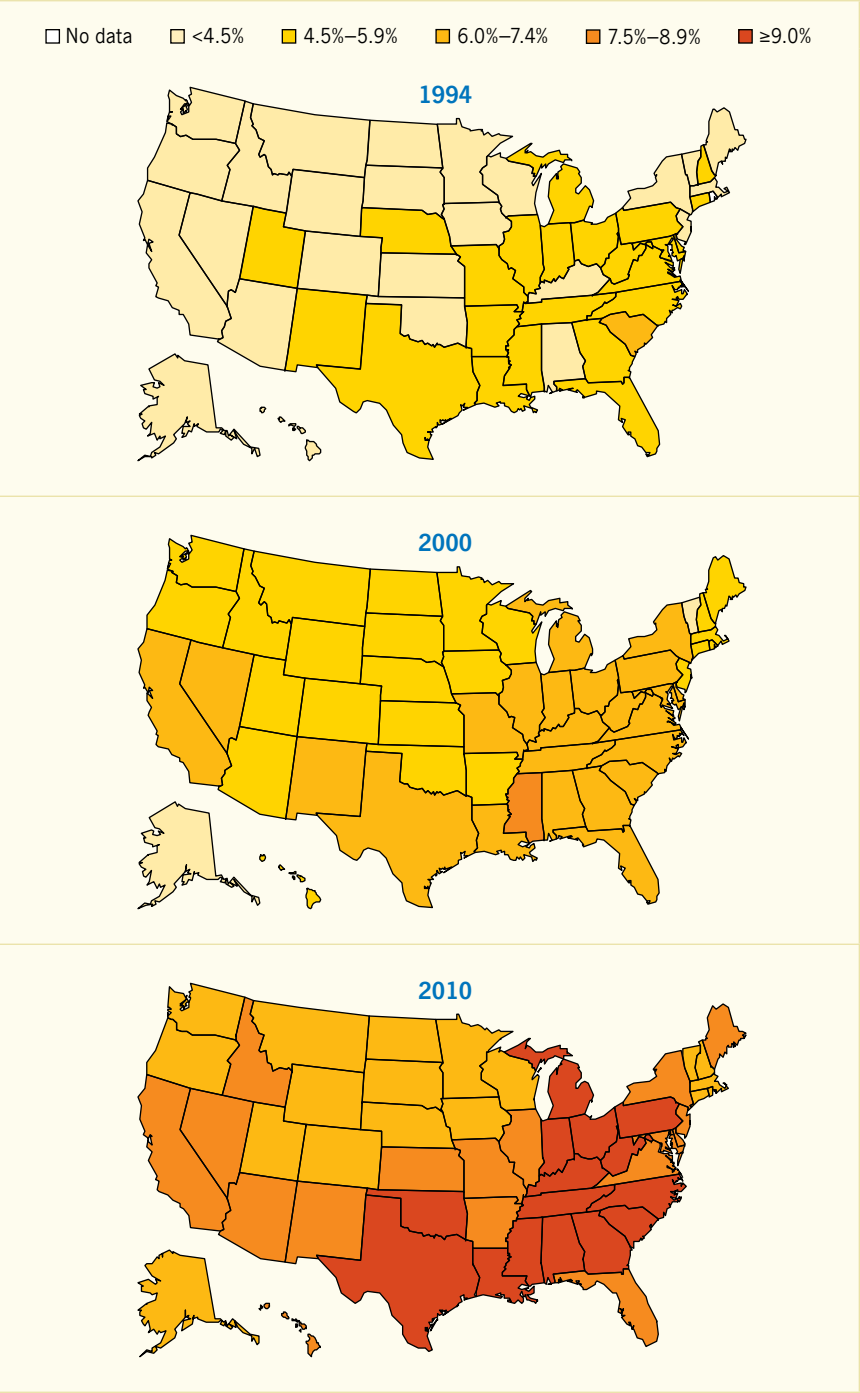
responses to behavioral and lifestyle risk factors vary, likely due to many factors, including differences among individuals in physiology, intervention adherence, and the possibility of complex gene-environment interactions that are not clearly understood (3). Research on novel biomarkers and intermediate conditions associated with diabetes risk may provide additional information on the disease progress and etiology (4,5).

Despite advances in the field, multiple challenges and knowledge gaps remain. This chapter reviews developments in understanding type 2 diabetes risk factors, limitations of present data, and continued challenges involved in investigating risk factors for diabetes and its causes and consequences. Cross-sectional national survey data are included to provide an overview of demographic characteristics of those at increased risk of diabetes. Large-scale prospective data from the United States are used to discuss genetic, behavioral, and metabolic risk factors for developing type 2 diabetes. Meta-analyses and longitudinal international collaboration data are also included to help fill the gaps and strengthen the discussion.

FIGURE 13.1. Age-Standardized Prevalence of Diagnosed Diabetes Among Adults Age ≥18 Years, U.S., 1994, 2000, and 2010



Data are from adults age ≥18 years based on self-report by telephone survey. Prevalence estimates are age-standardized to the 2000 U.S. Standard Population using age categories 18–44, 45–64, 65–74, and ≥75 years.

SOURCE: Reference 1 and Behavioral Risk Factor Surveillance System 1994, 2000, 2010

DEMOGRAPHIC RISK FACTORS

Among individuals age ≥20 years in the United States, 29 million people had diabetes, based on National Health and Nutrition Examination Surveys (NHANES) 2009–2012 estimates applied to 2012 U.S. Census data (6). A detailed description of prevalence and incidence of type 2 diabetes is provided in Chapter 3 *Prevalence and Incidence of Type 2 Diabetes and Prediabetes*. The demographic characteristics of individuals with type 2 diabetes are described in Chapter 8 *Sociodemographic Characteristics of Persons With Diabetes*. This section presents information on the association of each of these characteristics as a risk factor for developing type 2 diabetes.

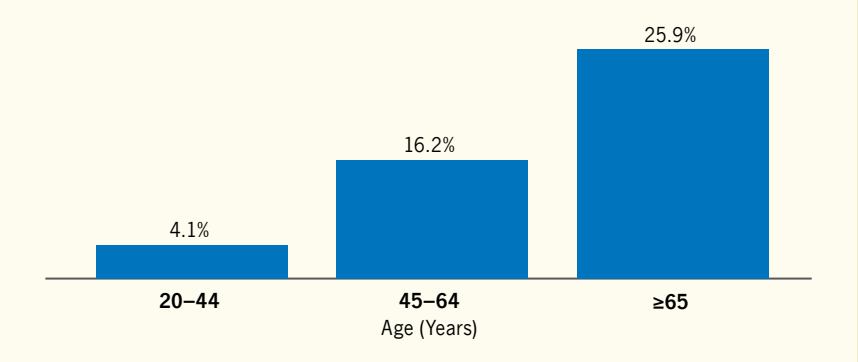
AGE

Based on NHANES data, the prevalence of diabetes increases with age (Figure 13.2) (6). In most populations, the incidence of type 2 diabetes is low before age 30 years but increases rapidly and continuously with older age (7,8). Prospective observational studies have generally reported age to be a strong risk factor, independent of major correlated lifestyle risk factors, including obesity. This is a particular concern at a time when life expectancy is increasing. The International Diabetes Federation estimated that the number of adults with diabetes in the United States will increase from 23.7 million in 2011 to 29.6 million by 2030 (9), largely attributed to the population aging. Median ages at diagnosis of diabetes vary among non-Hispanic white, non-Hispanic black, and Hispanic Americans based on estimation using data from the National Health Interview Survey (NHIS) of the National Center for Health Statistics, Centers for Disease Control and Prevention, as illustrated in Figure 13.3 (1).

SEX

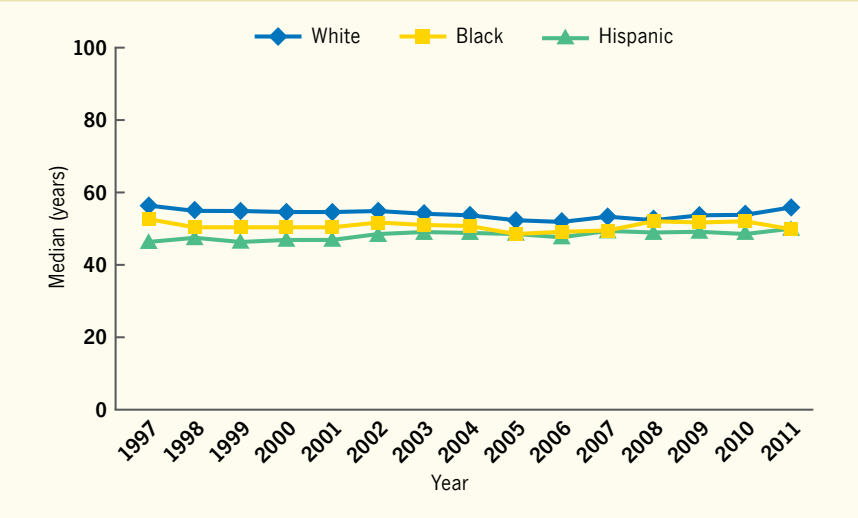
In the European Prospective Investigation into Cancer and Nutrition (EPIC), higher risk of diabetes in men compared with women was observed consistently across different European countries (10). However, this consistency was not as clearly evident in the United States population because the incidence of diabetes among men compared to women was higher in 2010 but lower in 2013, based on NHIS data. Table 13.1 summarizes the crude and age-standardized incidence of diagnosed diabetes by sex in the United States, 1993–2013 (1).

FIGURE 13.2. Estimated Percentage of Adults With Diagnosed and Undiagnosed Diabetes, by Age, U.S., 2012



SOURCE: Reference 6 and National Health and Nutrition Examination Surveys 2009–2012 estimates applied to 2012 U.S. Census data.

FIGURE 13.3. Median Age at Diagnosis of Diabetes Among Adult Incident Cases, by Race/Ethnicity, U.S., 1997–2011



Data are self-reported from adults age 18–79 years.

SOURCE: Reference 1 and National Health Interview Surveys 1997–2011

RACE AND ETHNICITY

National survey data from 2007–2009 for people age ≥20 years indicate that 7.1% of non-Hispanic whites, 8.4% of Asian Americans, 11.8% of Hispanics/Latinos, and 12.6% of non-Hispanic blacks had diagnosed diabetes (6). Thus, diabetes is approximately twice as common in non-Hispanic blacks and Hispanics as in non-Hispanic whites in the United States. Based on national data from 2011–2012, total diabetes prevalence (combining diagnosed and undiagnosed diabetes) was also found to be twice as high in Asian Americans as in non-Hispanic whites (11). Ethnic differences can be explained only in part by differences in the prevalence of obesity, behavioral risk factors, and socioeconomic status (SES). For example, higher risk observed in non-Hispanic black women compared to non-Hispanic white women from the NHANES III was attenuated when controlled for differences

in socioeconomic characteristics (12). However, this was not the case among men. In the Nurses' Health Study (NHS), self-reported Asian, Hispanic, and black ethnicity were each associated with higher diabetes risk compared to whites after adjustment for differences in age, body mass index (BMI), family history of diabetes, and lifestyle risk factors (i.e., alcohol consumption, smoking, physical activity, and diet) (13). In the Multiethnic Cohort Study of volunteers living in Hawaii and California, diabetes risk for Japanese Americans and Pacific Islanders was about two to three times higher compared to whites, and these associations remained after adjustment for BMI and education (14). In addition, diabetes prevalence varies widely among countries worldwide (Figure 13.4) (9). The contributions of genetics, migration, and acculturation on type 2 diabetes risk are discussed later in this chapter.

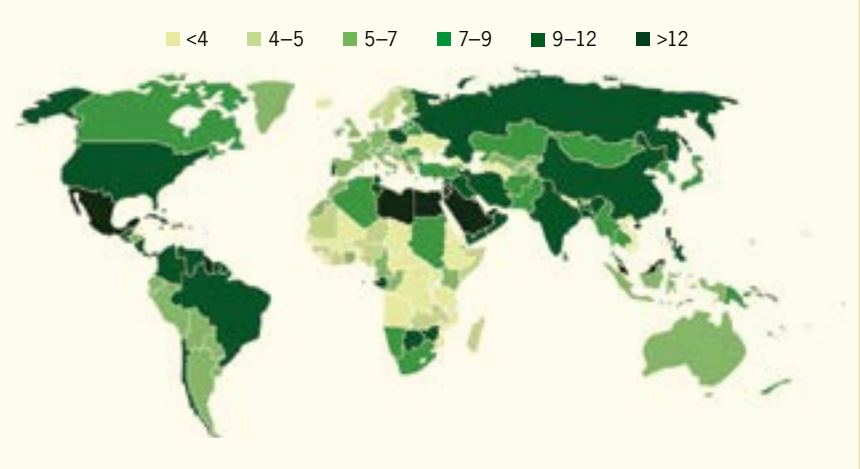
TABLE 13.1. Crude and Age-Standardized Incidence of Diagnosed Diabetes Per 1,000 Population Age 18–79 Years, by Sex, U.S., 1993–2013

	INCIDENCE (STANDARD ERROR)			
	Men		Women	
YEAR	Crude	Age-Standardized	Crude	Age-Standardized
1993	3.8 (0.5)	4.2 (0.5)	4.8 (0.5)	4.9 (0.5)
1994	4.1 (0.5)	4.6 (0.6)	5.4 (0.5)	5.5 (0.6)
1995	3.7 (0.5)	4.1 (0.6)	5.2 (0.6)	5.3 (0.6)
1996	4.0 (0.5)	4.4 (0.6)	4.9 (0.5)	5.0 (0.5)
1997	4.6 (0.5)	5.0 (0.5)	4.4 (0.4)	4.5 (0.4)
1998	5.0 (0.3)	5.3 (0.4)	5.2 (0.3)	5.3 (0.3)
1999	5.5 (0.4)	5.9 (0.4)	5.2 (0.3)	5.3 (0.3)
2000	6.1 (0.4)	6.5 (0.4)	5.9 (0.3)	6.0 (0.3)
2001	6.9 (0.4)	7.2 (0.5)	6.2 (0.4)	6.3 (0.4)
2002	7.1 (0.5)	7.4 (0.5)	6.8 (0.4)	6.8 (0.4)
2003	7.1 (0.5)	7.4 (0.5)	7.0 (0.4)	7.0 (0.4)
2004	7.0 (0.5)	7.3 (0.5)	7.5 (0.4)	7.4 (0.4)
2005	7.3 (0.5)	7.4 (0.5)	7.8 (0.5)	7.7 (0.4)
2006	7.8 (0.5)	7.9 (0.5)	7.7 (0.5)	7.6 (0.5)
2007	8.1 (0.6)	8.2 (0.6)	8.1 (0.5)	7.9 (0.5)
2008	9.2 (0.7)	9.1 (0.7)	8.2 (0.7)	7.9 (0.6)
2009	9.2 (0.7)	9.1 (0.7)	8.1 (0.6)	7.8 (0.6)
2010	8.7 (0.7)	8.6 (0.6)	8.0 (0.6)	7.7 (0.6)
2011	7.1 (0.4)	7.0 (0.4)	7.9 (0.5)	7.5 (0.5)
2012	6.6 (0.4)	6.4 (0.4)	8.0 (0.5)	7.6 (0.5)
2013	6.6 (0.5)	6.4 (0.5)	7.5 (0.6)	7.2 (0.5)

Data are age-standardized to the 2000 U.S. Standard Population.

SOURCE: Reference 1 and National Health Interview Surveys 1993–2013

FIGURE 13.4. Global Prevalence of Diabetes, International Diabetes Federation, 2011



Comparative prevalence (%) of diabetes is reported.

