AMERICAN UNIVERSITY OF BEIRUT

FRUCTOSE INTAKE AND RISK OF METABOLIC SYNDROME IN LEBANESE ADULTS: A CROSS SECTIONAL STUDY

by
RITA RONY AOUN

A thesis
submitted in partial fulfillment of the requirements
for the degree of Master of Sciences
to the Department of Nutrition and Food Sciences
of the Faculty of Agricultural and Food Sciences
at the American University of Beirut

Beirut, Lebanon
September 2019

AMERICAN UNIVERSITY OF BEIRUT

FRUCTOSE INTAKE AND RISK OF METABOLIC SYNDROME IN LEBANESE ADULTS: A CROSS SECTIONAL STUDY

by

RITA RONY AOUN

Approved by:

Dr. Lara Nasreddine, Associate Professor — Advisor
Nutrition and Food Sciences

Dr. Lamis Jomaa, Assistant Professor — Member of Committee
Nutrition and Food Sciences

Dr. Hani Tamim, Associate Professor — Member of Committee
Internal Medicine

Date of thesis defense: September 02, 2019

AMERICAN UNIVERSITY OF BEIRUT

THESIS, DISSERTATION, PROJECT RELEASE FORM

Student Name: _____Aoun_____Rita_____Rony _____

Last First Middle

(X) Master's Thesis ( ) Master's Project ( ) Doctoral Dissertation

[ ] I authorize the American University of Beirut to: (a) reproduce hard or electronic copies of my thesis, dissertation, or project; (b) include such copies in the archives and digital repositories of the University; and (c) make freely available such copies to third parties for research or educational purposes.

[X] I authorize the American University of Beirut, to: (a) reproduce hard or electronic copies of it; (b) include such copies in the archives and digital repositories of the University; and (c) make freely available such copies to third parties for research or educational purposes after:
One --- years from the date of submission of my thesis, dissertation, or project;
Two - --years from the date of submission of my thesis, dissertation, or project;
Three ~~-~~ years from the date of submission of my thesis, dissertation, or project.

_____ 11/09/2019

Signature Date

ACKNOWLEDGMENTS

To my life-coach, my brother Joey Aoun: because I owe it all to you. I can't thank you enough!

To my beloved family: my parents and my brothers who have always supported me spiritually and mentally throughout my life. Many thanks! I hope I have made you proud.

Very special gratitude goes out to my advisor Dr. Lara Nasreddine, for her patience, motivation, and guidance. Without her immense knowledge and continuous support, I would not have been able to complete this thesis.

Besides my advisor, I would like to thank my thesis committee: Dr. Hani Tamim and Dr. Lamis Jomaa who have widen my research from various perspectives through their questions and insightful comments.

And finally, last but not least, I am also thankful to the following research assistance: Maha Makki and Aurelie Mailhac for their assistance in the statistical data analysis.

AN ABSTRACT OF THE THESIS OF

Rita Rony Aoun for Master of Science
Major: Nutrition

Title : Fructose intake and risk of Metabolic Syndrome in Lebanese adults: a cross-sectional study

The parallelism between the increase in the consumption of fructose and the rise in obesity and metabolic syndrome (MetS) over the past 20 years, proposed excessive fructose intake as one of the potential causes for metabolic abnormalities. The evidence, however, remains inconclusive. The objectives of this study were to (1) assess dietary intake of fructose in a sample of Lebanese urban adults and (2) investigate the association of total, added and natural fructose intakes with MetS and its components.

This cross-sectional population-based study was conducted on 283 participants ≥ 18 years old with no prior history of chronic disease. Using standardized techniques, anthropometric and biochemical data were collected. Dietary intake was assessed by trained dietitians using a culture-specific 82-items semi-quantitative FFQ. Natural fructose intake (g/day) from fruits and vegetables was determined using NutriPro software. Added fructose intake was estimated to be 50% of added sugars in food products. Total dietary fructose intake was calculated by summing up natural and added fructose intakes.

Mean intake of total dietary fructose was 51.42 ± 35.54 g/day, which represents 6.58 ± 3.71 % of the total energy intakes. Natural and added fructose intakes were estimated at 12.29 ± 8.57 and 39.12 ± 34.10 g/day (1.78 ± 1.41% and 4.80 ± 3.56%), respectively. Compared with those in the lowest quartile of fructose intakes, participants in the highest quartile of total and added fructose intake, had respectively 2.450 (95% CI 1.047- 5.734) and 2.609 (95% CI 1.081- 6.298) higher risk of MetS, after adjustment for confounding variables. In contrast, natural fructose intake was not associated with MetS in the study sample. When examining each abnormality alone (hypertension, hyperglycemia, dyslipidemia), no significant association was found with fructose intake, even after adjustment for potential confounders.

A high fructose consumption was observed among Lebanese urban adults. The observed positive association between high fructose intake and the risk of MetS highlights the need for immediate public health strategies aimed at limiting sugar intake from industrialized foods and promoting healthier dietary patterns in Lebanon.

CONTENTS

TABLES

FIGURES

Figure Page

ABBREVIATIONS

MetS: *Metabolic syndrome*

HTN: *Hypertension*

IDF: *International Diabetes Federation*

CHO: *Carbohydrate*

HFCS: *High Fructose Corn Syrup*

CVD: *Cardiovascular Disease*

T2DM: *Type 2 Diabetes Mellitus*

WHO: *World Health Organization*

IGT: *Impaired glucose tolerance*

EGIR: *European Group for the Study of Insulin Resistance*

NCEP ATP III: *National Cholesterol Education Program Adult Treatment Panel III*

WC: *Waist circumference*

VF: *Visceral fat*

AHA/NHLBI: *American Heart Association/National Heart, Lung, and Blood Institute*

NCDs: *Non-communicable diseases*

NHANES: *National Health and Nutrition Examination Survey*

FFA: *Free fatty acids*

TNF-α: *Tumour Necrosis Factor alpha*

IL: *Interleukin*

PA: *Physical activity*

SSBs: *Sugar sweetened beverages*

SFA: *Saturated fatty acids*

BP: *Blood pressure*

HDL: *High density lipoproteins*

LDL: *Low density lipoprotein*

TG: *Triglycerides*

DNL: *De novo lipogenesis*

VLDL: *Very low density lipoprotein*

SREBP-1c: *Sterol Receptor Element–Binding Protein-1c*

CHREBP: *Carbohydrate responsive element binding protein*

LPL: *Lipoprotein lipase*

DAG: *Diacylglycerol*

NO: *Nitric oxide*

VAT: *Visceral adipose tissue*

SAT: *Subcutaneous adipose tissue*

SNS: *Sympathetic Nervous System*

BPA: *Bisphenol A*

AUB: *American University of Beirut*

NFSC: *Department of Nutrition and Food Sciences*

FFQ: *Food frequency questionnaire*

EI: *Energy intake*

Q4: *Quartile 4*

NCDs: *Non-communicable diseases*

To my beloved parents

CHAPTER I

INTRODUCTION

Metabolic syndrome (MetS), is a cluster of cardiometabolic risk factors, that contributes to type 2 diabetes and CVD (Xu et al., 2018; Grundy et al. 2004; Mottillo et al., 2010) . The criteria components include hypertension (HTN), atherogenic dyslipidemia, hyperglycemia and central adiposity (Alberti et al., 2009; Kaur, 2014). Worldwide, MetS prevalence have continued to grow to the point of becoming a primary public health concern. According to the International Diabetes Federation (IDF), approximately 25% of the world's population has been diagnosed with this syndrome (O'Neill et al., 2015) with high rates being reported in the Middle East countries, including Lebanon (Sibai et al., 2008; Naja et al., 2013).

Pathogenesis of MetS involves various complex interactions between genetic and environmental factors (Kaur, 2014). Many contributors have been proposed, with the diet being a major one. Indeed, several reviews have concluded that individual nutrients or food items were associated with increased risk of MetS (Malik et al., 2010; Baudrand et al., 2014; Cheng et al., 2017). The relationship between fructose intake and MetS in individuals is a current debate among researchers. In the last three decades, the rising level of fructose consumption in industrialized nations have paralleled the rise in MetS and obesity (Hu and Malik, 2010; Rippe, 2010), and epidemiologic studies have inconsistently linked these observations. Several studies have reached the conclusion that excessive intake of fructose was associated with increased adverse metabolic effects (Hu and Malik, 2010; Stanhope and Havel, 2008; Stanhope and Havel, 2010) , while others showed no association (Dolan et al., 2010; Jones, 2009; Tappy and Le, 2010; Tappy et al., 2010).

Fructose, the sweetest tasting carbohydrate (CHO), is consumed in significant amounts in humans' diets (Miller and Adeli, 2008). Fructose occurs naturally in fresh fruits, vegetables and honey and recently, has been widely used in industrialized foods [as sucrose or High Fructose Corn Syrup (HFCS)]. Fructose has become a major public health concern, painted as toxin in scientific publications mainly due to its lipogenic and low satiating effect (Rizkalla, 2010) (Lustig et al., 2012). However, there is no fully relevant data presented to establish a direct association between current amounts of dietary fructose and features of MetS (Rizkalla, 2010) (Feinman & Fine 2013).

Considering the lack of data on dietary fructose intake in Lebanese adults, the present study has two main objectives. First, it aims at assessing dietary fructose intake of Lebanese adults living in Beirut and estimate their added fructose intake. Second, the study aims at investigating the association of total and added fructose consumption with MetS and its components; abdominal obesity, fasting blood lipid levels, fasting glycemia and BP among Lebanese adults living in Beirut.

CHAPTER II

LITERATURE REVIEW

A. The Metabolic Syndrome

1. Historical perspectives and concept evolution [1]

The MetS concept saw the light in 1920, when a Swedish physician, Kylin, described the coexistence of the various components of the syndrome resulting in a triad of metabolic disorders 'hypertension–hyperglycaemia–hyperuricaemia" (Sarafidis and Nilsson, 2006). Later, in 1947, Vague described the association between android obesity and the development of the metabolic abnormalities found in cardiovascular disease (CVD) and Type 2 diabetes mellitus (T2DM) (Sarafidis and Nilsson, 2006). Following this, in the mid-1960s, the MetS became an important concept in the scientific research field. Several scientists worldwide published their observations on this condition at that time giving it various names. After several years of research, in 1988, Reaven introduced the concept of insulin resistance as the main contributor for this group of disorder, consisting of lipid abnormalities, HTN, and impaired glucose tolerance. Reaven named the sum of these disorders as "Syndrome X." A year later, Kaplan added a significant abnormality to the disorders described by Reaven, which is central obesity. He renamed this cluster "the deadly quarter" consisting of central obesity, lipid abnormalities, HTN and impaired glucose tolerance (Kaur, 2014). However, in 1992, several scientists renamed the syndrome "The Insulin Resistance Syndrome," believing that insulin resistance is the main contributor for the remaining disorders (Kaur, 2014). Finally, the name "Metabolic syndrome" has gained international acceptance in the past two decades. Ever since, the diagnostic criteria for the Mets remained a subject of interest for many researchers (see figure 1).

[1]. see Appendix I for the overall Literature review mind map diagram

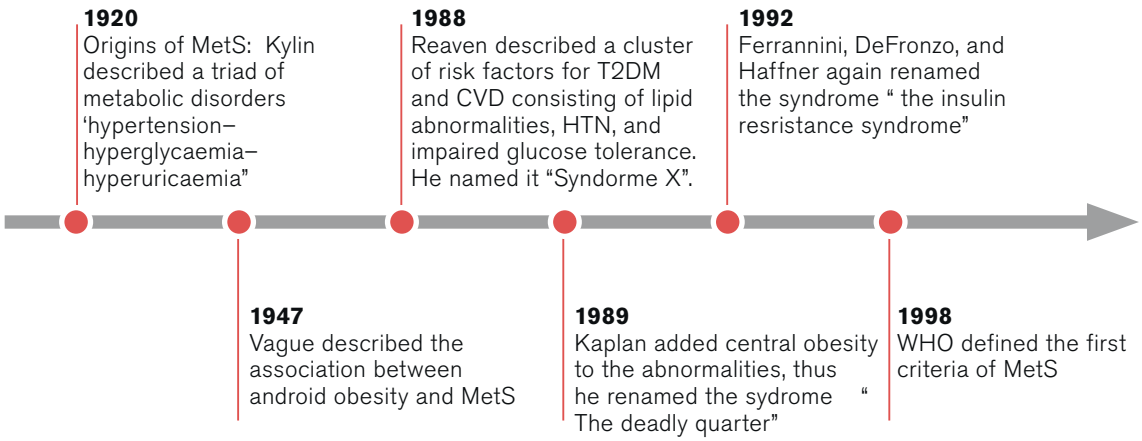

Figure 1 Historical timeline and concept evolution of MetS

2. *Various definitions of metabolic syndrome*

The MetS, is the presence of a cluster of metabolic risk factors for CVD and diabetes (Alberti et al., 2009). Over the years, many definitions have been proposed for MetS with each one of them providing different diagnostic criteria. The first definition of MetS was formulated in 1998 by the World Health Organization (WHO) (Alberti and Zimmet, 1998). According to the WHO definition, insulin resistance (impaired glucose tolerance (IGT) or T2DM) is one of the major underlying risk factors to MetS (Alberti, Zimmet, & Shaw, 2005). In addition to insulin resistance, at least two other factors should be present for the diagnosis of MetS to be made (see table 1). In 1999, the European Group for the Study of Insulin Resistance (EGIR) proposed a modified version to the WHO definition (Balkau and Charles, 1999). EGIR definition placed greater emphasis on central obesity and in contrast to WHO excluded all the patients with T2DM. The EGIR underlined hyperinsulinemia (plasma insulin more than 75 percentile) as the major contributor to MetS and required evidence of hyperinsulinemia for diagnosis. Both WHO and EGIR definitions required insulin resistance determined by an oral glucose tolerance test and hyper-insulinemic-euglycemic clamp. However these measurements were not practical for physicians and are primarily used in a research environment (Ritchie SA

and Connell JMC, 2007). In 2001, a more straightforward definition was announced by the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) (Cleeman et al., 2001). The NCEP ATP III was not “glucose-centric”, thus insulin resistance was not required for the diagnosis of MetS to be made. Moreover, it clearly stated that pro-inflammatory state and prothrombotic state are not among the criteria mandatory for the determination of MetS. Importantly, the NCEP ATP III definition used the waist circumference (WC) as the measure of central obesity instead of the waist to hip ratio used in the WHO definition. In contrast, to WHO and EGIR, the ATPIII definition facilitated diagnosis in clinical practice since it uses measurements and laboratory results more practical and applicable for physicians (Ritchie SA and Connell JMC, 2007). The various definitions of MetS has led to significant confusion. Therefore, in 2005 the IDF released a global consensus for a more practical definition of the MetS (Zimmet et al., 2005). The IDF made central obesity an essential component required in the diagnosis. Indeed, visceral fat (VF) accumulation in both genders has been demonstrated to have a strong association with various metabolic risk factors such as HTN, impaired blood glucose and lipid metabolism (Zimmet et al., 2005). Importantly, IDF have placed emphasis on developing criteria that would be applicable across all the ethnicities. Since different ethnicities have different distributions of norms for central obesity, IDF has proposed a new set of criteria that includes WC cutoffs specific by gender and ethnicity (Zimmet et al., 2005). In 2009, the IDF and the American Heart Association/National Heart, Lung, and Blood Institute (AHA/NHLBI) attempted to resolve the remaining differences between definitions and settled a harmonized description of the MetS (Alberti et al., 2009). The IDF and AHA agreed on the criteria for the clinical diagnosis of the MetS characterized by the presence of at least 3 of 5 risk factors as shown in Table 1.

Table 1 **Various definitions of MetS and criteria evaluation**

	WHO (1998)	EGIR (1999)	NCEP ATP III (2001)	IDF (2005)	Harmonized (2009)
Absolutely required	Insulin resistance (IGT, T2DM or other evidence of IR)	Hyperinsulinemia (plasma insulin more than 75 percentile)	None	Central obesity-Elevated WC * ethnicity specific **	None
Criteria	Insulin resistance plus ≥ 2 of the following	Hyperinsulinemia plus ≥ 2 of the following	≥ 3 of the following	Central obesity plus ≥ 2 of the following	Any 3 of the following
Fasting blood glucose	Already required (IGT, IFG or T2DM)	≥ 110 mg/dl but nondiabetic	≥ 110 mg/dl including diabetic	≥ 100 mg/dl or previously diagnosed type 2 diabetes	≥ 100 mg/dl or previously diagnosed type 2 diabetes
Blood pressure	≥ 140/90 mm Hg	≥ 140/90 mm Hg Or on treatment	≥ 130 mmHg systolic or ≥ 85 mmHg diastolic	≥ 130 mmHg systolic or ≥ 85 mmHg diastolic Or treatment	≥ 130 mmHg systolic or ≥ 85 mmHg diastolic Or treatment
Triglycerides	≥ 150 mg/dl	≥ 150 mg/dl Or treatment	≥ 150 mg/dl	≥ 150 mg/dl Or treatment	≥ 150 mg/dl Or treatment
HDL cholesterol	Men: < 35 mg/dl Women < 39 mg/dl	< 39 mg/dl in men or women Or treatment	Men: < 40 mg/dl Women < 50 mg/dl	Men: < 40 mg/dl Women < 50 mg/dl Or treatment	Men: < 40 mg/dl Women < 50 mg/dl Or treatment
Obesity	Men: WHR > 0.9 Women: WHR > 0.85 And/or BMI > 30 kg/m	Men: WC ≥ 94 cm Women: WC ≥ 80 cm	Men: WC > 102 cm Women: WC > 88 cm	Men: WC ≥ 94 cm Women: WC ≥ 80 cm	Elevated WC ethnicity and population specific
Other criteria	Microalbuminuria ***				
Criteria evaluation (Diagnostic limit or criticism of the criteria)	Microalbuminuria only included in this definition and considered by some to be controversial. In clinical practice or in epidemiological studies it is hard to determine IR that is measured by clamp techniques. The WHR may not be relevant index of the absolute amount of visceral fat.	Small differences from the WHO definition, thus it did not meet wide international use.	Did not include a measure of IR as a component, thus it is easier to be used in clinical practice. Includes WC as the measure of obesity which is a better index for abdominal obesity. However, it has unified criteria for different ethnic groups.	Places central obesity as the main criteria Proposed a new set of criteria with ethnic/racial specific cut-offs for WC	Obesity and IR are not pre-requisites for diagnosis The risk for MetS with a specific WC will differ in various ethnicities

EGIR, European Group for the Study of Insulin Resistance; HDL, high-density lipoprotein; IDF, International Diabetes Federation; MetS, metabolic syndrome; NCEP:ATPIII, National Cholesterol Education Program – Third Adult Treatment Panel; T2DM, type 2 diabetes mellitus; WC, waist circumference; WHR, waist to hip ratio; WHO, World Health Organization; IR, insulin resistance; BMI, body mass index;

* If BMI > 30 kg/m2 then central obesity can be assumed, and waist circumference does not need to be measured.

** Waist circumference are specific for each population; values given are for European men and women.

*** Microalbumineria: Urinary excretion rate of >20 mg/min or albumin: creatinine ratio of >30 mg/g.

3. The Global Epidemic of the Metabolic Syndrome

The disease pattern worldwide has changed significantly over the past 40 years. Non-communicable diseases (NCDs) have replaced infectious diseases and have become the primary cause of mortality and morbidity worldwide (Saklayen, 2018). According to the WHO, NCDs cause 70 % of all annual death worldwide (around 40 million people die per year due to NCDs) (WHO, 2018). The MetS is recognized as a major risk factor to several NCDs. Worldwide MetS prevalence ranges from <l0% to as much as 84%, depending on gender, age, ethnicity of the population studied the region, and the criteria used for the definition of MetS (Desroches et al., 2007; Kolovou et al., 2007). In fact, the prevalence of MetS is estimated to be higher when using the IDF and the harmonized definition since they suggest lower thresholds for central obesity (Brown et al., 2010). Based on the IDF, 25% of the world's population has been diagnosed with MetS (O'Neill et al., 2015).

Of concern is the observed increasing trend of MetS globally. According to the data from National Health and Nutrition Examination Survey (NHANES), the age adjusted prevalence of MetS increased from 26.7% in 1999-2000 to 32.9 % in 2003-2004 and has reached 34.7% in 2011-2012 in U.S. adults based on the ATP III criteria (Ford et al., 2004) (Aguilar et al., 2015). The pandemic of MetS has been as well increasing in most Asia Pacific region. A secular increase in prevalence is observed in China, Taiwan and South korea. According to the Korean National Health and Nutrition Examination Survey (KNHANES), the prevalence of MetS in Korea increased by 6.4 % in 9 years (from 1998 to 2007) using the ATP III criteria (Lim et al., 2011). In China, a significant increase in the prevalence of MetS, from 13.7% in 2000-2001 to 21.3% in 2009, was also reported (Xi et al., 2009). A similar result was observed in Taiwan (Yeh et al., 2011).

Furthermore, high rates of MetS were reported in the Middle East countries. According to a meta-analysis of 59 cross-sectional studies, prevalence of MetS was shown to be high in Turkey, Saudi Arabia, Pakistan, Qatar, Emirates and Iran with

a pooled estimate of 25% (Ansarimoghaddam et al.,2017). Recent studies have also suggested high rates of MetS in Lebanon. According to a cross-sectional survey conducted by Naja et al. in 2013, 34.7% out of 323 Lebanese participants were diagnosed as having MetS, using IDF criteria. Similar findings were also noted in a study conducted by Sibai et al. (2008) where a prevalence of 31.2 % was observed amongst Lebanese adults aged 18-65 years old recruited from health care centers. In the letter, Sibai also relied on the IDF definition (Sibai et al., 2008).

4. Etiology of metabolic syndrome

Obesity and MetS

Over the past three decades, the prevalence of overweight and obesity has dramatically increased worldwide in developed and underdeveloped countries. Indeed, over a third of the world's population today is obese or overweight (Ng M et al., 2014). If such trends continue linearly, by 2030, 58% of the world's adult population will be either obese or overweight (Kely et al., 2008). Prevalence of obesity has increased significantly across several countries around the world mainly United States of America (USA), United Kingdome (UK) and Australia (Ng M et al., 2014). An identical trend was also seen in Lebanon. Indeed, Nasreddine et al. reported an increase in the prevalence of overweight and obesity from 54.4 % to 65% over the past decade in Lebanon (1997 and 2009) (Nasreddine et al., 2012). The observed increase in obesity could be explained by the dramatic change in people's way of eating and activity patterns (Popkin et al., 2012). This alarming increase in obesity prevalence represents a major public health concern since it is considered to be a major risk factor for the development of MetS. Indeed, the development of MetS depends on two features: accumulation of body fat and predisposition to locate this fat intra-abdominally (Han & Lean 2016). Hypotheses relating obesity to the MetS focus on the understanding that visceral adipose tissue secretes a range of

adipocytokines such as free fatty acids (FFA), tumor Necrosis Factor alpha (TNF-α) and interleukin (IL) which are factors that impairs insulin action and increases metabolic disorders (Alberti et al., 2006). Furthermore, excessive VF is associated with a decreased production of adiponectin which has been shown to have anti-diabetic and anti-inflammatory functions (Alberti et al., 2006).

Physical activity and metabolic syndrome

Various studies have demonstrated that physical inactivity and sedentary behaviors are risk factors for developing MetS. The association of sedentary behaviors with MetS is positively related, independent of physical activity level. Indeed, a study conducted on 1,367 men and women, who participated in the 2003–2006 NHANES found that people with MetS spent a higher percentage of their time as sedentary compared to people without MetS (67.3 vs. 62.2%) (Bankoski et al., 2011). Moreover, it has consistently been shown that there is an inverse association between physical inactivity and MetS. Studies reported a greater occurrence of MetS in groups with a low level of physical activity (PA) (Kwang-Jun Ko at al., 2016).

Diet and metabolic syndrome

With the nutrition transition and the adoption of westernized diet major dietary shifts have occurred in most countries. Although Western diet has various definitions, it is often characterized by high consumption of sugar sweetened beverages (SSBs), refined grains, red and processed meat, with concurrently low intake of whole grain, fruits and vegetables (Wirfalt et al., 2013). Many recent studies have shown a positive association between Western dietary pattern and cardiometabolic abnormalities (Drake et al., 2018) (Rodríguez-Monforte et al., 2017). Moreover, another dietary pattern the fast food/dessert pattern that resembles the Western pattern is also reported to be positively associated with MetS in a sample of Lebanese adults (Naja et al., 2013).

Western dietary pattern are typically high in saturated fatty acids (SFA). Various studies have demonstrated positive association between high SFA intake and metabolic factors constitutes of the MetS such as elevated central obesity, elevated fasting glucose concentration and reduced insulin sensitivity (Noel et al., 2010) (Poledne, 2013) (Oliveria Junior et al., 2013). The effects of SFA on inducing the MetS could be partly explained by its effect on insulin resistance and inflammation markers (Nourmohammdi et al., 2015).

Another modifiable factor for MetS is sodium intake. According to a study conducted by Oh et al., 2015 a strong association was shown between high sodium intake and all the components of MetS. A positive association has been reported between sodium intake and blood pressure (BP), central obesity, fasting glucose, and triglycerides (TG) levels and an inverse association between sodium intake and high density lipoproteins (HDL) levels (Oh et al., 2015).

Over the last 40 years, soft drinks consumption has increased substantially (Basu et al., 2013). A systematic review and meta-analysis by Narain et al. in 2017, was performed to evaluate the association of soft drink consumption with the development of MetS. The results of this review suggested that soft drink consumption is positively associated with development of MetS (Narain et al., 2017). SSB consumption leads to a high caloric intake which results in a positive energy balance. Weight gain contributed by these soft drinks has been demonstrated to be a primary trigger for MetS (Malik et al., 2010). Moreover, SSBs may increase the risk of MetS because of their high content of sucrose and HFCS (Malik et al., 2010). Different factors explained in further details in section C.2 may explain this association.

B. Fructose

1. Sugar history

Sugar has always been present in the human diet since the origin of man. It was consumed as a component of wild fruits, vegetables and on occasion in wild honey and it constituted of glucose, fructose, and sucrose.

Sugar consumption became more popular when sugar cane was cultivated which is a high source of sucrose. Sugarcane was firstly domesticated about 8,000 years ago by the indigenous people in New Guinea, then it was gradually spread to India, Southeast Asia, and China (White, 2014).During the Golden age of India year 350 AD granulated sugar crystals were developed and have become a major trade item (White, 2014). In the middle age, it was imported to Europe and North America, where it was considered a luxury product and only consumed by royalty and very wealthy people. However, in 1500 with the discovery of America, sugar production began to expand. Its consumption increased rapidly worldwide, and it was no longer a luxury product. In 1800, sugar became widely used in processed food, beverages, and confection; it became a food necessity (White, 2014). Indeed, in England, the average consumption per capita of sugar increased from 1.8 Kgs in 1700 to 8.1 Kgs in 1800 (Johnson et al., 2007). Sugar consumption continued to grow in 1900, and its use became commonplace around the world. Finally, it was only in the 1960s that an additional sweetener, HFCS, was introduced in the United States (Vuilleumier, 1993). HFCS is a mixture of fructose and glucose with various fructose-to-glucose ratios. Due to its organoleptic properties, low cost and ability to confer a long shelf life it has been added to various manufactured food products and its consumption has increased at the expense of sucrose (Tappy et al., 2010).

