Chapter 9

Risk Factors for Non-Insulin-Dependent Diabetes

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SUMMARY

There is no single cause of non-insulin-dependent diabetes mellitus (NIDDM). More than 60 specific diseases have been associated with the NIDDM phenotype, but these account for <1% of all cases. The main form of NIDDM, associated with insulin resistance and secondary β-cell failure, may also comprise several etiologic entities. This chapter reviews the descriptive, analytical, and human experimental data concerning risk factors for NIDDM. Both genetic and nongenetic factors are presented as well as models for their interactions. Only some components of the pathomechanisms leading to NIDDM are known. It remains unknown whether interventions focused on these components, e.g., weight loss and increased physical activity, can prevent diabetes in at-risk persons or reverse the pathology in those already diagnosed with diabetes.

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INTRODUCTION

This review of the risk factors for NIDDM summarizes findings related to the epidemiology and natural history of the disease. Risk factors influence the risk of disease occurrence but, in most cases, are not the causal factors. For instance, prosperity and abundance of food do not directly cause obesity but may increase its incidence by making the causal exposure (food intake) more likely. A narrower definition of risk factor assumes that modification of the factor is possible and that such modification will change disease occurrence. In this sense, demographic characteristics such as age, gender, and ethnicity are not risk factors.

NIDDM is a heterogeneous disease caused by several pathomechanisms. Each of these pathomechanisms probably consists of a few components, and some components may play a role in two or more pathomechanisms. For instance, a high-fat diet may interact with two distinct genes involved in two distinct causal mechanisms, while each gene is unique to one mechanism. In fact, most components of the processes leading to NIDDM are currently unknown.

In this chapter, findings concerning genetic, metabolic, and behavioral risk factors for NIDDM are reviewed and integrated into a comprehensive model of causation. In the two final sections of this chapter we suggest preventive approaches. Although these proposals may be modified or rejected, they may facilitate the synthesis of a large body of information into simpler concepts.

HETEROGENEITY OF NIDDM

Several lines of evidence indicate that heterogeneity exists within the NIDDM phenotype: 1) the majority of NIDDM cases are believed to result from a combination of insulin resistance and β-cell failure that is not related to autoimmunity, and these two components are themselves highly heterogeneous, 2) β-cell autoimmunity, characteristic of insulin-dependent diabetes mellitus (IDDM), is present in up to 10%-33% of subjects diagnosed clinically with NIDDM, 3) heterogeneity is evident even in infrequent subtypes of NIDDM, such as maturity-onset diabetes of the young (MODY), and 4) >60 rare genetic syndromes, involving both nuclear and mitochondrial genes, are associated with glucose intolerance. Evaluation of risk factors requires careful attention to the heterogeneity of NIDDM in families and populations.

THE MAIN TYPE OF NIDDM

The focus of this chapter is on what is believed to be the main type of NIDDM, estimated traditionally to account for ~90% of all adult diabetes and characterized by initial insulin resistance and hyperinsulinemia with secondary β-cell failure. The very existence of a distinct and homogeneous "main type of NIDDM" is questionable. Both insulin resistance and β-cell failure have multiple genetic and nongenetic causes[1,2]. In addition, some newer data suggest that β-cell defect may not be secondary to insulin resistance but rather is concurrent with or even precedes development of insulin resistance.

Similar to most infectious and chronic diseases, clinical NIDDM appears to be only part of a broad spectrum of pathology. As many as 20%-60% of people in the general population may be genetically susceptible to NIDDM. However, relatively few develop impaired glucose tolerance (IGT) and even fewer progress to diabetes. About half of adults who fulfill World Health Organization (WHO) criteria for diabetes do not have symptoms sufficient to make a clinical diagnosis. The vast majority of IGT cases remains undiagnosed, and evidence has accumulated that IGT may remit without progressing to diabetes. It is very likely that the pathologic process specific to the main form of NIDDM affects a large proportion of the general population. In most cases, however, the number of susceptibility genes, their penetrance, and the environmental and lifestyle/behavioral exposures may be insufficient to produce clinical diabetes within an individual's life span.

