ASSOCIATION OF DIET QUALITY WITH HbA1c AND ILLNESS PERCEPTION WITH CARDIOVASCULAR RISK FACTORS IN PRE-DIABETES AND AT-RISK OF PRE-DIABETES SUBJECTS VISITING PUSAT SEJAHTERA, USM

SANIA SIDDIQUI

UNIVERSITI SAINS MALAYSIA

2019

ASSOCIATION OF DIET QUALITY WITH HbA1c AND ILLNESS PERCEPTION WITH CARDIOVASCULAR RISK FACTORS IN PRE-DIABETES AND AT-RISK OF PRE-DIABETES SUBJECTS VISITING PUSAT SEJAHTERA, USM

by

SANIA SIDDIQUI

Thesis submitted in fulfillment of the requirements
for the degree of
Master of Science

December 2019

ACKNOWLEDGEMENT

All praise to Allah S.W.T, the Most Gracious and the Most Merciful, for giving me opportunity, courage and strength to complete this thesis. It was a challenging, long and bumpy journey and would be a daunting task without the guidance of my supervisors, and support from my family.

I would like to express my deepest appreciation to my main supervisor, Dr. Hadzliana Zainal for her invaluable guidance, encouragement, and support in steering me throughout my research candidature. I am also grateful to my co-supervisor Dr. Sabariah Noor Harun for her clinical advice, and assistance during the research period. I would also like to thank Dr. Siti Maisharah Sheikh Ghadzi (Research co-investigator) for her insightful comments and guidance during study.

Endless thanks to my beloved parents and my siblings for their full support from the beginning of my journey until the end. Without their support, I hardly can endure this journey. Finally, I would also like to acknowledge School of Pharmaceutical Sciences and Universiti Sains Malaysia Incentive Bridging Grant for supporting this research project.

TABLE OF CONTENTS

LIST OF TABLES

Page

LIST OF FIGURES

Page

LIST OF ABBREVIATIONS

ADA	American Diabetes Association
AHA	American Heart Association
AMA	American Medical Association
ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
BIPQ	Brief Illness Perception Questionnaire
BMI	Body Mass Index
CDC	Centre of Diabetes Control and prevention
CDQDPS	China Da Qing Diabetes Prevention Study
CKD	Chronic Kidney Disease
CVD	Cardiovascular Disease
DR	Dietary Recall
DPP	Diabetes Prevention Program
DQI	Diet Quality Index
DQI-R	Diet Quality Index Revised
FA	Fatty Acid
FFQ	Food Frequency Questionnaire
FPG	Fasting Plasma Glucose
GI	Glycemic Index
GIP	Gastric Inhibitory Polypeptide
GL	Glycemic Load

GLP-1	Glucagon Like Peptide- 1
HEI	Healthy Eating Index
HR	Hazardous Ratio
HDL	High Density Lipoprotein
HOMA	Homeostatic Model Assessment
HOMA-β	Homeostatic Model Assessment of β-cell function
HOMA-IR	Homeostatic Model Assessment for Insulin Resistant
IFG	Impaired Fasting Glucose
IGT	Impaired Glucose Tolerance
I-IFG	Isolated Impaired Fasting Glucose
I-IGT	Isolated Impaired Glucose Tolerance
IPQ-R	Illness Perception Revised Questionnaire
IQR	Interquartile Range
IRAS	Insulin Resistant Atherosclerosis Study
M-HEI	Healthy Eating Index for Malaysians
MBIPQ	Malaysian Brief Illness Perception Questionnaire
MANS	Malaysian Adult Nutrition Survey
MDG	Malaysian Dietary Guideline
MUFA	Mono-Unsaturated Fatty Acid
NHMS	National Health Medical Survey
NHANES	National Health Morbidity Survey
NIDDM	Non-Insulin Dependent Diabetes Mellitus
NGT	Normal Glucose Tolerance
OGTT	Oral Glucose Tolerance Test

OR	Odds Ratio
PUFA	Poly Unsaturated Fatty Acid
RNI	Recommended Nutrient Intake
SFA	Saturated Fatty Acid
SQ	Semi-quantitative
SSBS	Sugar Sweetened Beverages
SSMM	Sweet, Solid fat, Meat and Mayonnaise
T2DM	Type 2 Diabetes Mellitus
TEI	Total Energy Intake
UDM	Undiagnosed Diabetes Mellitus
USDA	United State Department of Agriculture
VFL	Vegetable, Fruit, Legume
WHO	World Health Organization
WHR	Waist to Hip Ratio

HUBUNGAN ANTARA KUALITI DIET DENGAN HbA1c DAN PERSEPSI PENYAKIT DENGAN FAKTOR RISIKO KARDIOVASKULAR DALAM KALANGAN SUBJEK PRA-DIABETES DAN BERISIKO PRA-DIABETES YANG MELAWAT PUSAT SEJAHTERA

ABSTRAK

Kepentingan pengubahsuaian makanan dalam pencegahan dan penangguhan perkembangan diabetes sudah difahami sepenuhnya. Namun begitu, hubungan antara kualiti diet dan HbA1c dalam kalangan pra-diabetes penduduk Malaysia masih tidak jelas. Persepsi penyakit mungkin didapati berbeza dalam kalangan individu berdasarkan status pra-diabetes mereka. Kaitannya dengan faktor risiko penyakit kardiovaskular (CVD) dalam kalangan pesakit pra-diabetes jarang diteliti. Kajian ini bertujuan untuk mengenalpasti dan membandingkan kualiti diet yang diukur oleh Indeks Makanan Sihat untuk orang dewasa di Malaysia dalam kalangan populasi kajian, dan untuk mengenal pasti hubungan antara HEI dan HbA1c pada tahap pra-diabetes yang berlainan (iaitu pra-diabetes, berisiko untuk pra-diabetes, kencing manis yang tidak didiagnosis dan normoglisemik yang sihat). Objektif kedua kajian ini adalah untuk mengenal pasti dan membandingkan persepsi penyakit yang berkaitan dengan pra-diabetes dan hubungan dengan faktor risiko CVD yang berkaitan dalam kalangan pra-diabetes dan berisiko terhadap pra-diabetes. Kajian keratan rentas dilakukan antara Oktober 2018-Mac 2019 di Pusat Sejahtera USM. Sejumlah 147 peserta yang memenuhi kriteria kajian yang diinginkan dan sukarelawan untuk mengambil bahagian direkrut dalam kajian ini. Data berkenaan pemakanan, persepsi penyakit, antropometrik dan profil biokimia diukur dengan menggunakan soal selidik

