB, Franz M, Sampson L, Hennekens CH, Manson J. A prospective study of dietary glycemic load, carbohydrate intake, and risk of coronary heart disease in US women. *American Journal of Nutrition*. 2000;71(6):1455-1461.

[120] Levitan EB, Cook NR, Stampfer MJ, Ridker PR, Rexrode KM, Buring JE, Manson JE, Liu S. Dietary glycemic index, dietary glycemic load, blood lipids, and C-reactive protein. *Metabolism Clinical and Experimental*. 2008;57:437-443.

[121] Griffith JA, Ma Y, Chasan-Taber L, Olendzki BC, Chiriboga DE, Stanek III EJ, Merriam PA, Ockene IS. Association between dietary glycemic index, glycemic

load, and high-sensitivity C-reactive protein. *Nutrition.* 2008;24:401-406.

[122] Liu S, Manson JE, Buring JE, Stampfer MJ, Willett WC, Ridker PM. Relation between a diet with a high glycemic load and plasma concentrations of high-sensitivity C-reactive protein in middle-aged women. *The American Journal of Clinical Nutrition.* 2001;75:92-98.

[123] Sieri S, Pala V, Brighenti F, Pellegrini N, Muti P, Micheli A, Evangelista A, Grioni S, Contiero P, Berrino F, Krogh V. Dietary glycemic index, glycemic load, and the risk of breast cancer in an Italian prospective cohort study. *American Journal of Clinical Nutrition.* 2007;86:1160-1166.

[124] Sieri S, Pala V, Brighenti F, Agnoli C, Grioni S, Berrino F, Scazzina F, Palli D, Masala G, Vineis P, Sacerdote C, Tumino R, Giurdanella M, Mattiello A, Panico S, Krogh V. cohort, High glycemic diet and breast cancer occurrence in the Italian EPIC. *Nutrition, Metabolism and Cardiovascular Diseases*. 2012; doi:10.1016/j.numecd.

[125] Wen W, Shu XO, Li H, Yang G, Ji BT, Cai H, Gao YT, Zheng W. Dietary carbohydrates, fiber, and breast cancer risk in Chinese women. *Clinical Nutrition*. 2009;89:283-289.

[126] Augustin LS, Maso LD, LaVecchia C, Parpinel M, Negri E, Vaccarell S, Kendall CW, Jenkins DJ, Franceschi S. Dietary glycemic index and glycemic load, and breast cancer risk: A case-control study. *Annals of Oncology*. 2001;12(11):1533-1538.

[128] Ward H, Keogh , Lentjes M, Luben R, Wareham N, Khaw K. Fibre intake in relation to serum total cholesterol levels and CHD risk: A comparison of dietary

assessment methods. *European Journal of Clinical Nutrition.* 2011;66:296-304.

[129] Wolk A, Manson JE, Stampfer MJ, Colditz GA, Hu FB, Speizer FE, Hennekens CH, Willett WC. Long-term intake of dietary fiber and decreased risk of coronary heart disease among women. *Journal of American Medical Association*. 1999;281(21):1998-2004.

[131] King DE, Egan BM, Woolson RF, Mainous III AG, Al-Solaiman Y, Jesri A. Effect of a high-fibre diet vs a fibre-supplemented diet on C-reactive protein level. *Archives of Internal Medicine*. 2007;167(5):502-506.

[132] Belle FN, Kampman , Mc Tiernan A, Bernstein L, Baumgartner K, Baumgartner R, Ambs A, Ballard-Barbash R, Neuhouser ML. Dietary fibre, carbohydrates, glycemic index, and glycemic load in relation to breast cancer prognosis in the HEAL Cohort. *Cancer Epidemiol Biomarkers and Prevention*. 2011;20:890-899.

[133] Cade JE, Burley VJ, Greenwood DC. Dietary fibre and risk of breast cancer in the UK Women's Cohort Study. *International Journal of Epidemiology.* 2007;36(2):431-438.

[135] Hvidtfeldt UA, Tolstrup JS, Jakobsen MU. Alcohol intake and risk of coronary heart disease in younger, middle-aged, and older adults. *Circulation.* 2010;121:1589-1597.

[136] Ikehara S, Iso H, Toyoshima H, Date C, Yamamoto A, Kikuchi S, Kondo T, Watanabe Y, Akio K, Wada , Inaba Y, Tamakoshi A. Alcohol consumption and the mortality from stroke and coronary heart disease among Japanese men and women: The Japan Cohort Study. *Stroke.* 2008;39:2936-2942.

[137] Arriola L, Martinez-Camblor P, Larranage N, Basterretxea M, Amiano P, Moreno-Iribas C, Carracedo R, Agudo A, Ardanaz E, Barricarte A, Buckland G, Cirera L, Chirlaque MD, Martinez C, Molina E, Navarro C, Quiro's JR, Rodriguez L, Sanchez MJ, Tormo MJ, Gonzalez CA, Dorronsoro M. Alcohol intake and the risk of coronary heart disease in the Spanish EPIC cohort study. *Heart.* 2010;96:124-130.

[140] Imhof A, Froehlich M, Brenner H, Boeing H, Pepys MB, Koenig W. Effect of alcohol consumption on systemic markers of inflammation. *Lancet.* 2001;357:763-767.

[143] Imhof A, Woodward M, Doering A, Helbecque N, Loewel H, Amouyel P, Lowe GD, Koenig W. Overall alcohol intake, beer, wine, and systemic markers of inflammation in western Europe: Results from three MONICA samples (Ausburg, Glasgow, Lille). *European heart journal*. 2004;25:2092-2100.

[144] Tanasescu M, Leitzmann MF, Rimm EB, Willet WC, Stampfer MJ, Hu FB. Exercise type and intensity in relation to coronary heart disease in men. *Journal of the American Medical Association.* 2002;288:1994-2000.

[145] Manson JA, Hu FB, Rich-Edwards JW, Colditz GA, Stampfer MJ, Willet WC. A prospective study of walking as compared with vigorous exercise in the prevention of coronary heart disease in women. *New England Journal of Medicine*. 1999;341:650-658.

[146] Noda H, Iso H, Toyoshima H, Date C, Yamamoto A, Kikuchi S, Koizumi A, Kondo T, Watanabe Y, Wada Y, Inaba Y, Tamakoshi A. Walking and sports participation and mortality from coronary heart disease and stroke. *Journal of the American College of Cardiology.* 2005;46(9):1761-1767.

[147] Sesso HD, Paffenbarger RS. Physical activity and coronary heart disease in men: The Harvard Alumni Health Study. *Circulation.* 2000;102:975-980.

[148] Zheng H, Orsini N, Amin J, Wolk A, Nguyen VTT, Ehrlich F. Quantifying the dose-response of walking in reducing coronary heart disease risk: Meta-analysis. *European Journal of Epidemiology*. 2009;24(4):181-192.

[149] Geffken DF, Cushman M, Burke GL, Polak JF, Sakkinen PA, Tracy RP. Association between physical activity and markers of inflammation in a healthy elderly population. *American Journal of Epidemiology*. 2001;153(3):242-250.

[153] Pischon T, Hankinson SE, Hotamisligil GS, Rifai N, Rimm EB. Leisure-TimePhysical activity and reduced plasma levels of obesity-related inflammatory markers. *Obesity Research*. 2003;11(9):1055-1064.

[155] Verloop J, Rookus MA, van der Kooy K, van Leeuwen FE. Physical activity and breast cancer risk in women aged 20–54 years. *Journal of the National Cancer Institute.* 2000;92(2):128-135.

[156] Awatef M, Olfa G, Rim C, Asma K, Kacem M, Makram H, Leila BF, Amel L, Slim AB. Physical activity reduces breast cancer risk: A case-control study in Tunisia. *Cancer Epidemiology*. 2011;35:540-544.

[157] Eliassen AH, Hankinson SE, Rosner B, Holmes MD, Willett WC. Physical activity and risk of breast cancer among postmenopausal women. *Archives of Internal Medicine.* 2010;170(19):1758-1764.

[158] Kruk J. Lifetime physical activity and the risk of breast cancer: A case control study. *Cancer Detection and Prevention*. 2007;3:18-28.

[159] Mc Tiernan A, Kooperberg C, White E, Wilcox S, Coates R, Adams-Campbell LL, Woods N, Ockene J. Recreational physical activity and risk for breast cancer in postmenopausal women. *Journal of the American Medical Association*. 2003;290:1331-1336.

[161] Tsai JS, Guo FR, Chen SC, Chiu TY, Chen CY, Hung SH, Chuang LM. Smokers show reduced circulating adiponectin levels and adiponectin mRNA expression in peripheral blood mononuclear cells. *Atherosclerosis.* 2011;218(1):168-173.

[162] Takefuji S, Yatsuya H, Tamakoshi K, Otsuka R, Wada K, Kunihiro M, Sugiura K, Hottaa Y, Mitsuhashi H, Oiso Y, Toyoshima H. Smoking status and adiponectin in healthy Japanese men and women. *Preventitive medicine*. 2007;45(6):471-475.

[163] Estathiou SP, Skeva II, Dimas C, Dimas C, Panagiotou A, Parisi K, Tzanoumis L, Kafouri A, Bakratsas K, Mountokalakis TD. Smoking cessation increases serum adiponectin levels in apparently healthy Greek population. *Atherosclerosis*. 2009;205(2):632-636.

[164] Kubzanski LD, Kawachi I, Spiro III A, Weiss ST, Vokonas PS, Sparrow D. Is worrying bad for your heart? A prospective study of worry and coronary heart disease in the Normative Aging Study. *Circulation*. 1997;95:818-824.

[165] Einvik G, Ekeberg O, Klemsdal TO, Sandvik L, Hjerkinn EM. Physical distress is associated with cardiovascular events in a high risk population of elderly men. BMC *Cardiovascular Disorders*. 2009;9:14-20.

[166] Vogelzangs N, Seldenrijk A, Beekman ATF, van Hout HPJ, de Jonge P, Penninx BWJH. Cardiovascular disease in persons with depressive and anxiety disorders. *Journal of Affective Disorders*. 2010;125(1-3):241-248.

[167] Roest AM, Martens EJ, De Jonge P, Denollet J. Anxiety and risk of incident coronary heart disease, a meta-analysis. *Journal of the American College of Cardiology.* 2010;76(2):38-46.

[168] Versteeg H, Pedersen SS, Denollet J, Spek V. Type D personality and health status in cardiovascular disease populations: A meta-analysis of prospective studies. *European Journal of Cardiovascular Prevention and Rehabilitation.* 2011: doi: 10.1177/1741826711425338.

[169] Kubzanski LD, Koenen KC. Is posttraumatic stress disorder related to development of heart disease? An update. *Cleveland Clinical Journal of Medicine*. 2009;76(2):S60-S65.

[170] Rodondi N, Marques-Vidal P, Butler J, Sutton-Tyrrell K, Cornuz J, Satterfield S, Harris T, Bauer D, Ferrucci L, Vittinghoff E, Newman AB. Markers of atherosclerosis and inflammation for prediction of coronary heart disease in older adults. *American Journal of Epidemiology*. 2010;171(5):540-549.

[171] Roivainen M, Viik-Kajander M, Palosuo T, Toivanen P, Leinonen M, Saikku P, Tenkanen L, Manninen V, Hovi T, Manttari M. Infections, inflammation, and the risk of coronary heart disease. *Circulation.* 2000;101:252-257.

[172] Koenig W. Inflammation and coronary heart disease: An overwiew. *Cardiology*. 2001;9(1):31-35.

[173] Kruk J, Aboul-Enein HY. Psychological stress and the risk of breast cancer a case–control study. *Cancer Detection and Prevention*. 2004;28:399-408.

[174] Metcalfe C, Smith GD, Macleod J, Hart C. The role of self-reported stress in the development of breast cancer and prostate cancer: A prospective cohort study of employed males and females with 30 years of follow-up. *European Journal of Cancer.* 2007;43:1060-1065.

[175] Lillberg K, Verkasalo PK, Kaprio J, Teppo , Helenius H, Koslenvuo M. Stress of daily activities and risk of breast cancer: A prospective cohort study in Finland. *International Journal of Cancer*. 2001;91:888-893.

[176] Phillips AC, Batty D, Gale CR, Deary IJ, Osborn D, MacIntyre K, Carroll D. Generalised anxiety disorder, major depressive disorder, and their comorbidity as predictors of all-cause mortality: The Vietnam experience. *Psycosomatic Medicine.* 2009;71(4):395-403.

[180] Pelzer R, Mathews EH, Liebenberg L. Preliminary application of a new bolus insulin model for type 1 diabetes. *Diabetes Technology and Therapeutics.* 2011;13(5):527-535.

[181] Kroenke CH, Chu NF, Rifai N, Spiegelman D, Hankinson SE. A cross sectional study of alcohol consumption patterns and biological markers of glycaemic control among 459 women. *Diabetes Care*. 2003;26(7):1978-1978.

[182] Greenfield JR, Samras K, Jenkins AB, Kelly P, Spector TD. Moderate alcohol consumption, estrogen replacement therapy, and physical activity are associated with increased insulin sensitivity: Is abdominal adiposity the mediator? *Diabetes*

Care. 2003;26(10):2734-2740.

[183] Nayak S, Ramsingh D, Gooding S, Bissram S, Mohammed A, Raychaudhuri A, Sahadeo B, Pandohie V, Figaro K. Plasma adiponectin levels are related to obesity, inflammation and insulin in type 2 diabetic and non-diabetic Trinidadians. *Primary Care Diabetes.* 2010;4(3):187-192.

[184] Engeli S, Feldpausch M, Gorzelniak K. Association between Adiponectin and mediators of inflammation in obese women. *Diabetes.* 2003;52(4):942-947.

[185] Polak J, Kobacova Z, Holst C, Verdich C, Astrup A, Blaak E. Total adiponectin and adiponectin multimeric complexes in relation to weight-loss induced improvements in insulin sensitivity in obese women: The NUGENOB Study. *European Journal of Endocrinology*. 2008;158:533-541.

[186] Drinking and driving. International Center for Alcohol policies. 1995-2012. http://www.icap.org/PolicyIssues/DrinkingandDriving. (Accessed April 13, 2012).

[187] South Africans Against Drunk Driving. Units of Alcohol. SADD. 2011. Available at: http://www.sadd.org.za/index.php?option=com_content&view=article&id=15&Itemid=15. (Accessed April 13, 2012).

[188] Ambrose JA, Barua RS. The pathophysiology of cigarette smoking and cardiovascular disease. *Journal of the American College of Cardiology*. 2004;43(10):1731-1737.

[189] Pope III CA, Burnett RT, Turner MC. Lung cancer and cardiovascular disease mortality associated with ambient air pollution and cigarette smoke: Shape of

exposure-response relationships. *Environmental Health Perspective*. 2011;1616-1621.

[192] Volp PA, de Oliviera EF, Alves DM, Bressan EY. Energy expenditure: components and evaluation methods. *Nutricion Hospitalaria*. 2011;26(3):430-440.

[202] Ma Y. Association between dietary fiber and markers of systemic inflammation in the Women's Health Initiative Observational Study. *Nutrition*. 2008;24(10):941-949.

[204] Butcher JL, Beckstrand RL. Fiber's impact on high-sensitivity C-reactive protein levels in cardiovascular disease. *American Academy of Nurse Practitioners*. 2010;22(11):566-572.

[219] Véronique RL, Go AS, Lloyd-Jones DM, Adams RJ, Berry JD, Brown TM, Carnethon MR, Shifan D, de Simone G, Ford ES, Fox CS, Fullerton HJ, Gillespie C, Greenlund KJ, Hailpern SM, Heit JA, Ho MP, Howard VJ, Kissela BM, Kittner SJ, Lackland DT, Lichtman JH, Lisabeth LD, Makuc DM. Heart disease and stroke statistics 2011 update. *Circulation*. 2011;123:e18-e209.

[220] Nielsen NR, Zhang ZF, Kristensen TS, Netterstrom B, Schnohr P, Gronbaek M. Self-reported stress and risk of breast cancer: prospective cohort study. *British Medical Journal.* 2005;1:1-5.

[221] Kiechl S, Willeit J, Poewe W, Egger G, Oberhollwnzer F. Insulin sensitivity and regular alcohol consumption: Large, prospective, cross sectional population (Bruneck study). *British Medical Journal*. 1996;313:1040-1044.

6. CONCLUSION

This chapter is a conclusion for the entire study. In this chapter, an overview of the study will be provided. The important results obtained will be highlighted and suggestions into further investigations will be given.

6.1. Conclusions

CHD is responsible for approximately 3.8 million deaths in men and 3.4 million deaths in women annually worldwide [3]. BC is the most frequent cancer among women and statistics from 2008 show that approximately 1.38 million people were diagnosed with BC globally [5].

Published studies show several factors which play a major role in the development of CHD. These factors are all influenced by BG [6]. The factors include insulin resistance, high blood viscosity [26], [27], blood coagulation [28], [29], hypertension [30], dyslipidaemia [31], endothelial dysfunction [32] and inflammation [33].

There are also several key factors which have been associated with the development of BC namely: Insulin resistance [78], inflammation [79], [80], endogenous hormones (i.e. oestrogen) [81] and lipid profiles [82]. BG plays a role in each of these factors.

The available literature shows that excessive food intake, psychological stress and cigarette smoking increase BG levels. Lifestyle factors associated with higher BG levels are also linked to increased inflammation, RR for CHD and RR for BC. Dietary fibre intake, moderate alcohol consumption and physical exercise have a BG lowering effect. These factors are shown to be anti-inflammatory and decrease RR for CHD and BC (see paragraph 3.4 and 3.5).

The aim of this dissertation was, therefore, to develop a comprehensive model that accounts for the variety of systemic influences on CHD and BC –with the emphasis of the model being on the lifestyles and the inflammatory state. The interconnected nature of the lifestyle effects and of inflammatory pathways necessitates the development of a unifying system property, chosen to be BG.

The BG quantification was done through the use of the —ets model. This state of the art unit is easy to interpret, understand and visualise. Lifestyle factors such as excessive food intake, psychological stress, cigarette smoking, physical exercise, dietary fibre intake and moderate alcohol consumption can be quantified in terms of their glycaemic effect in this one common

unit. This state of the art method of quantification allows the effect of the different lifestyle factors on chronic disease to be compared.

To compile a meta-analysis, a literature search strategy was employed. Literature searches were done using databases such as ScienceDirect, Scopus, EBSCO, Google Scholar and IEEE Xplore. Subject headings related to the lifestyle factors (i.e. excessive food intake, dietary fibre intake, alcohol consumption, psychological stress, cigarette smoking and physical exercise) and chronic diseases (i.e. inflammation, BC and CHD) were used. A set of inclusion criteria was followed to ensure that applicable data were compared to one another. The —ets model was then used to transform the variety of different lifestyles units into one common unit. The result being the effects of the different lifestyle factors of different published studies, quantified in terms of —ets on inflammation (hs-CRP levels), RR for CHD and RR for BC.

The consolidated graphs obtained in which the lifestyle factors glycaemic effects on inflammation, RR for CHD and RR for BC can be compared are illustrated in Figure 27, 35 and 41 these are here repeated in Figures 42-44.

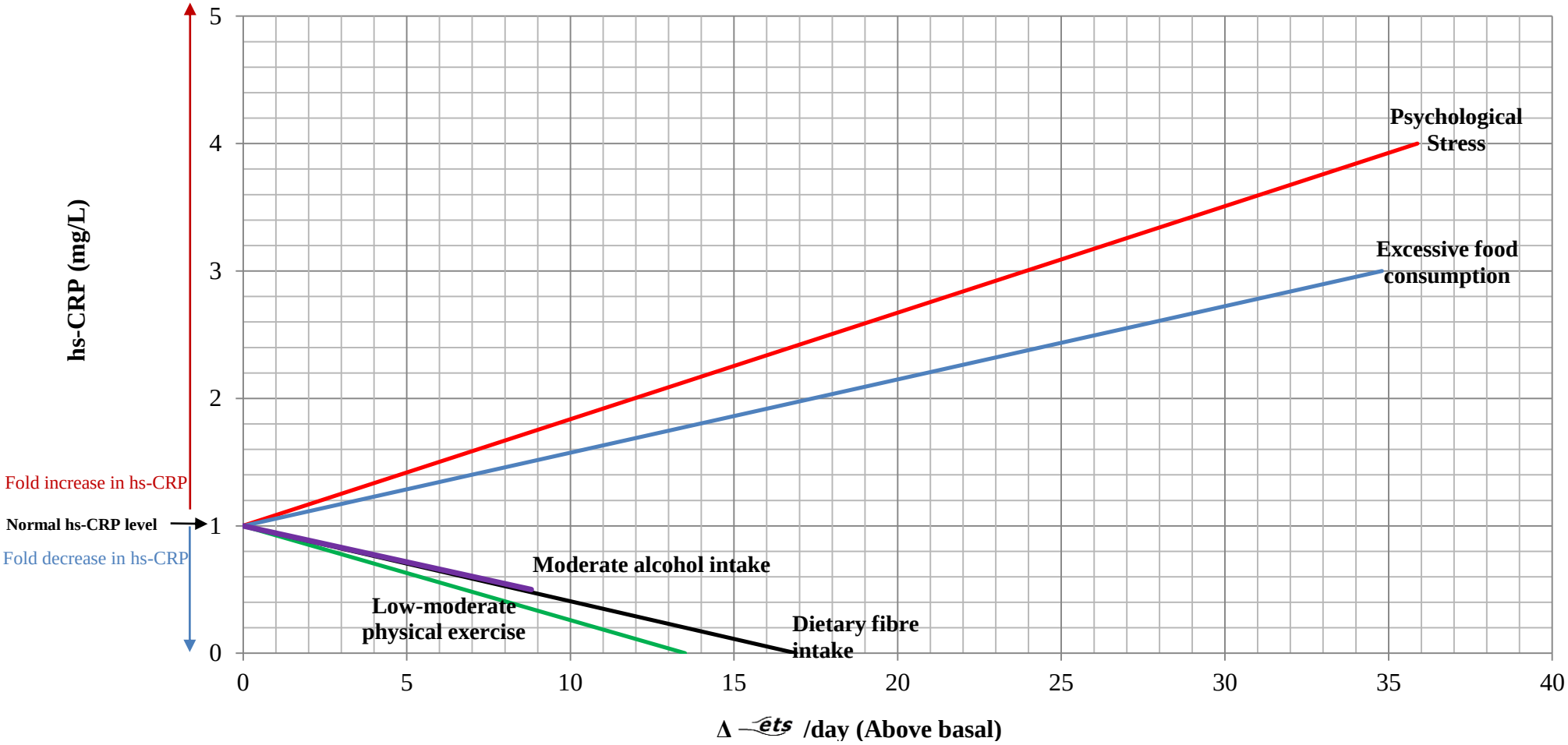


Figure 42: Consolidation of the effects of the different lifestyle factors on inflammation (hs-CRP)

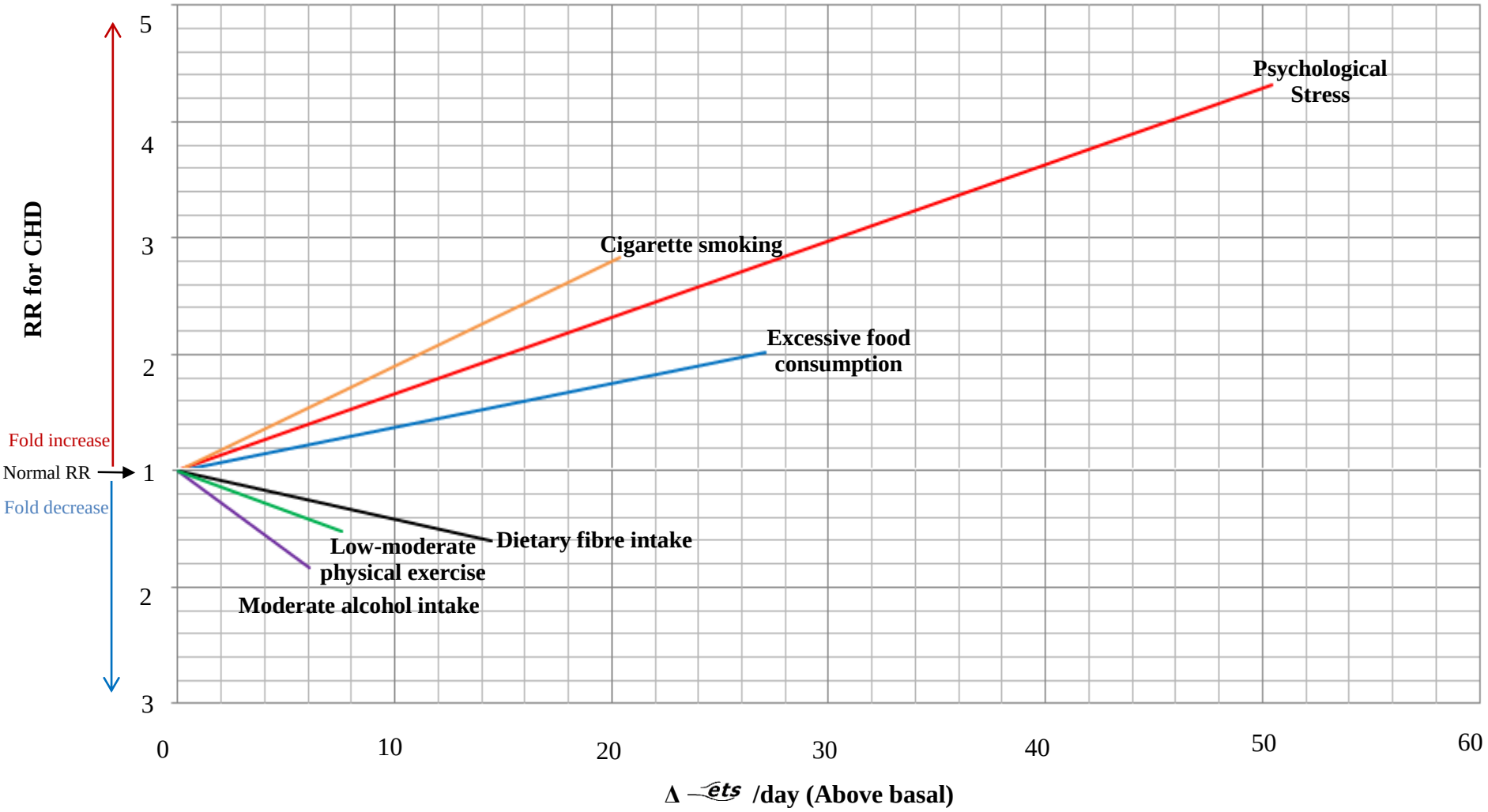


Figure 43: The consolidation of the glycaemic effect (in terms of –ets) of the different lifestyle factors on the RR of CHD