NIDDM ASSOCIATED WITH β-CELL AUTOIMMUNITY

It has been traditionally accepted that IDDM represents <10% of adult diabetes. This belief may change soon. In Caucasian populations, β-cell autoantibodies are found in 10%-33% of adult-onset diabetic patients not treated with insulin[3-7]. The presence of autoantibodies predicts a more rapid decline in β-cell function[7] and subsequent insulin dependency[4]. The older, qualitative islet cell antibody (ICA) assays are being replaced by more reproducible antigen-specific assays[8]. Large representative samples of NIDDM patients from different ethnic groups need to be screened using these assays to investigate the generalizability of these findings and establish precise estimates of the proportion of NIDDM cases that are actually latent IDDM. It is plausible that after β-cell autoimmunity is triggered in early childhood, those persons in whom the disease process is slow will present with IDDM as adults, develop diabetes that does not require insulin treatment, or even fail to develop diabetes altogether[9].

MATURITY-ONSET DIABETES OF THE YOUNG

MODY, an infrequent autosomal dominant syndrome of early-onset nonketosis-prone diabetes[10], has long been used as evidence of the heterogeneity of NIDDM. At least three genes have been linked to the apparently homogeneous MODY phenotype. These discoveries offer a preview of the complexities likely underlying the genetics of the main form of NIDDM.

A systematic screening identified close linkage between markers on chromosome 20q and MODY[11] in the RW pedigree in Michigan[10]. Even within this well-studied pedigree, evidence of heterogeneity of diabetes existed. Although linkage to chromosome 20q markers was demonstrated in all three branches of this pedigree, two branches appeared to have later onset of diabetes than typical MODY[11], suggesting that other genes and/or nongenetic factors may modify the age at onset of diabetes in this pedigree. Members of the RW family with MODY are insulin sensitive and display insulin secretion defect[11,12]. This is in contrast to Pima Indians, who develop diabetes early in life but are insulin resistant and hyperinsulinemic. No evidence of linkage to the 20q markers was found in Pima Indians[13]. No linkage to the 20q markers could be demonstrated in other U.S., Danish, and British MODY pedigrees and all but one French pedigree[14-16]. The likely MODY locus on chromosome 20q is close to the adenosine deaminase gene (ADA)[17]. However, the responsible gene is unlikely to be ADA itself, since diabetes is not a characteristic of ADA deficiency in humans or animal models. Linkage with the phospholipase C gene on chromosome 20 (in proximity to the ADA locus) has been shown[18]. This is a plausible candidate because of its involvement in glucose-stimulated insulin secretion.

The glucokinase (GCK) gene polymorphism in exon 7 was linked to MODY in 25%-45% of French MODY families studied[16,19,20] and in one U.K. family[21] where no linkage to ADA was seen[15]. In the French MODY families where linkage with GCK could not be detected, the age of diabetes onset was later than in those with the linkage. An uncommon nonsense mutation in exon 7 (one of at least 17 different mutations identified in the GCK gene) is associated with lower levels of the enzyme and an alteration of the setpoint for glucose-induced insulin secretion[22,23]. Low insulin response due to mutant GCK as the glucose sensor

may be the cause of MODY[24] in some families. The heterogeneity of genetic associations seen among MODY families suggests that several genes, and possibly nongenetic factors, are involved[25].

OTHER FORMS OF NIDDM

Approximately 50% of first-degree relatives of NIDDM patients diagnosed before age 35-40 years have diabetes or IGT, twice as many as among first-degree relatives of late-onset probands[26-28] (see Appendix 9.3). This may indicate a distinct type of diabetes with greater penetrance and/or earlier age of onset. The relatives with only mild IGT have β-cell dysfunction, which on its own may not lead to NIDDM. However, in the face of factors such as obesity or lack of exercise, this β-cell dysfunction could lead to the diabetic phenotype.

Some adult African Americans initially presenting with diabetic ketoacidosis and HLA genes associated with IDDM, but without autoimmunity, have a subsequent clinical course characteristic of NIDDM[29-31]. This group of diabetic persons may represent a distinct form of NIDDM.

A large number of rare genetic syndromes are associated with glucose intolerance, but together these account for a very small percentage (<1%) of NIDDM in the population[32,33] (see Chapter 5 for a detailed discussion).

