Epidemiology of Diabetes

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60.1 Introduction

Diabetes is a heterogeneous group of metabolic diseases which share a common characteristic: hyperglycemia. Hyperglycemia develops as a result of various defects in insulin secretion by pancreatic beta-cells or from changes in insulin action. Either defect jeopardizes the delicate interplay between insulin secretion and insulin action which is essential for the maintenance of normoglycemia. Normal pancreatic beta-cells can adapt to changes in insulin action. For example, under regular circumstances, a decrease in insulin sensitivity in target organs such as muscle is compensated by upregulation of insulin secretion and, alternatively, a decrease in secretory function of beta-cells can be counterbalanced by increases in insulin sensitivity. This hyperbolic relationship between insulin secretion and insulin action is deteriorated in patients with diabetes, resulting in chronically higher than normal levels of glycemia (Stumvoll et al. 2005). Type 2 diabetes, the most common form of diabetes, is characterized by a relative loss of beta-cell function which leads to insufficient compensation for increased insulin resistance. Type 1 diabetes is characterized by an absolute deficiency of insulin secretion resulting from autoimmune destruction of pancreatic beta-cells. Due to the different pathophysiology and causative factors involved, a detailed description of the epidemiology of type 1 diabetes is beyond this chapter. Interested readers should refer to previous reviews (Ekoé et al. 2008; Maahs et al. 2010).

Knowledge about the possible causes of type 2 diabetes has greatly advanced over the past few decades largely due to findings from experimental and observational prospective studies in diabetes epidemiology. Unhealthy diet and lifestyle are the most important modifiable factors for type 2 diabetes, and observational studies and randomized clinical trials have demonstrated that diabetes is largely preventable through lifestyle interventions. Accordingly, several countries have responded by implementing national diabetes programs (Colagiuri et al. 2010) and developing guidelines for diabetes prevention (Paulweber et al. 2010). However, despite our improved understanding of the determinants for type 2 diabetes, obesity and physical inactivity have continued to grow in most parts of the world. Particularly in developing countries that are experiencing an economic transition, the current diabetes trend is exceedingly alarming and deserves immediate attention.

The following section describes criteria for diagnosing diabetes and the rationale behind diagnostic cut-offs; the third section discusses current estimates of prevalence and incidence; the fourth section lays out common methodological approaches in diabetes epidemiology; the fifth section presents evidence for different lifestyle risk factors; biochemical and genetic biomarkers as risk factors for type 2 diabetes are discussed in Sects. 60.6 and 60.7, respectively; Sect. 60.8 summarizes evidence from observational and experimental studies on the preventability of type 2 diabetes; Sect. 60.9 discusses approaches for screening to detect undiagnosed cases and high-risk individuals; and the final section draws some conclusions from the chapter.

60.2 Diagnostic Criteria of Diabetes

Classic symptoms of diabetes are polyuria, dehydration, and increased thirst due to glycosuria. Glycosuria occurs if the glucose concentration in the blood is raised beyond the renal threshold, which may vary substantially between individuals (Butterfield et al. 1967). The diagnostic criteria applied today with regard to fasting plasma glucose concentrations are considerably lower than the renal threshold (about 162–180 mg/dL/[9–10 mmol/L]) for most patients (Table 60.1).

All diagnostic criteria for diabetes are dependent on a threshold value that is not clearly linked to symptoms but instead are based on a continuous distribution of blood glucose values. Justification of the diagnostic thresholds has been a long-standing matter of debate. The original approach defined abnormal glucose values as those greater than the mean + 2 SD in a given population. This approach has not been found to correlate well with symptoms (Siperstein 1975). An alternative statistical approach, to be used if the distributions of glucose values follow a bimodal distribution with clear separation of diabetes patients and diabetes-free individuals, is the use of the anti-mode (McCance et al. 1994). This approach, however, is dependent upon population characteristics and is, therefore, unlikely to yield generalizable thresholds (Barr et al. 2002). The clinical approach widely used today is based on the assumption that there exists a threshold above which diabetic complications occur at an increased rate. Chronic exposure to hyperglycemia as a result of diabetes is associated with long-term damage, dysfunction, and failure of different organs, particularly the eyes, kidneys, nerves, heart, and blood vessels. However, diagnosing diabetes based on the relation of glucose values to diabetes complications remains problematic. Although patients with diabetes are at a two- to

Table 60.1 Diagnostic criteria of diabetes and prediabetes from the American Diabetes Association and the world Health Organization

	American Diabetes Association (2011)		World Health Organization/ International Diabetes Federation (2006, 2011)	
	Diabetes	Prediabetes	Diabetes	Prediabetes
Fasting plasma glucose	≥126 mg/dL (7.0 mmol/L)	100–125 mg/dL (5.6–6.9 mmol/L)	≥126 mg/dL (7.0 mmol/L)	110–125 mg/dL (6.1–6.9 mmol/L)
2h plasma glucose after ingestion of a 75-g glucose load	≥200 mg/dL (11.1 mmol/L)	140–199 mg/dL (7.8–11.0 mmol/L)	≥200 mg/dL (11.1 mmol/L)	140–199 mg/dL (7.8–11.0 mmol/L)
Hemoglobin A1c	≥6.5%	5.7–6.4%	≥6.5%	–

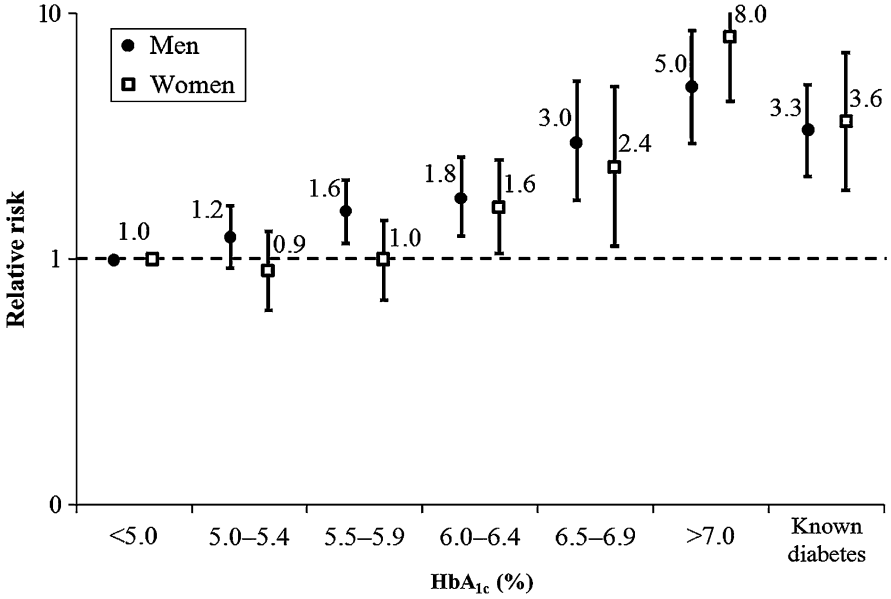

Fig. 60.1 Age-adjusted relative risk of cardiovascular disease events by categories of HbA_{1c} concentrations and known diabetes, EPIC-Norfolk Study (Khaw et al. 2004)

four-fold increased risk of coronary heart disease (Haffner and Cassells 2003; Hu 2002), there appears to be a relationship between glycemia and cardiovascular risk that extends well into the area that is clinically considered non-diabetic (Levitan et al. 2004; Sarwar et al. 2010). This association appears to be more evident when using hemoglobin A_{1c} (HbA_{1c}) compared to 2h plasma glucose (2hPG) during an oral glucose tolerance test or fasting plasma glucose (FPG) values (Sarwar et al. 2010). In the EPIC-Norfolk Study (Khaw et al. 2004), the largest prospective study which evaluated HbA_{1c}, there was a stepwise increase in risk for CVD with higher HbA_{1c} values over a follow-up period of 8 years. A 60–80% increase in risk was shown for HbA_{1c} values between 6.0% and 6.4% compared to participants with HbA_{1c} <5% (Fig. 60.1). Thus, the relationship between glycemia and cardiovascular risk does not provide evidence to substantiate a diagnostic threshold for diabetes.