kekerapan makanan dan borang ingatan 24 jam, Kaji Selidik Persepsi Penyakit Ringkas Malaysia (MBIPQ) dan kaedah piawai masing-masing. Tidak terdapat perbezaan yang signifikan dan hubungan antara skor komposit HEI dan HbA1c diperhatikan setelah analisis disesuaikan dengan faktor-faktor yang bercanggah dalam kalangan kumpulan kajian. Dimensi MBIPQ seperti kawalan peribadi yang tinggi dan kebimbangan penyakit dikaitkan dengan penurunan HbA1c ($r = -0.424$, $p = 0.039$), dan tekanan darah diastolik ($r = -0.433$, $p = 0.034$) dalam kalangan subjek pra-diabetes. Begitu juga, identiti penyakit yang lebih kuat (mengalami lebih banyak simptom yang berkaitan dengan diabetes) dan akibat penyakit yang serius, dikaitkan dengan BMI ($r = 0.297$, $p = 0.024$) dan tekanan darah sistolik ($r=0.287$, $p=0.035$) yang lebih tinggi dalam kalangan subjek berisiko pra-diabetes. Melalui regresi logistik, umur dan BMI didapati secara langsung dikaitkan dengan pra-diabetes, berisiko pra-diabetes dan diabetes yang tidak didiagnosis ($p <0.01$), manakala trigliserida dan jantina wanita membawa risiko yang lebih tinggi untuk diabetes yang tidak didiagnosis ($p<0.05$). Sebagai kesimpulan, skor HEI gagal meramalkan HbA1c. Ini menunjukkan, tabiat pemakanan secara keratan rentas tidak mungkin menjadi faktor risiko yang kuat untuk mendapat pra-diabetes dan diabetes. Hubungan antara dimensi MBIPQ dan faktor risiko CVD mencadangkan implikasinya dalam penjagaan pesakit. Umur, BMI, trigliserida dan jantina wanita adalah faktor utama dalam meramalkan pra-diabetes, berisiko diabetes pra-diabetes dan diabetes tidak didiagnosis yang perlu diberi keutamaan dalam pesakit pra-diabetes untuk mencapai kemungkinan pembalikan.

ASSOCIATION OF DIET QUALITY WITH HbA1c AND ILLNESS PERCEPTION WITH CARDIOVASCULAR RISK FACTORS IN PRE-DIABETES AND AT-RISK OF PRE-DIABETES SUBJECTS VISITING PUSAT SEJAHTERA, USM

ABSTRACT

Importance of dietary modification in prevention and delay of diabetes development is fully understood in literature. However, association between diet quality and HbA1c among pre-diabetic Malaysian population remains unclear. Illness perception may have found to be vary among individuals according to their pre-diabetes status. Its association with cardio vascular disease (CVD) risk factors among pre-diabetic patients was rarely studied. This study aims to identify and compare diet quality measured by Healthy Eating Index for Malaysian adults (HEI) among study population, and to identify association between HEI and HbA1c in distinct pre-diabetes states (i.e. pre-diabetes, at-risk of pre-diabetes, undiagnosed diabetes and healthy normoglycemic) .The secondary objective of this study was to identify and compare pre-diabetes related illness perception and its association with relevant CVD risk factors among pre-diabetic and at-risk of pre-diabetic subjects. Cross-sectional study was conducted between October 2018-March 2019 at Pusat Sejahtera USM. A total of 147 participants who met desired study criteria and volunteer to participate were recruited in this study. Data on diet, illness perception, anthropometric and on biochemical profile was measured by using Food frequency questionnaire and 24-hour recall form, Malaysian Brief illness perception questionnaire (MBIPQ) and standardized methods respectively. No significant difference and association between

HEI composite score and HbA1c were observed upon analysis after adjusting for confounding factors among study groups. MBIPQ dimensions such as high personal control, and disease concern was significantly associated with lower HbA1c ($r = -0.424$, $p = 0.039$), and diastolic blood pressure ($r = -0.433$, $p = 0.034$) among pre-diabetic subjects. Similarly, stronger disease identity (experiencing more pre-diabetes related symptoms) and serious diseases consequences, was significantly associated with higher BMI ($r = 0.297$, $p = 0.024$), and systolic blood pressure ($r = 0.287$, $p = 0.035$) among at-risk of pre-diabetes subjects. On logistic regression, age and BMI was found to be directly associated with pre-diabetes, at-risk of pre-diabetes and undiagnosed diabetes ($p<0.01$), while triglyceride and female gender carried higher risk of undiagnosed diabetes ($p<0.05$). In conclusion, HEI score failed to predict HbA1c. This suggests that cross-sectionally, dietary habits may not be a strong risk factor for the development of pre-diabetes and diabetes. MBIPQ dimensions association with CVD risk factors suggests its implication in routine clinical setting. Age, BMI, triglycerides and female gender are key factors in predicting pre-diabetes, at-risk of pre-diabetes and undiagnosed diabetes that needed to be prioritized in managing pre-diabetes to achieve possible reversion.

CHAPTER 1

INTRODUCTION

1.1 Background

Pre-diabetes is an intermediate glycemic state in which blood glucose concentrations are higher than normal but not of a magnitude that would correspond to the diagnosis of type 2 diabetes. It is considered as a risk state for the future development of type 2 diabetes and the chances are even more higher if the impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) exist together (Tabák *et al.*, 2012). Each year around 5-10% of individuals with pre-diabetes progresses to type 2 diabetes (Forouhi *et al.*, 2007). Nevertheless, the conversion rate varied by population characteristics and by the definitions of pre-diabetes used for the diagnostic purpose (Tabák *et al.*, 2012).

Understanding of basic pathophysiology of pre-diabetes (IFG/IGT) is important. It helps in determining the strategies to prevent the conversion spectrum of pre-diabetes to diabetes. Development of diabetes from normal glucose tolerance state (NGT) is a continuous process (Fonseca, 2009). Individuals with type 2 diabetes, showed increased fasting and post load plasma glucose levels, with decreased insulin sensitivity and increased insulin secretion even during their early follow-up i.e. almost 13 years before the onset of diabetes as reported in research studies (Ferrannini *et al.*, 2004; Tabák *et al.*, 2009). This notion favors that insulin resistance due to beta cell dysfunction was present years before the development of diabetes i.e. in the pre-diabetic state.

