Association of Alcohol Consumption with Glucose Homeostasis: A Systematic Review and Meta-Analysis

by

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A thesis submitted in conformity with the requirements for the degree of Master of Science
Institute of Medical Science
University of Toronto

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Abstract

Impaired glucose homeostasis is associated with increased risk of type 2 diabetes and cardiovascular diseases. Therefore, having in-depth knowledge about different risk factors involved in the pathogenesis of impaired glucose homeostasis is necessary. No systematic review has evaluated observational studies for the long-term effects of alcohol consumption on glucose homeostasis. We aimed to conduct a systematic review and meta-analysis to assess the association of alcohol consumption with different parameters of glucose homeostasis. Medline and Embase were searched for cohort and case-control studies about association of alcohol consumption with glucose homeostasis parameters. Identified articles with the outcome of impaired fasting glucose (IFG) were quantitatively summarized in a meta-analysis.

Our study suggests an overall increase in the incidence of IFG in association with alcohol consumption. For other indicators of glucose homeostasis (e.g. serum insulin and HbA1C), the number of included studies were low and the results were inconsistent.
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Contributions

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<th>Description</th>
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<tbody>
<tr>
<td>ATP</td>
<td>adenosine triphosphate</td>
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<tr>
<td>AMP</td>
<td>adenosine mono phosphate</td>
</tr>
<tr>
<td>FFA</td>
<td>free fatty acid</td>
</tr>
<tr>
<td>GIP</td>
<td>glucose-dependent insulinotropic polypeptide</td>
</tr>
<tr>
<td>GLP-1</td>
<td>glucagon-like peptide-1</td>
</tr>
<tr>
<td>cAMP</td>
<td>cyclic adenosine monophosphate</td>
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<tr>
<td>GLUT</td>
<td>glucose transporter</td>
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<tr>
<td>IFG</td>
<td>Impaired fasting glucose</td>
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<tr>
<td>IGT</td>
<td>Impaired glucose tolerance</td>
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<tr>
<td>CDA</td>
<td>Canadian diabetes Association</td>
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<tr>
<td>HbA1C</td>
<td>Glycated hemoglobin</td>
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<tr>
<td>OGGT</td>
<td>oral glucose tolerance test</td>
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<tr>
<td>FPG</td>
<td>fasting plasma glucose</td>
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<tr>
<td>NCEP</td>
<td>National Cholesterol Education Program</td>
</tr>
<tr>
<td>NIAAA</td>
<td>National Institute on Alcohol Abuse and Alcoholism</td>
</tr>
<tr>
<td>CVD</td>
<td>cardiovascular disease</td>
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<tr>
<td>PG</td>
<td>plasma glucose</td>
</tr>
<tr>
<td>NAD</td>
<td>Nicotinamide adenine dinucleotide</td>
</tr>
<tr>
<td>PRISMA</td>
<td>Preferred Reporting Items for Systematic review and Meta-Analysis</td>
</tr>
<tr>
<td>BBB</td>
<td>blood brain barrier</td>
</tr>
<tr>
<td>MetS</td>
<td>Metabolic syndrome</td>
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<tr>
<td>ECG</td>
<td>electrocardiography</td>
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<tr>
<td>BMI</td>
<td>body mass index</td>
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<tr>
<td>HOMA</td>
<td>homeostatic model assessment</td>
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<tr>
<td>SNP</td>
<td>single nucleotide polypeptides</td>
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<tr>
<td>PCO</td>
<td>Polycystic ovary syndrome</td>
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<tr>
<td>HDL</td>
<td>high-density cholesterol</td>
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<tr>
<td>Abbreviation</td>
<td>Description</td>
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<tr>
<td>LDL</td>
<td>low-density cholesterol</td>
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<tr>
<td>GI</td>
<td>Glycemic index</td>
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<tr>
<td>GL</td>
<td>Glycemic load</td>
</tr>
<tr>
<td>RR</td>
<td>Relative risk</td>
</tr>
<tr>
<td>hs-CRP</td>
<td>high-sensitivity C-reactive protein</td>
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Chapter 1

1. Introduction

1.1. Glucose Homeostasis

Homeostasis is defined as the tendency of an organism to maintain the equilibrium of different internal systems by using various biochemical and physical processes. Glucose homeostasis, also known as blood glucose regulation relies on the balance and interaction of two main hormones-insulin and glucagon-to maintain a healthy blood glucose level (Szablewski, 2011).

Glucose is an essential metabolic substance for all cells in the body. The amount of glucose in the blood should be in balance with the amount of glucose that the cells need for their metabolism in normal healthy individuals. Therefore, the amount of glucose should constantly be in a narrow normal range (Szablewski, 2011).

Several factors play role in achieving normal glucose homeostasis in the body. These factors include hormone regulations, glucose uptake during gastrointestinal ingestion and absorption, the rate of glucose uptake by peripheral tissues, and the rate of glucose uptake or release by liver or kidneys (Hers, 1990; Szablewski, 2011).

The hormone insulin, produced by beta cells of the pancreas, facilitates the transport of glucose into the cells (Hers, 1990). Insulin keeps post-prandial glucose in a normal range by three mechanisms: it increases glucose uptake of insulin-sensitive peripheral tissues such as skeletal muscles, it increases glycogenesis in the liver and it also inhibits glucagon production which stops glycogenolysis and gluconeogenesis (Aronoff, Berkowitz, Shreiner, & Want, 2004).

Glucagon, produced by alpha cells in the pancreas, is the other side of the equation in glucose homeostasis which is also produced by the pancreas (Hers, 1990). Glucagon works in a similar but opposite manner to insulin. When blood glucose levels are low, the pancreas releases glucagon. It stimulates the liver to release glucose stored within its cells, thus raising blood glucose levels to a normal level (Hers, 1990).

In normal circumstances, these hormonal interactions and adjustments maintain a constant and optimal blood glucose level. Glucose is needed constantly in most tissues and organs, such as the brain as an important source of energy. Low blood concentrations of glucose can cause seizures, loss of consciousness, and death, while a long-lasting elevation of blood glucose concentrations can result in blindness, renal failure, vascular disease, and neuropathy (Szablewski, 2011).
1.2. Role of Glucose in Metabolism

The most common clinical roles of glucose in the metabolism are glucose as a source of cellular energy, glycolysis, gluconeogenesis, glycogenesis, glycogenolysis, lipogenesis and lipolysis.

1.2.1. Glucose as source of cellular energy

Glucose produces adenosine triphosphate (ATP), as a high-energy end-product for the metabolism of different cells in the body. Glucose metabolism occurs in two different pathways: aerobic and nonaerobic. If it occurs aerobically (in the presence of oxygen), 36 molecules of ATP will be produced, but if it occurs anaerobically (in the absence of oxygen) 2 molecules of ATP will be produced (Hers, 1990; Szablewski, 2011).

1.2.2. Glycolysis

Glycolysis regulates insulin secretion and metabolic functions by a simple process of glucose metabolism. Regulatory enzymes which increase glycolysis might be good targets for diabetes medications (Guo et al., 2012).

Glycolysis takes place in the cytoplasm of the cells. This pathway has three stages. Stage one is the conversion of glucose to fructose 1, 6 biphosphate. Stage two is the breakdown of the 1, 6 biphosphate to two three-carbon fragments. Stage three is ATP production, and pyruvate is also produced (Berg, Tymoczko, & Stryer, 2002).

Glycolysis can occur in both aerobic and anaerobic situations. The end product of glycolysis is two molecules of ATP and two molecules of nicotinamide adenine dinucleotide-reduced form (Hers, 1990; Szablewski, 2011).

1.2.3. Gluconeogenesis

Gluconeogenesis, as a metabolic pathway, produces glucose from non-carbohydrates such as lactate, glycerol and glucogenic amino acids. The glucose produced from gluconeogenesis is released into the blood stream and then it will be taken up by muscles (Hers, 1990; Szablewski, 2011).

Gluconeogenesis occurs in both the liver and kidneys (Aber, Morris, & Housley, 1966). In post-absorptive situations, gluconeogenesis is responsible for 40 to 50% of total glucose release and renal gluconeogenesis is responsible for 20 to 25% of systemic glucose release which indicates that the kidneys are responsible for almost half of gluconeogenesis and therefore, these organs are as important as the liver in gluconeogenesis (M Stumvoll, 1998).
Renal gluconeogenesis is stimulated by epinephrine and is inhibited by insulin. Renal gluconeogenesis and glucose uptake are enhanced post absorptive and postprandial states. The most significant renal gluconeogenic precursors are lactate, glutamine and glycerol (Mitrakou, 2011).

Glucose release by the liver and kidneys are related. Therefore, a decrease in glucose release of one organ is related to an increase in the other one. This relationship between the liver and kidneys to keep glucose homeostasis in balance is called hepatorenal glucose reciprocity (Shrayyef & Gerich, 2010).

Control of gluconeogenesis occurs mostly at the level of conversion of fructose 6-phosphate and fructose 1, 6-bisphosphate under the enzymatic action of phosphofructokinase 1 and fructose 1, 6-bisphosphatase. Fructose 2, 6-bisphosphate is a strong stimulator of the phosphofructokinase 1 and fructose 1, 6-bisphosphatase and an inhibitor of phosphofructokinase 1 and fructose 1, 6-bisphosphatase. These two enzymes are portions of a protein which is a substrate for cyclic adenosine mono phosphate (AMP)-dependent protein kinase (Hers, 1990).

Cyclic AMP-dependent protein kinase phosphorylation causes the inactivation of phosphofructokinase 2 and the activation of fructose 2, 6-bisphosphatase, resulting in the disappearance of fructose 2,6-bisphosphate. One other significant part of these two enzymes is fructose 6-phosphate, which is the substrate of phosphofructokinase 2 and a strong inhibitor of fructose 2,6-bisphosphatase; they allow the formation of fructose 2,6-bisphosphate when the level of glycaemia and fructose 6-phosphate is high (Hers, 1990).

1.2.4. Glycogenesis

The process of glycogen synthesis, in which glucose molecules are added to chains of glycogen to be stored in the liver and muscles, is called glycogenesis (Hers, 1990; Szablewski, 2011).

Liver glycogenesis plays a significant role in glucose homeostasis and it is mostly regulated by glycogen synthase (Zhang et al., 2013).

1.2.5. Glycogenolysis

The process of breakdown of glycogen to produce glucose, while the blood sugar is low, is called glycogenolysis (Hers, 1990; Szablewski, 2011).
1.2.6. Lipogenesis and lipolysis

The process of converting glucose to fatty acids is called lipogenesis (Szablewski, 2011). This process is stimulated by high glucose diet and is inhibited by polyunsaturated fatty acids and fasting (Szablewski, 2011).

Hormones regulate Lipogenesis; for instance, insulin increases lipogenesis and growth hormone and leptin decreases that. Obesity also changes the process of lipogenesis and lipolysis by developing insulin resistance (Kersten, 2001).

Brown adipose tissue also plays a significant role in glucose homeostasis; it plays a role as an antidiabetic tissue. Its activation also causes more insulin sensitivity and more whole body glucose disposal (Mauvais-Jarvis, 2015).

Other examples for roles of glucose in the metabolism are oxidative decarboxylation, Krebs cycle, electron transport chain, metabolism of lactate, pentose phosphate pathways (Hers, 1990; Szablewski, 2011).

1.3. Normal Physiology of Glucose Homeostasis

Glucose in blood circulation is derived from three sources: intestinal absorption, glycogenolysis, and gluconeogenesis. The rate of gastric emptying is the main factor of how quickly glucose appears in blood circulation during intestinal absorption. Other factors involved in this process are glycogenolysis, the breakdown of glycogen, which is the polymerized storage form of glucose; and gluconeogenesis, which is the formation of glucose from lactate and amino acids during the fasting state (Aronoff et al., 2004).

Glucagon controls glycogenolysis and gluconeogenesis. Glycogenolysis is the primary mechanism by which glucose becomes available during the first 8-12 hours of fasting. If fasting lasts for longer periods, gluconeogenesis will be involved and glucose will be released from the liver (Aronoff et al., 2004).

Amylin is the other hormone involved in the normal process of glucose homeostasis and is associated with the decrease in postprandial glucagon, and lowers the rate of gastric emptying (Triplitt, 2012). Incretin hormones are a group of hormones which keep postprandial glucose in a low and constant level by regulating the release of insulin and gastrointestinal motility (Holst, Gribble, Horowitz, & Rayner, 2016). They include glucose-dependent insulinogetic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1). They regulate the levels of insulin and glucagon. Both GIP and GLP-1 are glucose independent hormones and they are produced when normal fasting levels rise above normal range but they do not directly affect insulin secretions. They are stimulated by meals by activating some specific receptors, called G protein-coupled, which exist on the beta cells of the pancreas and affect insulin secretions. On the other hand, when blood glucose is low, GLP-1 and GIP are lowered as well (Triplitt, 2012).
Glucose homeostasis involves both insulin dependent and non-insulin dependent processes. Central and peripheral nerve systems are not responsive to insulin but muscle and adipose tissue are insulin dependent (Bano, 2013).

Main glucose uptake of peripheral tissue (almost 80%) occurs in skeletal muscle. In skeletal muscle, glucose may be used immediately or for glycogenesis. Skeletal muscle is insulin dependent and it needs insulin to activate the main enzymes such as glycogen synthase (Triplitt, 2012).

Muscles play the main role in glucose uptake (≥ 80%); they may use glucose in a very short time or may store it as glycogen. Skeletal muscles, are insulin dependent and they use insulin to activate the main enzymes such as glycogen synthase and to regulate glycogenesis (Triplitt, 2012).

Adipose tissue is also responsible for small amounts of peripheral glucose uptake (2 to 5%). It produces fatty acids from triglycerides to increase the rate of gluconeogenesis. (Goude, Fagerberg, & Hulthe, 2002; Triplitt, 2012).

The liver plays a significant role in both short-term and long-term glucose metabolism; it works with the pancreas, muscles, adipose tissue and other organs in accordance to keep glucose homeostasis in balance. It also has a significant role in gluconeogenesis, glycogenesis, and it is directly involved in regulating peripheral insulin sensitivity (Levine & Haft, 1970; Postic, Dentin, & Girard, 2004).

The Liver does not use insulin for glucose uptake but it requires insulin for glucose output. For instance, in low levels of insulin concentrations, the liver increases the glucose output. Insulin in the liver, however facilitates glycogenesis (Triplitt, 2012).

Hepatic glucose production accounts for almost 80 percent of post absorptive glucose release in the blood circulation. However, 50 percent of this glucose release is because of glycogenolysis and the remaining proportion is due to gluconeogenesis. Gluconeogenesis quickly increases if the duration of fasting increases. In the first 24 hours of fasting, gluconeogenesis is responsible for approximately 70 percent of total glucose release in the circulation and after 48 hours it is responsible for almost 90 percent of glucose release in the circulation (Shrayyef & Gerich, 2010).

The main organ for glucose uptake is brain, which consumes glucose in both fasting and post-absorptive phases, and it accounts for almost 50 percent of the body’s glucose use. Another 25 percent of glucose use occurs in the splanchnic area (liver and gastrointestinal tract) and the other 25 percent of glucose use takes place in insulin dependent areas, such as skeletal muscle and adipose tissue (Triplitt, 2012).

Under physiologic conditions, the brain uses glucose as the main metabolic substance but it cannot produce glucose or store glycogen more than a few minutes. Therefore, the brain is dependent on a continuous amount of glucose in the blood (Shrayyef & Gerich, 2010)
Glucose needs assistance from insulin and a group of transport proteins called facilitated glucose transporter (GLUT) molecules, to be able to diffuse more easily through cell membranes. Twelve different GLUTs are recognized so far. Among them, GLUT4 is a main glucose transporter for adipose, muscle and heart tissues; and the hormone of insulin facilitates its function. GLUT 1, 2, 3 and 8 are responsible to transport glucose to other organs such as the brain and liver (Triplitt, 2012).

After glucose entry into the cells, it phosphorylates by the enzyme glucokinase in the hepatocytes and hexokinase in other cells (Triplitt, 2012).

On the other hand, the gastrointestinal tract is one of the significant sources of regulation of postprandial glucose. Gastric emptying plays a major role in this process. Gastrointestinal function is regulated by metabolic, hormonal and neuronal impulses produced by gut or vagal activity, these impulses influence appetite, pancreatic hormonal activities and gastrointestinal motility (Holst et al., 2016).

The kidneys regulate glucose by gluconeogenesis, glucose uptake, glucose reabsorption in proximal tubules and glucose excretion in the urine whenever glucose concentration rises almost above 180 mg/dL during chronic hyperglycemia such as type 2 diabetes (Triplitt, 2012).

The kidneys play a significant role in clearing and degrading insulin (Rabkin, Ryan, & Duckworth, 1984). Kidneys are the other organ involved in glucose homeostasis and gluconeogenesis. The liver releases about four times as much as the kidney under post-absorptive conditions, however, renal gluconeogenesis increases in prolonged fasting situations (Shrayyef & Gerich, 2010). Normal glucose homeostasis is also represented in Figure 1.1.
1.4. Key Regulators of Glucose Homeostasis

1.4.1. Insulin

Insulin is the main anabolic hormone in glucose homeostasis pathways. It has both direct and indirect effects on glucose metabolism. In a normal condition, insulin is immediately broken down by the liver and kidneys and it has a short half-life (3 to 10 minutes) (Cydlulka & Maloney Jr, 2002).

Insulin binds its receptors in the liver, kidneys, muscles and adipose tissue and it activates the signaling pathways involved in a complex cascade of protein kinases and regulatory proteins. The number of its receptor cites on different peripheral tissues are related to the sensitivity of that specific tissue to insulin (Cydlulka & Maloney Jr, 2002).
By activating this cascade, it suppresses glucose release from the liver and kidneys, trans-locates glucose transporters in muscle and adipose tissue to increase their glucose uptake, and inhibits release of FFA into the circulation due to suppression of the activity of hormone-sensitive lipase and it also increases their clearance from circulation. Insulin stimulates glucose uptake, storage and use by other insulin-sensitive tissues such as adipose tissue and skeletal muscle (Cydulka & Maloney Jr, 2002).

Insulin also promotes glycogen accumulation by inhibiting glucose-6-phosphatase and phosphorylase (glycogenolysis enzymes) while stimulating glycogen synthase (Shrayyef & Gerich, 2010).

**Effects of insulin on different enzymes of glucose synthesis (Shrayyef & Gerich, 2010):**

- **Blue arrow:** Phosphorylase
- **Red arrow:** Glycogen synthase
- **Green arrow:** Phosphoglucomutase
- **Orange arrow:** Glucose-6-phosphatase

Insulin indirectly lowers glucose release into circulation and promotes glucose removal by its effect on circulating FFA levels. FFA stimulates gluconeogenesis and reduces glucose transport into cells, (Shrayyef & Gerich, 2010).

Effects of insulin on different organs (e.g. liver, skeletal muscle and adipose tissue) are summarized in Table 1.1.

**Table 1.1. Effects of insulin on different organs (liver, skeletal muscle and adipose tissue) (Shrayyef & Gerich, 2010)**

<table>
<thead>
<tr>
<th></th>
<th>Stimulates</th>
<th>Inhibits</th>
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<tr>
<td><strong>Liver</strong></td>
<td>Glycogen synthesis</td>
<td>Glycogenolysis</td>
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<td></td>
<td></td>
<td>Gluconeogenesis</td>
</tr>
<tr>
<td><strong>Skeletal muscle</strong></td>
<td>Glucose uptake</td>
<td>Glycogenolysis</td>
</tr>
<tr>
<td></td>
<td>Glycogen synthesis</td>
<td></td>
</tr>
<tr>
<td><strong>Adipose tissue</strong></td>
<td>Glucose uptake</td>
<td>Lipolysis</td>
</tr>
</tbody>
</table>

1.4.2. Glucagon

Glucagon, produced by alpha cells of the pancreas, is the main catabolic hormone counterpart to insulin which regulates plasma glucose frequently (Cydulka & Maloney Jr, 2002).

Glucagon is released due to hypoglycemia, stress, trauma, infection, exercise, and starvation. Its secretion is inhibited by an increase in plasma level of glucose and stimulated by a decrease in glucose plasma level (Cydulka & Maloney Jr, 2002).

Glucagon has exclusive action on the liver by binding to its receptors and activating adenylate cyclase and increasing cyclic adenosine monophosphate (cAMP) which results in increasing in hepatic gluconeogenesis (Shrayyef & Gerich, 2010).

Hepatic glycogenolysis is the most significant immediate function (within minutes) of glucagon to increase plasma glucose (Shrayyef & Gerich, 2010).

Glucagon increases both glycogenolysis and gluconeogenesis in the liver but has no effect on kidneys (Shrayyef & Gerich, 2010).

Effects of insulin and glucagon on glucose homeostasis is compared and represented in Table 1.2.

Table 1.2. Effects of insulin and glucagon on glucose homeostasis (Shrayyef & Gerich, 2010)

<table>
<thead>
<tr>
<th>Insulin release due to high blood glucose:</th>
<th>Glucagon release due to low blood glucose:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increase in glycogen storage</td>
<td>Decrease in glycogen storage</td>
</tr>
<tr>
<td>Increase in gluconeogenesis</td>
<td>Decrease in gluconeogenesis</td>
</tr>
<tr>
<td>Decrease in glycogenolysis</td>
<td>Increase in glycogenolysis</td>
</tr>
<tr>
<td>End results: glucose uptake/storage</td>
<td>End results: glucose production</td>
</tr>
</tbody>
</table>
1.4.3. Catecholamine

Catecholamine release is regulated by the sympathetic nervous system and increases during stress and hypoglycemia. It inhibits insulin secretion while decreasing insulin action and it affects both glucose release and glucose removal and it indirectly increases gluconeogenic substrate availability and plasma FFA (Shrayyef & Gerich, 2010).

Catecholamine is also a potent stimulator of gluconeogenesis both directly and indirectly and it is more potent in renal glucose release than hepatic glucose release. In skeletal muscles, catecholamine lowers glucose uptake and increases glycogenolysis which results in an increase in the release of lactate; the major gluconeogenic precursor. In adipose tissue, it also stimulates lipolysis by activating hormone sensitive lipase which results in the release of FFA and glycerol which are both gluconeogenic precursors (Shrayyef & Gerich, 2010).

1.4.4. Growth hormone and cortisol

Glucagon and Catecholamine both have usually immediate regulatory actions but growth hormone and cortisol become evident for regulatory actions after several hours. Growth hormone and Cortisol reduce insulin’s ability to suppress glucose release, stimulate glucose uptake and inhibit lipolysis. They both increase the synthesis of gluconeogenesis enzymes and reduce glucose transport (Shrayyef & Gerich, 2010).

Glucocorticoids regulate glycogen metabolism; in the liver they enhance glycogen storage but in skeletal muscle they promote catecholamine-induced glycogenolysis and/or decrease insulin-stimulated glycogen synthesis (Kuo, McQueen, Chen, & Wang, 2015).

1.4.5. Free fatty acids (FFA)

Increases in plasma FFA have significant metabolic consequences. For instance, they stimulate hepatic and renal gluconeogenesis, inhibit muscle glucose transport, and compete with glucose as an oxidative fuel. Catecholamine and growth hormone increase circulating FFA but insulin reduces that by suppressing lipolysis and increasing FFA clearance, and hyperglycemia (Shrayyef & Gerich, 2010). In general, adipose tissue plays a significant role in the regulation of glucose homeostasis (Rosen & Spiegelman, 2006).

Different effects of key regulators of glucose homeostasis are summarized in Table1.3. In addition, the effects of glucose homeostasis on different organs are represented in Figure1.2.
Table 1.3. Key regulators of glucose homeostasis (Shrayyef & Gerich, 2010)

<table>
<thead>
<tr>
<th>Metabolic Regulators</th>
<th>Glucose Production</th>
<th>Glucose Utilization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin</td>
<td>↓</td>
<td>↑</td>
</tr>
<tr>
<td>Glucagon</td>
<td>↑</td>
<td>—</td>
</tr>
<tr>
<td>Epinephrine</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>Cortisol</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>Growth Hormone</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>FFA</td>
<td>↑</td>
<td>↓</td>
</tr>
</tbody>
</table>
Figure 1.2: Effects of glucose homeostasis on different organs (Shrayyef, 2010)
1.5. Impaired Glucose Homeostasis

Any defects in glucose homeostasis may cause the following problems:

Hyperglycemia, impaired fasting glucose, impaired glucose tolerance, prediabetes, diabetes mellitus type 1, type 2 diabetes mellitus, insulin resistance and metabolic syndrome, gestational diabetes, MODY (maturity onset diabetes of the young), neonatal diabetes mellitus, and hypoglycemia (Szablewski, 2011).