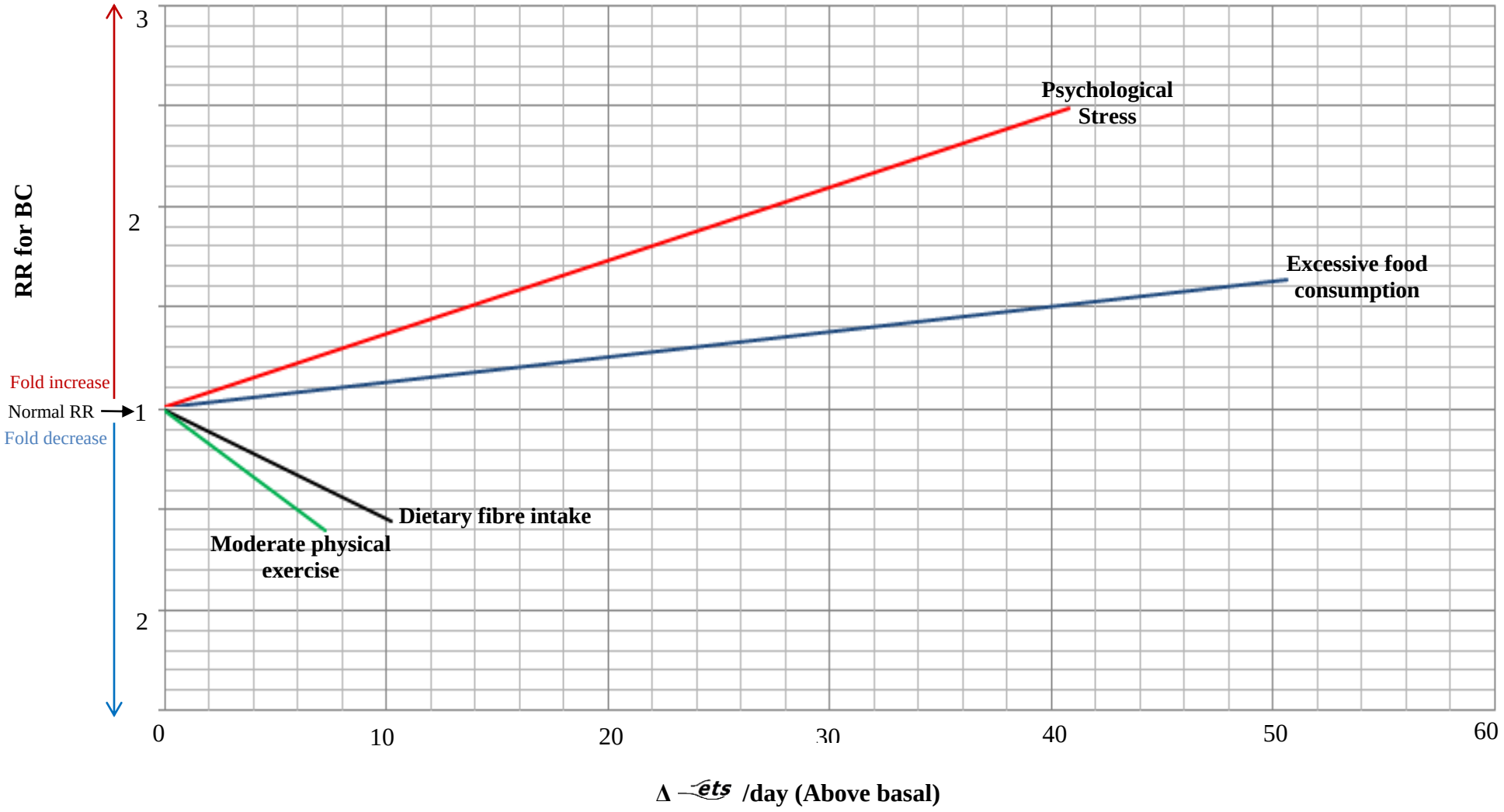


Figure 44: Consolidated effects of the different lifestyle factors on the RR for BC in terms of ets .

From these consolidating figures, it is clear that lifestyle factors that have BG lowering effects reduced inflammation and the risk for BC and CHD, as suspected. The lifestyle factors which are responsible for increasing BG levels had a pro-inflammatory effect and increased the risk for CHD and BC.

Psychological stress proved to have one of the strongest glycaemic effects inducing large $\overline{ets}$ values and was also the primary contributor to inflammation, CHD and BC. Chronic psychological stress increased hs-CRP levels four-fold, RR for CHD more than four-fold and more than doubled RR for BC.

Low to moderate physical exercise has a very strong anti-inflammatory effect lowering hs-CRP levels rapidly. It also had the largest impact on the reduction of BC risk, showing an approximate two-fold reduction. Even though exercise was not associated with the greatest reduction in CHD risk, it still proved to have a significant impact.

Moderate alcohol consumption is particularly important in protecting against CHD and also has anti-inflammatory properties. With the emphasis being on moderate, as excessive alcohol consumption has the opposite effect.

Generally the results were accurate, reflecting the important role of BG in the development of inflammation, CHD and BC. The results are also consistent with the glycaemic effects of the lifestyle factors discussed in the literature study with some exceptions. The exceptions can be attributed to two things: (1.) The results are only as accurate as the clinical data investigated, (2.) it is not a perfect model and other inflammatory, atherogenic and carcinogenic properties associated with the different lifestyle factors should also be taken into consideration in the development of inflammation, BC and CHD.

Overall, the systems engineering approach was successful in portraying the lifestyle effects on BG and, in turn, its effect on the development of the chronic diseases at a micro- and macroscopic level. It enabled all the lifestyle effects to be consolidated into a process diagram, giving an overarching illustration of the inter-connectedness of the pathways associated with the two chronic diseases. The systems engineering approach, in combination with the consolidated results obtained, verifies the pivotal role of BG in CHD and BC development.

6.2. Recommendations

There are several recommendations that can be made for further studies. These include:

1. Some of the studies done were on a relatively small number of subjects; larger groups of test subjects will supply more accurate results.
2. Studies should aim to publish data for the same lifestyle factor in the same unit so more accurate comparisons can be drawn.
3. Further research should be done into treatments for psychological stress as a preventative measure for inflammation, CHD and BC.
4. Physical exercise should be researched in more detail as a treatment and precaution for inflammation, CHD and BC.

6.3. References

[3] Bramkamp M, Radovanovic D, Erne P, Szucs TD. Determinants of costs and the length of stay in acute coronary syndromes: A real life analysis of more than 10 000 patients. *Cardiovascular Drugs and Therapy*. 2007;21(5):389-398.

[5] Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. *International Journal of Cancer*. 2010;127(12):2893-2917.

[6] Aronson D, Rayfield EJ. How hyperglycemia promotes atherosclerosis: Molecular mechanisms. *Cardiovascular Diabetology*. 2002;1(1):1-10.

[26] Stoll G, Bendszus M. Inflammation and atherosclerosis: Novel insights into plaque formation and destabilization. *Stroke*. 2006;37:1923-1932.

[27] Koenig W, Sund M, Birgit F, Doring A, Lowel H, Ernst E. Plasma viscosity and the risk of coronary heart disease. *Journal of the American Heart Association*. 1997;18:768-772.

[28] Dahlbäck B. Blood coagulation. *Lancet*. 2000;355:1627-1632.

[29] Spronk HMH, van der Voort D, ten Cate H. Blood coagulation and the risk of atherothrombosis: A complex relationship. *Thrombosis Journal*. 2004;2(12):1-12.

[30] Kaperonis EA, Liapis CD, Kakisis JD, Dimitroulis D, Papavassiliou VG. Inflammation and atherosclerosis. *European Journal of Vascular and Endovascular*

Surgery. 2006;31(4):386-393.

[31] Vega GL, Sirtori C. Dyslipidemia and coronary heart disease. *Current Opinion in Lipidology*;1996;7(4):179-182.

[32] McGorisk M, Treasure CB. Endothelial dysfunction in coronary heart disease. *Current Opinion in Cardiology*. 1996 ;11(4).

[33] Hansson GK. Inflammation, atherosclerosis and coronary artery disease. *New England Journal of Medicine*. 2005;352:1685-95.

[78] Larsson SC, Bergkvist L, Wolk A. Glycemic load, glycemic index and breast cancer risk in a prospective cohort of Swedish women. *International Journal of Cancer*. 2009;125(1):153-157.

[79] Patel SA, Heinrich C, Reddy Y, Srinivas B, Heidaran , Rameshwar. Breast Cancer Biology: The Multifaceted Roles of Mesenchymal Stem Cells. *Journal of Oncology*. 2008; doi:10.1155/2008/425895.

[80] Kundu JK, Surh YJ. Inflammation: Gearing the journey to cancer.*Mutation Research*. 2008;659:15-30.

[81] Nicolas Dıaz-Chico B, German Rodrıguez F, Bilbao C, Gonzalez A, Ramırez R, Cabrera de Leon A, Aguirre Jaime A, Chirino R, Navarro D, Dıaz-Chico JC. Androgens and androgen receptors in breast cancer. *Journal of Steroid Biochemistry and Molecular Biology*. 2007;105(1-5):1-15.

[82] Danilo C, Frank PG. Cholesterol and breast cancer development. *Current Opinion in Pharmacology*. 2012; doi:10.1016/j.coph:1-6.

APPENDIX A

The glycemic effect of several lifestyle factors on inflammation

EH Mathews, JM Espach, and L Liebenberg

Authors contracted to North-West University, Suite No 91, Private Bag X30, Lynnwood Ridge, 0040, South Africa and consultants to MCI (Pty) Ltd and TEMM International (Pty) Ltd

ehmathews@researchtoolbox.com; jespach@researchtoolbox.com; *LLiebenberg@researchtoolbox.com*

Corresponding author. Tel.: +27 12 809 0995; Fax: +27 86 515 5799

E-mail: LLiebenberg@researchtoolbox.com (L. Liebenberg)

Abstract

Aims: A number of published articles suggest that inflammation is linked to various chronic illnesses (i.e., coronary heart disease). The lifestyle factors which influence inflammation have been extensively investigated. It is however unclear which factor has the most significant impact on inflammation. The aim of this study is to use a common unit to compare the influence of the following lifestyle factors on inflammation: food and moderate alcohol consumption, physical exercise, psychological stress and fiber intake.

Methods: Before any comparisons between the lifestyle factors and inflammation could be made, a common unit was developed. This energy unit is known as equivalent teaspoons sugar (—ets) and it allowed the lifestyle factors to be expressed in terms of their effect on blood glucose (BG). The unit is easy to visualize and interpret especially for the non-technical person. The —ets values for each lifestyle factor was developed and plotted against its effect on C-reactive protein (hs-CRP) level. hs-CRP was used as the marker for inflammation.

Results: All the lifestyle factors influencing BG were shown to have an effect on inflammation. Food and stress have a pro-inflammatory effect while fiber intake, alcohol consumption and exercise reduce inflammation. The Pearson-R^2 values for the analyzed data varied between 0.47 for exercise and 0.81 for food.

Conclusion: The effects of food and alcohol consumption, stress, exercise and fiber (all *via* BG) on inflammation could be established using one consistent theory. To verify the theory experimental data from various studies were used. The lifestyle factors which influence inflammation can be quantified and compared in a common easy to interpret unit (—ets). The effect of the different lifestyle factors on inflammation could be placed in perspective especially the effect of psychological stress.

Key words: Inflammation, blood glucose (BG), High sensitivity C-reactive protein (hs-CRP), lifestyle factors, stress, exercise, alcohol, food, dietary fiber

Introduction

Inflammation is a protective tissue response causing redness, heat and swelling to an injured or infected part of the body (Vodovotz *et al*. 2009). It is a regulatory process responsible for the elimination of foreign substances which invade the body during infection as well as enhancing the repair of tissue damage caused by injury (Rodriguez-Vita & Lawrence 2010).

The inflammatory response promotes optimal healing but can also cause irreversible tissue damage if it persists, a state known as systemic or chronic inflammation (Kanterman *et al*. 2012). Systemic inflammation is linked to various chronic diseases such as cardiovascular disease, rheumatoid arthritis, diabetes mellitus and cancer (Rodriguez-Vita & Lawrence 2010, Vodovotz *et al*. 2009). The ability to measure the level of inflammation in the body is therefore important.

High sensitivity C-reactive protein (hs-CRP) is synthesized in the liver, and has been identified as the first marker for low-grade inflammation (Kluft & de Maat 2002). It has been widely studied and is currently one of the only trustworthy markers for chronic inflammation (Kluft & de Maat 2002). Levels lower than 1 mg/L are regarded as normal; levels between 1-3 mg/L are considered to be slightly elevated and above 3 mg/L are known as high hs-CRP levels and associated with chronic inflammation (Verma *et al.* 2004).

It is suggested that high blood glucose (BG) is associated with elevated levels of hs-CRP and consequently systemic inflammation (Brunengraber *et al*. 2009). High BG levels are known to induce pro-inflammatory cytokines such as Interleukin-6 (IL-6), which in turn is responsible for the regulation of hs-CRP and thus any increase in hs-CRP (Shanmugam *et al*. 2003).

The primary focus of this paper is on the various lifestyle factors that influence BG (and therefore inflammation). These include excessive food intake, alcohol intake, dietary fiber added to a meal, physical exercise and psychological stress.

Each lifestyle factor is however, quantified in a different unit, making it difficult to draw a comparison. Food intake is expressed in grams of carbohydrate; glycemic index or glycemic

load; alcohol in grams of ethanol; dietary fiber in grams; physical exercise in METs or kcal expended; and stress levels as high, medium and low.

A unit has been developed in previous papers suggesting that all these factors can be expressed in terms of their effect on BG (Mathews & Pelzer 2009). This unit is known as equivalent teaspoons sugar (ets). Because these lifestyle factors can now be quantified in the same unit, the effect of each factor on inflammation can be analyzed and discussed individually.

In this study we will look at several published studies which investigated what the effect of different lifestyles have on hs-CRP levels. Each factor will be quantified in terms of BG and ets in order to draw a comparison between the effects they have on inflammation.

Effect of Carbohydrate (CHO) intake on blood glucose metabolism

Carbohydrates (CHOs) can be classified as refined and unrefined CHOs (Hu 2010). The quality of a CHO is often determined by its GI value that depends on the rate at which a particular food is digested and absorbed. Unrefined CHOs are usually foods with compact granules containing high soluble fiber, which takes longer to digest and therefore have lower GI values. Refined CHOs on the other hand, are foods that have less compact granules contributing to faster digestion rates and higher GI values (Hu 2010).

Ingestion of CHOs with high GI values (i.e., refined CHOs) is associated with significantly higher levels of hs-CRP in comparison with low-GI CHOs (Liu *et al*. 2001, Levitan *et al*. 2008). However, according to the FDA all metabolized CHOs release the same amount of energy namely 4 kcal/g CHO (Wheeler 2010). If this is true, then why are refined CHOs associated with increased hs-CRP levels? The new ets energy model will be used to deliberate the refined and unrefined CHO issue.

Previously, an energy unit termed ets (or equivalent teaspoons sugar) was developed (Mathews & Pelzer, 2009). This energy unit was developed for several different reasons. (i.) To introduce a more correct energy value for metabolized CHO; (ii.) It can be used as a

common unit for all the lifestyle factors' BG effect; (iii.) It is also easier for the non-technical person to visualize a teaspoon of sugar, rather than glycemic index or load; (iv.) Practicality: ets is easier to count and therefore to keep track of a person's CHO consumption.

The relationship between the BG energy metabolized from CHOs and ets can be expressed as (Mathews & Pelzer 2009):

$$ets_{CHO} = \frac{\eta_{CHO}}{\eta_{Sugar}} \times \frac{m_{CHO}}{5} = \frac{GI_{CHO} m_{CHO}}{325} \quad (1)$$

Where all the *GI* values are referenced to the glucose standard.

η_{CHO} and η_{sugar} are the metabolic efficiencies of the CHO and the sugar, respectively.

GI_{CHO} is the glycemic index and m_{CHO} the mass of the CHO.

From this relationship it is clear that CHOs with higher GI values (refined) consist of a higher metabolic efficiency and will therefore release more energy, (ets_{CHO}), than unrefined CHOs. This would explain why consumption of refined CHOs is linked to higher levels of hs-CRP.

Studies were found which investigated the effect of metabolized CHO energy consumption on hs-CRP levels (Liu *et al*. 2001, Levitan *et al*. 2008, Griffith *et al.* 2008). Using Equation (1) the CHO intake from the studies could be expressed in terms of Δets_{CHO}. Figure A 1 could then be compiled that shows the effect of daily Δets_{CHO} consumption on hs-CRP levels.

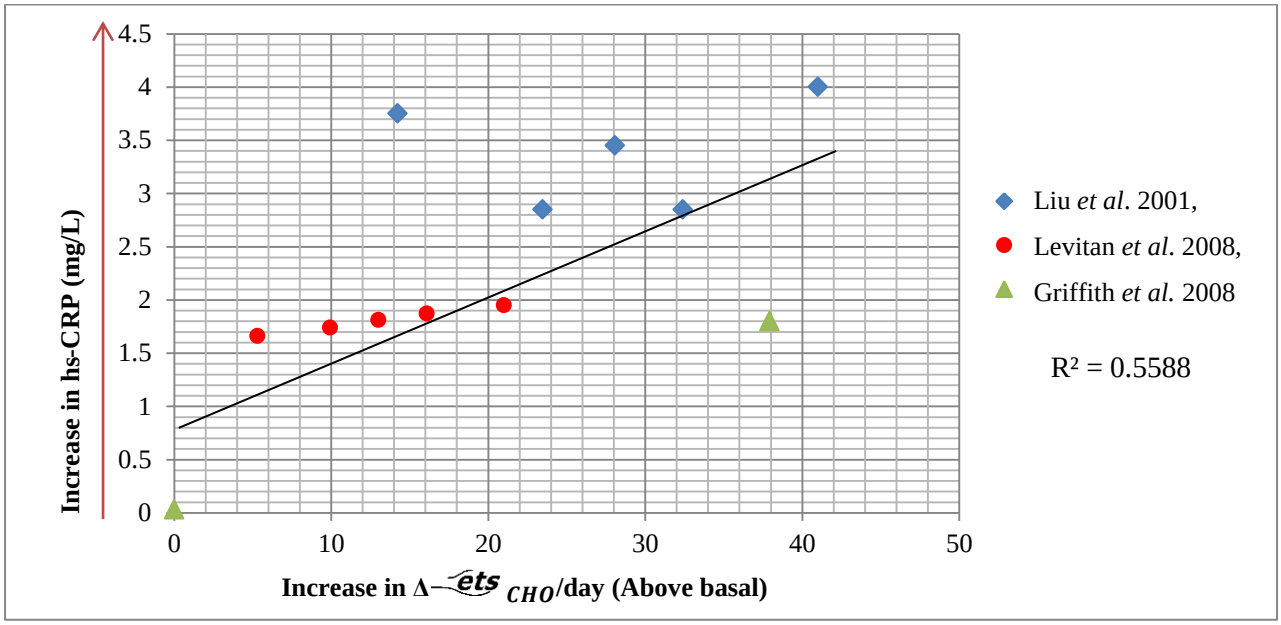


Figure A 1: The linearized relationship between daily Δets_{CHO} consumption and hs-CRP levels from published clinical trials.

The relationship between Δets_{CHO} and hs-CRP was plotted and a linear regression model which gave a R^2 value of 0.81 was obtained. The assumption of a linear fit was chosen in order to simplify interpretation and implementation of data. (If a second-degree polynomial fit is implemented it would give a slightly better R^2 value.) Figure A 1 suggests that hs-CRP levels increase proportionally with increasing energy (Δets_{CHO}) released by metabolized CHO. hs-CRP levels start to increase after a daily consumption of approximately 40 Δets_{CHO}. This is approximately the Δets_{CHO} count of one medium-sized fast food burger meal (burger, fries and cola). It was previously shown that average basal energy necessary for normal activity levels for men and women are approximately 23 Δets (Mathews & Liebenberg 2012). Other studies suggest that this figure is closer to 28 Δets (Volp et al. 2011).

Figure A 1 indicates that when basal —ets consumption is exceeded, the hs-CRP levels enter high levels of inflammation (> 3 mg/L). After the consumption of 28 —ets $_{CHO}$, the hs-CRP levels double with the intake of another 36—ets $_{CHO}$.

Table A 1 was compiled to draw attention to the —ets $_{CHO}$ values for some of the typical food choices. There are in fact —ets $_{CHO}$ values for an excess of 4000 different foods (this information can be accessed at http://www.diabetic-edutool.com).

Table A 1: Typical energy values for some popular foods

Food	**Equivalent teaspoons sugar —ets $_{CHO}$, per serving**
340 ml can of typical soda	8
Fresh apple, with skin (medium fruit)	2
Cheeseburger	7
Medium French fries	14
Blueberry muffin (medium serving)	10
Medium slice of white bread	3

The effect of fiber on metabolized BG energy and its influence on inflammation will be investigated in the following section.

Impact of fiber intake and metabolized BG on inflammation

High-fiber diets are associated with lower levels of hs-CRP and therefore inflammation (King *et al*. 2007, Butcher *et al.* 2010, Ajani *et al*. 2004). There are two possible explanations for this reduction in hs-CRP levels. First, dietary fiber is known to modify the adipocytokines in adipose tissue which increases the enterohepatic flow of lipids and lipophilic substances preventing inflammation (Ma *et al*. 2008).

Second, it is theorized that fiber reduces the metabolic efficiency of a meal reducing the BG metabolized from the CHO in the meal (Mathews & Pelzer 2009). Lower levels of metabolized BG are related to lower hs-CRP levels resulting in less inflammation. A reduction in metabolic efficiency is also *inter alia* linked to a lower GI value for the meal and as previously discussed, leads to reduced levels of hs-CRP (Jenkins *et al.* 2002, Ma *et al*. 2008). It should be noted that the fiber must be eaten with the meal to have an effect on the metabolic efficiency. Fiber eaten on its own at other times of the day will not make much of an impact.

Jenkins *et al.* 2002 added fiber to different foods and measured the resulting glucose response. One gram of fiber added to 50 grams of CHO, reduced the GI of a typical meal by four units. This can be translated to a reduction of 0.6 $\overset{\sim}{ets}$ per gram of extra fiber added to a meal.

A new variable, $\overset{\sim}{ets}_{Fib\ added}$, can now be defined.

$$\overset{\sim}{ets}_{Fib\ added} = 0.6 \times m_{Fib\ added} \tag{2}$$

Where $m_{Fib\ added}$ is the mass of the fiber added in grams.

Data were obtained from several studies that investigated the influence that fiber intake has on hs-CRP levels and thus on inflammation (King *et al*. 2007, Ajani *et al*. 2004, Butcher *et al.* 2010). Equation (2) was used to express the fiber intake reported in the studies in $\overset{\sim}{ets}_{Fib\ added}$. The $\overset{\sim}{ets}_{Fib\ added}$ values were then plotted against the published hs-CRP values as shown Figure A 2.

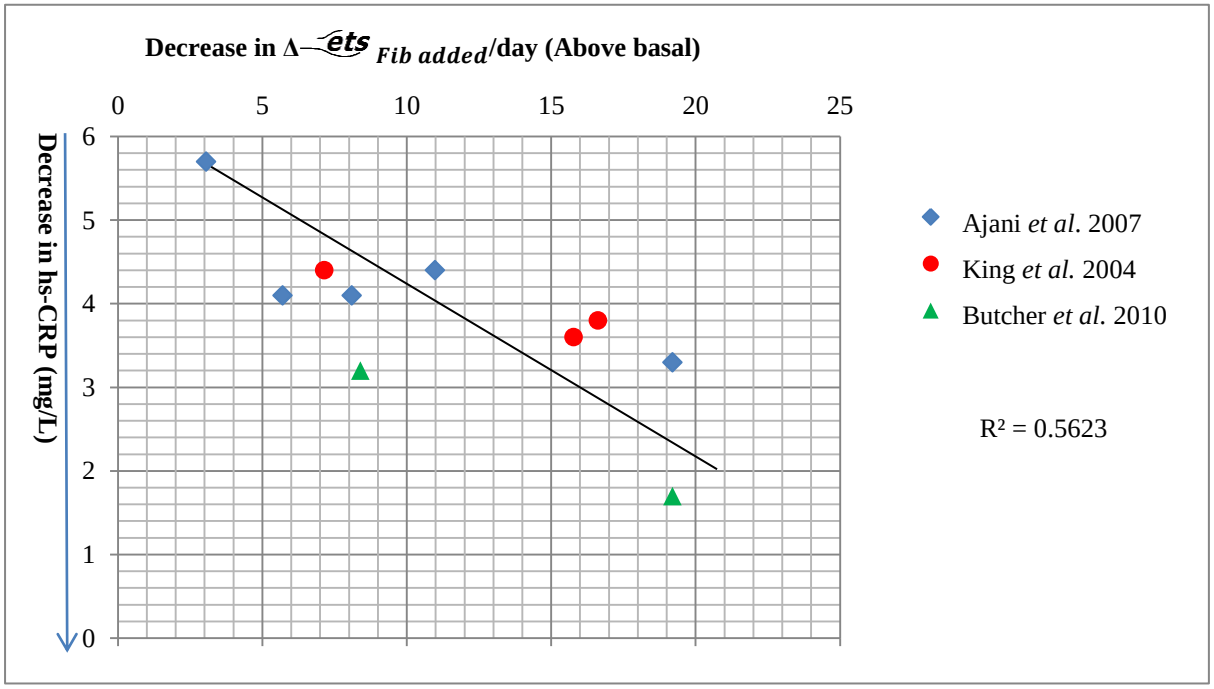


Figure A 2: The average linearized relationship between fiber intake and hs-CRP levels, taken from a number of published studies.