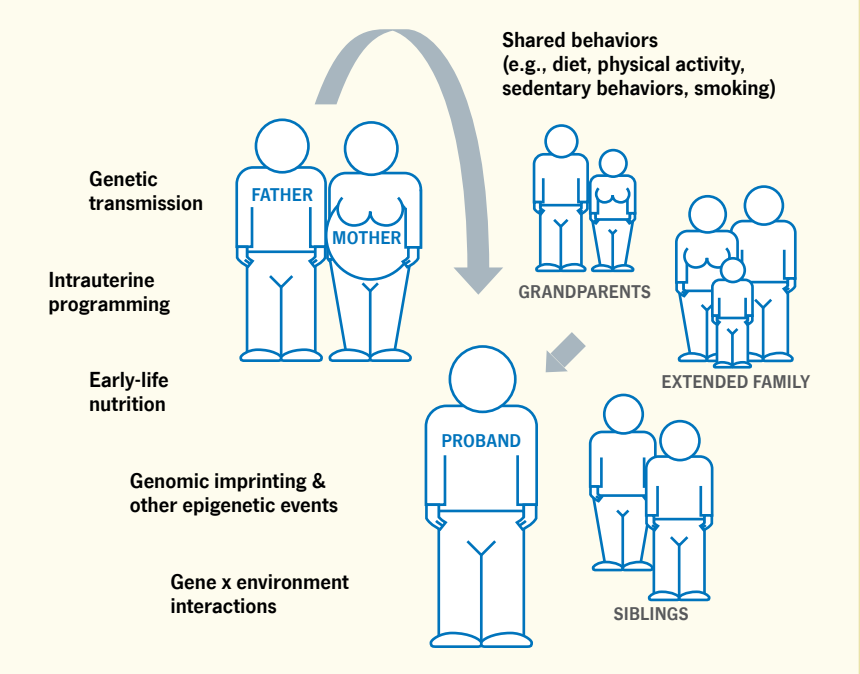
SOURCE: Reference 9, copyright © 2011 International Diabetes Federation, reprinted with permission

GENETIC RISK FACTORS

Detailed information on genetic risk factors is provided in Chapter 14 *Genetics of Type 2 Diabetes*. This section briefly summarizes genetics in the development of type 2 diabetes and discusses its interaction with environmental risk factors. A family history of diabetes has been linked with increased risk for type 2 diabetes (15). The concordance rates of type 2 diabetes are about 34%–58% in monozygotic twins and 12%–20% in dizygotic twins (16,17). Early efforts to identify genetic variants for type 2 diabetes heritability in epidemiologic studies involved genome-wide linkage and candidate gene approaches. With the introduction of studies incorporating high-throughput, parallel genotyping technologies, including genome-wide association studies (GWAS), the field has rapidly advanced, identifying and replicating multiple novel loci associated with type 2 diabetes (3,15,18,19,20,21,22,23,24,25,26,27,28), as discussed further in Chapter 14. Many common genetic variants predisposing to type 2 diabetes uncovered initially by GWAS have been located near genes implicated in beta cell function (29). Subsequently, genetic variants implicated in insulin resistance pathways were uncovered by accounting for differences in BMI (30).

In addition to genetic risk for type 2 diabetes, family members often share nongenetic environmental risk factors that contribute to risk for diabetes (Figure 13.5) (31).

FIGURE 13.5. Diabetes Risk in the Proband and the Complex Interplay Between Genes, Shared Environment, Shared Behaviors, and Epigenetic Effects



SOURCE: Reference 31, copyright © 2010 American Diabetes Association, reprinted with permission from the American Diabetes Association

GENE-ENVIRONMENT INTERACTIONS

Individuals vary in their susceptibility to environmental risk factors. These genetic variations may influence modifiable risk factors for type 2 diabetes. Therefore, understanding gene-environment interactions has the potential to benefit strategies for the prevention of type 2 diabetes.

Gene-environment interaction studies experience methodologic challenges when investigating small effects of common gene variants, which require a large sample size to uncover (32). Collaborative efforts have been made to address these challenges, including the Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) consortium. The consortium conducted a meta-analysis of 14 cohort studies comprising about 48,000 participants of European descent and reported a nominal interaction between *GCKR* (rs780094) variant and whole grain intake on fasting insulin (p=0.006) (33). The CHARGE consortium used a similar approach to report that higher total zinc intake may attenuate the glucose-raising effects of the zinc transporter variant, *SLC30A8* (rs11558471) (34). Constructing a risk score is another approach that has been used to investigate gene-environment interactions. In a nested case-control study within the Health Professionals Follow-up Study (HPFS) and the NHS, a genetic risk score was calculated on the basis of 10 polymorphisms in nine loci (35). The association between genetic score and type 2 diabetes was strengthened with the BMI increase in this study of individuals of European descent (35). In an intervention trial, the Diabetes Prevention Program (36), a high genetic risk score was associated with increased risk of developing type 2 diabetes, but a lifestyle intervention attenuated this risk.

Although it is questionable whether information on gene-environment interactions improves the prediction of type 2 diabetes (37), better understanding of genetic susceptibility to the disease and its influence on environmental risk factors may assist in developing future prevention strategies for type 2 diabetes.

BEHAVIORAL AND LIFESTYLE RISK FACTORS

The type 2 diabetes epidemic has been attributed to urbanization and environmental transition leading to sedentary behavior and overnutrition (38). These environmental transformations include work pattern changes from heavy labor to sedentary, increased computerization and mechanization, and improved public transportation accompanied by easy access to fast foods and other energy-dense and nutrient-poor foods (38). The lifestyle characteristics of people with type 2 diabetes are described in Chapter 10 *Lifestyle Characteristics Among People With Diabetes and Prediabetes*.

This section presents information on behavioral and lifestyle factors in relation to the risk of developing type 2 diabetes.

NUTRITION

Dietary intake has been suspected as a major lifestyle risk factor for type 2 diabetes for a long time, but evidence from prospective studies evaluating diet in relation to the incidence of diabetes has vastly accumulated since the 1990s (2). These studies investigated the roles of nutrients, foods, and dietary patterns on type 2 diabetes progression.

Dietary Carbohydrate and Fiber

Several prospective observational studies investigated the relation between total carbohydrate intake (expressed as the proportion of carbohydrate intake of total energy intake or as energy-adjusted intake quantity in grams per day) and risk of type 2 diabetes. The majority of these studies suggested that the relative carbohydrate proportion of the diet does not influence the risk of diabetes (39). A few prospective cohort studies also investigated specific nutrient substitutions with heterogeneous results. For example, no significant relation of higher carbohydrate intake at the expense of protein with risk of diabetes was observed in the NHS II (40), but such an isocaloric exchange was associated with reduced risk in the EPIC-Potsdam Study (41).

A meta-analysis of eight prospective cohort studies, including five from the United States and one each from Finland, Australia, and Germany, demonstrated an inverse association of the intake of dietary fiber from cereal products with risk of type 2 diabetes (42). Participants with higher intake had a relative risk (RR) of 0.67 (95% confidence interval [CI] 0.62–0.72) comparing highest versus lowest intake categories (42). In contrast to cereal fiber, total fiber or fiber from fruits or vegetables was not associated with diabetes risk (42). The protective effect of cereal fiber was confirmed by subsequent cohort studies (43,44), although some prospective studies did not detect a protective effect of cereal fiber (45,46).

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 (47), whereas the glycemic load is the cross-product of the glycemic index of a specific food and the amount of carbohydrates, which therefore reflects on both quality and quantity of the carbohydrates. The associations of glycemic index and load with risk of diabetes have been evaluated by a number of prospective studies. Meta-analyses of these studies demonstrated that diets with low average glycemic index and glycemic load might be associated with reduced risk for diabetes compared with high glycemic index and load (48,49,50). These associations appear to be independent of the amount of dietary fiber in the diet.

Dietary Fat

While higher total fat intake has been hypothesized to contribute to diabetes directly by inducing insulin resistance and indirectly by promoting weight gain, metabolic studies in humans do not support the idea that high-fat diets have a detrimental effect on insulin sensitivity (51). In most observational prospective studies, total fat intake was not associated with diabetes risk (Table 13.2). Strong evidence also comes from the large-scale, randomized Women's Health Initiative (WHI). The incidence of treated diabetes was not different among women who consumed a low-fat diet (24% energy from fat) compared to women who consumed a standard U.S. diet (35% energy from fat) (RR 0.96, 95% CI 0.90–1.03) (52). The specific type of fat may be more important than the total intake. Prospective studies suggest that diets that favor plant fats over animal fats are advantageous (53,54).

Whether changing the relative proportions of different fatty acid subgroups is related to diabetes risk remains a matter of debate. A higher intake of polyunsaturated fatty acids (PUFA) was related to lower diabetes risk in the NHS (55) and the Iowa Women's Study (56). Also, exchanging saturated fatty acids with PUFA was related to lower risk in some studies (53). However, the relationship between long-chain n-3 PUFA and diabetes risk has been inconsistent: a meta-analysis including 16 prospective cohorts with 440,873 participants and 21,512 cases of incident diabetes reported a combined relative risk of 1.04 (95% CI 0.97–1.10), comparing the highest versus lowest intake categories (57).

Micronutrients

Emerging evidence supports the associations of specific minerals with type 2 diabetes risk using assessments of dietary intake and/or biomarkers. A meta-analysis of four prospective studies conducted in the United States demonstrated that higher heme-iron intake was associated with increased risk of developing type 2 diabetes (RR 1.31, 95% CI 1.21–1.43), comparing the highest and lowest intake categories (58). In the same meta-analysis paper, higher iron stores, reflected by elevated ferritin concentrations, were associated with increased risk of developing type 2 diabetes (RR 1.66, 95% CI 1.15–2.39).

A meta-analysis of five prospective studies conducted in the United States also provided evidence that magnesium intake was inversely associated with risk of developing type 2 diabetes (RR 0.78, 95% CI 0.73–0.84) (59). This association was more pronounced among participants with BMI ≥25 kg/m^2 but was not significant among those with BMI <25 kg/m^2 (59).

TABLE 13.2. Summary of Prospective Cohort Studies of Total Fat Intake and Type 2 Diabetes

STUDY (REF.)	POPULATION	RESULTS	COMMENTS
San Luis Valley Diabetes Study (273)	Follow-up 11–40 months (1984–1988); 134 men and women with impaired glucose tolerance; 20 incident cases	Participants with diabetes at study end had higher total fat intake (43.4% energy) compared to participants with impaired glucose tolerance (40.6%) or normal glucose tolerance (38.9%); p=0.02	Adjusted for age, sex, race/ethnicity
Seven Countries Study (274)	Follow-up 20 years (baseline 1958–1964); 338 men; 26 incident cases	Men with newly diagnosed diabetes at study end had higher total fat intake (41.2% energy) compared to diabetes-free men (38.7%); p=0.10	Adjusted for age, cohort
Iowa Women's Health Study (56)	Follow-up 11 years (baseline 1986); 35,988 women; 1,890 incident cases	RR for Q5 vs. Q1: 0.89 (95% CI 0.75–1.05)	Adjusted for age, total energy, waist-to-hip ratio, BMI, physical activity, smoking, alcohol, education, marital status, residential area, hormone replacement therapy, dietary magnesium, cereal fiber
Nurses' Health Study (55)	Follow-up 14 years (baseline 1980); 84,204 women; 2,507 cases	RR for Q5 vs. Q1: 0.97 (95% CI 0.85–1.11)	Adjusted for age, time period, BMI, smoking, family history, alcohol, physical activity, percentage protein intake, total energy intake, dietary cholesterol
Nurses' Health Study (275)	Follow-up 20 years (baseline 1980); 85,059 women; 4,670 cases	RR for decile 10 vs. decile 1: 0.91 (95% CI 0.79–1.06)	Adjusted for age, BMI, smoking, postmenopausal hormone use, physical activity, alcohol intake, family history, protein intake, total calories
Kuopio Ischaemic Heart Disease Risk Factor Study (276)	Follow-up 4 years (baseline 1984–1989); 895 men; 56 cases with impaired fasting glucose, 34 diabetes cases	Men with diabetes (34.7% energy) or impaired fasting glucose (34.2%) at study end had no different total fat intake at baseline than men with normal glucose tolerance (33.7%); p=0.49.	Unadjusted
Health Professionals Follow-up Study (277)	Follow-up 12 years (baseline 1986); 42,504 men; 1,321 cases	RR for Q5 vs. Q1: 0.97 (95% CI 0.79–1.18)	Adjusted for age, total energy intake, time period, physical activity, smoking, alcohol, hypercholesterolemia, hypertension, family history, intake of cereal fiber and magnesium, BMI
EPIC-Norfolk Study (278)	Follow-up 3–7 years (baseline 1993–1997); 23,631 men and women; 414 cases	OR per 1-standard deviation change: 1.01 (95% CI 0.99–1.03)	Adjusted only for total energy intake
EPIC-Potsdam Study (41)	Follow-up 7 years (1994–1998); 25,067 men and women; 844 cases	Isoenergetic substitution of 5% energy with carbohydrates for fat: RR >1, but nonsignificant	Adjusted for age, sex, education, occupational activity, sport activity, cycling, smoking, alcohol intake, total energy intake, fiber intake, magnesium intake, protein intake, PUFA:SFA ratio, MUFA:SFA ratio
Melbourne Collaborative Cohort Study (279)	Follow-up 4 years (baseline 1990–1994); 3,737 men and women; 346 cases	RR for Q5 vs. Q1: 1.12 (95% CI 0.76–1.73)	Adjusted for age, sex, country of birth, family history of diabetes, physical activity, alcohol intake, BMI, waist-to-hip ratio

BMI, body mass index; CI, confidence interval; EPIC, European Prospective Investigation into Cancer and Nutrition; MUFA, monounsaturated fatty acids; OR, odds ratio; PUFA, polyunsaturated fatty acids; Q, quintile; RR, relative risk; SFA, saturated fatty acids.

SOURCE: References are listed within the table.

Vitamin D is classically known for its role in bone metabolism and regulation of calcium, and a potential role for vitamin D in glucose metabolism has also come to light. In the Framingham Offspring Study, higher levels of 25-OH vitamin D were associated with lower incidence of type 2 diabetes after accounting for potential confounders (60). This protective effect was also reported in the NHS, but mainly in the upper levels of circulating 25-OH vitamin D and with a stronger effect in overweight/obese women (61). In contrast, 25-OH vitamin D levels were not associated with type 2 diabetes incidence in the WHI, despite analysis of various cutoffs and subgroups (62). In addition, intervention trials investigating the impact of vitamin D supplementation have been mainly inconclusive, leaving the question about the link between vitamin D status and risk of type 2 diabetes unresolved (63).

As for the proposed mechanism, it is unclear whether vitamin D influences beta cell function and/or insulin resistance in type 2 diabetes pathophysiology. Vitamin D may be a marker of an overall healthy lifestyle, such as frequent outdoor physical activities that expose an individual to sunlight. In addition, nutrient-based associations with type 2 diabetes might be confounded by other unaccounted nutrients in food. For example, dairy products are not only rich in vitamin D, but also macronutrients and many other micronutrients (e.g., magnesium), which have been associated with diabetes risk as previously discussed (59).

TABLE 13.3. Summary of Meta-Analyses of Prospective Cohort Studies on Food and Beverage Intake and Type 2 Diabetes

FOOD (REF.)	POPULATIONS	RELATIVE RISK (95% CI)	COMMENTS
Processed red meat (67)	8 cohort studies	1.51 (1.25–1.83) per 50 g/d	Each cohort study consistently had relative risk above 1.00.
Unprocessed red meat (67)	9 cohort studies; 442,101 participants; 28,228 diabetes cases	1.19 (1.04–1.37) per 100 g/d	
Fish/seafood (57)	13 cohort studies; 481,489 participants; 20,830 diabetes cases	1.12 (0.94–1.34) per 100 g/d	Regional differences were observed (p for interaction=0.007): the associations were positive in North America and Europe, but inverse in Asia.
White rice (66)	7 cohort studies; 352,384 participants; 13,284 diabetes cases	1.11 (1.08–1.14) per each serving/d	Stronger associations in Asian populations were observed (p for interaction=0.038).
Green leafy vegetables (70)	4 cohort studies; 169,807 participants; 7,422 diabetes cases	0.86 (0.77–0.97) comparing extreme categories	
Green leafy vegetables (71)	Case-cohort, pooled analysis of five European cohorts; 18,955 diabetes cases	0.84 (0.74–0.94) comparing extreme categories	Total fruits and vegetables had a weaker overall effect: RR 0.93 (95% CI 0.87–1.00).
Dairy products (69)	6 cohort studies	0.86 (0.79–0.92) comparing extreme categories	Yogurt was associated with diabetes risk: RR 0.83 (95% CI 0.74–0.93).
Whole grains (65)	10 cohort studies	0.68 (0.58–0.81) per 3 servings/d	Inverse associations were observed for subtypes, including whole grain bread, whole grain cereals, wheat bran, and brown rice.
Sugar-sweetened beverages (81)	8 cohort studies; 310,819 participants; 15,043 diabetes cases	1.26 (1.12–1.41) comparing extreme categories	Sugar-sweetened beverages are mostly sweetened by high fructose corn syrup in the United States, while they are mostly sweetened by sucrose in Europe.
Sugar-sweetened beverages (82)	Case-cohort, pooled analysis of eight European cohorts; 11,684 diabetes cases	1.18 (1.06–1.32) per 336 g (12 oz)/d	
Alcohol (86)	20 cohort studies; 477,200 participants; 12,556 diabetes cases	0.60 (0.52–0.69) at 24 g/d for women 0.87 (0.76–1.00) at 22 g/d for men compared to abstainers	A U-shape relationship was observed: moderate consumption was the most beneficial.
Decaffeinated coffee (79)	11 cohort studies	0.80 (0.70–0.91) comparing extreme categories	
Total coffee (79)	28 cohort studies; 1,109,272 participants; 45,335 diabetes cases	0.70 (0.65–0.75) comparing extreme categories	Inverse associations were in a dose-response manner for both caffeinated and decaffeinated coffee consumption.