Chronic hyperglycemia has long-term complications such as dysfunction of the eyes, kidneys, nerves, heart, and blood vessels. Inadequate insulin secretion (insulin deficiency) and/or reduced responses of tissues to insulin (insulin resistance) (Triplitt, 2012).

Hyperinsulinemia and insulin resistance usually coexist which may cause impaired glucose homeostasis and type 2 diabetes (Triplitt, 2012).

Increased hepatocyte glucose output and adipocyte dysfunction is one other underlying mechanism for impaired glucose dysfunction and type 2 diabetes (Triplitt, 2012).

Insulin is secreted into the portal vein and then it is taken up by the liver and will suppress glucose uptake in the liver. Increased glucose output of the liver is related to type 2 diabetes and is strongly associated with severe fasting hyperglycemia (Triplitt, 2012).

Post-absorptive chronic hyperinsulinemia in mild hyperglycemia (less than 140 mg/dL or 7.8 mmol/L) offsets hepatic insulin resistance and keeps the normal basal rate of glucose output of the liver. However, moderate increase in fasting plasma glucose is related to an enhanced hepatic glucose output (Triplitt, 2012).

Increased fasting glucose (>140 mg/dL) may cause an excessive rate of hepatic glucose output as a major abnormality for elevated fasting glucose. In type 2 diabetes both hyperinsulinemia and hyperglycemia occur which are both strong inhibitors of glucose output of the liver and they may cause hepatic insulin resistance (Triplitt, 2012).

The pancreas has a significant ability to adapt to an increased demand for insulin (due to obesity, pregnancy, cortisol excess) to keep normoglycemic states (Triplitt, 2012).
Progressive loss of beta cell function and mass occurs due to glucotoxicity, lipotoxicity, proinflammatory cytokines, leptin and islet cells amyloid (Triplitt, 2012). This progressive impaired function of beta cells may lead to impaired glucose homeostasis and type 2 diabetes (Triplitt, 2012). In addition, adipocyte dysfunction changes fat deposition and impairs glucose tolerance and type 2 diabetes. Adipocytes are then resistant to antilipolytic effects of insulin, and increased free fatty acids may cause gluconeogenesis, induce hepatic and muscle insulin resistance and impair insulin secretion (Triplitt, 2012).

Other than the mechanism mentioned above, dysfunctional adipocytes induce inflammatory, atherosclerotic provoking cytokines and impair secretion of normal amounts of insulin-sensitizing adipocytokines (adiponectin). The pattern of fat disposition will be also impaired due to type 2 diabetes, because of enlarged insulin resistant adipocytes in visceral fat and decreased capacity to store fat which causes lipid overflow in muscles, liver and beta cells (Triplitt, 2012). The increased in free acid levels in the liver convert to triglycerides, and they will be stored there and may cause steatosis or fatty liver disease which may increase risk of non-alcoholic hepatitis and even cirrhosis (Triplitt, 2012).

Alterations in hepatic glucose metabolism, increased post-absorptive glucose and impaired inhibition of hepatic glucose in accordance with reduced glucose uptake after carbohydrate ingestion and overproduction of glucose and fatty acids in the liver may cause further insulin resistance. These are all examples of impaired glucose homeostasis due to hepatic dysfunction (Postic et al., 2004).

Impaired glucose homeostasis and type 2 diabetes involve muscles, the liver, beta cells, adipocytes, incretin deficiency and resistance, hyperglucagonemia, increased renal glucose reabsorption, and brain insulin resistance (Triplitt, 2012).

In general, dysfunction of different organs may cause impaired glucose homeostasis, which is summarized in Figure 1.3.
Figure 1.3. Different organs involved in glucose homeostasis (Michael Stumvoll, Goldstein, & van Haeften, 2007; Szablewski, 2011)
1.5.1. Impaired fasting glucose (IFG)

Impaired fasting glucose (IFG) was defined in 1997 by the American Diabetes Association to classify individuals with fasting glucose levels between normal and diabetes (Gavin III, Alberti, Davidson, & DeFronzo, 1997). The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus defined IFG as FPG levels between 6.1–6.9 mmol/L ((Goldenberg & Punthakee, 2013), (A. Cheng, 2013); CDA guideline, 2016). Different categories of fasting plasma glucose are represented in Table 1.4.

American Diabetes Association (ADA) changed the definition of IFG in 2003 as fasting plasma glucose of 100 to 125 mg/dL. (Nathan et al., 2007).

However, it should be noted that the World Health Organization (WHO) and numerous diabetes organizations define the IFG cutoff at 110 mg/dL (6.1 mmol/L) ((Goldenberg & Punthakee, 2013). The Canadian Diabetes Association defines IFG as an FPG value of 6.1 to 6.9 mmol/L due to the higher risk of developing diabetes in these individuals compared to defining IFG as an FPG value of 5.6 to 6.9 mmol/L (Goldenberg & Punthakee, 2013).

On the other hand, the reduction in IFG threshold might lead to early detection of people at high risk of diabetes to prevent or delay type 2 diabetes (C.-M. Chen & Yeh, 2013).

Table 1.4. Different categories of Fasting plasma glucose (FPG) (CDA guidelines, 2016, (A. Cheng, 2013))

<table>
<thead>
<tr>
<th>Normal</th>
<th>Less than 6.1mmol/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prediabetes</td>
<td>6.1 to 6.9mmol/L</td>
</tr>
<tr>
<td>diabetes</td>
<td>≥7mmol/L</td>
</tr>
</tbody>
</table>

1.5.2. Impaired glucose tolerance (IGT)

In 1997 and 2003, the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus defined impaired glucose tolerance (IGT) as 2-hour plasma glucose after glucose loading in a 75-g oral glucose tolerance test (OGTT) from 7.8 to 11mmol/L (CDA guideline, 2016, (A. Cheng, 2013; Costa, Conget, &
Different categories of the oral glucose tolerance test are summarized in Table 1.5. IGT is the first simply recognizable factor in pathogenesis of type 2 diabetes (Costa et al., 2002).

**Table 1.5. Different categories of oral glucose tolerance test (OGTT) (A. Cheng, 2013), CDA guidelines, 2016**

<table>
<thead>
<tr>
<th>Category</th>
<th>Glucose Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>Less than 7.8mmol/L</td>
</tr>
<tr>
<td>Prediabetes</td>
<td>7.8 to 11mmol/L</td>
</tr>
<tr>
<td>Diabetes</td>
<td>≥11.1mmol/L</td>
</tr>
</tbody>
</table>

1.5.3. HbA1C

Over 40 years ago, glycated hemoglobin (HbA1c) was identified as unusual hemoglobin in patients with diabetes. After discovering HbA1c, some studies were conducted correlating it to glucose measurements, which have led to the idea that HbA1c could be used as an objective measure of glycemic control. HbA1c reflects average plasma glucose over the previous eight to twelve weeks. It can be measured at any time of the day and does not need any specific preparation such as fasting and it has been the preferred test for assessing glycemic control in people with diabetes. More recently, it has been considered as a diagnostic test for diabetes and as a screening test for persons at high risk of diabetes (Selvin et al., 2010). Different categories of HbA1c are represented in Table 1.6.

**Table 1.6. Different categories of HbA1C (A. Cheng, 2013), CDA guidelines, 2016**

<table>
<thead>
<tr>
<th>Category</th>
<th>HbA1c Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>Less than 6%</td>
</tr>
<tr>
<td>Prediabetes</td>
<td>6 to 6.4%</td>
</tr>
<tr>
<td>Diabetes</td>
<td>6.5% or higher</td>
</tr>
</tbody>
</table>
1.5.4. Prediabetes

Prediabetes is defined as having IFG, IGT or an A1C of 6.0% to 6.4% (Goldenberg & Punthakee, 2013). IFG and IGT are intermediate states of abnormal glucose regulation between normal glucose homeostasis and diabetes ((A. Cheng, 2013), CDA guidelines, 2016).

The prevalence of both IFG and IGT are increasing worldwide (Nathan et al., 2007). This prevalence varies in different age, sex and ethnic groups. For instance, the prevalence of both IFG and IGT is higher in older people and also IGT is more frequent in women than in men (Nathan et al., 2007).

The same as those who are diagnosed with IFG and/or IGT, individuals with an A1C of 6–6.4% should be informed of their increased risk for diabetes and cardiovascular diseases and counseled about effective strategies to lower their risks ((A. Cheng, 2013), CDA guidelines, 2016). People with prediabetes, and especially those who are considered as having metabolic syndrome, would benefit from cardiovascular risk factor modifications (Alshehri, 2010; Ford, Zhao, & Li, 2010; Grundy, 2012; Rydén et al., 2007).

Different categories of prediabetes are shown in Table1.7.

**Table1.7. Prediabetes categories ((A. Cheng, 2013), CDA guidelines, 2016)**

<table>
<thead>
<tr>
<th>Categories of Increased Risk for Diabetes (Prediabetes)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FPG</strong></td>
<td><strong>2hPG</strong></td>
</tr>
<tr>
<td>6.1-6.9mmol/L</td>
<td>7.8-11.0mmol/L</td>
</tr>
<tr>
<td>Impaired fasting glucose (IFG)</td>
<td>Impaired glucose tolerance (IGT)</td>
</tr>
</tbody>
</table>
1.5.5. Metabolic syndrome

Metabolic syndrome according to NCEP criteria is defined as having at least 3 components of the following criteria (P. L. Huang, 2009):

1) Waist circumference >40 inches in men and >35 inches in women
2) Triglyceride ≥150 mg/dL
3) HDL cholesterol <40mg/dL in men, <50mg /dL in women
4) Blood pressure of ≥130 systolic or ≥ 85 mmHg
5) Fasting Plasma Glucose ≥ 110mg/dL

Impaired glucose homeostasis may lead to insulin resistance and metabolic syndrome. Whenever muscle, adipose tissue, or the liver does not use the insulin produced by the pancreas properly, insulin resistance may occur and also impaired in regulations of glycogenolysis and gluconeogenesis may lead to hepatic insulin resistance (Basu, Chandramouli, Dicke, Landau, & Rizza, 2005). In other words, insulin resistance is the core part of metabolic syndrome (J. R. Greenfield et al., 2003).

When insulin resistance occurs, more insulin is needed to metabolize the same amount of glucose, and thus, insulin resistance increases blood glucose levels. Impaired glucose homeostasis, in association with insulin resistance, leads to both hyperglycemia and hyperinsulinemia, and it increases the risk of type 2 diabetes mellitus. Genetic factors play important roles in glucose homeostasis, insulin resistance and metabolic syndrome (Norris & Rich, 2012; Romeo, Lee, & Shoelson, 2012).

In conclusion, hyperinsulinemia, insulin resistance and impairment of glucose stimulated insulin release are closely associated as seen in Figure 1.4.
1.5.6. Diabetes, definition and diagnostic criteria

Diabetes mellitus is one of the most significant clinical manifestations of impaired glucose homeostasis (Szablewski, 2011). Diabetes mellitus occurs as a result of impaired glucose homeostasis and is defined as a metabolic disorder characterized by the presence of hyperglycemia due to impaired insulin secretion, defective insulin action or both (Ramlo-Halsted & Edelman, 2000). The definition of diabetes is represented in Table 1.8.
The chronic hyperglycemia of diabetes is associated with relatively specific long-term microvascular complications affecting the eyes, kidneys and nerves, as well as an increased risk for cardiovascular disease (CVD). The diagnostic criteria for diabetes are based on thresholds of glycaemia that are associated with microvascular disease, especially retinopathy (Goldenberg & Punthakee, 2013), (CDA guideline 2016).

The global prevalence of diabetes worldwide is estimated to double from 2000 to 2030 (2.8% in 2000 and 4.4% in 2030). The total number of people with diabetes is estimated to increase from 171 million in 2000 to 366 million in 2030 (Wild, Roglic, Green, Sicree, & King, 2004).

One most important reason for this estimated demographic change might be because of the increase in the proportion of people older than 65 years of age (Wild et al., 2004). Therefore, in total the global prevalence of diabetes continues to increase (Whiting, Guariguata, Weil, & Shaw, 2011).

Diabetes is responsible for some severe complications such as blindness (Bäcklund, Algvere, & Rosenqvist, 1997), kidney failure, and non-traumatic limb amputations (Fowler, 2011). End stage complications of diabetes have significant burdens for quality of life in patients; however, comprehensive diabetes treatment has also negatively impacted quality of life in diabetic patients (E. S. Huang, Brown, Ewigman, Foley, & Meltzer, 2007).

A systematic review by Kiadaliri et al. (2013) represented that socioeconomic status and good care for cardiovascular diseases were associated with health related quality of life in patients with diabetes (Kiadaliri, Najafi, & Mirmalek-Sani, 2013).

In general, appropriate education to manage how to improve physical, psychological and social well beings are crucial for a higher quality of life in diabetic patients (Debono & Cachia, 2007). On the other hand, diabetes has a great financial burden on society. The cost of diabetes is greater than the cost of both annual coronary heart diseases (108.9 billion) and cancers (48.1 billion) (Heidenreich et al., 2011).

In summary, according to Canadian Diabetes Association (CDA) guidelines 2016, "Diabetes mellitus is a metabolic disorder characterized by the presence of hyperglycemia due to defective insulin secretion, defective insulin action or both"(A. Cheng, 2013). Ongoing patient self-management education and support are critical to preventing acute complications and reducing the risk of long-term complications (Goldenberg & Punthakee, 2013).
Table 1.8. Diagnosis of diabetes (CDA guidelines 2016, (A. Cheng, 2013))

Criteria for Diabetes Diagnosis: 4 Options

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>FPG ≥ 7.0 mmol/L *</td>
<td>Fasting is defined as no caloric intake for ≥ 8 hours</td>
</tr>
<tr>
<td>2-hr PG ≥ 11.1 mmol/L during OGTT (75-g) *</td>
<td>Using a glucose load containing the equivalent of 75g anhydrous glucose dissolved in water</td>
</tr>
<tr>
<td>A1C ≥ 6.5% (48 mmol/mol) *</td>
<td>Using a standardized, validated assay</td>
</tr>
<tr>
<td>Random PG ≥ 11.1 mmol/L</td>
<td>Any time of the day, without regard to the interval since the last meal</td>
</tr>
</tbody>
</table>

*In the absence of symptomatic hyperglycemia results should be confirmed by using repeat testing

1.6. Alcohol Consumption

Alcohol consumption is one of the most common modifiable risk factors for several health problems worldwide (Rehm, 2011).

According to the National Institute on Alcohol Abuse and Alcoholism (NIAAA) report in 2014, in the United States “almost 87.6 percent of people ages 18 or older were drinking alcohol at some point in their
lifetime; 71.0 percent reported that they consumed alcohol in the past year; 56.9 percent reported that they consumed alcohol in the past month”.

Based on the NIAAA report in 2014, in the United States,” 24.7 percent of people ages 18 or older reported that they were engaging in irregular heavy drinking behaviors (binge drinking) in the past month; and 6.7 percent reported that they were engaging in regular heavy drinking in the past month “.

In addition, according to Statistics Canada (2014), 17.9 percent of people ages 12 or older were engaged in heavy drinking occasions (both regular and irregular).

1.6.1. Alcohol consumption measurements

There are different methods to measure alcohol consumption. Alcohol consumption is usually measured in terms of volume or average volume of consumption.

Although having information about the standard drink amounts might be useful for following health guidelines, they do not always reflect customary serving sizes and there is a significant variability in alcohol content within each type of beverage (e.g., beer, wine, distilled spirits). On the other hand, the ethanol content of drinks varies from country to country; therefore, when standard drink is used as a screening tool, additional information should be obtained to increase the accuracy of alcohol consumption measurements (Gual, Martos, Lligoña, & Llopis, 1999).

Several factors influence the reliability and validity of alcohol measurements in surveys including reference period, the approach used to measure alcohol consumption, use of beverage-specific questions versus overall questions, open-ended versus categorical, measurement of standard versus actual drink sizes and also features of the overall survey design such as method of interview (i.e., in person versus by telephone), the use of computerized surveys, and measures to confirm confidentiality (Dawson, 2003).

On the other hand, heavy drinkers (both regular and irregular heavy drinking behaviors) usually underestimate their drinking behavior, whereas lower drinkers tend to overestimate it (Boniface, Kneale, & Shelton, 2014; Caldwell, Rodgers, Power, Clark, & Stansfeld, 2006).

Average daily alcohol consumption is usually calculated based on self-reports of the quantity (number of drinks consumed per drinking-day) and frequency (number of drinking-days) of alcohol consumption within a given time. However, this method may underestimate average daily alcohol consumption (and in turn, the prevalence of heavy drinking), because studies demonstrate that respondents do not typically include binge drinking occasions in estimates of their ‘usual’ or ‘average’ daily alcohol consumption (Rehm, Room, et al., 2003; Stahre, Naimi, Brewer, & Holt, 2006).

According to the NIAAA, “moderate drinking is defined as up to one drink per day for women and up to two drinks per day for men and a maximum of 14 drinks per week for men and 7 drinks per week for women”. But, “heavy drinking or high-risk drinking is defined as the consumption of 4 or more drinks per
day or 8 or more drinks per week for women and 5 or more drinks per day or 15 or more drinks per week for men”.

Patterns of drinking, especially heavy drinking occasions, are important terms to be considered (Rehm & Gmel, 2003), but unfortunately, patterns of drinking have been underestimated in most of the epidemiological studies (Rehm, Room, et al., 2003).

The NIAAA defines heavy drinking occasions (binge drinking) as a pattern of drinking that brings blood alcohol concentration (BAC) levels to 0.08 g/dL. This typically occurs after four drinks for women and five drinks for men in about 2 hours.

The graduated quantity–frequency approach is a suggested way to consider measuring the frequency of drinking and drinking patterns (T. K. Greenfield, 2000). Measuring drinking patterns are more complex than estimating the amount of alcohol consumed. In the 2000 Comparative Risk Assessment in the Global Burden of Disease Study, a measure of drinking patterns – the patterns of drinking score (PDS) – was developed (Rehm, Rehn, et al., 2003). The drinking pattern score is measured by calculating the frequency of drinking, average quantity per occasion, frequency of risky single drinking occasions, frequency of drinking with meals and frequency of drinking in public (Astudillo, Kuntsche, Graham, & Gmel, 2010; Gmel, Room, Kuendig, & Kuntsche, 2007).

1.7. Alcohol Consumption and Glucose Homeostasis

High amount and frequency of alcohol consumption especially in the long term are harmful to almost all cells in the body. On the other hand, low to moderate drinking has protective effects against cardiovascular diseases or ischemic stroke (Fujita & Takei, 2011).

Acute or chronic alterations in glucose homeostasis (such as hypoglycemia and hyperglycemia) may cause adverse effects on different cells in the body. Alcohol consumption also affects different pathways of glycemic control and insulin actions by affecting key regulators of glucose homeostasis. These effects of alcohol consumption are related to the duration of time that different cells in the body have had exposure to alcohol (Steiner, Crowell, & Lang, 2015).

1.7.1. Alcohol and glucose concentrations

The effects of alcohol consumption on glucose concentrations are still controversial. Alcohol interferes with all three main sources of glucose metabolism including glucose ingestion from food, gluconeogenesis and glycogenolysis (Gordon & Lieber, 1992).

Alcohol consumption may cause severe and sustained hypoglycemia after fasting situations for about 3 to 4 days (Searle, Shames, Cavalieri, Bagdade, & Porte, 1974). Alcohol-induced hypoglycemia usually
occurs in diabetic and non-diabetic people who consume alcohol in fasting states and without eating for long periods. In this situation blood glucose concentrations provide enough energy to the brain by glycogenolysis and gluconeogenesis (Emanuele, Swade, & Emanuele, 1998).

According to a review study by Badawy et al. (1997), alcohol consumption is related to an initial hyperglycemia following later hypoglycemic effects and therefore these findings represent that alcohol consumption has various effects on glucose concentrations (BADAWY, 1977).

Chronic alcohol drinking in high amounts increases the ratio of NAD+/NADH which reduces the gluconeogenesis rate and thus may lead to hypoglycemia (Kandi & Ramana, 2014) and also alcohol consumption decreases hepatic gluconeogenesis by reducing the concentration of pyruvate (Emanuele et al., 1998). However, the risk of hypoglycemia is higher in individuals with alcohol use disorders and people with impaired liver functions (H. E. Williams, 1984).

Chronic alcohol consumption with a long time of fasting may cause severe hypoglycemia leading to brain damage and persistent vegetative states (Jain, Beriwal, & Singh, 2002).

Most studies also suggest that alcohol consumption decreases glucose uptake by the brain cells (Steiner et al., 2015). Acute alcohol consumption decreases glucose arterial-jugular vein difference which indicates malfunction and neurological impairment (Muneer, Alikunju, Szlachetka, & Haorah, 2011).

It has been also suggested that alcohol consumption reduces the basal metabolism of the brain especially in heavy drinkers (Volkow et al., 2015). Decrease in glucose uptake due to alcohol consumption might be explained by reducing glucose transporter 1 (GLUT1) which may lead to blood brain barrier (BBB) dysfunction and neurological impairments (Muneer et al., 2011).

Several studies suggest that alcohol consumption reduces whole liver glycogen contents (Van Horn, Ivester, & Cunningham, 2001), it occurs both in periportal and perivenous hepatocytes by reducing basal glycogen synthase activity (Steiner et al., 2015).

Alcohol consumption lowers postprandial glucose by 16 to 37% (Brand-Miller et al., 2007). Acute alcohol consumption also decreases glucose uptake from some specific muscles (such as red quadriceps and soleus) but not others (such as gastrocnemius and white quadriceps) (Spolarics et al., 1994; Steiner et al., 2015). Chronic alcohol consumption, on the other hand, has no effect on basal glycogen content in skeletal muscles (Martin, Levi, Slavin, & Peters, 1984).

1.7.2. Alcohol and changes in basal insulin and glucose tolerance

Alcohol can reduce gastric emptying and gastric absorption; therefore, it may affect the results of oral glucose tolerance test. However, the effects of alcohol consumption on glucose tolerance are
 Alcohol consumption may improve, impair or not change glucose tolerance (Steiner et al., 2015).

In some studies, it has been shown that short-term (several hours) or long-term (1 to 3 weeks) infusion of alcohol may not have any changes on glucose tolerance in healthy non-diabetic individuals (J. Beulens, De Zoete, Kok, Schaafsma, & Hendriks, 2008). On the other hand, some studies have suggested that moderate alcohol consumption improves glucose tolerance which may be the result of increased insulin secretion by the pancreas (Facchini, Chen, & Reaven, 1994; Friedenberg, Metz, Mako, & Surmaczynska, 1971).

Facchini et al., (1994) evaluated the association between alcohol consumption and insulin sensitivity and plasma glucose concentrations among 40 adults, by oral glucose tolerance test. Among them, eleven women and nine men reported being light to moderate drinkers, consuming 10-30 g alcohol/day or 0.7-2.1 drinks per day, whereas the other half reported being non-drinkers. This study found plasma glucose was significantly lower in the light to moderate drinkers (120.7mg/dl ±14.4) compared to non-drinkers (192.8mg/dl ±21.6), (p<0.01) (Facchini et al., 1994).

Some other studies have revealed an opposite result. For instance, it has been shown that chronic alcohol consumption impairs glucose tolerance following oral glucose tolerance test (Andersen et al., 1983; Pezzarossa, Cervigni, Ghinelli, Molina, & Gnudi, 1986) and Kim et al, (2014) have suggested that even after a single dose of alcohol, impaired glucose tolerance has been reported (J. Y. Kim et al., 2014).

Some studies show that mild alcohol consumption may reduce insulin concentration and induce alcohol-related hypoinsulinemia (Michael J Davies et al., 2002). According to a cross-sectional study of men aged between 48 to 82 years, the frequency of alcohol consumption was inversely associated with insulin concentrations and also men who consumed alcohol almost every day had lower fasting insulin concentrations compared to irregular drinkers (K. A. Meyer et al., 2003). Another study by Bonnet et al, also represented the same results and they suggested that low to moderate alcohol consumption in healthy women increases insulin sensitivity, lowers basal insulin secretions and lowers fasting plasma glucagon concentrations which may lead to reduced risk of diabetes and in men increasing alcohol consumption also increased insulin sensitivity (Bonnet et al., 2012).

However, most of the other studies indicate that basal post absorptive insulin concentrations do not change significantly due to alcohol consumption (Kuhl & Andersen, 1974; Metz, Berger, & Mako, 1969). Furthermore, 1-3 weeks of moderate alcohol consumption had no effect on basal insulin concentration (J. Beulens et al., 2008; DEH Flanagan et al., 2002) and also plasma concentration of insulin did not alter even after long-term moderate alcohol consumption (Facchini et al., 1994).

On the other hand, in some other studies the association between alcohol consumption and basal insulin consumption has been defined as a J or U shape, which means that mild to moderate alcohol drinking...
decreases fasting insulin, whereas no drinking, low drinking or regular heavy drinking may increase that (Michael J Davies et al., 2002; Kiechl et al., 1996; Schrieks, Heil, Hendriks, Mukamal, & Beulens, 2015).

