Introduction
Hyperglycemia and diabetes mellitus
A high blood glucose level, as referred to by hyperglycemia, is the main characteristic of diabetes mellitus. There are two main types of diabetes mellitus, type 1 and type 2. Type 1 diabetes is characterized by destruction of insulin-producing pancreatic beta-cells (1). As a result, insulin secretion is minimized or even absent, leading to hyperglycemia.

Hyperglycemia in type 2 diabetes is due to an insufficient insulin secretion, which coincides with a decreased insulin sensitivity (2). The insulin secreting beta-cells try to compensate for the decrease in insulin sensitivity by upwards regulating insulin secretion. When insulin secretion becomes relatively inappropriate, hyperglycemia will occur (2;3). In this thesis, only type 2 diabetes will be discussed.

Markers of hyperglycemia
There are three main markers of hyperglycemia: fasting plasma glucose, postload plasma glucose (glucose levels 2 hours after the ingestion of 75-grams of glucose, referred to as the oral glucose tolerance test (OGTT)) and glycated hemoglobin (HbA1c). Fasting and postload glucose form the basis for the diagnosis of glucose metabolism disorders (4). Normal glucose metabolism is defined by a fasting plasma glucose < 6.1 mmol/l and a postload plasma glucose < 7.8 mmol/l. Type 2 diabetes is diagnosed when fasting plasma glucose concentrations are ≥ 7.0 mmol/l or postload plasma levels are ≥ 11.1 mmol/l. In between normal glucose metabolism and type 2 diabetes, intermediate hyperglycemia can be diagnosed. Intermediate hyperglycemia is defined by fasting plasma glucose levels between 6.1 and 7.0 mmol/l and/or postload plasma glucose levels between 7.8 and 11.1 mmol/l. Individuals diagnosed with intermediate hyperglycemia are at high risk of developing type 2 diabetes in the upcoming years (5).

HbA1c is another marker of hyperglycemia and is the result of the binding of glucose to hemoglobin, which is present in human erythrocytes. During the lifecycles of the erythrocytes, the bonding of glucose to hemoglobin accumulates. HbA1c is therefore thought to reflect the average glucose levels.
over the past 2-3 months. In daily practice, HbA1c is used to monitor glycemia in type 2 diabetes patients, with a level of ≤ 7.0 % as the target for optimal disease management (6). Recently, an expert committee recommended to use an HbA1c level of ≥ 6.5% for the diagnosis of type 2 diabetes (7), an advice which was adopted in the official diabetes guidelines of the American Diabetes Association in 2010 (8).

Burden of disease

The International Diabetes Federation estimated that in 2000 approximately 151 million people worldwide had type 2 diabetes, and they expect this number to have increased to 438 million in 2025, representing 6.6% of adult population in the entire world (9). In the Netherlands, an increase in the prevalence of type 2 diabetes is also expected. Recently, the National Institute for Public Health and the Environment of the Netherlands estimated that in 2025 about 1 million people in the Netherlands will suffer from type 2 diabetes, compared to 600,000 in the year 2003 (10). An increase in the prevalence of type 2 diabetes is expected to be a result of several worldwide trends: aging of the population, (11;12), increased life-expectancy of patients with type 2 diabetes (13), earlier detection of type 2 diabetes (14) and increases in the prevalence of the main risk factors for type 2 diabetes, i.e. adiposity and lack of physical activity (11).