Pre-diabetic patients have hyper pro-insulinemia in addition to insulin resistance (Ming *et al.*, 2016). Proposed hypothesis for this effect is the increased secretory demand on pancreatic β-cells that results in release of "readily releasable" insulin from reserve pool (concentrated in immature insulin) that eventually leads to increase in plasma pro-insulin and lower insulin level (Breuer *et al.*, 2010). Lower than the physiologic concentration of insulin decreases the inhibitory effect of insulin on gluconeogenesis and glycogenolysis. Thus, results in hyperglycemia, less peripheral glucose uptake due to deposition of free fatty acids and increase complications associated with glucotoxicity (Srihardyastutie.A, D.W.Soeatmadji, Fatchiyah, 2014).

Heterogenous pathophysiology was associated with isolated IFG (I-IFG) and isolated IGT (I-IGT). Both are characterized by reduced insulin secretion and increase insulin resistance (Færch, Holst and Vaag, 2009). However, the site of insulin resistance and pattern of insulin secretion is different in both the states. Individuals with I-IFG have normal peripheral insulin sensitivity, as 50% of glucose uptake is occurred in insulin insensitive brain cells during fasting state. In contrast to I-IGT major uptake of glucose after an OGTT is to be done by peripheral cells (David M. Nathan *et al.*, 2007). Studies that were using euglycemic- hyperinsulinemic clamp have reported a steep decline in peripheral insulin sensitivity among I-IGT individuals (Abdul-Ghani *et al.*, 2006; Færch, Holst and Vaag, 2009). Moreover, hepatic insulin sensitivity is usually decline in I-IFG individuals when tested by Homeostatic Model Assessment (HOMA) indexed of insulin sensitivity, this results in elevated hepatic end-glucose production and fasting hyperglycemia (Kærch *et al.*, 2009).

Pattern of insulin secretion is also different in both intermediate states. The first phase (30 min) insulin response to oral glucose is reduce in I-IFG which preserve to normal in later phase (60-120min) during OGTT testing. However, in I-IGT insulin secretion in response to glucose load weakened in first phase and declined further in late phase. Combined effect of defective insulin response with weakened peripheral insulin sensitivity resulted in prolonged hyperglycemia in I-IGT after glucose load on OGTT (David M. Nathan *et al.*, 2007).

Beta cell function normally declines in both I-IFG and I-IGT states. The likely reason for this effect, is the progressive loss in beta cell volume (Tabák *et al.*, 2012). Glucagon secretion is higher in both states due to increase in pancreatic alpha cell mass which results in abnormality in function of alpha cells and upregulation of glucagon secretion. Secretions of Glucagon like peptide 1 (GLP-1) hormone and concentration of glucose dependent insulin-tropic polypeptide (GIP) elevated in both the pre-diabetic states due to activation of compensatory mechanism to overcome reduced beta cell function (Færch, Holst and Vaag, 2009).

Etiology associated with I-IFG and I-IGT is also different in both states. Set of causes responsible for I-IFG is more likely due to genetic factor, smoking and male sex. In contrast, for I-IGT physical inactivity and unhealthy dietary habits are main responsible factors (Færch, Holst and Vaag, 2009). The summary of pathophysiology associated with I-IFG, I-IGT and IFG/IGT summarized in Figure 1.1

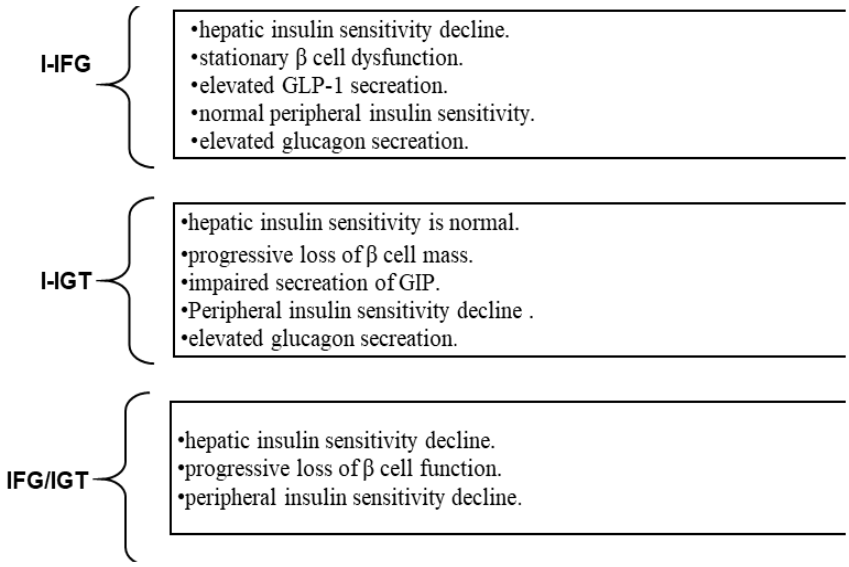

Figure 1.1 Pathophysiology associated with I-IFG, I-IGT, IFG/IGT in pre-diabetic patients [source: (Færch, Holst and Vaag, 2009)]

1.2 Definition and diagnosis of pre-diabetes

Pre-diabetes defined as the condition of abnormal blood glucose homeostasis in which blood glucose levels are higher than normal but below than diabetes threshold (Bagheri *et al.*, 2016). Pre-diabetes includes impaired fasting glucose and/or impaired glucose tolerance. IFG is characterized by the presence of fasting plasma glucose level between 5.6-6.9 mmol/L while IGT defines as 2-hour post load plasma glucose levels between 7.8-11.0 mmol/L on OGTT testing (American Diabetes Association, 2005). The term pre-diabetes has been criticized severely in literature. Initially it was used by *Alberti* to denote the strong family history of type 2 diabetes and to define abnormalities associated with pregnancy (such as high birth weight and hydraminos