1.7.3. Alcohol consumption and insulin sensitivity

Several studies have suggested the association of acute alcohol consumption with a decrease in insulin-stimulated glucose uptake might be indicative of whole body insulin resistance (Shelmet et al., 1988; Yki-Jarvinen & Nikkila, 1985).

Compared to nondrinking, low or heavy drinking; moderate alcohol consumption caused a higher fasting insulin resistance index and fasting insulin (Lazarus, Sparrow, & Weiss, 1997).

It has been suggested that acute alcohol consumption does not associate with hepatic insulin resistance (Avogaro et al., 1987), however, acute alcohol consumption decreases glucose uptake and glucose storage by muscles in a hyperinsulinemic state and this mechanism is not associated with reduced glycogen synthase activity (Boden, Chen, Desantis, White, & Mozzoli, 1993). Therefore, in general acute and chronic alcohol consumption induce skeletal muscle insulin resistance (Steiner et al., 2015).

On the other hand, according to a cross over partial diet controlled study by Sierksma et al. (2004), alcohol consumption improved insulin sensitivity in insulin resistant middle-aged men which might be due to an increase in adiponectin levels (Sierksma et al., 2004). Another cross over interventional study on middle-aged healthy men, revealed that no effect of alcohol was related to insulin sensitivity index (ISI), HOMA-IR, fasting glucose or insulin (Zilkens, Burke, Watts, Beilin, & Puddey, 2003).

According to Flanagan et al., (2000), insulin sensitivity was positively associated with alcohol consumption. However, no relationship was detected between alcohol consumption and fasting glucose, fasting insulin and glucose tolerance (DE Flanagan et al., 2000).

In general, in the previous literature, it has been suggested that low to moderate drinking increases insulin sensitivity (Hendriks, 2007; S. H. Kim, Abbasi, Lamendola, & Reaven, 2009) or anti-inflammatory factors such as adiponectin. Adiponectin has been shown to increase insulin receptor substrate in the liver and aid in transporting glucose out of the blood (Hendriks, 2007; Sierksma et al., 2004). However, excessive alcohol consumption has been shown to decrease insulin sensitivity and increase the risk of type 2 diabetes (Baliunas et al., 2009; J. W. Beulens et al., 2007; Facchini et al., 1994; M. Joosten, Beulens, Kersten, & Hendriks, 2008).

Metabolic syndrome, as a combination of obesity, hypertension, dyslipidemia, and hyperglycemia increases the risk of cardiovascular diseases and it has been suggested that alcohol consumption and metabolic syndrome are associated with a J shape pattern (Fujita & Takei, 2011).
According to a cross-sectional study of 4510 participants, however, alcohol consumption was associated with lower prevalence of metabolic syndrome (Djoussé et al., 2004).

### 1.7.4. Alcohol consumption and diabetes

As mentioned above alcohol consumption has various effects on different parameters of glucose homeostasis and consequently it might play an important role in the pathogenesis of diabetes.

Effective prevention from diabetes needs a global strategy to pinpoint the modifiable risk factors that can easily and cost effectively be controlled. Alcohol consumption may be one of the most common modifiable lifestyle factors that can affect many aspects of a diabetic patient’s life.

Even though, low to moderate drinking is suggested to have a protective effect on the incidence of diabetes, regular or irregular heavy drinking occasions increase that risk; however, not enough information is available regarding regular or irregular heavy drinking occasions in association with incidence of diabetes (Baliunas et al., 2009; Howard, Arnsten, & Gourevitch, 2004; Klatsky, 2007; Rehm, Sempos, & Trevisan, 2003).

A prospective study, also found that compared to lifelong abstainers, low to moderate drinkers had a lower risk for type 2 diabetes (S. G. Wannamethee, Camargo, Manson, Willett, & Rimm, 2003). In general, some previous studies, represent that moderate alcohol consumption is associated with reduced risk of diabetes (Carlsson, Hammar, Grill, & Kaprio, 2003; Rimm, Chan, Stampfer, Colditz, & Willett, 1995). On the other hand, some other studies have suggested a non-linear relation between alcohol intake and the risk of type 2 diabetes. This non-linear association was explained by reduction in risk of type 2 diabetes with moderate drinking and the adverse effect of regular and irregular heavy drinking occasions (S. Wannamethee, Shaper, Perry, & Alberti, 2002).

A systematic review of 15 cohort studies published in 2005 by Koppes et al, found a U shape association between alcohol drinking and diabetes. However, the risk of diabetes type 2 for heavy drinkers (≥48g/day) was similar to nondrinkers (Koppes, Dekker, Hendriks, Bouter, & Heine, 2005).

Another systematic review and meta-analysis of 20 cohort studies by Baliunas et al, in 2009 also confirmed the results of the previous systematic review mentioned above by finding a U shape association for both men and women. This study revealed that compared to lifelong abstainers, among men who consumed average of 22g/day alcohol, alcohol consumption had a protective effect but for heavy drinkers higher than 60 g/day it had a harmful effect. In addition, among women who consumed in average of 24g/day of alcohol the relative risk (RR) was lower than for those who consumed higher than 50 g/day (Baliunas et al., 2009).

On the other hand, a recent systematic review and meta-analysis of 38 observational studies by Knott et al. (2015) indicated that among moderate alcohol consumers, reducing the risk of diabetes may be only
limited to women and non-Asian populations or it may be overestimated by studies using a reference group mixed with less healthy former drinkers (Knott, Bell, & Britton, 2015).

In summary, as the incidence and prevalence of diabetes is rapidly growing, it might be necessary to identify its different risk factors to decrease premature mortality and delay its morbidities. Diabetes is a significant economic and public health burden, therefore, to understand the underlying physiologic mechanism of alcohol drinking on diabetes, having more information about the effects of alcohol on different parameters of glucose homeostasis might be necessary. This might also lead to decreasing public expenditures on health care costs and reducing indirect costs due to diabetes disabilities. Furthermore, this would decrease the economic and emotional burden on families.

1.8. Rationale

As one can discern from the discussion above, there are widely conflicting data regarding the relationship between alcohol consumption and glucose homeostasis. In terms of alcohol drinking and glucose homeostasis, only one systematic review and meta-analysis has been published (Schrieks et al., 2015), however, even in this systematic review only interventional studies were included and they have assessed the association of alcohol drinking (excluding heavy drinkers) on glucose homeostasis in short term periods with a duration of 2 to 12 weeks (Schrieks et al., 2015), which may not be relevant for longer-term developments in natural courses.

In sum, a systematic review of interventional studies already exists in this field but no systematic review has evaluated real-life data (i.e. observational studies) for the long-term effects alcohol consumption on glucose homeostasis parameters. On the other hand, as explained above, significant inconsistency exists in the previous literature for the association of alcohol consumption with glucose homeostasis.

To determine the long-term effects of dose response alcohol drinking on implicit changes of different parameters of glucose homeostasis including fasting glucose, serum insulin, insulin sensitivity and HbA1C, we conducted the following systematic review and meta-analysis. This relationship may help develop a better understanding of the risk factors associated with type 2 diabetes.

1.8.1. Research objective

To sum up all available observational studies (cohort and case-control studies) related to the association of alcohol consumption and glucose homeostasis parameters.
1.8.2. Research question

Is alcohol consumption compared to non-drinking associated with implicit changes of glucose homeostasis parameters including blood glucose level, insulin sensitivity, serum insulin, and HbA1C in patients with no diabetes?

1.8.3. Hypotheses

- Compared to non-drinkers, low to moderate alcohol consumers have a higher incidence of impaired glucose homeostasis parameters (by increasing the incidence of impaired fasting glucose, impaired glucose tolerance, insulin resistance, and increasing serum insulin concentrations and HbA1C levels).

- Compared to low to moderate drinkers, heavy drinkers (both regular and irregular heavy drinkers) have a higher incidence of impaired glucose homeostasis parameters (by increasing the incidence of impaired fasting glucose, impaired glucose tolerance, insulin resistance, and increasing serum insulin concentrations and HbA1C levels).
Chapter 2

2. Materials and Methods

We have used an established methodology for conducting systematic reviews, which include a clear research question, comprehensive, and explicit search strategy, criterion-based inclusion/exclusion criteria uniformly applied, rigorous and transparent critical appraisal, explicit and appropriate syntheses methods, and evidence-based inferences.

This systematic review, followed Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guideline (Moher, Liberati, Tetzlaff, & Altman, 2009). The PRISMA checklist (recommended items to address in a systematic review protocol) is provided in Appendix A.

We also did a mock submission to PROSPERO, an international prospective register of systematic reviews. However, as we had finished our systematic review we could not register the current review (Stewart, Moher, & Shekelle, 2012). The PROSPERO submission can be found in Appendix-C.

2.1. Search Strategy

The research team initially developed all its search strategies in consultation with the health research librarians at the University of Toronto and CAMH who had previous experience conducting systematic reviews.

Before running the searches, we held a first meeting with the knowledge users group to provide them the opportunity to comment on the search strategies and suggest terms, databases, or resources. Our electronic searching was followed by hand searching for references found in the included and relevant articles.

We systematically searched Medline and Embase from their inception up to February 2016. Additionally, we searched reference lists of identified articles and published meta-analyses and reviews. We conducted appropriate search key words for alcohol consumption and different glucose homeostasis parameters and we focused our review on observational studies.

We adapted the P.I.C.O. structure of reviews for our search strategy; PICO stands for Population, Intervention, Comparison and Outcomes (Stone, 2002).

For this systematic review, the P.I.C.O format was operationalized as follows:

“P”: What is the population of our interest?
We included adult human samples. Therefore, we limited our search to “humans”. Among them, we were looking for those who were not diabetic at baseline.

To find studies reflecting this population, we had specific search key words for diabetes including “diabetes mellitus” or “type 2 diabetes” or “non-insulin resistance diabetes” or “niddm” (section 2.1.1, the list of search terms).

“I”: What are the intervention/exposure?

For this systematic review, the exposure was alcohol consumption for which we used specific search keywords of “alcohol drinking” or “consumption” or “intake” or “intoxication” or “heavy drinking” or “binge drinking” or “alcoholic beverages” (section 2.1.1, the list of search terms).

“C”: What is the comparator or control group?

For this systematic review, the comparator would be those who were not drinking alcohol (non-drinkers).

“O”: What are the outcomes of our study?

The outcome of our interest was glucose homeostasis parameters (including blood glucose levels, serum insulin, insulin sensitivity and HbA1C).

Therefore, we used search key words of “glycaemia” or “hypoglycemia” or “hyperglycemia”, or “euglycemia”, “glucose” or “blood glucose”, “glucose homeostasis” or “glucose retake or uptake”, “insulin”, “glucagon”, “HbA1C”, “hemoglobin A1C” or “glycated” or “glycosylated hemoglobin” or “Hemoglobin A, Glycosylated” (section 2.1.1, the list of search terms).

We also limited our search to cohort or case-control studies and thus excluded other types of studies, as our objective was to study the natural course of the impact of alcohol on different parameters of glucose homeostasis. Specific reasons for inclusion and exclusion of study types are discussed below.

For identification of relevant studies, health research librarians at University of Toronto and CAMH have helped us to conduct all search strategies in the indexed databases.

The list of search terms can be found in the following page.
2.1.1 The List of Search Terms (OVID at University of Toronto)

Method terms:
exp Case-Control Studies/ or case control.mp.
exp cohort studies/ or exp follow-up studies/ or exp longitudinal studies/ or exp prospective studies/ or exp retrospective studies/ or cohort study.mp.

Exposure terms:
exp Alcohol Drinking/
exp Alcoholic Intoxication/
exp binge drinking/
(alcohol* adj3 (drink* or consum* or intake)).mp.
heavy drinking.mp.
alcoholic beverages/

Outcome terms:
insulin.mp. or exp insulin/
exp glucagon/ or glucagon.mp.
HbA1C.mp. or exp hemoglobin A1c/
glyc?emi$.mp
glycated h?emoglobin.mp.
Hemoglobin A, Glycosylated.mp. or exp glycosylated hemoglobin/
exp hypoglycemia/
exp hyperglycemia/
euglycemi*.mp.
Glucose.mp. or exp Glucose/
blood glucose.mp. or exp glucose blood level/ or exp Blood Glucose/
glucose homeostasis.mp. or exp glucose homeostasis/
(glucose adj2 (regulate* or uptake)).mp
Diabetes Mellitus/ep, et, mo, pc
diabetes mellitus/ep, et, pc
exp diabetes mellitus, type 2/
(diabetes adj2 type 2).mp.
niddm.mp.
exp non insulin dependent diabetes mellitus/

2.2. Study Selection

2.2.1. Inclusion criteria

- Population (type of participants):
  Adult human samples

- Type of literatures:
  Observational studies (cohort and case-control studies)

- Publication date:
  We did not have any date restrictions.

- Language of literature:
  Articles published in English (Due to limited support for translation, we restricted our search to English language articles. Language limits can impose information bias; however, we found that most articles in this field were written in English). For the peer-reviewed journal articles, it is assumed that high impact research in this field will have been translated into English. Therefore, it is believed that no high impact papers will be disregarded from the review based on the language restriction.

- Content of literature:
Articles that have assessed the association of alcohol drinking with any parameters of glucose homeostasis (blood glucose level, serum insulin level, insulin sensitivity or HbA1C) in patients who were free of diabetes at baseline.

2.2.2. Exclusion criteria

Cross-sectional studies, clinical trials, letters, editorials, grey literatures, abstract meetings and review articles were excluded.

We also excluded articles which have assessed the association of alcohol drinking with glucose homeostasis parameters exclusively in diabetic patients at baseline.

Articles, which had combined glucose homeostasis parameters with a diagnosis of diabetes in one outcome, were excluded as well.

2.2.2.1 Justification for excluding cross-sectional studies

As we were looking for the long-term effects of alcohol consumption on incidence of or change in impaired glucose homeostasis parameters, we excluded cross-sectional studies because cross-sectional studies assess the relationship of alcohol and glucose homeostasis parameters at a single point in time and the cause and effect relationships cannot be measured by cross-sectional studies (Sedgwick, 2014). Of course, longitudinal studies still have problems in assessing causality, but at least one criterion of causality – temporality – is controlled.

2.2.2.2 Justification for excluding clinical trials

As we were looking for the long-term effects of alcohol consumption on glucose homeostasis parameters, we excluded clinical trial studies because these tend to have a short time. For example, the recent systematic review and meta-analysis of interventional studies on the effects of alcohol consumption on different parameters of glucose homeostasis (Schrieks et al., 2015) had a follow-up time of 2 to 12 weeks, which is not sufficient for our objectives, as we are looking for the natural course, i.e., for long-term effects of alcohol consumption on different parameters of glucose homeostasis.

2.2.2.3 Justification for excluding studies not published as full papers including letters, editorials, grey literatures, and meeting abstract

Although including non-peer review articles and grey literature may reduce selection bias, because of the limited time-line that we had, we only included peer review articles. Moreover, the sampling frame for grey literature is not clear, and contrary to systematic searches of electronic databanks, a systematic search for grey literature is problematic. As for letters, editorials and abstracts, these types of literature usually do not have the information necessary to be included in this review.
2.2.2.4 Justification for excluding articles, which had diabetic patients at baseline, and articles, which had combined glucose homeostasis parameter with diabetes in one outcome

As we wanted to assess the association of alcohol consumption with changes of glucose homeostasis, we had to exclude those articles with diabetic patients at baseline, since glucose homeostasis parameters are affected in diabetic patients.

As we were mainly concerned for the effects of alcohol consumption on different parameters of glucose homeostasis, we excluded those studies, which had combined any parameters of glucose homeostasis with diabetes in one outcome.

We initially screened papers for inclusion by title and abstract followed by full text review. Two independent reviewers conducted all phases of study selection, critical appraisal and data extraction of the literature independently. When disagreement between reviewers occurred, consensus was attempted. If consensus was not reached, a third reviewer was consulted.

2.3. Data Extraction

Data were extracted according to the variables that had been agreed upon by the team members for all papers included in this study.

During the process of data extraction, we had regular team meetings to resolve issues related to locating the data in the text, establishing the nature and type of the data, ascertaining reliability of data extraction and, checking data extraction in preparation for analysis.

From all included studies, we extracted authors’ names, year of publication, country, years of follow up, age, sex, setting, number of cases and total participants, assessment of alcohol drinking, description of different categories of alcohol drinking if applicable, assessment of glucose homeostasis parameters, adjustment factors for potential confounders, relative risk (RR) and its standard error (SE). The most adjusted reported RRs were used.
2.3.1 Justification for using the most adjusted RR with cons and pros of this decision

To reduce the effects of different confounders for the association of alcohol consumption with different parameters of glucose homeostasis, we used the most adjusted RR if adjustment was done for true confounders and not for factors which were on the causal pathway. One consequence of this decision was that it was not possible to include articles with the same adjustments.

Using the best controlled estimate intended to reduce over-or-under estimate of true effects of alcohol consumption on different parameters of glucose homeostasis. Due to the distortion of the effects of alcohol consumption on glucose homeostasis parameters by confounders, we used the most adjusted RR for each study in our meta-analysis.

However, as indicated above, using the most adjusted effect size might cause over adjusting for some factors, which affect the causal pathways, and which are not the true confounders. Therefore, factors affecting only the causal pathways as a mediator should not be adjusted for.

Among the studies that we have included in our meta-analysis, only one study (B. J. Kim, Kim, & Kang, 2012) might be over adjusted due to adjustments for each component of metabolic syndrome, which means that in this study, some factors that have effects on causal pathway of alcohol consumption and impaired glucose homeostasis, such as low HDL, and high triglyceride have also been considered as confounders. However, the only model that did not have adjustments for components of metabolic syndrome in this study was age-adjusted only and it was not adjusted for other important factors such as weight, and lifestyle status (diets, smoking, and exercise) (Table 3.12).

This method of using most adjusted risk relations may lead to biased attributable fractions, but this statistic is not in the major objectives of this work. The reasons are that Levin’s original formulas for population attributable fractions are only valid in the absence of confounding and effect modification. Commonly, the approach used to address this concern is to use a confounder adjusted relative risk and the prevalence of exposure in the study or population, referred to hereafter as the partially adjusted method. However, if there is confounding or effect modification affecting the relative risk, then the estimate of the attributable fraction is potentially biased even if the relative risk has been adjusted for confounding (Benichou, 2001).

On the other hand, as indicated above, different studies might have used different adjustments, leading to heterogeneity in pooled estimates or meta-analysis (Rothman, 2012). In addition, we were faced with the problem that control for confounding was incomplete in some studies, also leading to heterogeneity. However, this is a risk of any pooling of different epidemiological studies.
2.4. Exposure Assessment

When alcohol consumption were reported as number of drinks, we used the mid-points (mean) of each category and converted these to grams per day (g/day) using reported conversions or country-specific conversions (Alcohol Guidelines. Eleventh Report of Session 2010–12: Report, Together with Formal Minutes, Oral and Written Evidence, 2012). For open-ended categories, we added three-quarters of the previous category to the lower bound.

Depending on the country, one standard drink is approximately 10–14 g of pure alcohol (WHO, 2000). To standardize alcohol intake across studies, we used 12 g/day as a standard drink and created four categories of average alcohol intake: abstainers (reference), ≤1 drink/day, >1 to ≤2 drinks/day, >2 to ≤3 drinks/day and >3 drinks/day.

We also considered alcohol consumption as a continuous variable in a separate linear regression analysis.

2.5. Outcome Assessment

Glucose homeostasis parameters’ outcomes were categorized into the following groups:

1) Blood glucose levels
2) Serum insulin level
3) HbA1C

For our meta-analysis, we included those articles that have evaluated the association of alcohol consumption with incidence of fasting glucose of ≥100 mg/dL at follow up, in those patients who were free of diabetes at baseline.

For those studies with the outcome of serum insulin or HbA1C, which were not combined in our meta-analysis, we used GRADE methods for evidence-based synthesis.

2.6. Quality Assessment

We used Newcastle-Ottawa Scale (NOS) to critically appraise the included studies for our current systematic review and meta-analysis (Wells et al., 2000).

(http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp, last accessed on 31.12.16.)
Use of Newcastle-Ottawa Scale (NOS) for critically appraising the observational studies has been endorsed by Cochrane collaboration in its 2011 handbook (Higgins & Green, 2011) and it has a separate version for cohort and case-control studies. For cohort studies, it has three items for “selection”, “comparability” and “outcome”.

Based on Newcastle-Ottawa Scale (NOS), high-quality responses earn a star, and in total they gain up to nine stars, (the comparability question earns up to two stars in total). The range of possible scores is from 0 through 9.

Two independent investigators evaluated the quality of each study for the assessment of potential biases, and disagreements were solved by consensus.

We also used GRADE methods for qualitatively synthesizing the results.

### 2.7. Statistical Analysis

We used the most adjusted RRs reported and the most comprehensive data available for each analysis, and gave priority to estimates where adjusted data and lifetime abstainers as the risk reference group were used. If necessary, RRs within studies were re-calculated based on the method described by Hamling and colleagues (Hamling, Lee, Weitkunat, & Ambühl, 2008). Reports of stratified analyses by sex were treated as independent samples.

We conducted categorical meta-analyses based on total alcohol consumption and although we had low number of studies for a subgroup analyses, we performed linear generalized least squares meta-regression analyses stratified by sex treating alcohol categories as a continuous variable (Orsini, Bellocco, & Greenland, 2006).

RRs were pooled with inverse-variance weighting using DerSimonian-Laird random-effect models to allow for between-study heterogeneity (DerSimonian & Laird, 1986).

Variation in the effect size because of heterogeneity between-studies was quantified using the Q- and I² statistic (J. Higgins & S. G. Thompson, 2002). Publication bias was examined using Egger’s regression-based test (Egger, Smith, Schneider, & Minder, 1997) and visual inspection of the funnel plot.

All meta-analyses were conducted on the natural log scale in Stata statistical software, version 14.1, and p< 0.05 (two-sided) was considered statistically significant.
Chapter 3

3. Results

We had 2893 articles (2890 articles from the electronic search after removal of duplicates, and 3 articles from hand search). Figure 3.1 represents the flowchart of search strategy. After reviewing the title and abstract 402 articles were retrieved for full text review (325 articles had no measure of alcohol and glucose homeostasis, 2 articles were from same cohort, 7 conference abstracts, 1 pilot study, 40 cross-sectional studies, 1 clinical trial, 10 articles from non-English studies, and 3 articles had combined outcome for glucose homeostasis parameters and diabetes diagnosis). In total 13 unique articles were included in our systematic review and among them seven articles were included in our meta-analysis.

Our included articles were categorized into three groups based on the outcomes: Seven articles with the outcome of incidence of fasting glucose ≥100mg/dL (Baik & Shin, 2008; Barrio-Lopez et al., 2013; Buja et al., 2010; Cullmann, Hilding, & Östenson, 2012; B. J. Kim et al., 2012; Marques-Vidal, Vollenweider, & Waeber, 2015; Shuval et al., 2012), three articles with the outcome of serum insulin (Balkau et al., 2006; Møller & Jespersen, 1995a; Rankinen et al., 1997), and three articles with the outcome of HbA1C (M. M. Joosten et al., 2011; Kiechl et al., 1996; Suwazono et al., 2009).

The detailed information based on different indicators of glucose homeostasis is summarized in Table 3.1.

We performed meta-analysis for those articles with the outcome of incidence of fasting glucose ≥100 mg/dL (seven articles).

Among those studies included in our meta-analysis, two studies included only men, five studies both men and women (three studies had data for both men and women separately and two studies had data for men and women combined) (Table 3.11).

Among those included articles in our meta-analysis, two studies were conducted in Korea, one in Italy, one in U.S, one in Sweden, one in Switzerland, and one in Spain. The total number of participants in our meta-analysis was 32,958 with a mean age of 50.2 and an average follow up time of 5.8 years. The detailed information about those included articles in our meta-analysis is summarized in Table 3.11.
Figure 3.1. Flowchart of the search strategy and process of selecting articles for association of alcohol consumption and glucose homeostasis parameters
Table 3.1. Included articles based on different indicators of glucose homeostasis

<table>
<thead>
<tr>
<th>Indicator</th>
<th>Number of included studies</th>
<th>Type of studies</th>
<th>Meta-analysis (Yes/No)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting glucose</td>
<td>7</td>
<td>All cohorts</td>
<td>Yes</td>
</tr>
<tr>
<td>Serum insulin</td>
<td>3</td>
<td>All cohorts</td>
<td>No</td>
</tr>
<tr>
<td>HbA1C</td>
<td>3</td>
<td>All cohorts</td>
<td>No</td>
</tr>
</tbody>
</table>
3.1. Alcohol Consumption and Different Parameters of Glucose homeostasis

In the following passage, the results of all articles that fulfilled our inclusion criteria are summarized. We performed meta-analysis for those included articles with the outcome of incidence of fasting glucose ≥100 mg/dL.