To accurately investigate whether the above mentioned trends have indeed resulted in an increase in the prevalence of type 2 diabetes and intermediate hyperglycemia, population-based studies using random samples of the population and an oral glucose tolerance test (OGTT) for the diagnosis of type 2 diabetes and intermediate hyperglycemia are needed. However, such studies in recent years are lacking worldwide. In Chapter 2 of this thesis, we describe changes in the prevalence of OGTT-diagnosed type 2 diabetes and intermediate hyperglycemia in two random samples of the population of the Netherlands in 1989 and 2006, and investigated whether these changes coincided with changes in risk factors for glucose metabolism disorders.
Risk factors of type 2 diabetes

Adiposity

In the past decades, many risk factors for type 2 diabetes have been identified, such as high age, family history of diabetes and obesity. One of the major risk factors for the development of type 2 diabetes is overweight, defined by a high body mass index (BMI), and especially abdominal overweight, defined by a large waist circumference. Several studies have observed increased risks of developing type 2 diabetes on a population level in people with a high BMI and/or large waist circumference as compared to those with a normal BMI and waist circumference (15;16). These population risks are important to gain insight into the importance of a risk factor in the etiology of a disease. However, for public health and daily care, differences in absolute risk are of importance, including questions like: what are the chances of not developing type 2 diabetes on an individual level when a person is overweight (how can I prevent getting type 2 diabetes)? Which person with overweight will develop type 2 diabetes? Which other risk factors have to be considered for this prediction? In Chapter 3 of this thesis, the role of adiposity in assessing the individual risk of developing type 2 diabetes is described. Moreover, we describe whether combining several risk factors for type 2 diabetes in a risk score like the FINDRISK (15), improves the prediction of incident type 2 diabetes on a population level.

Family history of diabetes

People with a family history of diabetes have a high risk of developing type 2 diabetes themselves (17). The underlying cause of this association is generally thought to be genetic. However, the clustering of body fatness in families, which can be due to both shared genetic and shared environmental influences, may also contribute to the relationship between family history and the development of type 2 diabetes. In cross-sectional studies, greater adiposity was observed in persons with a family history of diabetes than
in those without a family history (18;19). Prospective studies are needed to unravel the role of adiposity in the association between a family history of diabetes and the development of type 2 diabetes. Chapter 4 of this thesis describes the contribution of adiposity to the association between a family history of diabetes and incident type 2 diabetes in a large prospective cohort study.

Genetic risk factors

With the rise of publications of genomewide association (GWA) studies, in which tremendous numbers of single-nucleotide polymorphisms (SNPs) in large population samples are tested in relation to diseases, more and more insight has been gained in genetic factors in relation to the risk of type 2 diabetes. For example, specific genomic locations (loci’s) have been found to be associated with levels of fasting plasma glucose and incident type 2 diabetes (20). However, identified risk alleles only slightly improve the prediction of type 2 diabetes as compared to traditional risk factors (21). Therefore, more research is needed to investigate the role of identified loci’s in the pathophysiology of type 2 diabetes and the combination of loci’s on disease-risk. In Chapter 5 of this thesis, we describe the cross-sectional association between 4 identified genetic loci, GCK, GCKR, G6PC2 and MTNR1B, and fasting plasma glucose levels. Furthermore, the same 4 loci’s are tested in relation to the risk of type 2 diabetes.

The role of HbA1c in the diagnosis of type 2 diabetes

Recently, the role of HbA1c in the diagnosis of type 2 diabetes was recommended (7) and introduced in the guidelines of the American Type 2 diabetes Association (8). This recommendation was based on the strong association between HbA1c and retinopathy risk found in previous studies. In addition, HbA1c was recently found to be highly correlated to mean glucose levels in a sample of mainly type 2 diabetes patient (22). It may however be questioned whether HbA1c reflects glycemia in people with normal or slightly
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elevated glucose levels and whether it can therefore be used to identify people with undiagnosed type 2 diabetes. Previous studies have found that HbA1c might be determined by other factors not related to glycemia, for example age, genetic factors and erythrocyte life-span (23-25). In addition, although trajectories of fasting glucose and postload glucose before the diagnosis of type 2 diabetes have been studied, indicating a rapid increase in glucose 2-3 years before the diagnosis of type 2 diabetes (26), the developmental pattern of HbA1c before onset of type 2 diabetes is unknown. Therefore, more research into the association between glucose and HbA1c in people without type 2 diabetes and the diagnostic value of HbA1c compared to glucose is needed to further investigate the use of HbA1c in the diagnosis of type 2 diabetes. In Chapter 6 of this thesis, the correlation between fasting plasma glucose, postload plasma glucose and HbA1c is determined and the diagnostic value of HbA1c compared to glucose in a non-diabetic population is described. In Chapter 7, we prospectively investigated 10-year changes in fasting plasma glucose, postload plasma glucose and HbA1c before the diagnosis of type 2 diabetes.