CI, confidence interval; RR, relative risk.

SOURCE: Reference 2, reprinted from The Lancet copyright © 2014, with permission from Elsevier; references are listed within the table for individual food items.

Food Items and Groups

Intake of several individual food items or food groups is linked to diabetes risk. The evidence for these associations has been summarized by a number of meta-analyses (Table 13.3) (2). Similar to cereal fiber, intake of whole grains has been associated consistently with lower diabetes risk in prospective studies (64,65), even after adjustment for potential confounders, including obesity. Conversely, higher intake of white rice, which is a processed grain, was associated with increased risk of developing type 2 diabetes (66), especially among Asian populations with markedly higher amounts of white rice consumption (RR 1.55, 95% CI 1.20–2.01). Frequent consumption of red and processed meats was also associated with higher diabetes risk in prospective cohort studies (67).

The combined analysis of 13 prospective studies (six from the United States, three from Asian countries, and two from European countries) has shown that fish and/or seafood consumption was not significantly associated with increased risk of developing type 2 diabetes (57). Interestingly, differences in the direction of the association between fish/seafood consumption and type 2 diabetes risk were observed among geographic regions (p-interaction=0.007) (57). Higher fish/seafood consumption was associated with increased risk of developing type 2 diabetes in North America and Europe (RR 1.38, 95% CI 1.13–1.70), while it was associated with decreased risk in Asia (RR 0.89, 95% CI 0.81–0.98) (57). Similar regional variation was reported by a meta-analysis of fish consumption and type 2 diabetes risk (68). This regional variation might be explained by varying types of fish consumed and cooking preparation methods used within different geographic locations, although further investigation is needed to confirm this hypothesis.

Dairy consumption has been associated with moderately lower type 2 diabetes risk (69), and the benefits of yogurt seem to be more consistent than other types of dairy products.

Although the total intake of fruit and vegetables was not associated with risk of type 2 diabetes, higher green leafy vegetable intake was associated with reduced risk of developing type 2 diabetes (70,71). Further, consumption of anthocyanin-rich foods, particularly blueberries and apples/pears, was associated with lower risk of type 2 diabetes (72).

Consumption of nuts, which are high in PUFA and monounsaturated fatty acid, has been linked with lower risk of diabetes (73). However, few prospective studies have directly evaluated this hypothesis to date, with available data providing inconsistent results. For example, higher nut consumption was associated with reduced risk for type 2 diabetes in the NHS (RR comparing extreme categories 0.73, 95% CI 0.60–0.89) (74), but this significant association was not observed in the Physicians' Health Study (75). In the PREvención con DIeta MEDiterránea (PREDIMED) trial, supplementation with nuts significantly reduced incidence of type 2 diabetes (76). However, the nuts were supplemented in the context of the Mediterranean diet in this trial, and therefore, it is difficult to conclude that the beneficial results were solely due to nut consumption.

Coffee

Coffee consumption has been associated with lower diabetes risk in a number of prospective studies (Table 13.3). Meta-analyses clearly indicated a potential preventive role of coffee consumption (77,78,79). In addition, both caffeinated and decaffeinated coffee consumptions were associated with lower diabetes risk (79). While the active components of coffee that offer protection from diabetes have not been identified, caffeine does not appear to be a factor, and residual confounding is unlikely to explain the reduced risk observed among coffee consumers. Regular coffee consumption is generally associated with unfavorable lifestyle habits in most populations, and therefore, coffee consumption is more likely related to increased risk if confounded.

Sugar-Sweetened Beverages

About 20% of young adults (age 20–34 years) and 12% of adults (age ≥35 years) in the United States consume ≥500 calories per day from sugar-sweetened beverages based on NHANES 2007–2008 data (80). Prospective studies suggest that consuming sugar-sweetened beverages increases the risk of developing type 2 diabetes (Table 13.3) (81,82). Sugar-sweetened beverages, such as soft drinks, fruit drinks, and energy and vitamin water drinks, contain naturally derived caloric sweeteners, including sucrose, high fructose corn syrup, and/or fruit juice concentrates. An analysis suggested that substituting plain water, coffee, or tea for sugar-sweetened beverages was associated with lower risk of diabetes (83). The intake of sugar-sweetened beverages may contribute to diabetes risk by altering glucose metabolism when large amounts of rapidly absorbable carbohydrates are consumed and by promoting weight gain by incomplete compensation of liquid calories resulting in increased total caloric intake (84). Interaction between genetic predisposition and sugar-sweetened beverage intake was investigated in relation to BMI using a genetic predisposition score calculated based on 32 BMI-associated loci (85). Higher sugar-sweetened beverage intake was associated with more pronounced genetic predisposition to increased BMI and risk for obesity.

Alcohol Consumption

A U-shaped relation between alcohol consumption and type 2 diabetes has been reported from observational studies (86). Based on a meta-analysis of 20 prospective cohort studies (nine from the United States, six from Europe, three from Asia, and two from Australia), the amount of alcohol consumption was most protective of diabetes at 24 g per day among women and at 22 g per day among men, equating to approximately one and one-half U.S. standard drinks per day (Table 13.3) (86). However, risk of diabetes was particularly high at an alcohol consumption level above 50 g per day for women and 60 g per day for men, approximately four U.S. standard drinks per day (86). Therefore, the authors concluded that moderate alcohol consumption is protective against type 2 diabetes (86). However, the interpretation of the U-shape association must be taken with caution, because it might be confounded by some abstainers who might be "sick quitters." In a longitudinal analysis of HPFS participants, increasing alcohol consumption over time was associated with lower risk of type 2 diabetes among initially rare and light drinkers (87). In addition, moderate alcohol consumption has been shown to attenuate the positive association between dietary glycemic load and risk of diabetes (88). EPIC-InterAct study investigators reported that the association of alcohol consumption with type 2 diabetes might be stronger among women (89). Further, alcohol consumption was more strongly associated with reduced risk for type 2 diabetes among overweight compared with normal weight men and women (89). Therefore, body fatness may impact the relationship between alcohol consumption and type 2 diabetes risk, although further investigation is needed to confirm the role of body fat in the observed link between alcohol and diabetes. In terms of alcohol types, wine consumption might be most strongly associated with reduced risk for type 2 diabetes (89,90).

Dietary Patterns

Instead of considering individual food items in isolation, the application of dietary pattern techniques has revealed a variety of dietary patterns related to diabetes risk. The strongest evidence for beneficial effects of a particular dietary pattern has been accumulated for the Mediterranean diet, which is characterized by high consumption of minimally processed plant-based foods; olive oil as the principal source of fat; low-to-moderate consumption of dairy products, fish, and poultry; low consumption of red meat; and low-to-moderate consumption

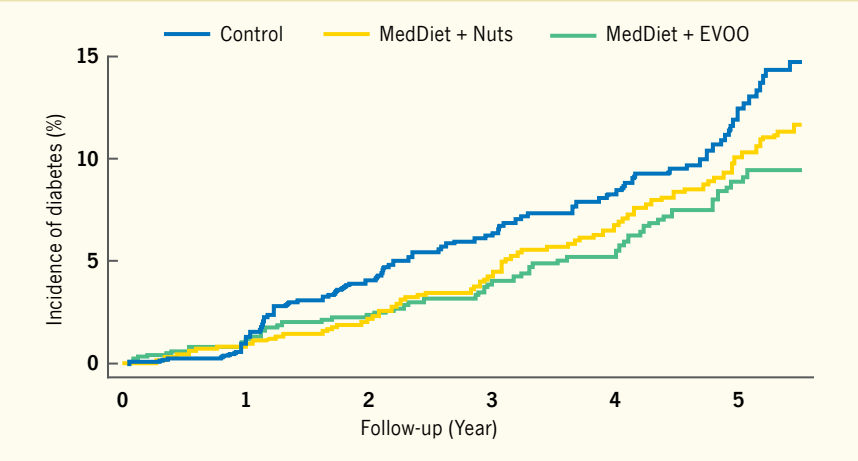
of wine with meals. Conclusions from prospective cohort studies (91,92,93) are supported by results of the PREDIMED randomized trial from Spain (Figure 13.6) (76,94). In this trial, after a median 4.1-year follow-up, participants assigned to a Mediterranean diet without calorie-restriction had a significant diabetes risk reduction with extra-virgin olive oil supplementation (hazard ratio [HR] 0.60, 95% CI 0.43–0.85) and a nonsignificant risk reduction with mixed nut supplementation (HR 0.82, 95% CI 0.61–1.10) compared to a low-fat control diet with adjustment for potential confounders (94). Studies using exploratory methods to define dietary patterns further support the notion that dietary patterns that favor fruits, vegetables, whole grains, and vegetable fats at the expense of red meats, refined grains, and sugared soft drinks reduce the risk of type 2 diabetes (95,96,97,98,99), while "Westernized" diets rich in red and processed meats, sugary drinks, and refined grains are related to higher diabetes risk (100,101). In addition, an analysis in the HPFS indicated that eating patterns, such as breakfast omission, were associated with increased risk of type 2 diabetes in men (102).

PHYSICAL INACTIVITY

The prevalence of leisure-time physical inactivity is increasing rapidly in the United States, as illustrated in Figure 13.7 (1). Sedentary behaviors, including increased screen time, are a risk factor for type 2 diabetes. In a meta-analysis of four prospective cohort studies, including three studies from the United States and one from Germany, higher television viewing time was associated with increased risk for type 2 diabetes (RR per 2 hours 1.20, 95% CI 1.14–1.27) (103). Based on a worldwide estimate, physical inactivity, defined as insufficient physical activity to meet present global recommendations by the World Health Organization 2010 (104), is responsible for 7% (95% CI 3.9%–9.6%) of the burden of type 2 diabetes (105).

Physical activity of moderate intensity can reduce the risk of developing type 2 diabetes based on a meta-analysis of 10

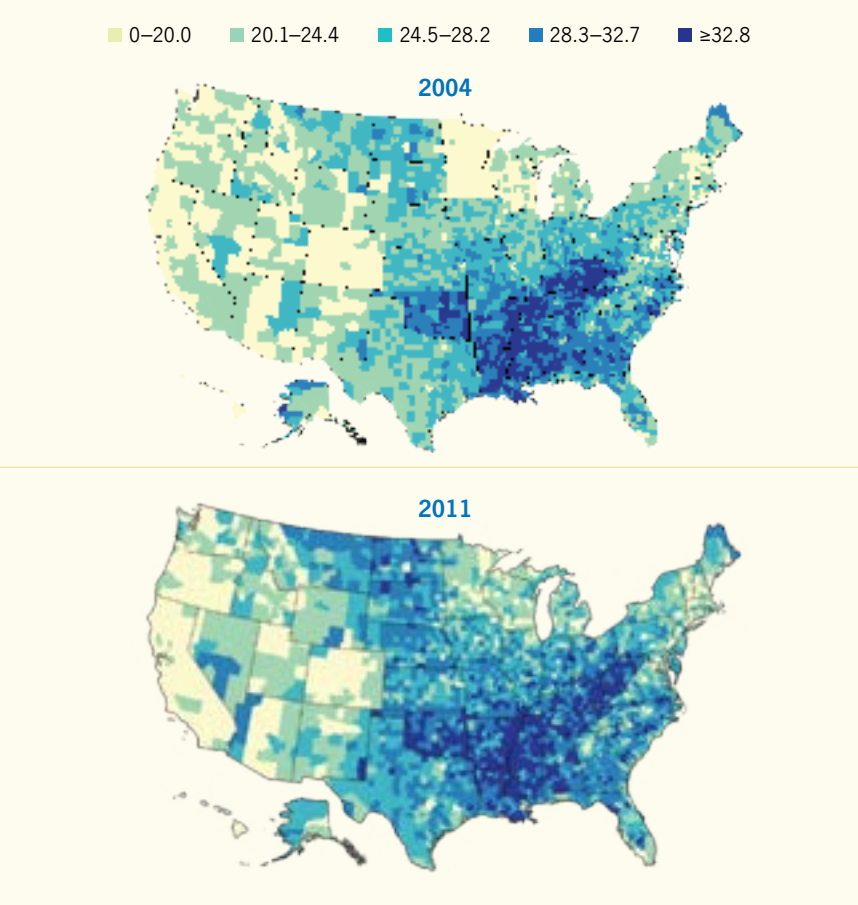
FIGURE 13.6. Cumulative Incidence of Diabetes by Group of Intervention, PREDIMED, 2003–2009



Nelson-Aalen curves are shown with the outcome of new-onset diabetes by exposure to each MedDiet intervention versus the control diet. From 2003 to 2009, participants were enrolled in the trial. EVOO, extra virgin olive oil; PREDIMED, Prevención con Dieta Mediterránea trial.

SOURCE: Reference 76, copyright © 2011 American Diabetes Association, reprinted with permission from the American Diabetes Association

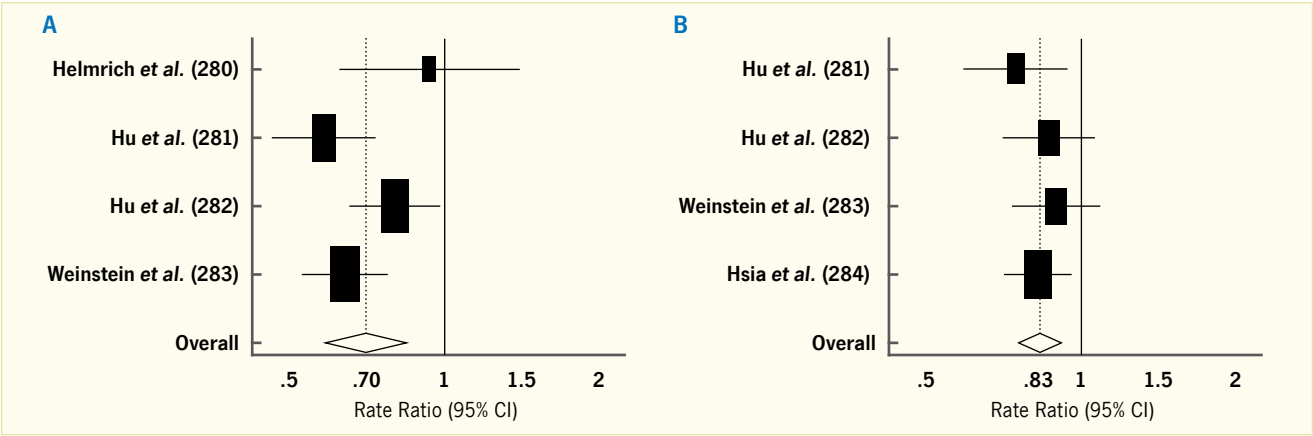
FIGURE 13.7. Age-Standardized Estimates of the Percentage of Adults Age ≥20 Years Who Are Physically Inactive, U.S., 2004 and 2011



Data are from adults age ≥20 years based on self-report by telephone survey. Physical inactivity is defined as no reported leisure-time physical activity. Rates were age adjusted by calculating age-specific rates for the following three age groups: 20–44, 45–64, and ≥65 years. A weighted sum based on the distribution of these three age groups from the 2000 Census was then used to standardize the rates by age using the weights 0.52, 0.31, and 0.17, respectively.

SOURCE: Reference 1 and Behavioral Risk Factor Surveillance System 2004 and 2011

FIGURE 13.8. Relative Risks for Walking and Incidence of Type 2 Diabetes for Individual Cohort Studies and All Studies Combined, (A) Without and (B) With Adjustment for Body Mass Index



Regular walking is defined as ≥2.5 hours per week of brisk walking. CI, confidence interval.