during pregnancy) (Grundy, 2012). However, in 1980 WHO discarded this term as many people with the border line glucose level may not necessarily proceed to diabetes and may unnecessarily alarmed them (WHO, 2006). In 2005, ADA used term pre-diabetes to covered group of individuals with IFG and IGT but not include other risk factors for diabetes development (American Diabetes Association, 2005). In 2008, WHO again repudiated the term and discarded its use, instead they suggest the term "Intermediate Hyperglycemia" to signify individuals with IFG and IGT (WHO, 2006). However, ADA continues to use term pre-diabetes to denote individuals with IFG, IGT and now, adding additional criteria i.e. HbA1c 5.7-6.4% to classify individuals with glycemia in between higher cut-off of normal and lower cut-off of diabetic threshold (American Diabetes Association, 2005). As pre-diabetes is not considered as a clinical entity by its own right, its diagnosis in asymptomatic individual is quite crucial. ADA recommended criteria for screening of pre-diabetes in asymptomatic adults with BMI $\geq$ 23kg/m^2 and have one or more additional diabetes related risk factors. These criteria were i) first-degree relative with diabetes ii) high-risk race/ethnicity (e.g., African American, Latino, Native American, Asian American, Pacific Islander) iii) history of CVD iv) hypertension ($\geq$140/90 mmHg or on therapy for hypertension) v) HDL cholesterol level $\leq$ 0.90 mmol/L and/or a triglyceride level $\geq$ 2.82 mmol/L vi) women with polycystic ovary syndrome vii) physical inactivity viii) Other clinical conditions associated with insulin resistance (e.g. severe obesity, acanthosis nigricans) (American Diabetes Association, 2019). As, the above defined criteria can help in identifying individuals with undiagnosed pre-diabetes/diabetes. Multiple health association organizations including ADA, American Medical Association (AMA), Centre for diabetes control and prevention (CDC) recommended

to utilize these criteria as a risk assessment test of pre-diabetes/ diabetes in clinical setting for earlier recognition (American Diabetes Association, 2018). Previously published study was also used these criteria in categorizing their study participants as at-risk of diabetes to monitor them in primary care setting and aimed at providing possible implications for earlier reversion (Strauss *et al.*, 2015).

1.2.1 Impaired fasting glucose

IFG is a state in which fasting plasma glucose levels are higher than normal but lower than diabetes threshold (WHO, 2016).In 1997, ADA identifies group of individuals with fasting plasma glucose levels in between the normal glucose homeostasis and diabetes i.e. (FPG=6.1-6.9 mmol/L). In 1999, World Health Organization (WHO) adopted ADA diagnostic criteria for IFG and IGT diagnosis (WHO, 2006) . In 2003, ADA revised their diagnostic criteria of IFG by dropping the threshold of the FPG to 5.6 mmol/L from 6.1 mmol/L (American Diabetes Association, 2005). The rationale of doing this is based on several reasons. Firstly, they claimed that fasting plasma glucose level between 5.6-6.9 mmol/L carries higher diabetes risk as compared to normoglycemia. Secondly, reverse operating analysis of several studies have demonstrated that FPG criteria (5.6-6.9 mmol/L) have maximum sensitivity and specificity in predicting pre-diabetes. Lastly, the expert committee of the ADA postulated that by lowering threshold of FPG could bring the concordance in the rate of prevalence of IFG and IGT in designated population (Grundy, 2012).

However, WHO does not adopt this change as the expert panel for review of WHO diagnostic and recommended guidelines fails to identify evidence of disease

progression and adverse outcome associated by reducing the cut-off point for FPG. They advocate to use FPG 6.1-6.9 mmol/L for the diagnosis of IFG (WHO, 2006).

1.2.2 Impaired glucose tolerance

Normoglycemia was defined as fasting plasma glucose level <5.6 mmol/L and 2-hour post-load plasma glucose level (2-HPP) <7.8 mmol/L. IGT categorized individuals with intermediate 2-HPP, 7.8-11.0 mmol/L after ingestion of standard glucose solution on OGTT (Grundy, 2012). Post load plasma glucose level considered as a reliable method for predicting type 2 diabetes. However, necessity of doing OGTT may somehow, limits its use as diagnostic criteria in normal daily routine setting.

1.2.3 Glycosylated hemoglobin (HbA1c)

In 2009, ADA expert committee added HbA1c as the additional diagnostic criteria for individuals at risk of diabetes. The level of threshold initially defined for intermediate state was 6.0-6.4% (WHO, 2011). Several studies conducted, failed to capture previously diagnosed IFG and IGT individuals in accordance to this HbA1c level (Lipska *et al.*, 2010). The Diabetes prevention program (DPP) demonstrated that interventions to prevent prognosis of pre-diabetes towards diabetes are effective in individuals with HbA1c around 5.9%. Thus, to enhance the efficiency of preventive interventions ADA defines HbA1c cut-off of 5.7-6.4% for the diagnosis of pre-diabetes (Grundy, 2012). However, as the sensitivity and specificity of HbA1c in identifying individuals with pre-diabetes is lower. To improve diagnostic accuracy, it is recommended to used HbA1c test in conjunction with FPG or OGTT test (Barry *et al.*, 2016). Table 1.1 displays diagnostic criteria for normal, pre-diabetes and diabetes proposed by ADA and WHO as given below.

Table 1.1 Diagnostic criteria for pre-diabetes by ADA and WHO

Diagnostic Test	HbA1c %	FPG (mmol/L)	2-hour post-load plasma glucose (mmol/L)
ADA			
Normal	< 5.7	< 5.6	< 7.8
Pre-diabetes	5.7-6.4	5.6-6.9	7.8-11.0
Diabetes	≥ 6.5	≥7.0	≥11.1
WHO			
Normal	<6.0	<6.1	< 7.8
Pre-diabetes	6.0-6.4	6.1-6.9	7.8-11.0
Diabetes	≥ 6.5	≥7.0	≥11.1

Abbreviations: ADA: American Diabetes Association, WHO: World health organization.

1.3 Health risk associated with pre-diabetes

1.3.1 Progression to diabetes

Based upon the prospective studies published in between 1979-2004, the annual incidence rate of diabetes was much higher in individuals having both IFG and IGT (15-19%) than those having IGT (4-6%) or IFG (6-9%) alone (Bansal, 2015). Other studies also analyzed their data in the similar manner. DPP outcome study reports 11% incidence rate of diabetes among pre-diabetic patients (Knowler, William C,Sarah E flower, 2009). In the US multi-ethnic study of atherosclerosis, the incidence rate was 6% among participants with IFG (Schoepp *et al.*, 2016). Japanese population-based study indicated that the incidence rate was 9% among participants with IFG and 7% in those with HbA1c 5.7-6.4% (Salem, 2012). They suggest the risk of diabetes development based on HbA1c is approximately similar to that posed by FPG, and 2-HPP. The large heterogeneity in estimates among studies is due to the variation in the criteria used to defined type 2 diabetes.