3.1.1. Justification for not performing meta-analysis for other indicators of glucose homeostasis (serum insulin and HbA1C)

As there was low number of studies for other categories of glucose hemostasis parameters (serum insulin and HbA1C) and also those studies were not homogenous, we did not perform a separate meta-analysis for each separate outcome and instead we only used GRADE methodologies for evidence based synthesis for those studies.

3.1.2. Alcohol consumption and serum insulin

We found three cohort studies (Balkau et al., 2006; Møller & Jespersen, 1995a; Rankinen et al., 1997) for association of alcohol consumption with serum insulin.

In a cohort study by Rankinen et al. (1997), 146 non-diabetic men aged 50-60 years at baseline participated. Plasma insulin was checked at baseline and then at 30 months later. Logistic regression analysis was performed to assess the odds ratio (OR) to measure changes in insulin levels during follow-up. Those participants who were drinking higher than 12 g/day had an odds ratio for high fasting plasma insulin of 12.8 (with 95%CI of 1.7-94.5) and a P value of 0.012. In general, the results of this study suggest that regular alcohol consumption increases the likelihood of an increase in plasma insulin (Rankinen et al., 1997).

More information about the results of this study is summarized in Table 3.2.
Table 3.2. Logistic regression analysis for the plasma insulin increase at 2.5-year follow-up in 146 middle-aged men (Rankinen et al., 1997)

<table>
<thead>
<tr>
<th>Alcohol intake</th>
<th>OR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>&lt;12g/d</td>
<td>0.9 (0.3-2.8)</td>
<td>0.909</td>
</tr>
<tr>
<td>≥12g/d</td>
<td>12.8 (1.7-94.5)</td>
<td>0.012</td>
</tr>
</tbody>
</table>

Another cohort study by Møller et al. (1995) investigated 577 men born in 1936 in Copenhagen, and among them 427 participated at both examinations at age 40 (in 1976) and then at age 51 (in 1987). Those participants who were on antidiabetic agents were excluded. The results indicated that a change in alcohol consumption was not significantly associated with a change in fasting serum insulin (Møller & Jespersen, 1995a).

Another follow-up study from DESIR cohort conducted in France, assessed the association of alcohol consumption in 3-year average and 3-year change with fasting insulin on 1917 men and 2006 women who were not using any anti-diabetic medications at baseline or at follow-up. However, it did not find a statistically significant change in fasting serum insulin in association with 3-year average or 3-year change in alcohol consumption (Balkau et al., 2006).

The detailed critical appraisal for these studies are shown in Table 3.3, Table 3.4, and Table 3.5.
### Table 3.3. Critical appraisal for the study of Rankinen et al, (1997) about association of alcohol consumption with serum insulin (based on Newcastle-Ottawa Scale (NOS))

<table>
<thead>
<tr>
<th>Selection</th>
<th>Comparability</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1) b*</td>
<td>1) a, b**</td>
<td>1) b*</td>
</tr>
<tr>
<td>2) a*</td>
<td></td>
<td>2) a*</td>
</tr>
<tr>
<td>3) c</td>
<td></td>
<td>3) b*</td>
</tr>
<tr>
<td>4) a*</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Reason for scoring less than 9:
3. Self-reported questionnaires (4-day diary food records) for alcohol consumption
Table 3.4. Critical appraisal for the study of Moller and Jepersen et al, (1995) about association of alcohol consumption with serum insulin (based on Newcastle-Ottawa Scale (NOS))

<table>
<thead>
<tr>
<th>Moller and Jepersen (1995) Score 8 out of 9</th>
<th>Selection</th>
<th>Comparability</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1) b*</td>
<td>1) a, b**</td>
<td>1) b*</td>
</tr>
<tr>
<td></td>
<td>2) a*</td>
<td></td>
<td>2) a*</td>
</tr>
<tr>
<td></td>
<td>3) d</td>
<td></td>
<td>3) b*</td>
</tr>
<tr>
<td></td>
<td>4) a*</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Reason for scoring less than 9:
3. No description for ascertainment of exposure (alcohol consumption)
Table 3.5. Critical appraisal for the study of Balkau et al, (2006) about association of alcohol consumption with serum insulin (based on Newcastle-Ottawa Scale (NOS))

<table>
<thead>
<tr>
<th>Balkau (2006)</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Score 7 out of 9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Selection</td>
<td>Comparability</td>
<td>Outcome</td>
</tr>
<tr>
<td>1) b*</td>
<td>1) a, b*</td>
<td>1) b*</td>
</tr>
<tr>
<td>2) a*</td>
<td></td>
<td>2) a*</td>
</tr>
<tr>
<td>3) c</td>
<td></td>
<td>3) b*</td>
</tr>
<tr>
<td>4) a*</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Reason for scoring less than 9:
3. Self-reported questionnaires and food frequency questionnaires (FFQ) for alcohol consumption

Study has only adjustments for age and educational levels
3.1.3. Alcohol consumption and HbA1C

We included three cohort studies about association of alcohol consumption with HbA1C (M. M. Joosten et al., 2011; Kiechl et al., 1996; Suwazono et al., 2009).

A cohort study included in this field, prospectively examined 1188 men with no diagnosis of diabetes or cancer at baseline and showed that HbA1C had a better profile among non-drinkers (abstainers) and low drinkers (initially consuming <15g/day) who modestly increased their drinking compared to men who were drinking ≥15g/day at baseline (M. M. Joosten et al., 2011). Detailed information is summarized in Table 3.6.

Table3.6. Mean increment (±Standard error of mean) per 7.5 g/d increase in alcohol consumption over 4 years of follow-up (M. M. Joosten et al., 2011)

<table>
<thead>
<tr>
<th>Alcohol consumption (g/d) in 1990</th>
<th>HbA1C (%)</th>
<th>Number of participants</th>
</tr>
</thead>
<tbody>
<tr>
<td>None (0)</td>
<td>-0.04±0.02</td>
<td>267</td>
</tr>
<tr>
<td>&lt;1 drink/day (0.1 to 14.9 g/d)</td>
<td>-0.02±0.02</td>
<td>610</td>
</tr>
<tr>
<td>≥1 drink/day (≥15g/d)</td>
<td>0.01±0.01</td>
<td>311</td>
</tr>
</tbody>
</table>

Another cohort study in this field evaluated 7104 male workers at a Japanese company by excluding those who were on anti-diabetic agents before or in the year of entry, and those who had anti-diabetic agents in the subsequent year. The participants were followed up for 14 years (from 1991-2005). The results of this study represented that daily alcohol consumption may protect against an increase in HbA1c level compared to less than daily drinking (Suwazono et al., 2009). The results of this study are shown in Table3.7.
Table 3.7. Association of alcohol consumption and increase in HbA1C (Suwazono et al., 2009)

<table>
<thead>
<tr>
<th>Drinking habits (every day/not every day)</th>
<th>Increase by ≥10%</th>
<th>Increase by ≥15%</th>
<th>Increase by ≥20%</th>
<th>Increase by ≥25%</th>
<th>Increase by ≥30%</th>
</tr>
</thead>
<tbody>
<tr>
<td>OR (95%CI):</td>
<td>OR (95%CI):</td>
<td>OR (95%CI):</td>
<td>OR (95%CI):</td>
<td>OR (95%CI):</td>
<td></td>
</tr>
<tr>
<td>1.09 (1.01, 1.18)</td>
<td>0.99 (0.91, 1.08)</td>
<td>0.85 (0.76, 0.95)</td>
<td>0.80 (0.69, 0.94)</td>
<td>0.74 (0.60, 0.90)</td>
<td></td>
</tr>
<tr>
<td>P value: 0.021</td>
<td>P value: 0.838</td>
<td>P value: 0.005</td>
<td>P value: 0.005</td>
<td>P value: 0.002</td>
<td></td>
</tr>
</tbody>
</table>

On the other hand, the prospective design of the study conducted by Kiechl et al, among non-diabetic participants in Italy, represented that after five years of follow-up, although alcohol consumption decreased HbA1C levels, it did not have a statistically significant effects on that (Kiechl et al., 1996). The critical appraisals for each study included in this field (association of alcohol consumption with HbA1C) are shown in Table 3.8, Table 3.9 and Table 3.10.
Table 3.8. Critical appraisal for the study of Joosten et al, (2011) about association of alcohol consumption with HbA1C (based on Newcastle-Ottawa Scale (NOS))

<table>
<thead>
<tr>
<th>Selection</th>
<th>Comparability</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1) c</td>
<td>1) a, b**</td>
<td>1) b*</td>
</tr>
<tr>
<td>2) a*</td>
<td>2) a*</td>
<td></td>
</tr>
<tr>
<td>3) c</td>
<td>3) b*</td>
<td></td>
</tr>
<tr>
<td>4) a*</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Reason for scoring less than 9:
1. Selected group of users (only male health professionals)
3. Food frequency questionnaires (FFQ) for alcohol consumption
### Table 3.9. Critical appraisal for the study of Suwasono et al, (2009) about association of alcohol consumption with HbA1C (based on Newcastle-Ottawa Scale (NOS))

<table>
<thead>
<tr>
<th>Suwasono (2009)</th>
<th>Selection</th>
<th>Comparability</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Score 7 out of 9</td>
<td>1) c</td>
<td>1) a, b**</td>
<td>1) b*</td>
</tr>
<tr>
<td></td>
<td>2) a*</td>
<td></td>
<td>2) a*</td>
</tr>
<tr>
<td></td>
<td>3) c</td>
<td></td>
<td>3) b*</td>
</tr>
<tr>
<td></td>
<td>4) a*</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Reason for scoring less than 9:**

1. Selected group of users (only male shift workers at a Japanese steel company were enrolled)
2. Self-reported questionnaires for alcohol consumption
Table 3.10. Critical appraisal for the study of Kiechl et al, (1996) about association of alcohol consumption with HbA1C (based on Newcastle-Ottawa Scale (NOS))

<table>
<thead>
<tr>
<th>Selection</th>
<th>Comparability</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1) b*</td>
<td>1) a, b**</td>
<td>1) b*</td>
</tr>
<tr>
<td>2) a*</td>
<td></td>
<td>2) a*</td>
</tr>
<tr>
<td>3) b*</td>
<td></td>
<td>3) b*</td>
</tr>
<tr>
<td>4) a*</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Reason for scoring less than 9: Not applicable
3.2. The GRADE methods to synthesize results qualitatively

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach developed by GRADE working group, provides a systematic approach for rating quality of evidence and strength of recommendations that is explicit, comprehensive, transparent, and pragmatic. It is used worldwide as the most effective method for linking evidence-quality evaluations to clinical recommendations (Guyatt et al., 2008).

The GRADE method specifically evaluates methodological flaws between studies, consistency of results across different studies, generalizability of study results to more patient base and how effective the exposure/intervention could be (Guyatt et al., 2008).

Different components, which are assessed for GRADE scoring, are as follows:
Type of evidence, risk of bias reports, consistency, directness, effect size and precision of results. Based on these components, the final quality of evidence could be categorized as high, moderate, low and/or very low categories.

Evidence from observational studies usually start at low, and we either go down or up (based on those categories mentioned above) (Guyatt et al., 2008).

3.2.1. The GRADE methods for association of alcohol consumption and serum insulin

All three studies included in this field were cohort studies (Balkau et al., 2006; Møller & Jespersen, 1995a; Rankinen et al., 1997). Therefore, as they were all observational studies, for type of evidence category our rating was low. And also these three studies did not have consistency in their results and moreover two of those studies also did not have a statistically significant results (Balkau et al., 2006; Møller & Jespersen, 1995a).

Therefore, for these studies, quality of evidence was rated down and in overall; the final quality of evidence for these studies could be categorized as low/very low GRADE rates.
3.2.2. The GRADE methods for association of alcohol consumption and HbA1C

All three studies included in this field were cohort studies (M. M. Joosten et al., 2011; Kiechl et al., 1996; Suwazono et al., 2009). Therefore, for type of evidence our rating was low. Two of these studies used selected participants, one of them had only male health professionals as the baseline participants (M. M. Joosten et al., 2011) and one other enrolled only shift worker men at a Japanese company (Suwazono et al., 2009). Therefore, in terms of generalizability of study results to wider patient base, these studies did not have strong quality.

And also these three studies had conflicting data and one of those studies (Kiechl et al., 1996) did not have a statistically significant results. Therefore, in overall, for these studies, quality of evidence was rated down and the final quality of evidence for these studies could be categorized as low/very low GRADE rates.

3.2.3. The GRADE methods for association of alcohol consumption and fasting glucose

For those seven studies that we have combined in our meta-analysis with the outcome of incidence of fasting glucose ≥100mg/dL, we started from low rates (as they were all observational studies). However, as most of the studies had high quality of evidence and most but not all the studies had consistent results and also most of the studies had statistically significant results, the overall GRADE rates for these studies was moderate.
Table 3.1. Characteristics of included studies in our systematic review and meta-analysis for the association between alcohol consumption and glucose homeostasis parameters

<table>
<thead>
<tr>
<th>First Author (Year of Publication)</th>
<th>Location</th>
<th>Sex, age at baseline (years)</th>
<th>Cases per total participants</th>
<th>Population at baseline</th>
<th>Follow up (Average years)</th>
<th>Alcohol consumption (Description of categories)</th>
<th>Setting, name of cohort</th>
<th>Adjustment</th>
<th>Outcome measured</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kim (2012)</td>
<td>Korea</td>
<td>M, Median age: 44</td>
<td>310/4391</td>
<td>Free of MetS, none were taking lipid lowering drugs for dyslipidemia</td>
<td>3</td>
<td>g/day: 1 or less occasion per month and &lt;28.25 g of alcohol per time, 1-14.9, 15-29.9, ≥30</td>
<td>Inhabitants of either Seoul or Kyung-gi province visited Kangbuk Samsung Hospital</td>
<td>Age, baseline weight, lifestyle status (diets, smoking and exercise), and each component of MetS at baseline, LDL-C, hsCRP, ALT, uric acid and HOMA-IR</td>
<td>Fasting glucose ≥110 mg/dL, At baseline and follow-up, blood samples were obtained in the morning following a 12-h fast. Serum fasting glucose was measured by the hexokinase method (Hitachi 747</td>
</tr>
<tr>
<td>Baik (2008)</td>
<td>Korea</td>
<td>Combined M &amp; W, 40-69</td>
<td>202/5227</td>
<td>4 g/day: Non-drinkers (Individuals who consumed &lt;1 drink/mo in their lives or who have abstained in the past 30d), 0.1-5, 5.1-15, 15.1-30, &gt;30</td>
<td>Korean citizens participating in a comprehensive health examination and having onsite interviews at Korea University Ansan Hospital, Korean Genome Epidemiology Study (KoGES)</td>
<td>Age, sex, BMI, income, occupation (white-collar, blue-collar, housekeeping), marital status (married, other status), education (&lt; 9 y, ≥9 y), smoking status (never smoker, former smoker, current smoker: &lt;20 cigarettes/y, ≥20 cigarettes/y), quartiles of physical activity, quartiles of total energy intake, quartiles of fat</td>
<td>automatic analyzer, Hitachi, Japan)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-------------</td>
<td>-------</td>
<td>----------------------</td>
<td>----------</td>
<td>------------------------------------------------</td>
<td>---------------------------------</td>
<td>---------------------------------------------------------------------------------------------------------------------------------</td>
<td>--------------------------------</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

All participants had at least an 8-h fasting period before the beginning of blood collection.
whose anthropometric measurements were not completed at the health examination, or whose smoking status was not reported were also excluded. Other than that, those with abnormal concentrations of blood albumin and total bilirubin at baseline were excluded as well.

intake, quartiles of dietary fiber intake, frequency (<1/mo, 1–3/mo, 1–2/wk, ≥2/wk) of red meat intake, frequency of fish intake, frequency of nut intake, family history of diabetes (no family history, diagnosis of diabetes in parents or siblings), and family history of hypertension (no family history, diagnosis of hypertension in parents or siblings)
<p>| Shuval (2012) | U. S | M, Mean age: 42.3 | Total (N): 3411 | Free of MetS or at least one of its components, patients with abnormal ECG, reporting a personal history of cancer, MI or stroke, subjects who did not reach 85% of their maximal heart rate on the treadmill test at baseline, and patients with &lt;1 y of follow up were excluded. | Drink/week: Non-drinkers (not consuming alcohol), ≤3, 3 to 14, &gt;14 | Patients from Cooper Clinic (Dallas, TX, USA) who were enrolled in the Aerobics Center Longitudinal Study. | Age, examination year, smoking status, family history of cardiovascular disease, alcohol or fitness in respective models, and BMI. | Fasting glucose ≥100 mg/dL | Serum samples were analyzed for glucose using automated bioassays |</p>
<table>
<thead>
<tr>
<th>Cullmann (2012)</th>
<th>Sweden</th>
<th>M, W, 35-56</th>
<th>414/5128</th>
<th>Free of prediabetes, and subjects with foreign origin and/or unclear (incomplete answers) or insufficient (only one second-degree relative with known diabetes) family history of diabetes were excluded whereas at follow up the exclusion criteria were newly diagnosed Type 2</th>
<th>9</th>
<th>Residents of Stockholm County, Stockholm Diabetes Prevention Program (SDPP)</th>
<th>Age, BMI, tobacco use, physical activity, family history of diabetes and education.</th>
<th>Prediabetes: impaired fasting glucose (fasting glucose 6.1–6.9 and 2 h glucose &lt;7.8 mmol/l), impaired glucose tolerance (fasting glucose &lt; 6.1 and 2 h glucose 7.8–11.0 mmol/l), both impaired fasting glucose and impaired glucose tolerance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Buja (2010)</td>
<td>Italy</td>
<td>M, W, 65-84</td>
<td>987/2443</td>
<td>Free of MetS, all former drinkers and patients with high aminotransferase levels were excluded.</td>
<td>3.5</td>
<td>Drinks/week: 0, ≤12, 13-24, &gt;24</td>
<td>A random sample of individuals of eight municipalities: Genova, Segrate (Milano), Selvazzano-Rubano (Padova), Impruneta</td>
<td>Age, waist circumference, smoking, education, consumption of fish, coffee, vegetables, olive oil, cheese and cured meats, and oral anti-diabetes and insulin therapy</td>
</tr>
</tbody>
</table>
| Marques-Vidal (2015) | Switzerland | M, W, 35-75 | 780/4255 | No IFG or diabetes, subjects with missing data were excluded | 5.5 | Units/week: Nondrinkers (0 drink/week), 1-13, 14-27, ≥28 | Lausanne inhabitants, CoLaus study | Age, BMI, waist circumference; maternal and paternal diabetes; hypertension; heart rate; smoking status; educational level and physical activity | Impaired Fasting Glucose (IFG): defined by fasting plasma glucose between 6.1 and 6.9 mmol/L without anti-diabetic treatment. Glucose measurement was...
Barrio-Lopez (2013) | Spain | Combined M/W, Mean age: 35.4 | Total participants: 8103 | Free of any MetS criteria, Subjects with baseline total energy intake of out of predefined limits were excluded and only participants within the range of 500 6-8 | Continuous (linear) | Graduates of the University of Navarra, registered nurses from some Spanish provinces and university graduates from other | Age, sex, baseline body mass index, smoking, physical activity, total energy intake, adherence to the Mediterranean dietary pattern | conducted after an over-night fast in Modular P apparatus (Roche Diagnostics, Switzerland) Using enzymatic methods. | Fasting glucose $\geq$100 mg/dL
to 3500 kcal/day for women and 800 to 4000 kcal/day for men were included and participants lost to follow up were excluded.

universities and associations, SUN (Seguimiento Universidad de Navarra)

<table>
<thead>
<tr>
<th>Serum insulin</th>
<th>Finland</th>
<th>M, 50--60</th>
<th>NA/146</th>
<th>Non-diabetic</th>
<th>2.5</th>
<th>g/day: Non-drinkers, &lt;12, ≥12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rankinen (1997)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Eastern finish men living in the city of Kuopio and a nearby suburban community</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Baseline insulin level, cardiovascular health status, change in body weight, smoking, age and follow-up time</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Fasting plasma insulin level (mU/l), plasma insulin level was determined radioimunologically after 12 hours fast and 30-minute rest in supine position (Phadeseph Insulin</td>
</tr>
<tr>
<td>Moller and Jeperson (1995)</td>
<td>Denmark</td>
<td>M, 40 years</td>
<td>NA/425</td>
<td>Those on anti-diabetic medications were excluded.</td>
<td>11</td>
<td>Continuous (linear)</td>
</tr>
<tr>
<td>---------------------------</td>
<td>---------</td>
<td>-------------</td>
<td>--------</td>
<td>-----------------------------------------------</td>
<td>----</td>
<td>-------------------</td>
</tr>
</tbody>
</table>

Fasting serum insulin (mU/l), after 12 hours of fasting and abstinence from smoking, Serum insulin concentrations were measured using radio-immunoassay either by means of a double antibody technique or using a commercially available kit (CIS, bio International, Gif-sur-Yvette, France).
<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Gender</th>
<th>Age</th>
<th>Inclusion Criteria</th>
<th>Age, Body Mass Index, Mean</th>
<th>Serum Insulin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Balkau (2006)</td>
<td>France</td>
<td>M, W</td>
<td>30—65 years</td>
<td>Those on anti-diabetic medications were excluded.</td>
<td>Age and educational level</td>
<td>Serum insulin (centrally measured, specific enzyme immunoassay with an IMX; Abbott, Rungis, France)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NA/3923</td>
<td>3</td>
<td>Continuous (linear)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HbA1C</td>
<td>Japan</td>
<td>M,</td>
<td>NA/7104</td>
<td>Those receiving a drinking habit (everyday)</td>
<td>Age, body mass index, mean</td>
<td>HbA1c (%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>14</td>
<td>Male workers with</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Suwasono (2009)</td>
<td>Mean age: 36.5</td>
<td>health examination for the first time in the final year of the follow-up period, those who had pharmacologic therapy initiated for diabetes mellitus before or in the year of entry, those who had therapy initiated for diabetes mellitus in the subsequent year, those with any missing data in the year of /not every day)</td>
<td>alternating shift workers at a Japanese steel company who attended annual health examinations during the observation period were enrolled in the study</td>
<td>arterial pressure, total serum cholesterol, creatinine, alanine aminotransferase, g-glutamyl transpeptidase, uric acid, smoking habit, and habitual exercise</td>
<td>By considering normal HbA1C: 4.3–5.8%, measured by the latex agglutination method</td>
<td></td>
</tr>
</tbody>
</table>
entry, those who did not receive a health examination in the subsequent year, and those for whom the measurement of HbA1c was missing the subsequent year.

<table>
<thead>
<tr>
<th>Study (2011)</th>
<th>Country</th>
<th>Gender</th>
<th>Age Range</th>
<th>Participants</th>
<th>Follow-up</th>
<th>Data Analysis</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Joosten</td>
<td>U. S</td>
<td>M</td>
<td>40-75</td>
<td>Men with missing data on BMI and physical activity at baseline and men who had implausible nutritional</td>
<td>4</td>
<td>Drink/day: Non-drinkers (0 drink/day), &lt;1, ≥1</td>
<td>U. S male health professionals who returned a mailed questionnaire about diet</td>
</tr>
</tbody>
</table>
information (≥70 missing food items or estimated daily energy intake <800 or >4,200 kcal) were excluded. In addition, men who had died or had been diagnosed with diabetes or cancer (except for those with non-melanoma skin cancer) were excluded, Health Professionals and medical history hypercholesterolemia, dietary glycemic load, fiber intake, trans fat intake, ratio of polyunsaturated to saturated fat, coffee intake and total energy intake.
<table>
<thead>
<tr>
<th>Study</th>
<th>Location</th>
<th>Sex, Age</th>
<th>Subjects</th>
<th>Follow-Up Study</th>
<th>Measurements</th>
<th>Additional Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kiechl (1996)</td>
<td>Italy</td>
<td>M, W 40—79 years</td>
<td>NA/771</td>
<td>Subjects with cerebrovascular disease, incomplete data collection, unavailable insulin measurements, and diabetes mellitus was excluded</td>
<td>5 g/day: abstainers, 1-50, 51-99, ≥100</td>
<td>The town of Bruneck is in an alpine region in the north of Italy (Bolzano province)</td>
</tr>
</tbody>
</table>
3.3. Meta-analysis

We performed a meta-analysis on seven cohort studies with the outcome of incidence of impaired fasting glucose.

Characteristics of all included studies in our quantitative meta-analysis are summarized in Table 3.11. In the following passage, each of those seven included articles in our meta-analysis is summarized separately.