A linear curve fit was once again implemented (R^2= 0.56). Figure A 2 shows that hs-CRP levels (indicative of inflammation) are reduced with the increased fiber intake (expressed in $\overset{ets}{}_{Fib\ added}$).

Figure A 2 also suggests that with the consumption of 10 grams of fiber with every meal, three times daily (by means of Equation (2) 10 × 3 × 0.6 = 18 $\overset{ets}{}_{Fib\ added}$), a two-fold reduction can be seen in hs-CRP levels.

The effect of exercise on blood glucose and inflammation

Several studies have shown that physical activity is associated with a reduction in hs-CRP levels and therefore suggests that it has an anti-inflammatory effect (Pischon *et al.* 2003, Geffken *et al.* 2001).

It is proposed that energy is expended through exercise, lowering BG levels in the body and thus lowering hs-CRP levels. Energy expended through exercise can also be quantified in terms of —ets.

It is known that through participation in physical activity almost 20% of the energy comes from BG ($0.2 \times kcal_{Exercise}$) (Noakes 2001). Using the energy expended during exercise in [$kcal_{Exercise}$], a relationship between the BG expended in —ets can be obtained. The following conversion exists between *kcal* and —ets (taken from equation (11) in Mathews & Pelzer 2009)

$$1\text{—ets} = E_{Teaspoon\ Sugar} = 0.65 \times 5g \times 4kcal/g = 13kcal \quad (3)$$

Resulting in:

$$\text{—ets}_{Exercise} = 0.2 \times kcal_{Exercise} \times (\text{—ets}/kcal) = 0.2 \times kcal_{Exercise} \times \frac{1}{13} = \frac{kcal_{Exercise}}{65} \quad (4)$$

$kcal_{Exercise}$ accounts for the type, duration and intensity of the exercise, it also takes into consideration the body mass of the test subject (ACSM 2007).

BG consumption through exercise can be quantified in terms of energy expended (above basal needs) in —ets through Equation (4). Published studies which investigated the effect of physical activity (expressed in kcal) on hs-CRP levels can be used to compile Figure A 3 (Pischon *et al*. 2003, Geffken *et al*. 2001). Only the effect of low-intensity exercise on inflammation was considered as this is more practical for most people to achieve.

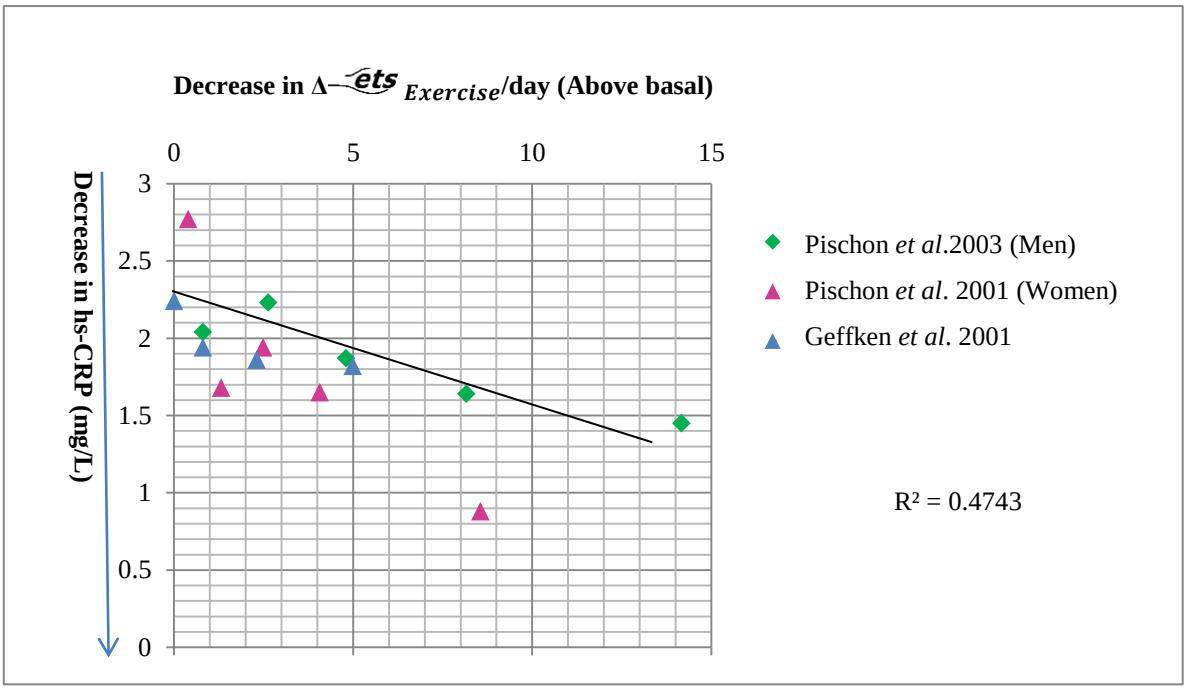


Figure A 3: The linearized relationship between low-intensity exercises expressed in ets and levels of hs-CRP for a number of published studies.

A linearized curve fit was implemented (R^2 = 0.47). Figure A 3 shows that an increase in energy expended through exercise ($ets_{Exercise}$) induces a decrease in hs-CRP levels. Figure A 3 also suggests that by expending approximately 6 $ets_{Exercise}$ daily, which corresponds to around 60 minutes of walking at a pace of 6 km/h for a 70 kg male, hs-CRP levels can be reduced by 0.5 mg/L.

Table A 2 provides an indication of energy expended in $ets_{Exercise}$ for some popular physical activities.

Table A 2: Typical ets values for physical exercises

Activity, for a duration of 60 min	**Equivalent teaspoons sugar $ets_{Exercise}$ energy expended by an 70-kg male**
Cycling at 21 km/h, level road	6
Swimming (crawl)	6
Tennis	9
Walking at 6 km/h	8
Running at 11 km/h	17

The effect of moderate alcohol consumption on BG and inflammation

Moderate alcohol consumption has been linked to lower levels of inflammation (Oliveira *et al*. 2010). Alcohol suppresses the ability of the liver to produce BG and the secretion of IL-6 is inhibited, which in turn reduces hs-CRP levels (Oliveira *et al*. 2010, Krebs *et al*. 1969, Bollen *et al*. 1998, Siler *et al*. 1998)

High alcohol consumption however, enhances inflammatory effects on the liver which is responsible for increased tissue inflammation through peroxidation of lipids (Oliveira *et al*. 2010). A U- shaped profile is therefore expected between alcohol consumption and hs-CRP levels (Albert *et al*. 2003).

This article focuses on moderate alcohol consumption as it is linked to lower hs-CRP levels. Several studies investigated the effect of alcohol consumption, in grams/day, of ethanol and hs-CRP levels. These results are summarized in Table A 3.

Table A 3: Alcohol consumption in ethanol (g/day) and measured hs-CRP levels (mg/L)

References	Imhof *et al.* 2004 (All)		Imhof *et al.* 2001 (Men)		Imhof *et al*. 2001 (Women)		
Ethanol (g/day)	0	20	0	20	40	0	20
hs-CRP (mg/L)	1.63	1.25	1.39	1.3	1.09	1.29	1.25

A linear relationship is assumed between alcohol consumption (*Alcohol*) and hs-CRP levels (*hs-CRP*), especially as only low to moderate alcohol consumption was considered. The correlation between alcohol consumption and hs-CRP levels can be expressed as:

$$hs - CRP = f_1 Alcohol \tag{5}$$

Now that the relationship between hs-CRP and alcohol is established the BG effect of alcohol can be determined and expressed in terms of $-\overset{ets}{\frown}$. Reduction of BG can be related to less insulin secretion. From a previous article the following relationship was deduced between BG and insulin (Mathews & Pelzer 2009):

$$\Delta I = f_2 . \Delta BG \tag{6}$$

Where:

ΔI is the change in insulin.

ΔBG is the change in blood glucose levels.

It is also known that that there is a direct relation between changes in BG level (ΔBG) and change in $-\overset{ets}{\frown}$ ($\Delta -\overset{ets}{\frown}$) (Pelzer *et al*. 2011):

$$\Delta BG = f_3 . \Delta -\overset{ets}{\frown} \tag{7}$$

Substituting equation (7) into equation (6) results in the following:

$$\therefore \Delta I = f_4.\Delta \text{ets} \tag{8}$$

The f_4 value corresponds to the insulin sensitivity which has to be determined so that the insulin levels can be linked to ets levels. Continuous glucose monitors were used on 11 test subjects. The measurements that were obtained after three days could be used to determine the average insulin sensitivity. Table A 4 gives an indication of how the average insulin sensitivity factor was calculated.

Table A 4: Insulin sensitivity *(f_4)* related to Δ ets levels

Subject	**ΔI /Δ ets**
1	0.77
2	0.83
3	0.67
4	0.53
5	0.77
6	0.30
7	1.43
8	0.56
9	0.43
10	0.77
11	0.56
Average = f_4	**0.69**

The average insulin sensitivity f_4 is 0.69. Now that the relationship between insulin and ets has been established, the relationship between alcohol consumption and insulin can be investigated.

Several studies have been published which relate the effect of alcohol consumption on insulin secretion. The change in insulin secretion with alcohol consumption is shown in Table A 5.

Table A 5: The effect of ethanol consumption on insulin secretion.

References	**(Kroenke *et al*. 2003)**		**(Greenfield *et al*. 2003)**	
Ethanol (g/day)	15.0	35.0	11.4	22.9
ΔI, Reduction in insulin secretion per day (mU/l)	3.89	4.32	5.9	5.6

The relationship between alcohol consumption and change in insulin levels can therefore be established as:

$$\Delta I = f_5 Alcohol \tag{9}$$

The reduction in insulin secretion corresponds to a reduction in BG which can be expressed in Δ–ets by using Equation (8).

Now that these relationships have been determined, Equations (8) & (9) can be substituted into Equation (5) to give the correlation between alcohol consumption expressed in terms of –ets and hs-CRP levels:

$$hs - CRP = f_6 \text{–ets}_{Alcohol} \tag{10}$$

Figure A 4 plots Equation (10) based on data from several studies.

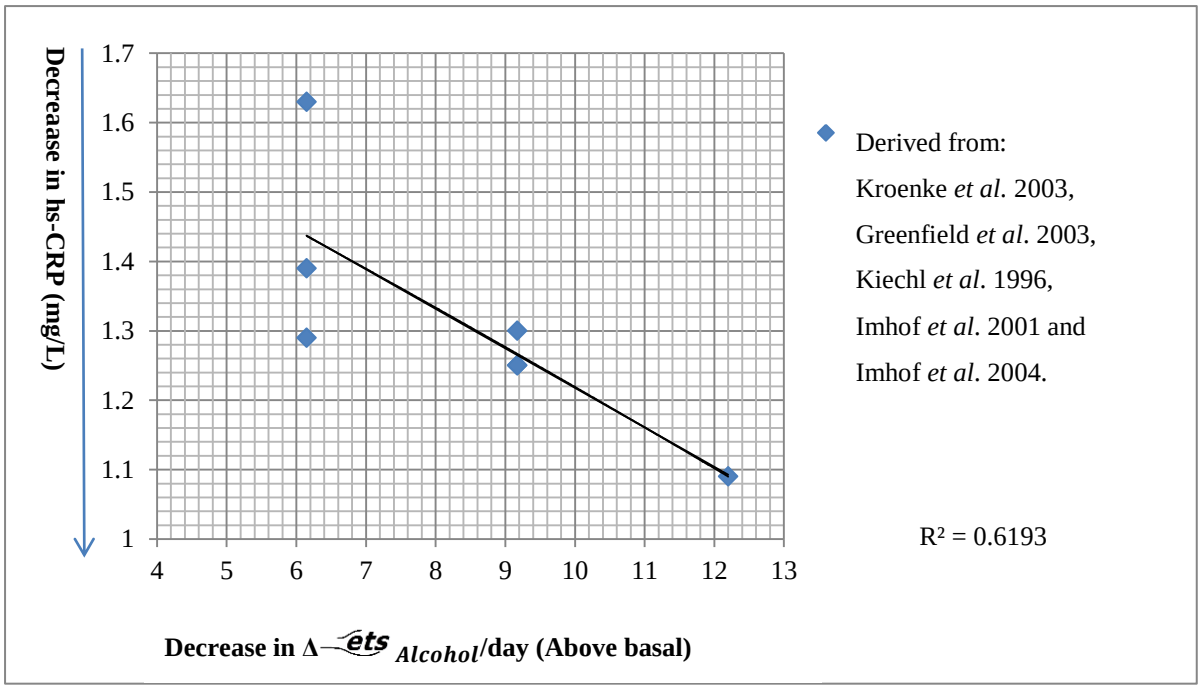


Figure A 4: The effect of alcohol (in terms of $ets_{Alcohol}$) on hs-CRP levels.

From Figure A 4 it can be deduced that moderate alcohol consumption lowers hs-CRP levels and therefore also inflammation. A $\Delta\ ets_{Alcohol}$ value of 6 corresponds to a reduction in hs-CRP from 1.44 to 1.1 mg/L. The practical inference from Figure A 4 is that by drinking approximately one small glass of wine (125 ml) that consists of 12 % alcohol (30 g ethanol = 6 $ets_{Alcohol}$), a person's hs-CRP levels can be reduced and therefore reduce inflammation.

As previously discussed high levels of ethanol consumption will have a negative effect on inflammation. These results however are not presented graphically but they do suggests that when consuming 40 grams of ethanol per day, (12 $ets_{Alcohol}$ or 330 ml of wine containing 12% alcohol), an individual's hs-CRP levels will start to rise (Imhof *et al*. 2001).

The effect of psychological stress on BG and on inflammation

It is known that chronic stress plays an important role in the BG which is produced particularly by the liver (McEweb 2008, Black 2003, Raikkonen *et al*. 1996, Saltiel & Kahn 2001, Mathews & Liebenberg 2012). Chronic stress induces the release of cortisol which inter alia stimulates BG production (McEweb 2008, Black 2003, Raikkonen et al. 1996,Saltiel & Kahn 2001, Mathews & Liebenberg 2012).

Investigations were conducted to determine whether increased levels of stress would increase hs-CRP levels. It was difficult to find sufficient published articles on the effect of stress on hs-CRP which can be quantified in terms of its effect on BG. Therefore, another route was considered.

As previously mentioned, hs-CRP is not only a marker for inflammation but also for Coronary heart disease (CHD). Published studies, linking hs-CRP levels to the relative risk of CHD are illustrated in Table A 6 by relationship A. The effect of stress in terms of ets, (and its effect on BG) on the relative risk (RR) of CHD is also known and presented as relationship B in Table A 6. With this information a correlation between stress, in terms of ets on hs-CRP levels, could be made. This is shown in Table A 6 link C.

Table A 6: The relationship between ets Stress and hs-CRP levels

hs-CRP (mg/L)	RR for CHD	ets Stress/day
0.6	1.2	3.0
1	1.17	2.6
1.1	1.8	12.1
2	1.7	10.6
2.2	2	15.2
3	1.31	4.7
3.8	3.56	38.8
4.5	2.6	24.3

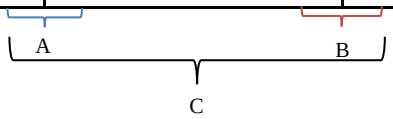


Table A 6 is compiled from the following studies: Kubzanski *et al.* 1997, Roest *et al.* 2010, Kubzanski *et al.* 2009, Einvik *et al.* 2009, Vogelzangs *et al*. 2010, Versteeg *et al.* 2011, Phillips *et al.* 2009, Roivainen *et al.* 2012, Koenig *et al.* 2001, and Rodondi *et al.* 2010.

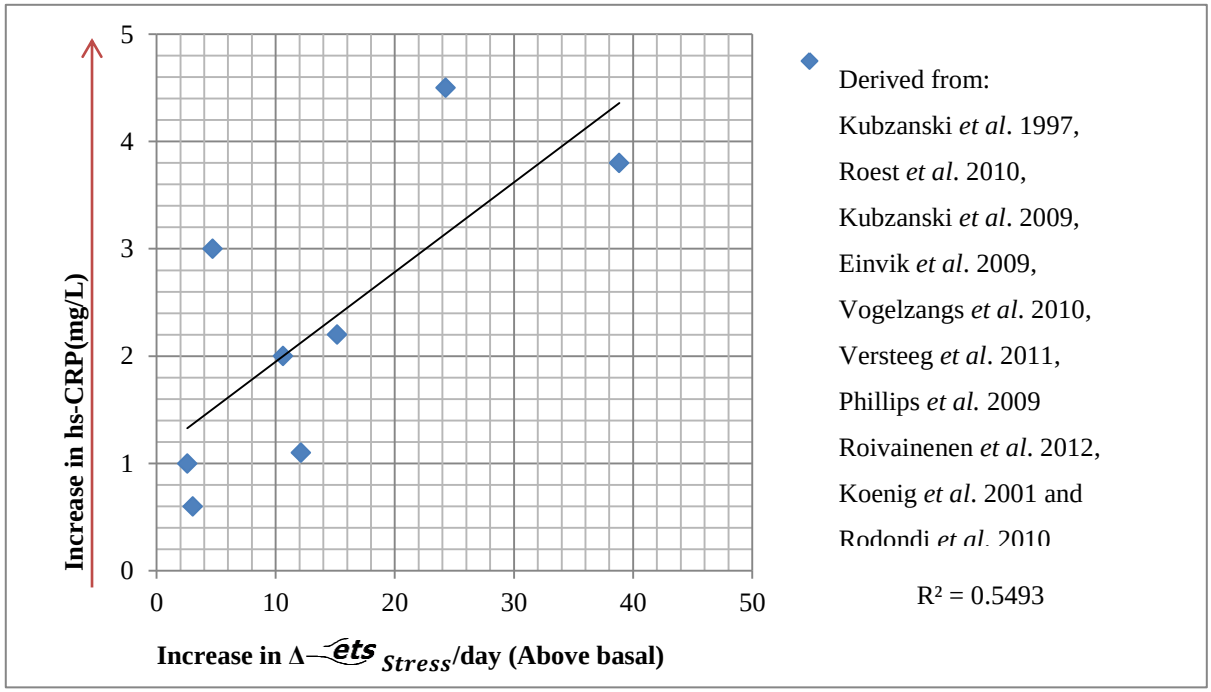


Figure A 5: The effect of stress quantified in $\widetilde{ets}_{Stress}$on hs-CRP levels.

Now that stress has been quantified in terms of $\widetilde{ets}_{Stress}$, and can be linked to hs-CRP levels, Figure A 5 could be compiled (R^2 = 0.55). Figure A 5 suggests that with increasing levels of stress (in terms of $\widetilde{ets}_{Stress}$) the level of hs-CRP is also increased. An increase of 16 $\widetilde{ets}_{Stress}$ (corresponding to low/medium levels of stress), leads to a two-fold increase in hs-CRP levels.

Discussion

Figures A 1 to A 5 were combined, resulting in Figure A 6. The graph has been normalized to 1 on the y-axis, where 1 represents normal hs-CRP levels. From Figure A 6, the five lifestyle factors can now be quantitatively compared. Stress and food increase hs-CRP levels, which correspond to a pro-inflammatory effect. Alcohol, fiber and exercise however, decrease hs-CRP levels corresponding to a decrease in inflammation.

From the range of the graphs shown in Figure A 6, one can deduce the relative effect that each lifestyle factor has on the secretion of BG above basal needs (in terms of Δ ets). It can be seen that stress rapidly induces very high levels of ets above basal needs. This suggests that stress is one of the most important contributors to inflammation. Stress treatments should therefore be investigated more extensively for the reduction of inflammation.

The graphs for stress and exercise have the steepest gradients and almost mirror one another, showing that these two factors have the largest effect on hs-CRP levels and inflammation. The reason for this could be that stress and exercise have an effect on the insulin sensitivity of a person, which also plays a role in inflammation. Stress decreases insulin sensitivity contributing to insulin resistance (Versteeg *et al*. 2011) and exercise has the opposite effect improving insulin sensitivity (Bordenave *et al*. 2008, Pedersen & Saltin 2006)

Food and fiber closely follow stress and exercise and are also almost mirror images of one another.

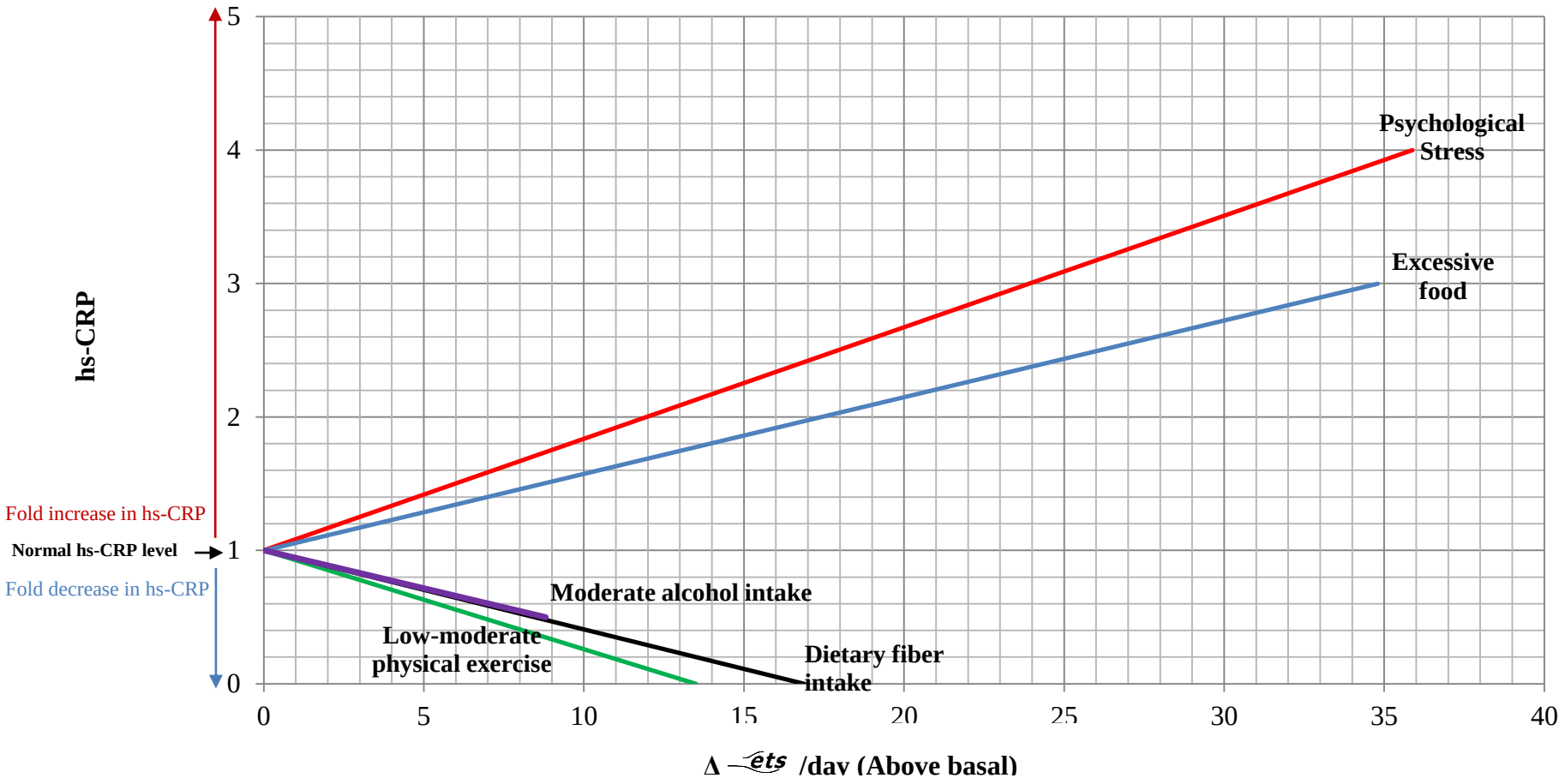


Figure A 6: Combined effect of the five lifestyle factors in terms of Δ ets /day on hs-CRP levels and therefore on inflammation.

Conclusion

In conclusion this study shows the effect of several lifestyle factors on inflammation, these factors include; food, dietary fiber, physical exercise, alcohol and psychological stress. Several different studies, including their corresponding clinical data, were investigated. hs-CRP was used as the marker for inflammation, with higher levels of hs-CRP suggesting an increase in inflammation.

The ets model made it possible to quantify the lifestyle factors in a common unit, enabling a comparison to be made between the effects of each factor on inflammation. The consolidated results accentuated the pivotal role of BG in inflammation. From the lifestyle factors investigated, high levels of psychological stress proved to have the largest and most significant effect on inflammation. Stress treatments should be seriously considered as treatments for the reduction of inflammation.

Acknowledgements

The “angel” investor for this project was Dr. Arnold van Dyk. Corlia Mathews initiated our thinking and developed the extensive food database.

As the underlying theory is relevant to other problems (e.g., cancer, diabetes, feeding programmes, etc.), it will also be reported elsewhere for better understanding of these problem areas.

References

ACSM. Metabolic Calculations Handbook Americand College of Sports Medicine. 1 ed. Baltimore, Maryland,: Lippincott Williams & Wilkins; 2007.

Ajani UA, Ford ES, Mokdad AH. Dietary fiber and C-reactive protein: Findings from National Health and Nutrition Examination survey data. *Nutritional Epidemiology*. 2004;134:1181-1185.

Albert MA, Glynn RJ, Ridker PM. Alcohol consumption and plasma concentration of C-reactive protein. *Circulation*. 2003;107:443-447.

Black PH. The inflammatory response is an integral part of the stress response: Implications for atherosclerosis, insulin syndrome, type II diabetes and metabolic X syndrome. *Brain, Behaviour and Immunity*. 2003;17:350-364.

Bollen M, Keppens S, Stalmans W. Specific features of glycogen metabolism in the liver. *Biochemical Journal*. 1998;336(1):19-31.