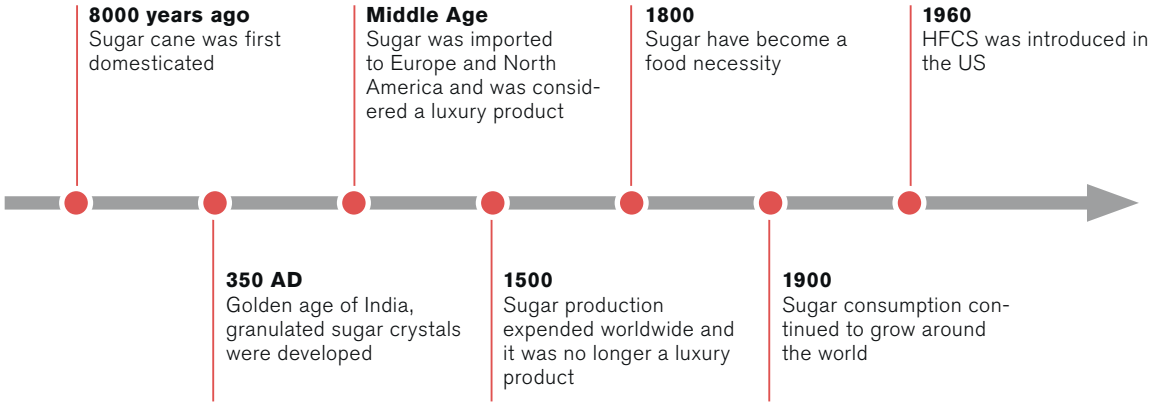

Figure 2 Historical timeline and concept evolution of sugar

2. *Evolution of fructose consumption*

According to United States Department of Agriculture (USDA), sucrose intake in the U.S. has declined by almost 50% (90g/day to 50g/day) between 1970 and 1985 (Tappy et al., 2010). This decrease in sucrose was countered with a sharp increase in HFCS. Based on the analysis of food dietary records obtained in USDA Nationwide Food Consumption Survey in 1977–78, the mean fructose intake for the United States population was 37 g/day in 1977–78 (Park et al., 1993). Evolution of fructose intake between 1977 and the 1990s was assessed by the third National Health and Nutrition Examination Survey, performed in 1988 –94 (NHANES III) (Vos et al., 2008). Investigators found that over a 10- to 16-year period, fructose consumption had increased by 46%. The average daily fructose intake jumped from 37g/day (which represent 8% of total energy intake) in 1977-1978 to 54.7 g/day (which represent 10.2% of total energy intake) in 1988 –94. Data collected from the NHANES 1999–2004 study reported a recent estimation of average fructose intake of 49 g/day (Marriot et al., 2009). Moreover, it stated that HFCS consumption has accounted for 42% of total caloric sweetener consumption in 1999 –2004 versus 16% in 1977–1978. A cross-sectional study of U.S. participants conducted by Welsh et al. in 2008 reported a slight decrease in fructose consumption between 1999-2000 and 2007-2008 (Welsh et al., 2011). However, despite this minor reduction added sugar and fructose consumption are still considered to be high.

3. Fructose Metabolism

Fructose absorption

Ingested fructose is absorbed from the gut through a specific fructose transporter GLUT 5 expressed mainly in enterocytes (Burant et al., 1992). Contrary to glucose, fructose absorption is passive, does not require ATP hydrolysis and is not sodium dependent. However, compared with glucose, the intestinal capacity to absorb fructose is limited. In fact, an adult can absorb between 5 to 50g of fructose per day (Rumessen et al., 1986). Several factors are reported to affect this capacity such as age, diet, specifically the presence of glucose, and overall health. After fructose loading, unabsorbed fructose may contribute to gastrointestinal symptoms such as diarrhea and flatulence (Rumessen et al., 1992).

Intermediary fructose metabolism

Once inside the enterocyte, fructose is released into the portal circulation through GLUT 2 at the basolateral membrane of the enterocytes (Corpe et al., 1999). The majority of the fructose present in blood is extracted by the liver resulting in only small amounts of fructose in circulation. Thus, fructose concentration in the blood is about 0.01 mmol/L, unlike glucose concentration which is about 5.5 mmol/L (Bray et al., 2007). Although fructose metabolism occurs primarily in the liver, enterocytes can metabolize up to 30% of it (Mavrias et al., 1973).

Hepatic metabolism

Fructose uptake by hepatocytes occurs via the glucose transporter GLUT2. Its metabolism differs from that of glucose as illustrated in Figure 3. Fructose is rapidly metabolized by the enzyme fructokinase (also known as ketohexokinase) into fructose 1 phosphate (Kolderup & Svihus, 2015). However, this first step is unregulated since there is no feedback mechanism regulating the phosphorylation

of fructose. The fructokinase enzyme is in fact not inhibited by energy status (ATP and citrate levels) (Samuel, 2011). Fructose 1 phosphate is metabolized into dihydroxyacetone phosphate (DHAP) and glyceraldehyde 3-phosphate (G3P) through the action of aldolase B. These fructose derived metabolites enter the glycolytic cycle bypassing phosphofructokinase, the main controlling step in glycolysis. Thus, the liver will metabolize dietary fructose in an unregulated manner, resulting in large amounts of trioses phosphate in hepatocytes. These latter can enter 3 different metabolic pathways in the liver: gluconeogenesis, lactic acid production or de novo lipogenesis (DNL) (Tappy et al., 2010). Fructose continuously entering the glycolytic pathway will result in excess energy flux and unregulated amounts of TCA intermediates which will lead to fatty acid synthesis (Softic et al., 2016).

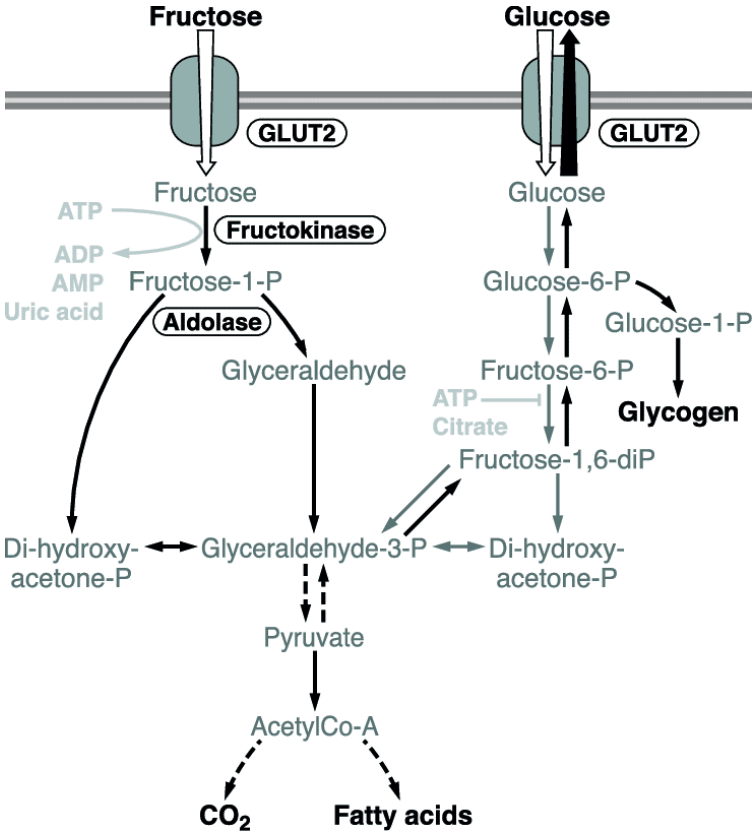

Figure 3 **Metabolism of fructose and glucose in the liver.**

Adapted from Rippe, J. M., & Angelopoulos, T. J. (2013). Sucrose, high-fructose corn syrup, and fructose, their metabolism and potential health effects: what do we really know?. Advances in nutrition (Bethesda, Md.), 4(2), 236–245.

4. Is fructose a concern ?

Fructose is a monosaccharide that has been part of the human diet for many years. Recently, it has received a lot of attention and has been claimed to be of public health concern.

First, in the 1980s, HFCS has primarily replaced sucrose in SSBs. Over the past 40 years, the intake of HFCS especially from SSB has risen across the globe. Indeed, in the US, the per capita consumption of SSBs between the late 1970s and 2006 have increased by two fold from 64.4 kcal/d to 141.7 kcal/d (Popkin, 2010). Similar patterns have been shown in many developing countries such as China and India where the volume of carbonated drinks sold increased by 14 and 18% respectively (Bray, 2007). Time trend data have shown an obesity epidemic in parallel with rising levels of HFCS consumption (Hu and Malik, 2010) (Rippe, 2010). Data to support this temporal association were illustrated in a graphic form (Figure 4). However, over the last 10 years SSB consumption has decreased whereas obesity rates are still increasing, thus questioning this association (Van et al., 2014).

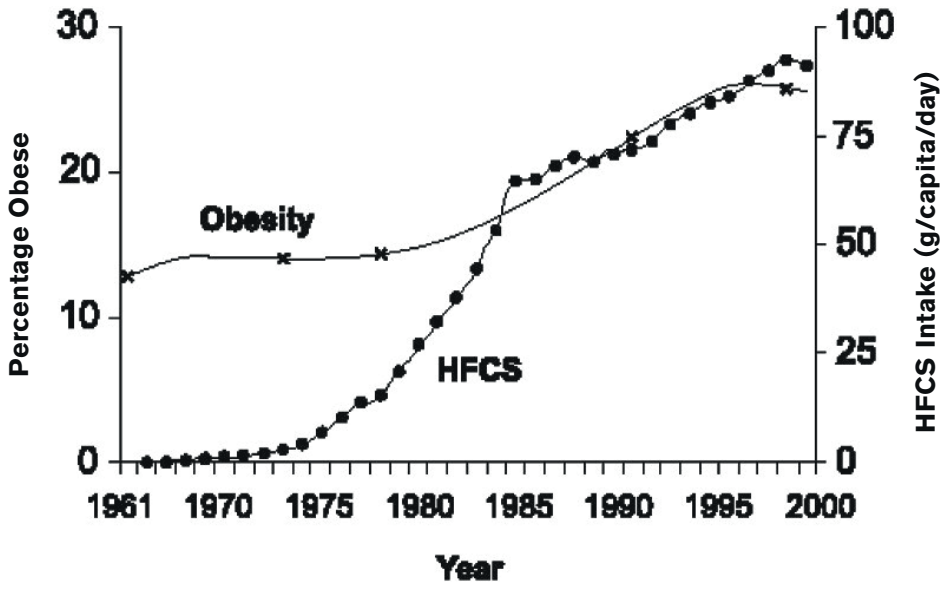

Figure 4 **Temporal association between increased consumption of high-fructose corn syrup (HFCS) and prevalence of obesity.**

Adapted from Rippe JM. (2010). The health implications of sucrose, high fructose corn syrup, and fructose: What do we really know? J Diabetes Technol. 4 Issue 4

Second, many researchers argued that the metabolism of dietary fructose has been shown to increase the likelihood of obesity, diabetes, CVD and MetS (Rippe, 2010) (Olsen and Heitmann, 2009) (Malik et al., 2010). Several studies have demonstrated that the ingestion of large quantities of fructose activates lipogenesis, induces insulin resistance and are associated with higher odds of HTN (Herman et al., 2016) (Hannou et al., 2018) (Jalal et al., 2010). Moreover, fructose metabolism stimulates uric acid production leading to hyperuricemia (Caliceti et al., 2017). This latter is suggested to be an independent risk factor for many pathological conditions such as chronic kidney disease, MetS and CVD (Borghi, 2015). However, in many studies the association between sugar intake and cardiometabolic risk factors lost significance when the analysis was adjusted for body weight (Forshee et al., 2008) (De Koning et al., 2011). This suggests that obesity may be responsible for the development of these cardiometabolic factors rather than sugar intake. Furthermore, the metabolic effects of fructose found in normal human diets contradict the effects observed in human and animal trials, where they have used unrealistically high amounts of pure fructose (Van et al., 2014). Therefore, more research is needed to better understand the metabolic effects of fructose.

C. Fructose and metabolic syndrome

1. Previous studies investigating fructose and metabolic syndrome

(see table 2 in the following page).

CHAPTER II

LITERATURE REVIEW

A. The Metabolic Syndrome

1. Historical perspectives and concept evolution [1]

The MetS concept saw the light in 1920, when a Swedish physician, Kylin, described the coexistence of the various components of the syndrome resulting in a triad of metabolic disorders 'hypertension–hyperglycaemia–hyperuricaemia" (Sarafidis and Nilsson, 2006). Later, in 1947, Vague described the association between android obesity and the development of the metabolic abnormalities found in cardiovascular disease (CVD) and Type 2 diabetes mellitus (T2DM) (Sarafidis and Nilsson, 2006). Following this, in the mid-1960s, the MetS became an important concept in the scientific research field. Several scientists worldwide published their observations on this condition at that time giving it various names. After several years of research, in 1988, Reaven introduced the concept of insulin resistance as the main contributor for this group of disorder, consisting of lipid abnormalities, HTN, and impaired glucose tolerance. Reaven named the sum of these disorders as "Syndrome X." A year later, Kaplan added a significant abnormality to the disorders described by Reaven, which is central obesity. He renamed this cluster "the deadly quarter" consisting of central obesity, lipid abnormalities, HTN and impaired glucose tolerance (Kaur, 2014). However, in 1992, several scientists renamed the syndrome "The Insulin Resistance Syndrome," believing that insulin resistance is the main contributor for the remaining disorders (Kaur, 2014). Finally, the name "Metabolic syndrome" has gained international acceptance in the past two decades. Ever since, the diagnostic criteria for the Mets remained a subject of interest for many researchers (see figure 1).

[1]. see Appendix I for the overall Literature review mind map diagram

2. Mechanisms linking fructose to metabolic syndrome

Effects of fructose on lipid metabolism

The earliest metabolic perturbation associated with a single load of fructose is postprandial hypertriglyceridemia (Stanhope & Havel, 2008). According to a meta-analysis and systematic review of 14 controlled feeding trials, the rise in postprandial TG occurs only in hypercaloric trials, where fructose intake provides additional calories and is at high doses around 175 g/day. However, fructose in iso-caloric exchange with other CHO was not found to lead to hypertriglyceridemia (Wang et al., 2014). Similar results were reported in another meta-analysis, where adverse effects on lipids were only shown when fructose intake increased energy intake by 21 to 35% (Chiavaroli et al., 2015). Hypertriglyceridemia can be the result of increased DNL, enhanced very low density lipoprotein (VLDL) synthesis, reduced clearance of TG and decreased VLDL catabolism.

Hepatic DNL induced by high intake of fructose leads to a significant increase in plasma TG. Unregulated hepatic metabolism of fructose leads to accumulation of pyruvate and acetyl CoA resulting in an increased conversion of acetyl CoA into fatty acids (Softic et al., 2016) (Rosset et al., 2016). Furthermore, fructose upregulates the lipogenic transcriptional factor Sterol Receptor Element–Binding Protein-1c (SREBP-1c) independently of insulin and carbohydrate responsive element binding protein (ChREBP), stimulating the conversion of acetyl CoA into TG (Carvalho et al., 2018) (Rosset et al., 2016). Thus, fructose contributes to DNL both by providing metabolites for FA synthesis and by increasing the transcriptional regulation of DNL (Figure 5). DNL, in turn, enhances VLDL production which results in the atherogenic lipid triad: low HDL (High clearance by the kidney), elevated TG and increased small dense LDL levels (Malik et al., 2010). Another route by which fructose promotes hypertriglyceridemia is by decreasing VLDL catabolism. The activity of lipoprotein lipase (LPL) that is responsible for VLDL hydrolyzes is

upregulated by insulin. Reduced activation of this enzyme secondary to low insulin activation after fructose intake, results in a decreased plasma TG clearance (Chong et al., 2007) (Hannou et al., 2018). The consequences of fructose metabolism are illustrated in figure 3.

Effects of fructose on glucose homeostasis

It has been known for several years that fructose has a lower glycemic index than glucose. Therefore, it will increase blood glucose and insulin levels less than isocaloric amounts of glucose (Teff, Elliott, Tschöp, et al., 2004). This lower glycemic and insulin responses have a positive effect on glucose homeostasis and glycemic control (Sievenpiper et al., 2014). However, it is also reported that high fructose administration may affect glucose homeostasis negatively by decreasing insulin sensitivity (Hannou et al., 2018). According to a systematic review and meta-analysis of diet-intervention trials, fructose consumption, in energy matched exchange for other CHO or in hypercaloric trials, induces hepatic insulin resistance in non-diabetic adults (Horst et al., 2016). These results indicate that insulin resistance caused by the consumption of extra calories from fructose is not attributed only to excess energy intake (weight gain). Similar results have been reported by a cross-sectional study conducted on a sample of 12000 Spanish adults. This study highlighted that the large added amounts of fructose mediate the positive association between habitual SSB consumption and insulin resistance since no association was found between artificially sweetened beverages and insulin levels (Lana et al., 2014). The mechanisms by which fructose induces insulin resistance remain uncertain.

Hepatic lipid accumulation induced by fructose is suggested to be the primary underlying mechanism of insulin resistance development. In the context of steatosis, in addition to TG, hepatic diacylglycerol (DAG) accumulate in hepatocytes. The build-up of DAG is strongly correlated with the development of hepatic insulin resistance via activation of hepatic protein kinase Cε, which inhibit hepatocellular insulin signaling (Petersen & Shulman, 2017) (Ter Horst et al., 2017).

Moreover, as shown in figure 5, fructose metabolism stimulates uric acid production leading to hyperuricemia (Caliceti et al., 2017). This latter induces mitochondrial oxidative stress which in turn is linked with insulin resistance (Hoehn et al., 2009). In addition, hyperuricemia will decrease endothelial nitric oxide (NO) release, which will decrease the contact between glucose and GLUT4, increasing insulin resistance (Duplain et al., 2001).

Effects of fructose on visceral adiposity and appetite

Many RCTs, cross-sectional and prospective studies have shown that excessive fructose intake, especially from SSB, increases visceral adipose tissues (Ma et al., 2016) (Ma et al., 2014) (Odegaard et al., 2012) (Maersk et al., 2012). A recent prospective observational study conducted on 1000 participants of the Third Generation cohort of the Framingham Heart Study, showed that daily SSB intake is associated with adverse changes in visceral adiposity. SSB daily consumers over six years had a 27 % greater increase in visceral adipose tissue compared to non-consumers (Ma et al., 2016). Similarly, a cross-sectional study conducted among 2500 participants of the Framingham Heart Study showed that daily SSB consumers have greater VF and greater visceral adipose tissue: subcutaneous adipose tissue (VAT: SAT) ratio after adjustment for age, sex, energy intake, alcohol intake, physical activity level, educational level, and current smoking status compared to non-consumers (Ma et al., 2014).

Various potential mechanisms may explain this positive association between fructose intake and visceral adiposity. As already discussed, fructose consumption promotes postprandial hypertriglyceridemia. LPL, regulated by insulin, is responsible for fat accumulation in VAT. In normal circumstances, LPL in VAT is less sensitive to insulin than LPL in SAT (Mead et al., 2002). However, in the case of insulin resistance, induced by high fructose consumption, LPL activity in SAT is reduced; therefore TG deposition in VAT will be more significant (Mead et al., 2002).

Another possible mechanism is that fructose may increase activation of intracellular glucocorticoids, which increases the activity of LPL (Senesi et al., 2010). The concentration of glucocorticoids receptors in VAT is higher than SAT; thus TG will be stored in VAT in cases of excess fructose intake.

Furthermore, it has been proposed that fructose may increase weight gain by altering appetite and satiety, resulting in overeating behavior. Unlike glucose, high fructose intake is not effective in stimulating insulin secretion, a hormone that increases satiety (Labouebe et al., 2013). The satiety hormone leptin is also reduced after fructose intake (Figlewicz and Benoit, 2009). Another mechanism that increases food intake is ATP depletion, which occurs after the administration of fructose (Cha et al., 2008).

Effects of Fructose on Blood Pressure

Epidemiological evidence suggests that there is a link between fructose consumption and hypertension. A cross-sectional study conducted on NHANES population reported that a high intake of fructose from added sugar ≥74 g/day is significantly associated with higher risk of HTN after adjusting for demographics, comorbidities, PA, total kilocalorie intake and dietary confounders (Jalal et al., 2010). Other studies have not shown this association, and this could be explained by the difference in the pattern of dietary intake, where the majority of fructose consumed in the NHANES population comes from added sugars rather than from fruits (Jalal et al., 2010). Fructose may contribute to the rise in BP via several mechanisms, including increased intestinal salt absorption, endothelial dysfunction and chronic activation of the sympathetic nervous system (SNS).

High fructose feeding in rats has been shown to stimulate sodium and chloride absorption, resulting in HTN (Cabral et al., 2014) (Soleimani, 2011) (Soleimani and Alborzi, 2011). A high fructose diet upregulates the sodium transporter, sodium-hydrogen exchanger 3 (NHE3), and the chloride transporter,

putative anion transporter 1 (PAT1) which in turn increases sodium absorption and chloride absorption respectively (Soleimani, 2011) (Soleimani and Alborzi, 2011). Indeed, in both GLUT 5 and PAT 1 knockout mice this associated HTN was prevented (Barone et al., 2009). Hyperuricemia induced by fructose metabolism is believed to increase mitochondrial oxidative stress and to reduce endothelial NO release, resulting in endothelial dysfunction (Jia et al., 2014). Moreover, it has been suggested that uric acid induces inflammatory reactions. Thus, the high serum level of uric acid increases the expression of inflammatory biomarkers such as C-reactive protein in endothelial cells, which in turn inhibits NO generation (Figure 5) (Spiga et al., 2017). High intake of fructose induces insulin resistance resulting in hyperinsulinemia, which in turn lead to chronic activation of the SNS. This latter, stimulate norepinephrine release that is believed to induce vasocontraction and to impair endothelial function (Klein & Kiat, 2015).

(see figure 5 in the following page)

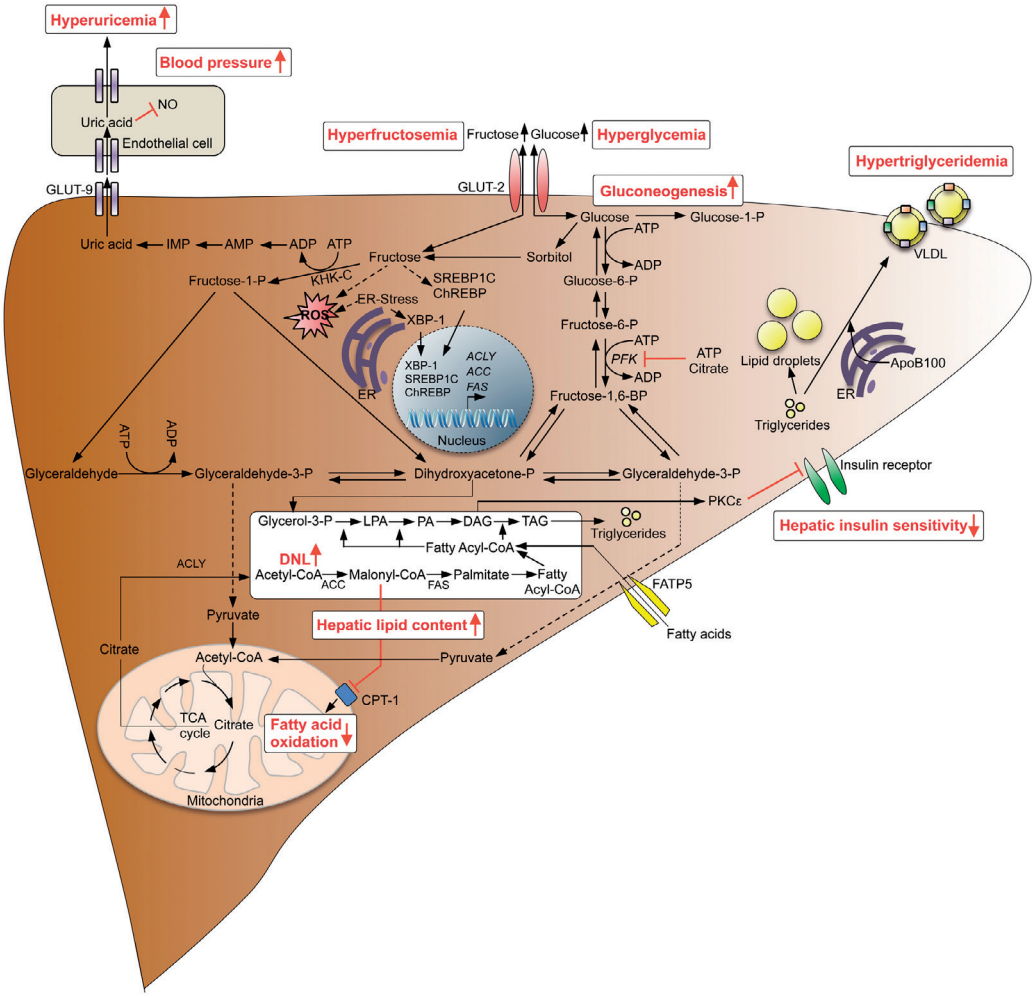

***Figure 5* Consequences of hepatic fructose metabolism**

Adapted from Mirtschink P., Jang C., Arany Z., Krek W., (2018). Fructose metabolism, cardiometabolic risk, and the epidemic of coronary artery disease, European Heart Journal, Volume 39, Issue 26, Pages 2497–2505. ACC, acetyl-coa carboxylase; ACLY, ATP citrate lyase; CPT1, carnitine-palmitoyltransferase 1; ChREBP, carbohydrate-responsive element-binding protein; DAG, diacylglycerole; FAS, fatty acid synthase; FATP5, fatty acid transport protein 5; GLUT2, glucose transporter 2; GLUT9, glucose transporter 9; LPA, lysophosphatidic acid; NO, nitric oxide; PFK, phosphofructokinase; PA, phosphatidic acid; PKCε, protein kinase C epsilon type; SREBP1, sterol regulatory element binding transcription factor 1; TAG, triacylglycerole; XBP-1, X-box binding protein 1.

CHAPTER III

MATERIAL AND METHODS

Data for the current study were obtained from the cross sectional survey "Assessment of Bisphenol A (BPA) levels and their association with the health status among the Lebanese population" that was conducted between March and May 2014 on a representative sample of Lebanese adults residing in the Greater area of Beirut. The survey protocol was approved by the Institutional Review Board of the American University of Beirut. All participants included in the study signed an informed consent form and had the right to withdraw at any time (Appendix II and III).