SOURCE: Reference 106, copyright © 2007 American Diabetes Association, reprinted with permission from the American Diabetes Association; references for individual studies are listed within the figure.

prospective cohort studies, including one from Japan, three from European countries, and the others from the United States (106). Regular walking, defined as ≥2.5 hours per week of brisk walking, was associated with reduced risk for type 2 diabetes compared to almost no walking (RR 0.70, 95% CI 0.58–0.84) (106). This association remained significant after adjustment for BMI (Figure 13.8) (106).

Moderate to high intensity exercise is well known to have beneficial effects on type 2 diabetes prevention (107,108). In addition to aerobic exercise (e.g., brisk walking, jogging, running, bicycling, swimming, tennis, squash, and rowing), weight training has been associated with lower risk of developing type 2 diabetes (109). In the HPFS, engaging in weight training and doing aerobic exercise for ≥150 minutes per week were independently associated with reduced risk of developing type 2 diabetes by 34% (95% CI 7%–54%) and 52% (95% CI 45%–58%), respectively (109). These independent effects of endurance and resistance trainings may be explained by the involvement of distinctive pathways. Aerobic exercise increases the mitochondrial density and oxidative enzyme activity, improving fatty acid oxidation, and stimulates insulin-independent, as well as insulin-dependent, skeletal muscle glucose uptake. Resistance training increases the skeletal muscle mass and glycolytic capacity, enhancing glucose uptake (110).

OBESITY

The prevalence of obesity in the United States increased considerably from 1994 to 2010, as illustrated in Figure 13.9 (1). Excessive body fat is the single largest risk factor for type 2 diabetes. The diabetes risk associated with excessive body fat, measured by BMI (the ratio of body weight in kilograms to squared height in meters) or anthropometric indicators, such as a 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 25–29.9 kg/m^2, and obesity ≥30 kg/m^2) are associated with a stepwise increase in diabetes risk. However, diabetes risk increases even within the normal body weight range. In the NHS, the relative risk of diabetes among women with BMI 23.0–24.9 kg/m^2 was 2.67 (95% CI 2.13–3.34) compared to women with BMI <23.0 kg/m^2 (111). Also, the majority of diabetes cases develop in individuals at the normal weight and overweight ranges, not among obese individuals (112).

Duration of Obesity

In addition to the level of overweight and obesity, longer duration of retaining high body weight is also an important risk factor for type 2 diabetes. Several prospective cohort studies reported an increased risk with longer duration of obesity, independent of the BMI attained at baseline (113,114,115,116). The relative risk per additional 2-year duration of obesity was 1.11 (95% CI 1.05–1.16) among men and 1.06 (95% CI 1.02–1.11) among women in the Framingham Heart Study (FHS) after adjustment for age at the onset of obesity (113). In the EPIC-Potsdam Study, weight gain during early adulthood age 25–40 years was more strongly associated with diabetes risk (RR 1.25, 95% CI 1.21–1.30 in men and RR 1.24, 95% CI 1.20–1.27 in women) compared with weight gain during later adulthood age 40–55 years (RR 1.13, 95% CI 1.10–1.16 in men and RR 1.11, 95% CI 1.08–1.14 in women) (117).

Body Fat Distribution

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 from various geographic regions, including the United States, Europe, and Asia, suggested that the relative risk associated with a higher waist circumference was slightly stronger than that associated with higher BMI (Table 13.4) (118). On the other hand, the association of waist-to-hip ratio with type 2 diabetes was slightly weaker compared to BMI.

These findings suggest that waist circumference is a valid alternative to BMI when assessing type 2 diabetes risk in a clinical setting or at a population level. However, the combination of BMI and waist circumference can be informative, since both

measures are independently associated with risk. Given the strong correlation between BMI and waist circumference, normal weight individuals who have abdominal obesity or vice versa are relatively uncommon. However, among overweight individuals, measuring waist circumference in addition to BMI allows for further stratification on diabetes risk. The prospective EPIC Study suggested that individuals with overweight and abdominal obesity (waist circumference ≥102 cm among men, ≥88 cm among women) have a similar risk compared to obese individuals (BMI ≥30 kg/m²) (119).

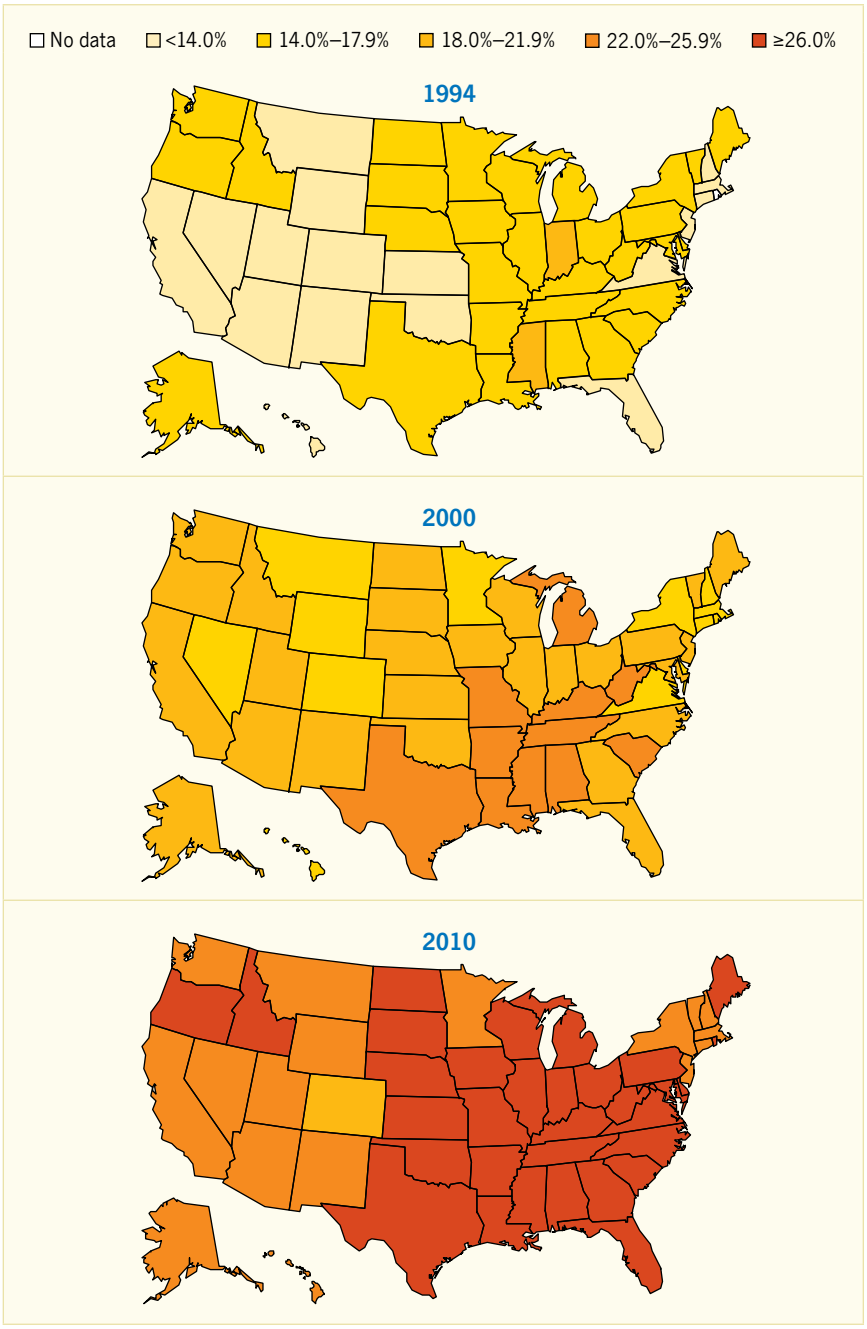
EARLY-LIFE ENVIRONMENT

With the increased prevalence of obesity at a population level, more women are experiencing metabolic abnormalities during pregnancy, such as gestational diabetes (120,121,122,123), which is described in detail in Chapter 4 *Gestational Diabetes*. Children who experienced intrauterine exposure to maternal diabetes are more likely to have large-for-gestational age birth weight (124), childhood overweight (125), and impaired glucose tolerance (IGT) in early adulthood (126). Since obesity and IGT are risk factors for gestational diabetes (124), these metabolic abnormalties in young adults likely contribute to the increasing rates of gestational diabetes (120,121,122,123) and, subsequently, type 2 diabetes. Therefore, this vicious cycle may continue to the next generation.

Intrauterine Exposure

Maternal diabetes in pregnancy has been associated with higher adiposity in offspring (125,127,128,129,130). In the multicenter, multinational Hyperglycemia and Adverse Pregnancy Outcome (HAPO) Study, as described in Chapter 4, maternal glucose intolerance between 24 and 32 weeks gestation at glucose concentrations less severe than traditional diabetes diagnostic thresholds was associated with neonatal adiposity (sum of skin folds >90th percentile or percent body fat >90th percentile) (131). Children exposed to maternal diabetes in pregnancy are more likely to have IGT later in life, as discussed in Chapter 15 *Diabetes in Youth* (126,132).

FIGURE 13.9. Age-Standardized Prevalence of Obesity Among Adults Age ≥18 Years, U.S., 1994, 2000, and 2010



Data are from adults age ≥18 years with body mass index ≥30 kg/m² based on self-report by telephone survey. Prevalence is age-standardized to the 2000 U.S. Standard Population using age categories 18–44, 45–64, 65–74, and ≥75 years.

SOURCE: Reference 1 and Behavioral Risk Factor Surveillance System 1994, 2000, 2010

TABLE 13.4. Relative Risk of Type 2 Diabetes Per Standard Deviation in Obesity Indicators, Meta-Analysis of Prospective Studies, 1985–2004

OBESITY INDICATORS	NUMBER OF STUDIES INCLUDED IN META-ANALYSIS	POOLED RELATIVE RISK (95% CONFIDENCE INTERVAL)
Waist circumference	18	1.87 (1.58–2.20)
Body mass index		1.72 (1.47–2.02)
Waist-to-hip ratio	25	1.88 (1.61–2.19)
Body mass index		1.98 (1.70–2.30)

SOURCE: Reference 118, copyright © 2007 Oxford University Press, reprinted with permission

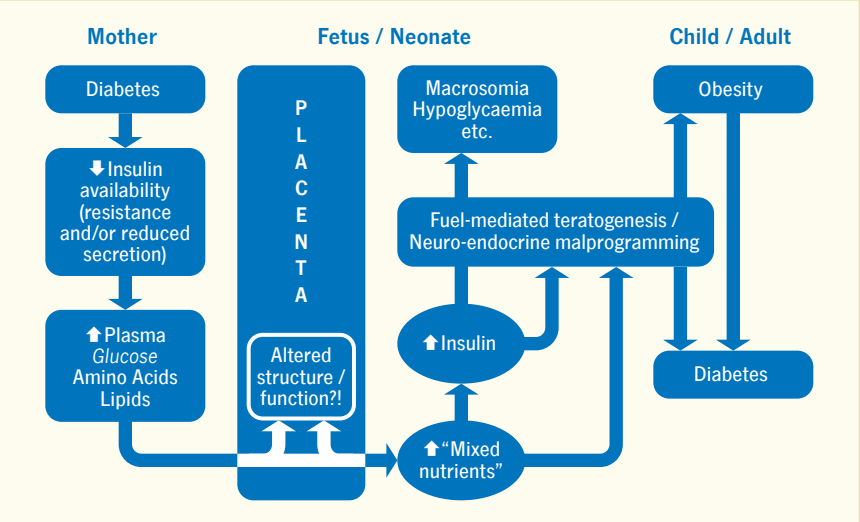
In the multiethnic SEARCH for Diabetes in Youth Case-Control Study, intrauterine exposure to maternal diabetes (odds ratio [OR] 5.7, 95% CI 2.4–13.4) and obesity (OR 2.8, 95% CI 1.5–5.2) were associated with type 2 diabetes in youth age 10–22 years (133). The adolescent and young adult offspring of mothers with type 1 diabetes had an increased occurrence of IGT, a defective insulin secretory response (134), higher adiposity, and insulin resistance (135). These studies indicate that the effect of the intrauterine and early postnatal exposure to maternal diabetes and related disorders may be related to increased diabetes risk in offspring.

Fetal exposure to famine also has been associated with increased risk of diabetes later in life. In an investigation among individuals born around the time of famine in the Netherlands during 1944–1945, prenatal exposure to famine, especially during late gestation, was associated with compromised glucose tolerance in adulthood (136). Similarly, fetal exposure to the severe Chinese famine during 1959–1961 was associated with increased risk of hyperglycemia in adulthood (137). Further, the association appears to be exacerbated by a nutritionally rich environment in later life (137). This association may be mediated through epigenetic programming (138).

Birth Weight

Meta-analyses including different populations from Europe, North America, and Asia have reported a U-shaped relation between birth weight and risk of developing type 2 diabetes later in life (139,140). Compared with a normal birth weight (2,500–4,000 g), a low birth weight <2,500 g was associated with increased risk of type 2 diabetes (OR 1.47, 95% CI 1.26–1.72), while a birth weight >4,000 g was also associated with increased risk (OR 1.36, 95% CI 1.07–1.73) (139). A low birth weight by fetal undernutrition during critical periods of development could lead to structural and physiological adaptations and increased diabetes risk later in life (141). Similarly, a positive association between birth weight and type 2 diabetes at a birth weight >4,000 g is also biologically plausible. The fetus in the environment of maternal diabetes is likely exposed to higher concentrations of glucose because glucose travels freely across the placenta from the mother to the fetus (124). In response to increased glucose, the fetus increases its own insulin production, which can cause the fetus to grow excessively, resulting in macrosomia (124) and, subsequently, glucose intolerance later in life (126), as illustrated in Figure 13.10 (142).

FIGURE 13.10. Maternal Diabetes and Perinatal Programming



SOURCE: Reference 142, copyright © 2011 Elsevier, reprinted with permission

Although adjusting for SES did not alter the reported association of birth weight with type 2 diabetes (140), the authors acknowledge that individual socioeconomic markers might not have captured all dimensions of social position across the life course. Therefore, the potential effect of residual socioeconomic confounding cannot be excluded.

Early Postnatal Exposure

Women from Prospect-EPIC who were exposed to the 1944–1945 Dutch famine between ages 0 and 21 years were at increased risk for developing type 2 diabetes later in life (143). Therefore, a short period of severe undernutrition during postnatal development may also increase type 2 diabetes risk in adulthood.

Early postnatal behavioral exposures, such as breastfeeding, may have a long-term protective effect against obesity and type 2 diabetes later in life (144,145,146). Previous meta-analyses have demonstrated that being breastfed during early life has a protective effect on obesity over a wide range of ages (144,145). In addition to childhood obesity, breastfeeding was associated with lower preprandial blood glucose and insulin concentrations among infants (146), and breastfed children and adults without diabetes had lower fasting insulin concentrations than those who were formula-fed (146). A meta-analysis of seven studies reported that being breastfed compared to formula-fed was associated with a reduced risk of type 2 diabetes later in life (OR 0.61, 95% CI 0.44–0.85) (146). However, a randomized breastfeeding promotion intervention in Belarus was not able to reduce childhood obesity assessed at age 6.5 years (147). The authors, therefore, have commented that previous findings on beneficial effects of breastfeeding on childhood obesity may have been caused by confounding and selection bias (147), including demographic, socioeconomic, educational, ethnic, cultural, and psychological factors in addition to maternal and infant physical and emotional health (148). Moreover, differences in the maternal populations might also affect child care practices, access to medical care, and child health status (148), which could subsequently influence anthropometric and adiposity status of the child. Therefore, it is difficult to extrapolate the

findings of the intervention study from Belarus to the setting of the childhood obesity epidemic in the United States. Further studies are needed to confirm these observed associations.

SOCIOECONOMIC STATUS

The socioeconomic characteristics of people with type 2 diabetes are described in Chapter 8. This section presents information on the associations of these factors with risk of type 2 diabetes.