Bordenave S, Brandou F, Manetta J, Fedou C, Mercier, Brun JF. Effects of acute exercise on insulin sensitivity, glucose effectiveness and disposition index in type 2 diabetic persons. *Diabetes and Metabolism*. 2008;34:250-257.

Brunengraber LN, Robinson AV, Chwals WJ. Relationship of serum C-reactive protein and blood glucose levels with injury severity and patient morbidity in a pediatric trauma population. *Journal of Pediatric Surgery*. 2009:992-996.

Butcher JL, Beckstrand RL. Fiber's impact on high-sensitivity C-reactive protein levels in cardiovascular disease. *American Academy of Nurse Practitioners*. 2010;22(11):566-572.

Einvik G, Ekeberg O, Klemsdal TO, Sandvik L, Hjerkinn EM. Physical distress is associated with cardiovascular events in a high risk population of elderly men. *BMC Cardiovascular Disorders.* 2009;9(14):1-6.

Geffken DF, Cushman M, Burke GL, Polak JF, Sakkinen PA, Tracy RP. Association between physical activity and markers of inflammation in a healthy elderly population. *American Journal of Epidemiology*. 2001;153(3):242-250.

Greenfield JR, Samras K, Jenkins AB, Kelly P, Spector TD. Moderate alcohol consumption, estrogen replacement therapy, and physical activity are associated with increased insulin sensitivity: Is abdominal adiposity the mediator? *Diabetes Care*. 2003;26(10):2734-2740.

Griffith JA, Ma Y, Chasan-Taber L, Olendzki BC, Chiriboga DE, Stanek III EJ, Merriam PA, Ockene IS. Association between dietary glycemic index, glycemic load, and high-sensitivity C-reactive protein. *Nutrition*. 2008;24:401-406.

Hu FB. Are refined carbohydrates worse than saturated fat*? The American Journal of Clinical Nutrition*. 2010;91:1541-1542.

Imhof A, Froehlich M, Brenner H, Boeing H, Pepys MB, Koenig W. Effect of alcohol consumption on systemic markers of inflammation. *Lancet*. 2001;357:763-767.

Imhof A, Woodward M, Doering A, Helbecque N, Loewel H, Amouyel P, Lowe GD, Koenig W. Overall alcohol intake, beer, wine, and systemic markers of inflammation in Western Europe: results from three MONICA samples (Ausburg, Glasgow, Lille). *European Heart Journal*. 2004;25:2092-2100.

Jenkins AL, Zdravkovic U, Wursch P, Vuksan V. Depression of the glycaemic index by high levels of β-glucan Fibre in two functional foods tested in type 2 diabetes. *European Journal of Clinical Nutrition*. 2002;56(7):622-628.

Kanterman J, Sade-Feldman M, Baniyash M. New insights into chronic inflammation-induced immunosuppression. *Seminars in Cancer Biology*. 2012;doi:10.1016/j.semcancer.2012.02.008.

Kiechl S, Willeit J, Poewe W, Egger G, Oberhollwnzer F. Insulin sensitivity and regular alcohol consumption: Large, prospective, cross sectional population (Bruneck study). *British Medical Journal*. 1996;313:1040-1044.

King DE, Egan BM, Woolson RF, Mainous III AG, Al-Solaiman Y, Jesri A. Effect of a high-fibre diet vs a fibre-supplemented diet on C-reactive protein level. *Archives of Internal Medicine*. 2007;167(5):502-506.

Kluft C, de Maat MPM. Sensitive markers of inflammation make it possible to study the chronic process: The rise of interest in low levels of C-reactive protein. *Vascular Pharmacology*. 2002;39(3):99-104.

Koenig W. Inflammation and coronary heart disease: An Overview. *Cardiology*. 2001;9(1):31-35.

Krebs HA, Freedland RA, Hems R, Stubbs M. Inhibition of hepatic gluconeogenesis by ethanol. *Biochemical Journal*. 1969;112(1):117-124.

Kroenke CH, Chu NF, Rifai N, Spiegelman D, Hankinson SE. A cross sectional study of alcohol consumption patterns and biological markers of glycaemic control among 459 women. *Diabetes Care*. 2003;26(7):1978-1978.

Kubzanski LD, Kawachi I, Spiro III A, Weiss ST, Vokonas PS, Sparrow D. Is worrying bad for your heart? A prospective study of worry and coronary heart disease in the Normative Aging Study. *Circulation*. 1997;95:818-824.

Kubzanski LD, Koenen KC. Is posttraumatic stress disorder related to development of heart disease? An update. *Cleveland Clinical Journal of Medicine*. 2009;76(2):S60-S65.

Levitan EB, Cook NR, Stampfer MJ, Ridker PR, Rexrode KM, Buring JE, Manson JE, Liu S. Dietary glycemic index, dietary glycemic load, blood lipids, and C-reactive protein. *Metabolism Clinical and Experimental*. 2008;57:437-443.

Liu S, Manson JE, Buring JE, Stampfer MJ, Willett WC, Ridker PM. Relation between a diet with a high glycemic load and plasma concentrations of high-sensitivity C-reactive protein in middle-aged women. *The American Journal of Clinical Nutrition.* 2001;75:92-98.

Ma Y, Hebert JR, Li W, Bertone-Johnson ER, Tinker L, Rosal MC, Ockene IS, Ockene JK, Griffith JA, Liu S. Association between dietary fiber and markers of systemic inflammation in the Women's Health Initiative Observational Study. *Nutrition*. 2008;24:941-949.

Mathews H, Liebenberg L. A Practical quantification of blood glucose production due to high-level chronic stress. *Stress Health*. 2012;doi:10.1002/smi.2415.

Mathews EH, Pelzer R. A new model to estimate bolus insulin need. Diabetes *Technology and Therapeutics*. 2009;11(12):813-817.

McEweb BS. Central effects of stress hormones in health and disease: Understanding the protective and damaging effects of stress and stress mediators. *European Journal of Pharmacology*. 2008;583:174-185.

Noakes TD. Lore of Running. Oxford, UK: Oxford University Press; 2001.

Oliveira A, Rodriguez-Artalejo F, Lopes C. Alcohol intake and systemic markers of inflammation: Shape of the association according to sex and body mass index. *Pharmacology and Cell Metabolism*. 2010;45(2):119-125.

Pedersen B, Saltin B. Evidence for prescribing exercise as therapy in chronic disease. *Scandinavian Journal of Medicine and Science in Sports*. 2006;16(1):3-63.

Pelzer R, Mathews EH, Liebenberg L. Preliminary application of a new bolus insulin model for type 1 diabetes. *Diabetes Technology and Therapeutics*. 2011;13(5):527-535.

Phillips AC, Batty D, Gale CR, Deary IJ, Osborn D, MacIntyre K, Carroll D. Generalized anxiety disorder, major depressive disorder, and their comorbidity as predictors of all-cause mortality: The Vietnam experience. *Psychosomatic Medicine*. 2009;71(4):395-403.

Pischon T, Hankinson SE, Hotamisligil GS, Rifai N, Rimm EB. Leisure-time physical activity reduces plasma levels of obesity-related inflammatory markers. *Obesity Research*. 2003;11(9):1055-1064.

Raikkonen K, Keltikangas-Jarvinen L, Adlercreutz H, Hautanen A. Psychological stress and the insulin resistance syndrome. *Metabolism*. 1996;45(12):1533-1538.

Rodondi N, Marques-Vidal P, Butler J, Sutton-Tyrrell K, Cornuz J, Satterfield S, Harris T, Bauer D, Ferrucci L, Vittinghoff E, Newman AB. Markers of atherosclerosis and inflammation for prediction of coronary heart disease in older adults. *American Journal of Epidemiology*. 2010;171(5):540-549.

Rodriguez-Vita J, Lawrence T. The resolution of inflammation and cancer. *Cytokine and Growth Factor Reviews*. 2010;21(1):61-65.

Roest AM, Martens EJ, De Jonge P, Denollet J. Anxiety and risk of incident coronary heart disease, a meta-analysis. *Journal of the American College of Cardiology*. 2010;76(2):38-46.

Roivainen M, Viik-Kajander M, Palosuo T, Toivanen P, Leinonen M, Saikku P, Tenkanen L, Manninen V, Hovi T, Manttari M. Infections, inflammation, and the risk of coronary heart disease. *Circulation*. 2000;101:252-257.

Saltiel AR, Kahn CR. Insulin signalling and the regulation of glucose and lipid metabolism. *Nature*. 2001;414:799-806.

Shanmugam N, Reddy MA, Guha M, Nararajan R. High glucose-induced expression of proinflammatory cytokine and chemokine genes in monocytic cells. *Diabetes*. 2003;52(5):1256-1264.

Siler SQ, Neese RA, Christiansen MP, Hellerstein MK. The inhibition of gluconeogenesis following alcohol in humans. *Endocrinology and Metabolism*. 1998;276(5):E897-E907.

Verma S, Szmitko PE, Yeh ET. C-Reactive protein. *Circulation*. 2004;109:1914-1917.

Versteeg H, Pedersen SS, Denollet J, Spek V. Type D personality and health status in cardiovascular disease populations: A meta-analysis of prospective studies. *European Journal of Cardiovascular Prevention and Rehabilitation.* 2011:doi:10.1177/1741826711425338.

Vodovotz Y, Constantine G, Rubin J, Csete M, Voit EO, An G. Mechanistic simulations of inflammation: Current state and future prospects. *Mathematical Biosciences*. 2009;217(1):1-10.

Vogelzangs N, Seldenrijk A, Beekman ATF, van Hout HPJ, de Jonge P, Penninx BWJH. Cardiovascular disease in persons with depressive and anxiety disorders. *Journal of Affective Disorders*. 2010;125(1-3):241-248.

Volp PA, de Oliviera EF, Alves DM, Bressan Ey. Energy expenditure: Components and evaluation methods. *Nutricion Hospitalaria*. 2011;26(3):430-440.

Wheeler ML. What are net carbs? *Diabetes Forecast*. 2010.

APPENDIX B

Blood glucose and Coronary Heart Disease: Comparing lifestyle effects

EH Mathews, G Mathews, L Liebenberg, JM Espach

Authors contracted to North-West University, Suite No 91, Private Bag X30, Lynnwood Ridge, 0040, South Africa and consultants to MCI (Pty) Ltd and TEMM International (Pty) Ltd

ehmathews@researchtoolbox.com; jespach@researchtoolbox.com; *LLiebenberg@researchtoolbox.com*

Corresponding author. Tel.: +27 12 809 0995; Fax: +27 86 515 5799

E-mail: LLiebenberg@researchtoolbox.com (L. Liebenberg)

Abstract

Aim: Research shows that high levels of low density lipoproteins (LDL) and low levels of high density lipoproteins (HDL), as well as high insulin, inflammation and blood viscosity levels are, among others, risk factors for coronary heart disease (CHD). It is unclear which one is the major risk factor. However, high blood glucose (BG) levels adversely influence all of them. Therefore, some important lifestyle factors which influence BG were investigated, *e.g.*, food and alcohol consumption, exercise, stress as well as fiber intake.

Problems addressed were: (1) current thinking on BG released from carbohydrates (CHO) does not lead to an acceptable explanation for the difference in CHD risk of refined and unrefined CHO; (2) the lifestyle factors are measured in diverse measuring units; and (3) the effect on BG of the different lifestyle factors is not quantified. These problems make it difficult to: (1) formulate a single consistent CHD risk theory, (2) to compare the impacts of the different lifestyle factors, and (3) to develop practical, quantifiable lifestyle suggestions for the five factors. Our aim is to solve these problems.

Method: A common unit to describe BG effect (and which is easy for anyone to visualize and understand), namely the equivalent teaspoons sugar (—ets), was developed for the five lifestyle factors. The glucose hypothesis was tested using calculated —ets values and CHD risk data from clinical trials of others.

Results: All the lifestyle factors influencing BG were shown to affect the risk for CHD. The Pearson-R^2 values for the analyzed data varied between 0.55 for fiber and 0.96 for stress. Psychological stress proved to have the greatest impact on the development of CHD with a more than four-fold increase in relative risk (RR) for CHD.

Conclusion: One consistent theory to quantify the lifestyle effects of food and alcohol consumption, psychological stress, low to moderate exercise and fiber intake (all *via* BG) on CHD was established. Clinical trial data from several publications were used

to verify the theory. Quantifiable and easy-to-understand lifestyle suggestions for prevention of CHD were established. Introducing the comparative quantification unit, —ets, the relative effect of especially prolonged high-level stress on CHD could be placed into perspective.

Key words: Coronary heart disease (CHD), blood glucose (BG), lifestyle factors, stress, exercise, alcohol, food, dietary fiber.

Introduction

Coronary Heart Disease (CHD) is the leading cause of death in the Western world (Roberts and Barnard 2005). One cause of Coronary Heart Disease is the pathogenic process associated with the development of arteriosclerotic plaque in the arteries (Stoll and Bendszus 2006, Shah and Forrester 1991, Falk 1989).

High blood viscosity creates regions of low wall shear stress in the arteries (Reneman and Hoeks 2008, Gnasso *et al.* 1997) which are prone to arteriosclerotic lesion formation (Malek *et al.* 1999, Chatzizisis *et al.* 2007). Therefore, high blood viscosity has been shown to correspond to increased risk of coronary heart disease (Stoll and Bendszus 2006, Koenig *et al.* 1997). Research shows that there is a significant correlation between blood glucose (BG) levels and blood viscosity (Cinar *et al.* 2001).

Furthermore, high levels of Low Density (LDL) "bad" cholesterol and low levels of High Density (HDL) "good" cholesterol are also known to increase the relative risk of coronary heart disease (Willerson and Ridker 2006, Manninen *et al.* 1992). High BG levels reduce HDL cholesterol levels and enhance the synthesis of Very Low Density (VLDL) cholesterol (Avramoglu *et al.* 2006) with adverse effects on RR for CHD (Frost *et al.* 1999, Garg *et al.* 1992).

A high insulin level is also shown to be a risk factor for CHD (Ruige *et al.* 1998, Perry *et al.* 1996). Insulin levels increase with an increasing BG level. High BG levels also increase the potential for inflammation which has also been shown to increase the risk of CHD (Mazonne *et al.* 2008).

Furthermore, high BG engenders adverse metabolic events within endothelial cells, promoting atherogenesis (Beckman *et al.* 2002; Holman *et al.* 2008; Ouriel 2001). It is unclear which of the above mentioned constitutes the major CHD risk factor. However, what we know is that high BG levels adversely influence all of them.

We also know that various lifestyle factors influence blood glucose (BG), including food (Denova-Gutierrez *et al.* 2010) and alcohol intake (Kroenke *et al.* 2003), dietary fiber added to a meal (Jenkins et al. 2002), physical exercise (Roberts and Barnard 2005) and psychological stress (Roberts and Barnard 2005).

However, these lifestyle factors are all measured in different units, *e.g.*, for food intake we use grams of carbohydrates (CHO) and the Glycemic Index (GI); for fiber we use grams; for alcohol consumption we use grams of ethanol; for exercise it is kcal (or METs) expended; and stress is usually reported as being low, moderate (medium), high, *etc.*

Before we can compare the impact of these factors (*via* BG) on coronary heart disease, we must develop a common unit to describe the BG effect of all these factors. We start off by investigating food intake.

There are studies linking a diet, high in refined carbohydrates (CHO), to an increased risk of CHD (Liu *et al.* 2002). But why refined CHOs? Do they metabolize more glucose energy than unrefined CHOs, thus raising the blood viscosity, reducing HDL, increasing VLDL and increasing insulin and inflammation levels?

Unfortunately, conventional practice as required by the FDA (Wheeler 2010) assumes that all CHOs release BG with an energy content of approximately 4 kcal per gram into the body (FAO 2004, FAO 2003, Livesey 2001, Livesey *et al.* 2000). This means that the metabolized glucose energy from refined and unrefined CHOs is apparently the same.

This can thus not explain the difference in CHD risks (*via* BG) for these two food types, refined and unrefined. But is this conventional wisdom regarding CHO-to-BG energy metabolism correct? This will be discussed in the next section and then applied to the risk of CHD.

CHD risk and the correct metabolized glucose energy from CHOs

We developed a more correct way than the one used during the past century (Atwater and Bryant 1900, Livesey 1990, Livesey *et al.* 2000) to calculate the BG energy metabolized from a CHO by a living creature (Mathews and Pelzer 2009). It was shown that, contrary to popular belief, the metabolized BG energy from different CHOs can differ vastly. This could explain the refined/unrefined CHO effect on CHD.

In the previous paper (Mathews and Pelzer 2009) we defined an energy unit termed —ets (or equivalent teaspoons sugar). This is a practical unit as it is easier to visualize a teaspoon of sugar than grams of CHO and Glycemic Index. Let us now briefly discuss the new —ets model to investigate in more detail the link between CHD and BG as a result of CHO ingestion.

To obtain the metabolized BG energy from any CHO in terms of an equivalent teaspoons sugar (—ets), the following relation holds (Mathews and Pelzer 2009):

$$—ets_{CHO} = \frac{\eta_{CHO}}{\eta_{Sugar}} \frac{m_{CHO}}{5} = \frac{GI_{CHO}\, m_{CHO}}{325} \qquad (1)$$

Where η_{CHO} and η_{sugar} are the metabolic efficiencies of the CHO under investigation and sugar, respectively. GI_{CHO} is the glycemic index whilst the mass of the CHO is given by m_{CHO}. All *GI* values are referenced to the glucose standard.

The higher the GI value (*i.e.*, the more refined the CHO), the higher the metabolic efficiency (η_{CHO}) and the more BG (measured in —ets) becomes available. This could explain the different CHD risks for refined versus unrefined CHO ingestion.

Studies were identified which report sufficient information to enable the computation of the participants' metabolized CHO energy consumption as described by the —ets equation (Equation 1). The studies investigated the effects of metabolized CHO

energy consumption on coronary heart disease (Liu *et al.* 2000, Mursu *et al.* 2011, Sieri *et al.* 2010, and Denova-Gutierrez *et al.* 2009).

The η_{CHO} (≈ $GI_{CHO}/100$) and m_{CHO} values were obtained from the clinical trials investigated, and the average daily ets consumption was computed using Equation (1). The results, shown in Figure B 1, indicate the effect of daily ets consumption on the risk of CHD using trial data of the various studies.

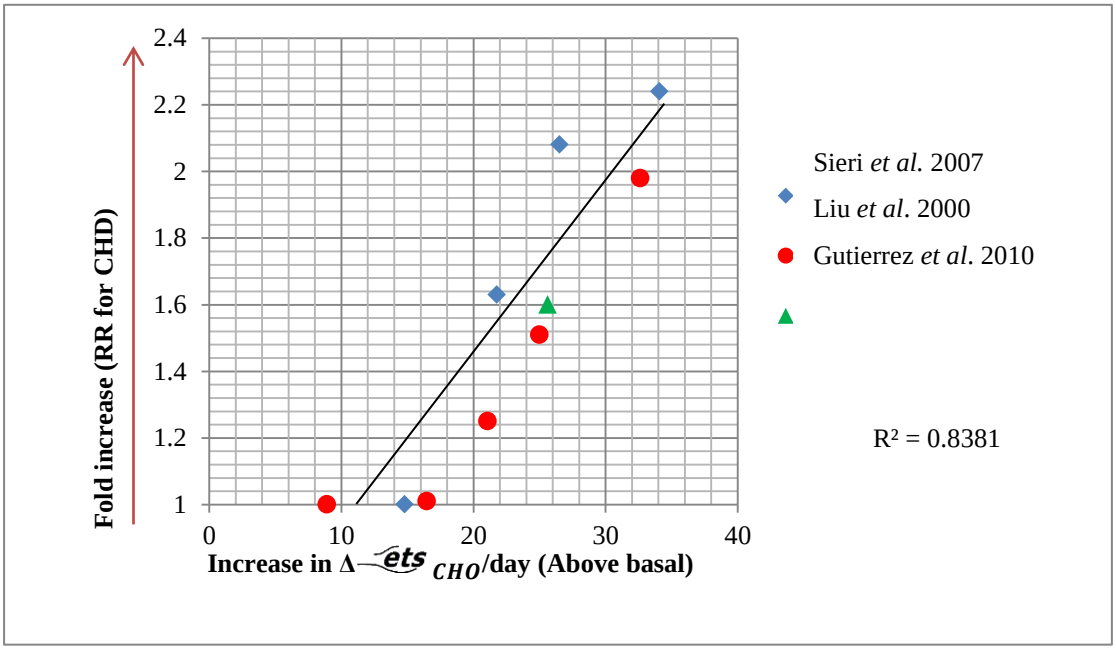


Figure B 1: The linearized relationship between daily ets_{CHO} consumption and the relative risk of Coronary Heart Disease (CHD) for a number of clinical trials.

Figure B 1 (with R^2 = 0.84) suggests that the risk of coronary heart disease increases with blood glucose energy metabolized from CHO as expressed in ets_{CHO} (which increases as the food becomes more refined). The CHD risk starts to increase from consumption of about 36 ets per day. This is approximately the ets_{CHO} count of one medium-sized fast food burger meal (burger, fries and cola). The relative risk doubles (RR = 2) when a person consumes an additional upsized fast food burger meal per day.

We previously showed that the average basal energy requirement for men and women at average activity levels is about 23 —ets per day (Mathews and Liebenberg 2012). New evidence which has become available to us shows that this is closer to 28 —ets per day (Pinheiro Volp *et al.* 2011). It is apparent that consumption of more BG than the body requires for basal needs, increases the relative risk of CHD.

The idea behind the —ets concept was not only to develop a more correct metabolized CHO energy value and a common unit for all the lifestyle factors but also to develop a unit which is easy to understand, interpret and implement. Keeping track of your daily —ets consumption is simple and assists in making smart food and portion size choices.

More than 4 000 different foodstuffs have been analyzed for their —ets $_{CHO}$ content. Table B 1 shows the —ets $_{CHO}$ values for a few popular foods. It can be seen that the values are typically small and easy to add. (If one uses the mass of CHO, the values become on average five-fold larger!)

Table B 1: Typical—ets energy values for some popular foods

Food	**Equivalent teaspoons sugar —ets $_{CHO}$, per serving**
340 ml can of typical soda	8
Fresh apple, with skin (medium fruit)	2
Cheeseburger	7
Medium French fries	14
Blueberry muffin (medium serving)	10
Medium slice of white bread	3

The theory to calculate the correct metabolized blood glucose values for CHO ingestion and its relevant risk for CHD is now in place. The effect of fiber on metabolized BG energy and its impact on CHD will now be investigated in the next section.

Fiber: Blood glucose metabolism and its impact on coronary heart disease

Several authors have shown that dietary fiber reduces the risk of coronary heart disease (Ward *et al.* 2011, Kokubu *et al.* 2011, Pereira *et al.* 2004, Anderson 2000, and Truswell 2002). Different reasons are proposed for this phenomenon (Brownlee 2011, Guarner and Malagelada 2003, Luo *et al.* 1996, Englyst and Englyst 2005, Roberts and Barnard 2005).

Our hypothesis is that the fiber in a meal reduces the metabolic efficiency of the meal and thus reduces the BG metabolized from the CHO in the meal. A reduction in metabolized BG will reduce the risk of CHD. The metabolic efficiency is *inter alia* dependent on the GI value of the food (Mathews and Pelzer 2009), which is reduced when fiber is added to the meal (Jenkins *et al.* 2002).

Jenkins *et al.* (2002) added fiber to different foods and measured the resulting glucose response. One gram of fiber added to 50 grams of CHO reduced the GI of a typical meal by 4 units. This can be translated to a reduction of 0.6 $\overset{\frown}{ets}$ per gram of extra fiber added to a meal.

A new variable, $\overset{\frown}{ets}_{Fib\ added}$ can now be defined. It is described by the following equation:

$$\overset{\frown}{ets}_{Fib\ added} = 0.6 \times m_{Fib\ added} \tag{2}$$

Where $m_{Fib\ added}$ is the mass of the fiber added in grams.

Published measured data were obtained for CHD relative risk (RR) against dietary fiber intake (Ward *et al.* 2011, Kokubu *et al.* 2011). Using Equation (2) and the published data, $\overset{\sim}{ets}_{Fib\ added}$ values can be calculated and plotted against the published RR measurements (Figure B 2).

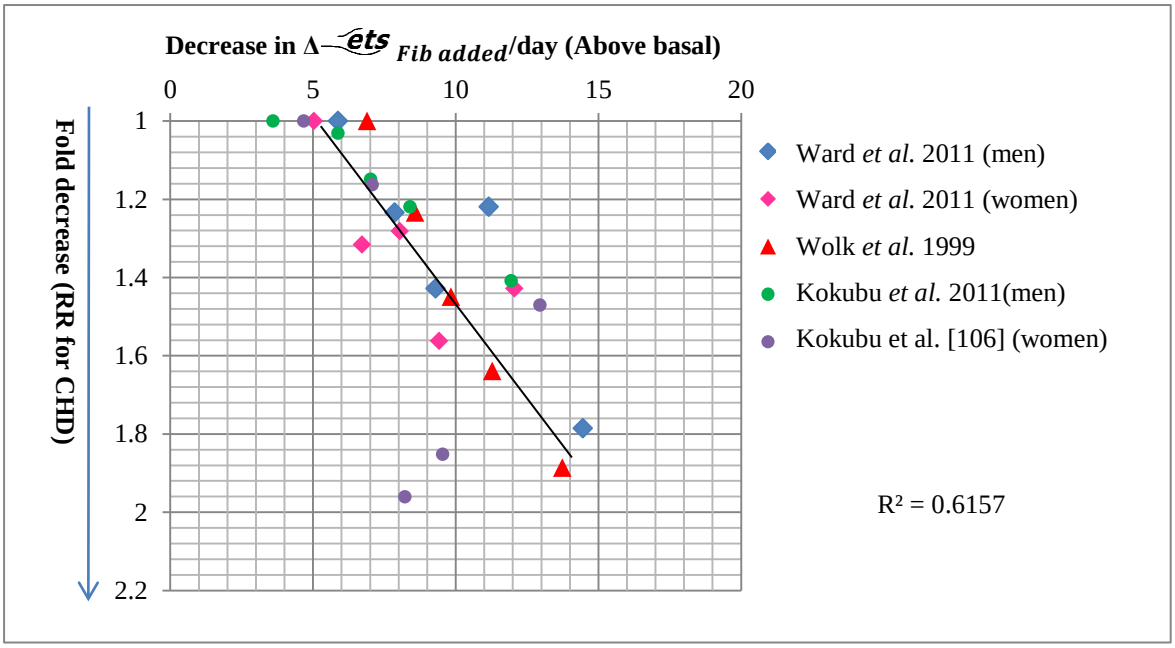


Figure B 2: The average linearized relationship between fiber intake and RR of CHD for a number of published studies.