1.3.2 Cardiovascular disease (CVD)

Pre-diabetes is considered as a risk factor for CVD mortality (Brunner *et al.*, 2006). A national population-based study, Australian diabetes, obesity and life style study (AusDiab) conducted in 1999, to determine association of abnormal glucose tolerance with CVD mortality. They found positive association among impaired fasting glucose (HR= 1.6, 95% CI 1.0 to 2.4) and impaired glucose tolerance (HR= 1.5, 95% CI 1.1 to 2.0) with CVD mortality after median follow-up of 5.2 years (Barr *et al.*, 2007).

1.3.3 Nephropathy

Similar to diabetes, pre-diabetes is linked to an increased risk of chronic kidney disease (CKD) (M.Gabir *et al.,* 2000). NHANES study showed that 17.7% cases of CKD were among pre-diabetic population. Other studies also supported the presence of increased albuminuria and reduced glomerular filtration rate, the early marker of CKD among pre-diabetic population (Plantinga *et al.*, 2010). Longitudinal studies also proven that pre-diabetes is a subsequent risk factor for CKD (Fox *et al.*, 2005; Thomas *et al.,* 2011). However, the causal relationship of this effect is unclear whether this prospective association is due to pre-diabetes itself or reflection of diabetes development or due to other factors contributing to hyperglycemia and kidney pathology (Tabák *et al.*, 2012).

1.3.4 Neuropathies

Various forms of neuropathies such as diabetic neuropathy, polyneuropathy, small fiber neuropathy, autonomic neuropathy was observed among pre-diabetic patients (Grundy, 2012). A study for monitoring trends and determinant in cardiovascular disease (MONICA) reports 13% prevalence of polyneuropathy in IGT and 11.3% cases among IFG population in comparison to 7.4% cases among NGT (Ziegler *et al.*, 2008). There is also evidence of increase prevalence of painful sensory neuropathy and small fiber neuropathy among pre-diabetic patients due to involvement of demyelinated nerve fibers that carry pain to regulate autonomic neuronal functions (Hoffman-snyder *et al.*, 2006).

1.4 Management of pre-diabetes

Preventive strategies are becoming important as the trajectory of pre-diabetes towards diabetes increases. Both pre-diabetes and diabetes can be controlled by improving dietary habits, physical activity and by maintaining healthy weight and BMI (Diabetes Prevention Research Group, 2002).

1.4.1 Lifestyle intervention

Many studies have shown that approximately two-thirds of pre-diabetic subjects can delay diabetes by making improvements in their lifestyle (Lindström *et al.*, 2003), (Snehalatha *et al.*, 2009). However, many pre-diabetic people are unaware of to which extent lifestyle modification can prevent diabetes progression.

Even though, progression of pre-diabetes towards diabetes is a continuous process, individuals with pre-diabetes can revert to normoglycemia by adopting changes in their lifestyle (Bansal, 2015). Several intervention trials favors the efficacy of lifestyle modification by demonstrating reduction in risk of development of diabetes among pre-diabetic individuals (Tabák *et al.*, 2012).“China Da Qing diabetes prevention study” demonstrated that 43% risk reduction among IGT individuals who followed lifestyle intervention for period of 6 years (Li *et al.*, 2008). Diabetes prevention study reflects positive association of lifestyle changes with reduce incidence of diabetes among IGT individuals whereas, individuals in the intervention group receives individualized dietary counselling to limit the intake of fat, saturated fat and increase consumption of dietary fiber and physical activity. The overall risk reduction was 58% ($p<0.001$) observed in the intervention group during intervention trial (Tuomilehto *et al.*, 2001). Some other studies also reported, the beneficial effects of lifestyle interventions in relation to improvement in beta cell function and increase in insulin sensitivity among pre-diabetic population (Diabetes Prevention Research Group, 2006; Snehalatha *et al.*, 2009).

1.4.2 Pharmacotherapy

Several antidiabetic medicines such as biguanides, alpha glucosidase inhibitors, GLP-1 and non-antidiabetic drugs such as anti-obesity and bariatric surgery were studied in literature for their effectiveness in reversion of abnormal glucose tolerance to normoglycemia (Tabák *et al.*, 2012). Metformin has been used previously among diabetic individuals and found to be effective in IGT individuals because of its favorable outcome in reducing BMI and improving lipid profile (Salpeter *et al.*, 2008).

Alternative treatment was also suggested to be account if the patient is non-responsive or intolerant to the metformin therapy. Thiazolidinedione reduces the incidence of diabetes by 70% in at risk population, but this drug class does not provide a good safety profile and will lead to the risk of hepatotoxicity, weight gain, edema, heart failure which underline its beneficial effects (R.A. *et al.*, 2011). Alpha glucosidase inhibitors reduce glucose absorption by prolonging carbohydrate digestion and thus results in decrease postprandial blood glucose level (Rahul L Gajbhiye, Anand G, 2018). A study to prevent Non-Insulin Dependent Diabetes Mellitus (STOP-NIDDM trial), shows 25% risk reduction among IGT individuals by using acarbose over 3.3-year follow-up. However, this drug also shows several gastrointestinal side effects which decrease drug adherence among consumers (Josse and Gomis, 2003).

1.5 Diet quality

Diet quality is the "comprehensive evaluation of the individual's diet, quantified with multidimensional approach by involving selection of dietary components with the respective cut-offs or scores to determine how closely it align with national dietary guideline" (Wirt and Collins, 2009).

According to WHO, burden of chronic disease is increasing globally. In 2001, 60% of total death cases was accounted for chronic diseases with 46% of the global disease burden. Almost half of the total chronic disease deaths are attributed to CVD and diabetes (WHO, 2016). This observing worrying trends is not only because they affect large proportion of population but also, they affect individuals in the earlier phases of their life. Epidemiological data suggest that adherence to recommended dietary guidelines, a marker of diet quality plays a vital role in maintaining good health

outcome and may reduce the risk of developing chronic disease and associated pre-mature deaths (Gopinath *et al.*, 2013).