In contrast to macrovascular complications, the associations between different measures of glycemia and the prevalence of microvascular complications are markedly non-linear (Barr et al. 2002). Still, defining optimal diagnostic thresholds from the shape of the associations has been challenging. For example, recent data from the DETECT-2 study (Fig. 60.2), a consortium of several studies with ~45,000 participants, suggest that the risk of diabetes-specific retinopathy increases around an HbA_{1c} of 6.5% and a 2hPG in the range of 10.1–11.2 mmol/L. These findings support current diagnostic thresholds (Colagiuri et al. 2011). However, the optimal

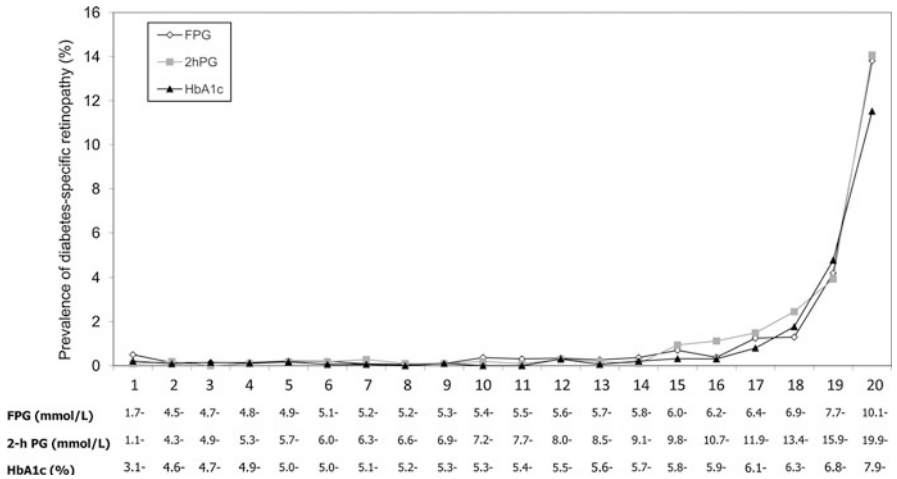

Fig. 60.2 Prevalence of diabetes-specific retinopathy (moderate or more severe retinopathy) by vigintiles of the distribution of FPG, 2hPG, and HbA_{1c} (Colagiuri et al. 2011)

cut-off for FPG in the DETECT-2 study was found to be around 6.5 mmol/dL (117 mg/dL), which is considerably lower than the current diagnostic cut-off of 7.0 mmol/dL (126 mg/dL).

60.3 Prevalence and Incidence of Diabetes Across the World

According to estimations of the International Diabetes Federation, the global prevalence of diabetes in 2010 was 6.4% for adults between 20 and 79 years of age (International Diabetes Federation 2009). In absolute terms, approximately 285 million people in this age range are estimated to have diabetes. There are substantial regional differences in diabetes prevalence. The highest age-adjusted prevalence has been observed in the North American and Caribbean region (10.2%) and the Middle East and North African region (9.3%) (Table 60.2). Global projections predict that the total number of affected individuals will continue to increase over the coming years. The International Diabetes Federation estimates that by the year 2030, 438 million people will have diabetes, accounting for 7.7% of the total population in this age range. These projections probably underestimate the impact of the diabetes epidemic as they are only based on the expected population growth and age-specific demographic changes as determinants of disease prevalence, without taking changes in the prevalence of behavioral and lifestyle risk factors into account. Large differences in diabetes prevalence exist when people from rural and urban geographical areas (with the same or similar ethnicity) are compared. This indicates that the ongoing transition in behavioral, environmental, economic, and social risk factors (urbanization, unhealthy diets, physical inactivity, obesity) will most likely

Table 60.2 Worldwide prevalence of diabetes in 2010 and 2030 among adults (20–79 years) (International Diabetes Federation 2009)

	2010		2030	
Region	Population (millions)	Diabetes prevalence[a] (%)	Population (millions)	Diabetes prevalence[a] (%)
Africa	379	3.8	653	4.7
Europe	646	6.9	659	8.1
Middle East and North Africa	344	9.3	533	10.8
North America and Caribbean	320	10.2	390	12.1
South and Central America	287	6.6	382	7.8
Southeast Asia	838	7.6	1,200	9.1
Western Pacific	1,531	4.7	1,772	5.7
Total	4,345	6.4	5,589	7.7

[a]Prevalence adjusted to world population in 2010 and 2030

result in accelerated growth in diabetes prevalence in many parts of the world, particularly in developing countries.

Representative data on type 2 diabetes incidence rates are lacking from most parts of the world. Many prospective cohort studies collect diabetes incidence data; however, participants are usually selected based on specific geographical regions, age ranges, or individual characteristics. Thus, prospective cohort studies are frequently conducted in populations that are not nationally representative. Countries with nationally representative studies generally draw from cross-sectional survey data, medical records, registries, or health administration data to reflect the current incidence of diagnosed diabetes. For example, estimates of diabetes incidence in the US are based on the representative National Health Interview Survey. The survey data are continuously available; however, the survey does not distinguish whether increases in diabetes incidence rates are due to an actual increase in the number of cases or to improved case ascertainment or a combination of these factors. Based on this survey, the incidence of diagnosed diabetes has increased in the USA from 4.9 to 6.9 per 1,000 adults (18–79 years) between 1997 and 2003 (Geiss et al. 2006). These data, in combination with trend data on the ratio of diagnosed and undiagnosed diabetes (Gregg et al. 2004), provide strong evidence that diabetes incidence has substantially increased during recent years in the USA, likely due to increased obesity and changes in behavioral risk factor prevalence.

There are several methodological difficulties in the assessment of diabetes prevalence and incidence which hinder the comparability of country- or region-specific estimates (Table 60.3). For example, the data sources used by the International Diabetes Federation in determining the country-specific prevalence rates draw from considerably heterogeneous study populations and diabetes assessment techniques (International Diabetes Federation 2009). While representative studies are likely to produce reliable prevalence estimates, such studies are not available for many

Table 60.3 Methodological problems in estimation of diabetes prevalence and incidence (Schulze et al. 2010a)

Problem	Comment
Unknown diabetes	• Clinical diagnosis is made frequently by chance • Considerable proportion of cases are likely unknown • Proportion of unknown cases depends on the availability and acceptability of population-wide screening
Diagnostic parameters	• Guidelines offer a variety of alternative parameters with changes over time (e.g., recent inclusion of HbA_{1c}) • Different parameters do not identify similar case groups • Prevalence of known diabetes in a population depends on the parameters commonly used in clinical practice
Diagnostic thresholds	• Changes in diagnostic thresholds affect prevalence estimates (e.g., increasing prevalence after lowering the threshold for FPG from 140 to 126 mg/dL)
Reliability of measures	• Clinical diagnosis requires confirmatory measurement • Reproducibility of elevated glycemia levels: ~50% • Reproducibility is different for different parameters (e.g., higher for FPG than for 2hPG) and depending on time

countries. Frequently, data from selected study populations are not generalizable to the national level. For countries where representative studies have been conducted, a difference in time intervals or diagnostic parameters makes cross-country comparisons challenging.

Universal glucose screening has not been common practice in most countries, and insurance coverage of screening programs is frequently low. Thus, individuals meeting diagnostic criteria may remain undetected in the general population at any point in time. For example, in a representative study in a region of southern Germany, the prevalence of undetected diabetes has been estimated to be as high as the prevalence of diagnosed diabetes (Meisinger et al. 2010; Rathmann et al. 2003). In the USA, undiagnosed diabetes cases account for about 1/5 of all diabetes cases in NHANES 2003–2006 (overall prevalence among adults ≥20 years of age is 9.6%) (Cowie et al. 2010). To estimate the total population level of prevalence and incidence, representative studies would need to identify all individuals previously diagnosed with diabetes as well as those currently meeting the diagnostic criteria. Data from the US-based NHANES 2005–2006 indicate that there is limited overlap across the three diagnostic parameters FPG, 2hPG, and HbA_{1c} (Cowie et al. 2010). Of the three diagnostics, 2hPG results in the highest prevalence of undiagnosed diabetes (4.9%), followed by FPG (2.5%) and HbA_{1c} (1.6%).

The actual proportion of undiagnosed diabetes in a population is a function of the true total prevalence and the extent to which diabetes cases are identified within the health care system through screening programs. In most cases, survey estimates for the prevalence of undiagnosed diabetes rely on a single diagnostic measurement. Studies have suggested that about half of the cases detected through screening utilizing 2hPG as the diagnostic criterion will be confirmed

in a second measurement (Brohall et al. 2006; Eschwege et al. 2001). The results from the 2hPG diagnostic are less reproducible than the results from FPG or HbA_{1c} screening. Thus, diabetes prevalence is overestimated when glucose parameters are measured only once. To increase accuracy, repeated measurements that confirm screen-detected cases are necessary. Logistically, this clearly presents a challenge.

60.4 Approaches in Analytical Diabetes Epidemiology

While descriptive diabetes epidemiology describes the distribution, prevalence, and incidence of diabetes in populations, analytical epidemiology investigates the determinants of diabetes development. Observational prospective cohort studies have been widely used in diabetes epidemiology to investigate the determinants of disease (for a detailed description of cohort studies see chapter ▸Cohort Studies of this handbook). In addition, several randomized controlled trials have been conducted to evaluate the efficacy of lifestyle interventions and drug treatments in the prevention of diabetes. Prospective cohort studies are less prone to reverse causation and information bias (e.g., recall bias) than case-control or cross-sectional studies. Therefore, prospective cohort studies are considered the strongest study design among observational studies. Nested case-control studies and case-cohort studies (see chapter ▸Modern Epidemiological Study Designs of this handbook) can benefit from the efficient use of existing biological samples collected through prospective cohort studies. Although randomized clinical trials can provide the strongest evidence for causal inference, such trials are often infeasible for individual dietary and lifestyle factors due to high cost and lack of long-term compliance.