3.3.1. Alcohol consumption and fasting glucose

A cohort study with an average of three years of follow up, evaluated 4505 Korean men free of metabolic syndrome with a median age of 44 years at baseline. In this study, data for alcohol consumption was collected using a self-report questionnaire. Participants were divided into four different categories: Non-drinkers, light drinkers (1.0–14.9 g/day), moderate drinkers (15.0–29.9 g/day), and heavy drinkers (≥30.0 g/day). These categories were compared to non-drinkers as a reference group. The results of this study indicated that alcohol consumption has a positive association with incidence of fasting glucose≥110mg/dL(B. J. Kim et al., 2012). More details are summarized in Table 3.12.
Table 3.12. Logistic regression of association of alcohol consumption with incidence of fasting glucose ≥110mg/dL (B. J. Kim et al., 2012)

<table>
<thead>
<tr>
<th>Alcohol consumption</th>
<th>OR (95% CI), P value</th>
<th>OR (95% CI), P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Age-adjusted</td>
<td>Adjusted for age, baseline weight, lifestyle status (diets, smoking and exercise), each component of MetS at baseline, LDL-C, hsCRP, ALT, uric acid and HOMA-IR</td>
</tr>
<tr>
<td>Non-drinkers</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Light drinker</td>
<td>1.25 (0.88-1.76)</td>
<td>1.18 (0.82–1.69)</td>
</tr>
<tr>
<td></td>
<td>P: 0.211</td>
<td>P: 0.382</td>
</tr>
<tr>
<td>Moderate drinker</td>
<td>1.62 (1.09-2.42)</td>
<td>1.60 (1.05–2.44)</td>
</tr>
<tr>
<td></td>
<td>P: 0.018</td>
<td>P: 0.030</td>
</tr>
<tr>
<td>Heavy drinker</td>
<td>1.77 (1.03-3.06)</td>
<td>1.59 (0.88–2.87)</td>
</tr>
<tr>
<td></td>
<td>P: 0.041</td>
<td>P: 0.126</td>
</tr>
</tbody>
</table>

Another prospective cohort study included in our meta-analysis, evaluated 5227 Korean men and women aged 40-69 years with 4 years of follow-up, for association of alcohol consumption with incidence of fasting glucose ≥110mg/dL. All, were free of metabolic syndrome and were not on anti-diabetic agents at baseline. Drinking consumption (g/day) was categorized into four groups: very light (0.1 to 5), light (5.1 to 15), moderate drinker (15.1 to 30) and heavy drinker (>30). These different categories of drinking were compared to non-drinkers as a reference group (Baik & Shin, 2008).

The results represented that heavy drinking especially among liquor drinkers is significantly associated with incidence of fasting glucose ≥110mg/dL (Baik & Shin, 2008). The detailed information is represented in Table 3.13, Table 3.14 and Table 3.15.
Table 3.13. Association of alcohol consumption with incidence of fasting glucose ≥110mg/dL among all alcohol drinkers (Baik & Shin, 2008)

<table>
<thead>
<tr>
<th></th>
<th>Non-drinkers</th>
<th>Very light drinkers</th>
<th>Light drinkers</th>
<th>Moderate drinkers</th>
<th>Heavy drinkers</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>(0.1 to 5 g/day)</td>
<td>(5.1 to 15 g/day)</td>
<td>(15.1 to 30 g/day)</td>
<td>(&gt;30 g/day)</td>
</tr>
<tr>
<td>Number of cases/non-cases</td>
<td>64/2253</td>
<td>25/984</td>
<td>21/671</td>
<td>34/512</td>
<td>58/605</td>
</tr>
<tr>
<td>Multivariate OR* (95%CI)</td>
<td>Reference</td>
<td>0.81 (0.50-1.32)</td>
<td>0.85 (0.49-1.45)</td>
<td>1.57 (0.96-2.58)</td>
<td>2.37 (1.50-3.73)</td>
</tr>
</tbody>
</table>

*Adjusted for age, sex, BMI, income (wage <106 Won/mo, ≥106 Won/mo), occupation (white-collar, blue-collar, housekeeping), marital status (married, other status), education (< 9 y, ≥9 y), smoking status (never smoker, former smoker, current smoker: <20 cigarettes/y, ≥20 cigarettes/y), quartiles of physical activity, quartiles of total energy intake, quartiles of fat intake, quartiles of dietary fiber intake, frequency (<1/mo, 1–3/mo, 1–2/wk, ≥2/wk) of red meat intake, frequency of fish intake, frequency of nut intake, family history of diabetes (no family history, diagnosis of diabetes in parents or siblings), and family history of hypertension (no family history, diagnosis of hypertension in parents or siblings)

Table 3.14. Association of alcohol consumption with incidence of fasting glucose ≥110mg/dL among liquor drinkers (Baik & Shin, 2008)

<table>
<thead>
<tr>
<th></th>
<th>Non-drinkers</th>
<th>Very light drinkers</th>
<th>Light drinkers</th>
<th>Moderate drinkers</th>
<th>Heavy drinkers</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>(0.1 to 5 g/day)</td>
<td>(5.1 to 15 g/day)</td>
<td>(15.1 to 30 g/day)</td>
<td>(&gt;30 g/day)</td>
</tr>
<tr>
<td>Number of cases/non-cases</td>
<td>64/2253</td>
<td>19/633</td>
<td>20/545</td>
<td>33/462</td>
<td>52/527</td>
</tr>
<tr>
<td>Multivariate OR* (95%CI)</td>
<td>Reference</td>
<td>0.90 (0.53-1.55)</td>
<td>0.99 (0.57-1.74)</td>
<td>1.70 (1.02-2.82)</td>
<td>2.44 (1.51-3.92)</td>
</tr>
</tbody>
</table>

*Adjusted for age, sex, BMI, income (wage <106 Won/mo, ≥106 Won/mo), occupation (white-collar, blue-collar, housekeeping), marital status (married, other status), education (< 9 y, ≥9 y), smoking status (never smoker, former smoker, current smoker: <20 cigarettes/y, ≥20 cigarettes/y), quartiles of physical activity, quartiles of total energy intake, quartiles of fat intake, quartiles of dietary fiber intake, frequency (<1/mo, 1–3/mo, 1–2/wk, ≥2/wk) of red meat intake, frequency of fish intake, frequency of nut intake, family history of diabetes (no family history, diagnosis of diabetes in parents or siblings), and family history of hypertension (no family history, diagnosis of hypertension in parents or siblings)
history of diabetes (no family history, diagnosis of diabetes in parents or siblings), and family history of hypertension (no family history, diagnosis of hypertension in parents or siblings)

The other cohort study in this field assessed 3411 apparently healthy men aged 20 to 79 years from Cooper Clinic (Dallas, Texas) who were non-Hispanic white and well educated. This study (Shuval et al., 2012) had an average of nine years follow up. All individuals were free of metabolic syndrome or at least one component of metabolic syndrome at baseline, and patients with abnormal ECG, reporting a personal history of cancer, myocardial infarction or stroke, subjects who did not reach 85% of their maximal heart rate on the treadmill test at baseline, and patients with <1 y of follow up were excluded (Shuval et al., 2012). Alcohol consumption was categorized into three different categories of alcohol consumption: Light (≤3 drink/week), moderate (>3 to 14 drink per week) and heavy drinkers (>14 drink per week).

These different categories were compared to non-drinkers as a reference group (Shuval et al., 2012). This study revealed that lower alcohol consumption is associated with decreased risk of high fasting glucose level (Shuval et al., 2012). The details are summarized in Table 3.16.

Table 3.15. Association of alcohol consumption with incidence of fasting glucose ≥110mg/dL among non-liquor drinkers (Baik & Shin, 2008)

<table>
<thead>
<tr>
<th></th>
<th>Non-drinkers</th>
<th>Very light drinkers (0.1 to 5 g/day)</th>
<th>Light drinkers (5.1 to 15 g/day)</th>
<th>Moderate drinkers (15.1 to 30 g/day)</th>
<th>Heavy drinkers (&gt;30 g/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of cases/non-cases</td>
<td>64/2253</td>
<td>6/351</td>
<td>1/126</td>
<td>1/50</td>
<td>6/78</td>
</tr>
<tr>
<td>Multivariate OR* (95%CI)</td>
<td>Reference</td>
<td>0.62 (0.26-1.48)</td>
<td>0.24 (0.03-1.79)</td>
<td>0.45 (0.06-3.67)</td>
<td>2 (0.76-5.26)</td>
</tr>
</tbody>
</table>

*Adjusted for age, sex, BMI, income (wage <10^6 Won/mo, ≥10^6 Won/mo), occupation (white-collar, blue-collar, housekeeping), marital status (married, other status), education (<9 y, ≥9y), smoking status (never smoker, former smoker, current smoker: <20 cigarettes/y, ≥20, cigarettes/y), quartiles of physical activity, quartiles of total energy intake, quartiles of fat intake, quartiles of dietary fiber intake, frequency ( <1/mo, 1–3/mo, 1–2/wk, ≥2/wk) of red meat intake, frequency of fish intake, frequency of nut intake, family history of diabetes (no family history, diagnosis of diabetes in parents or siblings), and family history of hypertension (no family history, diagnosis of hypertension in parents or siblings)
Table 3.16. Incidence of fasting glucose ≥100mg/dL in association with alcohol consumption (Shuval et al., 2012).

<table>
<thead>
<tr>
<th>Alcohol consumption</th>
<th>HR* (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-drinker</td>
<td>0.81 (0.63–1.04)</td>
</tr>
<tr>
<td>Light</td>
<td>0.82 (0.65–1.04)</td>
</tr>
<tr>
<td>Moderate</td>
<td>0.99 (0.82–1.20)</td>
</tr>
<tr>
<td>Heavy</td>
<td>1</td>
</tr>
</tbody>
</table>

*Adjusted for age, examination year, smoking status, family history of cardiovascular disease, alcohol or fitness in respective models, and BMI

Another included study in this field, followed 2070 men and 3058 women aged 35-56 for 8-10 years (Cullmann et al., 2012). Participants with known diabetes or family history of diabetes at baseline were excluded (Cullmann et al., 2012).

Alcohol consumption, in this study, was categorized as occasional, low, medium and heavy drinking categories. Among men, these categories were defined as occasional (0.01 to 6.79 g/day), low (6.80 to 13.01 g/day), medium (13.02 to 22.13 g/day), and heavy drinking (≥22.14 g/day) (Cullmann et al., 2012).

For women, different categories of alcohol consumption were defined as occasional (0.01 to 1.49 g/day), low (1.50 to 4.71 g/day), medium (4.72 to 8.75 g/day), and heavy drinking (≥8.76 g/day). These different categories were compared to abstainers as a reference group (Cullmann et al., 2012).

In this study, the outcome was prediabetes and it was defined as impaired fasting glucose (fasting glucose 6.1–6.9 and 2 h glucose < 7.8 mmol/l), or impaired glucose tolerance (fasting glucose < 6.1 and 2 h glucose 7.8–11.0 mmol/l), or both impaired fasting glucose and impaired glucose tolerance (Cullmann et al., 2012).

The results of this study represented that, alcohol consumption increased the risk of abnormal glucose regulation in men but in women, the associations were more complex; the risk was decreased with low or medium alcohol consumption (Cullmann et al., 2012).

Detailed information about the results of this study is summarized in Table 3.17 and Table 3.18.
Table 3.17. Association of alcohol consumption with abnormal glucose regulation in men (Cullmann et al., 2012).

<table>
<thead>
<tr>
<th>Alcohol consumption (g/day) in men</th>
<th>OR* (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abstainers</td>
<td>1.73 (0.78–3.86)</td>
</tr>
<tr>
<td>Occasional (0.01-6.79)</td>
<td>1</td>
</tr>
<tr>
<td>Low (6.80-13.01)</td>
<td>1.33 (0.87–2.05)</td>
</tr>
<tr>
<td>Medium (13.02-22.13)</td>
<td>1.44 (0.95–2.20)</td>
</tr>
<tr>
<td>High ≥22.14</td>
<td>1.49 (0.98–2.25)</td>
</tr>
</tbody>
</table>

*Adjusted for age, BMI, tobacco use, physical activity, family history of diabetes and education.

Table 3.18. Association of alcohol consumption with abnormal glucose regulation in women (Cullmann et al., 2012).

<table>
<thead>
<tr>
<th>Alcohol consumption (g/day) in women</th>
<th>OR* (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abstainers</td>
<td>1.13 (0.50–2.56)</td>
</tr>
<tr>
<td>Occasional (0.01-1.49)</td>
<td>1</td>
</tr>
<tr>
<td>Low (1.50-4.71)</td>
<td>0.96 (0.63–1.48)</td>
</tr>
<tr>
<td>Medium (4.72-8.75)</td>
<td>0.85 (0.53–1.34)</td>
</tr>
<tr>
<td>High ≥8.76</td>
<td>0.83 (0.52–1.33)</td>
</tr>
</tbody>
</table>

*Adjusted for age, BMI, tobacco use, physical activity, family history of diabetes and education.
Another cohort study in this category assessed 2443 individuals, with the age of 65 to 84 years. All participants were free of metabolic syndrome at baseline. Former drinkers and patients with high aminotransferase levels were excluded. All individuals were followed for 3.5 years. The results of this study suggested a harmful effect in men for association of alcohol consumption (all categories) with impaired fasting glucose, however, this association was not statistically significant (Buja et al., 2010).

These different categories of alcohol consumption were compared to abstainers as a reference group (Buja et al., 2010). Table 3.19 and Table 3.20 contain more details about the results of this study.

**Table 3.19. Association of alcohol consumption with incidence of fasting glucose ≥110mg/dL in women (Buja et al., 2010)**

<table>
<thead>
<tr>
<th>Alcohol consumption</th>
<th>Abstainers</th>
<th>≤ 12 g/day</th>
<th>13 to 24 g/day</th>
<th>&gt;24 g/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence of fasting glucose ≥110mg/dL, RR (95%CI) *</td>
<td>Reference</td>
<td>1.15 (0.59–2.18)</td>
<td>1.45 (0.65–3.01)</td>
<td>0.41 (0.05–2.79)</td>
</tr>
<tr>
<td>N=203</td>
<td>N=228</td>
<td>N=99</td>
<td>N=31</td>
<td></td>
</tr>
</tbody>
</table>

*Adjusted for age, waist circumference, smoking, education, consumption of fish, coffee, vegetables, olive oil, cheese and cured meats, and oral anti-diabetes and insulin therapy.

**Table 3.20. Association of alcohol consumption with incidence of fasting glucose ≥110mg/dL in men (Buja et al., 2010)**

<table>
<thead>
<tr>
<th>Alcohol consumption</th>
<th>Abstainers</th>
<th>≤ 12 g/day</th>
<th>13 to 24 g/day</th>
<th>25 to 47 g/day</th>
<th>≥ 48 g/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence of fasting glucose ≥110mg/dL, RR (95%CI) *</td>
<td>Reference</td>
<td>5.04 (0.66–25.11)</td>
<td>4.92 (0.66–24.31)</td>
<td>6.71 (0.93–29.27)</td>
<td>4.49 (0.56–23.78)</td>
</tr>
<tr>
<td>N=55</td>
<td>N= 154</td>
<td>N= 207</td>
<td>N= 158</td>
<td>N= 110</td>
<td></td>
</tr>
</tbody>
</table>

*Adjusted for age, waist circumference, smoking, education, consumption of fish, coffee, vegetables, olive oil, cheese and cured meats, and oral anti-diabetes and insulin therapy.
Another cohort study in this field examined 4255 subjects aged 35 to 75 years. All, were free of impaired fasting glucose or diabetes at baseline. This study had average of 5.5 years of follow up. Alcohol consumption was categorized as 1-13, 14-27, ≥28 units per week; and non-drinkers (0 drinks per week) were considered as a reference group.

The results of this study for association of alcohol consumption and IFG are summarized in Table3.21 and Table3.22.

Table3.21. Association between alcohol consumption and 5.5-year incidence impaired fasting glucose among men (Marques-Vidal et al., 2015)

<table>
<thead>
<tr>
<th>Alcohol consumption</th>
<th>Non</th>
<th>1 to 13 drink/week</th>
<th>14 to 27 drink/week</th>
<th>≥28 drink/week</th>
<th>Linear trend</th>
<th>Quadratic trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORs* for incidence of IFG</td>
<td>1</td>
<td>1.07 (0.77 to 1.46)</td>
<td>1.56 (1.08 to 2.24)</td>
<td>1.56 (0.92 to 2.66)</td>
<td>0.04</td>
<td>0.84</td>
</tr>
</tbody>
</table>

*Adjusted for age, BMI, waist circumference; maternal and paternal diabetes; hypertension; heart rate; smoking status; educational level and physical activity.

Table3.22. Association between alcohol consumption and 5.5-year incidence impaired fasting glucose among women (Marques-Vidal et al., 2015)

<table>
<thead>
<tr>
<th>Alcohol consumption</th>
<th>Non-drinker</th>
<th>1 to 13 drink/week</th>
<th>14 to 27 drink/week</th>
<th>≥28 drink/week</th>
<th>Linear trend</th>
<th>Quadratic trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORs* for incidence of IFG</td>
<td>1</td>
<td>1.17 (0.89 to 1.54)</td>
<td>1.17 (0.69 to 1.99)</td>
<td>1.50 (0.31 to 7.21)</td>
<td>0.62</td>
<td>0.92</td>
</tr>
</tbody>
</table>

*Adjusted for age, BMI, waist circumference; maternal and paternal diabetes; hypertension; heart rate; smoking status; educational level and physical activity.
Another cohort study conducted in Spain, had 8103 participants with a mean age of 35.4 years. All were free of any metabolic syndrome criteria. This study revealed that after 6 to 8 years of follow-up, those participants who consumed ≥ 7 drinks/week, had 54% higher risk of incidence of fasting glucose ≥100 mg/dL (adjusted OR: 1.54 with 95% CI of 1.16 to 2.04) compared to those who never drink alcohol (Barrio-Lopez et al., 2013).

For this study (Barrio-Lopez et al., 2013), we used alcohol as a continuous variable in our meta-analysis.
3.3.2. Results of quality assessment for studies combined in meta-analysis

Newcastle-Ottawa Scale (NOS) for the observational studies included in our meta-analysis ranged from 7 to 9. Therefore, all the studies we combined in our meta-analysis had a high quality based on Newcastle-Ottawa Scale (NOS) for cohort studies.

For the “selection” of the cohorts, all studies gained stars, except two studies (Barrio-Lopez et al., 2013; Shuval et al., 2012), which were from selected users.

In addition, for demonstration that outcome of interest was not present at start of the study, all the studies gained stars except two studies (Buja et al., 2010; B. J. Kim et al., 2012). In those two studies, although it is mentioned in the article that participants with metabolic syndrome are excluded, it does not specifically mention if all participants had normal fasting glucose at baseline (Buja et al., 2010; B. J. Kim et al., 2012).

For ascertainment of exposure, none of the studies could gain a star as all the studies in our meta-analysis had self-report questionnaire for alcohol consumption assessments except one study which used interviewer-administered questionnaire instead of self-report questionnaires for measuring alcohol consumption (Baik & Shin, 2008).

All studies earned a star for comparability for age, which we considered as the most important factor for adjustment. All included studies earned a second star for additional adjustment.

The critical appraisals for all included studies in our meta-analysis are shown in Table3.23, Table3.24, Table3.25, Table3.26, Table3.27, Table3.28, and Table3.29.

However, in general quality scores are usually used for meta-analyses of randomized trials of interventions not for observational studies (Chalmers et al., 1981; Detsky, Naylor, O'Rourke, McGeer, & L'Abbé, 1992; Moher et al., 1998)

Furthermore, quality score use in meta-analyses is controversial (Greenland & O'rourke, 2001; Herbison, Hay-Smith, & Gillespie, 2006).
Table 3.23. Critical appraisal results for the study of Shuval et al, (2012) (based on Newcastle-Ottawa Scale (NOS))

<table>
<thead>
<tr>
<th>Shuval (2012) Score 7 out of 9</th>
</tr>
</thead>
<tbody>
<tr>
<td>Selection</td>
</tr>
<tr>
<td>1) c</td>
</tr>
<tr>
<td>2) a*</td>
</tr>
<tr>
<td>3) c</td>
</tr>
<tr>
<td>4) a*</td>
</tr>
</tbody>
</table>

Reasons for scoring less than 9:
1. Since it was a selected group of users (only men, non-Hispanic white, and well educated, are included)
2. Self-reported questionnaire of alcohol consumption
Table 3.24. Critical appraisal results for the study of Buja et al, (2010) (based on Newcastle-Ottawa Scale (NOS))

<table>
<thead>
<tr>
<th>Selection</th>
<th>Comparability</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1) b*</td>
<td>1) a, b**</td>
<td>1) b*</td>
</tr>
<tr>
<td>2) a*</td>
<td></td>
<td>2) a*</td>
</tr>
<tr>
<td>3) c</td>
<td></td>
<td>3) b*</td>
</tr>
<tr>
<td>4) b</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Reasons for scoring less than 9:
3. Self-reported questionnaires for alcohol consumption
4. Although it is mentioned in the article that participants with metabolic syndrome are excluded, it does not specifically mention if participants with high fasting glucose were also excluded.
Table 3.25. Critical appraisal results for the study of Barrio Lopez et al, (2013) (based on Newcastle-Ottawa Scale (NOS))

<table>
<thead>
<tr>
<th>Barrio Lopez (2013) Score 7 out of 9</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1) c</td>
<td>1) a, b**</td>
<td>1) b*</td>
</tr>
<tr>
<td>2) a*</td>
<td>2) a*</td>
<td>2) a*</td>
</tr>
<tr>
<td>3) c</td>
<td>3) b*</td>
<td>3) b*</td>
</tr>
<tr>
<td>4) a*</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Reasons for scoring less than 9:

1. Only University graduates were selected for the study, so they used selected group of users and this selection does not truly or somewhat representative of the average population.