1.6 Problem statement and rationale of study

Pre-diabetes is a modifiable risk factor for the development of type 2 diabetes and its associated complications (American Diabetes Association, 2005). Globally, prevalence of pre-diabetes and type 2 diabetes in conjunction with subsequent health consequences are considered as a public health problem and become epidemic globally (International Diabetes Atlas Committee, 2003). With an estimation, around 5-10% of pre-diabetic population turns to diabetes each year (Bansal, 2015). However, conversion rate of individuals from pre-diabetes to diabetes varies with the population characteristics and the criteria used to defined pre-diabetes among studies (David M Nathan *et al.*, 2007). Poor eating habits such as high intake of diet which is rich in carbohydrate, fat, high glycemic index, quality and the quantity of food consumed in relation to insulin response are more closely related factors of diabetes prognosis (Woo *et al.*, 2003). Early recognition and prevention of pre-diabetes is therefore, necessary to prevent or delay transition towards diabetes.

Non-pharmacological intervention programs exemplified as lifestyle modification reduces the risk of incidence of pre-diabetes and shows high efficacy to postpone or prevent type 2 diabetes (Tuomilehto *et al.*, 2001; Lindström *et al.*, 2003). In contrast, in the absence of any lifestyle modification the incidence of diabetes among pre-diabetic subjects was relatively higher. In China Da Qing Diabetes Prevention Study (CDQDPS), the cumulative incidence of diabetes over a period of 20-years was noted to be higher than 90% among pre-diabetic subjects as defined by

WHO in control group, versus 80% incidence among pre-diabetic subjects in intervention group (Li *et al.*, 2008) that proven the efficacy of lifestyle intervention in diabetes incidence. Short term lifestyle interventions extended over a period of 5 years also noted to reduce the conversion figure by 58% among pre-diabetic subjects as defined by ADA (Diabetes Prevention Research Group, 2002). The use of ADA vs WHO criteria to defined diabetes may also affect the incidence of diabetes among studies with lower incidence in individuals defined by ADA as compared to WHO criteria (Bansal, 2015).

Comprehensive dietary assessment is considered as an acceptable approach in implementation and development of individualized intervention program and for determining the role of diet with chronic disease (Gopinath *et al.*, 2013). To date, several international studies have been published, demonstrating association of dietary factors as determinant in disease progression among pre-diabetic population. A Japanese cross-sectional study conducted among pre-diabetic patients, evaluated the association of diet quality with glucose tolerance status. The study findings suggested that higher diet quality was associated with reduced risk of impaired glucose tolerance ($p=0.02$) (Sartorelli *et al.*, 2009). Another study conducted in Australia to identify the role of diet quality in disease progression, prospectively followed healthy individuals for 10 years until the diagnosis of pre-diabetes. The findings of study proposed, 2-point increase in total diet quality score was associated with 52% and 10-year risk reduction of pre-diabetes (Gopinath *et al.*, 2013). The findings of above described studies are significant in advocating the effect of diet on pre-diabetes but are not generalizable to other population due to differences in dietary habits and food

availability. This gap inclined the need of more studies to evaluate the association between diet quality and pre-diabetes among respective population.

Pre-diabetes is a host for major CVD risk factors including hypertension and dyslipidemia. Impairment in insulin secretion and increased insulin resistance overtime predisposes the risk of development of type 2 diabetes, mortality and morbidity associated with CVD (David M. Nathan *et al.*, 2007). Epidemiological studies including Paris Prospective Study (PPS) demonstrated that, elevated risk of CVD was associated with pre-diabetes as compared to NGT individuals (Dagogo-Jack, 2005). Primary preventions such as smoking cessation, healthy food choices, maintenance of ideal body weight, control of blood pressure and lipid profile proven to reduce CVD morbidity and mortality associated with pre-diabetes (Dagogo-Jack, 2005). However, adherence to these preventions depends upon individuals understanding and perception about illness (Petrie and Weinman, 2012). Illness perception reflects individual's views about illness and highlights disease related misconceptions (Broadbent *et al.*, 2006) . Literature has shown positive association of illness perception with CVD risk factors among type 2 diabetic patients and demonstrate it as an important framework for developing successful interventions and self-management in chronic diseases (Petricek *et al.*, 2009).

In Malaysia, studies regarding the association of diet quality with glycemic control is lacking. However, the increase prevalence of type 2 diabetes and pre-diabetes in this region and consumption of food patterns among inhabitants make it interesting to know about the association of diet quality score with increasing glycemia in non-diabetic ranges (Norlaila *et al.*, 2011). Association of illness perception with CVD among pre-diabetic population is scantly focused in literature. Lack of

availability of local and international studies on this topic emphasizes the necessity of more researches in this context, which helps in understanding the impact of individual's belief on CVD risk factor control in this population.

Results of this study will provide better understanding about diet disease relationship for the health care professionals and in managing and delaying progression of pre-diabetes. Additionally, by investigating the association of illness perception of pre-diabetes with control of CVD risk factors may help health care professionals in developing education/intervention programs to promote awareness about cardiovascular health among pre-diabetic patients.

1.7 Research Question

The primary research question of this study: whether there was any significant association exist between diet quality (measured in terms of HEI composite score) with the HbA1c among study participants?

A secondary research question: whether there was any significant difference in the diet quality measured by HEI among different study groups after adjusting for potential covariate such as age, BMI and total daily energy intake?

The final research question is there any association between pre-diabetes related illness perception measured by MBIPQ among pre-diabetic and At-risk of pre-diabetic group with CVD risk profile?

1.8 Objective

There are two main general objectives in this study:

Objective 1) To evaluate the association of diet quality of respondents assessed by using Healthy eating index for Malaysians (M-HEI) with their HbA1c.

Objective 2) To evaluate the association between pre-diabetes related illness perception measured by using MBIPQ (Malaysian brief illness perception questionnaire) with CVD risk factors.

The specific objectives were:

a) To identify and compare HEI score among study groups (pre-diabetic, at-risk of pre-diabetic, undiagnosed diabetic and healthy normoglycemic).

b) To find the association between diet quality measure by using HEI composite score (%) of respondents with their HbA1c.

c) To evaluate the association of CVD risk profile (HDL, LDL, BMI, waist circumference, systolic blood pressure (SBP), diastolic blood pressure (DBP)) with sub-scales of pre-diabetes related illness perception measured by using MBIPQ among pre-diabetic and at-risk of pre-diabetic respondents.