A. Participants

Participants were selected using a multistage probability sampling of adults in the Greater Beirut area, where the strata were the districts of the area. Within each district, a sample of neighborhoods, then households was chosen randomly based on a systematic random sampling approach. At the household level, the interviewer chose the one with the most recent month of birth to participate, if eligible. Participants on dialysis, mentally disabled or pregnant were excluded. Furthermore, subjects working in plastic or other chemical company were excluded since they have been exposed to BPA. For the current analysis, the selection of participants from the original population (n 501) was undertaken according to the following criteria:

1. Healthy, with no history of chronic disease
2. Having complete anthropometric, biochemical and dietary data
3. No under or over reporting of energy intake (EI)

In total, 283 participants, aged ≥ 18 years, were included in this study.

B. Data collection

Participants who agreed to participate in the study were requested to visit the American University of Beirut (AUB) for data collection, after an overnight fast. Data collection took place at the Department of Nutrition and Food Sciences (NFSC) in the Faculty of Agricultural and Food Sciences at AUB. Data collection forms were filled by trained personnel to minimize errors (Appendix IV and V).

1. Socio-demographic and lifestyle characteristics

The sociodemographic and lifestyle characteristics of the participants, including age (in years), gender, marital status (married, engaged and single, including divorcees and widowers), educational level, monthly household income (expressed in terms of U.S. dollars), smoking status (current smokers of cigarette or hookah vs past and non-smokers), crowding index, physical activity level, were collected by trained interviewers using a pretested questionnaire. Educational level was categorized into no schooling or primary school, intermediate school, secondary school or technical diploma and university degree. Monthly household income was divided into < 600$, 600$ ≤ income ≤ 2000$, > 2000$. Physical activity was categorized into 3 categories: low, moderate and high. Data about family and personal medical history of diseases were also obtained.

2. Anthropometric, BP and biochemical measurements

Weight was measured to the nearest 0.1 Kg using a calibrated electronic weighing scale (Inbody 3.0, Biospace Co. Ltd, Korea), while the subjects were wearing light clothes without shoes. Height was measured using a portable stadiometer (Seca 213, Germany) and recorded to the nearest 0.5 cm. The candidates were in a standing position, flat against the measuring board without shoes. BMI was calculated as weight (Kg) divided by square of the height (meters). WC was measured to the nearest 0.5 cm, at the umbilical level, using an unstretched tape meter (Seca

201, Germany). The tape was placed around the abdomen without exerting any pressure on the skin. Body fat was assessed using the Bioelectrical Impedance Analysis technique (Inbody 3.0, Biospace Co. Ltd, Alpha-Tec s.a.r.l.).

Levels of serum TG, HDL-C, LDL-C, and glucose were measured using an enzymatic spectrophotometric technique using Vitros 350 analyzer (Ortho-Clinical Diagnostics, Johnson and Johnson, 50–100 Holmers Farm Way, High Wycombe, Buckinghamshire, HP12 4DP, United Kingdom) at the NFSC department. As for hemoglobin A1c (HbA1c) analysis, it was measured using the BioRad Variant Hemoglobin Analyzer at AUBMC. Sitting BP was measured after a ten-minute rest using a standard digital sphygmanometer. All measurements were taken twice and the average of the two values was used.

3. Dietary intake assessment

Dietary data were collected using a semi-quantitative, culture specific food frequency questionnaire (FFQ) with 82-food items (Appendix IV and V). The participants completed the FFQ during one-on-one interview. The FFQ referred to participant's dietary intake during the past year. Participants were asked to record their intakes in terms of a reference portion size (expressed in household measures such as cups, spoons and plates) and/or customary packing size. The standard two-dimensional food portion visual chart, developed by Nutrition Consulting Enterprises, was used to assist in quantifying the reference portion size (Posner et al., 1992). Total energy and macronutrients intakes were computed using the Nutritionist Pro software, version 1.2.

Outliers, which refers to extreme values of EI that lie far from the majority of the other data points are excluded. Indeed, most of the literatures include only participants with plausible EI (between 500 and 5000 Kcals per day) and exclude individuals reporting an abnormally high or low EI (High >5,000 kcal for men, >4,000 kcal for women or low <800 kcal for men, <600 kcal for women) (Derghan

et al., 2017; Bell et al., 2014). In this study, the outliers were identified based on the Interquartile Range (IQR) method and hence individuals reporting >6,000 kcals were excluded.

C. Metabolic syndrome definition

MetS was defined based on the harmonized definition of the IDF. It was characterized as having at least 3 out of 5 of the metabolic abnormalities: 1) Abdominal obesity: WC ≥ 94 cm for men and WC ≥ 80 cm for women (Eastern Mediterranean and Middle Eastern populations are recommended to use European data), 2) elevated BP: ≥ 130 mmHg systolic or ≥ 85 mmHg diastolic, 3) elevated fasting blood sugar ≥ 100 mg/dl (5.6 mmol/L), 4) elevated TG ≥ 150 mg/dl (>1.69 mmol/L), 5) Low serum HDL: < 40 mg/dl (<1.04 mmol/L) for men and < 50 mg/dl (<1.29 mmol/L) for women (Alberti et al., 2009).

D. Estimation of added and natural fructose dietary intake

Fructose content data was available for 36 food items based on NutriPro software (i.e. total fructose). There was no data on added and natural fructose. Hence, for whole fruits and vegetables, natural fructose was assumed to be equal to total fructose (Hosseini-Esfahani et al, 2011) (Table 3). Acknowledging that the most common added sugar in commodities is sucrose, we have calculated the content of added fructose as 50% of added sugars (i.e. sucrose) in food items (Hosseini-Esfahani et al, 2011) (Sun et al, 2011).Table 4 shows the content of total and added fructose per food item.

Added fructose intake was calculated and was later categorized into first, second, third and fourth quartiles corresponding to <15.10 g of added fructose / day (Q1), 15.10 – 28.405 g of added fructose /day (Q2), 28.41 – 51.48 g of added fructose /day (Q3) and >51.48 g of added fructose /day (Q4). Natural fructose in fruits and vegetables was also categorized into first, second, third and fourth quartiles

corresponding to <6.39 g of natural fructose / day (Q1), 6.39 - 10.39g of natural fructose / day (Q2), 10.39 - 16.64 g of natural fructose / day (Q3) and >16.64 g of natural fructose / day (Q4). The sum of fructose consumption was calculated by summing up natural fructose and added fructose intake (Hosseini-Esfahani et al, 2011) and was also categorized, into four quartiles: < 26.74 g of fructose / day (Q1), 26.75 – 41.99 g of fructose / day (Q2), 41.99 – 65.05 g of fructose / day (Q3) and > 64.05 g of fructose / day (Q4).

Table 3 **Natural fructose content of food items (per 100g)**

Food item	**Natural fructose (in 100g)**
Citrus orange/ grapefruit	2.0795
Peach, plum, prunes	3.07
Strawberries	3.90
Grapes	8.13
Banana/ Apples	5.375
Salad, green: lettuce, mint, cucumber, green pepper, rocket, purslane, etc.	1.133
Tomatoes, fresh	1.37
Corn / Green peas, fresh	0.05
Corn/ Green peas, canned	0.05
Potatoes, baked / boiled/ mashed	0.34
Zucchini/ Eggplants, cooked	1.21
Cauliflower/ Cabbage/ Broccoli	1.21
Other canned vegetables (Mushroom, palmetto, asparagus, etc.)	0
Legumes: lentils, beans, chickpeas, etc., dried, cooked	0.1
Legumes, canned (beans, fava, chickpeas)	0.1
Wine, red / white/ blush	0.778
Mustard	0.18

Table 4 **Total and added fructose content of food items (per 100g)**

Food item	**Total sugar (g / 100g) (Assumed= added sugar)**	**Added fructose (g/ 100g) (assuming 50% of added sugar is fructose)**
Bread, brown	0.82	0.41
Traditional breads(markouk/tannour)	1.77	0.88
Breakfast cereals, regular/ sugar coated/ chocolate/ bran	10.50	5.25
Kaak	1.26	0.63
Fruits canned	17.14	8.57
Fruit juice canned	12.42	6.21
Fruit juice bottled	12.42	6.21
Cakes / Cookies/ Doughnuts / Muffins/ Croissant / Biscuits	24.85	12.42
Ice cream	19.16	9.58
Chocolate bar	57.82	28.91
Sugar, honey, jam, molasses, chocolate spread	99.80	49.9
Arabic sweets (Baklava, maamoul, knefe)	1.185	0.59
Soft drink, regular	11.55	5.77
Cocoa / Hot chocolate	70.38	35.19
Manaeesh, zaatar/ cheese	0.09	0.045
Energy & sports drinks	10.06	5.03
Pizza	1.98	0.99
Canned/ Pre-packed soups	1.54	0.77
Ketchup	22.77	11.38

E. Statistical analysis

Statistical analysis was performed using he Statistical Analysis Package for Social Sciences, version 24.0 (SPSS Inc., Chicago, IL, USA). Sociodemographic characteristics, anthropometric and biochemical measurements and dietary intake of the total study population and across MetS status were described using frequencies for categorical variables, means and standard deviations for continuous variables. The significant differences between the groups, was obtained using Independent t-test and Chi-square test for continuous variables and categorical variables respectively. In all the analyses, a p value less than 0.05 was considered statistically significant.

To investigate the association between total/added dietary fructose and each of the metabolic abnormalities, as categorical variables, binary logistic regression analysis was conducted with the MetS and its 5 components being the dependent variable with only two outcomes (yes/no, high/low, normal/abnormal) and fructose intake the independent variables. Associations were examined based on crude (unadjusted) models. Based on the results of crude association, multivariable models were performed while adjusting for variables that were shown to be significantly associated with MetS in crude models. Moreover, more variables were added based on the literature (Hosseini-Esfahani et al, 2011). To put more power and to fine tune the model, stepwise regression analysis was conducted. Thus, the nonsignificant variables were eliminated automatically. The OR of MetS and its components in each quartile of total fructose intake and added fructose intake were determined using logistic regression analysis.

CHAPTER III

RESULTS

A. Subject characteristics and dietary intakes/ Assessment of fructose intake

1. Socio-Demographic characteristics

Of the 283 eligible individuals, 102 were diagnosed with MetS. Thus, the prevalence of MetS in the current study was estimated at 36% according to the IDF definition (Alberti et al., 2009). General characteristics of the study population according to MetS status are presented in Table 5. Overall, the mean age of the participants was 41 ± 13.71 years, with a higher proportion of females than males (67.5 % vs 32.5 %). Only 9.1 % of the overall participants had a monthly income level higher than 2000$. Among lifestyle factors, most of the subjects were current smokers of either cigarettes or narghile (68.9%) and almost half of the subjects had low physical activity level (46.3%). Participants with MetS were significantly older as compared with participants without MetS (44.85 ± 14.64 vs. 38.84 ± 12.70 years), with a higher proportion being males (45.1% vs 25.4%). Also, a higher proportion of participants with higher education levels (university) was observed among participants without MetS compared with those with MetS (18.9 % vs. 4.9 %) (see table 5 in the following page).

***Table 5* Socio-demographic and lifestyle characteristics of the study sample[a]**

	Total [b] (n=283)	**MetS (n= 102)**	**No MetS (n= 181)**	**P-value [c]**
Age (years) (Mean ± SD)	41 ± 13.7	44.8 ± 14.6	38.8 ± 12.7	**< 0.001**
Gender				
Male	92 (32.5)	46 (45.1)	46 (25.4)	**0.001**
Female	191 (67.5)	56 (54.9)	135 (74.6)	
Marital Status				
Single [d]	90 (31.8)	36 (35.3)	54 (29.8)	0.344
Married	193 (68.2)	66 (64.7)	127 (70.2)	
Income Per Month				
< 600$	75 (28.4)	33 (33)	42 (25.6)	0.345
600$ ≤ income ≤ 2000$	165 (62.5)	60 (60)	105 (64)	
> 2000$	24 (9.1)	7 (7)	17 (10.4)	
Education				
No schooling or primary	89 (31.6)	38 (37.3)	51 (28.3)	**0.01**
Intermediate	77 (27.3)	31 (30.4)	46 (25.6)	
Secondary or technical diploma	77 (27.3)	28 (27.5)	49 (27.2)	
University degree	39 (13.8)	5 (4.9)	34 (18.9)	
Smoking status [e]				
Current smokers	195 (68.9)	70 (68.6)	125 (69.1)	0.641
Past smokers	25 (8.8)	11 (10.8)	14 (7.7)	
Never smoked	63 (22.3)	21 (20.6)	42 (23.2)	
Crowding Index				
≤ 1 person/room	109 (38.5)	45 (44.1)	64 (35.4)	0.146
> 1 person/room	174 (61.5)	57 (55.9)	117 (64.6)	
Engagement in Physical Activity				
None	42 (14.8)	20 (19.6)	22 (12.2)	0.09
Any	241 (85.2)	82 (80.4)	159 (87.8)	
Levels of physical activity				
Low-intensity activity	131 (46.3)	51 (50)	80 (44.2)	0.199
Moderate-intensity activity	88 (31.1)	34 (33.3)	54 (29.8)	
High-intensity activity	64 (22.6)	17 (16.7)	47 (26)	

[a] Data are reported as N(%): frequency and percentage within column for categorical variables or as Mean ± SD for continuous variables. SD: Standard deviation.

[b] Lack of corresponding sum of frequencies with total sample size is due to missing data.

[c] Significance was derived from chi-square for categorical variables and from independent t test for continuous variables.

[d] Single includes divorced, widowed and engaged.

[e] Current smokers of either cigarette or narghile, Past smokers of either cigarette or narghile.

2. Anthropometric Characteristics, Biochemical and Blood Pressure Data

Table 6 presents the anthropometric and biochemical measurements along with the blood pressure data of the study sample (n=283) according to their MetS status. The comparison of participants with and without MetS showed that those with MetS had significantly higher BMI (31.04 ± 5.40 vs. 26.37 ± 5.02 kg/m2) , BW (83.53 ± 15.76 vs. 68.49 ± 13.55 Kgs), WC (100.65 ± 11.39 vs. 87.10 ± 12.02 cm) and body fat (32.45 ± 11.14 vs. 24.16 ± 10.08 Kgs). Moreover, participants with MetS had significantly higher fasting BG (105.70 ± 17.71 vs. 93.99 ± 7.21 mg/dl), TG (164.39 ± 79.96 vs. 96.07 ± 50.91 mg/dl) , LDL (116.23 ± 38.25 vs. 101.78 ± 31.45 mg/dl) and TC levels (192.72 ± 43.165 vs. 178.06 ± 36.53 mg/dl) compared to participants without MetS. Higher systolic BP (124.51 ± 18.42 vs. 111.71 ± 13.17 mmHg) and diastolic BP (77.41 ± 10.33 vs. 70.35 ± 8.16 mmHg) level was also noted among participants with MetS than among those without.

(see table 6 in the following page)

Table 6 **Anthropometric characteristics, biochemical and blood pressure data of the study sample[a]**

	Total (n= 283)	**MetS (n=102)**	**No MetS (n=181)**	**P-value [b]**
Anthropometric characteristic				
BMI (Kg/ m^2) (Mean ± SD) [c]	28.05 ± 5.62	31.04 ± 5.40	26.37 ± 5.02	**< 0.001**
Body weight (Kg) (Mean ± SD)	73.91 ± 16.08	83.53 ± 15.76	68.49 ± 13.55	**< 0.001**
Waist Circumference (cm) (Mean ± SD)	91.99 ± 13.46	100.65 ± 11.39	87.10 ± 12.02	**< 0.001**
Body Fat (Kg) (Mean ± SD)	27.15 ± 11.18	32.45 ± 11.14	24.16 ± 10.08	**< 0.001**
Biochemical and BP data [d]				
Serum glucose levels (mg/dl) (Mean ± SD)	98.21 ± 13.31	105.70 ± 17.71	93.99 ± 7.21	**< 0.001**
HbA1c (%) (Mean ± SD)	5.47 ± 0.49	5.69 ± 0.60	5.35 ± 0.38	**< 0.001**
Insulin (mU/mL) (Mean ± SD)	26.33 ± 15.57	31.37 ± 22.12	23.40 ± 8.83	**< 0.001**
TC (mg/dl) (Mean ± SD)	183.34 ± 39.61	192.72 ± 43.165	178.06 ± 36.53	**0.003**
LDL (mg/dl) (Mean ± SD)	106.99 ± 34.69	116.23 ± 38.25	101.78 ± 31.45	**0.001**
HDL (mg/dl) (Mean ± SD)	51.89 ± 15.89	42.87 ± 10.87	56.98 ± 16.04	**< 0.001**
TG (mg/dL) (Mean ± SD)	120.70 ± 70.88	164.39 ± 79.96	96.07 ± 50.91	**< 0.001**
SBP (mmHg) (Mean ± SD)	116.68 ± 16.62	124.51 ± 18.42	111.71 ± 13.17	**< 0.001**
DBP (mmHg) (Mean ± SD)	72.89 ± 9.60	77.41 ± 10.33	70.35 ± 8.16	**< 0.001**

[a] Data are reported as Mean ± SD. SD: Standard deviation

[b] Significance was derived from independent t test

[c] BMI: Body Mass Index

[d] TC: Total Cholesterol; HDL-C: High Density Lipoprotein-Cholesterol; LDL-C: Low Density Lipoprotein-Cholesterol; TG: Triglycerides; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; HbA1c: glycated hemoglobin.

3. Dietary Energy and Macronutrient Intakes

Dietary intake of the study sample according to their MetS status are presented in Table 7. Mean intake of total dietary fructose was 51.42 ± 35.54 g/day which represents 6.58 ± 3.71 % of the total EI. Natural and added fructose intakes were estimated at 12.29 ± 8.57 g/day and 39.12 ± 34.10 g/day (1.78 ± 1.41% and 4.80 ± 3.56% EI), respectively. No significant difference in dietary intakes was observed comparing participants with MetS with those without.

(see table 7 in the following page)

Table 7 **Dietary energy and macronutrient intakes of the study sample [a]**

	Total (n= 283)	**MetS (n=102)**	**No MetS (n=181)**	**P-value [b]**
	Mean ± SD			
Energy (Kcal/day)	3134 ± 1301	3232 ± 1337	3080 ± 1281	0.34
Carbohydrates (g/day)	388.22 ± 158.16	407.40 ± 170.21	377.41 ± 150.37	0.12
Carbohydrate (% of energy)	50.37 ± 8.30	50.98 ± 8.40	50.03 ± 8.25	0.36
Protein (g/day)	102.83 ± 60.65	101.95 ± 50.44	103.33 ± 65.83	0.85
Protein (% of energy)	13.02 ± 3.64	12.67 ± 3.22	13.22 ± 3.86	0.22
Fat (g/day)	131.81 ± 64.97	134.82 ± 67.28	130.12 ± 63.77	0.56
Fat (% of energy)	39.10 ± 7.86	38.56 ± 8.11	39.41 ± 7.72	0.38
Dietary Fibers (g/day)	28.16 ± 11.78	28.70 ± 13.49	27.85 ± 10.72	0.56
Total sugar intake (g/day)	104.99 ± 58.45	111.18 ± 61.84	101.49 ± 56.32	0.18
Added fructose (g/day) [c]	39.12 ± 34.10	41.85 ± 33.70	37.59 ± 34.31	0.31
Added fructose (%Kcal/day)	4.80 ± 3.56	4.81 ± 2.97	4.79 ± 3.86	0.96
Natural fructose (g/day) [d]	12.29 ± 8.57	11.84 ± 7.88	12.55 ± 8.95	0.51
Natural fructose (%Kcal/day)	1.78 ± 1.41	1.61 ± 1.15	1.87 ± 1.53	0.12
Total fructose (g/day) (Added + Natural)	51.42 ± 35.54	53.69 ± 35.03	50.14 ± 35.85	0.42
Total fructose (%Kcal/day)	6.58 ± 3.71	6.42 ± 2.96	6.67 ± 4.07	0.59

[a] Data are reported as Mean ± SD. SD: Standard deviation

[b] Significance was derived from independent t test

[c] Added fructose from industrialized foods and beverages containing beet or cane sugar/ molasses, corn sweeteners and invert syrup

[d] Natural fructose in fructose-containing food such as fruits, vegetables, honey.

B. Association of fructose intake with metabolic syndrome

To determine the association between fructose intake with MetS and its components, first we performed binary logistic regression. Three models were presented with the crude model being the one without adjustments. Model 1 included the sociodemographic variables age and sex. Model 2 included the variables of model 1, in addition to BMI, CHO (g/day), fibers (g/day), energy intake (kcal/day), smoking (ex, current, never), education and PA (yes, no) (Hosseini-Esfahani et al, 2011). According to our results, fructose intake > 64.05 g/d (Quartile 4 (Q4)) was associated with higher odds of MetS after adjusting for confounders (Model 2). Indeed, binary logistic regression results in Table 8 showed that the risk of MetS increased by 2.84 fold for participants in the highest quartile of total fructose intake (Q4) [OR 2.84 (95% CI 1.017-7.940)]. Similarly, the risk of MetS was increased by 3.18 fold for added fructose intake at Q4 [OR 3.18 (95% CI 1.068-9.493)] after adjusting for confounders (Model 2) as shown in Table 9. However, no significant association was observed between Natural fructose with MetS even at the highest quartile and after adjustments for potential confounders [OR 1.047 (95% CI 0.414-2.645)] (Table 10). When examining each abnormality alone, no significant association was found, even after adjustment for confounders.

While adjusting for the 9 potential independent variables, a significant association was observed between fructose intake and MetS. However, to put more power and to fine tune the model by eliminating the nonsignificant variables, we used the stepwise regression analysis instead of the ordinary binary logistic regression. In this regression, the 9 potential independent variables were included in the model, and those who are not statistically significant were eliminated automatically, with no human intervention. After conducting the stepwise regression we were able to determine the variables which significantly influenced the MetS. These latter were BMI, age and sex. As shown in Tables 11 and 12 the risk of MetS increased by 2.450 fold for participants in the highest quartile of total fructose intake (Q4) ([OR 2.450 (95% CI 1.047- 5.734)]) and by 2.609 fold for participants in the highest quartile of added fructose intake (Q4) [OR 2.609 (95% CI 1.081- 6.298)].

Table 8 **Crude and adjusted ORs with 95%CI for MetS and each of its component according to total dietary fructose quartiles (g/day)**

	Dietary total fructose intake			
	Quartile 1 (n=70) <26.74	**Quartile 2** (n=71) 26.75 - 41.99	**Quartile 3** (n=72) 41.99 – 64.05	**Quartile 4** (n=70) >64.05
	OR (95% CI)			
Metabolic Syndrome				
Crude model [a]	1	0.66 (0.32 - 1.34)	0.79 (0.39 - 1.58)	1.50 (0.76 - 2.96)
Model 1 [b]	1	0.59 (0.27 - 1.25)	0.85 (0.40 - 1.79)	1.87 (0.86 - 4.02)
Model 2 [c]	1	1.02 (0.42 - 2.43)	1.09 (0.45 - 2.68)	**2.84 (1.01 - 7.94)**
Elevated triglycerides				
Crude model	1	0.79 (0.37 - 1.66)	0.72 (0.34 - 1.52)	1.06 (0.52 - 2.19)
Model 1	1	1.69 (0.31 - 1.49)	0.70 (0.32 - 1.52)	0.84 (0.37 - 1.87)
Model 2	1	1.06 (0.45 - 2.47)	0.81 (0.34 - 1.94)	1.02 (0.38 - 2.72)
Elevated waist circumference				
Crude model	1	0.88 (0.42 - 1.84)	0.62 (0.30 - 1.26)	0.76 (0.36 - 1.57)
Model 1	1	0.90 (0.42 - 1.92)	0.68 (0.33 - 1.43)	1.18 (0.53 - 2.60)
Model 2	1	1.84 (0.60 - 5.65)	0.54 (0.51 - 1.87)	0.92 (0.23 - 3.71)
Elevated fasting blood glucose				
Crude model	1	0.57 (0.27 - 1.18)	1.07 (0.54 - 2.12)	0.94 (0.54 - 2.12)
Model 1	1	0.51 (0.24 - 1.09)	1.19 (0.58 - 2.44)	1.09 (0.50 - 2.36)
Model 2	1	0.74 (0.33 - 1.68)	1.65 (0.74 - 3.70)	1.54 (0.60 - 3.96)
Elevated blood pressure				
Crude model	1	0.50 (0.22 - 1.14)	0.96 (0.46 - 1.99)	1.57 (0.77 - 3.18)
Model 1	1	0.39 (0.16 - 0.94)	1.01 (0.45 - 2.25)	1.47 (0.64 - 3.38)
Model 2	1	0.53 (0.20 - 1.39)	1.31 (0.53 - 3.26)	1.89 (0.67 - 5.34)
Reduced HDL				
Crude model	1	0.86 (0.43 - 1.72)	1.20 (0.61 - 2.372)	1.063 (0.537-2.104)
Model 1	1	0.87 (0.43 -1.75)	1.88 (0.60 - 2.34)	1.03 (0.50 - 2.13)
Model 2	1	1.06 (0.50 - 2.22)	1.22 (0.57 - 2.59)	1.02 (0.42 - 2.48)

[a] Crude model: No adjustments

[b] Model 1: Adjusted for age and sex

[c] Model 2: Adjusted for age, sex, BMI, CHO (g/day), fibers (g/day), energy intake (kcal/day), smoking (ex, current, never), education and PA (yes, no)

Table 9 **Crude and adjusted ORs with 95%CI for MetS and each of its component according to added dietary fructose quartiles (g/day)**

	Dietary added fructose intake			
	Quartile 1 (n=70) <15.10	**Quartile 2** (n=71) 15.10 – 28.40	**Quartile 3** (n=72) 28.41 – 51.48	**Quartile 4** (n=70) >51.48
	OR (95% CI)			
Metabolic Syndrome				
Crude model [a]	1	0.82 (0.41 - 1.66)	0.88 (0.44 - 1.76)	1.54 (0.78 - 3.04)
Model 1 [b]	1	0.80 (0.38 - 1.68)	1.00 (0.47 - 2.14)	2.10 (0.95 - 4.63)
Model 2 [c]	1	1.30 (0.55 - 3.04)	1.33 (0.53 - 3.34)	**3.18 (1.06 - 9.49)**
Elevated triglycerides				
Crude model	1	1.16 (0.54 - 2.47)	1.42 (0.67 -2.99)	1.27 (0.59 -2.69)
Model 1	1	1.10 (0.50 - 2.42)	1.36 (0.62 -2.99)	1.00 (0.62 -2.99)
Model 2	1	1.54 (0.66 - 3.62)	1.58 (0.65 -3.81)	1.19 (0.41 - 3.43)
Elevated waist circumference				
Crude model	1	0.65 (0.31 - 1.37)	0.54 (0.26 - 1.12)	0.60 (0.28 -1.25)
Model 1	1	0.65 (0.30 - 1.40)	0.66 (0.31 - 1.41)	0.99 (0.44 - 2.22)
Model 2	1	0.70 (0.23 - 2.15)	0.60 (0.17 - 2.03)	0.61 (0.14 - 2.59)
Elevated fasting blood glucose				
Crude model	1	0.73 (0.36 - 1.46)	0.68 (0.34 - 1.37)	1.02 (0.59 - 2.01)
Model 1	1	0.71 (0.34 - 1.46)	0.76 (0.36 - 1.60)	1.32 (0.60 - 2.89)
Model 2	1	0.91 (0.42 - 1.99)	1.05 (0.45 - 2.42)	1.95 (0.72 - 5.26)
Elevated blood pressure				
Crude model	1	1.00 (0.46 - 2.13)	0.92 (0.43 - 1.98)	1.74 (0.84 - 3.58)
Model 1	1	0.95 (0.42 - 2.14)	0.91 (0.39 - 2.12)	1.73 (0.73 - 4.09)
Model 2	1	1.35 (0.55 - 3.29)	1.15 (0.44 - 3.00)	2.04 (0.67 - 6.17)
Reduced HDL				
Crude model	1	0.93 (0.46 -1.88)	1.70 (0.86 - 3.34)	1.23 (0.61 - 2.44)
Model 1	1	0.94 (0.46 - 1.90)	1.68 (0.84 - 3.35)	1.22 (0.58 - 2.58)
Model 2	1	1.03 (0.49 - 2.16)	1.74 (0.81 - 3.76)	1.20 (0.47 - 3.05)