Note that in Figure B 2 a RR of 2 corresponds to a two-fold increase or reduction in relative risk when compared with normal risk (RR = 1). The R^2 for the correlation between fiber and relative risk for CHD was 0.55.

An important implication from our hypothesis is that additional fiber must be eaten with the meal to reduce the meal's metabolic efficiency and thus its net BG energy release. Fiber eaten on its own at other times of the day will have little effect according to our hypothesis.

What does this mean on a practical lifestyle level? One can now easily quantify the BG effect for fiber. For example, if one adds 7 g of fiber to three meals a day (*i.e.*

21 g additional fiber/day), by Equation (2) this gives a BG metabolism reduction equal to $0.6 \times 21 = 12.6$ —ets energy for the meals.

Figure B 2 shows that this will reduce the trial group's relative risk of CHD by a factor of approximately 1.6 (*i.e.* RR = 1.6). Figure B 2 also shows that extra fiber, equivalent to values less than 3 —ets, does not influence the RR.

The effect of exercise on blood glucose and coronary heart disease (CHD)

Lack of physical inactivity is an important risk factor for CHD (Pedersen and Saltin 2006, Haskell *et al.* 2007, Roberts and Barnard 2005, Sundquist *et al.* 2005, Fuster *et al.* 2005, Warburton *et al.* 2006, Libby *et al.* 2002). Our hypothesis regarding exercise is that it *inter alia* consumes one's available BG energy. Let us investigate this hypothesis by first quantifying the exercise effect on BG.

It has been shown that the energy effect of BG can be described in terms of the easy-to-use unit, —ets (Hildebrand and Mathews 2004). This relationship is utilized to quantify and investigate the effect on CHD risks of energy expended through exercise.

Approximately 20% of the energy expended during exercise ($0.2 \times kcal_{Excercise}$) comes from BG (Noakes 2001). The BG energy expressed in —ets expended by a test subject can then be calculated using the energy expended in $kcal_{Excercise}$ and applying the conversion between *kcal* and —ets, namely the following (equation (11) Mathews and Pelzer (2009)):

$$1\text{—ets} = E_{Teaspoon\ Sugar} = 0.65 \times 5g \times 4kcal/g = 13kcal \qquad (3)$$

This results in the following:

$$\text{ets}_{Exercise} = 0.2 \times kcal_{Exercisee} \times (\text{ets}/kcal) = 0.2 \times kcal_{Exercise} \times \frac{1}{13}$$

$$= \frac{kcal_{Exercise}}{65}$$

(4)

The value $kcal_{Exercise}$ is calculated by accounting for the type, duration and intensity of the exercise, as well as the body weight of the individual (ACSM 2007). Good approximations for BG consumption due to exercise can therefore be made for a specific person.

With the BG required for physical exercise quantified by Equation (4) for energy expended, ($\text{ets}_{Exercise}$), over and above basal needs, we can now investigate published clinical trials for exercise and CHD risk. Several researchers investigated the relationship between physical activity (type, duration, and intensity) and coronary heart disease (Manson *et al.* 2002, Tanasescu *et al.* 2002, Zheng *et al.* 2009).

These results were used to determine the average daily $\text{ets}_{Exercise}$ expenditure, using equation (4). We focus on low-intensity exercise (walking, jogging, *etc.*) as it is more practical to achieve for most people rather than high-intensity exercise (*e.g.*, kickboxing), (Kruk 2011, Pearce 2008, Miyazaki *et al.* 2001, Saltiel and Kahn 2001).

The results from these low-intensity exercise studies are given in Figure B 3. Again note that we define RR of 2 corresponds to a two-fold decrease in normal CHD risk (RR=1). The R^2 value is 0.60.

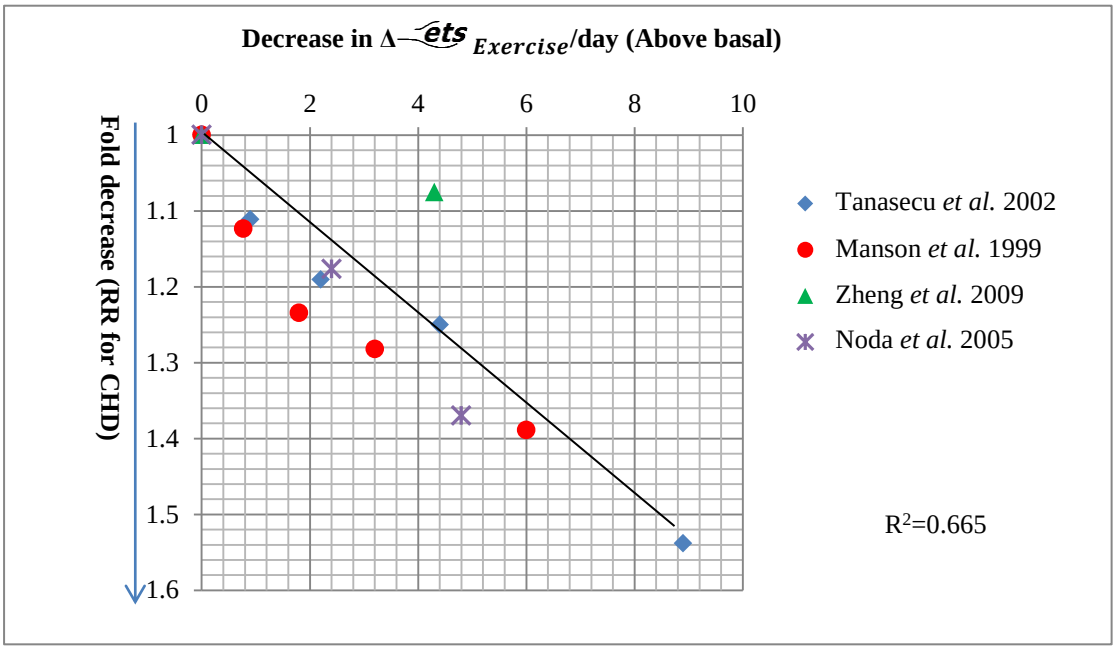


Figure B 3: The linearized relationship between low to moderate-intensity exercises in terms of $ets_{Exercise}$ (exercises above basal activity) and RR of CHD for a number of published studies.

What does Figure B 3 mean on a practical lifestyle level? Daily low to moderate-intensity exercise of approximately 7 $ets_{Exercise}$ energy reduces the risk for CHD by a factor of 1.5 (*i.e.* RR = 1.5), *cf.* Fig. 3. This is equivalent to approximately 60 minutes of walking at 6 km/h per day for a 70-kg male. Table B 2 provides examples of typical $ets_{Exercise}$ energy expended for some popular low-intensity exercises.

Table B 2: Typical $ets_{Exercise}$ values for physical exercises

Activity, for a duration of 60 min	**Equivalent teaspoons sugar $ets_{Exercise}$ energy expended by an 70-kg male**
Cycling at 21 km/h, level road	6
Swimming (crawl)	6
Tennis	9
Walking at 6 km/h	8
Running at 11 km/h	17

The effect of alcohol consumption on blood glucose (BG) and coronary heart disease (CHD)

Alcohol *inter alia* suppresses the ability of the liver to produce BG *via* gluconeogenesis and glycogenolysis (Krebs *et al*. 1969, Bollen *et al*. 1998, Siler *et al.* 1998). Our hypothesis thus suggests a favourable link between alcohol consumption and *RR* for CHD.

Published data indeed link *moderate* alcohol consumption (measured in grams of ethanol per day) with a lower relative risk (RR) for CHD (Hvidtfeld *et al.* 2010, Arriola *et al.* 2009, Ikehara *et al.* 2008). This is shown in Table B 3, or by the following equation:

$$\mathrm{RR} = f_1 Alcohol \tag{5}$$

Table B 3: Relative risk (RR) of CHD due to moderate alcohol consumption given in ethanol (g/day)

Reference	**Ikehara *et al.* (2008)**		**Hvidtfeld *et al.* (2010)**				**Arriola *et al. (*2009)**		
Ethanol g/d	0	22.9	0	4.9	19.9	29.9	0	5	30
RR	1	0.84	1	0.78	0.68	0.52	1	0.72	0.58

As with the previous lifestyle factors we want to relate the BG reduction effect of alcohol with the unit, $\overset{\frown}{ets}$. With less BG produced (ΔBG) by the liver, less insulin (ΔI) is needed and thus secreted by the pancreas. We can assume a linear relationship between BG production and insulin secretion (Mathews and Pelzer 2009). This is shown in equation (6):

$$\Delta I = f_2.\Delta BG \tag{6}$$

There is also a direct correlation between change in BG level and change in $\overset{\frown}{ets}$, (Pelzer *et al.* 2011):

$$\Delta BG = f_3.\Delta \overset{\frown}{ets} \tag{7}$$

Substituting equation (7) into equation (6) leads to the following equation:

$$\therefore \Delta I = f_4.\Delta \overset{\frown}{ets} \tag{8}$$

To relate insulin levels to $\overset{\frown}{ets}$ levels, we determined the insulin sensitivity, f_4. Eleven people were fitted with continuous glucose monitors for three days. From

these measurements the average insulin sensitivity was calculated as 0.69, (*cf.* Table B 4), and used as a guide for our calculations.

Table B 4: Insulin sensitivity (f_4) related to $\overline{ets}$ levels

Subject	$\Delta I / \Delta \overline{ets}$
1	0.77
2	0.83
3	0.67
4	0.53
5	0.77
6	0.30
7	1.43
8	0.56
9	0.43
10	0.77
11	0.56
Average = f_4	**0.69**

From the first two rows of Table B 5 we can find the correlation between alcohol consumption *(Alcohol)* and reduction in daily insulin secretion (ΔI):

$$\Delta I = f_5 Alcohol \tag{9}$$

The reduction in insulin *(* ΔI *) inter alia* reflects a reduction in BG (*i.e.* $\Delta\overline{ets}$) from especially the liver (Row 3 in Table B 5 using equation (8)). Substituting equations (5) and (8) into equation (9) gives the relative risk (RR) of CHD with alcohol consumption, expressed in one common unit, $\overline{ets}$:

$$RR = f_6 . \Delta \overline{ets}_{Alcohol} \quad (10)$$

Figure B 4 (with R^2 = 0.55) plots equation (10) for moderate alcohol intake (*e.g.*, fewer than two glasses of wine per day) using the data from Tables B 3 to B 5.

Table B 5: Alcohol consumption and insulin secretion

References	**(Kroenke *et al*. 2003)**		**(Greenfield *et al*. 2003)**	
Ethanol (g/day)	15.0	35.0	11.4	22.9
Δ*I*, Reduction in insulin secretion per day (mU/l)	3.89	4.32	5.9	5.6

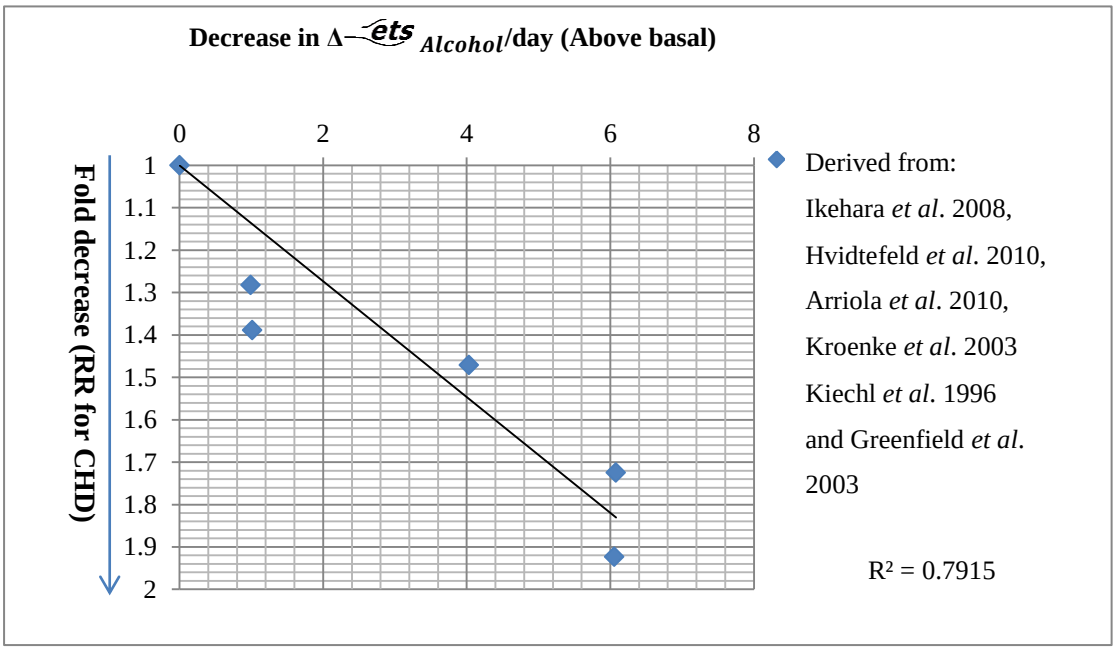


Figure B 4: Relative risk *(RR)* of CHD due to alcohol intake, quantified in terms of $\overline{ets}_{Alcohol}$.

What is the practical implication of Figure B 4? *Moderate* alcohol intake reduces the RR for CHD. Consuming one glass (approx. 200 ml) of dry white wine (12% ethanol per volume), is equivalent to 23 g of ethanol or approximately 8 $ets_{Alcohol}$ (*cf.* Table B 5). From Figure B 4 it can be seen that the RR for CHD reduces by approximately a factor 2 , from a normal risk (RR = 1).

Note that excessive alcohol intake increases the RR for CHD (Ikehara *et al.* 2008, Hvidtfeldt et al. 2010). We therefore do not recommend higher alcohol consumption also due to other potential negative effects.

Glucose energy released by counter regulation due to stress

Stress is *inter alia* an important contributor to the quantity of BG produced by especially the liver (McEwen 2008, Black 2003, Mathews and Liebenberg 2011, Saltiel and Kahn 2001, Räikkönen *et al.* 1996).

We quantified the BG production due to chronic, (in the order of weeks), high-level psychological stress using ets, (Mathews and Liebenberg 2012). Our research shows an average BG increase of 2.2 fold (or 50 ets_{Stress}) above basal needs for high levels of prolonged stress, which corresponds to a relative risk of 4.1.

Similar to our other work for high-level stress, we linearly scaled the relative risk factors for moderate and low levels of stress (from Kubzanski *et al.* 1997, Kubzanski *et al.* 2009, Envik *et al.* 2009, Vogelzang *et al.* 2010, Roest *et al.* 2010, Versteeg *et al.* 2011, and Phillips *et al.* 2009) against that of high-level stress. The extra ets_{Stress} secreted per day above daily basal need by the individuals as a result of stress (low-, moderate-, and high levels) is given in Figure B 5. The R^2 value is 0.96.

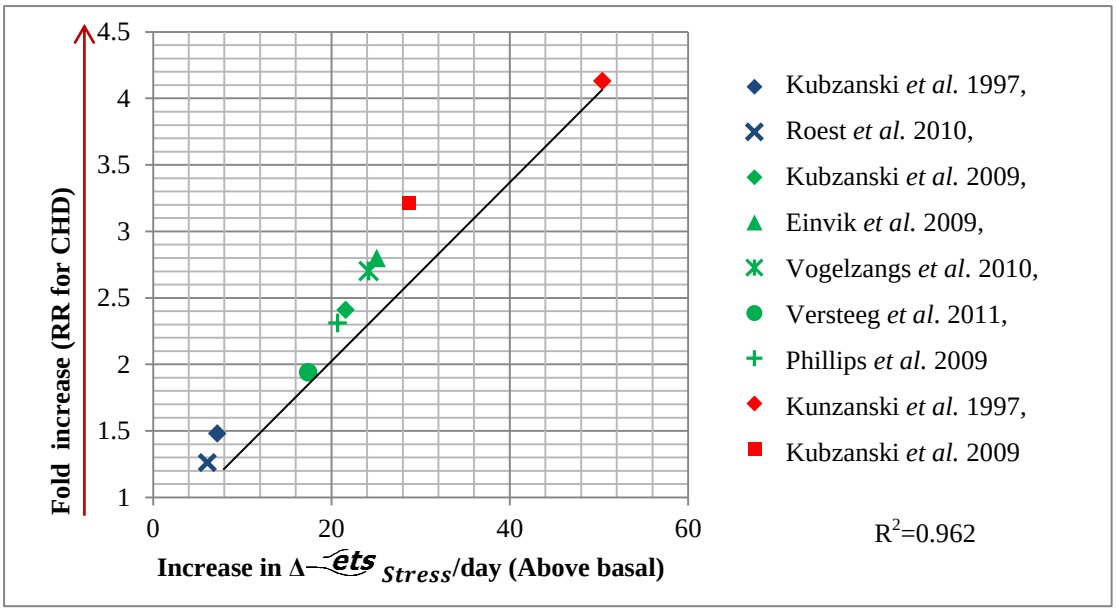


Figure B 5: The linearized relationship between prolonged stressful life events (low-, medium-, and high-intensity) and risk of Coronary Heart Disease (CHD) for a number of studies.

Now that stress has been quantified in terms of ets_{Stress}, it is easier to make quantitative and comparative predictions about the adverse effects of stress on CHD.

Discussion

Using the data from Figures B 1 to B 5, Figure B 6 could be constructed. The graphs start at a normal relative risk (*RR* = 1) and show the fold increase and decrease of the relevant contributors. The CHD risk of the five lifestyle BG contributors can now be compared quantitatively.

The lengths of the graphs in Figure B 6 give an idea of practical Δets values for the different lifestyle factors above basal needs (from the respective clinical trials). It can be seen that, in practice, stress can quickly induce very high levels of ets secreted above basal levels.

This is much higher than the practical $\Delta\overset{\frown}{ets}$ values for the other lifestyle-BG effects. Figure B 6 hints that treatment for stress (including anxiolytics) to reduce CHD risk may be more important than generally recognized.

The stress and exercise curves have similar absolute values of slopes. Similarly, the food and fiber curves are near-mirror images of each other. Exercise (Bordenave *et al.* 2008, Pedersen and Saltin 2006) and stress (Versteeg *et al.* 2011) both influence insulin sensitivity, albeit in opposite manners, thus explaining their larger slopes than those of the food and fiber curves.

Despite improving insulin sensitivity (Sierksma *et al.* 2004, Room *et al.* 2005), moderate alcohol consumption also has other antiatherosclerotic effects (O'Keefe *et al.* 2007, Stampfer *et al.* 2000, Mukamal *et al.* 2003), resulting in the large slope shown in Figure B 6.

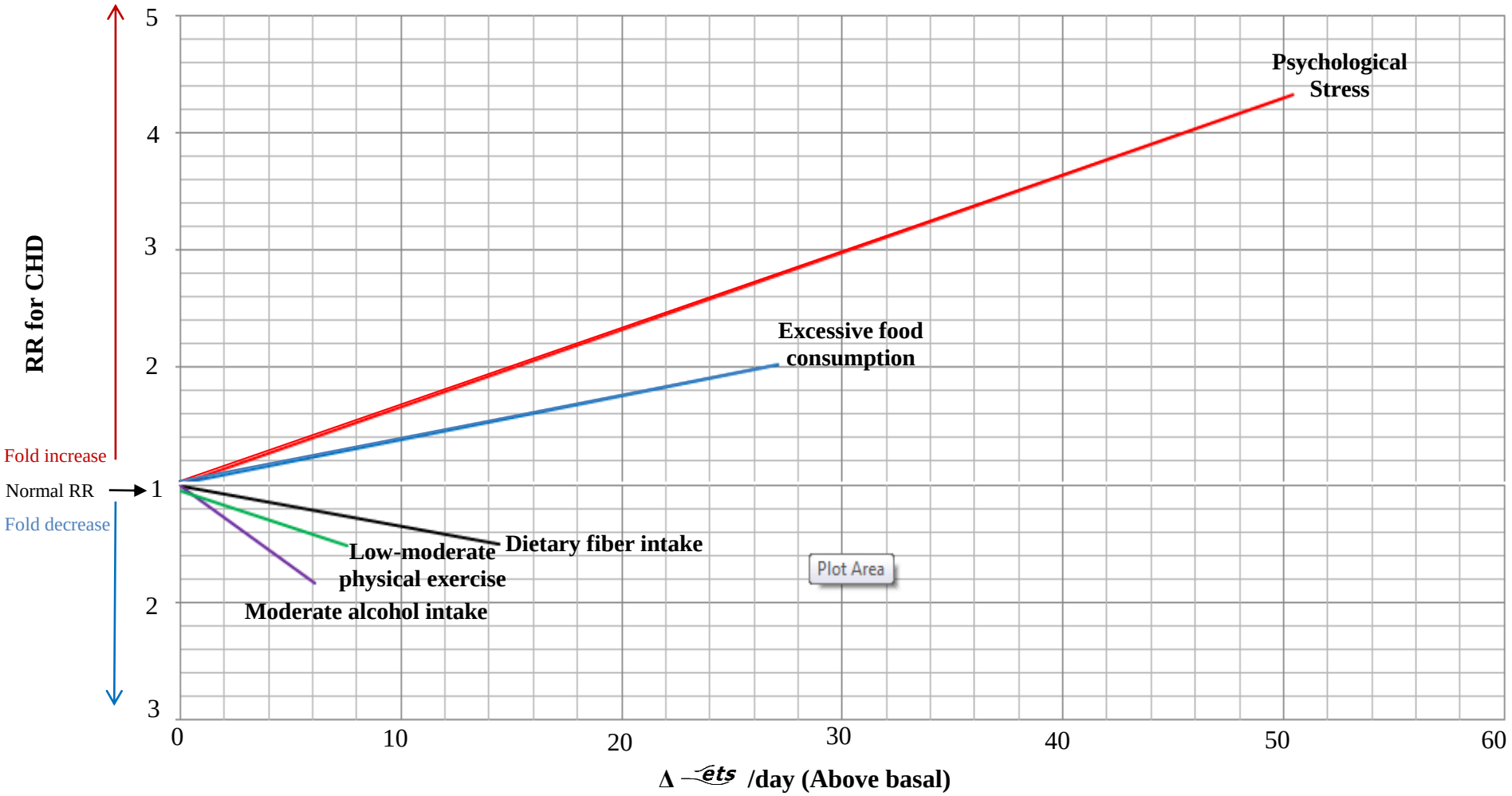


Figure B 6: The consolidation of the glycaemic effect (in terms of ets) of the different lifestyle factors on the RR of CHD

Conclusion

The most important contribution of this study is that a single, consistent and easy-to-understand, well verified and quantifiable theory was developed to explain the effect of food, alcohol, dietary fiber, physical exercise and psychological stress on relative risk for coronary heart disease (CHD). Quantification, using the (—ets) unit made it possible to compare lifestyle factors and to show the importance on CHD risk of prolonged high-level stress.

Although we have discussed glucose control as a measure to ensure a lifestyle concomitant with reduced CHD risk, it has not escaped our notice that this knowledge may lead to new solutions for controlling proliferative CHD. Details will be published later.

Acknowledgements

The "angel" investor for this project was Dr. Arnold van Dyk. Many co-workers helped with the research. Corlia Mathews initiated our thinking and developed the extensive food database. We thank Kobus Laubsher and Tarina van Zyl who assisted with the literature survey and data reduction. We are especially indebted to the many researchers whose published data we could use to independently verify our hypotheses. The following people reviewed the whole, or relevant parts of this manuscript, or gave us written feedback on our ideas: *Food:* Prof. Rury Holman (Churchill Hospital); *Stress:* Prof Anna Phillips (Birmingham University); *Dietary Fiber:* Dr Iain Brownlee (University of Newcastle-upon-Tyne); *Alcohol:* Prof. Eric Rimm (Harvard School of Public Health).

Because the underlying theory is relevant to other problems (*e.g.*, cancer, diabetes, feeding programmes, *etc.*), it will also be reported elsewhere for a better understanding of these problem areas.

References

ACSM. *Metabolic Calculations Handbook.* American College of Sports Medicine. Baltimore, Maryland, USA: Lippincott Williams & Wilkins; 2007.

Ambrose JA, Barua RS. The pathophysiology of cigarette smoking and cardiovascular disease-an update. *Journal of the American College of Cardiology.* 2004;43(10):1731-7.

Amici A, Cicconett P, Sagrafoli C, Baratta A, Passador P. Exaggerated morning blood pressure surge and cardiovascular events. A 5-year longitudinal study in normotensive and well-controlled hypertensive elederly. *Archives of Gerontology Geriatric.* 2009;49:e105-e109.

Anderson JW. High-Fiber diets for diabetic and hypertriglyceridemic patients. *Canadian Medical Association Journal.* 2000;123(10):975-979.

Anfossi G, Russo I, Bonomo K, Trovati M. The cardiovascular effects of metformin: Further reasons to consider an old drug as a cornerstone in the therapy of type 2 diabetes mellitus. *Curriculum of Vascular Pharmacology.* 2010;8:327-337.

Arriola L, Martinez-Camblor P, Larranage N, Basterretxea M, Amiano P, Moreno-Iribas C, Carracedo R, Agudo A, Ardanaz E, Barricarte A, Buckland G, Cirera L, Chirlaque MD, Martinez C, Molina E, Navarro C, Quiro's JR, Rodriguez L, Sanchez MJ, Tormo MJ, Gonzalez CA, Dorronsoro M. Alcohol intake and the risk of coronary heart disease in the Spanish EPIC cohort study. *Heart.* 2010;96:124-130.