1.9 Null Hypothesis

a) There was no significant difference in mean HEI score (%) among study groups.

b) There was no significant association between diet quality and HbA1c among study groups.

c) There was no significant association between dimensions of illness perception and CVD risk profile variables such as HDL, LDL, TC, TG, waist circumference and blood pressure and blood glucose levels among pre-diabetic and at-risk of pre-diabetic respondents.

CHAPTER 2

LITERATURE REVIEW

This chapter is divided into two main sections (Figure 2.1). The first section represents critical review of the literature to show current understanding about diet and pre-diabetes association. Specifically, this chapter focus on dietary factors that are associated with either increased or decreased risk of pre-diabetes. A brief description of dietary assessment methods used in nutritional epidemiology studies that were using FFQ in pre-diabetic dietary assessment was also discussed. Lastly, a brief description about diet quality indices and studies evaluating diet quality by using common indices such as DQI, HEI or M-HEI among Malaysian adult population was also discussed. The second section of this chapter focus on the studies that were showing association of CVD risk factors among pre-diabetic population and systematic review of studies evaluating relationship between illness perception as a predictor of CVD risk factors among pre-diabetic population.

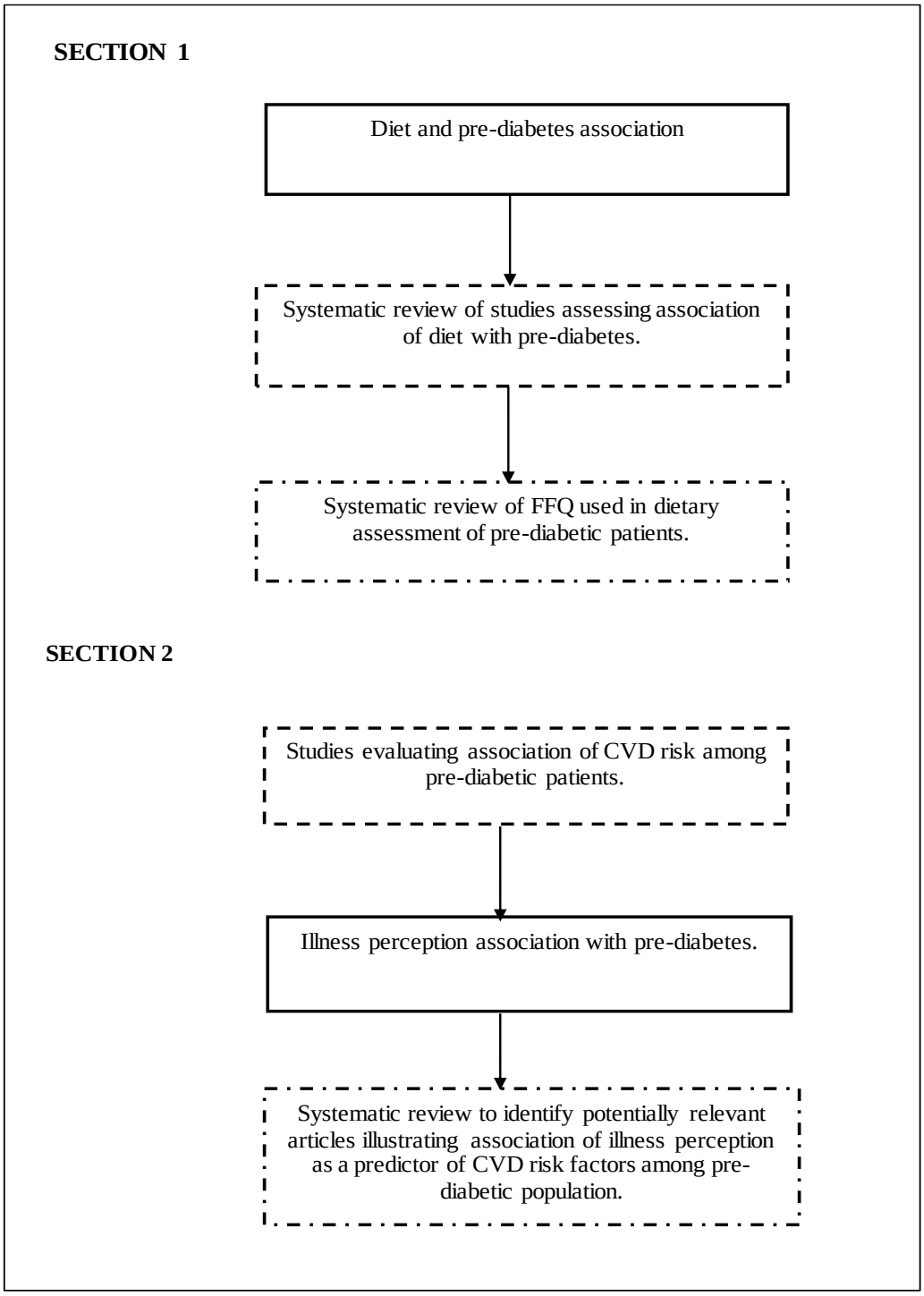

Figure 2.1 Outline of literature review

2.1 Association of diet with pre-diabetes

2.1.1 Introduction

Prevalence of pre-diabetes is increasing significantly in both developed and in developing countries. It is expected to affect 472 million adults globally by the end of 2025. Of these. more than half cases of pre-diabetes expected to be found in south east Asia and in West pacific region only (International Diabetes Atlas Committee, 2003). In the US alone, almost 23.7% of adult population above >20 years and 48.3% of adults ≥65 years and above were diagnosed as pre-diabetes in 2014. When this figure is applied to whole US population the reported statistics touched the figure of 84 million pre-diabetic cases in 2015 (Centre for Disease Control and Prevention, 2017). Prevalence of IFG and IGT in the US population varied with sex and with ethnicity, with 35.1% of IGT cases identified at age of above ≥75 years (Cowie *et al.*, 2009). According to National health and morbidity survey (NHANES) the overall, rate of prevalence of IGT in the U.S was 13.8% in adults age >20 years old (Cowie *et al.*, 2009). In Diabetes Epidemiology Collaborative Analysis of Diagnostic Criteria in Europe (DECODE) study, the rate of prevalence of IGT was rose from 2.9% in men aged 30-39 years old to 15.1% in adults aged 70-79 years older (The DECODE study group, 2003). This suggest that the risk of pre-diabetes increased with the increased in age. Conversion rates from pre-diabetes to type 2 diabetes was also higher with isolated IGT. In most of the western countries, conversion rate per anum with isolated IGT was in the range of 4.35-6.35%. Similarly, in DPP study the conversion rate was about 10% per year (Grundy, 2012).