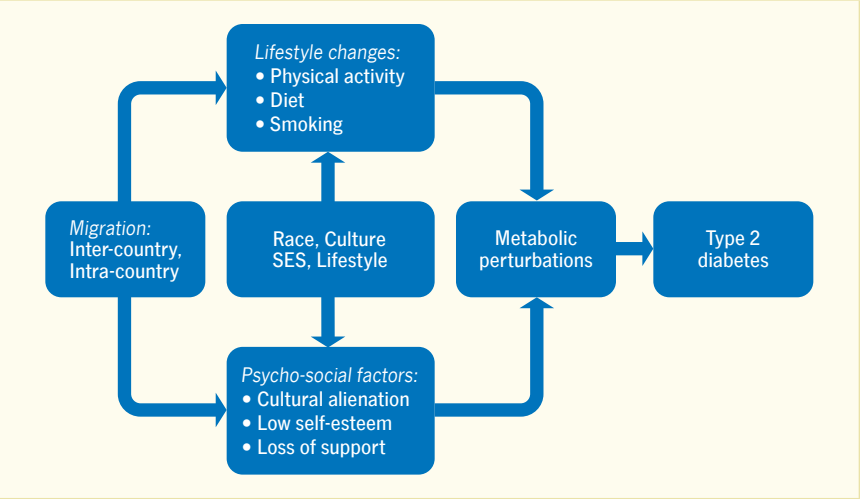
A meta-analysis of 23 prospective case-control and cohort studies from countries in Europe, Asia, Africa, and the Americas, including the United States, was conducted to summarize the overall association of SES with risk for type 2 diabetes (149). The overall risk of developing type 2 diabetes was increased among those in a lower socioeconomic position, including lower levels of education (RR 1.41, 95% CI 1.28–1.51), occupation (RR 1.31, 95% CI 1.09–1.57), and income (RR 1.40, 95% CI 1.04–1.88) (149). The associations remained consistent in the sensitivity analysis of studies from high-income countries, including the United States. Similarly, in the Black Women's Health Study (150), lower education, household income, and neighborhood SES were associated with increased risk of developing type 2 diabetes, although these associations were attenuated after adjustment for BMI.

Causal pathways of the association between SES and type 2 diabetes are not fully understood. However, SES may contribute to the development of type 2 diabetes through processes involving lack of access to health care services, healthy foods, places to exercise, and occupational opportunities, leading to unhealthy lifestyle practices (151).

MIGRATION AND ACCULTURATION

The process of urbanization and Westernization associated with inter- and intra-country migration is a contributing risk factor for type 2 diabetes (38,152). Among African descents, stepwise increases along the sociocultural gradient were observed in the prevalence of obesity (5% in Nigeria, 23% in Jamaica, and 39% in the United States) (153) and type 2 diabetes (1%, 12%, and 13%, respectively) (154). As migrants adopt the attitudes, values, customs, beliefs, and behaviors of a local culture, a process termed acculturation, their environmental risk exposure to type 2 diabetes is altered. This interplay of multiple factors after migration resulting in the metabolic syndrome and type 2 diabetes is illustrated in Figure 13.11 (155).

FIGURE 13.11. Migration and Its Impact on Type 2 Diabetes



SES, socioeconomic status.

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Acculturation is a complex and multidirectional process. For example, within the Hispanic ethnic group, the prevalence of diabetes varies by country of origin, based on NHIS 2000–2005 data (156). Acculturation among Hispanic Americans has been associated with suboptimal dietary practices and increased smoking, but also with improved physical activity levels (157). In addition, the process of acculturation within a migrant population varies in degrees of retaining their cultural roots and integrating the local mainstream culture (157). It must be also noted that the study participant selection process may not reflect general representation of the source population.

SLEEP

The association between sleep and diabetes is discussed in detail in Chapter 25 *Impact of Sleep and Circadian Disturbances on Glucose Metabolism and Type 2 Diabetes*. This section briefly summarizes studies of sleep disturbances as a risk for type 2 diabetes. Habitual sleep patterns have changed over the past several decades in the United States with an increased proportion of short sleepers (158), especially among full-time workers (159). A number of studies have reported that habitual sleep disturbances are associated with risk of developing type 2 diabetes (160).

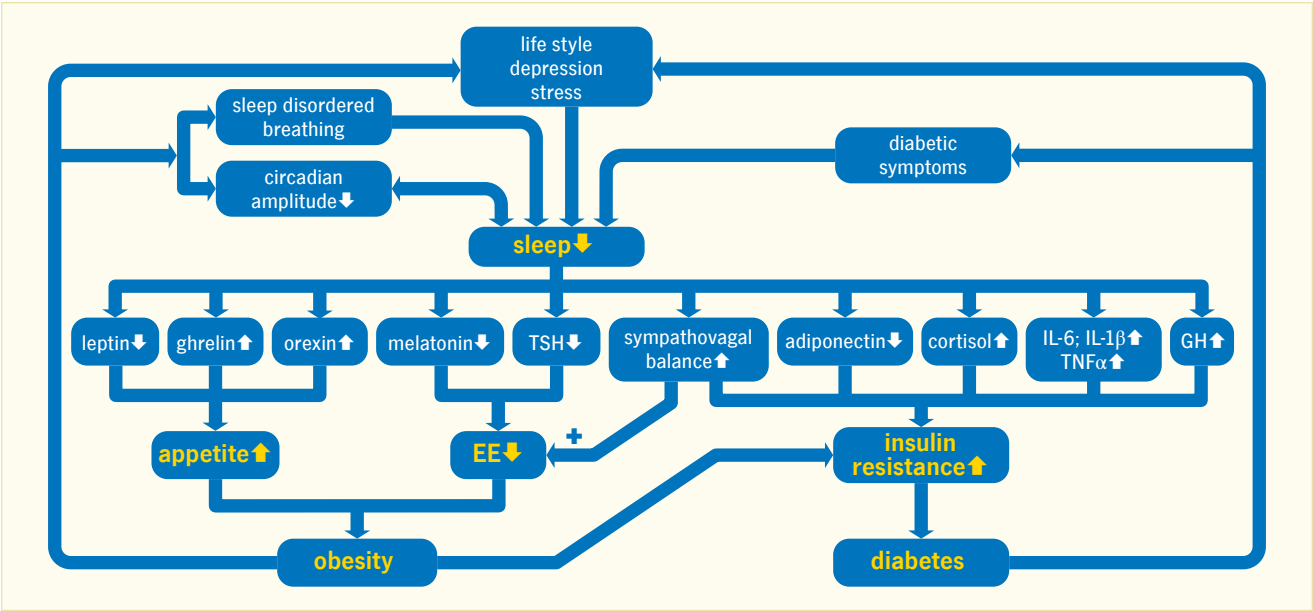
Obstructive Sleep Apnea

Obstructive sleep apnea, a sleep disorder characterized by repetitive upper airway obstructions leading to intermittent hypoxia and sleep fragmentation (161), is highly prevalent among obese adults (162). A meta-analysis of six prospective cohort studies was conducted, including 5,953 participants, 332 diabetes cases, and follow-up of 2.7–16 years (163). Moderate-to-severe obstructive sleep apnea was associated with increased risk for type 2 diabetes (RR 1.63, 95% CI 1.09–2.45) (163).

Sleep Quantity and Quality

A meta-analysis of 10 prospective cohorts of 107,756 male and female participants with a follow-up range of 4.2–32 years and 3,586 incident cases of type 2 diabetes was conducted to assess the associations of quantity and quality of sleep with the incidence of type 2 diabetes (160). Short duration of

FIGURE 13.12. Schematic Representation of Putative Pathways of Sleep Curtailment Linking With Obesity and Type 2 Diabetes



EE, energy expenditure; GH, growth hormone; IL, interleukin; TNF, tumor necrosis factor; TSH, thyroid-stimulating hormone.

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sleep (≤5–6 hours/night) was associated with increased risk of developing type 2 diabetes (RR 1.28, 95% CI 1.03–1.60), while long duration of sleep (>8–9 hours/night) was also associated with increased risk (RR 1.48, 95% CI 1.13–1.96) (160). Type 2 diabetes risk was also increased among those with difficulty in initiating (RR 1.57, 95% CI 1.25–1.97) or maintaining sleep (RR 1.84, 95% CI 1.39–2.43) (160). In addition, shift work, which disrupts the normal synchronization of the light-dark cycle and sleeping, may lead to a mismatch of circadian rhythms, triggering a cascade of endocrinologic effects (164). In the NHS I and II, performing night shift work for an extended period was associated with increased risk of developing type 2 diabetes (165).

Multiple potential mechanisms have been proposed linking sleep disturbances and type 2 diabetes, as illustrated in Figure 13.12 (166). The role of sleep curtailment has been linked to metabolic and endocrine alterations, including decreased glucose tolerance and insulin sensitivity, increased evening levels of cortisol, increased levels of ghrelin, decreased levels of leptin, and increased hunger and appetite (166,167). These changes may lead to increases in food intake and fatigue, favoring decreased energy expenditure, and subsequently to insulin resistance and type 2 diabetes. The underlying mechanism explaining the association between long sleep duration and type 2 diabetes is less clear. One possible explanation could be that psychiatric comorbidity, such as depression, might lead to spending excessive time in bed, which then leads to exacerbated sleep fragmentation and reduced daytime physical activity (168,169).

DEPRESSION AND ANTIDEPRESSANT MEDICATIONS

The psychiatric topic is discussed in detail in Chapter 33 *Psychiatric and Psychosocial Issues Among Individuals Living With Diabetes*. Briefly, the relation between depression and type 2 diabetes is bidirectional (170). In a meta-analysis of 13 studies representing 6,916 incident cases and follow-up of 3–15.6 years, baseline depression was associated with incident diabetes (RR 1.60, 95% CI 1.37–1.88), and baseline diabetes was also associated with incident depression (RR 1.15, 95% CI 1.02–1.30) (171). In addition, use of antidepressant medication was associated with increased risk of type 2 diabetes, based on results from the HPFS and the NHS and NHS II (HR 1.30, 95% CI 1.14–1.49) with multiple adjustment for diabetes risk factors (172).

SMOKING

Smoking behavior is associated with the development of type 2 diabetes. In a meta-analysis of 25 prospective cohort studies including 1.2 million participants from the United States, Europe, and Asia with 45,844 incident cases during follow-up ranging from 5 to 30 years, active smokers were at increased risk for developing type 2 diabetes compared with nonsmokers (RR 1.44, 95% CI 1.31–1.58) (173). Further, a dose-response relation was observed between smoking and type 2 diabetes. Heavier active smokers had higher risk for type 2 diabetes (RR 1.61, 95% CI 1.43–1.80), while the associations were weaker for lighter active smokers (RR 1.29, 95% CI 1.13–1.48) and former smokers (RR 1.23, 95% CI 1.14–1.33). Smoking cessation was associated with a short-term increased risk of diabetes, which is largely mediated through weight gain (174). Exposure to passive smoking at work or home was also associated with increased risk of developing diabetes (175).

The underlying mechanism whereby cigarette consumption increases type 2 diabetes risk is not entirely clear. In experimental studies, smoking was linked with IGT and insulin resistance (176,177). In a double-blind, cross-over,

placebo-controlled, randomized experimental study, nicotine infusion aggravated insulin resistance among participants with type 2 diabetes, but not among nondiabetic participants (177). Therefore, cigarette smoke may not initiate but instead promote the progression of the disease. In addition, it has been speculated that nicotine or other agents in cigarette smoke might directly induce pancreatic injuries (178) and affect insulin secretion by inducing oxidative stress in the pancreas and, subsequently, leading to loss of beta cell function (179).

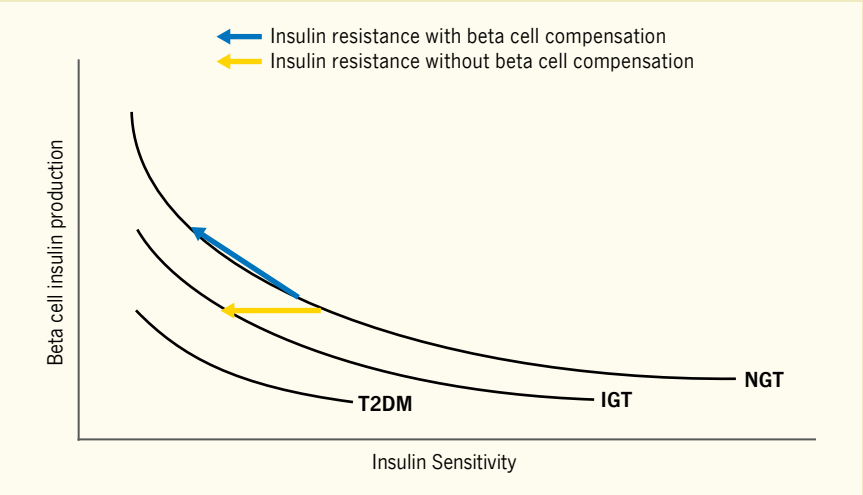
METABOLIC FACTORS ASSOCIATED WITH RISK OF TYPE 2 DIABETES

Novel biomarkers and intermediate conditions associated with diabetes risk offer the potential to detect diabetes risk at an early stage. These metabolic risk factors for type 2 diabetes are presented in this section.

METABOLIC PROGRESSION TO TYPE 2 DIABETES

Among individuals with normal glucose tolerance, a hyperbolic relation exists between beta cell function and insulin sensitivity (180). When deviation from this hyperbola occurs, deterioration of glucose tolerance and the progression to type 2 diabetes occur (Figure 13.13) (181).

FIGURE 13.13. Hyperbolic Relation Between Beta Cell Function and Insulin Sensitivity



IGT, impaired glucose tolerance; NGT, normal glucose tolerance; T2DM, type 2 diabetes mellitus.
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Impaired Fasting Glucose and Impaired Glucose Tolerance

Type 2 diabetes is a progressive disorder that is defined by specific cutoffs of glycemia. Impaired fasting glucose (IFG) and IGT are "prediabetes" states defined by glycemic levels higher than normal but below the actual cutoffs for diagnosis of diabetes. Multiple cutoffs and controversies have influenced the definitions of IFG and IGT over the years, but the American Diabetes Association Clinical Practice Recommendations define IFG as fasting glucose between 100 mg/dL (5.55 mmol/L) and 125 mg/dL (6.94 mmol/L) and IGT as glucose 2 hours after a standard 75 g oral glucose tolerance test (OGTT) between 140 mg/dL (7.77 mmol/L) and 199 mg/dL (11.04 mmol/L) (182). More details about diagnostic criteria and prevalence of type 2 diabetes are covered in Chapter 1 *Classification and Diagnosis of Diabetes* and Chapter 3.

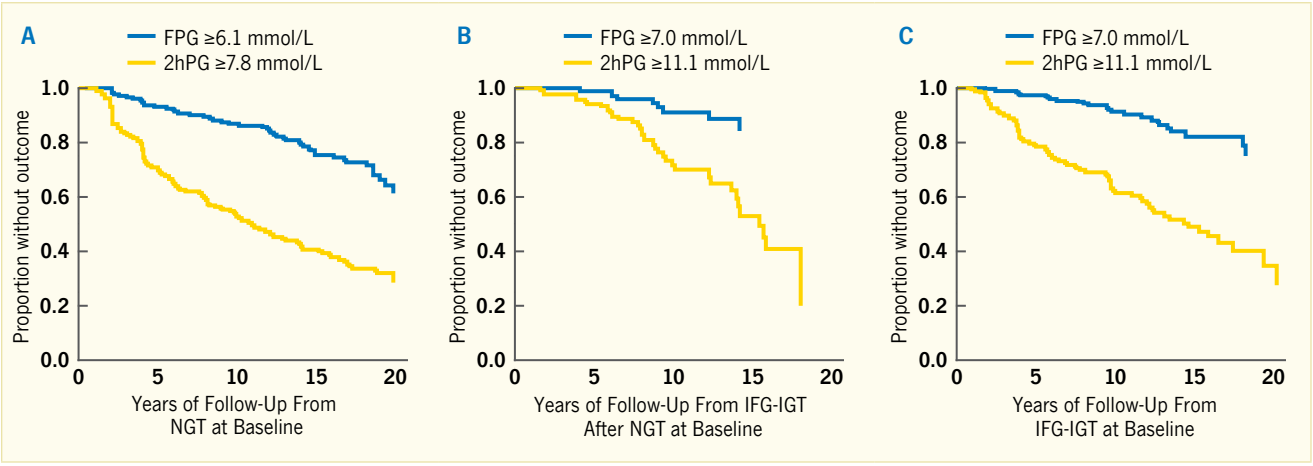
Based on the NHANES, an estimated 34.9% of the U.S. adult population had prediabetes in 2005–2006, after excluding type 2 diabetes (183). This means that more than one-third of U.S. adults should be classified as prediabetic. Unfortunately, very few were aware of their prediabetes status, since only 4.8% reported that their physician informed them about being at risk for type 2 diabetes (183), likely because testing for abnormal glucose levels is rare.