Lifestyle factors play an important role in the etiology of type 2 diabetes (see Sect. 60.5). Thus, methodological developments in assessment tools are essential to diabetes epidemiology. Optimal methods for collecting data on diet and physical activity have been a longstanding source of debate (see chapters ▸Nutritional Epidemiology and ▸Physical Activity Epidemiology of this handbook). Semiquantitative food frequency questionnaires are the most commonly used method to assess diet in nutritional epidemiological studies, but the validity of this method varies across different populations. To account for the correlations between intakes of energy and nutrients, adjustment of dietary data requires sophisticated statistical modeling (see chapter ▸Nutritional Epidemiology of this handbook). In addition, anthropometric measures such as weight, height, and waist and hip circumferences have been commonly used to assess body fat and fat distribution in epidemiological studies. These measures tend to have a high degree of intercorrelations, and simultaneous modeling of these variables is subject to various interpretations (see Sect. 60.5.1). Complex modeling of risk factors typically employs logistic (see chapter ▸Regression Methods for Epidemiological Analysis of this handbook) or Cox (see chapter ▸Survival Analysis of this handbook) regression models.

60.5 Major Lifestyle Risk Factors

60.5.1 Overweight and Obesity

Excessive body fat is the single largest risk factor for type 2 diabetes. For a detailed review on potential mechanisms by which obesity leads to insulin resistance and type 2 diabetes, the reader should refer to Kahn et al. (2006). The diabetes risk associated with excessive body fat, measured by the body mass index (BMI, the ratio of body weight in kg to squared height in meter) or anthropometric indicators such as waist circumference or skinfold thickness, increases in a continuous fashion. Clinical risk categories for BMI (normal weight 18.5–24.9 kg/m^2, overweight 25–29 kg/m^2, and obesity $\geq$30 kg/m^2) are associated with a stepwise increase in diabetes risk. However, studies have clearly shown that diabetes risk increases already within the normal body weight range (Hu et al. 2001a). Existing evidence from randomized controlled trials has convincingly demonstrated the benefits of weight reduction on diabetes incidence, but these studies were limited to high-risk individuals who were overweight (Knowler et al. 2002; Ramachandran et al. 2006; Tuomilehto et al. 2001).

Whether anthropometric measures that reflect body fat distribution are superior to measures of total or percent body fat has been a matter of debate. A meta-analysis of prospective observational studies suggests that the relative risk associated with higher waist circumference is slightly stronger than that associated with higher BMI (Vazquez et al. 2007). These findings suggest that waist circumference is a valid alternative to BMI when assessing type 2 diabetes risk in a clinical setting or at the population level, although the combination of BMI and waist circumference can be more predictive of diabetes risk. Waist-height ratio has also been investigated in a number of studies, although the added value beyond waist circumference alone remains unclear (Browning et al. 2010; Schulze et al. 2006; Taylor et al. 2010). Determining whether abdominal adiposity predicts type 2 diabetes independently of general adiposity has become a research priority. Numerous studies have used multivariable modeling to examine the role of body fat indices, but the colinearity of anthropometric measures is analytically challenging, and the interpretation of mutually adjusted body fat measurements is not straightforward (Table 60.4).

While BMI is the most frequently used clinical and epidemiological measure of body fat and is generally thought to be uncorrelated with height, studies indicate that BMI is slightly correlated with height in many populations, particularly among women (Diverse Populations Collaborative Group 2005). Height and diabetes risk have an inverse relationship (Schulze et al. 2006; Weitzman et al. 2010). Similarly, waist and hip circumferences are correlated with height (Heymsfield et al. 2011). These correlations have implications not only for defining clinical cut-offs for waist and hip circumferences but also for estimating the strength of the association between body fat measures and diabetes risk. Waist-hip circumference measures reflect fat accumulation in the abdominal region more accurately than BMI, but these measures are still imprecise as they are not specific enough to assess the

Table 60.4 Conceptual meanings of statistical models using various anthropometric variables to predict type 2 diabetes risk (Hu 2008)

Models	Interpretations
1. $Y =$ height + weight	Coefficient for weight can be interpreted as the association between overall body fatness and disease risk; the interpretation of height is unclear as, to some degree, it becomes a surrogate for lean body mass
2. $Y =$ height + BMI	BMI and height are uncorrelated. BMI is a measure of overall adiposity, while height can be interpreted as a surrogate of childhood and adolescent nutritional status
3. $Y =$ height + weight adjusted for height	The correlation between height and weight adjusted for height (residuals) from a regression model is zero. Weight adjusted for height is a marker of overall adiposity, while height is a surrogate of childhood and adolescent nutritional status
4. $Y =$ BMI + WC (or WHR)	BMI and WC (or WHR) are highly correlated. While WC is a measure of central obesity, the interpretation of BMI (holding WC constant) is complicated, as it largely reflects the effects of muscularity rather than body fatness, especially in the elderly
5. $Y =$ BMI + WC adjusted for BMI	BMI and WC adjusted for BMI (residuals) in a regression model is zero. WC residuals represent the effects of central obesity adjusted for overall adiposity, while BMI represents the effect of overall adiposity
6. $Y =$ WC + hip circumference	Waist and hip circumferences are moderately correlated. While WC is a measure of central obesity or abdominal fat, hip circumference (holding WC constant) largely represents the effects of gluteal muscularity and bone structure
7. $Y =$ baseline weight + current weight	After adjusting for baseline weight, current weight largely reflects the effects of change in body weight on disease risk
8. $Y =$ change in weight + change in WC	change in WC represents the effects of changes in body fat distribution on disease risk, while change in weight (holding change in WC constant) largely reflects changes in lean body mass (e.g., in the elderly, weight loss is largely due to muscle loss)

Y disease outcome (e.g., type 2 diabetes), *BMI* body mass index, *WC* waist circumference, *WHR* waist-to-hip circumference ratio

amount of visceral and subcutaneous fat. Studies have shown that visceral adipose tissue is metabolically more active than subcutaneous adipose tissue (Jain et al. 2009).

60.5.2 Physical Activity

The notion that physical activity is a central element in diabetes prevention is supported by evidence from multiple major lifestyle intervention trials (Knowler et al. 2002; Ramachandran et al. 2006; Tuomilehto et al. 2001), although it is difficult to disentangle the independent roles of physical activity and dietary interventions in these trials. In the Da Qing Study, a group-randomized trial of high-risk individuals with impaired glucose tolerance conducted in China, physical

activity intervention alone had a significant, beneficial impact on diabetes incidence in comparison with the standard intervention (Pan et al. 1997).

A large body of observational studies further supports the beneficial role of physical activity in diabetes prevention (Wareham 2007). Physical activity is a cornerstone of weight maintenance, and it is associated with increased insulin sensitivity (Maarbjerg et al. 2011). Several prospective studies have demonstrated a reduction in diabetes risk with higher levels of physical activity (reviewed in Gill and Cooper (2008) and Wareham (2007)). In most studies, a significant inverse association between physical activity and diabetes remained after adjusting for BMI, suggesting that the benefits of physical activity on diabetes are not entirely mediated through body weight.

Measuring physical activity by questionnaires is prone to measurement errors in epidemiological studies (see chapter ▸Physical Activity Epidemiology of this handbook), likely resulting in an underestimation of the true effect size. Thus, the amount of physical activity required to prevent diabetes remains unresolved. New technologies of activity assessment, e.g. heart rate monitoring and accelerometers, provide more accurate estimates of physical activity levels, although the applications of these technologies in large populations are expensive and logistically difficult. Nonetheless, the combination of self-reported and objectively measured physical activity data will provide further insights on the beneficial role of different amounts and intensities of physical activity in the development of diabetes.

The type of activity most strongly related to a reduction in diabetes risk remains unclear. Moderate to vigorous activity, including brisk walking, has consistently been related to lower diabetes incidence (Jeon et al. 2007). However, no study has examined the role of resistance training such as weight lifting versus aerobic exercise in diabetes risk. Sedentary behaviors, such as prolonged television watching, are associated with an increased risk of diabetes. This relationship is not explained by unhealthy eating patterns associated with television watching (Grøntved and Hu 2011). Appropriate control for different physical activities in analyses of a specific activity as exposure can be performed using isotemporal substitution models reflecting the displacement of time spent on different activities (Mekary et al. 2009). However, the multidimensional nature of physical activity (or inactivity) makes it hard to conclude whether the benefits are due to increased total energy expenditure (i.e., that any form of activity is advisable) or the fitness-producing effect of activities (i.e., that prevention efforts need to focus primarily on fitness-promoting recreational activities). Although several studies have suggested that higher fitness is associated with lower diabetes risk independently of body fatness (Carnethon et al. 2009; Lee et al. 2009a), the benefits of physical activity are likely due to the combination of both increased energy expenditure and improved physical fitness.