Consequences of hyperglycemia

Hyperglycemia results in serious micro- and macrovascular complications, such as retinopathy, nephropathy, neuropathy and cardiovascular disease (CVD). Compared to the general non-diabetic population, patients with type 2 diabetes have a 2 to 4 fold higher risk of death from CVD (27) and high levels of HbA1c and postload glucose have been found to be associated with a higher risk of CVD death in patients with type 2 diabetes (28-30). In people without type 2 diabetes, high levels of glucose and/or HbA1c are also related to future cardiovascular mortality (31;32). It is however largely unknown whether there is a relation between markers of hyperglycemia and non-fatal CVD in the general population. Moreover, it is unknown which marker of hyperglycemia is the best predictor of CVD in the general population without type 2 diabetes. Chapter 8 of this thesis describes fasting plasma glucose,
postload plasma glucose and HbA1c in relation to 10-year risk of fatal and non-fatal CVD in a population without type 2 diabetes at baseline.

Study populations
Three study populations were used in this thesis:

1) The Hoorn Study is a population-based cohort study among 2484 participants 50-75 years of age who lived in the town of Hoorn, The Netherlands (33). The baseline measurements, consisting of an oral glucose tolerance test (OGTT), blood collections, questionnaires and anthropometry measurements, were performed in 1989. Follow-up examinations were performed in 1996 (all surviving participants) and 2000 (all participants with type 2 diabetes or intermediate hyperglycemia in 1996 and a sample of those with normal glucose metabolism in 1996). Morbidity and mortality of all participants is registered continuously.

2) The New Hoorn Study is a cross-sectional population study performed in 2006 among 2807 randomly selected inhabitants of the town of Hoorn, The Netherlands, between 40 and 65 years of age (34). They visited the Diabetes Research Center in Hoorn, where an OGTT was performed, blood was collected and anthropometry measurements were performed. Questionnaires were used to collect information on demographic variables and issues related to the risk of type 2 diabetes (for example smoking habits and physical activity behaviour).

3) The Nurses’ Health Study. The Nurses’ Health Study is a prospective cohort study in the United States of America which was started in 1976 when 121,700 married female registered nurses aged 30-55 years received a questionnaire on health status and potential risk factors for major chronic diseases. Ever since, participants were sent questionnaires biennially. Over time, the data collection was extended with the collection of blood, urine and cheek cells in subsamples of the population.
**Scope of this thesis**

In this thesis, we aimed at expanding the knowledge on causes and consequences of hyperglycemia. In Figure 1, a schematic outline of this thesis is presented. We examined the prevalence of type 2 diabetes and intermediate hyperglycemia (Chapter 1) and assessed the role of adiposity (Chapter 3), family history of diabetes (Chapter 4) and 4 genetic loci’s (Chapter 5) as determinants of type 2 diabetes. Moreover, we focused on the three markers of hyperglycemia and investigated their role in the diagnosis of type 2 diabetes (Chapter 6), their trajectories before the onset of type 2 diabetes (Chapter 7) and their association with cardiovascular disease (Chapter 8). Last, the General Discussion describes methodological aspects of the studies in this thesis, (pathophysiological) mechanisms behind the results, clinical implications and suggestions for future research (Chapter 9).

**Figure 1.**

*Schematic outline of the thesis*
REFERENCE LIST


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Introduction


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Chapter 1