3. Self-reported questionnaires for alcohol consumption.

<table>
<thead>
<tr>
<th></th>
<th>Selection</th>
<th>Comparability</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baik (2008)</strong></td>
<td>1) b*</td>
<td>1) a, b**</td>
<td>1) b*</td>
</tr>
<tr>
<td></td>
<td>2) a*</td>
<td></td>
<td>2) a*</td>
</tr>
<tr>
<td></td>
<td>3) b*</td>
<td></td>
<td>3) b*</td>
</tr>
<tr>
<td></td>
<td>4) a*</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Score 9 out of 9</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Reason for scoring less than 9:</strong></td>
<td>Not applicable</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 3.27. Critical appraisal results for the study of Cullmann et al, (2012) (based on Newcastle-Ottawa Scale (NOS))

<table>
<thead>
<tr>
<th>Selection</th>
<th>Comparability</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1) b*</td>
<td>1) a, b**</td>
<td>1) b*</td>
</tr>
<tr>
<td>2) a*</td>
<td></td>
<td>2) a*</td>
</tr>
<tr>
<td>3) b</td>
<td></td>
<td>3) b*</td>
</tr>
<tr>
<td>4) a*</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Reason for scoring less than 9:
3. Self-reported questionnaires for alcohol consumption
Table 3.28. Critical appraisal results for the study of Marques-Vidal et al, (2015) (based on Newcastle-Ottawa Scale (NOS))

<table>
<thead>
<tr>
<th>Marques-Vidal (2015)</th>
<th>Score 8 out of 9</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Selection</strong></td>
<td><strong>Comparability</strong></td>
</tr>
<tr>
<td>1) b*</td>
<td>1) a, b**</td>
</tr>
<tr>
<td>2) a*</td>
<td>2) a*</td>
</tr>
<tr>
<td>3) b</td>
<td>3) b*</td>
</tr>
<tr>
<td>4) a*</td>
<td></td>
</tr>
<tr>
<td><strong>Reason for scoring less than 9:</strong></td>
<td></td>
</tr>
<tr>
<td>3. Self-reported questionnaires for alcohol consumption</td>
<td></td>
</tr>
</tbody>
</table>
Table 3.29. Critical appraisal results for the study of Kim et al, (2012) (based on Newcastle-Ottawa Scale (NOS))

<table>
<thead>
<tr>
<th>Kim (2012)</th>
<th>Score 7 out of 9</th>
</tr>
</thead>
<tbody>
<tr>
<td>Selection</td>
<td>Comparability</td>
</tr>
<tr>
<td>1) b*</td>
<td>1) a, b**</td>
</tr>
<tr>
<td>2) a*</td>
<td></td>
</tr>
<tr>
<td>3) b</td>
<td></td>
</tr>
<tr>
<td>4) b</td>
<td></td>
</tr>
</tbody>
</table>

Reason for scoring less than 9:
3. Self-reported questionnaires for alcohol consumption
4. Although it is mentioned in the article that participants were all free of metabolic syndrome, it does not specifically mention that if all had normal fasting glucose at baseline
3.3.3. Meta-analysis Results

Figure 3.2. Forest plot of the effects of alcohol consumption categories on the incidence of fasting glucose ≥ 100 mg/dL (n=6) Weights are from random-effects analysis CI, confidence interval; RR, relative risk
Table 3.30. Tests of Heterogeneity (for the effects of alcohol consumption categories on incidence of fasting glucose ≥100mg/dL)

<table>
<thead>
<tr>
<th>Category</th>
<th>Heterogeneity statistic</th>
<th>Degree of freedom</th>
<th>P value</th>
<th>I-squared</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 1 drinks/day</td>
<td>7.14</td>
<td>8</td>
<td>0.521</td>
<td>0.0%</td>
</tr>
<tr>
<td>&gt;1 - ≤2 drinks/day</td>
<td>5.32</td>
<td>5</td>
<td>0.378</td>
<td>6.1%</td>
</tr>
<tr>
<td>&gt;2-≤3 drinks/day</td>
<td>6.84</td>
<td>4</td>
<td>0.145</td>
<td>41.5%</td>
</tr>
<tr>
<td>&gt;3 drinks/day</td>
<td>7.56</td>
<td>5</td>
<td>0.183</td>
<td>33.8%</td>
</tr>
<tr>
<td>Overall</td>
<td>37.69</td>
<td>25</td>
<td>0.050</td>
<td>33.7%</td>
</tr>
</tbody>
</table>
Figure 3.3. Forest plot of linear effect (per 1 standard drink, 12 g/day) of alcohol consumption in comparison to abstainers on incidence of fasting glucose ≥100 mg/dL, by sex (n=7)
Table 3.31. Tests of Heterogeneity (for the linear regression effects of alcohol consumption on incidence of fasting glucose ≥100mg/dL by gender stratification (women, men and combined))

<table>
<thead>
<tr>
<th></th>
<th>Heterogeneity of statistics</th>
<th>Degree of freedom</th>
<th>P value</th>
<th>I-squared</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women</td>
<td>1.68</td>
<td>2</td>
<td>0.431</td>
<td>0.0%</td>
</tr>
<tr>
<td>Men</td>
<td>2.93</td>
<td>3</td>
<td>0.403</td>
<td>0.0%</td>
</tr>
<tr>
<td>Combined</td>
<td>0.33</td>
<td>1</td>
<td>0.564</td>
<td>0.0%</td>
</tr>
<tr>
<td>Overall</td>
<td>15.04</td>
<td>8</td>
<td>0.058</td>
<td>46.8%</td>
</tr>
</tbody>
</table>
Figure 3.4. Funnel plot for identification of publication bias (Test of H0: no small study effects, P=0.683)
Figure 3.5. Sensitivity analysis results (leaving one study out, one at a time)
3.3.4. Alcohol consumption impairs fasting glucose

Random-effects summary estimates are provided in Figure 3.2 and Figure 3.3. Our meta-analysis assessed the association of alcohol consumption with incidence of fasting plasma glucose of ≥100 mg/dL. Figure 3.2 provides the forest plot of the effects of alcohol consumption categories on the incidence of fasting glucose ≥100 mg/dL which includes 6 articles (Baik & Shin, 2008; Buja et al., 2010; Cullmann et al., 2012; B. J. Kim et al., 2012; Marques-Vidal et al., 2015; Shuval et al., 2012) that had data for different categories of alcohol consumption in association with incidence of fasting glucose ≥100 mg/dL.

The subtotal relative risk (RR) for the category of ≤1 drink/day was 1.05 with 95% CI of (0.92 to 1.19). For the categories of alcohol consumption, >1 to ≤2 drinks/day, >2 to ≤3, subtotal RRs were 1.32 with 95% CI of (1.11 to 1.57) and 1.30 (0.84 to 2.02) respectively. The RR increased with increasing alcohol consumption (RR = 1.61, 95% CI 1.21 to 2.13) for more than 3 drinks/day.

Those six studies (Baik & Shin, 2008; Buja et al., 2010; Cullmann et al., 2012; B. J. Kim et al., 2012; Marques-Vidal et al., 2015; Shuval et al., 2012), included in the forest plot for the effects of alcohol consumption categories on the incidence of fasting glucose ≥ 100 mg/dL, showed an overall association of RR = 1.25 (with 95% CI of 1.11 to 1.40) with any amount of alcohol consumption.

One additional study provided a linear regression coefficient (Barrio-Lopez et al., 2013). A linear test for trend using all seven studies stratified by sex was performed (Figure 3.3). This linear meta-regression treating alcohol consumption as a continuous variable, showed that for an increase in one standard drink (12 g pure alcohol), the RR for incidence of fasting glucose ≥100 mg/d was 1.10 (95% CI 1.05-1.15) in men, and 1.04 (95% CI 0.90-1.21) in women. Confidence intervals in studies among women were generally wider. For combined men and women, the RR for incidence of fasting glucose ≥100 mg/d was 1.29 with 95% CI of 1.17-1.42.

The overall effect, regardless of sex, was 1.15 (95% CI 1.08-1.22) per one standard drink increase in alcohol consumption in comparison to abstainers.

Therefore, the linear test for trend using all seven studies stratified by sex, showed a significant positive trend in men and studies that did not stratify by sex (combined men and women), and no significant trend in women (Figure 3.3).

Only one study differentiated between former drinkers and lifetime abstainers (Buja et al., 2010) which was in concordance with other studies with current abstainers as the reference group.

Exclusion of Kim (2012) because light drinkers were included in the reference group (B. J. Kim et al., 2012) and Cullmann (2012) because of inclusion of prediabetes (defined as IFG, IGT or both IFG and IGT) in the outcome definition (Cullmann et al., 2012) did not meaningfully change these risk relationships.

Omitting each study separately by performing sensitivity analysis, showed that none of the studies had an excessive influence on the overall association (Figure 3.5).
There was no evidence for small-study effects based on Egger’s test (P=0.68) or visual inspection of the funnel plot (Figure3.4).

3.3.5. Heterogeneity Assessment

The thresholds for the interpretation of I-squared can be misleading, because the importance of inconsistency depends on several different factors. A guide to interpretation based on Cochrane handbook is as follows (Higgins & Green, 2008):

0% to 40%: might not be important;

30% to 60%: may indicate moderate heterogeneity*;

50% to 90%: may indicate substantial heterogeneity*;

75% to 100%: indicates considerable heterogeneity.

*The importance of the observed value of I-squared depends on some factors such as the magnitude and direction of effects and the strength of evidence for heterogeneity.

Although, no universal rule exists for definition of ‘mild’, ‘moderate’ or ‘severe heterogeneity, mild heterogeneity might account for less than 30 percent of the variability in point estimates, and considerable heterogeneity substantially more than 50 percent (Higgins & Thompson, 2002).

The overall heterogeneity for the forest plot of our meta-analysis for association of alcohol consumption, based on different categories of alcohol consumption with incidence of fasting glucose of ≥100 mg/dL was 33.7% with P value of 0.05, which means that in overall low to moderate heterogeneity between studies, exists.

For our meta-regression analysis stratified by sex, the overall I-squared was 46.8% with the P value of 0.058, which also suggest the overall moderate heterogeneity between studies. The tests for heterogeneity are summarized in Table3.30 and Table3.31.
Chapter 4

4. Discussion

Our study is the first systematic review of observational studies (cohort and case-control studies) that has assessed the long-term effects of alcohol consumption on different parameters of glucose homeostasis.

4.1. Alcohol consumption and blood glucose levels

The studies included in our meta-analysis revealed an overall increase in incidence of fasting glucose $\geq 100 \text{mg/dL}$ in association with alcohol consumption.

However, a previous systematic review of interventional studies on non-diabetic patients at baseline represented that no association exists between alcohol consumption and fasting glucose (Schrieks et al., 2015).

One important reason for this difference between the results of the previous systematic review of interventional studies with our present study, might be due to the short duration of all those interventional studies included in the study of Schrieks et al. (2015) for assessing the effects of alcohol consumption on fasting glucose (which was in average 5.9 weeks), but in contrast to that, our present study has evaluated this effect in long-term with average follow-up of 5.8 years. One other difference between the results of our present meta-analysis and the previous systematic review in this field is the difference of the methodology of included studies. We have only included observational studies but Schrieks et al. (2015) have included interventional studies. Schrieks et al. (2015) have excluded heavy drinkers from their study, but in our current systematic review and meta-analysis, we did not have any restrictions based on the amount of alcohol consumption, however, even in our present meta-analysis, in most of the studies, we had lack of data regarding heavy drinkers. Differences in population at baseline among the included studies in the study of Schrieks et al. (2015) from our current meta-analysis might be another reason for having different results between these two studies.

In our present meta-analysis, for association of alcohol consumption with incidence of fasting glucose $\geq 100 \text{mg/dL}$, mild to moderate heterogeneity among the included studies exist which might be due to different methods used in each study, different countries that studies were conducted, different measurements of alcohol consumption, adjustment levels, and type of data measurements. However, the study type cannot be a source of heterogeneity because only cohort studies were included in our meta-analysis; therefore, the difference in follow-up time may have been contributed.
In terms of association of alcohol consumption with impaired glucose tolerance, we found two articles among our search (Kiyohara et al., 2003; Lu et al., 2003). One of these cohort studies which has been done among Native Americans indicated that the risk for worsening glucose tolerance (progression of normal glucose tolerance to IGT, normal glucose tolerance to diabetes, or IGT to diabetes) was not significantly associated with alcohol intake in comparison to lifetime abstainers, whether stratified by obesity status or not (Lu et al., 2003). Another cohort study about association of alcohol consumption and impaired glucose tolerance, was performed in Japan and it showed that among men, a 10 g/day increase in alcohol intake was associated with an OR = 1.19 (95% CI 1.08 – 1.33) for incident glucose intolerance (Kiyohara et al., 2003).

However, these two articles mentioned above had combined IGT with diagnosis of diabetes in one outcome. Therefore, based on our inclusion and exclusion criteria, we excluded these two articles. Impaired glucose tolerance by itself has been reported as a separate diagnostic tool for diabetes screening and is associated with increased risk of cardiovascular diseases including hypertension, hyperlipidemia, and central obesity (Costa et al., 2002). People with IGT have even higher mortality rates due to cardiovascular problems than others (Melanie J Davies & Gray, 1996). It is not completely known if treating IGT will prevent these cardiovascular complications but the main reason for identifying all risk factors associated with impaired glucose tolerance is preventing or delaying the onset of type 2 diabetes (Costa et al., 2002). Reduced growth in early life is another significant problem which is also strongly associated with impaired glucose tolerance (Hales et al., 1991).

IFG and IGT are both intermediate stages in glucose metabolism between normal glucose tolerance and overt diabetes with partial overlap (Abdul-Ghani, Tripathy, & DeFronzo, 2006).

IFG is a clinical health concern that requires significant attention but it has no specific clinical symptoms, therefore, its accurate diagnosis and early interventions are very important. Because IFG does not typically present with clinical symptoms, confirmation and interventions should begin at an early stage (C.-M. Chen & Yeh, 2013).

Recent data shows that the prevalence of IFG is increasing dramatically. Some specific factors affect the prevalence of IFG/IGT such as ethnic group, age and sex (Nathan et al., 2007). IFG is more prevalent among women and among older people. Although patients with IFG and IGT might have some overlap, these two terms do not define the same group (Nathan et al., 2007).

In the general population, IGT is more prevalent than IFG alone (Santaguida et al., 2005). The underlying mechanism for IFG/ IGT is beta cell dysfunction and insulin resistance and this pathogenesis mechanism is almost the same as type 2 diabetes (Abdul-Ghani et al., 2006).

Over a period of 3 to 5 years, 25% of both IFG and IGT progress to diabetes, 50% remain within the same IFG or IGT level, and 25% revert to a normal glucose state (Nathan et al., 2007). However, the risk of developing type 2 diabetes is doubled in those individuals with both IFG and IGT at the same time (Nathan et al., 2007).
According to a longitudinal population based study, IGT is more associated with future development of type 2 diabetes than IFG alone (Shaw et al., 1999). In particular, it has also been suggested that having both IFG and IGT at the same time, has a strong association with the development of diabetes (de Vegt et al., 2001).

Screening for IFG/IGT is the same as screening for diabetes. The tests of choice for screening prediabetes is FPG and 2-h OGTT for assessing hyperglycemia (Nathan et al., 2007). However, according to a cohort study 2-h BG is a better indicator for mortality due to cardiovascular problems than FPG alone (Group, 2001) and post challenge hyperglycemia is also a risk factor for cardiovascular diseases mortalities independent than other risk factors (Saydah et al., 2001).

Isolated IFG has a different pathophysiology than isolated IGT. People with IGT have more significant muscle insulin resistance than hepatic insulin resistance but on the other hand, people with IFG have severe hepatic insulin resistance but almost normal muscle insulin sensitivity (Abdul-Ghani et al., 2006). Furthermore, people with both IFG and IGT have both hepatic and muscle insulin resistance (Abdul-Ghani et al., 2006).

There is also a difference between IFG and IGT in the pattern of insulin secretion in response to intravenous glucose administration. Individuals with isolated IFG have a reduced first phase (0 to 10 minutes) and a lower early phase (first 30 minutes) but the late phase (60 to 120 minutes) after oral glucose tolerance test is normal.

On the other hand, people with isolated IGT have an abnormal early phase insulin response after oral glucose tolerance test which is significantly reduced in the late phase of insulin secretion (Nathan et al., 2007).

In addition, transition from impaired fasting glucose (IFG), and impaired glucose tolerance (IGT) to diabetes may take several years (Nathan et al., 2007). However, almost 70% of prediabetes subjects will eventually develop diabetes. Whenever diabetes type 2 is diagnosed, approximately 50 percent of the functional beta cells are reduced. The risk of cardiovascular disease is high during the prediabetes stage (Abdul-Ghani et al., 2006; Nathan et al., 2007) and when it reaches to the diabetes stage the risk of cardiovascular diseases including dyslipidemia (low HDL cholesterol, high triglyceride), high blood pressure, and other complications such as kidney problems, and neurological problems will be even higher (Nathan et al., 2007).

IGT is more likely linked to cardiovascular diseases than IFG alone (Tominaga et al., 1999). Those cardiovascular problems associated with IFG/IGT include atherothrombosis, non-stenotic atherosclerosis, unstable angina, myocardial infarction, heart failure and combination of these (Santaguida et al., 2005). Therefore, including glucose concentrations as well as diabetes is a good factor for predicting cardiovascular score mortality risks (Group, 2004).

Furthermore, intensive life style modifications in patients with IFG/IGT can prevent or delay the onset of diabetes and cardiovascular diseases (Nathan et al., 2007). Early interventions for IFG/IGT states have
the goal of delaying and preventing the need for treatment of type 2 diabetes, preserving more functional beta cells, and preventing and delaying microvascular and macrovascular complications such as cardiovascular disorders (Nathan et al., 2007). In patients with IFG, IGT, or prediabetes we should always consider cardiovascular risk factors, markers for atherosclerosis, and also clinical symptoms for cardiovascular diseases (Nathan et al., 2007).

The priority for early interventions in patients with early stages of impaired glucose homeostasis is reducing weight and obesity. Even in those obese or overweight people who have normal blood glucose, counseling about weight reduction and exercise is necessary. Weight reduction programs could be a part of community programs or school programs and would have lots of other health benefits (Nathan et al., 2007).

In general, 5 to 10 percent weight reduction along with approximately 30 minutes of physical activity a day is the treatment of choice for people with IFG/IGT (Nathan et al., 2007).

In terms of alcohol consumption and glycemic load or glycemic index, we also had one cohort study among our search, which indicated that a higher alcohol consumption attenuates the positive association between glycemic load and incidence of type 2 diabetes but it did not modify the association of glycemic index and type 2 diabetes (Mekary et al., 2011). However, as the outcome of this article was glycemic load and glycemic index in association with type 2 diabetes, we did not include this article in our systematic review.

Glycemic index (GI) is defined as a measure of the blood glucose-raising potential of carbohydrate content of a specific food compared to a reference food. For instance, taking a high-GI food will increase postprandial blood glucose that reduces rapidly but a low-GI food lowers blood glucose concentration that reduces slowly. Glycemic load (GL) is measured by multiplying GI by the amount of carbohydrate in a food. High GI or GL diets may lead to type 2 diabetes and cardiovascular diseases (Barclay et al., 2008; Liu et al., 2000; Monro & Shaw, 2008; Salmeron et al., 1997). Glycemic index plays an important role in the dietary management and prevention of diabetes (Marsh, Barclay, Colagiuri, & Brand-Miller, 2011). Low glycemic load and glycemic index have protective effects on diabetes and cardiovascular diseases (Barclay et al., 2008).

4.2. Alcohol consumption and serum insulin levels

As mentioned above, our systematic review had different outcomes. In terms of alcohol drinking and insulin concentration, we found inconsistent results among the literatures. Among cohort studies, one study found positive association (Rankinen et al., 1997), and two other did not suggest a significant
association between alcohol consumption and serum insulin (Balkau et al., 2006; Møller & Jespersen, 1995a).

This inconsistency between the results of the included studies in our present systematic review might be due to differences in the years of follow-up for evaluating the association of alcohol consumption and serum insulin, different participants based on their baseline health, race and the country of origins.

On the other hand, differences in drinking patterns and type of alcoholic beverages and standard drinks based on different countries and cultures might be one other reason for this inconsistency. The way serum insulin has been measured might be one other source of this conflicting data.

In addition, for each of these studies, different adjustments have been made which explain the inconsistency more.

On the other hand, the previous systematic review of interventional studies in this field indicated that alcohol consumption may decrease fasting insulin in overall and it may also improve insulin sensitivity in only women but not in men or in overall (Schrieks et al., 2015).

An inverse association between alcohol and non-fasting insulin has been shown in a cross-sectional study (S. Wannamethee et al., 2002) and one other cross-sectional study represented that alcohol consumption is inversely associated with risk of type 2 diabetes but alcohol consumption in association with fasting insulin level could not explain this relationship (J. W. Beulens, Rimm, Hu, Hendriks, & Mukamal, 2008).

Fasting insulin levels in healthy non-diabetic individuals could be an alternative marker for assessing insulin sensitivity (Laakso, 1993; Muniyappa, Lee, Chen, & Quon, 2008; Schrieks et al., 2015).

High levels of serum insulin are atherogenic (Perry et al., 1996) and linked to cardiovascular diseases morbidity and mortality (Møller & Jespersen, 1995b). Therefore, having more knowledge about the association of serum insulin and its risk factors such as alcohol consumption might be a good idea to prevent type 2 diabetes and cardiovascular complications.

According to a cross-sectional study, among non-diabetic men, those who were moderate alcohol consumers had the lowest fasting insulin resistance index and fasting insulin and lower risk of coronary heart disease (Lazarus et al., 1997) and one other study also indicated the same results by suggesting an inverse association between regular alcohol consumption and insulin resistance (DE Flanagan et al., 2000). It was also suggested that the protective effects of alcohol consumption on cardiovascular diseases including dyslipidemia and hypertension might be due to its effects on serum insulin and insulin sensitivity (DE Flanagan et al., 2000; Konrat et al., 2002; Lazarus et al., 1997).
Other cross-sectional studies also had the same results. They suggested that alcohol consumption is associated with lower fasting insulin and lower 2-hour post glucose insulin concentrations (Hodge, Dowse, Collins, & Zimmet, 1993; Kenkre, Lindeman, Yau, Baumgartner, & Garry, 2003). Another study also suggested that alcohol consumption is positively correlated with insulin-mediated glucose uptake (Goude et al., 2002).

Metabolic effects of alcohol consumption specifically wine consumption were assessed in a study of type 2 diabetic patients and it was suggested that chronic alcohol consumption caused reduces in serum fasting insulin. These results are consistent with other cross-sectional studies about the effects of alcohol consumption on serum insulin in non-diabetic patients (Bantle, Thomas, & Bantle, 2008).

In addition, in terms of alcohol consumption and insulin sensitivity (measured by modified HOMA-IR and HOMA-B) we found one article among our search which included participants from a nested case-control study of non-diabetic twin females, however, the association of alcohol consumption with insulin sensitivity (assessed by modified HOMA-IR and HOMA-B) was evaluated by a cross-sectional analysis. This study represented that moderate alcohol consumption increased insulin sensitivity (J. R. Greenfield et al., 2003). However, because of the cross-sectional design of the relationship between alcohol consumption with insulin sensitivity, we excluded that from our present systematic review.

High insulin concentrations is a strong factor in development of type 2 diabetes (Carnethon, Palaniappan, Burchfiel, Brancati, & Fortmann, 2002). It has been also suggested that there is higher insulin response and insulin resistance in glucose tolerant patients (Osei et al., 1993).

Insulin resistance and β cell dysfunction are the main reasons for the pathogenesis of type 2 diabetes. The homeostasis model assessment (HOMA) is the most applicable tool in assessing insulin sensitivity (Y. Song et al., 2007). Moderate to large increases in HOMA-IR are positively associated with developing type 2 diabetes (Morimoto et al., 2014).

Elevations of serum gamma-glutamyl transferase (GGT) in alcohol drinkers was suggested to be positively associated with HOMA-IR and insulin resistance (Yamada et al., 2004).

According to a cross-sectional study, alcohol consumption was negatively associated with insulin resistance measured by HOMA-IR scores and this finding was independent to central obesity, metabolic profiles, and fatty liver disease (Gunji et al., 2011). On the other hand, another cross-sectional study represented a U-shape association between alcohol consumption and HOMA-IR (Villegas, Salim, O'Halloran, & Perry, 2004).

One other impact of alcohol consumption on insulin concentrations and insulin sensitivity discussed in some literature is its effects on some mediators such as adiponectin. Alcohol consumption may improve insulin resistance by increasing adiponectin levels. Adiponectin is a plasma protein produced by
adipocytes (Bonnet et al., 2012). Low levels of adiponectin are reported in obese patients and individuals with type 2 diabetes (Bonnet et al., 2012).

Fasting plasma adiponectin is related to high basal and low insulin stimulated tyrosine phosphorylation of insulin receptors in skeletal muscle (Stefan et al., 2002). On the other hand, tumor necrosis factor (TNF-α) is associated with high basal tyrosine phosphorylation of insulin receptors in skeletal muscle and as a result it may cause insulin resistance (Hotamisligil, Shargill, & Spiegelman, 1993). According to in vitro studies, adiponectin may have some effects on reducing TNF-α (Ouchi et al., 2000).

A cross-over partially diet-controlled study has evaluated the effects of moderate alcohol consumption on adiponectin levels and has found that moderate alcohol consumption improves insulin sensitivity and increases adiponectin levels in insulin-resistant individuals (Sierksma et al., 2004). This results have been also approved in a large and more heterogeneous group of healthy subjects (Thamer, Haap, Fritsche, Haering, & Stumvoll, 2004).

One other insulin related effect of alcohol might be its inhibitory effect on incretin responses, especially if alcohol is consumed with meals (Dalgaard, Thomsen, Rasmussen, Holst, & Hermansen, 2004).

In terms of association of alcohol consumption and Fetuin A (Ley et al., 2014), among our search we had one study with a cohort analysis for association of alcohol consumption and incidence of type 2 diabetes and a cross-sectional analysis for association of alcohol consumption with Fetuin A (Ley et al., 2014). The study mentioned above (conducted by Ley SH et al. (2014)) suggested that moderate alcohol consumption was associated with lower plasma Fetuin-A (which inhibits insulin signaling, and is a biomarker for type 2 diabetes). Fetuin-A and insulin could explain a significant proportion of the association between alcohol consumption and incidence of type 2 diabetes. However, as discussed above, the association of alcohol consumption with Fetuin A in this study (Ley et al., 2014) was assessed in a cross-sectional design and thus we excluded that from our current systematic review.

Fetuin A is a new biomarker and a multifunctional glycoprotein that inhibits insulin receptors and is related to insulin resistance (Lorant et al., 2011; Mori et al., 2006; A. Song et al., 2011). It is exclusively produced by hepatocytes in humans (Denecke et al., 2003). Fetuin A has been suggested as an independent risk factor for type 2 diabetes (Stefan et al., 2008) and it has been found that Fetuin A is higher in diabetic patients (Lorant et al., 2011). It is also correlated with IGT and prediabetes stage other than type 2 diabetes (Postic et al., 2004; A. Song et al., 2011).

Fetuin A binds to insulin receptor tyrosine kinase in adipocytes and skeletal muscle. Therefore, it may cause insulin resistance in adipocytes, and skeletal muscle other than hepatocytes (Mathews et al., 2000).
4.3. Alcohol consumption and glycated hemoglobin (HbA1C)

The other outcome of our systematic review was glycated hemoglobin (HbA1C). Three studies included in this field, showed mixed findings.