60.5.3 Smoking

Active cigarette smoking has consistently been associated with increased diabetes incidence (for a systematic review the reader can refer to Willi et al. (2007)).

Although the relative risk for active smokers compared to never smokers is moderate (∼1.5), smoking accounts for a considerable proportion of diabetes cases due to its high prevalence in many populations. In the USA, where smoking prevalence is declining, smoking has been estimated to account for about 12% of all diabetes cases (Ding and Hu 2007).

Smoking cessation is associated with a modest increase in weight. There is a dose-response relationship among former smokers with weight gain being proportional to the number of cigarettes formerly smoked daily (Filozof et al. 2004). However, this weight gain typically occurs in the shortterm. While diabetes risk is particularly high among individuals who recently quit smoking (Yeh et al. 2010), the beneficial effects of smoking cessation outweigh the adverse effects of associated weight gain in the longterm, leading to a reduction of diabetes risk (Wannamethee et al. 2001; Will et al. 2001).

60.5.4 Alcohol Consumption

Moderate alcohol consumption (1–3 drinks/day) has consistently been associated with lower diabetes incidence. Most studies have observed a u-shaped association, where an increased risk of adverse health outcomes is observed for abstainers and for heavy alcohol consumers. The large number of prospective observational studies that addressed alcohol consumption and diabetes risk has been summarized by several meta-analyses (Baliunas et al. 2009; Carlsson et al. 2005; Koppes et al. 2005). In most studies, the increased risk among alcohol abstainers compared to moderate drinkers should be interpreted cautiously because of heterogeneity in the abstainer population (e.g., life-long abstainers, sickquitters, underreporters). Nonetheless, the benefits of moderate alcohol consumption on diabetes still persisted even when light drinkers (e.g., half a drink or less per day) were used as the reference group.

For moderate alcohol consumers, the reduced risk of type 2 diabetes could be due to increased insulin sensitivity (Davies et al. 2002; Joosten et al. 2008) and adiponectin concentrations (Beulens et al. 2008a). However, results from randomized controlled trials are not entirely consistent, particularly for male participants (Beulens et al. 2006, 2007, 2008b; Sierksma et al. 2004; Zilkens et al. 2003). Although some studies observed different associations depending on the type of alcoholic beverage consumed, randomized trials suggest that the underlying biological mechanism is most likely to be explained by the consumption of alcohol, regardless of the type (Beulens et al. 2006, 2007, 2008b; Davies et al. 2002).

60.5.5 Dietary Factors

It has been hypothesized that higher total fat intake contributes to diabetes, directly by inducing insulin resistance and indirectly by promoting weight gain. Results from metabolic studies in humans, however, are inconsistent and generally do not

support the idea that high-fat diets have a detrimental effect on insulin sensitivity (Lichtenstein and Schwab 2000; Riserus et al. 2009). Additionally, changing the dietary fat and carbohydrate composition in intervention studies generally had no effect on subsequent weight change over a long-term period (Howard et al. 2006). In most observational prospective studies, total fat or carbohydrate intake was not associated with diabetes risk (for an overview of the literature, the reader should refer to reviews on this topic (Hu et al. 2001b; Melanson et al. 2009; Schulze and Hu 2005)). This point is further supported by the Women's Health Initiative, a large randomized trial in which women who consumed a low-fat diet had similar diabetes incidence rates compared with women who consumed a standard USA diet (Tinker et al. 2008). The specific type of fat and carbohydrate may be more important than the total intake. Prospective studies suggest that diets that favor plant fats over animal fats (Hu et al. 2001b; Melanson et al. 2009) and that are rich in fiber, particularly from cereals (Schulze et al. 2007), are advantageous.

Carbohydrate quality can be determined by evaluating the physiologic response to carbohydrate-rich foods. The glycemic index reflects the quality of carbohydrates by ranking the ability of specific foods to raise postprandial blood glucose levels (Jenkins et al. 1981), whereas the glycemic load, a crossproduct of the glycemic index of a specific food and the amount of carbohydrates, reflects both quality and quantity of the carbohydrates. The relationship between glycemic index or load and risk of diabetes has been evaluated by a number of prospective studies, which showed that diets with low average glycemic index and glycemic load might be associated with lower risk for diabetes compared with high glycemic index/load diets (Dong et al. 2011a; Liu and Chou 2010). These associations appear to be independent of the amount of dietary fiber.

Though data are limited with regard to dietary protein, higher intake of animal protein has been observed to be associated with higher diabetes risk (Schulze et al. 2008; Sluijs et al. 2010; Song et al. 2004). In addition, cohort studies suggest that higher magnesium intake (Dong et al. 2011b; Larsson and Wolk 2007; Schulze et al. 2007) decreases diabetes risk, whereas higher iron intake – particularly from animal sources (iron bound to heme in oxygen-binding proteins myoglobin and hemoglobin) – increases diabetes risk (Rajpathak et al. 2009a). The relationship between antioxidative nutrients and diabetes risk has been evaluated in post hoc analyses of several randomized clinical trials. Generally, no benefits from vitamin C, vitamin E, or beta-carotene supplementation were found (Song et al. 2009), but supplementation with selenium was associated with increased risk of diabetes in one trial (Stranges et al. 2007).

A growing number of studies have evaluated the role of specific foods with regard to diabetes risk. Coffee consumption has been associated with lower diabetes risk in a large number of studies (Huxley et al. 2009; van Dam and Hu 2005). Residual confounding is unlikely to explain these results because regular coffee consumption is generally associated with unfavorable lifestyle habits in most populations. Whole grains have consistently been associated with lower diabetes risk in prospective studies (de Munter et al. 2007; Priebe et al. 2008). Similarly, dairy consumption

is associated with lower diabetes risk (Tong et al. 2011), although this benefit may be restricted to low-fat dairy products. Consumption of nuts has also been associated with lower risk of diabetes, although to date, very few prospective studies have directly evaluated this hypothesis (Kendall et al. 2010). In contrast, frequent consumption of red and processed meats has consistently been related to higher diabetes risk in prospective cohort studies (Aune et al. 2009; Micha et al. 2010; Pan et al. 2011). Prospective studies also suggest that consuming sugar-sweetened beverages increases the risk of developing type 2 diabetes (Malik et al. 2010). A meta-analysis indicates that higher consumption of fruits and vegetables is not significantly associated with diabetes risk (Carter et al. 2010), although green leafy vegetables were found to be protective. It should be noted that observational studies may not be able to capture the true effect of diet on disease risk due to measurement errors inherent in the use of questionnaires, which could potentially lead to an underestimation of the effect (Harding et al. 2008).

To capture an individual's exposure to overall diet, several methods have been developed to derive dietary patterns. For details on food pattern evaluation methods and studies that evaluate the relationship between dietary patterns and diabetes risk, the reader should refer to published reviews (Esposito et al. 2010; Kastorini and Panagiotakos 2009; Michels and Schulze 2005; Schulze and Hu 2002; Schulze and Hoffmann 2006). Studies that evaluate major eating patterns through the use of exploratory patterning methods (e.g., factor and cluster analysis) suggest that "Western" diets rich in red and processed meats, sugary drinks, and refined grains are related to higher diabetes risk (Fung et al. 2004; van Dam et al. 2002). Several authors have used the reduced rank regression technique, which allows the use of intermediate risk markers in pattern recognition to identify diabetes-related patterns (Heidemann et al. 2005; Imamura et al. 2009; Liese et al. 2009; McNaughton et al. 2008; Schulze et al. 2005). Most studies support the notion that dietary patterns that favor fruits, vegetables, whole grains, and vegetable fats at the expenses of red meats, refined grains, and sugared soft drinks reduce the risk of type 2 diabetes. While this evidence is observational, additional support for the beneficial effects of similar diet patterns (e.g., the Mediterranean diet) comes from intervention studies (Salas-Salvado et al. 2011).

Measuring dietary intake in observational studies has been a major focus of research in nutritional epidemiology (see chapter ▸Nutritional Epidemiology of this handbook). Semiquantitative food frequency questionnaires are the most commonly used method to assess diet in large-scale studies to date. Food frequency questionnaires can be self-administered by participants, are relatively easy to complete, can be processed by computer, and are inexpensive – features that make them particularly feasible for use in large epidemiological studies. However, the validity of this method may vary with different populations and cultures. In addition, because food frequency questionnaires lack the detail and specificity of diet records or recalls, they may not provide accurate estimates of absolute intake of some nutrients. As a consequence, food frequency questionnaires provide very useful information on relative ranking of usual nutrient and food intakes rather than precise amounts of intakes. While more quantitative methods (food records, 24h-recalls) are available,

they are short-term assessment instruments unlikely to reflect long-term usual intake and put considerable burden on study participants and investigators. New methodological developments focus on the combination of different assessment methods. For example, data from food frequency questionnaires can be used in combination with few repeated 24-h recalls to increase the validity of collected dietary data (Souverein et al. 2011).