Atwater WO and Bryant AP. The availability and fuel values of food materials, Connecticut Agricultural Experiment Station, *12th Annual Report 1900*;73-110.

Avramoglu RK, Basciano H, Adeli K. Lipid and lipoprotein dysregulation in insulin resistant states. *Clinica Chimica Acta.* 2006;368(1-2):1-19.

Bailey CJ. Metformin: Effects on micro and macrovascular complications in type 2 diabetes. *Cardiovascular Drugs and Therapy.* 2008;22:215-224.

Beckman JA, Creager MA, Libby P. Diabetes and atherosclerosis—epidemiology, pathophysiology, and management. *Journal of the American Medical Association.* 2002;287(19):2570-2581.

Black PH. The inflammatory response is an integral part of the stress response: Implications for atherosclerosis, insulin syndrome, type II diabetes and metabolic syndrome X. *Brain, Behavior, and Immunity.* 2003;17:350-364.

Bollen M, Keppens S, and Stalmans W. Specific features of glycogen metabolism in the liver. *Biochemical Journal.* 1998;336:19-31.

Bordenave S, Brandou F, Manetta J, Fédou C, Mercier, Brun J-F. Effects of acute exercise on insulin sensitivity, glucose effectiveness and disposition index in type 2 diabetic persons. *Diabetes and Metabolism.* 2008;34:250-257.

Boscarino JA. Posttraumatic stress disorder and physical illness. Results from clinical and epidemiologic studies. *Annals of the New York Academy of Sciences.* 2004;1032:141-153.

Brouns F, Bjorck I, Frayn KN, Gibbs AL, Lang V, Slama G, Wolever TMS. Glycaemic index methodology. *Nutrition Research Reviews.* 2005;15:145-171.

Brownlee IA. The physiological roles of dietary fiber. *Food Hydrocolloids.* 2011;25:238-250.

Charmandari, E., Tsigos, C., Chrousos, G. (2005). Endocrinology of the stress response. *Annual Review of Physiology.* 67(1):259-284.

Chatzizisis YS, Coskun AU, Jonas M, Edelman ER, Feldman CL, and Stone PH. Role of endothelial shear stress in the natural history of coronary atherosclerosis and vascular remodelling. *Journal of the American College of Cardiology.* 2007;49(25):2379-2393.

Cinar Y, Senyol AM, Duman K. Blood viscosity and blood pressure: role of temperature and hyperglycemia. *American Journal of Hypertension.* 2001;14:433-438.

Clark HE, Coates ME, Eva JK, Ford DJ, Miller CK, O'Donoghue PN, Scott PP, Ward RJ. Dietary standards for laboratory animals: Report of the Laboratory Animals Centre Diets Advisory Committee. *Laboratory Animal.* 1977;11:1-28.

Denova-Gutierrez E, et al. Dietary glycaemic index, dietary glycaemic load, blood lipids, and coronary heart disease. *J Nutrition and Metabolism.* 2010;8 pages, doi: 10.1155/2010/170680.

Einvik G, Ekeberg O, Klemsdal TO, Sandvik L, and Hjerkinn EM. Physical distress is associated with cardiovascular events in a high risk population of elderly men. *BMC Cardiovascular Disorders* 2009;9(14),6 pages, doi: 10.1186/1471-2261-9-14.

Englyst KN, and Englysts HN. Carbohydrate bioavailability. *British Journal of Nutrition.* 2005;94:1-11.

Falk E. Morphologic features of unstable atherothrombotic plaques underlying acute coronary syndromes. *American Journal of Cardiology.* 1989;63:114E-120E.

FAO. Energy in human nutrition. Report of a Joint FAO/WHO/UNU expert Consultation. Food and Nutrition Paper No. 78. Rome, 2004.

Frost G, Leeds AA, Dore CJ, Madeiros S, Brading S, Dornhorst, A. Glycaemic index as a determinant of serum HDL-cholesterol concentration. *Lancet.* 1999;353:1045-1048.

Garg A, Grundy SM, Koffler M. Effect of high carbohydrate intake on hyperglycemia, islet function, and plasma lipoproteins in NIDDM. *Diabetes Care.* 1992;15:1572-1580.

Giugliano M, Bove M, Grattarola M. Insulin release at the molecular level: metabolic-electrophysiological modelling of the pancreatic beta-cells. *IEEE Transactions on Biomedical Engineering.* 2000;47:611-623.

Gnasso A, Irace C, Carallo C, De Franceschi MS, Motti C, Mattioli PL, Pujia A. In vivo association between low wall shear stress and plaque in subjects with asymmetrical carotid atherosclerosis. *Stroke*. 1997;28:993-998.

Greenfield JR, Samras K, Jenkins AB, Kelly P, Spector TD. Moderate alcohol consumption, estrogen replacement therapy, and physical activity are associated with increased insulin sensitivity: Is abdominal adiposity the mediator? *Diabetes Care.* 2003;26(10):2734-2740.

Guarner F, and J-R Malagelada. Gut flora in health and disease. *Lancet.* 2003;361:512-519.

Haskell WL, Lee IM, Pate RR, Powell KE, Blair SN, Franklin BA, Macera CA, Heath GW, Thompson PD, Bauman A. Physical activity and public health: Updated recommendation for adults from the American College of Sports Medicine and The American Heart Association. *Circulation.* 2007;116:1081-1093.

Hildebrand GE, and Mathews EH. A new method to predict the carbohydrate needs for diabetics during exercise. *Proc. 64th Scientific Sessions American Diabetes Association*. 2004;53:A532.

Holman RR, Paul SK, Bethel MA, Matthews DR, and Neil HAW. 10-Year follow up of intensive glucose control in type 2 diabetes. *New England Journal of Medicine.* 2008;359:1-13.

Howard PA, Delafontaine P. Nonsteroidal anti-inflammatory drugs and cardiovascular risk. *Journal of the American College of Cardiology.* 2004;43(4):519-25.

Hvidtfeldt UA, Tolstrup JS, Jakobsen MU. Alcohol intake and risk of coronary heart disease in younger, middle-aged, and older adults. *Circulation*. 2010;121:1589-1597.

Ikehara S, Iso H, Toyoshima H, Date C, Yamamoto A, Kikuchi S, Kondo T, Watanabe Y, Akio K, Wada , Inaba Y, Tamakoshi A. Alcohol consumption and the mortality from stroke and coronary heart disease among Japanese men and women: The Japan Cohort Study. *Stroke.* 2008;39:2936-2942.

Jadhav S, Ferrell W, Greer IA, Petrie JR, Cobbe SM, Sattar N. Effects of metformin on microvascular function and exercise tolerance in women with angina and normal coronary arteries. *Journal of the American College of Cardiology*. 2006;48(5):956-63.

Jenkins AL, Jenkins DJA, Zdravkovic U, Würsch P, Vuksan V. Depression of the glycaemic index by high levels of β-glucan Fiber in two functional foods tested in type 2 diabetes. *European Journal of Clinical Nutrition.* 2002;56:622–628.

Kario K. Morning surge in blood pressure and cardiovascular risk-evidence and perspectives. *Hypertension.* 2010;56:765-773.

Kiechl S, Willeit J, Poewe W, Egger G, Oberhollenzer F, *et al*. Insulin sensitivity and regular alcohol consumption: large, prospective, cross sectional population (Bruneck study). *British Medical Journal.* 1996;313:1040-1044.

Koenig W, Sund M, Birgit F, Doring A, Lowel H, Ernst E. Plasma viscosity and the risk of coronary heart disease. *Arteriosclerosis Thrombosis and Vascular Biology.* 1997;18:768-772.

Krebs HA, Freedland RA, Hems R, and Stubbs M. Inhibition of hepatic gluconeogenesis by ethanol. *Biochemical Journal.* 1969;112:117-124.

Kroenke CH, Chu NF, Rifai N, Spiegelman D, Hankinson SE. A cross sectional study of alcohol consumption patterns and biological markers of glycaemic control among 459 women. *Diabetes Care*. 2003;26(7):1978-1978

Kruk J. Physical exercise and oxidative stress. *Medicina Sportiva.* 2011;15(1):30-40.

Kubzanski LD, Kawachi I, Spiro III A, Weiss ST, Vokonas PS, and Sparrow D. Is worrying bad for your heart? A prospective study of worry and coronary heart disease in the Normative Aging Study. *Circulation.* 1997;95:818-824.

Kubzansky LD and Koenen KC. Is posttraumatic stress disorder related to development of heart disease? An update. *Cleveland Clinical Journal of Medicine.* 2009;76(2):S60-S65.

Lee BM, Wolever TMS. Effects of glucose, sucrose and fructose on plasma glucose and insulin responses in normal human: Comparison with white bread. *European Journal of Clinical Nutrition.* 1998;52:924-928.

Libby P, Ridker PM, and Maseri A. Inflammation and atherosclerosis. *Circulation.* 2002;1135-2243, doi: 10.1161/hc0902.104353.

Liu S, Buring JE, Sesso HD, Rimm EB, Willet WC, and Manson JE. A prospective study of dietary Fiber intake and risk of cardiovascular disease among women. *Journal of the American College of Cardiology*. 2002;39(1):49-56.

Liu S, Willett WC, Stampfer MJ, Hu FB, Franz M, Sampson, Hennekens CH, Manson JE. A prospective study of dietary glycaemic load, carbohydrate intake, and risk of coronary heart disease in US women. *American Journal of Clinical Nutrition.* 2000;71(6)1455-1466.

Livesey G, Buss D, Coussement P, Edwards DG, Howlett J, Jonas DA, Kleiner JE, Mueller D and Sentko A. Suitability of traditional energy values for novel foods and ingredients. *Food Control.* 2000;11:249-289.

Livesey G. Energy values of unavailable carbohydrate and diets: An inquiry and analysis. *American Journal of Clinical Nutrition.* 1990;51:617-637.

Malek AM, Alper SL, Aikawa K, Izumo S. Hemodynamic Shear Stress and its role in Atherosclerosis. *Journal of the American Medical Association.* 1999;282:2035-2042.

Manninen V, Tenkanen L, Koskinen P, Huttunen JK, Manttari M, Heinonen OP, Frick MH. Joint effects of serum triglyceride and LDL cholesterol and HDL cholesterol concentrations on coronary heart disease risk in the Helsinki Heart Study. Implications for treatment. *Circulation.* 1992;85:37-45.

Manson JE, *et al*. Walking compared with vigorous exercise for the prevention of cardiovascular events in women. *New England Journal of Medicine.* 2002;347(10):716-725.

Mathews, EH. Accurate simulation of the blood glucose energy cycle can enhance diabetic drug and product discovery. *Proceedings of the 64th Scientific Sessions, American Diabetes Association*, Orlando, Florida, 2004, A1958-PO, A468.

Mathews EH and Pelzer R. A new model to estimate bolus insulin need. *Diabetes Technology and Therapeutics*. 2009;11(12):813-817.

Mathews H, Liebenberg L. A Practical quantification of blood glucose production due to high-level chronic stress. *Stress Health*. 2012;doi:10.1002/smi.2415.

Mazonne T, Chait A, Plutzky J. Cardiovascular disease risk in type 2 diabetes mellitus: insights from mechanistic studies. *Lancet*. 2008;371:1800-1809.

McEwen BS. Central effects of stress hormones in health and disease: understanding the protective and damaging effects of stress and stress mediators. *European Journal of Pharmacology.* 2008;583:174-185.

Merrill AL and Watt BK. Energy value of foods: Basis and derivation. Agriculture Handbook No. 74. Washington, DC, ARS United States Department of Agriculture, 1973.

Miyazaki H, et al. Strenuous endurance training in humans reduces oxidative stress following exhaustive exercise. *European Journal of Applied Physiology.* 2001;84:1-6.

Mougios V. Exercise Biochemistry, Champaign, IL, USA: Human Kinetics; 2006.

Mukamal KJ, Conigrave KM, Mittleman MA, Camargo CA, Stampfer MJ, Willett WC, and Rimm EB. Roles of drinking pattern and type of alcohol consumed in coronary heart disease in men. *New England Journal of Medicine.* 2003;348(2):109-118.

Noakes TD. Lore of running. Oxford, UK: Oxford University Press; 2001.

Noda H, Iso H, Toyoshima H, Date C, Yamamoto A, Kikuchi S, Koizumi A, Kondo T, Watanabe Y, WadaY , Inaba Y, Tamakoshi A. Walking and Sports Participation and Mortality from Coronary Heart Disease and Stroke. *Journal of the American College of Cardiology.* 1999;46:1761-1767.

O'Keefe JH, Bybee KA, Lavie CJ. Alcohol and cardiovascular health: The razor-sharp double-edged sword. *Journal of the American College of Cardiology*. 2007;50(11):1009-1014.

Ouriel K. Peripheral arterial disease. *Lancet.* 2001;358:1257-1264.

Park Y, Subar AF, Hollenbeck A, and Schatzkin A. Dietary Fiber intake and mortality in the NIH-AARP diet and health study. *Archives of Internal Medicine.* 2011;doi:10.1001/archinternmed.2011.18.

Pearce PZ. Exercise is Medicine. Current Sports Medicine Reports 2008;7(3):171-175.

Pedersen BK and Saltin B. Evidence for prescribing exercise as therapy in chronic disease. *Scandinavian Journal of Medicine Science and Sports.* 2006;16(1):3-63.

Pelzer R, Mathews EH, and Liebenberg L. Preliminary application of a new bolus insulin model for type 1 diabetes. *Diabetes Technology and Therapeutics.* 2011; 13(5):527-535.

Pereira MA, O'Reilly E, Augustsson K, Fraser GE, Goldbourt U, Heitmann BL, Hallmans G, Knekt P, Liu S, Pietinen P, Spiegelman D, Stevens J, Virtamo J, Willett WC, Ascherio A. Dietary fiber and risk of coronary heart disease. *Archives of Internal Medicine.* 2004;164:370-376.

Perry IJ, Wannamethee SG, Whincup PH, Shaper AG, Walker MK, Alberti KGMM. Serum Insulin and Incident Coronary Heart Disease in Middle-aged British Men. *American Journal of Epidemiology*. 1996;144:224-234.

Phillips AC, *et al*. Generalized anxiety disorder, major depressive disorder, and their comorbidity as predictors of all-cause and cardiovascular mortality: the Vietnam experience. *Psychosomatic Medicine.* 2009;71:395-403.

Pinheiro Volp AC, Esteves de Oliviera FC, Duarte Moreira Alves R, and Esteves y J. Bressan EA. Energy expenditure: components and evaluation methods. *Nutrición Hospitalaria.* 2011;26(3):430-440.

Räikkönen K, Keltikangas-Jarvinen L, Adlercreutz H, Hautanen A. Psychosocial stress and the insulin resistance syndrome. *Metabolism.* 1996;45(12):1533-1538.

Reneman RS and Hoeks APG. Wall shear stress as measured in vivo: consequences for the design of the arterial system. *Medical and Biological Engineering and Computing.* 2008;46:499-507.

Ridker PM, Cushman M, Stampfer MJ, Tracy RP, and Hennekens CH. Inflammation, aspirin, and the risk of cardiovascular disease in apparently healthy men. *New England Journal of Medicine.* 1997;336(14):973-9.

Roberts CK, and Barnard RJ. Effects of exercise and diet on chronic disease. *Journal of Applied Physiology.* 2005;98: 3-30.

Room R, Babor T, Rehm J. Alcohol and public health. *Lancet.* 2005; 365: 519–30.

Roest AM, Martens EJ, De Jonge P, Denollet J. Anxiety and risk of incident coronary heart disease, a meta-analysis. *Journal of the American College of Cardiology*. 2010;56(1):38-46.

Rubner M. Der Energiewet der Kost des Menschen, *Z. Biology.* 1901;42:261-308.

Ruige JB, Assendelft WJ, Dekker JM, Kostense PJ, Heine RJ, Bouter LM. Insulin and Risk of Cardiovascular Disease: A Meta-Analysis. *Circulation.* 1998;97:996-1001.

Saltiel AR, Kahn CR. Insulin signalling and the regulation of glucose and lipid metabolism. *Nature.* 2001;414:799-806.

Sesso HD, Paffenbarger RS, Lee I. Physical Activity and Coronary Heart Disease in Men: The Harvard Alumni Health Study. *Circulation.* 2000;102:975-980.

Shah PK, Forrester JS. Pathophysiology of acute coronary syndromes. *American Journal of Cardiology.* 1991;68:16C-23C.

Sieri S, *et al*. Dietary glycaemic load and index and risk of coronary heart disease in a large Italian cohort. *Archives of Internal Medicine.* 2010;170(7):640-647.

Siler SQ, Neese RA, Christiansen MP, and Hellerstein MK. The inhibition of gluconeogenesis following alcohol in humans. *Endocrinology and Metabolism.* 1998;38:E897-E907.

Southgate DAT and Durnin JVGA. Calorie conversion factors. An experimental re-assessment of the factors used in the calculation of the energy value of human diets. *British Journal of Nutrition.* 1970;24:517–535.

Stampfer MJ, Hu FB, Manson JE, Rimm EB, Willett WC. Primary prevention of coronary heart disease in women through diet and lifestyle. *New England Journal of Medicine.* 2000;343:16-22.

Stergiou GS, Vemmos KN, Pliarchopoulou KM, Synetos AG, Roussias LG, *et al*. Parallel morning and evening surge in stroke onset, blood pressure, and physical activity. *Stroke.* 2002;33:1480-1486.

Stoll G and Bendszus. Inflammation and atherosclerosis: novel insights into plaque formation and destabilization. *Stroke.* 2006;37:1923-1932.

Sundquist K, Qvist J, Johansson S-E, and Sundquist J. The long-term effect of physical activity on incidence of coronary heart disease: a 12-year follow-up study. *Preventative Medicine.* 2005;41:219-225.

Tanasescu M, Leitzmann MF, Rimm EB, Willet WC, Stampfer MJ, Hu FB. Exercise type and intensity in relation to coronary heart disease in men. *Journal of the American Medical Association*. 2002;288:1994-2000

Truswell S. Cereal grains and coronary heart disease, *European Journal of Clinical Nutrition.* 2002;56:1-14.

Versteeg H, Pedersen SS, Denollet J. Type D personality and health status in cardiovascular disease populations: a meta-analysis of prospective studies. *European Journal of Cardiovascular Prevention and Rehabilitation.* 2011;doi:10.1177/1741826711425338.

Vogelzangs N, Seldenrijk A, Beekman ATF, van Hout HPJ, de Jonge P, Penninx BWJH. Cardiovascular disease in persons with depressive and anxiety disorders. *Journal of Affective Disorders*. 2010;125(1-3):241-248.

Wallace TM, and Matthews DR. The assessment of insulin resistance in man. *Diabetic Medicine.* 2002;19:527-534.

Warburton DER, Nicol CW, Bredin SSD. Health benefits of physical activity: the evidence. *Canadian Medical Association Journal.* 2006;174(6):801-809.

Weismann, C. (1990). The metabolic response to stress: An overview and update. *Anaesth.* 73:308-327.

Wheeler ML. What are net carbs? *Diabetes Forecast*. August 15, 2010.

Willerson JT and Ridker PM. Inflammation as a cardiovascular risk factor. *Circulation.* 2004;109(II):II2-II10.

Wolever TMS, Bolognesi C. Source and amount of carbohydrate affect postprandial glucose and insulin in normal subjects. *Journal of Nutrition.* 1996;126:2798-2806.

Zheng H, Orsini N, Amin J, Wolk A, Nguyen VTT, and Ehrlich F. Quantifying the dose-response of walking in reducing coronary heart disease: Meta-analysis. *European Journal of Epidemiology*. 2009;24:181-192.

APPENDIX C

The effect of smoking on blood glucose and coronary heart disease

Edward H. Mathews[1,2], **Johanna Espach**[1,2], **Leon Liebenberg**[1,2]

Authors contracted to North-West University, Suite No 91, Private Bag X30, Lynnwood Ridge, 0040, South Africa and consultants to MCI (Pty) Ltd and TEMM International (Pty) Ltd

ehmathews@researchtoolbox.com; jespach@researchtoolbox.com;

LLiebenberg@researchtoolbox.com

Corresponding author. Tel.: +27 12 809 0995; Fax: +27 86 515 5799

E-mail: LLiebenberg@researchtoolbox.com (L. Liebenberg)

Abstract

Aim:

Smoking is associated with increased risk of coronary heart disease (CHD). It is hypothesized that the reason for this increased risk is primarily due to smoking causing high blood glucose (BG) levels through its insulin desensitizing properties. High BG levels are related to increased inflammation and thus increased atherosclerosis and CHD. The effect of smoking on BG and the latter's effect on CHD is investigated using a novel approach.

Method:

To express the effect which smoking has on BG, a common unit for BG energy quantification was developed, namely equivalent teaspoons of sugar (—ets). This is a practical unit due to the fact that a teaspoon of sugar is easy to visualize and thus to understand for an ordinary person. Published data were interpreted and processed; the —ets model was applied to find the relationship between smoking and BG on the RR for CHD. Linear curve fittings were assumed to make the data easier to interpret and understand.

Results:

From the results it is apparent that smoking can be quantified in terms of its effect on BG by using a state of the art model (—ets). Smoking increases BG levels, and this is thought to increase the risk for CHD. The data for smoking in terms of —ets against the relative risk (RR) for CHD were fitted linearly with an R^2 of 0.72. Cigarette smoking leads to an increase of approximately 20—ets above basal requirements and increase the RR for CHD more than two and a half-fold.

Conclusion:

A practical and easy-to-use unit was established and employed to quantify the effect that smoking has on BG and the latter's effect on CHD. Smoking apparently induces high BG levels and is thought to be through the insulin resistance state. Increased BG levels are associated with a higher risk for CHD. Cigarette smoking has other atherosclerotic properties apart from its glycemic effect and it is therefore expected to have even greater impact on CHD development.

Key words: Smoking, insulin resistance, coronary heart disease, blood glucose.

Introduction

Coronary heart disease (CHD) is the leading cause of death in the western world (Roberts and Barnard 2005, Barker 2012). Several epidemiologic studies suggest that smoking is one of the leading risk factors associated with CHD in both men and women (Ambrose and Barua 2004). A recent study showed that in regions such as South America, Eastern Europe and South-East Asia there were approximately twice as many deaths from CHD attributable to smoking, than from cancer or respiratory disease (Leif 2009). The number of smokers worldwide is increasing and is estimated to reach 1.7 billion by 2025 (Leif 2009). It is therefore becoming increasingly important to understand the risks associated with cigarette smoking.

It has been suggested that the key link between cigarette smoke and cardiovascular disease is insulin resistance (Reaven and Tsao 2003). Smoking reduces important anti-inflammatory markers such as adiponectin which is a protein produced in the adipose tissue, and is known for its anti-inflammatory and insulin sensitizing properties (Reaven and Tsao 2003). If adiponectin levels fall sufficiently insulin sensitivity is decreased which can lead to insulin resistance.

Insulin resistance causes chronic hyperglycemia (constant levels of high blood glucose), which is the state commonly attributed to diabetics (Funk *et al*. 2012). Hyperglycemia contributes to atherosclerosis, which includes thickening of artery walls and accumulation of plaque and is known as the primary cause for CHD (Funk *et al.* 2012).

Atherosclerosis and CHD are both commonly known as inflammatory diseases (Anuurad *et al*. 2009). Hyperglycemia is linked to inflammation through the reductase pathway. High blood glucose levels increase inflammation by influencing this pathway through the activation of protein kinase, the accumulation of diacylglycerol and increased glucose flux (Chait and Bornfeldt 2009). In the process inflammatory markers such as C-reactive protein (CRP), interleuken-6 (IL-6) and tumor necrosis factor alpha (TNF-α) are increased which enhance monocyte adhesion to endothelial cells resulting in accelerated fatty streak formation in arteries (Ambrose and Barua 2004, Chait and Bornfeldt 2009). These fatty streaks finally form lesions which then rupture and cause clinical manifestations of CHD (Chait and Bornfeldt 2009).

Figure C 1 illustrates a simplified mechanism of smoking on the relative risk (RR) for CHD through insulin resistance and inflammation (BG pathway).

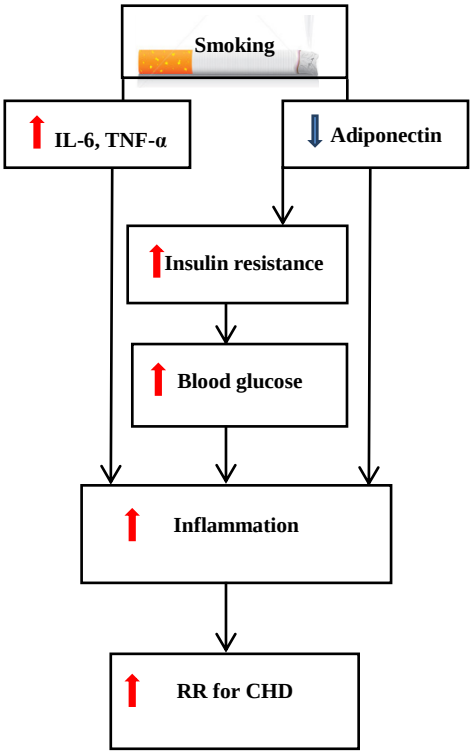


Figure C 1: A simplified pathway mechanism illustrating the effect of smoking through the BG pathway on the risk of CHD

Smoking contributes to CHD not only through insulin resistance and inflammation but also through:

Vasomotor dysfunction: Smoking decreases vasodilatory function in macro-vascular beds such as coronary and brachial arteries. Nitrogen Oxide, (NO), is responsible for vasodilation. Cigarette smoke decreases the availability of NO. Apart from the vaso-regulating properties NO also plays an important role in the regulation of inflammation, leukocyte adhesion, platelet adhesion and thrombosis (Ambrose and Barua 2004).

Modification of lipid profile: Smoking cause higher serum cholesterol and low density lipoprotein (LDL) levels, as well as low levels of high density lipoprotein (HDL). These can cause blockages in arteries causing atherosclerosis (Ambrose and Barua 2004).