[a] Crude model: No adjustments

[b] Model 1: Adjusted for age and sex

[c] Model 2: Adjusted for age, sex, BMI, CHO (g/day), fibers (g/day), energy intake (kcal/day), smoking (ex, current, never), education and PA (yes, no)

Table 10 **Crude and adjusted ORs with 95%CI for MetS and each of its component according to natural dietary fructose quartiles (g/day)**

	Dietary natural fructose intake			
	Quartile 1 (n=70) <6.39	**Quartile 2** (n=71) 6.39 - 10.39	**Quartile 3** (n=72) 10.39 - 16.64	**Quartile 4** (n=70) >16.64
	OR (95% CI)			
Metabolic Syndrome				
Crude model [a]	1	0.90 (0.45-1.78)	1.03 (0.52-2.05)	0.88 (0.44-1.76)
Model 1 [b]	1	0.88 (0.42-1.81)	0.96 (0.47-1.97)	0.77 (0.37-1.61)
Model 2 [c]	1	0.86 (0.38-1.95)	1.16 (0.49-2.76)	1.04 (0.41-2.64)
Elevated triglycerides				
Crude model	1	0.72 (0.34-1.51)	0.74 (0.35-1.54)	0.87 (0.42-1.79)
Model 1	1	0.71 (0.33 -1.53)	0.70 (0.32-1.519)	0.88 (0.41-1.88)
Model 2	1	0.79 (0.35 -1.77)	0.96 (0.41 -2.24)	1.30 (0.52 -3.23)
Elevated waist circumference				
Crude model	1	0.97 (0.48 -1.96)	1.09 (0.53 - 2.21)	1.14 (0.55 -2.33)
Model 1	1	0.93 (0.45 -1.91)	0.98 (0.47 -2.05)	0.91 (0.43 -1.93)
Model 2	1	1.24 (0.41 -3.75)	2.42 (0.79 -7.37)	1.60 (0.48 -5.31)
Elevated fasting blood glucose				
Crude model	1	0.96 (0.47 - 1.95)	1.50 (0.75 -3.00)	1.13 (0.56 -2.30)
Model 1	1	0.94 (0.44 -1.96)	1.43 (0.69 -2.95)	1.00 (0.47 -2.10)
Model 2	1	0.93 (0.43 -2.02)	1.58 (0.71 -3.50)	1.04 (0.43 -2.49)
Elevated blood pressure				
Crude model	1	0.68 (0.32 -1.41)	0.91 (0.45 -1.86)	0.60 (0.28 -1.28)
Model 1	1	0.63 (0.28 -1.39)	0.84 (0.39 - 1.82)	0.53 (0.23 -1.21)
Model 2	1	0.61 (0.26 -1.43)	0.79 (0.33-1.91)	0.57 (0.21 -1.54)
Reduced HDL				
Crude model	1	0.75 (0.38 -1.48)	0.770 (0.392-1.515)	0.741 (0.375-1.463)
Model 1	1	0.75 (0.38 -1.48)	0.78 (0.39 - 1.54)	0.76 (0.38 -1.51)
Model 2	1	0.76 (0.37-1.51)	0.88 (0.42 -1.85)	0.96 (0.43-2.13)

[a] Crude model: No adjustments

[b] Model 1: Adjusted for age and sex

[c] Model 2: Adjusted for age, sex, BMI, CHO (g/day), fibers (g/day), energy intake (kcal/day), smoking (ex, current, never), education and PA (yes, no)

Table 11 **Adjusted ORs with 95%CI for MetS and each of its component according to total dietary fructose quartiles (g/day) using the stepwise regression**

	Dietary total fructose intake			
	Quartile 1 (n=70) <15.10	**Quartile 2** (n=71) 15.10 – 28.40	**Quartile 3** (n=72) 28.41 – 51.48	**Quartile 4** (n=70) >51.48
	OR (95% CI)			
Metabolic Syndrome				
Model 2 [a]	1	0.86 (0.37-1.99)	1.02 (0.45-2.30)	**2.45 (1.04- 5.73)**
Elevated triglycerides				
Model 2	1	1.02 (0.45-2.32)	0.83 (0.37-1.87)	0.91 (0.40-2.05)
Elevated waist circumference				
Model 2	1	1.81 (0.63-5.17)	0.62 (0.22-1.76)	0.82 (0.28-2.34)
Elevated fasting blood glucose				
Model 2	1	0. 62 (0.28-1.35)	1.32 (0.63-2.75)	1.18 (0.53-2.59)
Elevated blood pressure				
Model 2	1	0.52 (0.20-1.30)	1.20 (0.52-2.77)	1.74 (0.72-4.16)
Reduced HDL				
Model 2	1	1.02 (0.50-2.08)	1.32 (0.66-2.64)	1.18 (0.58-2.37)

[a] Model 2: Adjusted for age, sex, BMI, CHO (g/day), fibers (g/day), energy intake (kcal/day), smoking (ex, current, never), education and PA (yes, no)

Table 12 **Adjusted ORs with 95%CI for MetS and each of its component according to added dietary fructose quartiles (g/day) using the stepwise regression**

	Dietary added fructose intake			
	Quartile 1 (n=70) <15.10	**Quartile 2** (n=71) 15.10 – 28.40	**Quartile 3** (n=72) 28.41 – 51.48	**Quartile 4** (n=70) >51.48
	OR (95% CI)			
Metabolic Syndrome				
Model 2 [a]	1	1.16 (0.51 - 2.65)	1.33 (0.57 - 3.09)	**2.60 (1.08 - 6.29)**
Elevated triglycerides				
Model 2	1	1.40 (0.61 - 3.21)	1.60 (0.71 - 3.62)	0.99 (0.42 - 2.32)
Elevated waist circumference				
Model 2	1	0.71 (0.25 - 2.01)	0.56 (0.19 - 1.61)	0.48 (0.16 - 1.44)
Elevated fasting blood glucose				
Model 2	1	0. 81 (0.38 - 1.71)	0.83 (0.38 - 1.79)	1.37 (0.62 - 3.05)
Elevated blood pressure				
Model 2	1	1.31 (0.55 - 3.12)	1.13 (0.46 - 2.77)	1.98 (0.79 - 4.92)
Reduced HDL				
Model 2	1	1.05 (0.51 - 2.16)	1.92 (0.95 - 3.88)	1.34 (0.66 - 2.72)

[a] Model 2: Adjusted for age, sex, BMI, CHO (g/day), fibers (g/day), energy intake (kcal/day), smoking (ex, current, never), education and PA (yes, no)

CHAPTER V

DISCUSSION

Worldwide, MetS prevalence has continued to grow to the point of becoming a primary public health challenge and is considered to be a major risk factor for type 2 diabetes mellitus, cardiovascular disease and all-cause mortality (Zimmet et al., 2005). Whether dietary fructose intake is associated with increased risk of MetS remains in dispute and studies are yielding contrasting results (Hu and Malik, 2010; Stanhope and Havel, 2008; Stanhope and Havel, 2010) (Dolan et al., 2010; Jones, 2009; Tappy and Le, 2010; Tappy et al., 2010).

In our study the prevalence of MetS in a healthy sample of Lebanese adults was estimated at 36% according to the harmonized definition of the IDF (Alberti et al., 2009). When compared with estimates reported from previous studies conducted in Lebanon, the MetS prevalence in the current study slightly exceeded that reported by Naja et al. (2013) (34.7%) and Sibai et al. (2008) (31.2%). It is important to note that all of these studies included healthy subjects with no previous disease and used the IDF criteria. Moreover, the prevalence estimate for MetS in our study was also higher than those reported from neighboring countries such as Qatar (33.7%) (Bener et al., 2009) and from developed countries such as Spain (16.46%) (Tauler et al., 2014).

This study aimed at assessing dietary total and added fructose intake among Lebanese urban adults aged 18 years and over. Total dietary fructose intake was estimated at 51.42 ± 35.54 g/day, which exceeds the upper limit of fructose intake (50g/day) that is proposed to be one of the main etiologies of MetS (Johnson et al., 2009). Moreover, the results of the current study highlights a slightly higher consumption of dietary fructose in Lebanon when compared to other countries worldwide. Indeed, as shown in Table 13 dietary intake of fructose in US was

estimated at 48.07 ± 35.73 g/day (Sun et al, 2011) and in Tehran dietary fructose intake was estimated at 46.5 ± 24.5 and 37.3 ± 24.2 g/day, in men and women respectively (Hosseini-Esfahani et al, 2011). Furthermore, compared to the European countries, our fructose intake is higher. Indeed, the range of fructose intake in Germany was estimated at 8.4 – 40.6 and 11 –34.8, in men and women respectively (Schulze et al., 2008) and in Finland the range of dietary fructose intake was estimated at 6 – 28.8 (Montonen et al., 2007). Few studies have estimated added fructose intake. Table 13 shows that added fructose intake as estimated in this study (39.12 ± 34.10 g/day) exceeded the estimate reported from Iran (26.9 ± 13.9 and 19 ± 13.7 g/day, in men and women respectively) (Hosseini-Esfahani et al, 2011). The observed high intake of total and added fructose amongst Lebanese adults raises concerns given the suggested association of high fructose intake with metabolic abnormalities such as hyperuricemia, oxidative stress and insulin resistance (Caliceti et al., 2017) (Castro et al., 2015) (Hannou et al., 2018) all of which may be involved in the pathophysiology of the MetS (McCracken et al., 2018).

(see table 13 in the following page)

Table 13 **Fructose intake as g/day and as %Kcal/day in different populations**

	Total Fructose	Natural Fructose	Added Fructose	Design of the study	Dietary intake assessment (at baseline)	Reference
Lebanon	**g/day**[*] 51.42 ± 35.54 **Men:** 65.43 ± 41.03 **Women:** 44.67 ± 30.45 **% Kcal /day** 6.58 ± 3.71 **Men:** 6.61 ± 4.19 **Women:** 6.56 ± 3.46	**g/day** 12.29 ± 8.57 **Men:** 12.49 ± 9.60 **Women:** 12.20 ± 8.06 **% Kcal /day** 1.78 ± 1.41 **Men:** 1.39 ± 1.25 **Women:** 1.96 ± 1.45	**g/day** 39.12 ± 34.10 **Men:** 52.93 ± 40.13 **Women:** 32.47 ± 28.59 **% Kcal /day** 4.80 ± 3.56 **Men:** 5.22 ± 4.05 **Women:** 4.60 ± 3.28	Cross sectional study	Semiquantitative FFQ	The current study
US	**g/day** 48.07 ± 35.73 **% Kcal /day** 8.53 ± 4.82	_____	_____	Descriptive statistics NHANES 1999-2006 database	_____	Sun et al, 2011
Tehran	**g/day** Men: 46.5 ± 24.5 Women: 37.3 ± 24.2 **% Kcal /day** 8 in men 7 in women	**g/day** Men: 19.5 ± 10.7 Women: 18.6 ± 10.5	**g/day** Men: 26.9 ± 13.9 Women: 19 ± 13.7	Cross sectional study	Validated Semiquantitative FFQ	Hosseini-Esfahani et al, 2011
Germany	**g/day** [**] **Men:** 8.4 – 40.6 **Women:** 11 –34.8	_____	_____	Cohort study for 7 – 11 years	Validated Semiquantitative FFQ	Schulze et al., 2008
Finland	**g/day** [**] 6 – 28.8	_____	_____	Cohort study for 12 years	Interview with questionnaire	Montonen et al

[*] Fructose exposure reported as mean ± SD,

[**] Fructose exposure reported as median (IQR) or as a range.

Despite the fact that in our study we did not find any significant association between fructose intake and each of the individual abnormalities of the MetS, our results showed a significant relationship between fructose (total/added) with the MetS as an entity, after adjustment for potential confounders. It should be emphasized that, the positive association was observed only in the fourth quartile of fructose intake (> 64.05 g of total fructose/day and >51.48 g of added fructose/day). The positive association between fructose consumption and increased risk of MetS is supported by several studies (Moreno and Hong 2013; Hu and Malik, 2010; Stanhope and Havel, 2008; Stanhope and Havel, 2010; Hosseini-Esfahani et al, 2011; Malik et al., 2010). These findings are consistent with those reported by a previous cross-sectional study conducted in 2011 by Hosseini-Esfahani et al., showing that men and women in the highest quartile of fructose intake, had 33% and 20% higher risk of developing MetS, respectively. Similar results were documented in a systematic review and meta-analysis of clinical trials which also concluded that high fructose consumption from industrialized products is the main contributor to MetS (Kelishadi et al., 2014). Moreover, among three studies evaluating MetS and fructose intake in a meta-analysis by Malik et al., the pooled RR was 1.20 [95% CI 1.02–1.42] comparing extreme quantile of SSB intake, which is considered an important source of added fructose in the human diet. This suggests that an increased risk of 20% of MetS is associated with higher consumption of SSB compared with lower consumption (Malik et al., 2010). An important mechanism that may explain this association between fructose intake and MetS is the altered appetite and satiety signals caused by high fructose intake which results in weight gain and visceral fat accumulation (Labouebe et al., 2013) (Figlewicz and Benoit, 2009). Interestingly, the association of Fructose with MetS became significant only after adjustment for confounders that included BMI, age and sex and BMI. The fact that the association became significant after adjustment for BMI, suggests that the association is driven by nutrient- specific mechanisms rather than merely excessive body weight. these nutrient-specific

mechanisms may include the unregulated hepatic fructose metabolism that causes hepatic lipid accumulation (Softic et al., 2016) (Rosset et al., 2016), hyperuricemia (Caliceti et al., 2017) (Jia et al., 2014) and decreased insulin sensitivity (Hannou et al., 2018), hence MetS. Hyperuricemia caused by excessive fructose intake induces mitochondrial oxidative stress which in turn is linked with insulin resistance (Hoehn et al., 2009). It will decrease endothelial nitric NO release, which will decrease the contact between glucose and GLUT4, decreasing insulin sensitivity (Duplain et al., 2001). Moreover, oxidative stress induced by hyperuricemia plays a major role in clinical manifestations such as coronary heart disease and diabetes (Roberts and Sindhu, 2009).

Worth noting that in the current study no positive association was identified between natural fructose and MetS even after adjustment for potential confounders. The sources of natural fructose are principally fruits and vegetables which are rich in various bioactive compounds such as phytochemicals, antioxidants and fibers (Devalaraja et al., 2011). This wide array of protective nutrients may offset metabolic abnormalities of fructose and may prevent the development of obesity, diabetes and MetS (Devalaraja et al., 2011; Salvin and Lloyd, 2012) . Furthermore, small amounts of natural fructose coming from fruits and vegetables have been shown to improve hepatic glucose handling by increasing the uptake of glucose into the liver and glycogen deposition (Geidl-Flueck & Gerber, 2017).

The high intake of added fructose (4.80 ± 3.56 %Kcal/day) compared to natural fructose (1.78 ± 1.41 %Kcal/day) in Lebanon may be a manifestation of the nutrition transition in the country. Indeed, Lebanon, like other countries of the Middle-East and North Africa Region (MENA), is undergoing modernization and urbanization which resulted in significant changes in diet during the past few decades (Nasreddine et al., 2014). A recent study showed that the diet in Lebanon is shifting towards higher energy, higher sugar and lower intakes of fruits and vegetables (Nasreddine et al., 2019). Thus, this increase in added caloric sweeteners

and decrease in fruits and vegetables may explain the current dietary pattern of Lebanese adults which is high in added fructose and low in natural fructose. The study findings illustrating the high intake of added fructose in Lebanon coupled with its association with a 3- fold increase in the odds of MetS is worrisome, may have implications on the disease burden in the country, particularly non-communicable diseases (NCDs). The MetS is in fact a risk factor for type 2 diabetes and cardiovascular diseases (Wilson et al., 2005) (Shin et al., 2013), which are highly prevalent in Eastern Mediterranean countries specially in Lebanon and are assuming an escalating secular trend (84% of death is caused by NCDs in Lebanon) (Boutayeb et al., 2013).

Our study have several strengths. To our knowledge, it is the first study that assessed fructose intake in Lebanese adults and investigated its association with MetS and its component. It is important to mention that participants with previous history of chronic disease were excluded since they could have received nutritional advice to follow a healthy diet low in sugar, and hence in fructose.

Despite its strength, our study has several limitations that deserve attention. First, since it is a cross-sectional design, the current study does not allow to determine causality between fructose intake, MetS and its components. Therefore, this study limits our ability to determine whether individuals with high fructose intake have a higher risk to develop the MetS or whether those diagnosed with MetS tend to follow an unhealthy eating pattern high in fructose. The second limitation in this study is the use of a semi quantitative food-frequency questionnaire (FFQ) for collecting dietary data. This latter, highlights the possibility of recall bias and may be associated with an overestimation of dietary intake (Kushi, 1994). However, FFQs were shown to be the most suitable dietary assessment tools in large epidemiological studies given that they allow for the estimation of dietary intake over a long period of time (Shim, Oh and Kim, 2014). Moreover, social desirability bias may have influenced our findings since participants may misreport their food intake in a

manner they perceive as favorable to the interviewer (Hebert et al., 1995). Even though this limitation is reported, it is worth mentioning that it is minimized since the data was collected by trained and experienced dietitians who enhanced quality control in data collection. Selection bias is also considered a limitation in the current study. Indeed, the likelihood of overweight and unhealthy subjects to participate in this study is higher than healthy subjects participation, which may explain why we had a higher prevalence of MetS compared to other studies. Finally, the cut off points used for WC were not specific to our study sample. We used the threshold values applicable to the European population. This latter may not be fully adapted to our sample, since some studies suggested lower WC cutoffs for ethnic Arabs (Al-Lawati & Jousilahti, 2008).

CHAPTER VI

CONCLUSION

This study is, the first in the Eastern Mediterranean region, to assess fructose intake and investigate its association with MetS. The current study documented a high intake of fructose amongst Lebanese urban adults, with almost quarter of the population (n=70) being classified in the highest quartile of fructose intake. It also showed a positive association between fructose (total/added) and MetS, whereas the risk of MetS increased by 2.450 and by 2.609 fold when the total fructose and added fructose were at 75th percentile, respectively.

These findings are supported by several studies (Moreno and Hong 2013; Hu and Malik, 2010; Stanhope and Havel, 2008; Stanhope and Havel, 2010; Hosseini-Esfahani et al, 2011). Therefore, restrictive guidelines on fructose intakes, could be an effective strategy to decrease the prevalence of MetS and obesity. Since the main sources of added fructose in the human diet include SSBs, a possible action to reduce the consumption of SSBs and products with high sugar levels is the inclusion of "sugar taxes" as they did in Mexico and Hungary (Carvalho et al., 2018) (Batis et al., 2016) (Falbe et al., 2016). These interventions are shown to be effective and has a strong influence on population's food choice, especially in low income groups (Mozaffarian et al., 2018). Banning SSBs or limiting their availability in public schools and across university campuses may also be effective in reducing sugar intake. Indeed, Britain, France, Los Angeles, and Miami have banned soft drinks in their schools (Vartanian et al., 2007). Moreover, food package nutrition fact panels, health claims and warning labels should be promoted because they may encourage industry to reformulate while also increasing consumer awareness (Mozaffarian et al., 2018). Indeed, the California State Senate have required to place a health warning label on sugary drinks (California State Senate, 2019). Such information

increases consumer education and would have a direct impact on consumer to make healthier choices. Last but not least, population education and promoting healthier eating via dietary guidelines can also be helpful (Mozaffarian et al., 2018).

The findings of the current study support recent dietary recommendation published by AHA and WHO to limit sugar consumption (Johnson RK. et al., 2009) (WHO, 2015). It provides further support for the development of restrictive guidelines and public health strategies aiming to encourage the decrease in the consumption of industrialized foods high in fructose in order to prevent MetS and obesity. However, one should consider the whole dietary pattern for health benefits and should not focus only on sugar content as the sole element of a healthy diet.

More studies are needed to design appropriate interventions. As a start, cohort studies may be helpful in indicating the temporal sequence between fructose intake and MetS. In addition intervention studies are needed. At this stage, short term intervention studies investigating the effect of fructose have highlighted it as a public health concern. However, there is a need for longer term intervention studies to better understand the effects of fructose on different aspects of metabolism and to better inform policy development.

BIBLIOGRAPHY

Alberti, K. G., & Zimmet, P. Z. (1998). Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. Diabet Med, 15(7), 539-553.

Alberti, K. G., Eckel, R. H., Grundy, S. M., Zimmet, P. Z., Cleeman, J. I., Donato, K. A., . . . Smith, S. C., Jr. (2009). Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. Circulation, 120(16), 1640-1645.

Alberti, Zimmet, Paul, & Shaw, Jonathan. (2006). Metabolic syndrome—a new world-wide definition. A consensus statement from the international diabetes federation. Diabetic Medicine, 23(5), 469-480.

Al-Lawati, J. A., & Jousilahti, P. (2008). Body mass index, waist circumference and waist-to-hip ratio cut-off points for categorisation of obesity among Omani Arabs. Public Health Nutr, 11(1), 102-108

Aguilar M, Bhuket T, Torres S, Liu B, Wong RJ. (2015). Prevalence of the Metabolic Syndrome in the United States, 2003-2012. JAMA. 313(19):1973–1974.

Ansarimoghaddam A, Ali Adineh H, Zareban I, Iranpour S, Hosseinzadeh A. (2017). Prevalence of metabolic syndrome in Middle-East countries: Meta-analysis of cross-sectional studies, Diab Met Syndr: Clin Res Rev. 12(2): 195-201

Barone S, Fussell SL, Singh AK, Lucas F, Xu J, Kim C, et al. (2009). Slc2a5 (GLUT5) is essential for the absorption of fructose in the intestine and generation of fructose-induced hypertension. J Biol Chem. 284:5056–5066

Balkau, B, & Charles, MA. (1999). for the European Group for the Study of Insulin Resistance Comment on the provisional report from the WHO consultation. Diabetic Medicine, 16, 442-443.

Bankoski, A., Harris, T. B., McClain, J. J., Brychta, R. J., Caserotti, P., Chen, K. Y., Berrigan, D., Troiano, R. P., … Koster, A. (2011). Sedentary activity associated with metabolic syndrome independent of physical activity. Diabetes care, 34(2), 497-503.

Basu S, McKee M, Galea G, Stuckler D. (2013). Relationship of soft drink consumption to global overweight, obesity, and diabetes: a cross-national analysis of 75 countries. Am J Public Health. 103:2071–2077.

Batis C, Rivera JA, Popkin BM, Taillie LS. First- year evaluation of Mexico's tax on nonessential energy-dense foods: an observational study. PLoS Med. 2016;13(7):e1002057.

Baudrand, R., Campino, C., Carvajal, C. A., Olivieri, O., Guidi, G., Faccini, G., . . . Fardella, C. E. (2014). High sodium intake is associated with increased glucocorticoid production, insulin resistance and metabolic syndrome. Clin Endocrinol (Oxf), 80(5), 677-684. doi: 10.1111/cen.12225

Bener, A., Zirie, M., Musallam, M., Khader, Y. S., & Al-Hamaq, A. O. (2009). Prevalence of metabolic syndrome according to Adult Treatment Panel III and International Diabetes Federation criteria: a population-based study. Metab Syndr Relat Disord, 7(3), 221-229.

Borghi C. (2015). The role of uric acid in the development of cardiovascular disease. Curr. Med. Res. Opin. 31(Suppl. S2):1–2.

Boutayeb, A., Boutayeb, S., & Boutayeb, W. (2013). Multi-morbidity of non communicable diseases and equity in WHO Eastern Mediterranean countries. International journal for equity in health, 12, 60. doi:10.1186/1475-9276-12-60

Bray G. A. (2007). How bad is fructose? The American Journal of Clinical Nutrition. 86 (4):895–896.

Brown TM, Voeks JH, Bittner V, Safford MM. (2010). Variations in prevalent cardiovascular disease and future risk by metabolic syndrome classification in the REasons for Geographic And Racial Differences in Stroke (RE- GARDS) study. Am Heart J. 159:385–391.

Burant, C. F., Takeda, J., Brot-Laroche, E., Bell, G. I., Davidson, N. O. (1992) Fructose transporter in human spermatozoa and small intestine is GLUT5. J. Biol. Chem. 267, 14523–14526

California State Senate, Legislation requiring safety warning label on sugary drinks introduced in California Senate
available at: https://sd17.senate.ca.gov/news/2019-02-20-legislation-requiring-safety-warning-label-sugary-drinks-introduced-california

Carvalho, C.T., Souza, Z.M., Arbex, N., Sá, D., de Souza Rodrigues, L.C., de Sá, D.A.R., de Sá, L.B.P.C. and Arbex, A.K. (2018) The Role of Fructose in Public Health and Obesity. Health, 10, 434-441.

Castro MC., Massa ML., Arbeláez LG., Schinella G., Gagliardino JJ., Francini F., (2015). Fructose-induced inflammation, insulin resistance and oxidative stress: A liver pathological triad effectively disrupted by lipoic acid. Life science, 137, 1-6

Cha SH, Wolfgang M, Tokutake Y, Chohnan S, Lane MD (2008). Differential effects of central fructose and glucose on hypothalamic malonyl-CoA and food intake. Proc Natl Acad Sci 105:16871-16875.

Cheng, M., Wang, H., Wang, Z., Du, W., Ouyang, Y., & Zhang, B. (2017). Relationship between dietary factors and the number of altered metabolic syndrome components in Chinese adults: a cross-sectional study using data from the China Health and Nutrition Survey. BMJ open, 7(5), e014911.

Chiavaroli, L., de Souza, R. J., Ha, V., Cozma, A. I., Mirrahimi, A., Wang, D. D., Yu, M., Carleton, A. J., Di Buono, M., Jenkins, A. L., Leiter, L. A., Wolever, T. M., Beyene, J., Kendall, C. W., Jenkins, D. J., … Sievenpiper, J. L. (2015). Effect of Fructose on Established Lipid Targets: A Systematic Review and Meta-Analysis of Controlled Feeding Trials. Journal of the American Heart Association, 4(9), e001700.

Cabral PD, Hong NJ, Khan MAH, Ortiz PA, Beierwaltes WH, Imig JD, et al. (2014). Fructose stimulates Na/H exchange activity and sensitizes the proximal tubule to angiotensin II. Hypertension. 63:e68–e73.