In epidemiological studies on diet and diabetes, the regression calibration approach can be used to correct measures of association for random and systematic errors inevitable in all dietary assessments (Qiu and Rosner 2010). However, this approach requires a validation study in a subsample of the study. Also, random measurement errors can also be reduced by repeated dietary assessment over the course of a study (Hu et al. 1999). For example, correction for measurement error by the regression calibration approach and by using repeated dietary assessments in comparison to baseline diet only yielded stronger associations between red and processed meat intake and type 2 diabetes risk (Pan et al. 2011).

Due to the multidimensional nature of dietary intake, observational studies on dietary risk factors and diabetes require careful statistical model building. Given that several dietary exposures have been observed to be related to diabetes risk, confounder adjustment is a central requirement. Besides control of confounding, adjustment for total energy intake also mimics differences in dietary composition under isocaloric situations. In the case that the effect of specific energy-providing macronutrients on disease outcome is modeled, effect estimates then reflect macronutrient substitutions. For example, adjustment of carbohydrate density (percentage of total energy) for total energy intake and specific other macronutrient densities allows to evaluate associations with diabetes risk for an isocaloric substitution of carbohydrates for fat or for protein (Schulze et al. 2008). Multivariable modeling can also be used to investigate the effect of a substitution of a serving of one food for another (Halton et al. 2006; Pan et al. 2011).

60.5.6 Emotional Stress and Sleeping Problems

Findings from prospective cohort studies suggest that different forms of emotional stress increase the risk of type 2 diabetes. Here, emotional stress refers to consequences of the failure to respond appropriately to emotional threats, with signs of stress defined at a cognitive, emotional, physical, or behavioral level (Pouwer et al. 2010). Depression has consistently been associated with higher diabetes incidence (Knol et al. 2006; Mezuk et al. 2008). Also, general emotional stress has been found to increase diabetes risk, although the data are not conclusive (Pouwer et al. 2010). There is some evidence that psychosocial stress at work is also associated with increased diabetes risk (Agardh et al. 2003; Heraclides et al. 2009). Emotional stress can affect sleep duration and sleep quality. Conversely, sleeping problems may not only be a consequence of emotional stress but are often experienced as a significant source of stress (Pouwer et al. 2010).

Prospective studies have consistently observed higher diabetes risk with short sleep duration (≤5–6 h/night) and long sleep duration (>8–9 h/night). There is also strong evidence that reduced sleep quality, e.g., difficulties in initiating or maintaining sleep, increases diabetes risk (Cappuccio et al. 2010). Potential mechanisms relating short sleep duration to increased risk include changes in circulating levels of leptin and ghrelin as well as cortisol metabolism and inflammation. While BMI is an important potential confounder because it can contribute to snoring problems and sleep apnea (and thus to sleeping problems), short sleep duration has generally been found to increase diabetes risk independently of body fatness. There is less clear indication of possible mechanisms mediating the risk-increasing effect of long sleep duration, although confounding by depressive symptoms, low socioeconomic status, unhealthy lifestyle patterns, and prevalent health conditions may be potential explanations (Pouwer et al. 2010).

60.6 Biochemical Predictors

In light of the increasing prevalence of diabetes worldwide, interest in identifying "novel" predictors is mounting. A growing number of studies have evaluated biochemical markers for associations with diabetes risk in recent years. Such research has mainly been targeted at improving our understanding of the pathogenesis of diabetes. Biochemical markers have also been increasingly used to evaluate potential mechanisms by which conventional risk factors might be related to diabetes risk. These investigations focus on etiology and can be separated from the debate on whether biomarkers have value as a screening tool for predicting future diabetes cases. The latter point is discussed later in this chapter.

The evaluation of biochemical markers in epidemiological studies involves a number of challenges which are often not sufficiently addressed (see chapter ▸Molecular Epidemiology of this handbook). These complex problems include: residual confounding, inappropriate adjustment for intermediate variables, and analytical measurement error and biological variation. For a more detailed discussion, the reader might refer to Sattar et al. (2008). While biochemical markers of diabetes risk may generally be measureable in different body tissues, the overwhelming majority of studies have focused on peptides, proteins, and metabolites measureable in peripheral blood. Parameters of glucose metabolism have been of particular interest because these are either directly relevant as diagnostic parameters (FPG, 2hPG, HbA_{1c}) or they reflect the primary underlying mechanisms of insulin resistance (reflected by different indices, e.g., HOMA insulin resistance index) and impaired β-cell function (reflected by fasting insulin, proinsulin, or HOMA β-cell function index). Additional biomarkers that have been found to predict diabetes incidence include blood lipids (i.e., triglycerides and HDL-cholesterol (Fagot-Campagna et al. 1997; Montonen et al. 2011; Schmidt et al. 2005; Stern et al. 2002; Wilson et al. 2007)), liver enzymes (alanine aminotransferase and gamma-glutamyltransferase (Fraser et al. 2009)) and other hepatic-derived predictors

(sex hormone-binding globulin (Ding et al. 2006)), the adipokine adiponectin (Li et al. 2009), and markers of subclinical inflammation, in particular CRP (Lee et al. 2009b). There is also emerging evidence that novel markers related to inflammation and endothelial dysfunction (e.g., IL-6, cellular adhesion molecules, white cell count (Goldberg 2009)), body iron stores (Forouhi et al. 2007; Jehn et al. 2007; Rajpathak et al. 2009b), hepatokine fetuin-A (Ix et al. 2008; Stefan et al. 2008), or PAI-1 (Festa et al. 2002; Kanaya et al. 2006) are associated with diabetes risk. For a detailed review of the literature, the reader may refer to published reviews (Herder et al. 2011; Sattar et al. 2008).

Current approaches focus on complementing candidate-based biomarker studies with hypothesis-free approaches. In particular, metabolomics has gained more interest because metabolites are considered to be the most proximal biomarkers of pathophysiological processes. The number of different metabolites (including lipids, sugars, nucleotides, amino acids, organic acids), their substantial chemical diversity in terms of polarity and water/lipid solubility, and their wide range of concentration levels across different human tissues make the application of metabolomics in large-scale epidemiological studies particularly challenging (see chapter ▸Molecular Epidemiology of this handbook). A recent prospective study using a targeted metabolomics approach indicated that branched-chain and aromatic amino acids in plasma could be used as predictors of risk of type 2 diabetes (Wang et al. 2011).

60.7 Genetic Predictors

In addition to biochemical markers, there has been a growing interest in genetic markers as predictors of diabetes. Several loci were identified in candidate association studies (PPARG, KCNJ11, TCF7L2, WFS1, and HNF1B), but the majority of the known susceptibility loci for type 2 diabetes have been identified by genome-wide association studies (GWAS) based on case-control studies (e.g., FTO, SLC30A8, HHEX-IDE-KIF11, CDKAL1, IGF2BP2, CDKN2A-CDKN2B, TSPAN8, ADAMTS9, NOTCH2, CDC123-CAMK1D, THADA, JAZF, KCNQ1, IRS1, DUSP9, ZFAND6, PRC1, CENTD2, TP53INP1, KLF14, ZBED3, BCL11A, HNF1A, CHCHD9, HMGA2, UBE2E2, C2CD4A-C2CD4B, and RBMS1-ITGB6) or by evaluating associations with diabetes-related quantitative traits, e.g., FPG, 2hPG, HbA_{1c}, and indices of insulin resistance and β-cell function (MTNR1B, DGKB-TMEM195, GCKR, GCK, PROX1, and ADCY5) (for a detailed description of genome-wide association studies see chapter ▸Statistical Methods in Genetic Epidemiology of this handbook). GWAS have resulted in a major paradigm shift in epidemiological research from hypothesis-driven investigations toward exploratory analyses and decision-making based on the presence or absence of statistical significance. The pooling of study populations has led to increased statistical power and the discovery of many new loci. These loci are typically associated with a small to moderate effect on diabetes risk, with most variants carrying an odds ratio of

Table 60.5 Genetic variants evaluated to predict type 2 diabetes in prospective cohort studies considering multiple loci simultaneously

Study	Number of genetic variants	Comparison	Relative risk (95% CI)
Rotterdam Study (van Hoek et al. 2008)	18	Per risk allele	1.04 (1.02–1.07)
Framingham offspring Study (Meigs et al. 2008) (de Miguel-Yanes et al. 2011)	18 40	Per risk allele	1.12 (1.07–1.17) <50 years: 1.24 (1.13–1.36) ≥50 years: 1.11 (1.03–1.19)
Malmö preventive project (Lyssenko et al. 2008)	11	Per risk allele	1.12 (1.08–1.15)
Botnia Study (Lyssenko et al. 2008)	11	Per risk allele	0.94 (0.84–1.04)
Health professionals follow-up Study (Cornelis et al. 2009a)	10	Per risk allele	1.19 (1.14–1.24)
Nurses' health Study (Cornelis et al. 2009a)	10	Per risk allele	1.16 (1.12–1.20)
EPIC-Potsdam Study (Schulze et al. 2009)	20	≥22 vs. <17 risk alleles	1.47 (1.12–1.93)
Whitehall II Study (Talmud et al. 2010)	20	Per risk allele	1.7 (0.9–2.5)

1.1–1.2 per risk allele. In addition, these risk alleles are usually common, often exceeding 25% prevalence in most populations (Herder et al. 2011). Interestingly, the majority of risk loci reflect variation in genes involved in β-cell function rather than insulin resistance (Florez 2008).