Even though smoking promotes CHD by means other than insulin resistance, these other effects are not discussed in this paper. It is hypothesized that the primary contribution made by smoking to the risk of CHD is through increased blood glucose levels. This paper quantifies the effects of smoking on CHD through a novel blood glucose quantification method.

Method

High blood glucose (BG) is a major contributor to CHD and, as suggested, the key link between smoking and CHD is insulin resistance (Reaven and Tsao 2003). It is therefore logical to first quantify smoking in terms of its effect on BG.

A common unit was developed to quantify the effect that several lifestyle factors have on BG. This common unit is called equivalent teaspoon sugar (—ets) (Mathews and Pelzer 2009). It is a practical unit because a teaspoon of sugar is easy to visualize and understand for the ordinary person.

Published data indicates that there is an accurate correlation between the number of cigarettes smoked and the relative risk (RR), of CHD. A linear relationship (R^2 = 0.75) was assumed to facilitate easy interpretation (Estathiou *et al.* 2009, Pope III *et al.* 2011).

Using this data, a mathematical equation describing the RR as a function of the number of cigarettes smoked per day is suggested:

$$RR = f_1.\text{Cigarettes} \quad (1)$$

Where f_1 is the proportionality constant.

As adiponectin plays such a definitive role in insulin resistance, published data are also available which depict the relationship between cigarette smoking and plasma adiponectin levels, *cf.* Table C 1. This relationship can be described by the following equation:

$$\Delta \text{ Adiponectin} = f_2 . \text{ Cigarettes} \quad (2)$$

Table C 1: Published data showing the relationship between the number of cigarettes smoked and adiponectin levels. (Adapted from Tsai *et al*. 2011, Takefuji *et al*. 2007, Estathiou *et al*. 2009).

Reference	**Tsai *et al.* 2011**		**Takefuji *et al.* 2007**		**Efstathiou *et al.* 2009**		
Number of cigarettes	0	25	7.5	19.5	16.5	27.1	37.7
Adiponectin (µg/ml)	11.47	8.35	8.65	8.05	8.7	7.2	5.7

The link between plasma adiponectin and fasting insulin levels can also be found from published literature and as shown in Table C 2.

Table C 2: Relationship between fasting insulin and adiponectin (Adapted from Nayak *et al.* 2010, Engeli *et al*. 2003, Polak *et al*. 2008)

Reference	**Nayak *et al.* 2010**			**Engeli *et al*. 2003**			**Polak *et al*. 2008**		
Adiponectin (µg/ml)	7.79	24.77	16.98	15	17.5	20	4.4	7.1	9.8
Insulin (µU/ml)	8.89	18.19	27.49	3.3	6.6	10	8.4	11.3	14.2

$$\Delta \text{ Adiponectin} = f_3 . \Delta I \quad (3)$$

Where ΔI = Change in insulin

By substituting equation (2) into (3):

$$\text{Cigarettes} = f_4 . \Delta I \quad (4)$$

Assuming a linear relationship between BG production and insulin secretion (Mathews and Pelzer 2009):

$$\Delta I = f_5 . \Delta BG \quad (5)$$

There is also a direct correlation between change in BG level and change in—ets (Pelzer *et al.* 2011):

$$\Delta BG = f_6 . \Delta\text{—ets} \quad (6)$$

Substituting equation (5) into equation (6) gives:

$$\Delta I = f_7.\Delta\text{—}ets \quad (7)$$

Combining equations (4) and (7):

$$\text{Cigarettes} = f_8.\Delta\text{—}ets \quad (8)$$

Finally substituting equation (8) into equation (1) the following relationship is established:

$$RR_{CHD} = f_9.\Delta\text{—}ets \quad (9)$$

The data from the different publications can now be interpreted and processed by the mathematical equations derived to establish the risk of smoking on CHD through—*ets*.

Results and discussion

Table C 3, obtained from equations 8 and 9, gives an indication of the number of cigarettes smoked per day expressed in equivalent Δ —*ets* per day and the corresponding RR for CHD.

Table C 3: The number of cigarettes with the equivalent in Δ_{ets} as well as the corresponding relative risks for CHD.

Number of cigarettes/day	Δ_{ets}/day	RR for CHD
1.5	0.76	1.58
5.5	2.80	1.73
10	5.09	2.01
15	7.64	1.99
20	10.19	2.42
25	12.74	2.33
30	15.28	2.17
35	17.83	2.52
40	20.38	2.37

Figure C 2 shows the significance of smoking on the RR for CHD using the data collected (from Nayak et al. 2010, Engeli et al. 2003, Pollak et al. 2008, Tsai et al. 2011, Takefuji et al. 2007, Estathiou et al. 2009, Pope III et al. 2011, Pelzer et al. 2011, Mathews and Pelzer 2009).

Figure C 2 assumes a normal relative risk, (RR = 1), and shows the fold increase in RR on the y-axis. A linear curve fitting (R2 = 0.72) was done to simplify interpretation of the data.

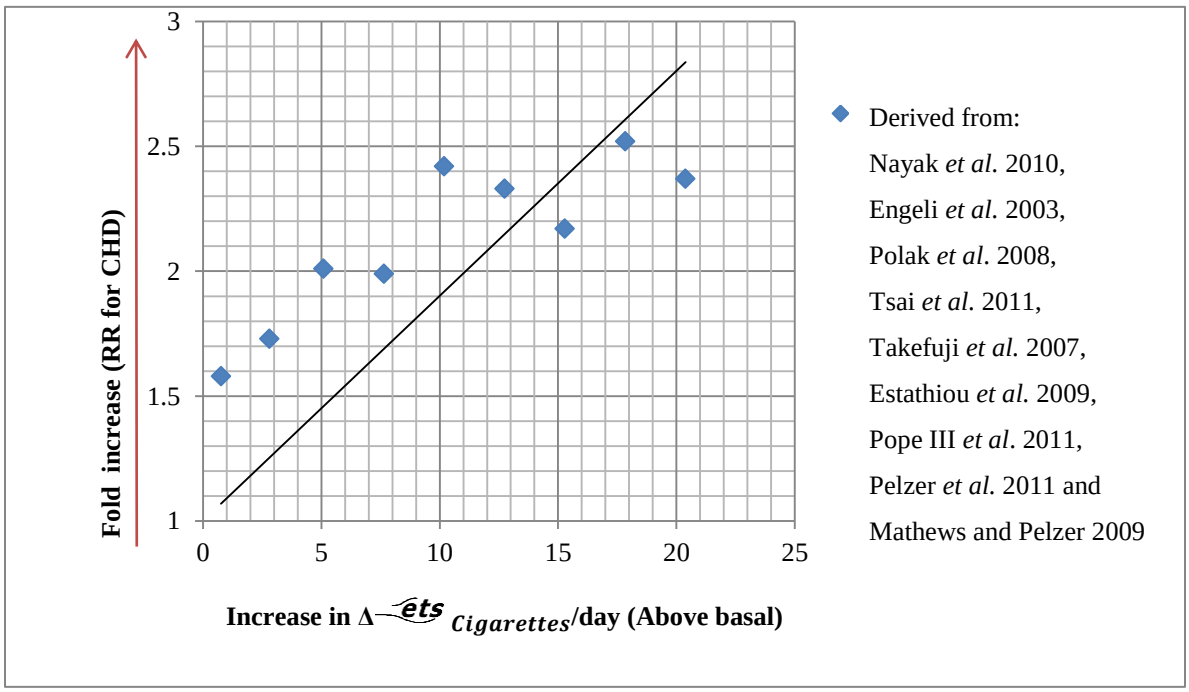


Figure C 2: The RR for CHD as a function number of cigarettes per day quantified in terms of blood glucose expressed in . Data from Nayak et al. 2010, Engeli et al. 2003, Polak et al. 2008, Tsai et al. 2011, Takefuji et al. 2007, Estathiou et al. 2009, Pope III et al. 2011, Pelzer et al. 2011, Mathews and Pelzer 2009.

From Figure C 2 it can be seen that with increasing the RR for CHD also increases, as expected. More importantly it shows that there is a strong correlation between smoking, BG and CHD.

However, the gradient of this graph is not as steep as expected. Suggesting that, the increase in BG, is not the only contribution that smoking has on the risk for CHD. There are other atherosclerotic effects that are also associated with cigarette smoking such as the vasomotor dysfunction and modification on the lipid profile (Ambrose and Barua 2004). The practical

implication of Figure C 2 is that smoking 20 cigarettes a day may cause BG levels to rise up to 20 $\overline{ets}$ above basal requirements, resulting in a more than an increase of two and a half times the normal RR for CHD.

Conclusion

The mathematical models presented in this paper indicate that there is a strong correlation between blood glucose levels ($\overline{ets}$) and cigarette smoking. From the data processed it is apparent that smoking induces high levels of blood glucose which result in increased relative risk for CHD. Even though all the effects that cigarette smoking has on the RR for CHD cannot be completely quantified through its glycemic impact, it is still a good indication of the negative effect of smoking on CHD.

References

Ambrose JA, Barua RS. The pathophysiology of cigarette smoking and cardiovascular disease. *Journal of the American College of Cardiology*. 2004;43(10):1731-1737.

Anuurad E, Tracy RP, Pearson TA. Synergistic role of inflammation and insulin resistance as coronary artery disease risk factors in African American caucasions. *Atherosclerosis*. 2009;205:290-295.

Barker D. Developmental origins of chronic disease. *Public Health*. 2012;126:185-189.

Bermudez EA, Rifai N, Buring JE. Relation between markers of systemic vascular inflammation and smoking in women. *American Journal of Cardiology*. 2002;89(9):1117-1119.

Chait A, Bornfeldt KE. Diabetes and atherosclerosis: Is there a role for Diabetes? *Journal of Lipid Research*. 2009;50:S335-S339.

de Maat MP, Kluft C. The association between inflammation markers, coronary artery disease and smoking. *Vascular Pharmacology*. 2002;39:137-139.

Engeli S, Feldpausch M, Gorzelniak K. Association between adiponectin and mediators of inflammation in obese women. *Diabetes*. 2003;52(4):942-947.

Estathiou SP, Skeva II, Dimas C, Dimas C, Panagiotou A, Parisi K, Tzanoumis L, Kafouri A, Bakratsas K, Mountokalakis TD. Smoking cessation increases serum adiponectin levels in apparently healthy Greek population. *Atherosclerosis*. 2009;205(2):632-636.

Funk SD, Yurdagul Jr A, Orr WA. Hyperglycemia and endothelial dysfunction in atherosclerosis: Lessons from type 1 diabetes. *International Journal of Vascular Medicine*. 2012;2012:1-19.

Leif E. Cigarette smoking: An undertreaten risk factor for cardiovascular disease. *Atherosclerosis*. 2009;205(1):23-32.

Mendall MA, Patel P, Asante M. Relation of serum cytokine concentrations to cardiovascular risk factors and coronary heart disease. *Heart.* 1997;78:273-277.

Nayak S, Ramsingh D, Gooding S, Bissram S, Mohammed A, Raychaudhuri A, Sahadeo B, Pandohie V, Figaro K. Plasma adiponectin levels are related to obesity, inflammation and insulin in type 2 diabetic and non-diabetic Trinidadians. *Primary Care Diabetes*. 2010;4(3):187-192.

Polak J, Kobacova Z, Holst C, Verdich C, Astrup A, Blaak E. Total adiponectin and adiponectin multimeric complexes in relation to weight-loss induced improvements in insulin sensitivity in obese women:the NUGENOB study. *European Journal of Endocrinology*. 2008;158:533-541.

Pope III CA, Burnett RT, Turner MC. Lung cancer and cardiovascular disease mortality associated with ambient air pollution and cigarette smoke: Shape of exposure-response relationships. *Environmental Health Perspective.* 2011;287(9):1616-1621.

Reaven G, Tsao PS. Insulin resistance and compensatory hyperinsulemia: The key player between cigarette smoking and cardiovascular disease. *Journal of the American College of Cardiology.* 2003;41(6):1044-1047.

Smith C, Fischer TH. Particulate and vapor phase constituents of cigarette mainstream smoke and risk of myocardial infarction. *Atherosclerosis*. 2001;158(2):257-267.

Takefuji S, Yatsuya H, Tamakoshi K. Smoking status and adiponectin in healthy Japanese men and women. *Preventitive Medicine*. 2007;45(6):471-475.

Tappia PS, Troughton KL, Langly-Evans SC. Cigarette smoking influences cytokine production and antioxidant defenses. *Clinical Science*. 1995;88(4):485-489.

Tracy RP, Psaty BM, Marcy E. Lifetime smoking exposure affects the association of C-reactive protein with cardiovascular disease risk factors and subclinical disease in healthy elderly subjects. *Artheriosclerosis Thrombosis and Vascular Biology*. 1997;17:2167-2176.

Tsai JS, Guo FR, Chen SC. Smokers show reduced circulating adiponectin levels and adiponectin mRNA expression in peripheral blood mononuclear cells. *Atherosclerosis*. 2011;218:168-173.

APPENDIX D

The effect of various lifestyle factors on blood glucose and breast cancer

EH Mathews, JM Espach, and L Liebenberg

Authors contracted to North-West University, Suite No 91, Private Bag X30, Lynnwood Ridge, 0040, South Africa and consultants to MCI (Pty) Ltd and TEMM International (Pty) Ltd

ehmathews@researchtoolbox.com; jespach@researchtoolbox.com;

LLiebenberg@researchtoolbox.com

Corresponding author. Tel.: +27 12 809 0995; Fax: +27 86 515 5799

E-mail: LLiebenberg@researchtoolbox.com (L. Liebenberg)

Abstract

Aims: Research publications suggest that blood glucose (BG) plays a significant role in breast cancer development. The lifestyle factors which influence the risk of breast cancer such as: Food, physical exercise, psychological stress and fiber intake have been extensively investigated. However, it is unclear which factor has the most significant impact on the risk for BC. All these lifestyle factors have one thing in common, they influence BG levels. The aim of this study is to quantify the risk factors in terms of their glycemic effect by using a common, single unit to compare their influences on BC risk.

Methods: A state of the art model known as —ets (equivalent teaspoons of sugar) was implemented to quantify each lifestyle factor in terms of its effect on BG. The advantage of using —ets is that it is easy to vizualize and interpret and allows the lifestyle effects on BC to be compared using a common unit. After the equivalent values for each factor was developed they were used to express the relative risk (RR) for BC as a function of —ets.

Results: The lifestyles responsible for increasing BG levels also increased the risk for BC. Whereas, the BG lowering lifestyle factors were inversely associated with the RR of BC. Psychological stress had the largest impact on the RR for BC, doubling the risk. Low to moderate physical activity was associated with the largest protective effect, reducing the risk by a factor of 0.6.

Conclusion: The glycemic effects of food, psychological stress, physical exercise and dietary fiber on the risk of BC could be established using one consistent state of the art unit,—ets. For verification of the theory clinical data from various research publications were used. The lifestyle factors which influence the RR of BC could be quantified and compared. The effect of the different lifestyle factors on BC could be placed in perspective especially the large impact of psychological stress.

Key words: Breast cancer (BC), blood glucose (BG), carcinogenesis, lifestyle factors, psychological stress, physical exercise, excessive food intake, dietary fibre and ets.

Introduction

Globally breast cancer (BC) is the most frequently diagnosed cancer among women. In 2008 statistics showed that nearly 1.38 million people were diagnosed with BC (Ferlay *et al*. 2010). BC is also the most common cause of death in women worldwide (Ferlay *et al*. 2010).

Cancer is not a single disease, it has become increasingly evident that it is organ and tissue specific (Weigelt & Mina 2008). BC is commonly known as a group of a variety of different diseases with different risk factors, clinical and pathological properties as well as different responses to treatment (Weigelt *et al*. 2010, Hanby *et al*. 2005, Weigelt & Mina 2008).

BC can be separated into subgroups by histological grade or type. Classification in terms of grade takes into consideration the degree of differentiation and proliferation (i.e. tubule formation, nuclear pleomorphism and mitotic index) (Weigelt *et al*. 2010). Histological type is more commonly used for classification and refers to the growth of the tumor (Weigelt *et al*. 2010).

Through histological type classification, BC can either be referred to as non-invasive (in situ) or invasive. Non-invasive BC is usually situated in the epithelial lining of the terminal duct or lobular unit and is usually where the carcinoma originates. Invasive BC refers to the cancerous cells growing through the ducts or lobules into the tissue of the breast (Bateman 2004). These cells, especially ductal carcinomas often continue to grow at a rapid pace and cause a lump or thickening and can metastasise through the blood or lymph nodes into other parts of the body (Bateman 2004).

It has been suggested that high blood glucose (BG) fuels carcinogenesis. More than 70 years ago the glucose metabolism was studied by Warburgh using aerobically incubated tumor slices

(Gatenby & Gillies 2004, Kim & Dang 2006, dos Santos *et al.* 2004). These tumor slices were responsible for the rapid production of high levels of lactate (Kim & Dang 2006, dos Santos *et al.* 2004). This high rate of glycolysis therefore became a biomarker for malignancies (dos Santos *et al* 2004). Furthermore, it showed high rates of glutamine utilisation. The combination of glutamine and glucose provide energy in the form of ATP for increased cell proliferation (dos Santos *et al* 2004).

In this study the focus will be on the effect of lifestyle factors glycemic effects on the development of BC. Several publications have studied different lifestyle effects and the development of BC. Lifestyle factors that are of particular importance in this study, due to their glycemic impact, are: Food intake, psychological stress, dietary fiber intake and physical exercise. Research shows that food intake (Sieri *et al*. 2007, Wen *et al*. 2009 , Sieri *et al.* 2012, Augustin *et al.* 2001, Larrson *et al.* 2009) and psychological stress (Lillberg *et al*. 2001, Metcalfe *et al*. 2007, Kruk *et al*. 2004) is associated with increased relative risk (RR) for BC. However dietary fiber intake (Wen *et al.* 2009, Cade *et al*. 2007 Belle *et al.* 2011) and physical exercise (Eliasen *et al*. 2010, Kruk *et al.* 2007, McTiernan *et al*. 2003, Awatef *et al*. 2011, Verloop *et al*. 2000, Carpenter *et al.* 2003) are both linked to reduced RR for BC.

These lifestyle factors are all expressed in different units making it difficult to draw a comparison between them. This, in turn, is confusing when attempting to establish which factor has the largest impact on BC development. Therefore, in this paper the lifestyle factors will be quantified in terms of their glycemic effect and a state of the art model known as ets (equivalent teaspoons of sugar). This common and easily understandable unit allows the glycemic effects of the different lifestyle factors to be vizualized and interpreted in a simplistic manner (in terms of teaspoons of sugar). It also ensures that the lifestyle impacts can be compared on an equal standard.

The lifestyle factors from the different clinical studies will therefore be modelled in terms of ets and the impact of the glycemic effect will be investigated using published data for the RR

of BC. The lifestyle factors which increase BG levels will be investigated first, followed by the lifestyles that reduce BG levels.

Lifestyle factors that increase BG levels

Effect of excessive food intake on BG

Carbohydrates (CHOs) are the primary source of energy in the diet of average person (Anderson *et al.* 2002). Carbohydrate intake is often quantified in terms of Glycemic index (GI) and Glycemic load (GL). Carbohydrates with high GI values are quickly broken down into glucose, causing spikes in blood glucose levels and an increase in short term satiety. On the other hand, low GI carbohydrates are broken down slowly resulting in sustained satiety in the long term (Ebbeling *et al.* 2003). GL takes into consideration both the mass of the food and the GI value (GL = Mass of CHO × GI) (Ebbeling *et al.* 2003).

Several publications show that with increased GL the RR for BC increases (Sieri *et al*. 2007, Wen *et al*. 2009 , Sieri *et al.* 2012, Augustin *et al.* 2001, Larrson *et al.* 2009). In this study, the data from the several research publications that express food intake in terms of GL, will be modelled in terms of its BG effect and its impact on the RR for BC.

A relationship between the blood glucose (BG) energy metabolised from Carbohydrates (CHOs) and ets already exist (Mathews & Pelzer 2009):

$$ets_{CHO} = \frac{\eta_{CHO}}{\eta_{Sugar}} \times \frac{m_{CHO}}{5} = \frac{GI_{CHO} m_{CHO}}{325} \tag{22}$$

All the *GI* values are referenced to the glucose standard. η_{CHO} and η_{Sugar} are the metabolic efficiencies of the CHO and the sugar, respectively. GI_{CHO} is the glycaemic index and m_{CHO} the mass of the CHO

Now that a relationship has been established between CHO metabolised and $\overline{ets}$, the data collected from the various research publications which link the RR for BC and GL can be used in Equation 1. The $\overline{ets}_{CHO}$ and RR for BC is plotted in Figure D 1**:** The linearized relationship between excessive food consumption above basal requirements in terms of $\overline{ets}$ and the RR for CHD.

A linearized function is assumed to simplify the interpretation and understanding of the results. The correlation coefficient (R^2) is low due to this linearized assumption. If the same results were used in a second order polynomial a higher R^2 value will be obtained, but the interpretation will be more complex.

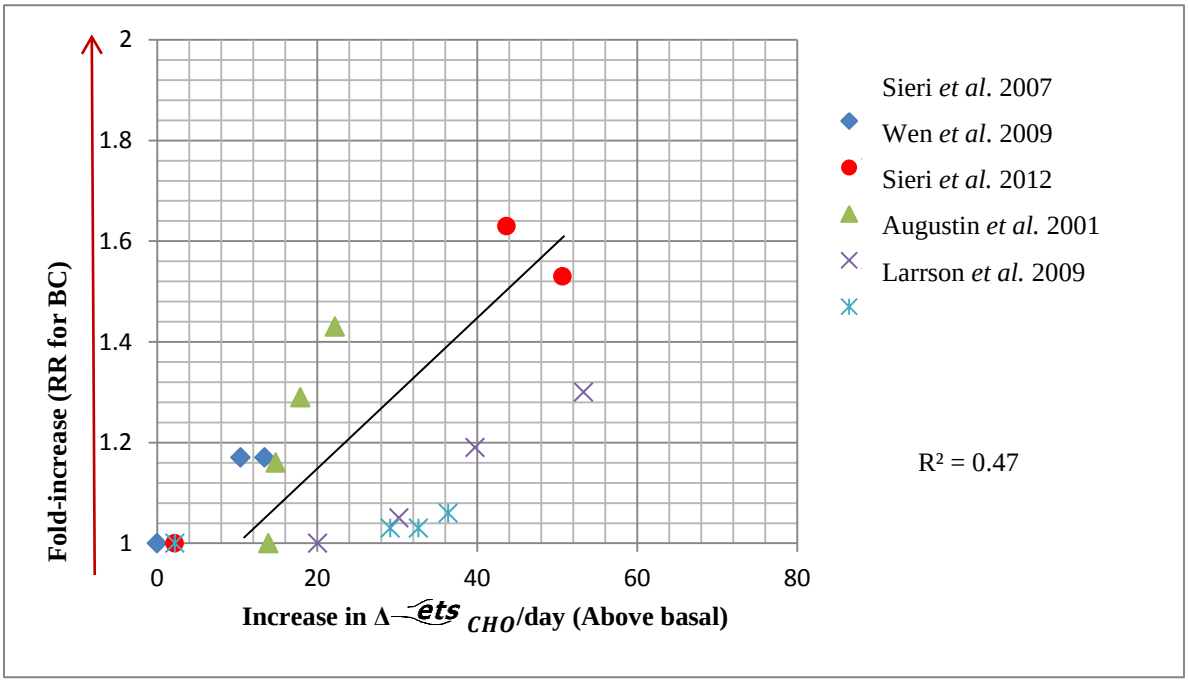


Figure D 1: The linearized relationship between excessive food consumption above basal requirements in terms of $\overline{ets}$ and the RR for CHD

Figure D 1**:** The linearized relationship between excessive food consumption above basal requirements in terms of $\overline{ets}$ and the RR for CHD implicates that with increased food intake the RR for BC increases. Figure D 1**:** The linearized relationship between excessive food

consumption above basal requirements in terms of —ets and the RR for CHD has been modified to take into consideration the basal energy requirements for everyday activities. It has been suggested that a person requires approximately 23 —ets to 28 —ets as basal energy (Mathews & Pelzer 2009, Volp *et al.* 2011).

Practically, Figure D 1**:** The linearized relationship between excessive food consumption above basal requirements in terms of —ets and the RR for CHD shows that with the consumption of an additional fast food burger meal corresponding to approximately 36—ets(burger, chips and cola), the RR for BC increases with a factor of 1.4 (RR=1.4).

Psychological stress

Prolonged psychological stress is associated with increased BG production especially in the liver (McEweb 2008, Black 2003, Raikkonen et al. 1996, Saltiel & Kahn 2001, Mathews & Liebenberg 2012). Cortisol a steroid hormone, which is secreted during psychological stress, is responsible for gluconeogenesis and glycogenolysis (Mathews & Liebenberg 2012). Therefore, with increased psychological stress, cortisol levels increase which, in turn, elevate blood glucose levels, glucagon, growth hormones and catecholamines (Mathews & Liebenberg 2012).

As mentioned previously, published studies show what the impact of psychological stress is on the RR for BC. This is presented in Table D 1.

Table D 1: The relationship between clinical data from published studies showing the impact of psychological stress on the RR for BC

Reference	Stress level	RR for BC
Lillberg *et al*. 2001	Low	1.09
	High	1.25
Metcalfe *et al*. 2007	Low	1
	Medium	2.04
	High	2.14
Kruk *et al*. 2004	Low	1.24
	Medium	2
	High	3.83

In order to quantify the stress level in terms of *ets*, an established relationship from Mathews & Liebenberg 2012 was used. This association is presented in Table D 2.

Table D 2: The relationship between clinical data from published studies showing the impact of psychological stress on the RR for BC

Reference	Stress level	—ets/day
Kubzanski *et al.* 1997	low	7.2
	medium	21.6
	high	50.4
Kubzanski *et al.* 2009	high	28.7
Einvik *et al.* 2009	medium	25.1
Vogelzangs *et al.* 2010	medium	24.2
Roest *et al.* 2010	low	6.1
Versteeg *et al.* 2011	medium	17.4
Phillips *et al.* 2009	medium	20.7

Combining Tables D 1 and D 2, psychological stress level is quantified in terms of —ets. This BG quantification of stress in terms of —ets can now be plotted with its corresponding RR for BC in Figure D 2. A linearized relationship was again assumed for a simplified interpretation and understanding.