One study included in our systematic review, represented that HbA1c decreased by 4% among previous non-drinkers and increased among drinkers of one or more drinks per day when consumption increased over a four-year period (M. M. Joosten et al., 2011). On the other hand, another cohort study in this field, suggests that daily alcohol consumption may protect against an increase in HbA1c level compared to less than daily drinking (Suwazono et al., 2009). However, one other cohort study included in our systematic review, indicated no statistically significant association between alcohol consumption and HbA1C (Kiechl et al., 1996).

Therefore, the results of these three included studies in this field were inconsistent. This conflicting data might be due to the differences in the population included, differences in race, country of origin, baseline heath of individuals, the way the exposure is measured (e.g. Joosten et al, has evaluated the change in alcohol consumption while the two other studies have only measured alcohol consumption at baseline), differences in drinking patterns, type of alcoholic beverages and standard drinks based on different countries might be other reasons for this inconsistency. Other than that, differences in length of follow-up and the way HbA1C is measured in each study might be another source of this inconsistency in the results.

In addition, different studies have used different adjustments, which might be an additional reason for this inconsistency.

The results of the systematic review of interventional studies on non-diabetic patients, in the category of alcohol and HbA1C, also represented that moderate drinking lowers HbA1C (Schrieks et al., 2015). On the other hand a clinical trial on type 2 diabetic patients at baseline, also had the similar results and revealed that moderate alcohol consumption reduces HbA1C (Shai et al., 2007).

According to a cross-sectional study glycated hemoglobin is lower in those who drink 42 or more units of alcohol per week than in those who did not drink alcohol (Gulliford & Ukoumunne, 2001).


Glycated hemoglobin (HbA1C) is a long-term factor for glucose control and a strong predicator for diabetes complications (Wolffenbuttel, Giordano, Founds, & Bucala, 1996). It is associated with both micro and macro vascular complications of diabetes and it also increases the risk of atherosclerosis.
HbA1C is also associated with cardiovascular diseases even in non-diabetic individuals (Selvin et al., 2010).

HbA1C and blood glucose levels are two distinguished factors involved in pathogenesis of type 2 diabetes. The reason for variations in HbA1C levels might be due to both genetic and non-genetic factors. Non-genetic factors are responsible for 40 to 60% of variations in HbA1C levels (Jansen et al., 2013). Red blood cell survival and blood glucose concentrations are the two main indicators for variations in HbA1C. However, several other factors may affect HbA1C variations such as age, BMI, smoking, alcohol consumption and race (Jansen et al., 2013). Some specific genetic factors may also play a significant role in this field (Jansen et al., 2013).

4.4. Confounding factors for the effects of alcohol consumption on glucose homeostasis

In general, possibility of biased measures due to cofounding effects should be taken into considerations. Confounders are defined as a set of additional factors, which can distort the effects of the exposure under study on a given outcome. Confounding factors may mask or falsely demonstrate a clear causal link between the exposure and outcome (Skelly, Dettori, & Brodt, 2012).

A true confounding factor predicts the outcome even in the absence of the exposure. A confounding factor is also associated with the exposure being studied and is unequally distributed between the exposed and unexposed group. However, a confounder cannot be a mediator between the exposure and the outcome (Skelly et al., 2012).

In our present systematic review, the included articles had different adjustments for potential confounders because it was impossible to include articles with the same adjusted risk factors.

No matter how many variables the included studies have adjusted for, there will be always risk of residual confounding, possibly by factors that are unknown and cannot be measured.

Potential confounders for association of alcohol consumption with different parameters of glucose homeostasis are categorized as demographic (e.g. age, gender), socioeconomic (e.g. smoking, diet, and physical activity), biologic determinants (e.g. genetics, BMI, and other underlying diseases) and medications.

Some factors such as dyslipidemia (including low HDL, high LDL and triglycerides) is considered as a mediator, which affects the causal pathway between alcohol consumption and impaired glucose homeostasis.
In the following passage, different confounders for the effects of alcohol consumption on different parameters of glucose homeostasis are discussed.

### 4.4.1. Demographic determinants

#### 4.4.1.1. Age

Aging increases the risk of impaired glucose homeostasis and incidence of type 2 diabetes. By increasing the average age of the populations in the world, the risk of impaired glucose homeostasis and type 2 diabetes will also increase and it may have a great burden on the economics of the whole society (C. Meyer, 2008).

An imbalance between beta cell function and insulin sensitivity is the underlying mechanism for IGT and type 2 diabetes which occurs by increased age (C. Meyer, 2008). Decrease in beta cell mass and/or function, however, may happen even during early years of life and it will increase by aging (C. Meyer, 2008).

On the other hand, annual decreases in insulin sensitivity and insulin clearance occur by aging and first and second phase insulin secretion will decrease in individuals with normal glucose tolerance by aging (C. Meyer, 2008).

Aging-induced impaired glucose homeostasis is more severe in those subjects with impaired glucose tolerance at baseline compared to people with normal glucose tolerance (C. Meyer, 2008).

Normal aging decreases beta cell mass and function but it does not lead to type 2 diabetes in all individuals (C. Meyer, 2008).

Increasing in age also increases the prevalence of impaired fasting glucose (IFG) (Alikor & Emem-Chioma, 2014; Escobedo et al., 2009).

According to a cross-sectional study aging is positively and strongly associated with increased glycated hemoglobin even after excluding those who have IFG, IGT or both (Pani et al., 2008).

Aging is also related to higher HbA1C even without hyperglycemia (Ravikumar, Bhansali, Walia, Shanmugasundar, & Ravikiran, 2011; Y.-C. Yang, Lu, Wu, & Chang, 1997) and it should always be taken into considerations in patients with prediabetes and diabetes in targeting the optimal points of HbA1C (Dubowitz et al., 2014).
4.4.1.2. Sex

In women, there is more adipose tissue, more FFA, and more intra-myocellular fat. Women also have two-thirds of the skeletal muscles of men. All these factors cause more predisposition to insulin resistance in women compared to men (Mauvais-Jarvis, 2015).

There is also a narrow range for beneficial effects of estrogen on glucose homeostasis in women between puberty and menopause stages (Mauvais-Jarvis, 2015).

In women after menopause, when estrogen levels are reduced, insulin resistance may develop. On the other hand, synthetic estrogens and supra physiologic estrogen levels in oral contraceptives may cause more severe insulin resistance in women compared to men (Mauvais-Jarvis, 2015).

In women, IGT is more prevalent than in men but, on the other hand, IFG is more prevalent in men. The reason for increased prevalence of IGT in women is less muscle mass in women and reduced insulin stimulated glucose disposal (Mauvais-Jarvis, 2015).

In women, central obesity and the prevalence of metabolic syndrome is two to ten times higher than men (Mauvais-Jarvis, 2015).

There is a sex difference in the amounts of HbA1C. In women, before menopause the level of HbA1C is lower than men (Y.-C. Yang et al., 1997).

4.4.2. Social determinants

4.4.2.1. Smoking

Smoking has long term effects on glucose homeostasis (Sargeant et al., 2001). A prospective cohort study revealed that smoking is associated with impaired fasting glucose and type 2 diabetes (Noriyuki Nakanishi, Nakamura, Matsuo, Suzuki, & Tatara, 2000). Similarly, another cohort study in Korean adults also suggested that smoking is positively correlated with impaired fasting glucose and diabetes (Park et al., 2008). Smoking is positively associated with conversion of normoglycemia to IFG (incidence of IFG) in non-diabetic patients at baseline (Rafalson et al., 2009).

However, in contrast to those studies mentioned above, one other study suggested that quitting smoking is correlated with increased diabetes and IFG (Stein et al., 2014).

According to a non-randomized control trial, smoking is associated with impaired glucose tolerance and increased insulin resistance (Frati, Iniestra, & Ariza, 1996). Another study in this field also had the same
results and represented that smoking is strongly correlated with incidence of metabolic syndrome, impaired glucose tolerance, impaired insulin sensitivity, and insulin secretion (Piatti et al., 2014).

Smoking is positively associated with high glycated hemoglobin (Gunton, Davies, Wilmshurst, Fulcher, & McElduff, 2002; Modan et al., 1988). It has been represented that smoking cessation may improve HbA1C (Gunton et al., 2002). In contrast to the above mentioned studies, one other study indicated that smoking has no significant direct effect on HbA1C (McCulloch, Lee, Higgins, McCall, & Schade, 2002).

Smoking is also correlated with severity of insulin resistance, and insulin levels (Eliasson, Attvall, Taskinen, & Smith, 1994). Chronic cigarette smoking is associated with increased severity of insulin resistance in non-insulin dependent diabetes (Targher et al., 1997).

It has also been suggested that cigarette smoking is associated with skeletal muscle insulin resistance, which will be reversed by quitting (Piatti et al., 2014).

One other study found the same results and represented that smoking is associated with increased risk of insulin resistance and metabolic syndrome by increasing central obesity (Piatti et al., 2014).

On the other hand, one other study represented a transient metabolic changes due to smoking cessation (Stadler et al., 2014).

Compared to non-smokers, smoking is associated with higher fasting glucose, fasting insulin, and HOMA-IR (Haj Mouhamed et al., 2015). However, according to a cross-sectional study, smoking was not associated with HOMA-IR and current smoking was related to decreased beta cell function (Wang et al., 2015). Individuals with vascular damage and insulin resistance may have more complications from acute effects of smoking (Seet et al., 2012). Current smokers, had lower levels of HOMA-IR than quitters and non-smokers (Kanervisto et al., 2015).

Smoking in pregnancy affects different glucose homeostasis parameters. More number of heavy smoker mothers had higher 2-hour glucose in the range of gestational diabetes and also higher numbers of heavy smoker mothers had a high glycated hemoglobin (Zarén, Lindmark, Wibell, & Følling, 2000). However, one other study, did not support this finding and suggested that smoking is not associated with gestational diabetes (Zarén et al., 2000).

According to a systematic review and meta-analysis of observational studies, heavy smokers compared to light smokers had increased incidence of type 2 diabetes and also active smokers compared to former smokers had a higher incidence of type 2 diabetes (Willi, Bodenmann, Ghali, Faris, & Cornuz, 2007).

4.4.2.2. Physical activity

Physical activity is inversely associated with IFG or diabetes by decreasing fasting glucose concentrations (N Nakanishi, Takatorige, & Suzuki, 2004).
According to a clinical trial, diet and physical activity reduce the incidence of diabetes over a 6-year period among individuals with IGT (Pan et al., 1997).

Another cross-sectional study also indicated the same results and revealed that physical activity and no sedentary life style have a protective effect on the risk of abnormal glucose metabolism (Dunstan et al., 2004). In individuals with IFG at baseline, regular daily physical activity improves fasting glucose (Liao et al., 2015). According to a follow-up study, physical activity reduces the development of impaired fasting glucose (Puterman, Adler, Matthews, & Epel, 2012).

Low physical activity is an independent indicator for impaired glucose tolerance (Annuzzi et al., 1985).

The underlying mechanism for the effects of exercise on IGT is by increasing GLUT4 proteins (GLUT 4 proteins facilitate the diffusion of glucose into the cells) on cell membranes and the intrinsic activity of the transporters. The greater the intensity of exercise, the greater the depletion of glycogen and therefore, insulin action will be better modified (Wright & Swan, 2001).

On the other hand, according to a systematic review of interventional studies, physical activity reduces HbA1C (Avery, Flynn, Van Wersch, Sniehotta, & Trenell, 2012). Cross-sectional studies also found the same results and indicated an inverse association between physical activity and HbA1C (Beraki, Magnuson, Särnblad, Åman, & Samuelsson, 2014).

Furthermore, resistance exercises reduce glycated hemoglobin more than aerobic exercises (Bweir et al., 2009).

Among subjects with prediabetes at baseline, insulin sensitivity was higher for those who had regular exercise training (Malin, Gerber, Chipkin, & Braun, 2012).

High intensity physical activity reduces HOMA-IR (Hessol et al., 2013; LeCheiminant & Tucker, 2011). The time spent on physical activity is an important factor associated with improved glucose metabolism and insulin sensitivity (Nelson et al., 2013; Rizzo, Ruiz, Oja, Veidebaum, & Sjöström, 2008).

4.4.2.3. Diet

Diet is one other significant factor involved in the etiology of impaired glucose homeostasis. Proteins and amino acids are strong modifiers for glucose regulations and prandial insulin secretions. In the short-term, they induce skeletal muscle insulin resistance and stimulate endogenous glucose production (Krebs et al., 2002).

To reduce the prevalence of insulin resistance and diabetes, intake of high sucrose, high fructose corn syrups, animal and trans-fats, mayonnaise salads, red meat, potatoes, lard, and/or butter should be restricted and intake of vegetables, vegetable oil, fish, fruit, whole grains and fiber should be increased (Asif, 2014).
Patients with IGT may respond better to dietary intervention than those with IFG (Eikenberg & Davy, 2013). In addition, decreases in carbohydrate intake decreases glycated hemoglobin (Power & Thomas, 2011).

Diet affects insulin sensitivity and beta cell function. Diet induced weight loss, improves insulin sensitivity and beta cell function. Low fat and low carbohydrate diets increase hepatic insulin sensitivity, reduce glucose production from the liver with almost 2% weight loss and increase skeletal muscle insulin sensitivity after a 7% weight loss (Eikenberg & Davy, 2013).

A diet with mostly saturated fatty acids disturbs insulin sensitivity. However, a diet with monounsaturated fatty acids has no significant impact on insulin sensitivity (Eikenberg & Davy, 2013).

Therefore, having a diet rich in polyunsaturated fats instead of saturated, taking 31.2 g insoluble fiber per day, and replacing of 6 to 10 daily servings of refined grains with whole grains could increase peripheral insulin sensitivity (Eikenberg & Davy, 2013).

There is a complex relationship between low glycemic index foods with risk of diabetes. Some studies suggest that foods with low glycemic index decrease the risk of type 2 diabetes, but some other studies do not report reduction in the risk of type 2 diabetes due to low glycemic index foods (Eikenberg & Davy, 2013).

4.4.3. Biological determinants

4.4.3.1. BMI

Increase in BMI is related to the development of impaired fasting glucose (Klein et al., 2004). According to a randomized clinical trial, BMI is an important modifiable risk factor related to the prevalence of metabolic syndrome and impaired fasting glucose (Thompson et al., 2007). Intra-abdominal fat is a major factor which impairs beta cell function and insulin sensitivity (Kahn, 2003).

According to a case-control study, BMI and waist circumference are associated with impaired fasting glucose (Qian et al., 2010). A cross-sectional study also revealed that obesity and waist hip ratio is correlated with diabetes and impaired glucose tolerance (Saadat, Salehi, Emami, & Azizi, 2005). Fasting glucose will be decreased by reducing weight (1.5 kg) and waist circumference (3cm) (Chae et al., 2012). Not only being obese, but also being slightly overweight is correlated with impaired glucose tolerance (Klein et al., 2004). Weight loss, independent of BMI, is a significant risk factor for improving glucose tolerance, insulin sensitivity, and beta cell function (Ferrannini & Camastra, 1998).

On the other hand, rapid increase of BMI in infants and adolescents may cause metabolic syndrome and impaired glucose tolerance (Fall et al., 2008). Therefore, there is a strong positive association between
impaired glucose tolerance and obesity (European & Group, 2002; Rivers, Hanna-Mahase, Frankson, Smith, & Peter, 2013).

BMI gain in childhood and adulthood is also associated with increased HbA1C (Power & Thomas, 2011). Increases in BMI is associated with higher insulin resistance hemostasis (HOMA-IR) and lower number of beta cells (Chung, Cho, Chung, & Chung, 2012).

Central obesity is also correlated with increases in first phase insulin secretion (Walton, Godsland, Proudler, Felton, & Wynn, 1992)

In summary, BMI is a strong and independent indicator for insulin sensitivity even in normal weight individuals (Risérus, Ärnlöv, & Berglund, 2007; Sinaiko et al., 2005).

4.4.3.2. Genetics

The role of genetics in glucose homeostasis is still unknown. However, some specific genes which play a role in increasing the risk of type 2 diabetes and inducing variations in fasting glucose levels in non-diabetic individuals have been recognized (Norris & Rich, 2012).

According to a meta-analysis performed in non-diabetic patients, specific loci were associated with fasting glucose, HOMA-B, fasting insulin and HOMA-IR. These genes are related to signal transduction, cell proliferation, development, glucose-sensing and circadian regulation (Dupuis et al., 2010).

Glucose transporters are tissue-specific membrane glycoproteins. Their specific genes are characterized by cDNA cloning. Among these proteins, the most common distributed is HepG2-type transporter (Mueckler, 1990).

Chromosome 6q21-q23, and 1q21-24 are related to impaired glucose homeostasis and type 2 diabetes (Xiang et al., 2004).

Therefore, underlying genetic factors play an important role in the occurrence of impaired glucose homeostasis (Sinasac et al., 2016).

Genetic predisposition has a significant role as a potential risk factor for diabetes. Some specific genes such as PPARγ, KCNJ11, CAPN10, HNF4A and TCF7L2 are linked to increasing the risk of type 2 diabetes (Arner, Arner, Hammarstedt, & Smith, 2011).

Another novel finding in this field is about the genetic predisposition for type 2 diabetes which particularly increases the sensitivity of individuals to environmental and caloric excess (Arner et al., 2011).
First-degree relatives of individuals with type 2 diabetes are almost three times more likely to develop the disease than those without a positive family history (Florez, Hirschhorn, & Altshuler, 2003; Gloyn, 2003; Hansen, 2003). Race and ethnicity also play an important role in the occurrence of impaired glucose homeostasis. For instance, it has been represented that impaired glucose homeostasis and type 2 diabetes is more common in African Americans than in White Americans (Healy, Osei, & Gaillard, 2015).

Allele frequencies of fasting glucose related single nucleotide polypeptides (SNPs) differ prominently by race and ethnicity (Q. Yang et al., 2010).

Racial and ethnic differences are also in association with HbA1C and blood glucose levels (Herman & Cohen, 2012).

4.4.3.3. Underlying diseases
Some underlying medical problems predispose different individuals to impaired glucose homeostasis. These problems include some diseases related to endocrinology such as Cushing syndrome, acromegaly, gigantism, hyperparathyroidism, hyperprolactinemia, hyperthyroidism, primary hyperaldosteronism, pheochromocytoma, poly cystic ovary syndrome (PCO), POEMS syndrome (a rare disorder including Polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal-plasma proliferative disease, and Skin changes).

Other than those mentioned above, some gastrointestinal problems (e.g. chronic pancreatitis), some types of cancers, and some other rare disorders such as hemochromatosis also increase the risk of impaired glucose homeostasis (Krysiak, Rudzki, & Okopień, 2011).

4.4.4. Medication
Some specific medications induce impaired glucose homeostasis. For instance, diuretics, alpha and beta blockers, ACE inhibitors, lipid lowering agents (e.g. statins), glucocorticoids, sympathomimetic, sex hormones, and quinin may cause impaired glucose homeostasis (Chan, Cockram, & Critchley, 1996).

Some serotonergic antidepressants such as fluoxetine reduce blood glucose and increase insulin sensitivity but some others such as noradrenergic antidepressants have opposite effects (McIntyre, Soczynska, Konarski, & Kennedy, 2006).

Therefore, drug-induced diabetes and its cardiovascular complications is an important field to take into consideration (Blackburn & Wilson, 2006).
Other than the confounding factors mentioned above, some other factors have effects on the intermediate causal pathway between alcohol consumption and impaired glucose homeostasis such as dyslipidemia.

Alcohol consumption may cause some changes in lipid profile. On the other hand, dyslipidemia has a dual relationship with impaired glucose homeostasis. Disturbed cholesterol homeostasis may cause impaired glucose homeostasis (Toffolo, de Aguiar-Nemer, & da Silva-Fonseca, 2012).

Dyslipidemia may reduce the function of beta cells by accumulation of cholesterols in the beta cells of the pancreas which may cause hyperglycemia, insulin resistance and beta cell apoptosis (Bardini, Rotella, & Giannini, 2012).

In addition, abnormal lipid metabolism is more prevalent in impaired glucose tolerance and non-insulin dependent diabetes (Nagai, Tomizawa, Minamide, Nakajima, & Mori, 1996).

Some forms of dyslipidemia are associated with prediabetes which are manifested by low HDL, increased level of triglyceride rich lipoproteins and dysmetabolism of triglyceride rich lipoprotein which causes increased amounts of denser and smaller LDls (Garber, 2011).

According to a cross-sectional study, patients with hyperlipidemia have an increased risk for high blood glucose levels and diabetes type 2. Therefore, specific interventions should be regulated to prevent the complications due to type 2 diabetes in patients with hyperlipidemia (G.-Y. Chen et al., 2015).

4.5. Factors affecting research related to alcohol

In terms of alcohol-related research studies, there is still potential to improve alcohol guidelines and to consider different factors for interpreting alcohol-related health consequences. These different factors are discussed below.

While performing alcohol related research, age is an important factor to be taken into considerations. Alcohol-related harms mostly occur in children, adolescents, and elderly people (Mustonen, 2000). Young people are also more engaged in irregular heavy drinking behaviors. On the other hand, older people drink alcohol more frequently than other age categories and also because of some changes in the physiologic function of their different organs, the effects of alcohol on old people’s health will also change (Sorock, Chen, Gonzalgo, & Baker, 2006).

The alcohol-related burden of disease among older people is a public health concern because of the increasing aging population in many countries around the world (WHO, 2012).

Women are likely to be more vulnerable to alcohol-related harm from a specific level of alcohol or a particular drinking pattern. Women’s predisposition to alcohol related harm is another major public health issue because of increases in the number of women who use alcohol as a result of economic
development and changing gender roles (Grucza, Bucholz, Rice, & Bierut, 2008). This can be a serious health and economic problem especially because of new born babies (Abel & Sokol, 1987). However, compared to women, men are less often abstainers, they drink more (in both amount and frequency), and so there is increased burden of disease among men (Nolen-Hoeksema, 2004). The vulnerability of women to alcohol related harm from a given amount of alcohol may be explained by several factors (Wilsnack, Wilsnack, & Kantor, 2014). Women usually have less body weight, lower liver capacity to metabolize alcohol, and a higher body fat, which may result in higher blood alcohol concentrations than men for the same amount of alcohol consumption and on the other hand, the more water available, the more diluted alcohol occurs in men (WHO, 2014).

In addition, women who drink during pregnancy may increase the risk of fetal alcohol spectrum disorder (Viljoen et al., 2005), therefore, mandatory health warnings for women’s drinking should be considered. Another significant vulnerability factor for alcohol related health problems is having a positive family history (Merikangas et al., 1998). Multiple genes play a role in alcohol use disorders and alcohol dependency and also some harmful parental drinking practices may lead to childhood psychological problems and later to harmful drinking patterns (Shin, Edwards, & Heeren, 2009).

There are more drinkers and also more heavy drinkers in higher socioeconomic areas and more abstainers exist in low socioeconomic groups (Grittner, Kuntsche, Graham, & Bloomfield, 2012). However, people with low socioeconomic status (SES) are usually more vulnerable to alcohol related harm which might be because of not having access to high quality health care services, having less support networks, and etc. (Schmidt, Mäkelä, Rehm, & Room, 2010).

Economic development is one other important factor associated with alcohol related harm. Greater economic wealth is mostly associated with higher levels of alcohol consumption and lower rates of abstention (WHO, 2014).

There is a dose–response relationship based on volume of alcohol consumption for most diseases and injuries related to alcohol consumption.

In addition, volume of drinking is not the only factor related to the harms of alcohol consumption. Other factors such as the pattern of drinking and the quality of drinking are also associated with some health problems (such as risk of cardiovascular diseases) (Rehm et al., 2010). Furthermore, the cardio protective effect of low to moderate amount of alcohol consumption disappears in the presence of heavy episodic drinking (HED) (Roerecke & Rehm, 2010).

Pattern of drinking while eating is suggested to be associated with less harm from chronic diseases than the same pattern but at other times (Stranges et al., 2004; Trevisan, Schisterman, Mennotti, Farchi, & Conti, 2001).
Therefore, the way of alcohol consumption (i.e., with meals or binging on weekends) might have significant impacts on different health disorders (Rehm, Gmel, Sempos, & Trevisan, 2003) and specifically on impaired glucose homeostasis parameters.

4.6. Limitations of the Study

In general, in our present systematic review and meta-analysis, the number of studies based on each indicator was low and consequently the whole study population may not be fully representative of the general population and also as in any meta-analysis, the strength of the current study is mostly determined by the quality and number of the included studies.

There was also inconsistency in the results of some indicators (such as serum insulin and HbA1C); therefore, it would be difficult to reach a firm conclusion specifically for these indicators.

In our current study, duration and dosing of the alcohol consumption and the characteristics of individuals were different. Therefore, it is possible that potential confounders such as age, smoking, BMI, physical activity, diet, genetic predisposition and underlying medical problems have affected our results.