Caliceti, C., Calabria, D., Roda, A., & Cicero, A. (2017). Fructose Intake, Serum Uric Acid, and Cardiometabolic Disorders: A Critical Review. Nutrients, 9(4), 395.

Carvalho, C. , de Souza, M. , Arbex, N. , Sá, D. , de Souza Rodrigues, L. , de Sá, D. , de Sá, L. and Arbex, A. (2018). The Role of Fructose in Public Health and Obesity. Health, 10, 434-441

Chong MF, Fielding BA, Frayn KN. (2007). Mechanisms for the acute effect of fructose on postprandial lipemia. Am J Clin Nutr. 85:1511–1520

Cleeman, JI, Grundy, SM, Becker, D, & Clark, LT. (2001). Expert panel on Detection, Evaluation and Treatment of High blood Cholesterol in Adults. Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP III). Jama, 285(19), 2486-2497.

Corpe CP, Burant CF, Hoekstra JH., (1999).Intestinal fructose absorption: clinical and molecular aspects. J Pediatr Gastroenterol Nutr 28: 364 –374.

Devalaraja S., Jain S., Yadav H. (2011). Exotic Fruits as Therapeutic Complements for Diabetes, Obesity and Metabolic Syndrome. Food Res. Int. 44:1856–1865.

Desroches S, Lamarche B. (2007) The evolving definitions and increasing prevalence of the metabolic syndrome. Applied Physiology, Nutrition and Metabolism. 32(1):23–32.

Drake, I., Sonestedt, E., Ericson, U., Wallström, P., & Orho-Melander, M. (2018). A Western dietary pattern is prospectively associated with cardio-metabolic traits and incidence of the metabolic syndrome. British Journal of Nutrition, 119(10), 1168-1176.

De Koning L, Malik VS, Rimm EB, et al. (2011) Sugar-sweetened and artificially sweetened beverage consumption and risk of type 2 diabetes in men. Am J Clin Nutr 93, 1321–1327

Dolan, L.C., Potter, S.M., Burdock, G.A., 2010. Evidence-based review on the effect of normal dietary consumption of fructose on development of hyperlipidemia and obesity in healthy, normal weight individuals. Crit. Rev. Food Sci. Nutr. 50 (1),53–84.

Duplain H, Burcelin R, Sartori C, et al. Insulin resistance, hyperlipidemia, and hypertension in mice lacking endothelial nitric oxide synthase. Cir- culation 2001;104:342–345

Ejtahed, H. S., Bahadoran, Z., Mirmiran, P., & Azizi, F. (2015). Sugar-Sweetened Beverage Consumption Is Associated with Metabolic Syndrome in Iranian Adults: Tehran Lipid and Glucose Study. Endocrinology and metabolism (Seoul, Korea), 30(3), 334-42.

Ervin R & Ogden C (2013) Consumption of added sugars among U.S. adults, 2005-2010. NCHS Data Brief 122, 1–8

Executive Summary of the Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). JAMA 2001; 285: 2486 – 2497

Falbe J, Thompson HR, Becker CM, Rojas N, McCulloch CE, Madsen KA. (2016). Impact of the Berkeley excise tax on sugar-sweetened beverage consumption. Am J Public Health. 106(10):1865–1871.

Figlewicz DP, Benoit SC (2009). Insulin, leptin, and food reward: update 2008. Am J Physiol Regul Integr Comp Physiol 296:R9-R19

Feinman, R., & Fine, E. (2013). Fructose in perspective. Nutrition & metabolism, 10(1), 45. doi:10.1186/1743-7075-10-45

Forshee RA, Anderson PA & Storey ML (2008) Sugar-sweetened beverages and body mass index in children and adolescents: a meta-analysis. Am J Clin Nutr 87, 1662–167

Ford ES, Giles WH, Mokdad AH (2004) Increasing prevalence of the metabolic syndrome among u.s. Adults. Diabetes Care 27: 2444-2449

Geidl-Flueck, B., & Gerber, P. A. (2017). Insights into the Hexose Liver Metabolism-Glucose versus Fructose. Nutrients, 9(9), 1026.

Hannou A., Haslam D., McKeown N., Herman M. (2018). Fructose metabolism and metabolic disease. J Clin Invest. 2018;128(2):545–555.

Han, T. S., & Lean, M. E. (2016). A clinical perspective of obesity, metabolic syndrome and cardiovascular disease. JRSM cardiovascular disease, 5.

Hebert J., Clemow l., Pbert l., Ockene I., Ockene J., (1995), Social desirability bias in dietary self-report may compromise the validity of dietary intake measures, International journal of epidemiology, 24, 2, 389–398

Herman, M. A., & Samuel, V. T. (2016). The Sweet Path to Metabolic Demise: Fructose and Lipid Synthesis. Trends in endocrinology and metabolism: TEM, 27(10), 719-730.

Hoehn KL, Salmon AB, Hohne-Behrens C, et al. (2009). Insulin resistance is a cellular antioxidant defense mechanism. Proc Natl Acad Sci USA; 106:17787–17792

Hosseini-Esfahani, F., Bahadoran, Z., Mirmiran, P., Hosseinpour-Niazi, S., Hosseinpanah, F., & Azizi, F. (2011). Dietary fructose and risk of metabolic syndrome in adults: Tehran Lipid and Glucose study. Nutrition & metabolism, 8(1), 50.

Horst K., Schene M., Holman R., Romijn J., Serlie M. (2016). Effect of fructose consumption on insulin sensitivity in nondiabetic subjects: a systematic review and meta-analysis of diet-intervention trials, Am Heart J. , 104, 6, 1562–157

Hu, F. B., & Malik, V. S. (2010). Sugar-sweetened beverages and risk of obesity and type 2 diabetes: epidemiologic evidence. Physiology & behavior, 100(1), 47-54.

Jalal, D. I., Smits, G., Johnson, R. J., & Chonchol, M. (2010). Increased fructose associates with elevated blood pressure. Journal of the American Society of Nephrology : JASN, 21(9), 1543-9.

Jia G, Aroor Annayya R, Whaley-Connell Adam T, Sowers James R. (2014). Fructose and uric acid: is there a role in endothelial function? Curr Hypertens Rep. 16:434.

Johnson R.J., Segal M.S., Sautin Y., Nakagawa T., Feig D.I., Kang D., Gersch M.S., Benner S., Sánchez-Lozada L.G., (2007). Potential role of sugar (fructose) in the epidemic of hypertension, obesity and the metabolic syndrome, diabetes, kidney disease, and cardiovascular disease. Am. J. Clin. Nutr. ;86:899–906

Johnson RJ, Perez-Pozo SE, Sautin YY, Manitius J, Sanchez-Lozada LG,

Feig DI, Shafiu M, Segal M, Glassock RJ, Shimada M, Roncal C, Nakagawa T., (2009). Hypothesis: could excessive fructose intake and uric acid cause type 2 diabetes? Endocr Rev, 30:96-116.

Johnson RK, et al. (2009). Dietary sugars intake and cardiovascular health: a scientific statement from the American Heart Association. Circulation. 120(11):1011–1020.

Jones, J.M., 2009. Dietary sweeteners containing fructose: overview of a workshop on the state of the science. J. Nutr. 139 (6), 1210S–1213S.

Kaur J. (2014). A comprehensive review on metabolic syndrome. Cardiology research and practice, 943162.

Kelly T, Yang W, Chen C-S, Reynolds K, He J. (2008). Global burden of obesity in 2005 and projections to 2030. Int J Obes 2005. 32(9):1431–7

Kelishadi R., Mansourian M., Heidari-Beni M., (2014), Association of fructose consumption and components of metabolic syndrome in human studies: A systematic review and meta-analysis; Volume 30, Issue 5, Pages 503-510

Khan, T. A., & Sievenpiper, J. L. (2016). Controversies about sugars: results from systematic reviews and meta-analyses on obesity, cardiometabolic disease and diabetes. European journal of nutrition, 55(Suppl 2), 25–43.

Khosravi-Boroujeni H, Sarrafzadegan N, Mohammadifard N, Alikhasi H, Sajjadi F, Asgari S, et al. (2012). Consumption of sugar-sweetened beverages in relation to the metabolic syndrome among Iranian adults. Obes Facts. 5:527–537

Klein, A. V., & Kiat, H. (2015). The mechanisms underlying fructose-induced hypertension: a review. Journal of hypertension, 33(5), 912-20.

Kolderup, A., & Svihus, B. (2015). Fructose Metabolism and Relation to Atherosclerosis, Type 2 Diabetes, and Obesity. Journal of nutrition and metabolism, 2015, 823081.

Kolovou GD, Anagnostopoulou KK, Salpea KD, Mikhailidis DP. (2007). The prevalence of metabolic syndrome in various populations. The American Journal of the Medical Sciences; 333(6):362–371.

Kushi, L. H. (1994). Gaps in epidemiologic research methods: design considerations for studies that use food-frequency questionnaires. Am J Clin Nutr, 59(1 Suppl), 180S-184S

Kwak, S. K., & Kim, J. H. (2017). Statistical data preparation: management of missing values and outliers. Korean journal of anesthesiology, 70(4), 407–411.

Kwang-Jun Ko, Eon-Ho Kim, Un-Hyo Baek, Zhao Gang, Seol-Jung Kang. (2016). The relationship between physical activity levels and metabolic syndrome in male white-collar workers. The Journal of Physical Therapy Science. 28: 3041–3046.

Labouebe G, Liu S, Dias C, Zou H, Wong JCY, Karunakaran S et al.: Insulin induces long-term depression of ventral tegmental area dopamine neurons via endocannabinoids. Nat Neurosci 2013, 16:300-308.

Lana A., Rodríguez-Artalejo F., Lopez-Garcia E. (2014). Consumption of Sugar-Sweetened Beverages Is Positively Related to Insulin Resistance and Higher Plasma Leptin Concentrations in Men and Nonoverweight Women, The Journal of Nutrition, 144, 7, 1099–1105

Lim S, et al. (2011). Increasing prevalence of metabolic syndrome in Korea: the Korean National Health and Nutrition Examination Survey for 1998–2007. Diabetes Care; 34(6):1323–8.

Lustig RH, Schmidt LA, Brindis CD. Public health: The toxic truth about sugar. Nature. 2012;482(7383):27–29.

Ma, J., Sloan, M., Fox, C. S., Hoffmann, U., Smith, C. E., Saltzman, E., Rogers, G. T., Jacques, P. F., … McKeown, N. M. (2014). Sugar-sweetened beverage consumption is associated with abdominal fat partitioning in healthy adults. The Journal of nutrition, 144(8), 1283-90.

Ma, J., McKeown, N. M., Hwang, S. J., Hoffmann, U., Jacques, P. F., & Fox, C. S. (2016). Sugar-Sweetened Beverage Consumption Is Associated With Change of Visceral Adipose Tissue Over 6 Years of Follow-Up. Circulation, 133(4), 370-7.

Maersk M, Belza A, Stodkilde-Jorgensen H, Ringgaard S, Chabanova E, Thomsen H, Pedersen SB, Astrup A, Richelsen B. Sucrose-sweetened beverages increase fat storage in the liver, muscle, and visceral fat depot: a 6-mo randomized intervention study. Am J Clin Nutr. 2012;95:283–289

Marriott BP, Cole N, Lee E. National estimates of dietary fructose intake increased from 1977 to 2004 in the United States. J Nutrl39: 1228 –1235, 2009.

Malik V., Bray G.A., Popkin B.M., Despres J.P., Hu F.B. (2010). Sweetened beverages and risk of metabolic syndrome and type 2 diabetes: a meta-analysis. Diab Care. 33:2477–83

Manikandan S. (2011). Measures of dispersion. Journal of pharmacology & pharmacotherapeutics, 2(4), 315–316.

Mavrias DA, Mayer RJ. Metabolism of fructose in the small intestine. (1973). The effect of fructose feeding on fructose transport and metabolism in rat small intestine. Biochim Biophys Acta. 291(2):531–537.

McCracken E., Monaghan M., Sreenivasan S., (2018), Pathophysiology of the metabolic syndrome, Clinics in Dermatology, 36 (1), 14-20

Mead JR, Irvine SA, Ramji DP. (2002). Lipoprotein lipase: structure, function, regulation, and role in disease. J Mol Med (Berl). 80:753–769.

Miller A, Adeli K. Title Dietary fructose and the metabolic syndrome. Current Opinion in Gastroenterology. 2008;24:204–209.

Mirtschink P., Jang C., Arany Z., Krek W., (2018). Fructose metabolism, cardiometabolic risk, and the epidemic of coronary artery disease, European Heart Journal, Volume 39, Issue 26, Pages 2497–2505

Montonen J., Järvinen R., Knekt P., Heliövaara M., Reunanen A. (2007). Consumption of Sweetened Beverages and Intakes of Fructose and Glucose Predict Type 2 Diabetes Occurrence, The Journal of Nutrition, 137 (6), 1447–1454.

Moreno J.A., Hong E. (2013) A single oral dose of fructose induces some features of metabolic syndrome in rats: Role of oxidative stress. Nutrition, Metabolism and Cardiovascular Diseases, 23 (6) , pp. 536-542.

Mozaffarian, D., Angell, S. Y., Lang, T., & Rivera, J. A. (2018). Role of government policy in nutrition-barriers to and opportunities for healthier eating. BMJ (Clinical research ed.), 361, k2426.

Mottillo, S., Filion, K. B., Genest, J., Joseph, L., Pilote, L., Poirier, P., . . . Eisenberg, M. J. (2010). The metabolic syndrome and cardiovascular risk a systematic review and meta-analysis. J Am Coll Cardiol, 56(14), 1113-1132.

Naja, F., Nasreddine, L., Itani, L., Adra, N., Sibai, A. M., & Hwalla, N. (2013). Association between dietary patterns and the risk of metabolic syndrome among Lebanese adults. Eur J Nutr, 52(1), 97-105.

Nasreddine L., Ayoub J.J., Hachem F., Tabbara J., Sibai A.M., Hwalla N., Naja F.(2019), Differences in Dietary Intakes among Lebanese Adults over a Decade: Results from Two National Surveys 1997–2008/2009. Nutrients 11, 1738.

Nasreddine, L., Naja, F., Chamieh, M. C., Adra, N., Sibai, A. M., & Hwalla, N. (2012). Trends in overweight and obesity in Lebanon: evidence from two national cross-sectional surveys (1997 and 2009). BMC Public Health, 12, 798.

Nasreddine L., Naja F., Sibai A., Helou K., Adra N., Hwalla N. (2014), Trends in nutritional intakes and nutrition-related cardiovascular disease risk factors in Lebanon: the need for immediate action, Leban Med J, 62, pp. 83-91

Narain A, Kwok CS, Mamas MA, (2017). Soft drink intake and the risk of metabolic syndrome: a systematic review and meta-analysis. Int J Clin Pract 71:e12927.

Noel SE, Newby PK, Ordovas JM, Tucker KL. Adherence to an (n-3) fatty acid/fish intake pattern is inversely associated with metabolic syndrome among Puerto Rican adults in the Greater Boston area. J Nutr. 2010; 140:1846

Nourmohammdi M, Ejtahed H-S, Mirmiran P, Hekmatdoost A. (2015). Dietary fatty acid composition and metabolic syndrome: a review. J Nutr Sci Diet .1(1):28-36.

Ng, M., Fleming, T., Robinson, M., Thomson, B., Graetz, N., Margono, C., . . . Gakidou, E. (2014). Global, regional, and national prevalence of overweight and obesity in children and adults during 1980-2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet, 384(9945), 766-781.

Odegaard AO, Choh AC, Czerwinski SA, Towne B, Demerath EW. Sugar-sweetened and diet beverages in relation to visceral adipose tissue. Obesity (Silver Spring) 2012;20:689–691.

O'Neill S., O'Driscoll L. Metabolic syndrome: a closer look at the growing epidemic and its associated pathologies. Obes. Rev. 2015;16(1):1–12

Oliveira Junior SA, Padovani CR, Rodrigues SA, et al. (2013). Extensive impact of saturated fatty acids on metabolic and cardiovascular profile in rats with diet-induced obesity: a canonical analysis. Cardiovasc Diabetol. 12:65.

Olsen NJ, Heitmann BL. Intake of calorically sweetened beverages and obesity. Obes Rev.2009;10:68–75

Oh, S. W., Han, K. H., Han, S. Y., Koo, H. S., Kim, S., & Chin, H. J. (2015). Association of Sodium Excretion With Metabolic Syndrome, Insulin Resistance, and Body Fat. Medicine, 94(39), e1650.

Park YK, Yetley EA. Intakes and food sources of fructose in the United States. Am J Clin Nutr 58, Suppl: 737S–747S, 1993.

Petersen, M. C., & Shulman, G. I. (2017). Roles of Diacylglycerols and Ceramides in Hepatic Insulin Resistance. Trends in pharmacological sciences, 38(7), 649-665

Perez-Pozo S., Schold J., Nakagawa T., Sanchez-Lozada L., Johnson R., Lillo J. (2010). Excessive fructose intake induces the features of metabolic syndrome in healthy adult men: role of uric acid in the hypertensive response. Int J Obes; 34:454–61.

Poledne R. A new atherogenic effect of saturated fatty acids. Physiol Res. 2013; 62:139-43.

Popkin BM. Patterns of beverage use across the lifecycle. Physiol Behav 2010;100:4-9

Popkin, B. M., Adair, L. S., & Ng, S. W. (2012). Global nutrition transition and the pandemic of obesity in developing countries. Nutrition reviews, 70(1), 3-21.

Ritchie SA, Connell JMC. The link between abdominal obesity, metabolic syndrome and cardiovascular disease. Nutrition, Metabolism and Cardiovascular Diseases. 2007;17(4):319–326

Rippe JM. (2010). The health implications of sucrose, high fructose corn syrup, and fructose: What do we really know? J Diabetes Technol. 4 Issue 4

Rippe, J. M., & Angelopoulos, T. J. (2013). Sucrose, high-fructose corn syrup, and fructose, their metabolism and potential health effects: what do we really know?. Advances in nutrition (Bethesda, Md.), 4(2), 236–245.

Rizkalla S. (2010). Health implications of fructose consumption: A review of recent data. Nutrition & metabolism, 7, 82.

Rodríguez-Monforte, M., Sánchez, E., Barrio, F. et al. (2017). Metabolic syndrome and dietary patterns: a systematic review and meta-analysis of observational studies. Eur J Nutr. 56(3), 925–947

Rosset, R., Surowska, A., & Tappy, L. (2016). Pathogenesis of Cardiovascular and Metabolic Diseases: Are Fructose-Containing Sugars More Involved Than Other Dietary Calories?. Current hypertension reports, 18(6), 44.

Rumessen JJ, Gudmand-Hoyer E. Absorption capacity of fructose in healthy adults. Comparison with sucrose and its constituent monosaccharides. Gut. 1986;27(10):1161–1168.

Rumessen JJ. Fructose and related food carbohydrates. Sources, intake, absorption, and clinical implications. Scand J Gastroenterol. 1992;27(10):819–828.

Saklayen M. G. (2018). The Global Epidemic of the Metabolic Syndrome. Current hypertension reports, 20(2), 12. doi:10.1007/s11906-018-0812-z

Sarafidis, P. A., & Nilsson, P. M. (2006). The metabolic syndrome: a glance at its history. J Hypertens, 24(4), 621-626.

Samuel V. T. (2011). Fructose induced lipogenesis: from sugar to fat to insulin resistance. Trends in Endocrinology and Metabolism. ;22(2):60–65

Schulze, M., Schulz, M., Heidemann, C., Schienkiewitz, A., Hoffmann, K., & Boeing, H. (2008). Carbohydrate intake and incidence of type 2 diabetes in the European Prospective Investigation into Cancer and Nutrition (EPIC)-Potsdam Study. British Journal of Nutrition, 99(5), 1107-1116

Senesi S, Legeza B, Balazs Z, Csala M, Marcolongo P, Kereszturi E, Szelenyi P, Egger C, Fulceri R, Mandl J, Giunti R, Odermatt A, Banhegyi G, Benedetti A. (2010). Contribution of fructose-6-phosphate to glucocorticoid activation in the endoplasmic reticulum: possible implication in the metabolic syndrome. Endocrinology.151:4830–4839

Shim, J. S., Oh, K., & Kim, H. C. (2014). Dietary assessment methods in epidemiologic studies. Epidemiology and health, 36, e2014009.

Shin, S., Kim, S. A., Ha, J., & Lim, K. (2018). Sugar-Sweetened Beverage Consumption in Relation to Obesity and Metabolic Syndrome among Korean Adults: A Cross-Sectional Study from the 2012–2016 Korean National Health and Nutrition Examination Survey (KNHANES). Nutrients, 10(10), 1467

Shin, J. A., Lee, J. H., Lim, S. Y., Ha, H. S., Kwon, H. S., Park, Y. M., … Son, H. Y. (2013). Metabolic syndrome as a predictor of type 2 diabetes, and its clinical interpretations and usefulness. Journal of diabetes investigation, 4(4), 334–343.

Sibai, Abla-Mehio, Obeid, Omar, Batal, Malek, Adra, Nada, Khoury, Dalia El, & Hwalla, Nahla. (2008). Prevalence and correlates of metabolic syndrome in an adult Lebanese population. CVD Prevention and Control, 3(2), 83-90

Silbernagel, G., Machann, J., Unmuth, S., Schick, F., Stefan, N., Häring, H., & Fritsche, A. (2011). Effects of 4-week very-high-fructose/glucose diets on insulin sensitivity, visceral fat and intrahepatic lipids: An exploratory trial. British Journal of Nutrition, 106(1), 79-8

Slavin J.L., Lloyd B. (2012). Health benefits of fruits and vegetables. Adv. Nutr. 3:506–516.

Softic, S., Cohen, D. E., & Kahn, C. R. (2016). Role of Dietary Fructose and Hepatic De Novo Lipogenesis in Fatty Liver Disease. Digestive diseases and sciences, 61(5), 1282-93

Soleimani M. (2011). Dietary fructose, salt absorption and hypertension in metabolic syndrome: towards a new paradigm. Acta Physiol. 201:55–62

Soleimani M, Alborzi P. (2011). The role of salt in the pathogenesis of fructose-induced hypertension. Int J Nephrol. 392708, 392708pp

Solberg H. & Lahti A., (2005), Detection of Outliers in Reference Distributions: Performance of Horn's Algorithm, Clinical Chemistry 51 (12) 2326-2332

Spiga R1, Marini MA1, Mancuso E1, Di Fatta C1, Fuoco A1, Perticone F1, Andreozzi F1, Mannino GC2, Sesti G1. (2017). Uric Acid Is Associated With Inflammatory Biomarkers and Induces Inflammation Via Activating the NF-κB Signaling Pathway in HepG2 Cells. Arterioscler Thromb Vasc Biol. 37(6):1241-1249.

Stanhope, K. L., & Havel, P. J. (2008). Fructose consumption: potential mechanisms for its effects to increase visceral adiposity and induce dyslipidemia and insulin resistance. Current opinion in lipidology, 19(1), 16-24.

Stanhope, K.L., Havel, P.J., (2010). Fructose consumption: recent results and their potential implications. Ann. NY Acad. Sci. 1190 (1), 15–24.

Sun S., Anderson G., Flickinger B., Williamson-Hughes P., Empie M., (2011). Fructose and non-fructose sugar intakes in the US population and their associations with indicators of metabolic syndrome, Food and Chemical Toxicology, 49 (11), 2875-2882.

Tappy, L., Le, K.A. (2010) Metabolic effects of fructose and the worldwide increase in obesity. Physiol Rev, 90, 23-46

Tappy, L., Le, K.A., Tran, C., Paquot, N. (2010). Fructose and metabolic diseases: new findings, new questions. Nutrition. 26 (11-12), 1044-1049

Tauler, P., Bennasar-Veny, M., Morales-Asencio, J. M., Lopez-Gonzalez, A. A., Vicente-Herrero, T., De Pedro-Gomez, J., . . . Aguilo, A. (2014). Prevalence of premorbid metabolic syndrome in Spanish adult workers using IDF and ATPIII diagnostic criteria: relationship with cardiovascular risk factors. PLoS One, 9(2), e89281.

Ter Horst, K. W., Gilijamse, P. W., Versteeg, R. I., Ackermans, M. T., Nederveen, A. J., la Fleur, S. E., Romijn, J. A., Nieuwdorp, M., Zhang, D., Samuel, V. T., Vatner, D. F., Petersen, K. F., Shulman, G. I., … Serlie, M. J. (2017). Hepatic Diacylglycerol-Associated Protein Kinase Cε Translocation Links Hepatic Steatosis to Hepatic Insulin Resistance in Humans. Cell reports, 19(10), 1997-2004.

Teff K., S. S. Elliott, M. Tschöp et al., "Dietary fructose reduces circulating insulin and leptin, attenuates postprandial suppression of ghrelin, and increases triglycerides in women," The Journal of Clinical Endocrinology & Metabolism, vol. 89, no. 6, pp. 2963–2972, 2004

Van Buul, V. J., Tappy, L., & Brouns, F. J. (2014). Misconceptions about fructose-containing sugars and their role in the obesity epidemic. Nutrition research reviews, 27(1), 119-30.

Vartanian, L.R., Schwartz, M.B. and Brownell, K.D. (2007) Effects of Soft Drink Consumption on Nutrition and Health: A Systematic Review and Meta-Analysis. American Public Health Association, 97, 4.

Vos M, Kimmons J, Gillespie C, Welsh J, (2008). Blanck H. Dietary fructose consumption among US children and adults: the Third National Health and Nutrition Examination Survey. Medscape J Med. 10(7):160

Vuilleumier S. (1993). Worldwide production of high-fructose syrup and crystalline fructose. Am. J. Clin. Nutr. ;58:733S–736S

Wang DD, Sievenpiper JL, de Souza RJ, Cozma AI, Chiavaroli L, Ha V, Mirrahimi A, Carleton AJ, Di Buono M, Jenkins AL, Leiter LA, Wolever TM, Beyene J, Kendall CW, Jenkins DJ. (2014). Effect of fructose on postprandial triglycerides: a systematic review and meta-analysis of controlled feeding trials. Atherosclerosis. 232(1): 125-133

Welsh, J. A., Sharma, A. J., Grellinger, L., Vos, M. B. (2011) Consumption of added sugars is decreasing in the United States. Am. J. Clin. Nutr. 94, 726–734

White J.S. (2014) Sucrose, HFCS, and Fructose: History, Manufacture, Composition, Applications, and Production. In: Rippe J. (eds) Fructose, High Fructose Corn Syrup, Sucrose and Health. Nutrition and Health. Humana Press, New York, NY

WHO, "Noncommunicable diseases," fact sheet, June 2018.

World Health Organization. Definition, Diagnosis and Classification of Diabetes Mellitus and its Complications. Report of a WHO consultation. Geneva: World Health Organization 1999

World Health Organization (2015). Guideline: Sugars Intake For Adults and Children. WHO Website. http://www.who.int/nutrition/publications/ guidelines/ sugars_intake/en/

Wirfalt E, Drake I & Wallstrom P (2013) What do review papers conclude about food and dietary patterns? Food Nutr Res 57, 10.3402/fnr.v57i0.20523

Wilson PW., Agostino RB., Parise H., Sullivan L., Meigs JB., (2005) Metabolic Syndrome as a Precursor of Cardiovascular Disease and Type 2 Diabetes Mellitus, AHA journals 112 (20); 3066-3072

Xi B, et al. Prevalence of metabolic syndrome and its influencing factors among the Chinese adults: the China Health and Nutrition Survey in 2009. Prev Med. 2013;57(6):867–71.