An obvious increment in the prevalence of pre-diabetes was also found in Malaysia. National health morbidity survey (NHMS) conducted between 1986-2015, reported that the prevalence of pre-diabetes defined by either IGT or by IFG. IGT was used to define pre-diabetes prevalence in first two surveys i.e. (NHMS I, 1986) and (NHMS II, 1996). The reported prevalence was 4.8% in NHMS I which was decreased to 4.3% in subsequent survey (Letchuman *et al.*, 2010). To omit the need of doing OGTT that is required for IGT evaluation, IFG was used to characterized pre-diabetes prevalence in NHMS III and IV. The rate of IFG prevalence was 4.7% in both surveys. (Letchuman *et al.*, 2010; NHMS; Ministry of Health Malaysia, 2015). Fasting blood capillary was used as a diagnostic test to identify IFG cases in NHMS III and IV. The test is preferable in large population survey due to their associated benefits in terms of easiness, less expensive and less invasive nature in obtainment of blood collection. However, its accuracy is questionable in diagnosing pre-diabetes as compared to standard method i.e. OGTT (Tirimacco *et al.*, 2010). To report overall prevalence of pre-diabetes based on OGTT testing, a cross-sectional survey was conducted in 2011 across the urban and rural areas of Malaysia. The overall prevalence of pre-diabetes in this survey was 22.1%, affecting 16.1 % of subjects with IGT, 3.4% with IFG and 2.6% with both the IFG and IGT. The prevalence was higher in women (69.8%) as compared to men (30.2%), affecting nearly half of the population (47.0 %) aged between 30-49 years (Norlaila *et al.*, 2011).

Pre-diabetes is known as a reversible condition that elevate individual's risk for diabetes development. If pre-diabetes is left untreated, it affects 37% of individuals with diabetes in succeeding years (Tuso, 2014). A systematic review was conducted previously, displays positive association of elevated level of HbA1c in pre-diabetic

range with the development of T2D and explained HbA1c level in between 5.5-6.0% was associated significantly with the increased the risk of progression of pre-diabetes towards diabetes (Zhang *et al.*, 2010). The 5-year conversion rate was about 9-25%. However, this risk increases further to 50% when the level of HbA1c is greater than or equal to 6% (Heianza *et al.*, 2011).

Progression of pre-diabetes to diabetes can be reduced by lifestyle modification. Intervention trials conducted in between 1997-2006, proven the efficacy of life style intervention in reducing disease progression by 40-70% among pre-diabetic population (Tabák *et al.*, 2012). DPP documented, 58% risk reduction of diabetes among pre-diabetic patients, through interventions in dietary habits and increasing physical activity (Hamman *et al.*, 2006). The Finnish diabetes prevention study (DPS) used achievement goals, to reduce disease progression among pre-diabetic subjects. The goals were weight reduction by 5%, total and saturated fat consumption less than 30% and 10 % of total energy intake, increasing physical activity to a threshold of more than 4h/week and enhancing fiber consumption up to 15g per 1000kcal. The higher goal achievements by study participant showed pronounced risk reduction in the intervention group (Tuomilehto *et al.*, 2001).

As, literature shown that diabetes can be prevented by adopting lifestyle modification. Consequently, adaptation of western life style and high consumption of saturated fatty acids, refined sugars, grain and red meat increased the risk of type 2 diabetes development in at risk population (Bagheri *et al.*, 2016). To hold the global prevalence of pre-diabetes, it is important to identify dietary factors as determinant in epidemiology and progression of pre-diabetes. Current literature is filled with the examples of showing an association of dietary factors with diabetes or incidence of

diabetes in apparently healthy individuals (Jannasch, Kro and Schulze, 2017). However, investigations in evaluating association of diet with pre-diabetes is limited. Lack of awareness and understanding the role of dietary factors in blood glucose dysregulation among pre-diabetic patients convey a considerable delay in adopting healthy dietary patterns in this population and thus, ultimately increases the incidence of type 2 diabetes. Furthermore, increasing awareness and risk stratification in pre-diabetic individuals can also help physicians to develop potential interventions. These interventions in-turn may be useful in decreasing percentage of patients in their panel sharing common risk factors for diabetes development (Tuso, 2014). A better understanding of how different dietary factors/dietary patterns influence blood glucose in this state could improve current knowledge regarding the effect of specific food group intake on pre-diabetic outcomes.

2.1.2 Search strategy

The objective of the current search strategy was to identify all the published literatures assessing relationship of dietary factors/patterns with glycemic parameters among pre-diabetic patients. The eligibility criteria were peer reviewed and English language studies that were published from the inception year of data base till April 13th, 2018. To identify potentially relevant articles, a computerized search strategy was implemented by using electronic data-bases i.e. PubMed, CINAHL, PsycINFO, ProQuest and Scopus.

Medical subject heading (MeSH) terms of major topic and free text terms were used which were categorized under four groups:

i. Food frequency questionnaire: “FFQ”

ii. Nutrition assessment: “Diet survey”, “Diet evaluation”, “Energy intake”.

iii. Diet: “Nutrition”, “Dietary pattern”, “Diet quality”, “Nutrition status”.

iv. Pre-diabetes (age ≥ 18 years): “Pre-diabetic state”, “Glucose intolerance “, “Insulin resistance”.

Search was conducted either by entering search terms separately or in combination with Boolean terms such as “AND”, “OR”. Keywords and search terms were identified in titles and abstracts. Studies that were not in the English language, using animal models, or not having full text were excluded. All the retrieved articles were then sent to Endnote X7.7.1 where duplicates were removed**.**

Studies with primary or secondary outcomes of (1) evaluating the relationship of diet with glycemic indices of pre-diabetes such as IFG, IGT and homeostasis model assessments, (Homeostatic Model Assessment of Insulin Resistant (HOMA-IR) and Homeostatic Model Assessment of β-cell function (HOMA-β) or (2) assessing odds of pre-diabetes with dietary pattern intake or (3) assessing diet as a risk factor for the development of pre-diabetes were included. However, studies assessing the relationship of diet with inflammatory markers, metabolic syndromes and CVD among pre-diabetic population were excluded as patients with above defined complications generally have restricted diet and may receive recommendations from dietetics to control disease (Amin *et al.*, 2010).