In prospective studies investigating the progression of type 2 diabetes, individuals progressed from normoglycemia to impaired glucose regulation (IFG and/or IGT) before reaching hyperglycemic levels of type 2 diabetes. Although individuals progressed from normal glucose tolerance to type 2 diabetes via IFG and/or IGT, one anomaly does not always precede the other, based on data from the Baltimore Longitudinal Study of Aging (BLSA) with a mean follow-up of 10 years (Figure 13.14) (184). In addition, many individuals with IFG and/or IGT do not progress to type 2 diabetes, and some even return to normoglycemia (184).

Both IFG and IGT in isolation predict an increased risk, but the combination of IFG and IGT signifies a particularly high-risk state. In the Framingham Offspring Study, a standard OGTT was performed at examination cycle 5. Follow-up assessment after 7–8 years demonstrated a type 2 diabetes incidence of 1.3% in participants with normal glucose tolerance at baseline, 4.3% in those with IGT (OR 3.34), 9.2% in those with IFG (OR 7.57), and 25.5% in individuals with both IGT and IFG (OR 25.6) (185). As mentioned, it should be kept in mind that the cutoffs used for defining IGT and IFG have been proposed to help clinicians to identify individuals at risk, but in biological terms, the relation between prediabetes hyperglycemia and the risk of developing type 2 diabetes is mostly continuous.

Further, the transition rate may vary across ethnic background. For example, the absolute conversion rate from IGT to type 2 diabetes was 3.58% per year in the BLSA (mainly Caucasian), while it was 8.73% per year in Pima Indians (186). Other risk factors predicting a higher conversion rate depend on the population but often include higher adiposity (defined by elevated BMI or waist circumference), weight gain, younger age (in

FIGURE 13.14. Cumulative Proportion of Subjects Progressing From Normal to Abnormal Glucose Tolerance Using Standard Diagnostic Criteria, Baltimore Longitudinal Study of Aging



(A) Progression from NGT to abnormal FPG (≥6.1 mmol/L) and abnormal 2hPG (≥7.8 mmol/L) among 488 subjects. (B) Progression from IFG-IGT after NGT baseline to diabetic FPG (≥7.0 mmol/L) and diabetic 2hPG (≥11.1 mmol/L) among 216 subjects. (C) Progression from IFG-IGT at baseline to diabetic FPG (≥7.0 mmol/L) and diabetic 2hPG (≥11.1 mmol/L) among 265 subjects. Conversions for glucose values are provided in *Diabetes in America Appendix 1 Conversions*. 2hPG, 2-hour plasma glucose; FPG, fasting plasma glucose; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; NGT, normal glucose tolerance.

SOURCE: Reference 184, copyright © 2003 American Diabetes Association, reprinted with permission from the American Diabetes Association

most contemporary cohorts), markers of insulin resistance, and reduced beta cell function (187).

Beta Cell Dysfunction

Type 2 diabetes is believed to originate from an imbalance between insulin resistance and the capacity of the beta cell to produce insulin in the face of demand. The etiologic factors leading to beta cell dysfunction are still a matter of important research, but genetic variants predisposing to type 2 diabetes are often located near genes implicated in beta cell function (28).

The acute insulin response (AIR) measured during a frequently sampled intravenous glucose tolerance test is a refined measure of insulin secretion capacity and represents the first-phase insulin response (188). A low AIR is associated with risk of developing type 2 diabetes based on prospective studies in Pima Indians and Insulin Resistance Atherosclerosis Study (IRAS) participants (189,190,191).

Indices of insulin secretion can also be derived from the OGTT. The most commonly used is the insulinogenic index calculated as [Δ insulin$_{0-30\,min}$] / [Δ glucose$_{0-30\,min}$]. The correlation between the insulinogenic index and the first-phase insulin secretion based on an intravenous glucose tolerance test (IVGTT) is estimated at r=0.58 (192). The San Antonio Heart Study (SAHS) included Mexican Americans and non-Hispanic whites who were followed for 7–8 years with multiple time points of an OGTT. In the SAHS, a low insulinogenic index was associated with increased risk of developing type 2 diabetes (193). Another report from the SAHS showed that the index estimating the later phase of insulin secretion during OGTT (60–120 minutes) was also associated with risk of developing type 2 diabetes, independent of the insulinogenic index (194).

Proinsulin

Beta cell dysfunction can be assessed by measuring proinsulin and other products of insulin processing. High proinsulin levels in relation to mature insulin circulating levels indicate beta cell stress, impaired beta cell function, and/or insulin processing and secretion abnormalities. In the NHS, women who developed type 2 diabetes had higher proinsulin levels, proinsulin-to-insulin ratios, and C-peptide levels at baseline (195). In the Women's Health Study, higher proinsulin levels were a risk factor for a more rapid transition to type 2 diabetes (196).

Although both AIR and proinsulin levels are markers of beta cell function, they seem to capture complementary information. In the IRAS, multivariable logistic regression models demonstrated that AIR and proinsulin levels were independently associated with risk of developing type 2 diabetes, even when adjusting for potential confounding factors, such as insulin sensitivity (197).

Insulin Sensitivity (or Insulin Resistance)

Increased insulin resistance usually precedes the development of type 2 diabetes by many years and is considered as a very early step in the progression towards disease onset. Various indices of insulin resistance have been proposed; their abilities to predict type 2 diabetes incidence are presented in Table 13.5 (198). The gold standard to measure insulin resistance is the M-value based on euglycemic hyperinsulinemic clamp studies: the lower the M-value, the higher the insulin resistance (or lower the insulin sensitivity, its reciprocal). Prospective studies in Pima Indians demonstrated that a low M-value predicts type 2 diabetes incidence (190,199). The mini-model during an IVGTT is another refined technique to estimate insulin sensitivity (S_I). In offspring from parents with type 2 diabetes with follow-up of up to 25 years, S_I was the strongest determinant of the progression to type 2 diabetes (200).

TABLE 13.5. Ability of Candidate Indices of Insulin Resistance to Predict Incident Type 2 Diabetes

	AROC CURVE				TOP 10% VERSUS BOTTOM 90%			
	IGT		NGT		IGT		NGT	
INDICES	AROC	Rank	AROC	Rank	RR	Rank	RR	Rank
-$ISI_{0,120}$	67.3	1	70.8*	2	1.96	1	2.93	1
-ISIgly_a	58.8	13	68.8	3	1.47	13	2.88	2
-SiM	64.8	5	71.2*	1	1.77	2	2.76	3
-ISIgly_b	65.4	2	68.7	4	1.59	7.5	2.74	6.5
-QUICKI	65.4	3	68.6	5	1.59	7.5	2.74	6.5
-Stum_nodem	56.0	17	67.2	7	1.26	18	2.52	12
-BFSI	63.9	6	67.0	8	1.61	4	2.65	9
-ISI-2h	56.6	15	65.2	13	1.26	17	2.53	10
-McAuley	62.2	8	66.5	11	1.45	14	2.46	16
ln(FI)	61.8	9	66.5	12	1.50	11	2.47	14.5
-Stum_wdem	56.0	16	68.4	6	1.27	16	2.40	17
-ISI	65.2	4	66.8	10	1.59	7.5	2.74	6.5
BMI	59.2	12	66.8	9	1.59	5	2.53	11
-Raynaud	62.2	7	64.6	14	1.50	11	2.47	14.5
FIRI	59.7	11	60.8	15	1.59	7.5	2.74	6.5
HOMA-IR	59.8	10	59.9	16	1.62	3	2.74	4
FI	58.1	14	59.9	17	1.50	11	2.47	13
IGR	55.8	18	55.2	19	1.32	15	1.80	19

Poisson regression analyses using data from the San Antonio Heart Study, Mexico City Diabetes Study, and Insulin Resistance Atherosclerosis Study. aROC, area under the receiver-operator-characteristic curve; BFSI, Bennett's fasting insulin sensitivity index; BMI, body mass index; FI, fasting insulin; FIRI, Duncan's fasting insulin resistance; HOMA-IR, homeostasis model assessment insulin resistance; IGR, insulin/glucose ratio; IGT, impaired glucose tolerance; $ISI_{0,120}$, insulin sensitivity index at 0 and 120 min; ISIgly_a, Belfiore (area); ISIgly_b, Belfiore (basal); NGT, normal glucose tolerance; QUICKI, quantitative insulin sensitivity check index; SiM, Avignon's insulin sensitivity index; Stum_nodem, Stumvoll's index without demographic variables; Stum_wdem, Stumvoll's index with demographic variables.

* aROC for $ISI_{0,120}$ and SiM are not significantly different. For the consistency in the direction of the association in the table, the negative indices are included.

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In most large-scale epidemiologic studies, it is impractical to perform clamp studies or a sophisticated, multisample IVGTT. Consequently, a number of simpler indices to estimate insulin resistance (or insulin sensitivity) are used. Most of these indices are derived from measures of insulin and glucose during the OGTT and sometimes use solely fasting measurements. Various insulin resistance indices were compared in their ability to predict type 2 diabetes incidence using three prospective studies (i.e., SAHS, IRAS, Mexico City Diabetes Study) that included multiple racial/ethnic backgrounds (i.e., non-Hispanic white, African American, Hispanic American, Mexican) (Table 13.5) (198). The Insulin Sensitivity Index ($ISI_{0,120}$; that uses the fasting and 120 minute post-OGTT insulin and glucose concentrations) proposed by Gutt *et al.* (201) offered the highest predictive values. However, the simpler indices frequently used are based only on fasting measures (198).

The homeostasis model assessment of insulin resistance (HOMA-IR), based simply on fasting insulin and glucose measurements (202), is commonly used and accepted as a marker of insulin resistance in large-scale epidemiologic studies. In the Framingham Offspring Study, individuals in the upper quartile of insulin resistance based on HOMA-IR were twice as likely (OR 2.05) to develop type 2 diabetes over 7 years of follow-up (using a multivariable model that included known type 2 diabetes clinical risk factors in addition to HOMA beta cell index, calculated using fasting insulin and glucose measurements as described by Matthews *et al.* (202)) (203). In the WHI Observational Study, higher HOMA-IR was associated with increased risk of developing type 2 diabetes across multiple ethnic groups, including white, black, Hispanic, and Asian/Pacific Islanders (204).

Fasting insulin is also used as a surrogate for insulin resistance in large-scale epidemiologic studies. Based on NHANES reports, the prevalence of hyperinsulinemia increased from 25.8% in the NHANES III to 34.8% in the NHANES 1999–2002 ($p<0.001$), a global increase of 35% in the U.S. adult population (205). The increase was particularly noted in non-Hispanic whites, but other racial/ethnic backgrounds had higher prevalences at both assessment periods.

ADIPOKINES, INFLAMMATORY, AND OTHER BIOMARKERS

Prediabetes and insulin resistance states are increasingly characterized by a subclinical pro-inflammatory condition, likely derived from adipose tissue dysregulation. With accumulation of excess weight, macrophages infiltrate adipose tissue and lead to secretion of pro-inflammatory cytokines and impaired secretion of adipokines, which are proteins secreted by the adipose tissue. The liver is likely involved in the process by secretion of C-reactive protein (CRP) and is sometimes characterized by abnormal fatty infiltration associated with increased liver enzymes in the circulation. The inflammatory process is often linked with endothelial dysfunction markers. Many epidemiologic studies have tested whether adipokines and other cytokines are early markers of risk for developing type 2 diabetes.

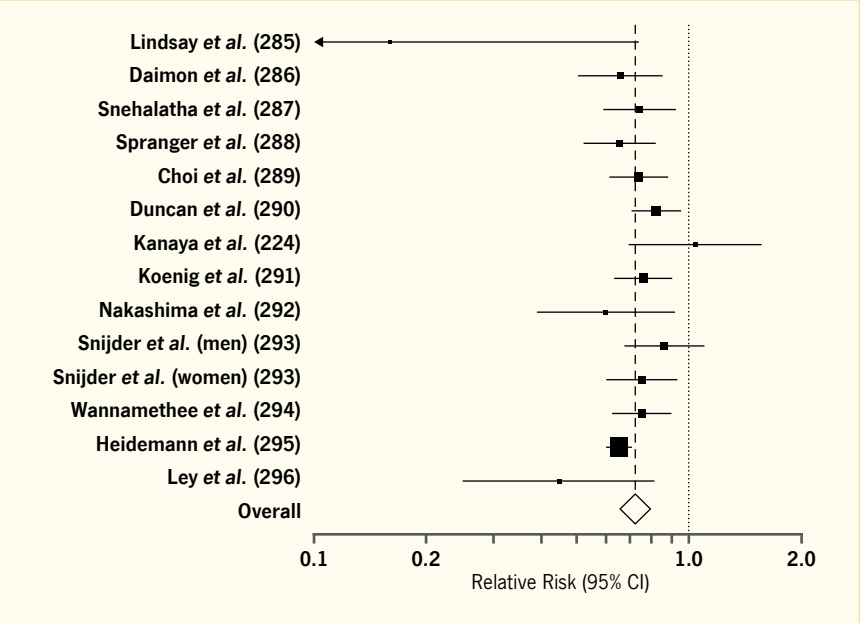
Adiponectin

Adiponectin is an adipokine mainly produced by adipocytes (206). In contrast to most adipokines and cytokines, circulating adiponectin levels are decreased in excess weight, especially if centrally distributed. Small "healthy" adipocytes produce high levels of adiponectin, which is believed to have anti-inflammatory and insulin-sensitizing effects, based on *in vitro* and animal studies (207,208,209).

In humans, adiponectin levels are inversely correlated to insulin resistance (210). In a meta-analysis reviewing 13 prospective studies conducted in countries from Europe, Asia, and America, including the United States, lower adiponectin levels were consistently associated with increased risk of developing type 2 diabetes in populations from various ethnic backgrounds and wide ranges of age, sex, and baseline glucose tolerance (Figure 13.15) (211).

In the Framingham Offspring Study and in the Cooperative Health Research in the Region of Augsburg (KORA) study, low adiponectin levels were associated with increased risk of developing type 2 diabetes among individuals who were insulin resistant at baseline (upper quartile of HOMA-IR), but not among insulin-sensitive individuals (212). In contrast, based on analyses from the Cardiovascular Health Study (CHS), the association between lower adiponectin levels and increased risk of type 2 diabetes was stronger in individuals with lower HOMA-IR (213). Using more refined measures of insulin sensitivity (S_i based on IVGTT), the association between adiponectin levels and the type 2 diabetes incidence was blunted and nonsignificant after adjusting for S_i in the IRAS multiethnic cohort, suggesting that insulin S_i mediated the association (214). The discrepancies between studies are difficult to explain, but they indicate that the interactions between adiponectin and insulin resistance and their association with type 2 diabetes incidence are complex.

FIGURE 13.15. Adiponectin and Risk of Type 2 Diabetes



Fourteen data points are included for the 13 studies because results for men and women are presented separately in the Hoorn Study (Ref. 293). CI, confidence interval.

SOURCE: Reference 211, reproduced with permission, copyright © 2009 American Medical Association. All rights reserved.References for individual studies are listed within the figure.

Pro-Inflammatory Cytokines

Tumor necrosis factor-alpha (TNFα) was one of the first proteins to be identified as part of the adipose tissue inflammatory pathways (215) and is suspected to directly and indirectly contribute to insulin resistance by acting on adipose tissue, liver, and skeletal muscles. In the adipose tissue, TNFα is produced primarily by adipose-infiltrating macrophages and is implicated in inflammation, cell cycle regulation, cytotoxicity, and production of other cytokines. Interleukin (IL)-6 is a pro-inflammatory cytokine that is produced by many cell types, including fibroblasts, endothelial cells, mononuclear phagocytes, neutrophils, hepatocytes, and lymphocytes. Both TNFα and IL-6 stimulate the synthesis and secretion of CRP by the liver. CRP is a sensitive marker of low-grade systemic inflammation.

Each of these three biomarkers—TNFα, IL-6, and CRP—was associated with increased risk of developing type 2 diabetes in prospective studies, but CRP seemed to offer stronger and more stable association (216). When including all three biomarkers in models, only CRP remained significantly associated with type 2 diabetes incidence in the NHS (217) and WHI Observational Study (218). In the EPIC-Norfolk cohort, the association between elevated CRP and risk for developing type 2 diabetes was attenuated to nonsignificance after adjustment for waist-to-hip ratio, serum gamma glutamyltransferase (GGT), and serum adiponectin (219). In the Multi-Ethnic Study of Atherosclerosis (MESA), IL-6 and CRP were associated with the type 2 diabetes incidence in white, black, and Hispanic individuals, but not in participants of Chinese origin (220). In a meta-analysis regrouping 16 prospective studies from various regions and populations from Europe, Asia, and America, high CRP levels were associated with increased risk of type 2 diabetes incidence but demonstrated significant heterogeneity among the studies, partly explained by the influence of sex distribution, uneven adjustments for adiposity distribution, and/or glycemia at baseline (219).