Several recent prospective studies have used genetic risk scores or risk allele scores to capture genetic risk at multiple loci simultaneously (Table 60.5) (Cornelis et al. 2009a; de Miguel-Yanes et al. 2011; Lyssenko et al. 2008; Meigs et al. 2008; Schulze et al. 2009; Talmud et al. 2010; van Hoek et al. 2008). Such scores can generally be calculated by either assuming equal contribution of each risk allele or weighting the risk alleles. The latter technique has been applied by assigning study-specific or literature-based weights. Given that most genetic variants are associated with a modest increase in risk of diabetes and that study-specific associations are frequently inconsistent with associations reported from large pooling projects for single loci, the use of study-specific weights is likely to introduce overoptimism in risk prediction when evaluating genetic risk scores (de Miguel-Yanes et al. 2011). Also, because there is very little difference in effect sizes between most variants, weighted genetic risk scores may not be substantially different in their associated risk compared to that for unweighted scores (Cornelis et al. 2009a; Talmud et al. 2010).

The risk variants identified to date only account for ~10% of observed familial clustering of type 2 diabetes (Voight et al. 2010). Thus far, the identified variants

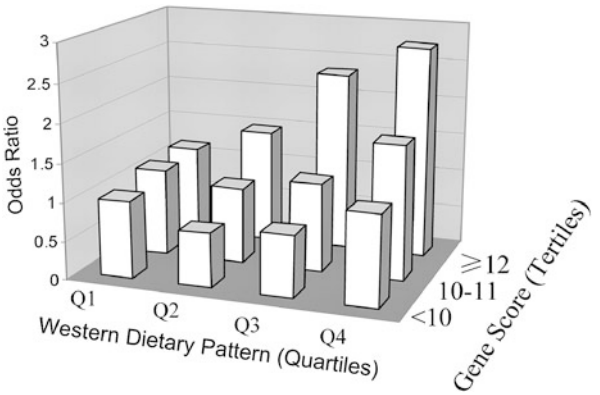

Fig. 60.3 Diabetes risk according to joint classification of a "Western" dietary pattern and genetic risk (Qi et al. 2009)

are common alleles (frequency >5%), and it remains unclear whether less common variants would have a stronger genetic effect on diabetes. Potentially, the combined effects of common and less common variants may explain a greater degree of heritability of diabetes, although rare variants with large effects are yet to be identified.

Current research is also focused on investigating the interplay between environmental risk factors and genetic susceptibility. For an overview of the literature, the reader should refer to reviews on this topic (Franks et al. 2007; Qi et al. 2008; Qi and Liang 2010). There is some evidence that the effectiveness of lifestyle interventions is dependent upon genetic variants (Florez et al. 2007). For example, prospective studies have observed that the beneficial effects of fiber-rich diets or diets with high carbohydrate quality (low glycemic index) may depend upon genetic variation in TCF7L2 (Cornelis et al. 2009b; Fisher et al. 2009). Additionally, the detrimental effects of adhering to a "Western" dietary pattern were stronger among individuals carrying a relatively large number of diabetes risk alleles compared to those with relatively few (Fig. 60.3) (Qi et al. 2009). Interactions between physical activity and genetic variants have also been found (Brito et al. 2009). Still, intensive lifestyle modification reduced diabetes risk irrespective of genetic susceptibility to diabetes in the Diabetes Prevention Program (Hivert et al. 2011). Although genetic predictors of diabetes have been identified by large consortia of cross-sectional and case-control studies in recent years, these studies are generally not suitable for evaluating gene-environment interactions because most of the studies did not collect exposure information on environmental factors, especially diet and lifestyle. Also, diet and lifestyle information assessed in case-control or cross-sectional studies is prone to recall bias and reverse causation. Analyses on gene-environment interactions require large prospective population-based studies with sufficient statistical power, detailed information on diet and lifestyle, and replication of the findings in various populations.

60.8 Prevention of Diabetes

60.8.1 Healthy Lifestyles and Preventability of Type 2 Diabetes

Epidemiological evidence strongly indicates that diabetes is associated with Western dietary and lifestyle habits. People who migrate to Western countries generally have more sedentary lifestyles and consume "Western" diets and, therefore, have a greater risk of developing type 2 diabetes compared with their counterparts who remain in their native countries (Manson and Spelsberg 1994). Populations undergoing westernization in the absence of migration have also experienced dramatic rises in obesity and type 2 diabetes (Gohdes et al. 1993; Collins et al. 1994; Hodge et al. 1994).

Although a large body of evidence from epidemiological studies has implicated individual dietary and lifestyle factors in the development of type 2 diabetes, only a few studies have examined multiple risk factors simultaneously (Ford et al. 2009; Gopinath et al. 2010; Hu et al. 2001a; Mozaffarian et al. 2009; Reis et al. 2011). All of these studies considered physical activity, diet, smoking, and overweight or obesity as modifiable risk factors (Table 60.6). Alcohol consumption was considered by three of the five studies as an additional risk factor (Hu et al. 2001a; Mozaffarian et al. 2009; Reis et al. 2011). Overall, participants who adhered to all of the low-risk behaviors had a dramatically lower risk of developing type 2 diabetes. The studies also observed that only a small fraction of participants fulfilled all low-risk behavior criteria and that the population attributable risk of not adhering to healthy lifestyles is very high.

In these studies, the definition of a healthy diet based on population percentiles is somewhat arbitrary, thus making the translation of findings into public health practice challenging. The categorization of continuous risk factors is also subjective as different cut-offs for BMI and waist circumference were used in different studies. Despite these limitations, the data provide strong epidemiological evidence that the majority of type 2 diabetes cases could be prevented by the adoption of a healthier lifestyle.

Several randomized trials have also demonstrated the preventability of diabetes through lifestyle modification (Table 60.7). In a group-randomized trial in China, intervention with diet alone, exercise alone, and diet-plus-exercise was associated with a 31%, 46%, and 42% reduction in the risk of developing diabetes compared to the control group (Pan et al. 1997). In the Finnish Diabetes Prevention Study, reduction in weight through dietary modification and increasing physical activity resulted in an overall diabetes risk reduction of 58% over 3 years (Tuomilehto et al. 2001). Similarly, in the US-based Diabetes Prevention Program, a lifestyle-modification program with the minimum goal of a 7% weight reduction and a minimum of 150 min of physical activity per week reduced diabetes incidence by 58% over 3 years (Knowler et al. 2002). In all of these studies, the effect was maintained several years beyond the active intervention period (Li et al. 2008; Lindstrom et al. 2006; Knowler et al. 2009). Similar effects of lifestyle modification on diabetes incidence have been observed in the Indian Diabetes Prevention

Table 60.6 Classification of low-risk, relative risk, and population attributable risk of type 2 diabetes mellitus in prospective studies for groups defined by combinations of modifiable risk factors

Lifestyle risk factors	Nurses' Health Study (Hu et al. 2001a)	Cardiovascular Health Study (Mozaffarian et al. 2009)	EPIC-Potsdam Study (Ford et al. 2009)	Blue Mountains Eye Study (Gopinath et al. 2010)	National Institutes of Health (NIH)–AARP Diet and Health Study (Reis et al. 2011)
Physical activity	Moderate-to vigorous exercise ≥30 min/day	≥median	≥3.5 h/week	≥3 times/week	20 min ≥ 3 times/week
Diet	Upper 2 quintiles of diet score	Upper 2 quintiles of diet score	>median of diet score	>median of diet score	Upper 2 quintiles of diet score
Smoking	No current	Never	Never	Never	Never or quit smoking >10 years ago
Overweight/obesity	BMI < 25 kg/m^2	BMI < 25 kg/m^{2}or waist circumference <88/92 cm	BMI < 30 kg/m^2	BMI < 30 kg/m^2	BMI 18.5–25 kg/m^2
Alcohol consumption	≥half a drink/day	Yes			Moderate
Percentage of population adhering to all factors	3.4%	3.4%	9.1%	11.4%	Men: 4.0% Women: 2.3%
Relative risk (95% CI)	5 factors vs. rest: 0.09 (0.05–0.17)	5 factors vs. rest: 0.11 (0.01–0.76)	4 factors vs. 0: 0.07 (0.05–0.12)	4 factors vs. 0: 0.17 (0.07–0.42)	5 factors vs. rest: Men: 0.28 (0.23–0.34) Women: 0.16 (0.10–0.24)
Population attributable risk % (95% CI)	91 (83–95)	89 (23–99)	Not reported	Not reported	Not reported