Xu, H., Li, X., Adams, H., Kubena, K., & Guo, S. (2018). Etiology of Metabolic Syndrome and Dietary Intervention. International journal of molecular sciences, 20(1), 128.

Yeh CJ, Chang HY, Pan WH. Time trend of obesity, the metabolic syndrome and related dietary pattern in Taiwan: from NAHSIT 1993–1996 to NAHSIT 2005–2008. Asia Pac J Clin Nutr. 2011;20(2):292–300.

Zimmet, P., Magliano, D., Matsuzawa, Y., Alberti, G., & Shaw, J. (2005). The metabolic syndrome: a global public health problem and a new definition. J Atheroscler Thromb, 12(6), 295-300.

Appendix I

Literature Review: Mind Map Diagram

Main Subject

Sub-sections/ Key Headers

Research Output

Temporal association between increased consumption of HFCS and prevalence of Obesity

Metabolism of Fructose increased obesity, CVD, Diabetes and MetS. However, some studies when they have adjusted for BW, they lost significance?

Is Fructose a concern?

Obesity Epidemic in parallel with rising levels of HFCS consumption. However, in the last 10 years, HFCS consumption decreases & Obesity increased?

1988 'syndrome X' by Reaven

1947 vague described android obesity

1989 'The deadly quarter' by kaplan

Historical perspective of MetS & concept evolution

Origins in 1920

1992 'The insulin resistance syndrome' by scientists

Historical timeline & concept evolution (timeline)

Fructose Effects on visceral adiposity & appetite

Consequences of Hepatic Fructose Metabolism

Fructose Effects on glucose homeostasis

Mechanisms linking Fructose to MetS

Effects of Fructose on Lipid Metabolism

Fructose Effects on Blood Pressure

8000 years ago, sugar cane first domesticated

Historical timeline & concept evolution (timeline)

Golden age of India, granulated sugar crystals

Historical perspective of sugars domestication

1960, high fructose corn syrup was introduced

1500, sugar production expended worldwide

1800, sugar becomes a food necessity

Diets and MetS

Physical activity and MetS

Etiology of MetS

Obesity and MetS

A *Metabolic Syndrome*

A+B

B *Fructose*

Fructose Metabolism in liver cells (Schematic diagram)

Fructose Metabolism

Fructose Absorption

Hepatic Metabolism

Intermediary fructose Metabolism

The global Epidemic of the MetS

Worldwide prevalence

Prevalence in a selection of countries worldwide

Middle East countries prevalence

WHO

EGIR

NSEP ATP III

Various definitions of MetS

IDF

Harmonized

Various definitions of MetS & criteria Evaluation (Table)

Perez pozo et al. 2010

Reflection on previous studies (t able)

Hosseini Esfahani et al. 2011

Previou studies investigating the association of fructose & MetS

Sun et al. 2011 & Shin et al. 2018

Ejtahed et al. 2015 & Silbernagel et al. 2011

Khosravi Boroujeni et al.2012

Mean Fructose Intake 1977-78 37g/day

Mean Fructose Intake 1988-94 54g/day

Sucrose Decreased & HFCS increased 1970-85

Evolution of Fructose Consumption

Mean Fructose Intake 1999-2004 49g/day

Evolution of the consumption of HFCS & sucrose in the US 1970-2006

Slight Decrease in Fructose intake 2008 onward

APPENDIX II

CONSENT FORM TO PARTICIPATE IN A RESEARCH STUDY (ARABIC)

1

أسس الموافقة على الإشتراك في دراسة تتعلق بالأبحاث الحيوية

تقييم مستويات ثنائي الفينول أ عند اللبنانيين وتقييم إرتباطه بالوضع الصحي لهم

رقم البروتوكول: IM.HT.03
الباحث: د. هاني تميم
العنوان: شارع القاهرة- بيروت – لبنان
تلفون : 01350000 ext: 5453
المكان الذي سوف تتم فيه الدراسة: المركز الطبي في الجامعة الأميركية في بيروت (AUBMC)

أنت مدعو(ة) للمشاركة ببحث علمي سريري سيجرى في الجامعة الأميركية في بيروت. الرجاء أن تأخذ(ي) الوقت الكافي لقراءة المعلومات التالية بتأن قبل أن تقرر(ي) إذا كنت تريد(ين) المشاركة أم لا. بإمكانك طلب إيضاحات أو معلومات إضافية عن أي شيء مذكور في هذه الإستمارة أو عن هذه الدراسة ككل.

إن الهدف من دراستنا هو قياس مستويات ثنائي الفينول أ (BPA) في عينة تمثل السكان اللبنانيين المقيمين في بيروت الكبرى، وتقييم إرتباط المستويات بمختلف الأمراض . كما نود أن نرى أيضا إذا كانت مستويات BPA تتغير مع مرور الوقت في كل شخص. ستتألف هذه الدراسة من مرحلتين، المرحلة الأولى عند بدء الدراسة والثانية بعد سنتين للمتابعة. سنقوم بتسجيل ما يقارب 500 مشارك في الدراسة التي ستتم في المركز الطبي في الجامعة الأميركية في بيروت (AUBMC) حيث سيتمّ حصر استخدام هذه الموافقة الموقعة ومعها البيانات التي يتمّ جمعها لغايات هذه الدراسة من دون أي استخدام آخر.

ال BPA مادة كيميائية مصنّعة تتعارض مع الهرمونات الطبيعية في الجسم. ومن الممكن العثور عليها في زجاجات من البلاستيك وحاويات المياه والزجاجات وأكواب الأطفال، والحاويات البلاستيكية، والبطانة الداخلية لعلب الطعام والمشروبات. قد يتناول البشر ال BPA إذا انتقل من الحاوية البلاستيكية إلى الطعام أو الشراب في ظل ظروف معينة. ويرتبط استهلاك ال BPA بالآثار الصحية الضارة بما في ذلك أمراض القلب وارتفاع ضغط الدم، ومرض السكري، والتغيرات في الكولسترول، والدهون الثلاثية، ومستوى هرمونات الغدة الدرقية. من الممكن أن مادة ال BPA تؤثر أيضا على المواد الجينية (DNA).

سيقوم الباحثون الميدانيون أصحاب شهادة (CITI) العاملون في شركة "الدولية للمعلومات" (Information International) المتعاقد معها استخدام الطريقة المباشرة لتعيين المشاركين. وسوف يقومون بزيارة المشاركين في مكان إقامتهم لشرح أهداف الدراسة وطريقة التنفيذ. ثم تأخذ موافقة المشاركين وسيتم إعطاء تفاصيل عن تاريخ ووقت الدراسة. و سيتم تسجيل اسم المشارك وتاريخ الميلاد، و أيام الأسبوع المتوافر فيها للمشاركة ورقم هاتف لإتاحة المجال للمتابعة. تحديد التاريخ الدقيق لتظيم الى المركز الطبي في الجامعة الأميركية في بيروت (AUBMC) وسوف تشمل كل زيارة 10 مشاركين سوف يقومون بالإجراءات المبينة أدناه.

إن مشاركتكم تعني أنكم ستقابلون شخصاً مؤهلاً يجري معكم دراسة تتضمّن العديد من الأسئلة حول الوضع الديمغرافي والاجتماعي والاقتصادي (العمر، والجنس، وموقع السكن، والتعليم، والمهنة والدخل)، ونمط الحياة (التدخين، الكحول، القهوة والنشاط البدني)، والحالة الصحية (التاريخ الطبي والأدوية)، والعادات الغذائية (الاستمارة الغذائية). وعلاوة على ذلك، سوف تخضعون لاختبار بدني لقياس الوزن والطول ومحيط الخصر وضغط الدم، ومعدل ضربات القلب. بالإضافة على ذلك سيتم فحص مستوى السكر بالدم بواسطة الاصبع، ويتضمن وخزة صغيرة واحدة في الاصبع لاخذ أقل من نقطة دم واحدة لإجراء الفحص. كما يطلب منكم الخضوع لسحب الدم الاختبارات الجينية المحددة (الحامض النووي) والفحوصات المخبرية (بما في ذلك مخزون السكر(HbA1c)، نسبة السكر الصباحي في الدم ، الكريانينين، الدهون، هرمونات الغدة الدرقية (TSH)، خمائر الكبد (SGPT و GGT)، الانسولين، الكريانينين البولية، الزلالي، فيتامين د (25 OH vit D)، الكورتيزول، الليبتين، البرولاكتين، البيتيد C. وعلاوة على ذلك، سيتم جمع البول لقياس مستويات ال BPA. وسوف تنجز هذه الفحوصات المخبرية مجانا، ولكن في وقت لاحق أثناء الدراسة.

خلال زيارتك، من المتوقع أن تكون مدة الانتهاء من الإجراءات خلال اليوم الواحد حوالي ساعة ونصف فقط، مقسمة بين 30 دقيقة لسحب الدم وجمع البول، و 60 دقيقة لملء الاستمارات لكل مشارك .ومن المتوقع ن تستغرق الزيارة مدة أقصاها 3 ساعات، بانتظار إلى أن سيكون هناك مشاركين آخرين يمرون بنفس العملية.

كانون الثاني 2014 رقم البروتوكول: IM.HT.03

بعد حوالي سنتين من الزيارة الأولى، سيتم الاتصال بكم هاتفياً لدعوتكم إلى استكمال الجزء الثاني من الدراسة وذلك من خلال زيارة المركز الطبي في الجامعة الأميركية في بيروت (AUBMC) والقيام بنفس الإجراءات التي قمتم بها في الزيارة الأولى.

على الرغم من أن أي دراسة قد تتوافق مع مخاطر لا يمكن التنبؤ بها، هذه الدراسة تحمل الحد الأدنى من المخاطر. لا تحمل أي من عمليات جمع البيانات أية مخاطر على المدى الطويل، وسوف يتم سحب الدم ضمن ظروف وقاية صحية صارمة وحجم الدم الإجمالي المطلوب هو 20 سم مكعب. ومن الآثار الجانبية الضئيلة التي من المحتمل أن تصيبكم: ألم معتدل، نزف محدود، رضّة خفيفة في موضع إدخال الإبرة. وقد تحدث في بعض الأحيان حالات إغماء أو دوار خفيف، ولكنها لا تدوم عادةً أكثر من دقائق قليلة.

ستقدم نتائج جميع الاختبارات التي أجريت مجاناً للمشاركين وذلك عبر الاتصال بهم وتزويدهم بنتائج الفحوصات المخبرية عند انتهائها. وعلاوة على ذلك، سيتم تعويض المشاركين عن نفقات التنقل بمبلغ 30,000 ليرة لبنانية عند وصولهم إلى المركز الطبي في الجامعة الأميركية في بيروت (AUBMC)، كما سيزود المشتركون بوجبة الفطور في ذات اليوم.

إذا وافقت على الإشتراك بهذا البحث سوف تبقى المعلومات سرية. وحدهم الأطباء بدائرة الأخلاقيات والمحققين في المؤسسات العامة يمكنهم الإطلاع على النتائج بناءً لأمر قانوني فقط.

سيتم تخزين كافة البيانات والعينات البيولوجية التي تم جمعها بطريقة سرية. وستتخذ جميع التدابير لضمان عدم حدوث أي خرق لخصوصية المشتركين. وعلاوة على ذلك، سيتم تخزين ما تبقى من عينات الدم والبول بشكل آمن إلى أجل غير مسمى في مختبر الدكتورة نادالي زغيب خويري في المركز الطبي في الجامعة الأميركية في بيروت (AUBMC). إذا اخترتم سحب موافقتكم من الدراسة، سيتم تدمير العينات الخاصة بك.

بناءً على طلبكم، سوف نزودكم بنتائج الفحوصات الجينية وشرح أهميتها لكم. سيتم الإبقاء على سرية المعلومات.

لوحظ أن أعرف ما إذا كنت على استعداد للمشاركة في هذه الدراسة. لديك الحق في قبول أو رفض المشاركة. في حال رفض المشاركة، لن يكون هناك أي خسارة للمنافع التي يقدمها المركز الطبي التابع للجامعة الأميركية في بيروت (AUBMC). كما يحق لكم الانسحاب من هذه الدراسة في أي وقت من دون خسارة المنافع التي يقدمها المركز الطبي التابع للجامعة الأميركية في بيروت (AUBMC). أيضاً، يحق للباحث انهاء مشاركتك بهذه الدراسة.

أوافق على المشاركة في هذه الدراسة والإجراءات المحددة أعلاه.
نعم_____ لا_____

أوافق على أن يتم التواصل معي للدراسات المستقبلية
نعم_____ لا_____

أوافق على أن يتم التواصل معي إذا كانت نتائج الفحوصات الجينية ذات أهمية طبية
نعم_____ لا_____

استخدام ما تبقى من عينات الدم والبول للدراسات المستقبلية
نود تخزين ما تبقى من عينات الدم والبول لاستخدام محتمل في دراسات مستقبلية. للقيام بذلك، قد يكون هناك في المستقبل متعاونين في الجامعة الأميركية في بيروت، أو في المؤسسات الأخرى في لبنان و/أو خارج لبنان. لن يتم أي عمليات وخز إضافية. وسيتم "ترميز" عينات الدم المخزّنة. *(تشير عبارة "ترميز" إلى قابلية التعريف والتعقب. لا يتم تعريف عينات الدم لغايات الأبحاث، ولكن يمكن ربطها بمصدرها عبر استخدام الرموز؛ إلا أن الباحث المسؤول أو المشرف الأساسي هو الوحيد الذي يحق له الحصول على اللائحة التي تحدد الرمز الخاص بكل مريض).*

أوافق على أن يتم استخدام ما تبقى من عينات الدم والبول للدراسات المستقبلية
نعم_____ لا_____

يمكن مشاركة عينات دمكم المرمزة مع باحثين آخرين لدراسات ذات صلة. ولن يعرف هؤلاء الباحثون هويتكم.

أوافق على مشاركة عينات دمي المرمزة مع باحثين آخرين لإجراء دراسات ذات صلة.
نعم_____ لا_____

إقرار المريض بالمشاركة في البحث:

أنا الموقع أدناه وبعد أن اطلعت واستوعبت كل جوانب هذا البحث وأجبت عن كل أسئلتي أوافق بملئ إرادتي على المشاركة في هذه الدراسة وأنا على علم تام بأنني أستطيع الإتصال بالدكتور هاني تميم على الرقم 01350000 المقسم 5453 أو بأي من ممثليه الضالعين بهذه الدراسة وذلك إذا أردت توجيه أي سؤال، كما أنني أعلم أنه فيما لو أن أسئلتي لم يجاوب عليها بطريقة مقنعة يمكنني الإتصال بأحد أعضاء لجنة الأخلاقيات على المقسم 5445. كما إنني أعلم أنه يمكنني الإنسحاب من المشاركة في هذه الدراسة في أي وقت شئت حتى بعد التوقيع على هذه الوثيقة وإن العناية التي أتلقاها لن تتأثر بهذا الإنسحاب وإنني سوف أزود بنسخة عن هذه الوثيقة.

_____ _____
إسم المريض أو ممثله القانوني/قريبه أو وصيه — التوقيع

_____
التاريخ و الساعة

_____ _____
إسم الشاهد — التوقيع
التاريخ و الساعة

إقرار الباحث باستلام التعهد بالإشتراك:

لقد أطلعت بالتفصيل على التعهد بالإشتراك في البحث مع _____ (إسم المريض، ممثله القانوني، قريبه، وصيه)، وأفهمت المريض الغاية من هذه الدراسة ومن أخطارها وفوائدها. لقد أجبت المشترك على جميع الأسئلة التي تقدم بها بوضوح تام وتعهدت له بإعلامه عن أي تغيير يطرأ في موضوع هذا البحث.

_____ _____
التوقيع — إسم الباحث أو ممثل المشترك

_____
التاريخ و الساعة

Institutional Review Board
American University of Beirut
17 FEB 2014
APPROVED

أسس الموافقة على الإشتراك في دراسة تتعلق بالأبحاث الجينية

تقييم مستويات ثنائي الفينول أ عند اللبنانيين وتقييم إرتباطه بالوضع الصحي لهم

رقم البروتوكول: IM.HT.03
الباحث: د. هاني تميم
العنوان: شارع القاهرة- بيروت – لبنان
تلفون : 01350000 ext: 5453
المكان الذي سوف تتم فيه الدراسة: المركز الطبي في الجامعة الأميركية في بيروت (AUBMC)

أنت مدعو(ة) للمشاركة ببحث علمي سريري سيجرى في الجامعة الأميركية في بيروت. الرجاء أن تأخذ(ي) الوقت الكافي لقراءة المعلومات التالية بتأن قبل أن تقرر(ي) إذا كنت تريد(ين) المشاركة أم لا. بإمكانك طلب إيضاحات أو معلومات إضافية عن أي شيء مذكور في هذه الإستمارة أو عن هذه الدراسة ككل.

إن الهدف من دراستنا هو قياس مستويات ثنائي الفينول أ (BPA) في عينة تمثل السكان اللبنانيين المقيمين في بيروت الكبرى، وتقييم إرتباط المستويات بمختلف الأمراض . كما نود أن نرى أيضا إذا كانت مستويات BPA تتغير مع مرور الوقت في كل شخص. ستتألف هذه الدراسة من مرحلتين، المرحلة الأولى عند بدء الدراسة والثانية بعد سنتين للمتابعة. سنقوم بتسجيل ما يقارب 500 مشارك في الدراسة التي ستتم في المركز الطبي في الجامعة الأميركية في بيروت (AUBMC) حيث سيتمّ حصر استخدام هذه الموافقة الموقّعة ومعها البيانات التي يتمّ جمعها لغايات هذه الدراسة من دون أي استخدام آخر.

ال BPA مادة كيميائية مصنّعة تتعارض مع الهرمونات الطبيعية في الجسم. ومن الممكن العثور عليها في زجاجات من البلاستيك وحاويات المياه والزجاجات وأكواب الأطفال، والحاويات البلاستيكية، والبطانة الداخلية لعلب الطعام والمشروبات. قد يتناول البشر ال BPA إذا انتقل من الحاوية البلاستيكية إلى الطعام أو الشراب في ظل ظروف معينة. ويرتبط استهلاك ال BPA بالآثار الصحية الضارة بما في ذلك أمراض القلب وارتفاع ضغط الدم، ومرض السكري، والتغيرات في الكولسترول، والدهون الثلاثية، ومستوى هرمونات الغدة الدرقية. من الممكن أن مادة ال BPA تؤثر أيضا على المواد الجينية (DNA).

سيقوم الباحثون الميدانيون أصحاب شهادة (CITI) العاملون في شركة "الدولية للمعلومات" (Information International) المتعاقد معها استخدام الطريقة المباشرة لتعيين المشاركين. وسوف يقومون بزيارة المشاركين في مكان إقامتهم لشرح أهداف الدراسة وطريقة التنفيذ. ثم تأخذ موافقة المشاركين وسيتم إعطاء تفاصيل عن تاريخ ووقت الدراسة. و سيتم تسجيل اسم المشارك وتاريخ الميلاد، و أيام الأسبوع المتوافر فيها للمشاركة ورقم هاتف لاتاحة المجال للمتابعة وتحديد التاريخ الدقيق لنقلهم الى المركز الطبي في الجامعة الأميركية في بيروت (AUBMC) وسوف تشمل كل زيارة 10 مشاركين سوف يقومون بالإجراءات المبينة أدناه.

إن مشاركتكم تعني أنّكم ستقابلون شخصاً مؤهّلاً يجري معكم دراسة تتضمّن العديد من الأسئلة حول الوضع الديمغرافي والاجتماعي والاقتصادي (العمر، والجنس، وموقع السكن، والتعليم، والمهنة والدخل)، ونمط الحياة (التدخين، الكحول، القهوة والنشاط البدني)، والحالة الصحية (التاريخ الطبي والأدوية)، والعادات الغذائية (الاستمارة الغذائية). وعلاوة على ذلك، سوف تخضعون لاختبار بدني لقياس الوزن والطول ومحيط الخصر وضغط الدم، ومعدل ضربات القلب. بالإضافة على ذلك سيتم فحص مستوى السكر بالدم بواسطة الاصبع، ويتضمن وخزة صغيرة واحدة في الاصبع لاخذ أقل من نقطة دم واحدة لإجراء الفحص. كما يطلب منكم الخضوع لسحب الدم الاختبارات الجينية المحددة (الحامض النووي) والفحوصات المخبرية (بما في ذلك مخزون السكر(HbA1c)، نسبة السكر الصباحي في الدم ، الكرياتينين، الدهون، هرمونات الغدة الدرقية (TSH)، خمائر الكبد (SGPT و GGT)، الانسولين، الكرياتينين البولية، الزلالي، فيتامين د (25 OH vit D), الكورتيزول، الليبتين، البروتاكتين، الببتيد C. وعلاوة على ذلك، سيتم جمع البول لقياس مستويات ال BPA. وسوف تنجز هذه الفحوصات المخبرية مجانا، ولكن في وقت لاحق أثناء الدراسة.

خلال زيارتك، من المتوقع أن تكون مدة الانتهاء من الإجراءات خلال اليوم الواحد حوالي ساعة ونصف فقط، مقسمة بين 30 دقيقة لسحب الدم وجمع البول, و 60 دقيقة لملء الاستمارات لكل مشارك .ومن المتوقع أن تستغرق الزيارة مدة أقصاها 3 ساعات، بالنظر إلى أن سيكون هناك مشاركين آخرين يمرون بنفس العملية.

بعد حوالي سنتين من الزيارة الأولى، سيتم الاتصال بكم هاتفياً لدعوتكم إلى استكمال الجزء الثاني من الدراسة وذلك من خلال زيارة المركز الطبي في الجامعة الأميركية في بيروت (AUBMC) والقيام بنفس الإجراءات التي قمتم بها في الزيارة الأولى.

على الرغم من أن أي دراسة قد تترافق مع مخاطر لا يمكن التنبؤ بها، هذه الدراسة تحمل الحد الأدنى من المخاطر. لا تحمل أي من عمليات جمع البيانات أية مخاطر على المدى الطويل، وسوف يتم سحب الدم ضمن ظروف وقاية صحية صارمة وحجم الدم الإجمالي المطلوب هو 20 سم مكعب. ومن الآثار الجانبية الضئيلة التي من المحتمل أن تصيبكم: ألم معتدل، نزف محدود، رضّة خفيفة في موضع إدخال الإبرة. وقد تحدث في بعض الأحيان حالات إغماء أو دوار خفيف، ولكنّها لا تدوم عادةً أكثر من دقائق قليلة.

ستقدم نتائج جميع الاختبارات التي أجريت مجاناً للمشاركين وذلك عبرالإتصال بهم وتزويدهم بنتائج الفحوصات المخبرية عند انتهائها. وعلاوة على ذلك، سيتم تعويض المشاركين عن نفقات التنقل بمبلغ 30,000 ليرة لبنانية عند وصولهم إلى المركز الطبي في الجامعة الأميركية في بيروت (AUBMC)، كما سيزود المشتركون بوجبة الفطور في ذات اليوم.

إذا وافقت على الإشتراك بهذا البحث سوف تبقى المعلومات سرية. وحدهم الأطباء ودائرة الأخلاقيات والمحققين في المؤسسات العامة يمكنهم الإطلاع على النتائج بناءً لأمر قانوني فقط.

سيتم تخزين كافة البيانات والعينات البيولوجية التي تم جمعها بطريقة سرية. وستتخذ جميع التدابير لضمان عدم حدوث أي خرق لخصوصية المشتركين. وعلاوة على ذلك، سيتم تخزين ما تبقى من عينات الدم والبول بشكل آمن إلى أجل غير مسمى في مختبر الدكتورة ناتالي زغيب خويري في المركز الطبي في الجامعة الأميركية في بيروت (AUBMC). إذا اخترتم سحب موافقتكم من الدراسة، سيتم تدمير العينات الخاصة بك.

بناءً على طلبكم، سوف نزودكم بنتائج الفحوصات الجينية وشرح أهميتها لكم. . سيتم الابقاء على سرية المعلومات.

أود أن أعرف ما إذا كنت على استعداد للمشاركة في هذه الدراسة. لديك الحق في قبول أو رفض المشاركة. في حال رفض المشاركة، لن يكون هنالك أي خسارة للمنافع التي يقدمها المركز الطبي التابع للجامعة الأميركية في بيروت (AUBMC). كما يحق لكم الانسحاب من هذه الدراسة في أي وقت من دون خسارة المنافع التي يقدمها المركز الطبي التابع للجامعة الأميركية في بيروت (AUBMC). أيضاً, يحق للباحث انهاء مشاركتك بهذه الدراسة.

أوافق على المشاركة في هذه الدراسة والإجراءات المحدّدة أعلاه.
نعم_____ **لا**_____

أوافق على أن يتم التواصل معي للدراسات المستقبلية
نعم_____ **لا**_____

أوافق على أن يتم التواصل معي إذا كانت نتائج الفحوصات الجينية ذات أهمية طبية
نعم_____ **لا**_____

استخدام ما تبقى من عينات الدم والبول للدراسات المستقبلية
نودّ تخزين ما تبقى من عينات الدم والبول لاستخدام محتمل في دراسات مستقبلية. للقيام بذلك، قد يكون هناك في المستقبل متعاونين في الجامعة الأميركية في بيروت، أو في المؤسسات الأخرى في لبنان و/أو خارج لبنان. لن يتمّ أي عمليات وخز إضافية. وسيتمّ "ترميز" عيّنات الدم المخزّنة. *(تشير عبارة "ترميز" إلى قابلية التعريف والتعقّب.لا يتمّ تعريف عينات الدم لغايات الأبحاث، ولكن يمكن ربطها بمصدرها عبر استخدام الرموز؛ إلاّ أنّ الباحث المسؤول أو المشرف الأساسي هو الوحيد الذي يحق له الحصول على اللائحة التي تحدّد الرمز الخاص بكل مريض).*

أوافق على أن يتم استخدام ما تبقى من عينات الدم والبول للدراسات المستقبلية
نعم_____ **لا**_____

ن مشاركة عينات دمكم المرمّزة مع باحثين آخرين لدراسات ذات صلة. ولن يعرف هؤلاء الباحثون هويتكم.

ق على مشاركة عيّنات دمي المرمّزة مع باحثين آخرين لإجراء دراسات ذات صلة.

_____ لا _____

إقرار المريض بالمشاركة في البحث:

أنا الموقع أدناه وبعد أن اطلعت واستوعبت كل جوانب هذا البحث وأجبت عن كل أسئلتي أوافق بملئ إرادتي على المشاركة في هذه الدراسة وأنا على علم تام بأنني أستطيع الإتصال بالدكتور هاني تميم على الرقم 01350000 المقسم 5453 أو بأي من ممثليه الضالعين بهذه الدراسة وذلك إذا أردت توجيه أي سؤال، كما أنني أعلم أنه فيما لو أن أسئلتي لم يجاوب عليها بطريقة مقنعة يمكنني الإتصال بأحد أعضاء لجنة الأخلاقيات على المقسم 5445. كما إنني أعلم أنه يمكنني الإنسحاب من المشاركة في هذه الدراسة في أي وقت شئت حتى بعد التوقيع على هذه الوثيقة وإن العناية التي أتلقاها لن تتأثر بهذا الإنسحاب وإنني سوف أزود بنسخة عن هذه الوثيقة.