IL-18 is another cytokine likely involved in pro-inflammatory and insulin resistance pathways. Its functions include augmentation of cell adhesion molecules, synthesis of nitric oxide, chemokine production, and stimulation of TNFα and IL-6 production. Elevated IL-18 levels have been associated with higher risk of incident type 2 diabetes in the NHS, independent of CRP levels and other measured cytokines/adipokines (221). In the Atherosclerosis Risk in Communities (ARIC) study, higher IL-18 levels were associated with increased risk of type 2 diabetes in whites, but not in African American descent participants, suggesting a potential difference between these ethnic backgrounds (222).

Coagulation Markers

Plasminogen activator inhibitor-1 (PAI-1) is mainly produced by endothelial cells but is also secreted by the adipose tissue. PAI-1 is an inhibitor of fibrinolysis by its

action on tissue plasminogen activator and urokinase-type plasminogen activator/urokinase. Von Willebrand factor is a glycoprotein involved in hemostasis, and increased circulating levels are also a marker of endothelial dysfunction. Fibrinogen is a key component of the coagulation cascade.

In the Framingham Offspring Study, higher levels of PAI-1 and von Willebrand factor were associated with increased risk of developing type 2 diabetes in multivariable models that included major diabetes clinical risk factors in addition to CRP levels (223). PAI-1 levels were strongly associated with risk of type 2 diabetes in multivariable models in the Health, Aging, and Body Composition Study of black and white older adults (224) and in the IRAS cohort (225). In contrast, circulating fibrinogen levels demonstrated weaker or nonsignificant associations with type 2 diabetes after accounting for other risk factors, including BMI (220,225).

Endothelial Dysfunction Markers

Endothelial dysfunction can be detected by measurement of elevated plasma levels of cellular adhesion molecules, including E-selectin, intercellular adhesion molecule 1, and vascular cell adhesion molecule 1. These markers were associated with risk of developing type 2 diabetes in the NHS (226) and the multiethnic WHI Observational Study (227).

Liver Enzymes

Nonalcoholic steatohepatitis is a liver condition strongly associated with insulin resistance and abnormal lipid metabolism characteristic of the metabolic syndrome, as described in Chapter 26 *Liver and Gallbladder Disease in Diabetes*. An increase in liver enzymes, mainly GGT and alanine aminotransferase (ALT), is one of the first clinical manifestations of nonalcoholic steatohepatitis.

In the Bogalusa Heart Study, liver enzymes were measured when participants were age 25 years on average. At follow-up exams (a mean of 16 years later), diabetes status was associated with higher baseline GGT or ALT levels, independently of potential confounding factors, including alcohol intake, BMI, triglyceride levels, and HOMA-IR (228). Similarly, the Coronary Artery Risk Development in Young Adults (CARDIA) study demonstrated that diabetes incidence was associated with higher GGT levels at baseline, independent of potential confounding factors (229). The associations between elevated liver enzymes and the risk of developing type 2 diabetes were observed consistently, as demonstrated in a meta-analysis of prospective cohorts of men and women from various countries in Europe and Asia, as well as the United States (230). Interestingly, a cross-sectional report from the NHANES III investigating the association between GGT levels and diabetes reported an interaction between BMI and GGT levels: higher diabetes prevalence was associated with high BMI only in individuals with higher GGT levels (231).

Fetuin-A

Fetuin-A, a glycoprotein secreted by the liver, has been linked with diabetes risk (232). In a meta-analysis of four prospective studies (three from the United States and one from Germany), a positive association was observed between high fetuin-A levels and type 2 diabetes risk (OR 1.69, 95% CI 1.39–2.05) comparing extreme categories (233). In the NHS, adjustment for liver enzymes did not modify this positive association (interaction p-values 0.91 for ALT and 0.58 for GGT) (233). The association between fetuin-A and diabetes was largely explained by fasting insulin and glycosylated hemoglobin (A1c) levels in this study, as further adjustment for these factors attenuated the significant association (233). In the EPIC-Potsdam study, however, fetuin-A remained significantly associated with diabetes risk after adjustment for multiple biomarkers, including high-density lipoprotein (HDL) cholesterol, triglycerides, glucose, A1c, GGT, and CRP (234). Further, the association was stronger among participants with higher than normal plasma glucose values, defined as ≥100 mg/dL (234).

Insulin-Like Growth Factor Axis

Insulin-like growth factors (IGF), which are proteins with high sequence similarity to insulin, are involved in the regulation of cell growth, proliferation, and survival, which affect multiple organs in the human body (235). IGF-1 shares structural homology with insulin, and laboratory models suggest that IGF-1 and IGF-binding proteins (IGFBP) may be linked to diabetes (235). In the NHS, total IGF-1 levels were not significantly associated with type 2 diabetes risk (236). However, free IGF-1 was inversely associated with type 2 diabetes risk among women with higher (above median: 4.6 µU/mL [27.6 pmol/L]) insulin levels (OR 0.48, 95% CI 0.26–0.90, comparing extreme quintiles), while it was positively associated with diabetes risk among those with lower insulin levels (OR 2.52, 95% CI 1.05–6.06, p-interaction= 0.003) (236). Lower IGFBP-1 and IGFBP-2 levels were associated with reduced risk for type 2 diabetes (OR 0.42, 95% CI 0.20–0.90, and OR 0.19, 95% CI 0.09–0.41, respectively, comparing extreme quintiles), and higher IGFBP-3 was associated with increased risk for diabetes (OR 2.07, 95% CI 1.16–3.71) (236). However, further investigation is needed to confirm these observational findings.

Sex Hormones

In men, higher risk of type 2 diabetes has been associated with hypogonadism, even in the subclinical range of testosterone levels. In the NHANES III, men in the lowest tertile of estimated free (or bioavailable) testosterone were about four times more likely to have type 2 diabetes compared with men in the upper tertile, adjusted for age, ethnic background, BMI, and waist-to-hip ratio (237). This report was in line with a meta-analysis demonstrating that low testosterone in men was associated with type 2 diabetes in both cross-sectional and prospective studies (238). The association between testosterone levels and risk of type 2 diabetes in women is less often investigated but seems to have the opposite trend. In the Rancho Bernardo Study, higher risk of type 2 diabetes was associated with higher bioavailable testosterone levels in postmenopausal women (239). In addition, higher levels of bioavailable estradiol were associated with higher risk of type 2 diabetes in women (239), but not in men (239,240).

Sex hormone-binding globulin (SHBG) is a protein that binds to circulating sex hormones, regulating the amount of free hormones available to engender their biologic effects. Higher insulin resistance has been associated with lower levels of SHBG. Lower levels of SHBG were associated with higher risk of type 2 diabetes; the relative risk derived from prospective studies was stronger in women than in men (238). Lower SHBG levels were associated with increased risk of developing type 2 diabetes in both the Physicians' Health Study and Women's Health Study, and genetic association analyses suggested that SHBG could be implicated in some of the metabolic pathways leading to type 2 diabetes, based on Mendelian randomization analyses (241).

POLYCYSTIC OVARY SYNDROME

Polycystic ovary syndrome (PCOS) is a syndrome of ovarian dysfunction characterized by the combination of hyperandrogenism, menstrual and ovulatory alterations, and polycystic ovarian morphology (242). PCOS has been associated with increased prevalence rates of IGT and type 2 diabetes based on meta-analysis results (243).

However, limited large-scale, long-term prospective data on PCOS and type 2 diabetes are available. After an 8-year follow-up of 97 women with PCOS and 95 controls (244), risk of developing type 2 diabetes among those with PCOS was elevated by twofold, but nonsignificant, potentially due to a small sample size. In a more recent prospective study following women with PCOS (n=255) (245), the age-standardized prevalence of type 2 diabetes at the end of a mean 17-year follow-up was 39.3%, which was significantly higher than 5.8% from the respective general population of a similar age.

GESTATIONAL DIABETES MELLITUS

Detailed information on gestational diabetes is provided in Chapter 4. This section briefly summarizes the data on gestational diabetes as a risk factor for type 2 diabetes.

Based on the large Kaiser Permanente Southern California database, in 2005, pregnancies were complicated by gestational diabetes in 4.9% of white, 5.2% of black, 8.6% of Hispanic, and 10.3% of Asian/Pacific Islander origin women (122). As reviewed (246), women with gestational diabetes are at increased risk for type 2 diabetes after the index pregnancy. The progression to type 2 diabetes is markedly increased within the first 5 years after delivery and then seems to level off. The incidence of progression to type 2 diabetes is estimated to be 40%–50% at 5 years in most cohorts but can reach up to 70% in Native Americans and with longer follow-up (246). Interestingly, a positive 50 g screening test (O'Sullivan test) during pregnancy is also associated with increased risk of developing type 2 diabetes, even if women did not reach gestational diabetes by the diagnostic criteria on the OGTT (247,248).

In view of this high risk of developing type 2 diabetes among women with a history of gestational diabetes, clinical guidelines recommend type 2 diabetes screening in postpartum (182). Unfortunately, this recommendation is poorly followed in clinical settings with postpartum type 2 diabetes screening performed in 33%–50% of women with gestational diabetes, even in academic centers (249,250,251).

THE METABOLIC SYNDROME AND ITS COMPONENTS

The "metabolic syndrome" refers to the phenomenon of risk factor clustering—the co-occurrence of metabolic traits in the same individual to a greater degree than expected by chance, hypothetically reflecting a unifying underlying pathophysiology. Metabolic traits that cluster in the metabolic syndrome include obesity (particularly central obesity assessed by waist circumference), high fasting glucose, high blood pressure, high triglyceride, and/or low HDL cholesterol levels. The co-occurrence of metabolic syndrome traits is closely linked to insulin resistance and obesity. Five different expert groups published proposed criteria for the metabolic syndrome, as shown in Table 13.6. The Third Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (ATP3) definition has been the most widely used definition in the medical literature. In 2009, expert groups agreed upon a definition of the metabolic syndrome (252). According to this definition, identical to the ATP3 definition shown in the first column of Table 13.6, the metabolic syndrome is present when at least three of five risk factors are present.

Prevalence of the Metabolic Syndrome in the United States

ATP3 metabolic syndrome risk factors and overall syndrome prevalence, examined in the NHANES 2003–2006, are shown in Tables 13.7 and 13.8 (253). Overall, 34.4% of adults age ≥20 years met diagnostic criteria for the metabolic syndrome. Age-adjusted prevalence was 35.1% for men and 32.6% for women. Metabolic syndrome prevalence increased with age. Among men, the age-specific prevalence was 20.3% among men 20–39 years, 40.8% for men 40–59 years, and 51.5% for men ≥60 years of age. Among women, the age-specific prevalence was 15.6% among women 20–39 years, 37.2% for women 40–59 years, and 54.4% for women ≥60 years of age.

The metabolic syndrome showed a complex distribution when stratified by race/ethnicity. It was less common among non-Hispanic white women (age-adjusted prevalence 31.5%) than non-Hispanic white men (37.2%), while it was more common among non-Hispanic black women (38.8%) and Mexican American women (40.6%) than among non-Hispanic black men (25.3%) and Mexican American men (33.2%). Overall, metabolic syndrome prevalence was highest among non-Hispanic black and Mexican American women.

Obese individuals had the highest prevalence of the metabolic syndrome of any subgroup. Age-adjusted prevalence was 65.0% among men and 56.1% among women with BMI ≥30 kg/m^2 compared with 6.8% among men and 9.3% among women with BMI <25 kg/m^2.

Community surveys demonstrate similar rates of the metabolic syndrome as the NHANES. In the FHS of middle-aged

TABLE 13.6. Five Definitions of the Metabolic Syndrome

	NCEP ATP3 2005 (REF. 297)	IDF 2006 (REF. 298)	EGIR 1999 (REF. 299)	WHO 1998 (REF. 300)	ACE 2003 (REF. 301)
Required		Waist ≥94 cm (men) or ≥80 cm (women)	Insulin resistance or fasting hyperinsulinemia in top 25%	Insulin resistance in top 25%; glucose ≥6.1 mmol/L (≥110 mg/dL); 2-h glucose ≥7.8 mmol/L (≥140 mg/dL)	High risk of insulin resistance or BMI ≥25 kg/m² or waist ≥102 cm (men) or ≥88 cm (women)
Number of abnormalities:	≥3 of:	and ≥2 of:	and ≥2 of:	and ≥2 of:	and ≥2 of:
Glucose	≥5.6 mmol/L (≥100 mg/dL) or drug treatment for elevated blood glucose	≥5.6 mmol/L (≥100 mg/dL) or diagnosed diabetes	6.1–6.9 mmol/L (110–125 mg/dL)		≥6.1 mmol/L (≥110 mg/dL); 2-h glucose ≥7.8 mmol/L (≥140 mg/dL)
HDL cholesterol	<1.0 mmol/L (<40 mg/dL) (men); <1.3 mmol/L (<50 mg/dL) (women); or drug treatment for low HDL-C	<1.0 mmol/L (<40 mg/dL) (men); <1.3 mmol/L (<50 mg/dL) (women); or drug treatment for low HDL-C	<1.0 mmol/L (<40 mg/dL)	<0.9 mmol/L (<35 mg/dL) (men); <1.0 mmol/L (<40 mg/dL) (women)	<1.0 mmol/L (<40 mg/dL) (men); <1.3 mmol/L (<50 mg/dL) (women)
			or	or	
Triglycerides	≥1.7 mmol/L (≥150 mg/dL) or drug treatment for elevated triglycerides	≥1.7 mmol/L (≥150 mg/dL) or drug treatment for high triglycerides	≥2.0 mmol/L (≥180 mg/dL) or drug treatment for dyslipidemia	≥1.7 mmol/L (≥150 mg/dL)	≥1.7 mmol/L (≥150 mg/dL)
Obesity	Waist ≥102 cm (men) or ≥88 cm (women)		Waist ≥94 cm (men) or ≥80 cm (women)	Waist-to-hip ratio >0.9 (men) or >0.85 (women) or BMI ≥30 kg/m²	
Hypertension	≥130/85 mmHg or drug treatment for hypertension	≥130/85 mmHg or drug treatment for hypertension	≥140/90 mmHg or drug treatment for hypertension	≥140/90 mmHg	≥130/85 mmHg
Comments	Treatment with one or more of fibrates or niacin; in Asian patients, waist ≥90 cm (men) or ≥80 cm (women)	For South Asian and Chinese patients, waist ≥90 cm (men) or ≥80 cm (women); for Japanese patients, waist ≥90 cm (men) or ≥85 cm (women)		Insulin resistance measured using insulin clamp; the presence of microalbuminuria is also counted as one of the two or more qualifying traits.	High risk of being insulin resistant is indicated by the presence of at least one of the following: diagnosis of CVD, hypertension, polycystic ovary syndrome, nonalcoholic fatty liver disease, or acanthosis nigricans; family history of type 2 diabetes, hypertension, or CVD; history of gestational diabetes or glucose intolerance; nonwhite ethnicity; sedentary lifestyle; BMI ≥25 kg/m² or waist circumference ≥94 cm (men) and ≥80 cm (women); and age 40 years.

Conversions for glucose, HDL cholesterol, and triglyceride values are provided in *Diabetes in America Appendix 1 Conversions.* ACE, American College of Endocrinology; BMI, body mass index; CVD, cardiovascular disease; EGIR, European Group for the Study of Insulin Resistance; HDL-C, high-density lipoprotein cholesterol; IDF, International Diabetes Federation; NCEP ATP3, National Cholesterol Education Program Adult Treatment Panel 3; WHO, World Health Organization.