Table 60.7 Major lifestyle modification trials for prevention of type 2 diabetes

	Da Qing Study (Pan et al. 1997; Li et al. 2008)	Finnish Diabetes Prevention Study (Tuomilehto et al. 2001; Lindstrom et al. 2006)	Diabetes Prevention Program (Knowler et al. 2002, 2009)	Indian Diabetes Prevention Program (Ramachandran et al. 2006)	Japanese Trial (Kosaka et al. 2005)
N, sex	577 men and women with impaired glucose tolerance	522 men and women with impaired glucose tolerance	3,234 men and women with impaired glucose tolerance	269 men and women with impaired glucose tolerance	458 men with impaired glucose tolerance
Age	>25 years	40–65 years	>25 years	33–55 years	>30 years
Country	China	Finland	USA	India	Japan
Weight reduction goal	BMI = 23 kg/m^2 for overweight subjects in diet group	≥5%	7%	Weight maintenance	Reduction in BMI to <22 kg/m^2
Intervention arms	Diet alone Exercise alone Diet + exercise Control	Lifestyle intervention Control	Lifestyle intervention Control	Lifestyle intervention Control	Lifestyle intervention Control
Dietary intervention	25–30% energy from fat; 55–65% energy from carbohydrate; specific advice on cereal, vegetable, meat, milk, and oil intake in subjects with BMI ≥25 kg/m^2	<30% energy from fat; <10% saturated fat; fiber ≥15 g/1,000 kcal; frequent intake of whole grain products, vegetables, fruits, low-fat milk and meat products, soft margarines, and vegetable oils	25% fat, low-calorie diet; healthy eating based on US Department of Agriculture Food Guide Pyramid	Avoidance of simple sugars and refined carbohydrates; total fat intake ≤20 g/day; restriction of saturated fat; fiber-rich food	Smaller meals; avoidance of fat-rich foods
Lifestyle intervention	1 unit physical activity daily (5–30 min depending on intensity); 2 units/day if possible for those <50 years of age with no evidence of cardiovascular disease	Moderate exercise ≥30 min daily	150 min/week physical activity	Brisk walking for ≥30 min each day	Walking 30–40 min/day or cycling 30 min at weekends
Follow-up (years)	6	3.2	2.8	2.5	4
Diabetes risk reduction with intervention compared with controls	Diet only: 31% Exercise only: 46% Diet + Exercise: 42%	63%	58%	28%	67%

Program (Ramachandran et al. 2006) and in a Japanese trial (Kosaka et al. 2005). These trials share the limitation that study participants were preselected based on their risk profile with prevalent impaired glucose tolerance being a prerequisite. Consequently, diabetes incidence – even with lifestyle intervention – was very high, and thus, these results may not be easily generalizable to other risk groups.

60.8.2 Drugs in the Prevention of Type 2 Diabetes

Several trials have evaluated the efficacy of drugs in the prevention or delay of type 2 diabetes (Table 60.8). Metformin treatment resulted in a diabetes risk reduction in the diabetes prevention program (Knowler et al. 2002) and in the Indian Diabetes Prevention Program (Ramachandran et al. 2006). Metformin improves hyperglycemia primarily by suppressing hepatic gluconeogenesis. In the Study to Prevent Non-Insulin-Dependent Diabetes Mellitus (STOP-NIDDM) (Chiasson et al. 2002), the acarbose intervention group experienced a 25% diabetes risk reduction compared with the placebo group. Treatment with voglibose resulted in a risk reduction in a Japanese study (Kawamori et al. 2009). Both acarbose and voglibose are alpha-glucosidase inhibitors that decrease the absorption of carbohydrates from the intestine, resulting in a slower and lower rise in blood glucose, particularly after meals. Thiazolidinediones were used as drug intervention in several studies. Both troglitazone (Buchanan et al. 2002; Knowler et al. 2005) and rosiglitazone (Gerstein et al. 2006) reduced the risk of incident diabetes by at least 50% over 3 years compared to placebo. Furthermore, a low-dose combination therapy with rosiglitazone and metformin reduced the risk of type 2 diabetes in patients with impaired glucose tolerance (Zinman et al. 2010). The primary mechanism of action of thiazolidinediones involves binding to the peroxisome proliferator-activated receptor gamma, a transcription factor that regulates the expression and release of mediators of insulin resistance originating in adipose tissue. Treatment with orlistat, a potent inhibitor of pancreatic lipases that prevents the absorption of fats from the human diet, reduced diabetes risk by about 40% in two intervention studies (Heymsfield et al. 2000; Torgerson et al. 2004). A diabetes risk reduction was also observed for valsartan, an angiotensin receptor blocker (McMurray et al. 2010). In contrast, nateglinide, which stimulates insulin secretion, (Holman et al. 2010) and ramipril, an angiotensin-converting enzyme inhibitor (Bosch et al. 2006), were not found to significantly reduce diabetes risk in randomized controlled trials.

While these trials provide evidence that type 2 diabetes can be prevented through pharmacological interventions in high-risk populations, lifestyle modifications are more efficacious than drug interventions (Knowler et al. 2002; Ramachandran et al. 2006), and they do not cause side effects that are common in drug treatments. In particular, troglitazone was withdrawn from the market in 2000 due to liver toxicity, and rosiglitazone has been found to increase risk of cardiovascular disease. In addition, the beneficial effects of drugs on diabetes were lost shortly after the drugs were stopped (i.e., a few weeks), whereas lifestyle interventions had sustained benefits on diabetes prevention even after the active intervention discontinued for

Table 60.8 Major drug trials for prevention of type 2 diabetes

Study (author)	Population	Intervention	Relative risk (95% CI) of intervention compared with placebo
Diabetes Prevention Program (Knowler et al. 2002, 2005)	$n = 3{,}234$ with impaired glucose tolerance, aged ≥25 years	850 mg metformin or placebo twice daily, mean 2.8 years	0.69 (0.57–0.83)
		400 mg troglitazone or placebo daily, mean 0.9 years	0.25 ($p < 0.001$)
Indian Diabetes Prevention Program (Ramachandran et al. 2006)	$n = 269$ native Asian Indians with impaired glucose tolerance, aged 35–55 years	250 mg metformin or placebo twice daily, median 30 months	0.74 (0.65–0.81)
Study to Prevent Non-Insulin-Dependent Diabetes Mellitus (STOP-NIDDM) (Chiasson et al. 2002)	$n = 1{,}429$ with impaired glucose tolerance, aged 40–70 years	100 mg acarbose or placebo three times daily, mean 3.3 years	0.75 (0.63–0.90)
Japanese Study (Kawamori et al. 2009)	$n = 1{,}780$ with impaired glucose tolerance, aged 30–70 years	0.2 mg voglibose or placebo three times daily, mean 48 weeks	0.60 (0.43–0.82)
Three trials (Heymsfield et al. 2000)	$n = 675$ with BMI ≥30, aged >18 years	120 mg orlistat or placebo three times daily, 582 days	0.39 ($p = 0.04$) among participants with impaired glucose tolerance at baseline
XENDOS (Torgerson et al. 2004)	$n = 3{,}305$ with BMI ≥30, aged 30–60 years	120 mg orlistat or placebo three times daily, 4 years	0.63 (0.46–0.86)
TRIPOD (Buchanan et al. 2002)	$n = 266$ hispanic women with previous gestational diabetes, aged ≥18 years	400 mg troglitazone or placebo once a day, mean 30 months	0.45 (0.25–0.83)
DREAM (Gerstein et al. 2006)	$n = 5{,}269$ with impaired fasting glucose or impaired glucose tolerance, aged ≥30 years	8 mg rosiglitazone or placebo daily	0.40 (0.35–0.46)
CANOE (Zinman et al. 2010)	$n = 207$ with impaired glucose tolerance, aged 30–75 years	2 mg rosiglitazone and 500 mg metformin or placebo twice daily, median 3.9 years	0.34 (0.20–0.59)
NAVIGATOR (Holman et al. 2010; McMurray et al. 2010)	$n = 9{,}306$ with impaired glucose tolerance, mean age 64 years	160 mg valsartan or placebo daily, median 5.0 years	0.86 (0.80–0.92)
		60 mg nateglinide or placebo three times daily, median 5.0 years	1.07 (1.00–1.15)
HOPE (Bosch et al. 2006)	$n = 5{,}269$ with impaired fasting glucose or impaired glucose tolerance, aged ≥30 years	15 mg ramipril or placebo daily, median 3 years	0.91 (0.81–1.03)

several years. Moreover, healthy diet and lifestyle modification is effective not only in preventing diabetes, but also in reducing the risk of other chronic diseases such as coronary heart disease (Ford et al. 2009; Stampfer et al. 2000).