On the other hand, among all those studies that fulfilled our inclusion criteria, no study had information about pattern of drinking or binge drinking (irregular heavy drinking occasions), which is a very important topic for assessing the effects of alcohol consumption on different diseases (Rehm & Gmel, 2003). Unfortunately, pattern of drinking has been underestimated in most of the epidemiological studies (Rehm, Room, et al., 2003).

Furthermore, we cannot reach any conclusion regarding the effects of alcohol consumption above 60 g/day because of the lack of data among our included articles in the meta-analysis.

On the other hand, in most of the included studies, we did not have data about association of specific alcoholic beverages on different parameters of glucose homeostasis. Moreover, the sugar content or caloric content of different drinks should also be considered especially in research related to association of alcohol consumption with glucose homeostasis.

In most of the alcohol research studies including the studies in our meta-analysis, non-drinkers are considered as a reference group. However, nondrinkers are mixed of both former drinkers and lifelong abstainers. Former drinkers usually have poorer health and higher mortality rates than nondrinkers and even moderate drinkers (Knott et al., 2015; Tsubono, Yamada, Nishino, Tsuji, & Hisamichi, 2001). Therefore, in some studies, the protective effects of moderate drinkers compared to nondrinkers has been overestimated due to mixing unhealthy former drinkers to nondrinkers as reference group.
One other limitation of our present study, is that in most of those included studies, change in alcohol consumption during follow-up, which is a very important criteria (Kerr, Fillmore, & Bostrom, 2002) was not measured, and it may lead to over or under estimation of alcohol consumption. On the other hand, self-reporting of alcohol consumption is not always reliable, because the possibility of underestimating alcohol consumption exists (Midanik, 1982).

Although, according to previous studies, the reproducibility and validity of self-administered data is acceptable (Giovannucci et al., 1991; Gronbaek & Heitmann, 1996; G. D. Williams, Aitken, & Malin, 1985), self-report of alcohol consumption may cause recall bias.

Finally, we have only included published studies, and thus there is potential for publication bias. Though we did not find apparent evidence for such bias, we still cannot completely exclude such a possibility.

4.7. Public health impacts and clinical implications

As mentioned before, early stages of impaired glucose homeostasis such as IFG, IGT or prediabetes usually have no clinical symptoms, but are associated with increased risk of type 2 diabetes and cardiovascular diseases.

On the other hand, early stages of impaired glucose homeostasis such as IFG, IGT and prediabetes are considered reversible situations. Therefore, more research is needed to investigate the risk factors associated with different indicators of impaired glucose homeostasis to find different effective strategies for early interventions to prevent or delay the development of type 2 diabetes and its complications.

Among different risk factors in association with impaired glucose homeostasis, alcohol consumption is one of the most common modifiable risk factors. The results of our current meta-analysis suggest that alcohol consumption, in overall, increases the incidence of impaired fasting glucose. Although, we still need more research studies to be able to confirm the results of our meta-analysis and to provide a strong public health impact, being more cautious about alcohol drinking behaviors is necessary.

4.8. Conclusion

Glucose homeostasis has different indicators and several factors are involved in the pathogenesis of impaired glucose homeostasis. In general, the association of alcohol consumption as one of the most common modifiable risk factors with glucose homeostasis parameters is complex. According to our meta-analysis results, alcohol consumption in overall has a positive association with incidence of impaired fasting glucose.
Our meta-analyses results showed that by increasing the amount of alcohol consumption, the risk for incidence of fasting glucose ≥ 100mg/dL also increased. This was shown in our regression analysis, which treated alcohol consumption continuously; moreover, in categorical analyses we found evidence, which commensurate with our hypotheses, although not all groups were significantly different from the abstainers group. While we could show an overall statistically significant result, the scarcity of underlying data, requires replication.

In addition, in terms of the association of alcohol consumption with other indicators of glucose homeostasis such as serum insulin and HbA1C, there were fewer studies available, and those had heterogeneous results. Therefore, we cannot reach any conclusion for these outcomes.

There is also lack of data on the association of alcohol consumption with some other indicators of glucose homeostasis such as impaired glucose tolerance (IGT), and insulin sensitivity (HOMA-IR and HOMA-B) in cohort or case-control studies. Therefore, all these different factors mentioned above preclude us from making firm judgements or conclusions on association of alcohol consumption with different indicators of glucose homeostasis and more research studies are needed to enable us to refute or corroborate our hypothesis.

4.9. Future Directions

The results of our systematic review and meta-analyses address that there is still a knowledge gap in terms of the association of alcohol consumption with glucose homeostasis.

Although there are considerable number of studies about the association of alcohol consumption and diabetes, in terms of association of alcohol consumption with different parameters of glucose homeostasis especially for early stages of impaired glucose homeostasis such as impaired fasting glucose, impaired glucose tolerance, and prediabetes stage there is a significant lack of data.

More research with higher quality in diverse ethnic populations is needed to further explain this relationship.

Thus, future research is necessary to consider the effects of alcohol consumption on separate indicators of impaired glucose homeostasis including impaired fasting glucose, impaired glucose tolerance, serum insulin levels, insulin sensitivity, and HbA1C, on non-diabetic patients at baseline. In this way, we will be able to evaluate the effects of alcohol consumption on each parameters of glucose homeostasis more effectively.

In particular, by replicating and confirming the results of our meta-analyses in more cohort studies with larger sample size we might be able to prevent or delay the progression of early stages of impaired
glucose homeostasis (such as impaired fasting glucose) to diabetes and its different severe complications by modifying alcohol drinking behaviors in people with early stages of impaired glucose homeostasis.

On the other hand, as discussed previously for designing the future research studies the role of different confounders such as age, sex, smoking, BMI, diet, physical activity, genetic, underlying medical problems and medications should also be considered. Therefore, appropriate adjustments by considering these confounders should be used for analyzing the results of future studies.

The other factor to be considered especially for longitudinal studies is considering the change in those specific mentioned confounders as well as the changes in overall health of the participants during the time of follow-up.

In addition, for developing further studies, we need to consider several factors related to alcohol consumption. Future research studies should assess the effects of alcohol consumption in chronic heavy drinking categories other than low to moderate categories. However, most of the previous research studies have only considered low to moderate effects of alcohol consumption on different glucose homeostasis parameters.

For example, even in the previous systematic review of interventional studies by Scriecks et al. (2015) in the field of association of alcohol consumption with glucose homeostasis, heavy drinkers have been excluded (Scriecks et al., 2015).

Moreover, one very important factor in developing further research studies in the field of association of alcohol consumption with glucose homeostasis, is considering the pattern of drinking or binge drinking (irregular heavy drinking occasions) other than restricting research to the amount of alcohol consumption.

For instance, the effects of alcohol consumption on incidence of impaired glucose homeostasis and diabetes might be more determined by pattern of drinking other than the amount of drinking. This would be similar to ischemic diseases, where it had been shown that any beneficial effect of light to moderate alcohol consumption disappears in people who had at least one binge drinking episode per month (Roerecke & Rehm, 2010).

Therefore, we should consider the specific questions regarding pattern of drinking such as measuring the frequency of drinking, the average quantity per occasion, the frequency of risky single drinking occasions, frequency of drinking with meals and frequency of drinking in public for designing future alcohol related questionnaires.

Furthermore, change in alcohol consumption during follow up is one other factor, which might be considered in developing future cohort studies. Change in alcohol consumption is a very important topic for developing future alcohol related research studies with long-term follow-ups.
The effects of various types of alcoholic beverages in association with separate parameters of impaired glucose homeostasis, is another significant point to be considered in future studies. Specifically sugar content and caloric content of these different types of alcoholic beverages play an important role on different parameters of glucose homeostasis, which should be addressed in future studies.

Therefore, specific questions about change in alcohol consumption after years of follow up and about different types of alcoholic beverages should also be added in alcohol related questionnaires for future studies in this field.

Moreover, for developing future alcohol related research studies, one specific factor to be considered is developing research studies by considering sex-stratification effects of alcohol consumption. Because as mentioned before, the effects of alcohol consumption might be different in different genders. For instance, although among women there are more abstainers rather than alcohol consumers, and women usually drink less than men (Nolen-Hoeksema, 2004), more evaluations are needed to consider female drinking in relation to different health problems and specifically impaired glucose homeostasis.

Therefore, further research is required to enable us to know more about sex-specific differences in the dose-response relationship between alcohol consumption and different parameters of glucose homeostasis.

In general, drinking cultures among different countries and populations is another important factor to be evaluated in future studies.

One other important factor for developing future studies is to distinguish lifetime abstainers than former drinkers while considering non-drinkers as reference group. Former drinkers might have more underlying health problems compared to lifetime abstainers. Therefore, we cannot strongly rely on the results of those previous literatures, which have considered non-drinkers as a combined population of former drinkers and lifetime abstainers, and it might be a good idea if we consider healthy lifetime abstainers as non drinker reference group in developing further research studies.

In addition, for developing future systematic reviews about association of alcohol consumption with glucose homeostasis, it might be better to include grey literatures as well as non-English studies and we would have a more comprehensive study if we search in more databases other than Medline and Embase.

In summary, more longitudinal studies with larger sample size, repeated measures of exposure, including more potentially relevant dimensions of alcohol consumption and applying more robust methods are needed to assess different parameters of glucose homeostasis in association with alcohol consumption and to enable us to reach a solid conclusion.
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Dubowitz, N., Xue, W., Long, Q., Ownby, J., Olson, D., Barb, D., . . . Jackson, S. (2014). Aging is associated with increased HbA1c levels, independently of glucose levels and insulin resistance, and also with decreased HbA1c diagnostic specificity. *Diabetic Medicine, 31*(8), 927-935.


## Appendices

### Appendix A-PRISMA Checklist

**PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol**

<table>
<thead>
<tr>
<th>Section and topic</th>
<th>Item No</th>
<th>Checklist item</th>
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<tbody>
<tr>
<td><strong>ADMINISTRATIVE INFORMATION</strong></td>
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<tr>
<td>Title:</td>
<td>1a</td>
<td>Identify the report as a protocol of a systematic review</td>
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<td>1b</td>
<td>If the protocol is for an update of a previous systematic review, identify as such</td>
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<tr>
<td>Registration</td>
<td>2</td>
<td>If registered, provide the name of the registry (such as PROSPERO) and registration number</td>
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<tr>
<td>Authors:</td>
<td>3a</td>
<td>Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author</td>
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<td>3b</td>
<td>Describe contributions of protocol authors and identify the guarantor of the review</td>
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<tr>
<td>Amendments</td>
<td>4</td>
<td>If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments</td>
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<tr>
<td>Support:</td>
<td>5a</td>
<td>Indicate sources of financial or other support for the review</td>
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<td>Provide name for the review funder and/or sponsor</td>
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<td>5c</td>
<td>Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol</td>
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<tr>
<td><strong>INTRODUCTION</strong></td>
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<td>Rationale</td>
<td>6</td>
<td>Describe the rationale for the review in the context of what is already known</td>
</tr>
<tr>
<td>Objectives</td>
<td>7</td>
<td>Provide an explicit statement of the question(s) the review will address regarding participants, interventions, comparators, and outcomes (PICO)</td>
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<tr>
<td><strong>METHODS</strong></td>
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<tr>
<td>Eligibility criteria</td>
<td>8</td>
<td>Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review</td>
</tr>
<tr>
<td>Information sources</td>
<td>9</td>
<td>Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage</td>
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<tr>
<td>Search strategy</td>
<td>10</td>
<td>Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated</td>
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<td>Study records:</td>
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<tr>
<td>Data management</td>
<td>11a</td>
<td>Describe the mechanism(s) that will be used to manage records and data throughout the review</td>
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<tr>
<td>Selection process</td>
<td>11b</td>
<td>State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)</td>
</tr>
<tr>
<td>Data collection process</td>
<td>11c</td>
<td>Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators</td>
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<tr>
<td>Data items</td>
<td>12</td>
<td>List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications</td>
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<tr>
<td>Outcomes and prioritization</td>
<td>13</td>
<td>List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale</td>
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<tr>
<td>Risk of bias in individual studies</td>
<td>14</td>
<td>Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis</td>
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<td>Data synthesis</td>
<td>15a</td>
<td>Describe criteria under which study data will be quantitatively synthesised</td>
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<td>If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I², Kendall’s τ)</td>
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<td></td>
<td>15c</td>
<td>Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)</td>
</tr>
<tr>
<td></td>
<td>15d</td>
<td>If quantitative synthesis is not appropriate, describe the type of summary planned</td>
</tr>
<tr>
<td>Meta-bias(es)</td>
<td>16</td>
<td>Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)</td>
</tr>
<tr>
<td>Confidence in cumulative evidence</td>
<td>17</td>
<td>Describe how the strength of the body of evidence will be assessed (such as GRADE)</td>
</tr>
</tbody>
</table>

*It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.*

Appendix B-Newcastle-Ottawa Scale (NOS)

NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE
COHORT STUDIES

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability

Selection

1) Representativeness of the exposed cohort
   a) truly representative of the average ______________ (describe) in the community *
   b) somewhat representative of the average ______________ in the community *
   c) selected group of users e.g. nurses, volunteers
   d) no description of the derivation of the cohort

2) Selection of the non-exposed cohort
   a) drawn from the same community as the exposed cohort *
   b) drawn from a different source
   c) no description of the derivation of the non-exposed cohort

3) Ascertainment of exposure
   a) secure record (e.g. surgical records) *
   b) structured interview *
   c) written self-report
   d) no description

4) Demonstration that outcome of interest was not present at start of study
   a) yes *
   b) no

Comparability

1) Comparability of cohorts on the basis of the design or analysis
   a) study controls for ______________ (select the most important factor) *
   b) study controls for any additional factor * (This criteria could be modified to indicate specific control for a second important factor.)

Outcome

1) Assessment of outcome
   a) independent blind assessment *
   b) record linkage *
   c) self-report
   d) no description

2) Was follow-up long enough for outcomes to occur
   a) yes (select an adequate follow up period for outcome of interest) *
   b) no

3) Adequacy of follow up of cohorts
   a) complete follow up - all subjects accounted for *
   b) subjects lost to follow up unlikely to introduce bias - small number lost - > ____ % (select an adequate %) follow up, or description provided of those lost) *
   c) follow up rate < ____% (select an adequate %) and no description of those lost
   d) no statement
Appendix C-PROSPERO

PROSPERO International prospective register of systematic reviews

Review title and timescale

1 Review title

Give the working title of the review. This must be in English. Ideally it should state succinctly the interventions or exposures being reviewed and the associated health or social problem being addressed in the review.

Association of alcohol consumption with glucose homeostasis: A systematic review and meta-analysis

2 Original language title

For reviews in languages other than English, this field should be used to enter the title in the language of the review. This will be displayed together with the English language title.

English

3 Anticipated or actual start date

Give the date when the systematic review commenced, or is expected to commence.

08/12/2015

4 Anticipated completion date

Give the date by which the review is expected to be completed.

01/12/2016

5 Stage of review at time of this submission

Indicate the stage of progress of the review by ticking the relevant boxes. Reviews that have progressed beyond the point of completing data extraction at the time of initial registration are not eligible for inclusion in PROSPERO. This field should be updated when any amendments are made to a published record.

The review has not yet started

Review stage				Started	Completed

Preliminary searches			No	Yes

Piloting of the study selection process		No	Yes

Formal screening of search results against eligibility criteria		No	Yes
Data extraction: No  Yes
Risk of bias (quality) assessment: No  Yes
Data analysis: No  Yes

Provide any other relevant information about the stage of the review here.

Review team details

6 Named contact

The named contact acts as the guarantor for the accuracy of the information presented in the register record.

Soudeh Taghdiri

7 Named contact email

Enter the electronic mail address of the named contact.

soodeh.taghdiri@gmail.com

8 Named contact address

Enter the full postal address for the named contact.

33 Russell Street, Rm 510 Toronto, Ontario, Canada M5S 2S1

9 Named contact phone number

Enter the telephone number for the named contact, including international dialing code.

416 535 8501

10 Organisational affiliation of the review

Full title of the organizational affiliations for this review, and website address if available. This field may be completed as 'None' if the review is not affiliated to any organisation.

Center for Addiction and Mental Health
Website address:

11 Review team members and their organisational affiliations

Give the title, first name and last name of all members of the team working directly on the review. Give the organisational affiliations of each member of the review team.

<table>
<thead>
<tr>
<th>Title</th>
<th>First name</th>
<th>Last name</th>
<th>Affiliation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ms.</td>
<td>Soudeh</td>
<td>Taghdiri</td>
<td>Institute of Medical Science, University of</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Toronto, Toronto, Canada</td>
</tr>
</tbody>
</table>
Dr. Jurgen Rehm  Institute for Mental Health Policy Research, Centre for Addiction and Mental Health (CAMH), Toronto, Canada

Mr. Omer Syed Hasan  Institute for Mental Health Policy Research, Centre for Addiction and Mental Health (CAMH), Toronto, Canada

Dr. Michael Roerecke  Institute for Mental Health Policy Research, Centre for Addiction and Mental Health (CAMH), Toronto, Canada

12 Funding sources/sponsors

Give details of the individuals, organizations, groups or other legal entities who take responsibility for initiating, managing, sponsoring and/or financing the review. Any unique identification numbers assigned to the review by the individuals or bodies listed should be included.

Internal funding for master's thesis

13 Conflicts of interest

List any conditions that could lead to actual or perceived undue influence on judgements concerning the main topic investigated in the review.

Are there any actual or potential conflicts of interest?

None known

14 Collaborators

Give the name, affiliation and role of any individuals or organisations who are working on the review but who are not listed as review team members.

<table>
<thead>
<tr>
<th>Title</th>
<th>First name</th>
<th>Last name</th>
<th>Organisation details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dr.</td>
<td>Gary</td>
<td>Lewis</td>
<td>Department of Medicine and Department of Physiology, University of Toronto</td>
</tr>
<tr>
<td>Dr.</td>
<td>Peter</td>
<td>Selby</td>
<td>Center for Addiction and Mental Health</td>
</tr>
<tr>
<td>Ms.</td>
<td>Sheila</td>
<td>Lacroix</td>
<td>Center for Addiction and Mental Health</td>
</tr>
<tr>
<td>Ms.</td>
<td>Zahra</td>
<td>Akhavian</td>
<td>Center for Addiction and Mental Health</td>
</tr>
</tbody>
</table>

Review methods
State the question(s) to be addressed / review objectives. Please complete a separate box for each question.

Is alcohol consumption compared to non-drinking associated with implicit changes of glucose homeostasis parameters including blood glucose level, serum insulin, insulin sensitivity and HbA1C in patients with no diabetes?

Search strategies were developed and conducted by the research team in consultation with the knowledge users group and experienced librarians. The search strategies were adapted from the P.I.C.O. structure of reviews which stands for Population, Intervention, Comparison and Outcomes. Medline and Embase were searched from their inception up to February 2016. We had no date restrictions. We limited our search to humans and cohort or case-control studies and not (bibliography or case reports or clinical conference or Conference Proceeding or clinical trial, all or comment or congresses or editorial or guideline or in vitro or letter or meta-analysis or "review" or systematic reviews). We have only included English studies.

If you have one, give the link to your search strategy here. Alternatively you can e-mail this to PROSPERO and we will store and link to it.

Give a short description of the disease, condition or healthcare domain being studied. This could include health and wellbeing outcomes.

Glucose homeostasis parameters including blood glucose levels, serum insulin levels, and HbA1C

Give summary criteria for the participants or populations being studied by the review. The preferred format includes details of both inclusion and exclusion criteria.

Adult human samples who were non-diabetic at baseline

Give full and clear descriptions of the nature of the interventions or the exposures to be reviewed

Alcohol consumption was considered as the exposure of our study.

Where relevant, give details of the alternatives against which the main subject/topic of the review will be compared (e.g. another intervention or a non-exposed control group).

Non-drinkers were considered as the comparator of our present study.
Types of study to be included

Give details of the study designs to be included in the review. If there are no restrictions on the types of study design eligible for inclusion, this should be stated.

Cohort and case-controls

Context

Give summary details of the setting and other relevant characteristics which help define the inclusion or exclusion criteria.

Articles that have assessed the association of alcohol drinking with any parameters of glucose homeostasis (blood glucose level, serum insulin level, insulin sensitivity or HbA1C) in patients who were free of diabetes at baseline were included.

We excluded articles, which have assessed the association of alcohol drinking with glucose homeostasis parameters exclusively in diabetic patients at baseline. Articles, which had combined glucose homeostasis parameters with a diagnosis of diabetes in one outcome, were excluded as well.

Primary outcome(s)

Give the most important outcomes.

Impaired fasting glucose, HbA1C, and serum insulin

Secondary outcomes

List any additional outcomes that will be addressed. If there are no secondary outcomes enter None.

Not applicable

Data extraction (selection and coding)

Give the procedure for selecting studies for the review and extracting data, including the number of researchers involved and how discrepancies will be resolved. List the data to be extracted.

From all included studies, we extracted authors' names, year of publication, country, years of follow up, age, sex, setting, number of cases and total participants, assessment of alcohol drinking, assessment of glucose homeostasis parameter, adjustments for potential confounders, relative risk (RR) and its standard error (SE) were reported.
Risk of bias (quality) assessment

State whether and how risk of bias will be assessed, how the quality of individual studies will be assessed, and whether and how this will influence the planned synthesis.

We have used Newcastle Ottawa Assessment Scale to critically appraise our studies. Two independent reviewers have assessed the risk of bias in included studies by considering the following characteristic:

- **Selection:**
  1. Representatives of the exposed cohort,
  2. Selection of the non-exposed cohort,
  3. Ascertainment of exposure
  4. Demonstration that outcome of interest was not present at start of study

- **Comparability:**
  Comparability of cohorts based on the design or analysis

- **Outcome:**
  1. Assessment of outcome
  2. Was follow-up long enough for outcomes to occur?
  3. Adequacy of follow up of cohorts

Disagreements between the review authors over the risk of bias, in some studies was resolved by discussion, with involvement of a third review author where necessary.

Strategy for data synthesis

Give the planned general approach to be used, for example whether the data to be used will be aggregate or at the level of individual participants, and whether a quantitative or narrative (descriptive) synthesis is planned. Where appropriate a brief outline of analytic approach should be given.

For the studies with the outcome of incidence of fasting glucose ≥ 100 mg/dL, we conducted meta-analyses. We used the most adjusted RR reported and the most comprehensive data available for each analysis, and gave priority to estimates where adjusted data and lifetime abstainers as the risk reference group were used. If necessary, RRs within studies were re-calculated based on the method described by Hamling and colleagues. Reports of stratified analyses by sex were treated as independent samples. We conducted categorical meta-analyses based on total alcohol consumption and linear generalized least squares meta-regression treating alcohol categories as a continuous variable. For those studies not combined with meta-analysis, we used GRADE method to synthesize results qualitatively.

Analysis of subgroups or subsets

Give any planned exploration of subgroups or subsets within the review. 'None planned' is a valid response if no subgroup analyses are planned.

We conducted linear generalized least squares meta-regression analyses stratified by sex treating alcohol categories as a continuous variable.

Review general information

Type and method of review

Select the type of review and the review method from the drop down list.
**Systematic review**

**Language**

Select the language(s) in which the review is being written and will be made available, from the drop down list. Use the control key to select more than one language.

**English**

Will a summary/abstract be made available in English?

Yes

**Country**

Select the country in which the review is being carried out from the drop down list. For multi-national collaborations select all the countries involved. Use the control key to select more than one country.

Canada

**Other registration details**

Give the name of any organisation where the systematic review title or protocol is registered together with any unique identification number assigned. If extracted data will be stored and made available through a repository such as the Systematic Review Data Repository (SRDR), details and a link should be included here.

Not applicable

**Reference and/or URL for published protocol**

Give the citation for the published protocol, if there is one.

Give the link to the published protocol, if there is one. This may be to an external site or to a protocol deposited with CRD in pdf format.

Not applicable

**Dissemination plans**

Give brief details of plans for communicating essential messages from the review to the appropriate audiences.

Our systematic review and meta-analysis will be submitted for publication in a peer-reviewed, open-access journal.

Do you intend to publish the review on completion?

Yes
36 Keywords
Give words or phrases that best describe the review. (One word per box, create a new box for each term)
Alcohol, glucose homeostasis, fasting glucose, insulin, HbA1C, meta-analysis, systematic review

37 Details of any existing review of the same topic by the same authors
Give details of earlier versions of the systematic review if an update of an existing review is being registered, including full bibliographic reference if possible.
Not applicable

38 Current review status
Review status should be updated when the review is completed and when it is published.
Completed but not published

39 Any additional information
Provide any further information the review team consider relevant to the registration of the review.
Not applicable

40 Details of final report/publication(s)
This field should be left empty until details of the completed review are available.
Give the full citation for the final report or publication of the systematic review.
Give the URL where available.
Not applicable