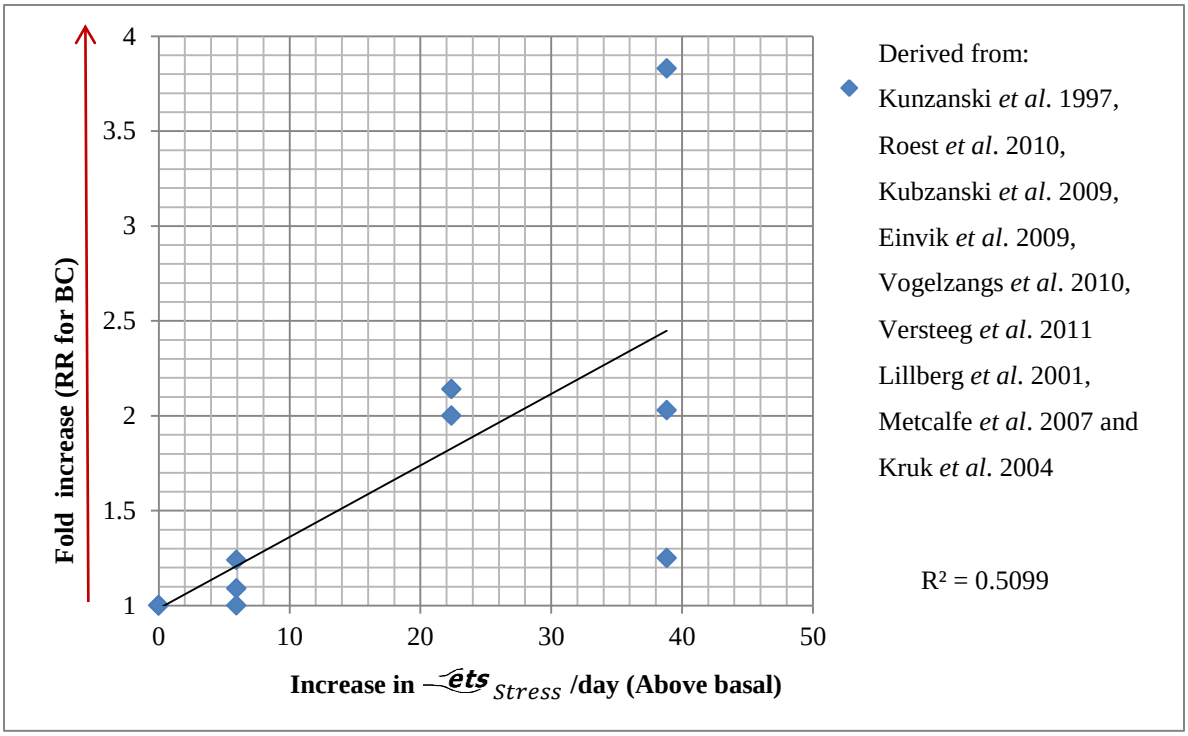


Figure D 2: The impact of psychological stress in terms of ets on the RR for developing BC.

Psychological stress is responsible for an increase in RR for BC, as can be seen from Figure D 2 ($R^2 = 0.51$). The glycaemic effect of psychological stress is substantial inducing ets values of almost 40 and a corresponding 2.5 fold increase in the RR fold. The practical implication of Figure D 2 is that low stress (≈ 11 ets) increases RR for BC by a factor of 1.5; medium levels (≈ 31 ets) are related to approximately a two-fold increase in the RR for BC, and high levels of stress a 2.5 fold increase.

Blood glucose lowering lifestyle factors

Dietary fiber intake

The viscosity of fiber is associated with lower absorption rates in the small intestine (Kendall *et al.* 2010). Food high in fibre is known to have a low GI value (Kendall *et al.* 2010, Mathews & Pelzer 2009, Jenkins *et al.* 2002). The slower food absorption rate is also responsible for reduced glucose absorption, lowering BG levels. This is *inter alia* accountable for increased insulin sensitivity and better BG control (Kendall *et al.* 2010).

Jenkins added fiber to different foods and measured the resulting glucose response (Jenkins *et al*. 2002). One gram of fiber, added to 50 grams of CHO, reduced the GI of a typical meal by 4 units. This can be translated to a reduction of 0.6 $\textit{ets}$ per gram of extra fiber added to a meal. A new variable $\textit{ets}_{Fib\ added}$ can now be defined:

$$\textit{ets}_{Fib\ added} = 0.6 \times m_{Fib\ added} \tag{23}$$

Where $m_{Fib\ added}$ is the mass of the fiber added in grams.

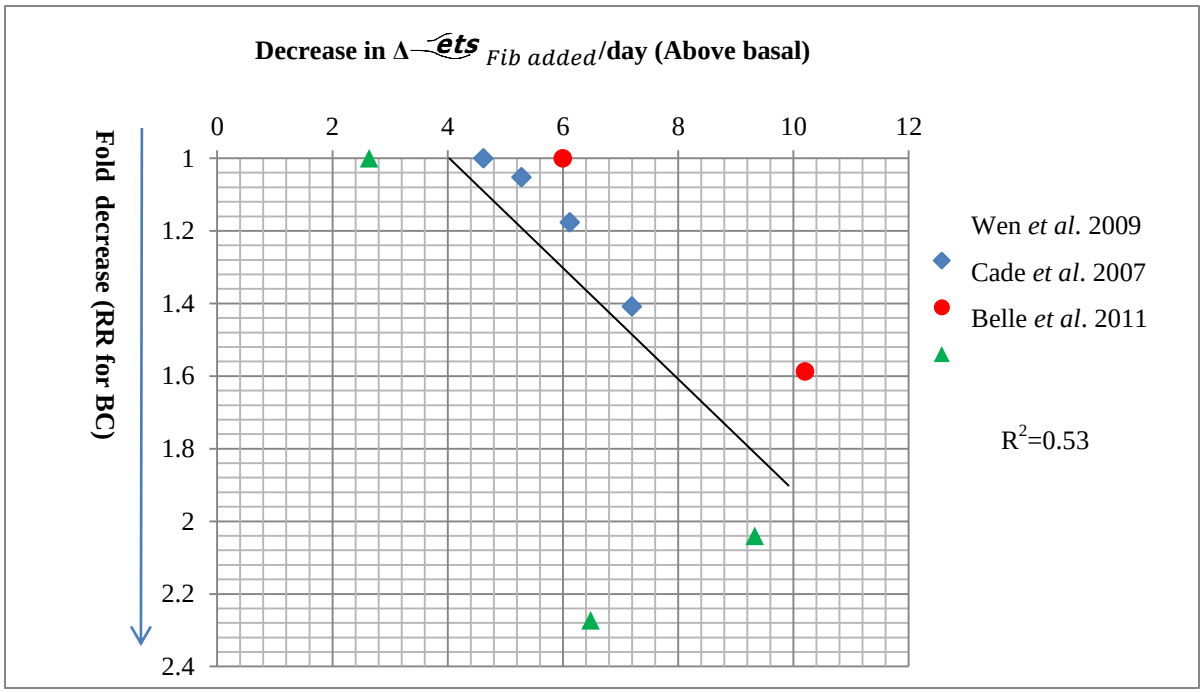


Figure D 3: The glycaemic effect in terms of ets of dietary fibre intake on the RR for BC.

A linearized relationship (R^2 = 0.53) between fiber intake in terms of ets and the RR for BC was once again assumed for ease of interpretation and understanding.

From Figure D 3 it is evident that fiber intake is inversely associated with the RR for BC. Dietary fiber intake only has an impact on the RR of BC after ingestion of the equivalent of 4 ets. With the consumption of 10 ets, which is the equivalent of 5.5 g of fiber added to three meals daily ($5.5g \times 3 \times 0.6 = 9.9$ ets), corresponds to an approximately two-fold reduction in the RR for BC.

Low to moderate intensity physical exercise

It is proposed that energy is expended through exercise, lowering BG levels in the body and thus lowering CRP levels. It is known that through participation in physical activity almost 20% of the energy comes from BG ($0.2\times kcal_{Exercise}$) (Noakes 2001). Using the energy expended during exercise in $kcal_{Exercise}$ a relationship between the BG expended in —ets can be obtained. The following conversion equation between *kcal* and —ets is obtained (taken from equation (11)).

$$1\text{—ets} = E_{Teaspoon\ Sugar} = 0.65 \times 5g \times 4kcal/g = 13kcal \tag{3}$$

Resulting in:

$$\text{—ets}_{Exercise} = 0.2 \times kcal_{Exercisee} \times (\text{—ets}/kcal) = 0.2 \times kcal_{Exercise} \times \frac{1}{3}$$

$$= \frac{kcal_{Exercise}}{65} \tag{4}$$

$kcal_{Exercise}$ accounts for the type, duration and intensity of the exercise, it also takes into consideration the body mass of the test subject (ACSM).

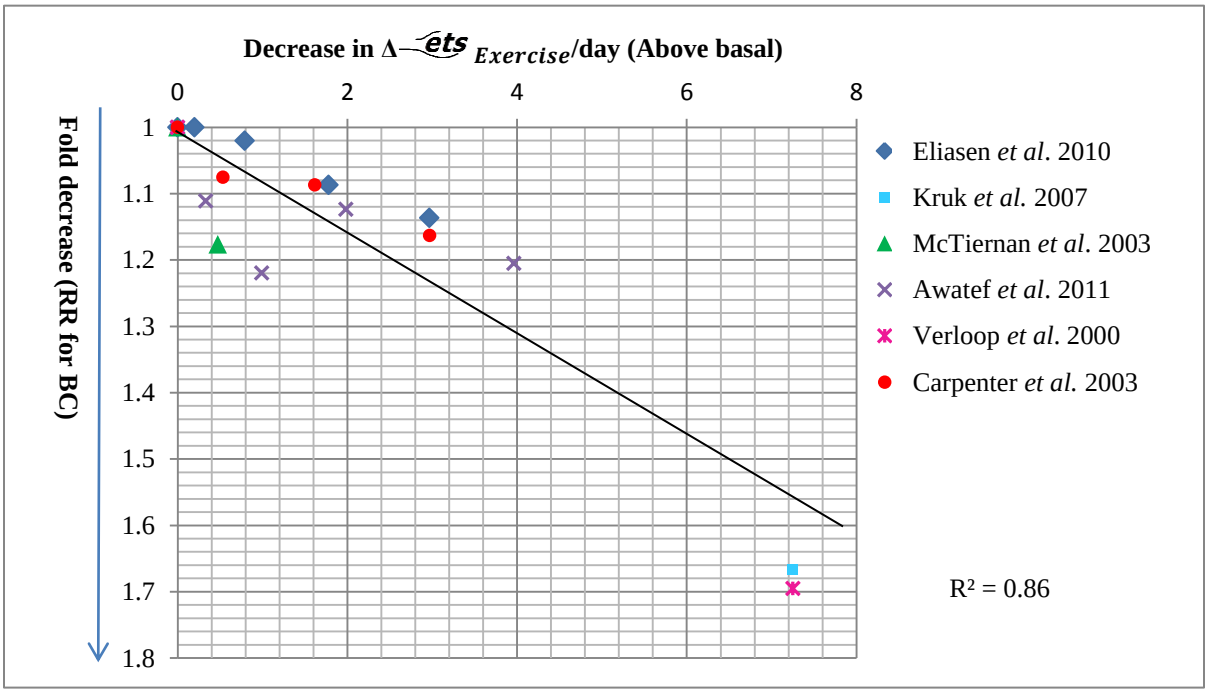


Figure D 4: The effect of low to moderate physical exercise in terms of —ets on the RR for BC

Only low to moderate intensity exercise is accounted for because this is what an average person will realistically achieve. An example of a low intensity exercise includes walking at 3 km/h for an hour. Moderate intensity exercise is classified as swimming for an hour.

From Figure D 4 it is apparent that physical activity reduces the risk of BC (R^2 = 0.86). Figure D 4 suggests that physical activity corresponding to approximately 7—ets (swimming at a moderate pace or cycling at 9 km/hr for 60 minutes) reduces BC risk by factor of 1.6 (RR = 1.6).

Consolidated results

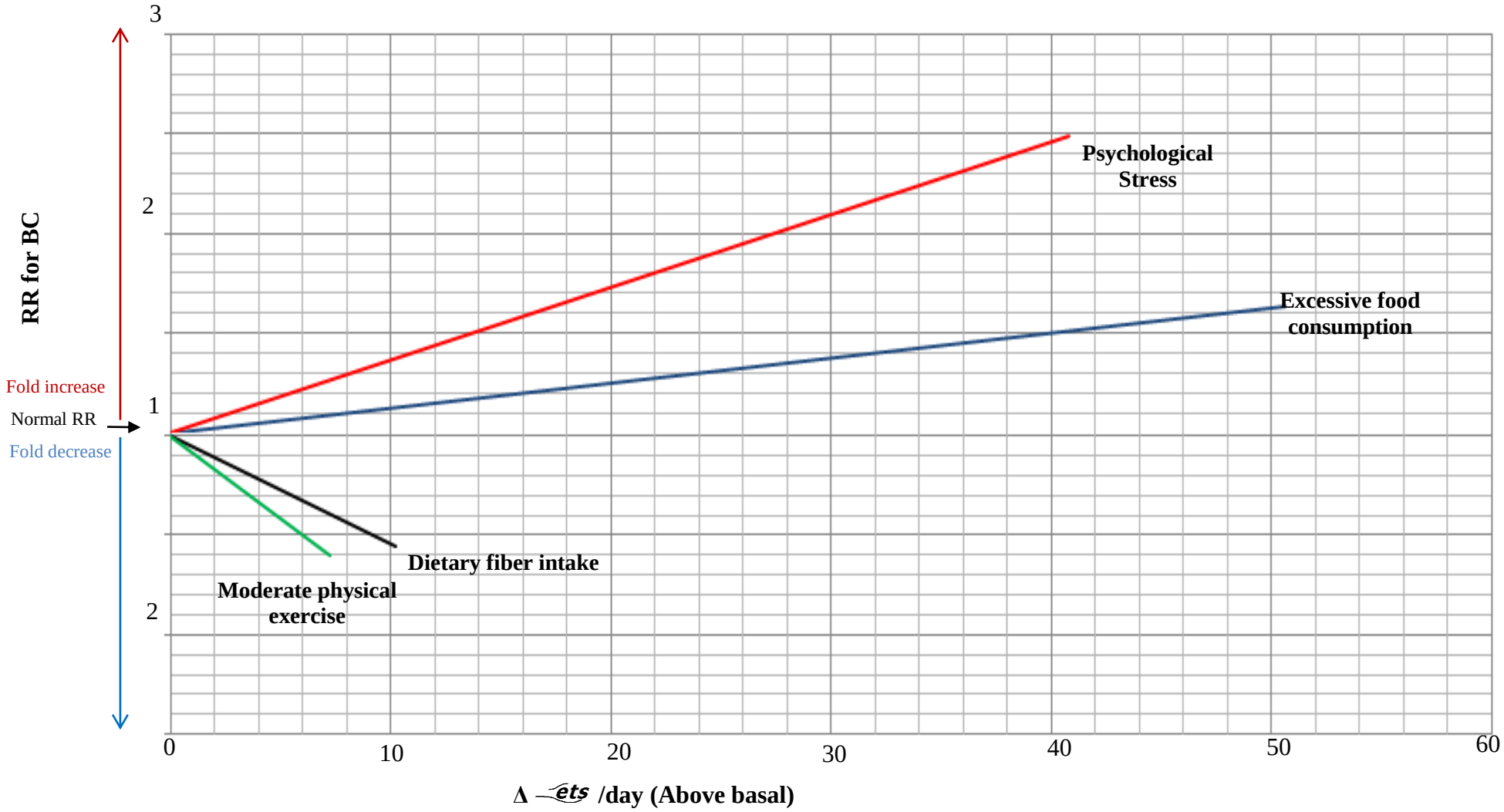


Figure D 5: Consolidated effects of the different lifestyle factors on the RR for BC in terms of ets.

The results of this study are based on previous studies and are only as accurate as the clinical data investigated. Furthermore, the model is not perfect and only accounts for the glycemic effects of the lifestyle factors investigated.

Figure D 5 is the consolidation of Figures D 1 to D 4. It is evident that the lifestyle factors associated with the increase of BG such as psychological stress and excessive food intake increase the RR for BC. The BG lowering lifestyles are related to a decrease in BC risk.

Psychological stress has the largest influence on carcinogenesis and the development of BC. It more than doubles the risk for BC, while inducing significantly large $\overline{ets}$ values. Excessive food consumption has a large glycaemic impact but a lower BC risk increase than stress. This could be attributed to inconsistencies in the clinical data investigated.

Low to moderate exercise is responsible for the greatest reduction in the risk for BC (with a factor of 1.6). Physical exercise, however, has a smaller effect on BG than dietary fiber intake. This shows that physical exercise has other anti-carcinogenic properties (such as anti-inflammatory properties (Das 2004)) in addition to its glycemic effect that accounts for its more rapid BC reduction.

Controlling psychological stress in combination with some low to moderate physical activity is suggested for pro-active prevention of BC.

Conclusion

Published studies have shown that BG plays a central role in BC development and protection. The state of the art, easy to visualize —ets model, used for the quantification of the different lifestyle factors' glycemic influences provided a way to draw a comparison between their impacts on BC. Psychological stress doubles the risk for BC and is considered the largest contributor to carcinogenesis. Low to moderate intensity physical exercise is responsible for the greatest risk reduction and protection against BC. Further investigations into treatments for psychological stress for the protection against BC are recommended.

References

ACSM. Metabolic Calculations Handbook Americand College of Sports Medicine. 1 ed. Baltimore, Maryland,: Lippincott Williams & Wilkins; 2007.

Augustin LS, Maso LD, LaVecchia C, Parpinel M, Negri E, Vaccarell S, Kendall CW, Jenkins DJ, Franceschi S. Dietary glycemic index and glycemic load, and breast cancer risk: A case-control study. *Annals of Oncology*. 2001;12 (11):1533-1538.

Awatef M, Olfa G, Rim C, Asma K, Kacem M, Makram H, Leila BF, Amel L, Slim AB. Physical activity reduces breast cancer risk: A case-control study in Tunisia. *Cancer Epidemiology*. 2011;35:540-544.

Bateman AC. Pathology of the breast. *Surgery*. 2004;22(7):iii-vii.

Belle FN, Kampman E, McTiernan A, Bernstein L, Baumgartner K, Baumgartner R, Ambs A, Ballard-Barbash R, Neuhouser ML. Dietary fibre, carbohydrates, glycemic index, and glycemic load in relation to breast cancer prognosis in the HEAL Cohort. *Cancer Epidemiology Biomarkers and Prevention*. 2011;20:890-899.

Black PH. The inflammatory response is an integral part of the stress response: Implications for atherosclerosis, insulin syndrome, type II daibetes and metabolic X syndrome. *Brain, Behaviour and Immunity*. 2003;17:350-364.

Cade JE, Burley VJ, Greenwood DC. Dietary fibre and risk of breast cancer in the UK Women's Cohort Study. *International Journal of Epidemiology*. 2007;36(2):431-438.

Carpenter CL, Ross RK, Paganini-Hill A, Bernstein L. Effect of family history, obesity and exercise on breast cancer risk among postmenopausal women. *International Journal of Cancer*. 2003;106:96-102.

Das UN. Anti-inflammatory nature of exercise. *Nutrition*. 2004;20(3).

dos Santos A, Borges JBR, de Almeida CG, Curi R. Metabolism of the microregions of human breast cancer. *Cancer Letters*. 2004 ;216:243-248.

Gatenby A, Gillies RJ. Why do cancers have high aerobic glycolysis? *Nature Reviews*. 2004;4:891-899.

Ebbeling CB, Leidig MM, Sinclair KB, Hangen JP, Ludwig DS. A reduced glycemic load diet in the treatment of adolescent obesity. *Archives of Pediatricians and Adolescent Medicine*. 2003;157(8):773-779.

Einvik G, Ekeberg O, Klemsdal TO, Sandvik L, Hjerkinn EM. Physical distress is associated with cardiovascular events in a high risk population of elderly men. *BMC Cardiovascular Disorders*. 2009;9(14):1-6.

Eliassen AH, Hankinson SE, Rosner B, Holmes MD, Willett WC. Physical activity and risk of breast cancer among postmenopausal women. *Archives of Internal Medicine*. 2010;170(19):1758-1764.

Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. *International Journal of Cancer*. 2010;127(12):2893-2917.

Jenkins AL, Zdravkovic U, Wursch P, Vuksan V. Depression of the glycaemic index by high levels of β-glucan fibre in two functional foods tested in type 2 diabetes. *European Journal of Clinical Nutrition*. 2002;56(7):622-628.

Kendall CW, Esfahani A, Jenkins J. The link between dietary fibre and human health. *Food Hydrocolloids*. 2010;24:42-48.

Kim Jw, Dang CV. Cancer's Molecular Sweet Tooth and the Warburg Effect. *Cancer Research*. 2006;66(18):8927-8930.

Kruk J, Aboul-Enein HY. Psychological stress and the risk of breast cancer a case-control study. *Cancer Detection and Prevention*. 2004;28:399-408.

Kruk J. Lifetime physical activity and the risk of breast cancer: A case control study. *Cancer Detection and Prevention.* 2007;31:18-28.

Kubzanski LD, Koenen KC. Is posttraumatic stress disorder related to development of heart disease? *An update. Cleveland Clinical Journal of Medicine*. 2009;76(2):S60-S65.

Larsson SC, Bergkvist L, Wolk A. Glycemic load, glycemic index and breast cancer risk in a prospective cohort of Swedish women. *International Journal of Cancer*. 2009;125(1):153-157.

Lillberg K, Verkasalo PK, Kaprio J, Teppo L, Helenius H, Koslenvuo M. Stress of daily activities and risk of breast cancer: A prospective cohort study in Finland. *International Journal of Cancer.* 2001;91:888-893.

Mathews EH, Liebenberg L. A practical quantification of blood glucose production due to high-level chronic stress. *Stress and Health*. in print 2012.

Mathews H, Liebenberg L. A Practical quantification of blood glucose production due to high-level chronic stress. *Stress and Health*. 2012; doi: 10.1002/smi.2415.

Mc Tiernan A, Kooperberg C, White E, Wilcox S, Coates R, Adams-Campbell LL, Woods N, Ockene J. Recreational physical activity and risk for breast cancer in postmenopausal women. *Journal of the American Medical Association*. 2003;290:1331-1336.

McEweb BS. Central effects of stress hormones in health and disease: Understanding the protective and damaging effects of stress and stress mediators. *European Journal of Pharmacology*. 2008;583:174-185.

Metcalfe C, Smith GD, Macleod J, Hart C. The role of self-reported stress in the development of breast cancer and prostate cancer: A prospective cohort study of employed males and females with 30 years of follow-up. *European Journal of Cancer*. 2007;43:1060-1065.

Noakes TD. Lore of Running. Oxford, UK: Oxford University Press; 2001.

Phillips AC, Batty D, Gale CR, Deary IJ, Osborn D, MacIntyre K, Carroll D. Generalized anxiety disorder, major depressive disorder, and their comorbidity as predictors of all-cause mortality: The Vietnam experience. *Psycosomatic Medicine*. 2009;71(4):395-403.

Raikkonen K, Keltikangas-Jarvinen L, Adlercreutz H, Hautanen A. Psycological stress and the insulin resistance syndrome. *Metabolism.* 1996;45(12):1533-1538.

Roest AM, Martens EJ, De Jonge P, Denollet J. Anxiety and risk of incident coronary heart disease, a meta-analysis. *Journal of the American College of Cardiology*. 2010;76(2):38-46.

Saltiel AR, Kahn CR. Insulin signalling and the regulation of glucose and lipid metabolism. *Nature.* 2001;414:799-806.

Sieri S, Pala V, Brighenti F, Agnoli C, Grioni S, Berrino F, Scazzina F, Palli D, Masala G, Vineis P, Sacerdote C, Tumino R, Giurdanella M, Mattiello A, Panico S, Krogh V. High glycemic diet and breast cancer occurrence in the Italian EPIC Cohort. *Nutrition, Metabolism and Cardiovascular Diseases.* 2012;doi:10.1016/j.numecd.

Sieri S, Pala V, Brighenti F, Pellegrini N, Muti P, Micheli A, Evangelista A, Grioni S, Contiero P, Berrino F, Krogh V. Dietary glycemic index, glycemic load, and the risk of breast cancer in an Italian prospective cohort study. *American Journal of Clinical Nutrition*. 2007;86(1160–6).

Verloop J, Rookus MA, van der Kooy K, van Leeuwen FE. Physical activity and breast cancer risk in women aged 20-54 years. *Journal of the National Cancer Institute*. 2000;92(2):128-135.

Versteeg H, Pedersen SS, Denollet J, Spek V. Type D personality and health status in cardiovascular disease populations: A meta-analysis of prospective studies. *European Journal of Cardiovascular Prevention and Rehabilitation*. 2011; doi: 10.1177/1741826711425338.

Vogelzangs N, Seldenrijk A, Beekman ATF, van Hout HPJ, de Jonge P, Penninx BWJH. Cardiovascular disease in persons with depressive and anxiety disorders. *Journal of Affective Disorders*. 2010;125(1-3):241-248.

Volp PA, de Oliviera EF, Alves DM, Bressan Ey. Energy expenditure: Components and evaluation methods. *Nutricion Hospitalaria*. 2011;26(3):430-440.

Weigelt B, Bissell MJ. Unraveling the microenvironmental influences on the normal mammary gland and breast cancer. *Seminars in Cancer Biology*. 2008;18:311-321.

Weigelt B, Geyer FC, Reis-Filho JS. Histological types of breast cancer: How special are they? *Molecular Oncology*. 2010;4(3):192-208.

Wen W, Shu XO, Li H, Yang G, Ji BT, Cai H, Gao YT, Zheng W. Dietary carbohydrates, fiber, and breast cancer risk in Chinese women. *Clinical Nutrition*. 2009;89:283-289.