Although lifestyle and drug interventions have been found to reduce the risk of diabetes among individuals at high risk, the benefits of these interventions for the prevention of cardiovascular events, death, or other long-term adverse health outcomes are yet to be demonstrated. For example, no difference in cardiovascular event rates was observed in the US Diabetes Prevention Program (Ratner et al. 2005); however, the study was not powered to examine cardiovascular outcomes. Treatment with acarbose reduced the risk of cardiovascular events in a post hoc analysis (Chiasson et al. 2003), but treatment groups had high attrition rates (33%). In the DREAM trial, cardiovascular event rates did not significantly differ between the rosiglitazone and placebo groups (Gerstein et al. 2006). Other studies among diabetic patients found that rosiglitazone treatment was associated with increased risk of myocardial infarction despite its glucose lowering effect (Nissen and Wolski 2007). On the other hand, lifestyle interventions, assuming a high adherence, are not only effective at reducing the risk of diabetes but also cost-effective at the population level. For a detailed discussion, the reader should refer to reviews on this topic (Waugh et al. 2007; Echouffo-Tcheugui et al. 2011; Norris et al. 2008).

60.9 Screening for Diabetes and Prediabetes

The benefits of early diabetes detection and treatment through screening programs compared to delayed treatment once cases become clinically diagnosed remains unclear because, to date, no randomized study has examined the effectiveness of screening programs. Results from the ADDITION study suggest that for screen-detected diabetes cases, intensive diabetes control did not significantly decrease the number of cardiovascular events beyond what has been achieved with standard care (Griffin et al. 2011). However, improvements in standard care over the study period may have resulted in small differences in patient care between the study groups. Notably, intensive glycemic control did not result in increased mortality risk – an effect that had been observed among patients with more advanced diabetes (Gerstein et al. 2008). As previously mentioned, thus far no randomized studies have compared screened and unscreened individuals with regard to long-term health benefits. The ongoing ADDITION-Cambridge study (Echouffo-Tcheugui et al. 2009) may shed more light on this question.

Despite uncertainties regarding the effectiveness of screening programs, a large body of literature has been published on screening techniques for undiagnosed diabetes. For an overview of the literature, the reader should refer to reviews on this topic (Echouffo-Tcheugui et al. 2009; Waugh et al. 2007). Point-of-care testing for FPG or HbA_{1c} is simple and convenient, but – as was discussed earlier in this chapter – they are unlikely to detect all prevalent diabetes cases. The 2hPG value is considered more reliable for diagnosing diabetes, but it requires an 8-h fast, commitment from the patient and the nursing staff, and has lower test-retest

reproducibility compared with other tests. There is also a growing body of literature on risk scores that do not require blood sampling (Echouffo-Tcheugui et al. 2011). Although none of these tools are optimal in detecting undiagnosed diabetes, they have acceptable validity and are particularly useful tools to screen populations for further glucose screening.

Screening for diabetes cases at baseline and during follow-up has also been common practice in many analytical epidemiological studies. However, as pointed out earlier, screening at a single time point can produce a substantial number of false-positive screens, particularly when 2hPG is used. Because the diagnosis of diabetes requires confirmation in a subsequent assessment, screen-positive study participants should be considered to be potential cases but not necessarily true cases. While this approach allows to include undiagnosed cases, particularly the subgroup with isolated elevated 2hPG levels, the misclassification might in fact bias relative risk calculations and might lead to an overestimation of absolute risk. In contrast, other studies used only self-reported clinical cases. This approach will miss undiagnosed cases which can only be detected through screening and who can be expected to be on average younger than clinical cases. Also, clinical cases will frequently exclude asymptomatic diabetes cases with isolated elevated 2hPG levels since this criterion is not commonly used in clinical practice. Thus, studies based only on self-reported diabetes are likely to underestimate absolute risk and may not represent specific subgroups of cases adequately. While both approaches have pros and cons, the prevalence of undiagnosed diabetes cases in studies based on verified self-reports will not bias estimates of relative risk if this misclassification is non-differential with regard to exposure status (Greenland and Lash 2008). In general, it is, therefore, more relevant to invest in increasing the specificity of the case definition (by verification) than its sensitivity (by additional screening). Still, if studies are also required to accurately reflect absolute risks and to represent all patient subgroups, screening based on all diagnostic parameters and confirmation of screen-detected cases would need to be included.

There is a growing interest in developing prediction models for incident diabetes. Glucose screening could be used as a method to detect individuals at high risk with intermediate states of abnormal glucose regulation that precede overt type 2 diabetes. Impaired fasting glucose (FPG 100 or 110–125 mg/dL/5.6 or 6.1–6.9 mmol/L), impaired glucose tolerance (2hPG 140–199 mg/dL/7.8–11.0 mmol/L), or elevated HbA_{1c} (5.7–6.4%) have been used widely in this context to define a "prediabetic" status (Table 60.1). A meta-analysis of prospective studies conducted in different populations estimated that the relative risk for diabetes compared to normoglycemic individuals was 6.35 in people with impaired glucose tolerance, 5.52 in people with isolated impaired glucose tolerance, 4.66 in people with impaired fasting glucose, 7.54 in people with isolated impaired fasting glucose, and 12.13 in people with both impaired fasting glucose and impaired glucose tolerance (Gerstein et al. 2007). Despite demonstrating a clear increase in risk, dichotomizing glucose values as either "normal" or "prediabetic" neglects the continuum of risk associated with higher values. For example, a steady increase in diabetes risk has been observed for FPG values well within the range considered

normal (Schulze et al. 2010b; Tirosh et al. 2005). Although current guidelines still include categories of prediabetes (Table 60.1), it is well established that risk is continuous, extending below the lower limit of the range for prediabetes and becoming disproportionately greater at the upper end of the range (American Diabetes Association 2011).

As an alternative to individual measures of blood glucose or HbA_{1c}, prediction models involving several diabetes risk factors hold significant promise for identifying those at high risk of developing type 2 diabetes. While several, moderately accurate diabetes prediction models have been developed based on risk factor information, there is evidence to suggest that these models could be improved with the addition of biochemical markers, in particular those reflecting hyperglycemia (Schmidt et al. 2005; Schulze et al. 2009). However, adding more complex markers of glucose and insulin metabolism, novel diabetes risk markers (such as CRP or adiponectin), or genetic information does not seem to further improve diabetes prediction. For a detailed review of prediction models, the reader should refer to Buijsse et al. (2011).

60.10 Conclusions

Similar to cardiovascular disease, overweight and obesity, diet, and lifestyle are predominant risk factors for type 2 diabetes. Diabetes epidemiology, therefore, shares important characteristics with other chronic disease epidemiology fields. Methodological developments to reduce misclassification in assessing dietary and lifestyle risk factors are of central interest to all fields of chronic disease epidemiology. Meanwhile, it is important to minimize confounding through improved study design and statistical analysis. Existing prospective cohort studies have increasingly been used for diabetes epidemiology although they may have initially been started as cancer epidemiology studies, e.g., the Nurses' Health Study or the European Prospective Investigation into Cancer (EPIC) study. The case-cohort study design for the evaluation of biochemical and genetic markers has increasingly been used to investigate type 2 diabetes and cardiovascular endpoints simultaneously to improve cost-efficiency. Recent advances in molecular and genetic epidemiology are of relevance to diabetes epidemiology, as they are to other fields.

Diabetes epidemiology also faces specific challenges. The definition of endpoints is heterogeneous across studies due to different diagnostic parameters and study-specific follow-up procedures. Based on current methodology, the misclassification of endpoints is almost unavoidable in diabetes epidemiology. This issue has also substantial implications for the estimation of population-level diabetes prevalence and incidence rates.

Diabetes epidemiology has played an essential role in demonstrating the importance of risk factors and the potential for prevention. The role of overweight and obesity in the etiology of type 2 diabetes has been demonstrated by numerous observational studies, and this link has also been causally established by intervention studies that focus on weight reduction among high-risk individuals. Physical

activity, specific components of the diet, smoking, and other lifestyle factors have also been implicated in the development of diabetes. Overall, the majority of type 2 diabetes cases in the general population is attributable to modifiable diet and lifestyle factors.

These findings have had important implications for public health initiatives. For example, the International Diabetes Federation prevention plan for type 2 diabetes is based on controlling modifiable lifestyle risk factors. The plan divides the population into two groups that should be targeted simultaneously: people at high risk of developing type 2 diabetes (high-risk approach of prevention) and the remaining population (population-wide approach of prevention) (Alberti et al. 2007). Similarly, European guidelines for the prevention of type 2 diabetes have highlighted lifestyle modifications as key elements, both in high-risk and population-wide prevention approaches (Paulweber et al. 2010).

Accurate tools used to quantify absolute risk are essential for establishing programs that target high-risk individuals. The field of diabetes epidemiology has developed a number of tools that frequently outperform similar prediction tools used in the fields of cardiovascular or cancer epidemiology. Therefore, identifying high-risk groups seems a feasible task for diabetes interventions. However, the changes required to reduce the risk of diabetes at the population level are unlikely to be achieved without major environmental changes to facilitate appropriate choices by individuals.

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