_____ _____

إسم المريض أو ممثله القانوني/قريبه أو وصيه — التوقيع

_____

التاريخ و الساعة

_____ _____

إسم الشاهد — التوقيع

التاريخ و الساعة

إقرار الباحث باستلام التعهد بالإشتراك:

لقد أطلعت بالتفصيل على التعهد بالإشتراك في البحث مع_____ (إسم المريض، ممثله القانوني، قريبه، وصيه)، وأفهمت المريض الغاية من هذه الدراسة ومن أخطارها وفوائدها. لقد أجبت المشترك على جميع الأسئلة التي تقدم بها بوضوح تام وتعهدت له بإعلامه عن أي تغيير يطرأ في موضوع هذا البحث.

_____ _____

التوقيع — إسم الباحث أو ممثل المشترك

_____

التاريخ و الساعة

Institutional Review Board
American University of Beirut
17 FEB 2014
APPROVED

كانون الثاني: 2014 رقم البروتوكول: IM.HT.03

APPENDIX III

CONSENT FORM TO PARTICIPATE IN A RESEARCH STUDY (ENGLISH)

Consent to participate in a genetic research study

Assessment of BPA levels and their association with the health status among Lebanese population

Protocol number: IM.HT.03
Investigator: Dr. Hani Tamim
Address: American University Hospital
Hamra Street
Beirut, Lebanon
Phone: (01) 350 000 ext: 5453

Site where the study will be conducted: AUBMC

You are being asked to participate in a clinical research study conducted at the American University of Beirut. Please take time to read the following information carefully before you decide whether you want to take part in this study or not. Feel free to ask the representative of the contracted company if you need more information or clarification about what is stated in this form and the study as a whole.

The aim of our study is to measure Bisphenol A (BPA) levels in a representative sample from the Lebanese population residing in Greater Beirut, and to assess if it is related to different diseases. We also would like to see if BPA measures change over time in any person. This study will be composed of 2 stages; at baseline and a 2-year follow up. We will be recruiting approximately 500 subjects and study will be conducted at AUBMC whereby this informed consent along with the data collected will be used for this study only.

BPA is a synthetic chemical that interferes with the natural hormones in the body. It can be found in plastic bottles and water containers, baby bottles and toddler cups, plastic ware, the inner lining of food cans and beverages. Humans may ingest BPA if it leaches from the plastic container into the food or drink under certain conditions. Consumption is associated with adverse health effects including heart disease, high blood pressure, diabetes, changes in cholesterol, triglycerides, and thyroid levels. BPA can also affect the expression of DNA material, called 'epigenetic effect.

The CITI certified field workers employed by the contracted company (Information International) will use the direct approaching method to recruit the cohort. They will visit the respondents in their residence to explain the study aims and method of implementation. Then the respondents will be consented and given the details of the date and time of the study. The name, date of birth, availability on week days and telephone number of the potential participant will be recorded for further follow up to specify the exact date for taking them to AUBMC. Each visit will include 10 participants who will complete the procedures described below.

Participating in this study means that you will sit with a certified research assistant who will conduct a survey which includes multiple questions about the demographic and socioeconomic status (Age, gender, location, education, occupation, income), lifestyle (smoking, alcohol, coffee, physical activity),

health status (medical history and medication), and dietary habits (Food Frequency Questionnaire). Moreover, you will undergo a physical exam to measure weight, height, waist circumference, blood pressure, and heart rate. Moreover, your blood sugar will be checked by a fingerstick, which means a very small prick will be done to your finger to get less than a drop of blood to do the test. You will also be asked to have blood withdrawn for specific genetic testing (DNA methylation) and clinical laboratory tests (including HBA1c, fasting blood sugar, creatinine, lipid profile, TSH, SGPT, GGT, fasting insulin, urinary creatinine, microalbuminuria, 25 OH vit D, Cortisol, leptine, C-peptide, prolactin). Moreover, urine will be collected for measuring BPA levels. These tests will be done free of charge, but will be done at a later time during the study.

During your visit, the duration for completing the procedures is expected to be for around an hour and a half over one day only, divided between 30 minutes for blood withdrawal and urine collection and 60 minutes for filling the surveys for each participant. Your total visit time to AUBMC is expected to be for a maximum of 3 hours, given that there will be other participants undergoing the same process.

After around 2 years from the baseline visit, you will be contacted by phone to be invited to complete the second part of the study (2-year follow-up stage) by visiting the AUBMC and going through the same process as the one described at baseline.

Although any study may be associated with any unforeseeable risk, this proposal has minimal risk. None of the data collection measures bare any long term hazards, and all blood withdrawal will be done under sterile hygienic conditions and the total volume required is 20 cc. Possible side effects include mild pain, bleeding, bruising at the site of the needle insertion. Fainting or light-headedness can sometimes occur, but usually last only a few minutes.

The results of all tests conducted will be freely provided to the participants by calling them and providing them with the results of the test upon its completion. Moreover, the participants will be compensated for travel expenses with 30,000 LBP upon arriving to AUBMC. In addition, we will provide the participants with breakfast the same day.

If you agree to participate in this research study, the information will be kept confidential. Unless required by law, only the study doctor and designee, the ethics committee and inspectors from governmental agencies will have direct access to your information collected.

All data and biological samples collected will be stored in a confidential manner. These measures will all be conducted ensuring there is no breach of participants' privacy. Moreover, the remaining blood and urine samples will be stored securely indefinitely in Dr. Nathalie Zgheib Khoueiry's laboratory at the AUBMC. If you elect to withdraw your consent for the study, your samples will be destroyed.

You may ask that we provide you with the genetic results and explain their significance to you. The information will be kept confidential.

I would like to know if you would be willing to participate in this study. You have the right to accept or decline participation. Refusing to participate will not involve any loss of benefits offered in the future by AUBMC. Moreover, you are entitled to withdraw from the study at any time without any loss of benefits offered by AUBMC at any time.

I agree to participate in this study and the procedures explained above.

YES ……. NO…….

I agree to be contacted for future studies

YES ……. NO…….

I would like to be contacted if the genetic test results are significant

YES ……. NO…….

Using remaining blood and urine for other future studies

We would like to keep the remaining blood and urine samples for potential use in other future studies. To do so, there might be future collaborators at AUB, at other institutions in Lebanon and/or outside Lebanon. There will be no extra prick. The stored blood and urine samples will be coded (*"Coded" means identifiable, traceable. Blood* and urine *samples that are unidentified for research purposes but can be linked to their source through the use of codes; however, the principal investigators or VMP will be the only ones to have the list linking patients to the codes assigned.)*

I agree to permit the use of the remaining blood and urine sample for future studies

YES ……. NO…….

Your coded blood and urine samples may be shared with other investigators for related studies. These investigators will not know your identity.

I agree to have my coded blood and urine samples shared with other investigators for related studies.

YES ……. NO…….

Patient's Participation:

I have read and understood all aspects of the research study and all my questions have been answered. I voluntarily agree to be a part of this research study and I know that I can contact Dr. Hani Tamim at 01350000 extension: 5453 or any of his/her designee involved in the study in case of any questions. If I felt that my questions have not been answered, I can contact the Institutional Review Board for human rights at 01350000 extension: 5445. I understand that I am free to withdraw this consent and discontinue participation in this project at any time, even after signing this form, and it will not affect the care I might receive at AUBMC. I also understand that my participation may be ended by investigator at anytime. I know that I will receive a copy of this signed informed consent.

_____ _____

Name of patient or Legal Representative or Parent/Guardian — Signature

_____

Date & Time

_____ _____

Witness's Name — Signature

_____

Date & Time

Investigator's Statement:

I have reviewed, in detail, the informed consent document for this research study with _____ _____ (name of patient, legal representative, or parent/guardian) the purpose of the study and its risks and benefits. I have answered all the patient's questions clearly. I will inform the participant in case of any changes to the research

_____ _____

Name of Investigator or designee — Signature

_____

Date & Time

Institutional Review Board
American University of Beirut
17 FEB 2014
APPROVED

APPENDIX IV

DATA COLLECTION FORM (ARABIC)

تقييم مستويات الBPA وارتباطها بالحالة الصحية بين السكان اللبنانيين

الاسم:	الحروف الأولى للإسم:	رقم المشارك:
رقم الهاتف:		التاريخ:

العوامل الديموغرافية:

تاريخ الميلاد:	الجنس: □ذكر □ أنثى
الحالة الاجتماعية: □ متزوج □ أعزب □ أرمل □ مطلق □ خاطب	

الاجتماعية والاقتصادية:

هل كنت مقيم خارج لبنان خلال العام الماضي : نعم كلا	
إذا كانت الإجابة بنعم، المكان _____ المدة _____	
مكان الإقامة _____	
طبيعة العمل _____	
ما هو دخلك في الأسرة	□ <600$ □ 600-999$ □ 1000-2000 $ □ >2000$ □ لا أعلم □ رفضت الإجابة
ما هو أعلى مستوى تعليمي أكملته؟	□ لم ألتحق بالمدرسة □ المرحلة الإبتدائية □ المرحلة المتوسطة □ المرحلة الثانوية □ دبلوم تعليم تقني/فني □ شهادة جامعية □ رفضت الإجابة
ما هو عدد الاشخاص الذين يسكنون في منزلكم (بما في ذلك الأقارب, أفراد العائلة أو الخدم الذين يسكنون معك بشكل جزئي)؟	
كم عدد الغرف في منزلكم (باستثناء المطبخ والحمامات والممرات والكراج والشرفات المفتوحة)؟	

تاريخ التدخين			
السجائر	هل تدخن(ي) السجائر حاليا ؟	□ نعم □ كلا	إذا كان الجواب نعم، كم سيجارة في اليوم؟_____ منذ متى؟_____
	إذا لا، هل أنت مدخن(ة) سجائر سابق(ة)؟	□ نعم □ كلا	إذا كان الجواب نعم، متى توقّفت؟_____
النرجيلة / الشيشة	هل تدخن(ي) النرجيلة حاليا ؟	□ نعم □ كلا	إذا كان الجواب نعم، كم نرجيلة في اليوم؟_____ منذ متى؟_____
	إذا لا، هل أنت مدخن(ة) نرجيلة سابق(ة)؟	□ نعم □ كلا	إذا كان الجواب نعم، متى توقّفت؟_____
الكحول			
هل تشرب الكحول حاليا؟		□ نعم □ كلا	إذا كانت الإجابة نعم، حدد النوع_____ كم كوب في اليوم؟_____ منذ متى؟_____
هل كنت تشرب الكحول سابقا		□ نعم □ كلا	إذا كان الجواب نعم، متى توقّفت؟_____
القهوة			
هل تشرب القهوة حاليا؟		□ نعم □ كلا	إذا كان الجواب نعم، كم كوب في اليوم؟_____
النشاط البدني			
خلال السبعة أيام الماضية، كم مرة مارست الأنشطة البدنية القوية مثل رفع الأوزان الثقيلة، والتمارين الرياضية، أو ركوب الدراجات بسرعة لفترة لا تقل عن 10 دقائق أو أي نشاط يتطلب الجهد البدني الشاق ويسبب صعوبة بالتنفّس)؟			_____ أيام في الأسبوع □ لم أمارس الأنشطة البدنية القوية كم من الوقت قضيت على المعدل لممارسة الأنشطة البدنية القوية؟ _____ساعات _____ دقائق؟ خلال ال 3 أشهر الماضية، كم عدد الأسابيع التي مارست بها الأنشطة البدنية القوية؟ _____ أسابيع
خلال السبعة أيام الماضية ، كم مرة مارست الأنشطة البدنية المعتدلة مثل رفع الأوزان الخفيفة، أو ركوب الدراجات، أو ممارس رياضة التنس أو أي نشاط يتطلب الجهد البدني المعتدل ويسبب صعوبة خفيفة بالتنفّس (لا تشمل المشي) ؟			_____ أيام في الأسبوع □ لم أمارس الأنشطة البدنية المعتدلة كم من الوقت قضيت على المعدل لممارسة الأنشطة البدنية المعتدلة ؟ _____ساعات _____ دقائق؟ خلال ال 3 أشهر الماضية، كم عدد الأسابيع التي مارست بها الأنشطة البدنية المعتدلة ؟ _____ أسابيع
خلال السبعة أيام الماضية ، كم مرة مارست رياضة المشي لفترة لا تقل عن 10 دقائق؟ و هذا يشمل المشي في المنزل و مكان العمل و المشي للتنقل اليومي أو الرياضة أو المتعة			_____ أيام في الأسبوع □ لم أمارس الأنشطة البدنية المعتدلة كم من الوقت قضيت على المعدل لممارسة رياضة المشي؟ _____ساعات _____ دقائق؟ خلال ال 3 أشهر الماضية، كم عدد الأسابيع التي مارست رياضة المشي؟ _____ أسابيع
خلال السبعة أيام الماضية ، ما هي الفترة الزمنية التي أمضيتها جالسا؟ و هذا يشمل الجلوس وراء مكتب أو خلال زيارة الأصدقاء أو الجلوس للقراءة أو مشاهدة التلفاز أو السفر على متن حافلة			_____ساعات _____ دقائق؟ خلال ال 3 أشهر الماضية، كم عدد الأسابيع التي اتبعت فيها هذا الكم من الوقت جالسا ؟ _____ أسابيع

التّاريخ الطبي:

مرض الشريان التاجي:

هل لديك أي من أفراد الأسرة الذين تم تشخيصهم بمرض الشريان التاجي أو ماتوا فجأة؟	□ نعم □ كلا إذا كان الجواب نعم حدد من:_____	في أي سن: _____
هل قيل لكم من قبل طبيب أنكم أصبتم بنوبة قلبية؟	□ نعم □ كلا	إذا كان الجواب نعم، حدد متى:_____
هل خضعت لعملية تمييل (قسطرة) شرايين القلب؟	□ نعم □ كلا	إذا كان الجواب نعم، حدد متى:_____
هل تم وضع رصور (الدعامة)؟	□ نعم □ كلا	إذا كان الجواب نعم، حدد متى:_____
هل خضعت لعملية جراحية لتغيير شرايين القلب؟	□ نعم □ كلا	إذا كان الجواب نعم، حدد متى:_____

ارتفاع ضغط الدم:

هل قيل لكم من قبل طبيب أو أحد العاملين في مجال الرعاية الصحية أن لديكم ارتفاع ضغط الدم؟	□ نعم □ كلا	إذا كان الجواب نعم، حدد متى:_____
هل خضعت لقياس ضغط الدم من قبل الطبيب أو أحد مقدمي الرعاية الصحية؟	□ نعم □ كلا	إذا كان الجواب نعم، حدد متى:_____ حدد النتيجة:_____
هل تخضعون لأي علاج لارتفاع ضغط الدم؟	□ نعم □ كلا	إذا كان الجواب نعم، حدد النوع: □ تعديل نمط الحياة □ الأدوية:_____

داء السكري:

هل قيل لكم من قبل طبيب أو أحد العاملين في مجال الرعاية الصحية أنكم تعانون من ارتفاع نسبة السكر في الدم أو من مرض السكري؟	□ نعم □ كلا	إذا كان الجواب نعم، حدد متى:_____
هل خضعت لقياس نسبة السكر في الدم من قبل طبيب أو العاملين في مجال الرعاية الصحية؟	□ نعم □ كلا	إذا كان الجواب نعم، حدد متى:_____ حدد النتيجة:_____
هل تخضعون لأي علاج لارتفاع السكر في الدم أو لمرض السكري؟	□ نعم □ كلا	إذا كان الجواب نعم، حدد النوع: □ تعديل نمط الحياة □ الأدوية:_____

ارتفاع مستوى الدهون في الدم:

هل قيل لكم من قبل طبيب أو أحد العاملين في مجال الرعاية الصحية أنكم تعانون من ارتفاع نسبة الكولسترول أو الدهون الثلاثية؟	□ نعم □ كلا	إذا كان الجواب نعم، حدد متى:_____
هل خضعت لقياس الكولسترول من قبل طبيب أو العاملين في مجال الرعاية الصحية؟	□ نعم □ كلا	إذا كان الجواب نعم، حدد متى:_____ حدد النتيجة:_____
هل تخضعون لأي علاج لارتفاع ارتفاع مستوى الدهون في الدم؟	□ نعم □ كلا	إذا كان الجواب نعم، حدد النوع: □ تعديل نمط الحياة □ الأدوية:_____

مرض الغدة الدرقية:

هل قيل لكم من قبل طبيب أو أحد العاملين في مجال الرعاية الصحية أنكم تعانون من مرض الغدة الدرقية؟	□ نعم □ كلا	إذا كان الجواب نعم، حدد متى:_____ حدد طبيعة المرض:_____
هل خضعت لقياس هرمونات الغدة الدرقية من قبل طبيب أو العاملين في مجال الرعاية الصحية؟	□ نعم □ كلا	إذا كان الجواب نعم، حدد متى:_____ حدد النتيجة:_____
هل تخضعون لأي علاج لمرض الغدة الدرقية؟	□ نعم □ كلا	إذا كان الجواب نعم، حدد النوع: □ تعديل نمط الحياة □ الأدوية:_____
هل لديك أي من أفراد الأسرة الذين تم تشخيصهم بمرض الغدة الدرقية؟ (أب، أم، اخ، أخت، جد، جدة)	□ نعم □ كلا	إذا كان الجواب نعم حدد من:_____

تاريخ أمراض السرطان:

هل قيل لكم من قبل طبيب أو أحد العاملين في مجال الرعاية الصحية أنكم تعانون من مرض السرطان ؟	□ نعم □ كلا	إذا كان الجواب نعم، حدد متى:_____ حدد طبيعة المرض:_____
هل تخضعون لعلاج كيمياني أو أي علاج آخر لمرض السرطان؟	□ نعم □ كلا	إذا كان الجواب نعم، حدد النوع: _____
هل لديك أي من أفراد الأسرة الذين تم تشخيصهم بمرض السرطان؟ (أب، أم، اخ، أخت، جد، جدة)	□ نعم □ كلا	إذا كان الجواب نعم حدد من:_____ حدد طبيعة المرض:_____

تاريخ الكسور:

هل عانيت من أيّ كسر في العظم؟	□ نعم □ كلا
إذا كان الجواب نعم	حدد أين:_____ العمر عند حصول الكسر:_____ كيف تم الكسر؟ (الوقوع من إرتفاع، حادث سير) _____

أمراض أخرى:

هل قيل لكم من قبل طبيب أو أحد مقدمي الرعاية الصحية أن لديك أي من التالي:		
السكتة الدماغية	□ نعم □ كلا	إذا كان الجواب نعم، حدد متى:_____
التهاب المفاصل	□ نعم □ كلا	إذا كان الجواب نعم، حدد متى:_____
التهاب الشعب الهوائية المزمن أو انتفاخ الرئة	□ نعم □ كلا	إذا كان الجواب نعم، حدد متى:_____
أمراض الكبد	□ نعم □ كلا	إذا كان الجواب نعم، حدد متى:_____

هل تعاني من أمراض أخرى؟

زيارة طبيب الأسنان:

هل قمت بزيارة طبيب الأسنان في العام الماضي؟	□ نعم □ كلا	إذا كان الجواب نعم، حدد متى:_____
هل تم وضع الحشوات في العام الماضي ؟	□ نعم □ كلا	إذا كان الجواب نعم، حدد متى:_____

الأدوية: (إذا لم تتوفر الأدوية الرجاء الاتصال بالمشترك)

الاسم (العلامة التجارية و الاسم العام)	الجرعة	تاريخ بدأ الاستعمال

مراجعة عامة:

هل شعرت بتغيير في الوزن خلال ال 3 أشهر الماضية؟		□ الوزن مستقر □ وزن مفقود:_____ كلغ □ وزن مكتسب:_____ كلغ
للنساء فقط	متى كانت آخر دورة شهرية؟_____	
	هل أنت في مرحلة: □ قبل انقطاع الطمث □ بعد انقطاع الطمث	إذا في مرحلة قبل انقطاع الطمث: □ الدورة الشهرية منتظمة □ الدورة الشهرية غير منتظمة
هل تعانين من:	□ حب الشباب □ الشعرانية	

إستفتاء حول وتيرة إستهلاك الطعام

الاسم:	الحروف الاولى للإسم:	رقم المشارك:

إستبيان وتيرة إستهلاك الطعام. يرجى منك التفكير بالنمط الغذائي الخاص بك الذي اتّبعته خلال **العام السابق**. الرجاء تحديد الكمية المتناولة عادةً **في اليوم** أو **الأسبوع** أو **الشهر** لكل من المواد الغذائية التالية

Code	الطعام	مرجع حجم الحصّة	حجم الحصّة	في اليوم	في الأسبوع	في الشهر	نادراً/أبداً
	مثال: أرز، أبيض، مطبوخ	Side A/ Page 5	1/2 A 11		3		
	جبن (غني بالدسم/صفراء)	حصة واحدة = مثلث/مربع	3 B1, thick 2	1			
	بقول: عدس، فاصوليا، حمّص، الخ، مطبوخة	Side A or B Side A/Page 4	1.5 cups		1		
1	**الخبز والحبوب**						
1.1	خبز أبيض	رغيف خبز عربي كبير/					
		رغيف خبز عربي وسط/					
		خبز فرنجي (baguette)					
		توست وسط					
1.2	خبز أسمر أو مصنوع من القمح الكامل	رغيف خبز عربي كبير/					
		رغيف خبز عربي وسط/					
		خبز فرنجي (baguette)					
		توست وسط					
1.3	تنور / مرقوق	رغيف					
1.4	حبوب الفطور، عادي/نخالة/ سكر	Side A					
		(علبة صغيرة 35g)					
1.5	منتوجات الكعك	Finger size: small/long Round kaak: small/medium Page 13					
1.6	أرز، أبيض، مطبوخ	Side A/ Page 5					
1.7	معكرونة، سادة، مطبوخة	Side A/ Page 5					
1.8	قمح، كامل، مطبوخ/برغل	Side A/ Page 5					
1.9	أرز/ معكرونة مصنوع من القمح الكامل	Side A/ Page 5					
2	**مشتقّات الحليب**						
2.1	حليب قليل الدسم (٢ % دهون)	Side A					
2.2	حليب كامل الدسم	Side A					
2.3	لبن قليل الدسم /خالٍ من الدسم	Side A					
		عيران					
2.4	لبن كامل الدسم	Side A					

Code	الطعام	مرجع حجم الحصّة	حجم الحصّة	في اليوم	في الأسبوع	في الشهر	نادراً/أبداً
		عيران					
2.5	جبن (غني بالدسم/صفراء)	حصة واحدة = مثلث/مربع Side A or B					
2.6	جبن (قليل الدسم/لايت/بيضاء)	حصة واحدة = مثلث/مربع Side A or B					
2.7	لبنه، عادي	Side A					
2.8	لبنه، لايت/ خالية الدسم	Side A					
3	**الفاكهة والعصائر**						
3.1	الحمضيّات: برتقال ,غريفون	حبّة واحدة وسط / Side A					
3.2	فاكهة ذات اللون الأصفر أو البرتقالي الداكن (درّاق، خوخ، الخ)	حبّة واحدة وسط / Side A					
3.3	فراولة	10 فراولة/ Side A					
3.4	عنب	10 عنب/ Side A					
3.5	فاكهة أخرى: موز، / تفاح، طازج	حبّة واحدة وسط					
3.6	فاكهة مجفّفة: زبيب ، تمر مشمش	زبيب (1 ملعقة طعام)، تمر/ مشمش (حبّة واحدة)					
3.7	عصير فاكهة طازج	Side A					
3.8	مشروبات بطعم الفاكهة: تنكة/بلاستيك	تنكة/Side A					
3.9	مشروبات بطعم الفاكهة: ممعبّأة في زجاجات /كرتونة	كرتونة / زجاجة صغيرة Side A					
3.10	فاكهة معلّبة	Peach/ apricot = ½ fruit, Pineapple = 1 slice					
4	**الخضار**						
4.1	سلطة خضراء: خس، فلفل أخضر، خيار،نعنع..	Side A/ Page 8					
4.2	خضار ذات اللون الأخضر أو الأصفر الداكن (سبانخ، هندبة، ملوخيّة، جزر...)	Side A/ Page 4					
4.3	بندورة، طازجة، حجم وسط	10 cherry/ حبّة واحدة					
4.4	ذرة / بازلاء خضراء، مطبوخة	Side A/ Page 4					
4.5	ذرة / بازلاء خضراء، معلّبة	Side A/ Page 4					
4.6	بطاطا مشويّة/ مسلوقة/ مهروسة	حبّة واحدة/ Side A					
4.7	قرع، كوسى، باذنجان/ مطبوخ	Side A/ 1 med. stuffed					
4.8	قرنبيط/ ملفوف/ بروكولي	Side A/ Page 4					
4.9	خضار أخرى معلّبة (بالميتو- فطر-هليون)	Side A/ Page 4					
4.10	عصير خضار طازج: بندورة/ جزر	Side A					
5	**اللحوم وبدائلها**						
5.1	بقول: عدس، فاصوليا، حمّص..مطبوخة/ غير معلبة	Side A/ Page 4					
5.2	بقول معلّبة (فول/ فاصوليا ...) تنك-زجاج	Side A/ Page4					

Code	الطعام	مرجع حجم الحصّة	حجم الحصّة	في اليوم	في الأسبوع	في الشهر	نادراً/أبداً
5.3	مكسّرات وبذور: فول سوداني، لوز/جوز ، بذور دوّار الشمس	Side A/ small bag Page 4					
5.4	لحم أحمر (بقر، عجل، غنم)	Side A– مفروم					
		Steak -Side B/ Thickness					
5.5	دواجن	ساق/فخذ/صدر/جوانح Thickness/Side B					
5.6	سمك/ ثمار البحر طازج	Side B/Thickness					
		قريدس: 1 وسط					
		كالماري: 1 وسط					
		كراب: 1 أصبع					
5.7	سمك، معلّب (تونا، سردين)	تنكة كبيرة/ تنكة صغيرة Page 19					
5.8	بيضة، كاملة	١ بيضة					
5.9	لحوم الأعضاء (كبد، كلاوي، نخاع)	Side B/ Thickness					
5.10	لحوم باردة: مرتديلا، جانبون، سلامي، حبش، الخ	شريحة واحدة Side B/ Thickness					
5.11	سجق، مقانق- غير معلب	حجم مقانق-Side B/ Thickness					
5.12	سجق، مقانق، هوت دوغ - معلّب	حجم مقانق-Side B/ Thickness حجم هوت دوغ					
6	**الدهون والزيوت**						
6.1	زيت نباتي: ذرة/ دوّار الشمس/ صويا	Side A					
6.2	زيت زيتون (يتضمن مع الزعتر)	Side A					
6.3	زيتون	1 حبة					
6.4	زبدة	Side A					
6.5	سمن	Side A					
6.6	مايونيز	Side A					
6.7	طحينة	Side A					
7	**الحلويات**						
7.1	كيك، كوكيز، دونات، مافن، كرواسان	Page 14, 15, 16 Side B/ Thickness					
7.2	بوظة	1 scoop/ Page 9 /1 stick					
7.3	لوح شوكولا	1 شوكولا وسط					
7.4	سكر، عسل، مربّى، دبس, كريمة شوكولا chocolate spread	Side A					
7.5	حلويات عربيّة، بقلاوة، معمول، كنافه	Thickness /Side B كنافه مع كعك					
8	**المشروبات**						
8.1	مشروبات غازيّة، عادي	Side A/ 1 can (330 mL)					

Code	الطعام	مرجع حجم الحصّة	حجم الحصّة	في اليوم	في الأسبوع	في الشهر	نادراً/أبداً
8.2	مشروبات غازيّة ، دايت	Side A/ 1 can (330 mL)					
8.3	قهوة تركية	Side A					
8.4	قهوة/نسكافيه أو شاي	Side A					
8.5	شراب الشوكولا أو الكاكاو الساخن	Side A					
8.6	بيرة، عادي	Side A/ 1 bottle					
8.7	نبيذ: أحمر، أبيض، أو وردي	Side A					
8.8	الخمور: ويسكي، فودكا، جين، رَم	Side A					
8.9	مياه	Side A/ bottle (0.5 L)					
9	**مأكولات أخرى**						
9.1	مناقيش، زعتر، جبنة	منقوشة كبيرة / صغيرة bouchee					
9.2	بطاطا مقليّة	Side A / Page 4					
9.3	رقائق البطاطا	XS/S/M/L/XL Page 20					
9.4	فلافل دون خبز	1 فلافل، حجم وسط					
9.5	سندويش شاورما	سندويش، حجم وسط					
9.6	برغر (لحمة، دجاج، سمك)	Side B /1 medium					
9.7	بيتزا	Side B/ Thickness					
9.8	حساء معلّب	Side A/ Page 3					
9.9	كاتشب	Side A					
9.10	خردل	Side A					

10.1. كم مرة تتبل طعامك مع صلصة الطماطم المكونة **من الطماطم والبصل والثوم مع زيت الزيتون؟**
---------- عدد مرات باليوم / الأسبوع / الشهر؟

10.2. هل تستهلك لحوم الدجاج أو الديك الرومي بدلا من اللحم الأحمر: البقر، العجل، لحم الخنزير، همبرغر، أو السجق؟
------ نعم ------ لا

هل هناك أي أطعمة أخرى غير تلك المذكورة أعلاه تتناولها **عادةً مرة في الأسبوع على الأقل؟**

مثال: ***باتيه، صلصة الكريمه، شوفان، coffee creamer, energy drink*** الخ (لا تشمل التوابل الجافّة). لا تسجّل الأطعمة التي تم ذكرها في القسم السابق.