SOURCE: References are listed within the table.

white individuals, the age- and sex-adjusted prevalence of ATP3 metabolic syndrome was 24%; among middle-aged non-Hispanic white individuals in the SAHS, prevalence was 23%, while among similarly aged Mexican American subjects in the SAHS, the age- and sex-adjusted prevalence was 31% (254). In the biracial ARIC Study, the overall prevalence of ATP3 metabolic syndrome was 36.3% among black individuals and 29.7% among white individuals (255). In the multiracial MESA, ATP3 metabolic syndrome prevalence was 30% among whites, 36% among African Americans, 43% among Latinos, and 26% among Chinese Americans (256). In the Metabolic Syndrome and Atherosclerosis in South Asians Living in America study, ATP3 metabolic syndrome prevalence was 41% (256). In another study of Asian Indian immigrants in seven U.S. cities, the age-adjusted prevalence of ATP3 metabolic syndrome was 33.1% among men and 32.2% among women (257). In the New York City Health and Nutrition Examination Survey 2004, the overall age-adjusted prevalence of ATP3 metabolic syndrome was 13.3% in whites, 18.0% in blacks, 23.0% in Hispanics, 17.7% in South Asians, and 9.6% in other Asian

TABLE 13.7. Prevalence of Individual Components of the Metabolic Syndrome Among Adults Age ≥20 Years, by Selected Characteristics, U.S., 2003–2006

CHARACTERISTICS	N	PERCENT (STANDARD ERROR)				
		Abdominal Obesity	Hypertriglyceridemia	Low HDL Cholesterol	High Blood Pressure or Medication Use*	High Fasting Glucose or Medication Use
Crude†	3,423	53.2 (1.3)	31.4 (1.0)	24.7 (0.9)	40.0 (1.3)	39.0 (1.9)
Age-standardized†‡	3,423	52.8 (1.1)	31.2 (1.0)	24.7 (0.9)	39.5 (1.1)	38.6 (1.6)
Sex‡						
Men	1,794	44.8 (1.3)	35.6 (1.5)	21.6 (1.5)	43.4 (1.4)	45.8 (1.8)
Women	1,629	60.7 (1.6)	26.5 (1.1)	27.8 (1.5)	35.2 (1.3)	31.3 (1.7)
Men						
Age (years)						
20–39	607	32.0 (2.2)	29.6 (2.1)	21.4 (2.5)	24.1 (2.0)	28.8 (1.8)
40–59	546	52.1 (2.5)	41.5 (2.5)	23.0 (1.9)	44.5 (2.7)	50.3 (3.3)
≥60	641	55.2 (2.4)	36.7 (2.1)	19.5 (1.3)	74.4 (2.7)	67.8 (1.9)
Race/ethnicity‡						
Non-Hispanic white	967	47.4 (1.4)	36.6 (1.7)	22.6 (1.9)	43.5 (1.7)	44.8 (2.2)
Non-Hispanic black	346	36.0 (2.9)	21.2 (2.4)	11.5 (1.6)	51.3 (2.8)	40.9 (2.3)
Mexican American	364	37.6 (3.6)	43.7 (2.8)	26.0 (2.8)	35.5 (2.7)	49.8 (3.1)
BMI‡						
Underweight/normal weight	532	§	18.0 (2.2)	9.4 (1.9)	32.0 (1.8)	35.0 (2.7)
Overweight	701	35.1 (1.8)	37.7 (1.8)	22.6 (2.7)	40.3 (2.2)	45.0 (2.2)
Obese/extremely obese	557	94.4 (1.1)	48.6 (2.7)	31.3 (3.3)	57.5 (2.4)	55.5 (2.0)
Women						
Age (years)						
20–39	488	49.8 (2.7)	17.8 (2.0)	29.4 (2.5)	6.8 (1.2)	13.4 (1.5)
40–59	542	64.1 (2.2)	27.3 (1.7)	29.4 (2.4)	43.2 (2.2)	35.5 (3.0)
≥60	599	74.0 (2.6)	40.1 (3.0)	22.7 (2.2)	71.0 (2.6)	55.1 (2.7)
Race/ethnicity‡						
Non-Hispanic white	846	58.0 (2.3)	27.3 (1.5)	27.6 (2.1)	33.0 (1.5)	28.7 (2.0)
Non-Hispanic black	348	76.3 (2.1)	14.4 (1.8)	26.8 (2.7)	53.4 (2.8)	38.7 (2.4)
Mexican American	306	74.9 (3.3)	34.6 (2.1)	39.6 (3.3)	32.1 (3.0)	41.7 (3.8)
BMI‡						
Underweight/normal weight	519	13.6 (1.5)	12.9 (1.3)	12.9 (1.7)	26.4 (1.9)	15.8 (1.7)
Overweight	474	77.7 (3.1)	32.3 (3.0)	30.5 (1.8)	31.7 (1.9)	31.2 (2.3)
Obese/extremely obese	634	99.6 (0.2)	36.8 (1.8)	43.1 (2.8)	46.8 (2.6)	46.9 (2.5)

BMI, body mass index: underweight and normal weight (BMI <25 kg/m²), overweight (BMI 25–29.9 kg/m²), and obese and extremely obese (BMI ≥30 kg/m²); HDL, high-density lipoprotein.

* Blood pressure measurement is the average of up to three blood pressure readings.

† Total includes racial and ethnic groups not shown separately, plus respondents with missing BMI values.

‡ Age-standardized estimates using the direct methods of adjustment to the 2000 U.S. Census

§ Indicates a relative standard error of 30% or more. Authors suppressed the estimate because they considered it highly unreliable.

SOURCE: Reference 253

groups (258). In a survey of community-dwelling women in California, the prevalence of the metabolic syndrome was 34% in Filipinas and 13% in white women (259).

Surveys of Native American populations show very high rates of the metabolic syndrome. In 1989–1992, among 3,945 adult men and women from three communities in Arizona, seven in Southwestern Oklahoma, and three in South and North Dakota studied in the Strong Heart Study, 44% of men and 63% of women met criteria for ATP3 metabolic syndrome (260). In 2003–2006, among 5,166 adults age 18–88 years residing on two Northern Plains American Indian reservations and a Southwestern American Indian community studied in the Education and Research Toward Health (EARTH) study, the age-adjusted prevalence of ATP3 metabolic syndrome was 53.2% among women and 44.6% among men (261).

Among children and adolescents, estimates of metabolic syndrome prevalence should be viewed with caution because about one-half of youth meeting criteria for the metabolic syndrome on one examination will not meet criteria on a second exam conducted within 1–5 years (262,263). Nonetheless, among 1,826 adolescents age 12–19 years included in the NHANES 1999–2002, 9.4% of youth met criteria for the metabolic syndrome, defined as at least three of: waist circumference ≥90th percentile for age and sex, blood pressure ≥90th percentile, triglycerides ≥150 mg/dL (≥1.70 mmol/L), HDL cholesterol ≤40 mg/dL (≤1.04 mmol/L), and fasting glucose ≥100 mg/dL (264). Metabolic syndrome prevalence was higher in boys (13.2%) than girls (5.3%), lower in black (5.2%) compared with white (10.7%) or Mexican American

(11.1%) children, and highly prevalent among overweight (BMI ≥85th percentile) (44.2%) versus normal weight (1.6%) children.

Risk of Incident Type 2 Diabetes Associated With the Metabolic Syndrome

The metabolic syndrome is a powerful risk factor for development of type 2 diabetes. A meta-analysis of prospective studies of the metabolic syndrome predicting incident diabetes over 2–20 years is shown in Figure 13.16 (5). The presence versus the absence of ATP3 metabolic syndrome among individuals without diabetes at baseline was associated with a 5.3-fold increased relative risk to develop type 2 diabetes over follow-up. In community studies, the metabolic syndrome determined by various definitions has been associated with increased risk for future type 2 diabetes in white individuals (203), black individuals (265), Mexican Americans (266), and Native Americans (267,268).

The metabolic syndrome demonstrates a positive dose-response gradient between the number of metabolic syndrome traits and diabetes risk. In the Framingham Offspring Study, among middle-aged men and women, the prevalence of ATP3 metabolic syndrome was 26.8% in men and 16.6% in women (269). Over 8 years of follow-up, compared with those with no metabolic syndrome traits, men with one or two traits had a fourfold increased risk of type 2 diabetes, and those with three or more traits had a 24-fold increased risk of diabetes. Among women, those with one or two traits had a sixfold increased risk of type 2 diabetes, and those with three or more traits had a thirtyfold increased risk of diabetes. The metabolic syndrome includes the category of IFG, itself a major type 2 diabetes risk factor. However, even individuals without IFG as part of their metabolic syndrome phenotype are at elevated diabetes risk. In the Framingham offspring, 13% of individuals had a large waist circumference and any other pair of traits not including IFG; this phenotype was associated with a fivefold increased risk of diabetes. Ten percent had high triglycerides, hypertension, and low HDL cholesterol, but not IFG or a large waist circumference; this phenotype was associated with a 3.5-fold increased relative risk of type 2 diabetes.

TABLE 13.8. Prevalence of the Metabolic Syndrome and Odds Ratios for Prevalence of the Metabolic Syndrome Among Adults Age ≥20 Years, by Selected Characteristics, U.S., 2003–2006

CHARACTERISTICS	PERCENT (SE)	ODDS RATIO (95% CI)
Crude*	34.4 (1.3)	
Age-adjusted*†	34.0 (1.1)	
Sex		
Men	35.1 (1.3)	1.00
Women	32.6 (1.6)	0.89 (0.73–1.07)
Men		
Age (years)		
20–39	20.3 (2.0)	1.00
40–59	40.8 (2.1)	2.70 (1.96–3.73)
≥60	51.5 (3.1)	4.18 (3.01–5.79)
Race/ethnicity†		
Non-Hispanic white	37.2 (1.6)	1.00
Non-Hispanic black	25.3 (2.0)	0.54 (0.40–0.73)
Mexican American	33.2 (2.9)	0.78 (0.57–1.07)
BMI†		
Underweight/normal weight	6.8 (1.1)	1.00
Overweight	29.8 (2.0)	6.17 (3.96–9.62)
Obese/extremely obese	65.0 (2.4)	31.92 (20.06–50.78)
Women		
Age (years)		
20–39	15.6 (1.8)	1.00
40–59	37.2 (2.6)	3.20 (2.32–4.43)
≥60	54.4 (2.8)	6.44 (4.75–8.72)
Race/ethnicity†		
Non-Hispanic white	31.5 (2.2)	1.00
Non-Hispanic black	38.8 (2.1)	1.44 (1.05–1.98)
Mexican American	40.6 (2.5)	1.55 (1.06–2.29)
BMI†		
Underweight/normal weight	9.3 (0.9)	1.00
Overweight	33.1 (2.9)	5.48 (3.75–8.02)
Obese/extremely obese	56.1 (2.6)	17.14 (12.54–23.44)

BMI, body mass index: underweight and normal weight (BMI <25 kg/m²), overweight (BMI 25–29.9 kg/m²), and obese and extremely obese (BMI ≥30 kg/m²); CI, confidence interval; SE, standard error.

* Total includes racial and ethnic groups not shown separately, plus respondents with missing BMI values.

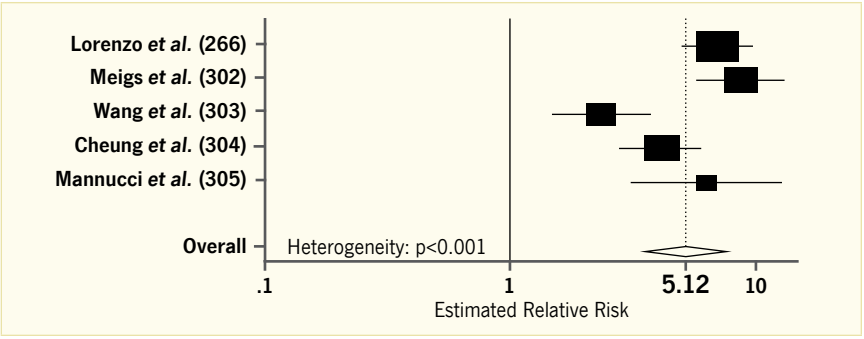
† Age-adjusted percent and standard error. The logistic regression models controlled for age group. Reference groups for logistic regression: sex—male; age—20–39 years; race/ethnicity—non-Hispanic white; BMI—underweight and normal weight.

SOURCE: Reference 253

When combined in prediction models for future risk of type 2 diabetes, metabolic syndrome traits have excellent discriminatory capacity. The ability of a prediction model to discriminate among individuals who will and will not develop disease in the future can be assessed by the model's c-statistic, or area under the receiver-operator-characteristic curve (aROC). The aROC is a function of the model's sensitivity (the probability that the model correctly identifies an individual with a subsequent outcome, or the true positive rate) and false positive rate. The aROC is the probability that a model correctly discriminates subjects developing an outcome from those without an outcome, where 0.5 is chance discrimination and 1.0 is perfect discrimination. In the FHS, a diabetes prediction model incorporating ATP3 metabolic syndrome traits, age, sex, and parental history of diabetes had an aROC of 0.85 (203). All FHS subjects are white; metabolic syndrome traits discriminated diabetes risk similarly in the biracial ARIC study (aROC 0.80) and

among Mexican Americans in the SAHS (aROC 0.82) (265,270). However, a review of several type 2 diabetes risk prediction tools concluded that risk scores probably need to be more carefully validated beyond populations in which they were developed (271).

FIGURE 13.16. ATP3 Metabolic Syndrome Increases Risk for Type 2 Diabetes



Horizontal bars represent 95% confidence intervals. ATP3, Adult Treatment Panel 3.

SOURCE: Reference 5, copyright © 2008 American Diabetes Association, reprinted with permission from the American Diabetes Association; references for individual studies are listed within the figure.

CONCLUSIONS AND IMPLICATIONS

Prospective studies have improved the understanding of behavioral and lifestyle risk factors for type 2 diabetes (272). However, there is great variation between individual responses to risk factor interventions, likely due to behavioral, physiologic, and genetic differences related to type 2 diabetes risk (3). Therefore, further advancement in the knowledge of gene-environment interactions may assist in the development of targeted prevention strategies for type 2 diabetes in the future. In addition, novel biomarkers and intermediate conditions associated with diabetes risk offer potential to detect diabetes risk at an early stage (4,5). Although type 2 diabetes cannot be cured at this time, the onset of type 2 diabetes may be delayed in many individuals at risk and may be prevented in some at-risk individuals through identifying metabolic risk factors at an early stage and intervening in the progression of the disease through modification of behavioral and lifestyle risk factors. Continued work to improve the understanding of type 2 diabetes risk may assist in the development of optimal strategies for type 2 diabetes prevention with a long-term goal of addressing this major public health concern.

LIST OF ABBREVIATIONS

A1c. . . . . glycosylated hemoglobin
AIR. . . . . acute insulin response
ALT. . . . . alanine aminotransferase
ARIC. . . . . Atherosclerosis Risk in Communities Study
aROC. . . . . area under the receiver-operator-characteristic curve
ATP3 . . . . . Third Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults
BLSA . . . . . Baltimore Longitudinal Study of Aging
BMI . . . . . body mass index
CHARGE . . . . . Cohorts for Heart and Aging Research in Genomic Epidemiology consortium
CI. . . . . confidence interval
CRP . . . . . C-reactive protein
EPIC. . . . . European Prospective Investigation into Cancer and Nutrition
FHS . . . . . Framingham Heart Study
GGT . . . . . gamma glutamyltransferase
GWAS . . . . . genome-wide association studies
HDL. . . . . high-density lipoprotein
HOMA-IR . . . . . homeostasis model assessment of insulin resistance
HPFS . . . . . Health Professionals Follow-up Study
HR . . . . . hazard ratio
IFG. . . . . impaired fasting glucose
IGF. . . . . insulin-like growth factor
IGFBP . . . . . insulin-like growth factor binding protein
IGT. . . . . impaired glucose tolerance
IL . . . . . interleukin
IRAS. . . . . Insulin Resistance Atherosclerosis Study
IVGTT. . . . . intravenous glucose tolerance test
MESA. . . . . Multi-Ethnic Study of Atherosclerosis
NHANES . . . . . National Health and Nutrition Examination Survey
NHIS . . . . . National Health Interview Survey
NHS. . . . . Nurses' Health Study
OGTT. . . . . oral glucose tolerance test
OR . . . . . odds ratio
PAI-1 . . . . . plasminogen activator inhibitor-1
PCOS. . . . . polycystic ovary syndrome
PREDIMED . . . Prevención con Dieta Mediterránea trial
PUFA . . . . . polyunsaturated fatty acids
RR . . . . . relative risk
SAHS. . . . . San Antonio Heart Study
SES . . . . . socioeconomic status
SHBG. . . . . sex hormone-binding globulin
S_i . . . . . insulin sensitivity assessed by IVGTT
TNFα . . . . . tumor necrosis factor alpha
WHI . . . . . Women's Health Initiative

CONVERSIONS

Conversions for glucose, HDL cholesterol, insulin, and triglyceride values are provided in *Diabetes in America Appendix 1 Conversions.*

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DUALITY OF INTEREST

Drs. Ley, Schulze, Hivert, Meigs, and Hu reported no conflicts of interest.

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