أطعمة أخرى تتناولها عادةً مرة في الأسبوع على الأقل	حجم الحصّة الإعتيادي	حصّة في الأسبوع

إستفتاء حول العادات الغذائيّة

1- هل تعلم ما هو ثناني الفينول أ (BPA) ؟	□ نعم □ كلا
2- هل أنت على علم بوجود زجاجات بلاستيكية/تابروير خالية من BPA؟	□ نعم □ كلا

		دائما 6-7 x/week	معظم الوقت 4- 5x/week	مرات قليلة 2-3 x/week	نادرا 1x/week to 2x/month	أبدا/ كلا	لا أعرف
3	هل تخزّن الأطعمة في حاويات بلاستيكيّة؟						
4	هل تسخّن الأطعمة في حاويات بلاستيكيّة؟						
5	هل تتأكّد من أنّ الحاويات البلاستيكيّة التي تستخدمها خالية من مادّة ال BPA؟						
6	هل تسخّن الأطعمة المغلّفة بنايلون لاصق؟						
7	هل تشرب المياه المعبّأة في قناني بلاستيكيّة؟						
	7.1 من المياه المعبأة في زجاجات البلاستيك: ---------- أكواب / يوم 7.2 من مبرد المياه: ---------- أكواب / يوم						
8	هل تعيد إستخدام قناني المياه البلاستيكيّة؟						
9	هل تشرب من قناني مياه قد تركتها في سيّارتك؟						
10	هل تتناول الطعام خارج المنزل؟ (في المطاعم، في الحانات التي تقدّم وجبات خفيفة، الخ)						
11	كم مرّة في الأسبوع تقوم بشراء الوجبات السريعة والجاهزة (delivery)؟						
12	هل تشتري المشروبات الغازيّة المعبّأة في علب تنك و في قناني بلاستيكيّة؟						
13	هل تستهلك معجون الطماطم/ رب البندورة المعلبة؟						

المأخوذ الغذائي خلال الأربع وعشرين ساعة الأخيرة

نرجو منك أن تتذكر ما تناولتِه من طعام أو شراب في الأمس منذ نهوضك في الصباح وحتى اليوم التالي.

التاريخ:----/----/----------

اليوم في الأسبوع:----------

الوقت	الطعام الذي تناولتِه	الكمية	طريقة التحضير

هل كان الأمس يوماً عادياً؟

- نعم
- لا، حدد: _____

- متى كانت آخر مرة تناولت فيها الطعام؟ _____

Physical Exam Form

Name of the participant: ---------- Initials:---------- Study ID number: ----------

		Results النتائج	Healthy ranges النطاقات الصحية
Body weight (kg	الوزن		
Height (cm):	الطول		
BMI:	مؤشر البدانة		*18.5-24.9 kg/m²*
Waist circumference (cm):	قياس دائرة الخصر		نساء *<80 cm*, رجال *<94 cm*
Body fat (kg):	نسبة الدهون في الجسم		نساء *<32%;* رجال *<25%*
Muscle mass (kg):	نسبة العضل في الجسم		نساء *24-30 %:* رجال *33-40%*
Waist to hip ratio:	قياس محيط الأوراك		نساء *<0.9*, رجال *<0.85*
Heart rate:	قياس نبض القلب		*60-100 bpm*
Blood Pressure – Measurement # 1	قياس ضغط الدم 1		
Systolic blood pressure (mmHg):	العالي		*120 mmHg*
Diastolic blood pressure(mmHg):	الواطي		*80 mmHg*
Blood Pressure – Measurement # 22	قياس ضغط الدم		
Systolic blood pressure (mmHg):	العالي		*120 mmHg*
Diastolic blood pressure(mmHg):	الواطي		*80 mmHg*

Time of urine collection	
Time of blood withdrawal	

APPENDIX V

DATA COLLECTION FORM (ENGLISH)

Assessment of BPA levels and their association with the health status among Lebanese population

Name:	Initials:	Study ID number:
Tel number:		Date:

Demographic Factors:

Date of birth:	Gender: □ Males □ Females
Marital status: □ Married □ Single □ Widow □ Divorced	□ Engaged

Socioeconomic:

Have you lived outside Lebanon for the past year: □ No □ Yes If yes, where_____ and for how long _____	
Which area do you live?	
What do you work?	
What is your income per family:	□ <600$ □ 600- 999.9$ □ 1000-2000$ □ >2000$ □ I don't know/ Not sure □ I prefer not to answer
What is your highest level of education?	□ No schooling □ Primary school □ Intermediate school □ Secondary school □ Technical diploma □ University degree □ I prefer not to answer
What is the total number of individuals living in your house? (Including relatives, family members and maids that frequently live with you on a semi-permanent basis)	
How many rooms are there in your house? (Excluding kitchens, bathrooms, hallways, balconies, and garage)	

Lifestyle:

Smoking history			
Cigarette	Do you currently smoke cigarettes?	□ No □ Yes	If yes, how many cigarettes/day? Since when?
	If no, are you a previous cigarette smoker?	□ No □ Yes	If yes, when did you stop?
Narghileh	Do you currently smoke narghileh?	□ No □ Yes	If yes, how many narghileh/day? Since when?
	If no, are you a previous narghileh smoker?	□ No □ Yes	If yes, when did you stop?
Alcohol			
Do you currently drink alcohol?		□ No □ Yes	
		If yes specify type? Since when?	How many glasses/week?
Previous drinker?		□ No □ Yes	If yes, when did you stop?
Coffee			
Do you currently drink coffee?		□ No □ Yes If yes how many cups/day?	
Physical activity			
During the last 7 days, on how many days did you do **vigorous** physical activities like heavy lifting, aerobics, or fast bicycling for at least 10 minutes (or any activity that take hard physical effort and make you breathe harder than normal)?		---------- days/week □ None - How much time in total did you usually spend on one of those days doing vigorous physical activities? _____ hours _____ minutes? - How many weeks did you spend doing vigorous physical activities during the last 3 months? ----------weeks	
During the last 7 days, on how many days did you do **moderate** physical activities like carrying light loads, bicycling at a regular pace, or tennis or any activity that take hard physical effort and make you breath harder than normal)? Do not include walking.		---------- days/week □ None - How much time in total did you usually spend on one of those days doing moderate physical activities? _____ hours _____ minutes? -How many weeks did you spend doing moderate physical activities during the last 3 months? ----------weeks	
During the last 7 days, on how many days did you **walk** for at least 10 minutes at a time? This includes walking at work and at home, walking to travel from place to place, and any other walking that you did solely for sport, exercise or leisure.		---------- days/week □None - How much time in total did you usually spend walking on one of those days? _____ hours _____ minutes? -How many weeks did you spend walking during the last 3 months? ----------weeks	
During the last 7 days, how much time in total did you usually spend sitting on a week day? This includes time spent sitting at a desk, visiting friends, reading traveling on a bus or sitting or lying down to watch television.		_____ hours _____ minutes? -How many weeks have you been spending the same time in terms of sitting during the last 3 months? ----------weeks	

Medical History:

Coronary artery disease:

Do you have any family member who has been diagnosed with coronary artery disease or died suddenly?	□ No □ Yes If yes: specify who	At what age:
Have you been told by a doctor that you had a heart attack?	□ No □ Yes If yes when:	
Did you undergo cardiac catheterization?	□ No □ Yes If yes when:	
Was a stent placed?	□ No □ Yes If yes when:	
Did you have coronary heart bypass surgery?	□ No □ Yes If yes when:	

Hypertension:

Have you been told by a doctor or a health care worker that you have high blood pressure?	□ No □ Yes If yes when:
Have you had your blood pressure measured by a doctor or a health care worker?	□ No □ Yes If yes when? What was it?
Are you taking any treatment for high blood pressure?	□ No □ Yes If yes specify: □ Life style modifications □ Drugs:

Diabetes Mellitus:

Have you been told by a doctor or a health care worker that you have raised blood sugar or diabetes?	□ No □ Yes If yes when:
Have you had your blood sugar measured by a doctor or a health care worker?	□ No □ Yes If yes when? What was it?
Are you taking any treatment for high blood sugar or diabetes?	□ No □ Yes If yes specify: □ Life style modifications □ Drugs:

Dyslipidemia:

Have you been told by a doctor or a health care worker that you have raised cholesterol or triglycerides?	□ No □ Yes If yes when:
Have you had your cholesterol measured by a doctor or a health care worker?	□ No □ Yes If yes when? What was it?
Are you taking any treatment for dyslipidemia?	□ No □ Yes If yes specify: □ Life style modifications □ Drugs:

Thyroid disease:

Have you ever been told by a doctor or ahealth care worker that you have thyroid disease?	□ No □ Yes If yes when? What was the disease?
Have you had your thyroid hormones measured by a doctor or a health care worker?	□ No □ Yes If yes when? What was it?
Are you taking any thyroid drug?	□ No □ Yes If yes specify:
Do you have any family history of thyroid disease? (Parents, siblings and grandparents)	□ No □ Yes If yes specify who:

Cancer history:

Have you ever been told by a doctor or ahealth care worker that you have cancer?	□ No □ Yes If yes when? What was the disease?
Are you taking any chemotherapy or other drug for cancer?	□ No □ Yes If yes specify
Do you have any family history of cance? (Parents, siblings and grandparents)	□ No □ Yes If yes specify the disease: Specify who:

Fracture history:

Did you ever sustain a fracture?	□No □Yes
If yes:	Where? Age at onset? How did it happen? (fall from height, accident…)?

Other diseases:

Have you been told by a doctor or a health care worker that you have any?	
Stroke?	□No □Yes If yes when:
Arthritis?	□No □Yes If yes when:
Chronic bronchitis or emphysema?	□No □Yes If yes when:
Liver disease?	□No □Yes If yes when:

Do you have any other illnesses?

Dentist visits:

Have you visited any dentist in the past year?	□ No □ Yes If yes when:
Did you have any fillings done in the past year?	□ No □ Yes If yes when:

Medications (if not brought, call the participant later)

Name (brand and generic)	Dose	Date started

Review of system:

Do you have any weight changes during the last 3 months?		□ Stable weight □ Lost weight How many Kgs? □ Gained weight How many Kgs?
For women:	When was your last menstrual period?	
	Are you: □ premenopausal □ postmenopausal	If premenopausal do you have □ Regular menses □ Irregular menses
	Do you have? □ Acne □ Hirsutism	

Physical Exam Form

Name of the participant: ---------- Initials:---------- Study ID number: ----------

		Results النتائج	Healthy ranges القياسات الصحية
Body weight (kg	الوزن		
Height (cm):	الطول		
BMI:	مؤشر الدهانة		*18.5-24.9 kg/m²*
Waist circumference (cm):	قياس دائرة الخصر		*رجال <94 cm, نساء <80 cm*
Body fat (kg):	نسبة الدهون في الجسم		*رجال <25%, نساء <32%*
Muscle mass (kg):	نسبة العضل في الجسم		*رجال 33-40%, نساء 24-30 %*
Waist to hip ratio:	قياس محيط الأورك		*رجال <0.85, نساء <0.9*
Heart rate:	قياس نبض القلب		*50-100 bpm*
Blood Pressure – Measurement # 1	قياس ضغط الدم 1		
Systolic blood pressure (mmHg):	العالي		*120 mmHg*
Diastolic blood pressure(mmHg):	الواطي		*90 mmHg*
Blood Pressure – Measurement # 22	قياس ضغط الدم		
Systolic blood pressure (mmHg):	العالي		*120 mmHg*
Diastolic blood pressure(mmHg):	الواطي		*90 mmHg*

Time of urine collection	
Time of blood withdrawal	

Sleep Habits and Berlin questionnaires

1- How many hours do you sleep per night on weekdays?					
4 hrs or less	5 to 6 hrs	5 to 7 hrs	7 to 8 hrs	8 to 9 hrs	9 hrs or more
2- How many hours do you sleep per night on weekends?					
4 hrs or less	5 to 6 hrs	5 to 7 hrs	7 to 8 hrs	8 to 9 hrs	9 hrs or more
3- Do you feel that you are not getting enough sleep?					
Never	Rarely (1 / month)	Sometimes (2-4 / month)	Frequently (5-15 /month)	Almost Always (16-30 / month)	
4- Do you have Trouble falling asleep?					
Never	Rarely (1 / month)	Sometimes (2-4 / month)	Frequently (5-15 /month)	Almost Always (16-30 / month)	
5- Do you wake up during the night and have difficulty resuming sleep?					
Never	Rarely (1 / month)	Sometimes (2-4 / month)	Frequently (5-15 /month)	Almost Always (16-30 / month)	
6- Do you wake up too early in the morning and be unable to resume sleep?					
Never	Rarely (1 / month)	Sometimes (2-4 / month)	Frequently (5-15 /month)	Almost Always (16-30 / month)	
7- Did your doctor tell you that you have sleep apnea?					
Yes	No				
8- Do you snore?					
Yes	No	Don't Know			
9- If you snore, your snoring is?					
a. Slightly louder than breathing	b. As loud as talking	c. Louder than talking	d. Very loud-can be heard in adjacent rooms		
10- If you snore, how often do you snore?					
a. Nearly every day	b. 3-4 times a week	c. 1-2 times a week	d. 1-2 times a month	e. Never or nearly never	
11- If you snore, has your snoring ever bothered other people?					
Yes	No	Don't Know			
12- Has anyone noticed that you quit breathing during sleep?					
a. Nearly every day	b. 3-4 times a week	c. 1-2 times a week	d. 1-2 times a month	e. Never or nearly never	
13- How often do you feel tired or fatigued after you sleep?					
a. Nearly every day	b. 3-4 times a week	c. 1-2 times a week	d. 1-2 times a month	e. Never or nearly never	
14- During your waking time do you fee tired, fatigued or not up to par?					
a. Nearly every day	b. 3-4 times a week	c. 1-2 times a week	d. 1-2 times a month	e. Never or nearly never	
15-Have you ever nodded off or fallen asleep while driving a vehicle?					
Yes	No				
16- If yes, how often does this occur?					
a. Nearly every day	b. 3-4 times a week	c. 1-2 times a week	d. 1-2 times a month	e. Never or nearly never	

FOOD FREQUENCY QUESTIONNAIRE

Name of the participant: ---------- Initials:---------- Study ID number: ----------

*Please think about your eating patterns during **the past year**. Please indicate your usual intake of each of the following food items per day, week, or month. Please be as precise as you can in your recall.*

Code	Food item	Reference Portion	Serving Size	Day	Week	Month	Rarely/Never
	Examples:						
	Rice, white, cooked	*A side*	*½ A 11*		*3*		
	Cheese, regular	*B side/ Thickness*	*B1 / Th. 2*	*4*			
	Legumes, canned (beans, peas)	*Side A/ Page 4*	*1.5 cups*		*2*		
1	**Bread and Cereals**						
1.1	Bread, white	1 large Arabic loaf					
		1 medium Arabic loaf					
		1 French baguette					
		1 pain de mie/ toast					
1.2	Bread, brown	1 large Arabic loaf					
		1 medium Arabic loaf					
		1 French baguette					
		1 pain de mie/ toast					
1.3	Traditional breads(markouk/tannour)	1 loaf					
1.4	Breakfast cereals, regular/ sugar coated/ chocolate/ bran	Side A					
		Carton (35 g)					
1.5	Kaak	Finger size Small round / Page 13					
1.6	Rice, white, cooked	Side A/ Page 5					
1.7	Pasta/ Noodles, plain, cooked	Side A/ Page 5					
1.8	Wheat/ Bulgur, cooked	Side A/ Page 5					
1.9	Rice/Pasta/Cereals, whole grain	Side A / Page 5					
2	**Dairy Products**						
2.1	Milk, skim/low-fat (0-2%)	Side A					
2.2	Milk, whole-fat	Side A					
2.3	Yogurt, fat-free/low-fat	Side A					
		Bottled ayran					
2.4	Yogurt, whole-fat	Side A					
		Bottled ayran					

2.5	Cheese, regular / yellow	Side A Side B / Thickness Cube/ triangular portion					
2.6	Cheese, low fat / white	Side A Side B / Thickness Cube/ triangular portion					
2.7	Labneh, regular	Side A					
2.8	Labneh, low fat	Side A					
3	**Fruits and Fruit Juices**						
3.1	Citrus orange/ grapefruit	Side A / 1 medium					
3.2	Peach, plum, prunes	Side A / 1 medium					
3.3	Strawberries	Side A / 10 strawberries					
3.4	Grapes	Side A / 10 grapes					
3.5	Banana/ Apples	Side A / 1 medium					
3.6	Dried Fruits	Raisins: 1 tbsp Dates: 1 portion Apricots: 1 portion					
3.7	Fruit juice, fresh	Side A					
3.8	Fruit juice, canned	1 can					
3.9	Fruit juice, bottled	1 bottle/ carton					
3.10	Fruits, canned	Peach/ apricot = ½ fruit Pineapple = 1 slice					
4	**Vegetables**						
4.1	Salad, green: lettuce, mint, cucumber, green pepper, rocket, purslane, etc.	Side A/ Page 8					
4.2	Dark green or deep yellow (spinach, Swiss Chard, Jew's mellow, carrots...)	Side A/ Page 4					
4.3	Tomatoes, fresh	1 medium / 10 cherry					
4.4	Corn / Green peas, fresh	Side A/ Page 4					
4.5	Corn/ Green peas, canned	Side A/ Page 4					
4.6	Potatoes, baked / boiled/ mashed	Side A / 1 medium					
4.7	Zucchini/ Eggplants, cooked	Side A/5 med. stuffed					
4.8	Cauliflower/ Cabbage/ Broccoli	Side A/ Page 4					
4.9	Other canned vegetables (Mushroom, palmetto, asparagus, etc.)	Side A/ Page 4					
4.10	Vegetable juice, fresh	Side A					
5	**Meat and Meat Alternatives**						
5.1	Legumes: lentils, beans, chickpeas, etc., dried, cooked	Side A/ Page 4					
5.2	Legumes, canned (beans, peas)	Side A/ Page 4					

5.3	Nuts & seeds: walnuts, peanuts, almonds, sunflower seeds, etc.	Side A/ Page 4 Pre-packed small bag					
5.4	Red meat, beef/ lamb/goat	Side A/ Ground					
		Steak - Side B/ Thickness					
5.5	Poultry	Leg/thigh/breast/wings Side B					
5.6	Fish/ Seafood, fresh	Side B/ Thickness					
		Shrimp: 1 medium					
		Calamari: 1 medium					
		Crab: 1 medium					
5.7	Fish, canned (tuna, sardines)	1 large can/ 1 small can Page 19					
5.8	Eggs	1 medium					
5.9	Organ meats (liver, kidneys, brain)	Side B/ Thickness					
5.10	Luncheon meats (mortadelle, turkey, salami, ham, etc.)	Side B/ Thickness Regular slice					
5.11	Sausages, makanek, uncanned	Side B/ Thickness Makanek size					
5.12	Sausages, makanek, hotdogs, canned	Hotdog size Makanek size Side B/ Thickness					
6	**Added Fats and Oils – Salads/ Cooking / Fries**						
6.1	Vegetable oil, corn/ sunflower/ soya	Side A					
6.2	Olive oil (including with thyme)	Side A					
6.3	Olives	5 olives					
6.4	Butter	Side A					
6.5	Ghee	Side A					
6.6	Mayonnaise	Side A					
6.7	Tahini	Side A					
7	**Sweets and Desserts**						
7.1	Cakes / Cookies/ Doughnuts / Muffins/ Croissant / Biscuits	Side B / Thickness Page 14-15-16					
7.2	Ice cream	1 scoop/ 1 stick/ Page 9					
7.3	Chocolate bar	1 medium					
7.4	Sugar, honey, jam, molasses, chocolate spread	Side A					
7.5	Arabic sweets Baklava, maamoul, kneife	Side B					

8	**Beverages**						
8.1	Soft drink, regular	Side A / 1 can (330 mL)					
8.2	Soft drink, diet	Side A / 1 can (330 mL)					
8.3	Turkish coffee	Side A					
8.4	Instant coffee / Tea	Side A					
8.5	Cocoa / Hot chocolate	Side A					
8.6	Beer	Side A / 1 bottle					
8.7	Wine, red / white/ blush	Side A					
8.8	Liquor, whiskey/ vodka/ gin/ rum	Side A					
8.9	Water	Side A / Bottle (0.5 L)					
9	**Miscellaneous**						
9.1	Manaeesh, zaatar/ cheese	1 regular / 1 bouché Page 17- 18					
9.2	French fries	Side A Page 4					
9.3	Potato chips / Tortilla	XS/ S/ M/ L/ XL bag Page 20					
9.4	Falafel, without bread	1 medium falafel					
9.5	Shawarma	1 medium sandwich					
9.6	Burgers (beef, chicken, fish)	1 medium burger					
9.7	Pizza	Side B / Thickness					
9.8	Canned/ Pre-packed soups	Side A / Page 3					
9.9	Ketchup	Side A					
9.10	Mustard	Side A					

10.1. How many times do you ***season your food with a tomato-based sauce*** (tomato, onion, garlic and simmered with olive oil)?
---------- number of times per day / week / month?

10.2. Do you actually consume chicken or turkey meat ***instead of*** veal, pork, hamburger, or sausage?
------ Yes ------ No

11. Are there any other foods/supplements that you regularly consume **[at least once per week]** and that were not mentioned in the FFQ list above?

Food Item	Usual serving size	Frequency of intake per week

Dietary Habits Questionnaire

1. Do you know what Bisphenol A (BPA) is? ----- No ----- Yes
2. Are you aware of BPA free bottles / plastic containers (Tupperware)? ----- No ----- Yes

		Always (6-7 times/week)	Most of the times (4-5 times/week)	Few times (2-3 times/week)	Rarely (1x/week to 2x/month)	Never	Don't know
3	Do you store foods in plastic containers?						
4	Do you heat foods in plastic containers?						
5	Do you make sure that the plastic containers you use are BPA-free?						
6	Do you heat foods that are wrapped in cling film?						
7	Do you drink bottled water?						
	7.1 From plastic- bottled water: ---------- cups/day 7.2 From water cooler: ---------- cups/day						
8	Do you reuse bottled water?						
9	Do you drink from bottles you left in your car?						
10	Do you eat outside home (snacks, restaurants, bars)?						
11	Do you order delivery foods?						
12	Do you purchase soft drinks in cans and/or plastic bottles?						
13	Do you consume canned tomato paste?						

24-Hours Dietary Recalls

Date: (dd/mm/yyyy) ---/---/-------

Day of the week: ----------

Time	Food eaten	Amount	Method of preparation

Was yesterday a usual eating day?

- Yes
- No, please specify ----------

- When was the last meal taken?

Lab work data collection

Name of the participant: ---------- Initials:---------- Study ID number:----------

Test	Unit	Result
Hba1c		
LDL		
SGPT		
Urinary creat		
FBS		
HDL		
GGT		
Spot microalbumin		
Fasting insulin		
Triglycerides		
CRP		
Creatinine		
Total cholesterol		
TSH		
25OHvit D		
Cortisol		
C-peptide		
Prolactin		
Leptin		

Physical Exam Form

Name of the participant: ---------- Initials:---------- Study ID number: ----------

		Results النتائج	Healthy ranges النطاقات الصحية
Body weight (kg	الوزن		
Height (cm):	الطول		
BMI:	مؤشر الدانة		*18.5-24.9 kg/m²*
Waist circumference (cm):	قياس دائرة الخصر		*نساء <80 cm, رجال <94 cm*
Body fat (kg):	نسبة الدهون في الجسم		*نساء <32%, رجال <25%*
Muscle mass (kg):	نسبة العضل في الجسم		*نساء 24-30 %: رجال 33-40%*
Waist to hip ratio:	قياس محيط الأورك		*نساء <0.9, رجال <0.85*
Heart rate:	قياس نبض القلب		*50-100 bpm*
Blood Pressure – Measurement # 1	قياس ضغط الدم 1		
Systolic blood pressure (mmHg):	العالي		*120 mmHg*
Diastolic blood pressure(mmHg):	الواطي		*90 mmHg*
Blood Pressure – Measurement # 22	قياس ضغط الدم		
Systolic blood pressure (mmHg):	العالي		*120 mmHg*
Diastolic blood pressure(mmHg):	الواطي		*90 mmHg*

Time of urine collection	
Time of blood withdrawal	