The demographic characteristics of people with NIDDM are described in Chapter 6. This section presents information on the association of these factors with risk of NIDDM.
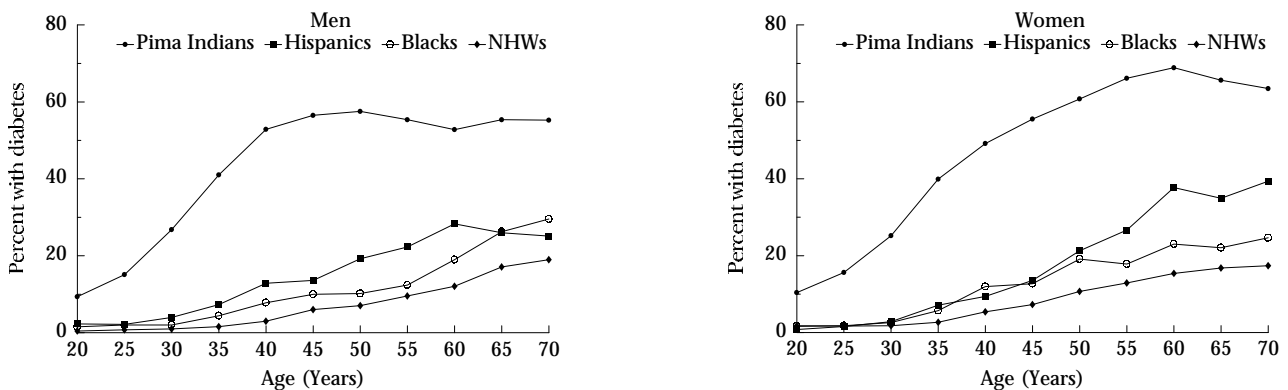
AGE

In most populations, NIDDM incidence is low before age 30 years but increases rapidly with older age. The prevalence of diabetes in Pima Indians age 25-29 years (13%) is, however, as high as that for U.S. non-Hispanic whites age 60-64 years[34] (Figure 9.1). In high-risk populations, susceptible persons develop NIDDM at earlier ages. Limited incidence data suggest that the relative risk of NIDDM in U.S. minority groups, compared with non-Hispanic whites, is highest at age <40 years and decreases thereafter.

ETHNICITY

Worldwide interpopulation differences in NIDDM prevalence are truly dramatic[34] (Figure 9.2). There are virtually no NIDDM cases in traditional societies such as Mapuche Indians in Chile and Bantu in Tanzania, compared with nearly half of the adult population affected among Pima Indians and Nauruans. In the United States, NIDDM is approximately twice as common in blacks and Hispanics as in non-Hispanic whites. These geographic and ethnic differences can, in large part, be explained by underlying differences in the prevalence of obesity and other behavioral risk

Figure 9.1
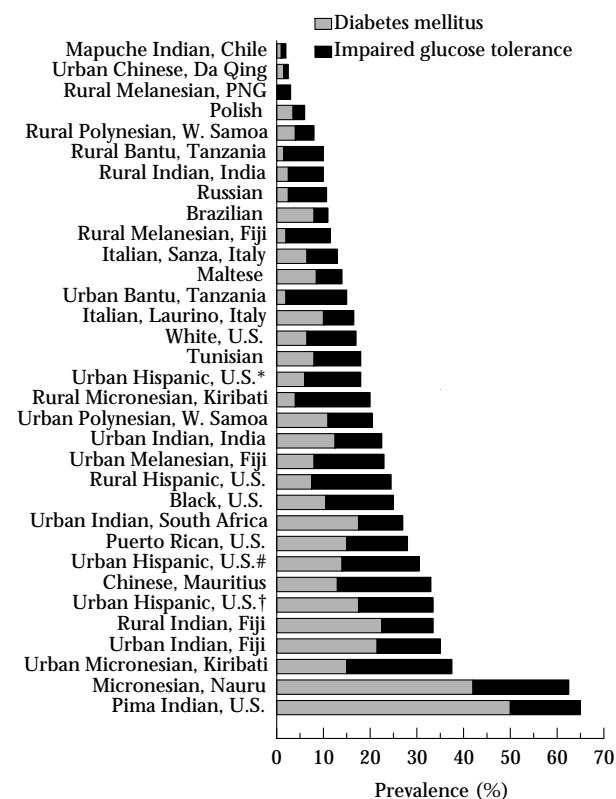**Prevalence of Diabetes in Men and Women in Four Ethnic Groups in the United States**

NHW, non-Hispanic whites.

Source: Reference 34

at higher levels of obesity[37]. It is conceivable that more accurate measurement of risk factors (e.g., deuterium dilution study rather than BMI, intra-abdominal fat by computerized tomography (CT) rather than waist-to-hip ratio, genotype rather than family history of diabetes, and accurate dietary and activity assessment in place of income and education) would better account for the ethnic differences. However, accurate measures of NIDDM risk factors are either not available (e.g., specific genotypes) or prohibitively expensive for use in population studies.

GENDER

There is little evidence that NIDDM risk differs between men and women when other factors are accounted for. Previously reported gender differences have been small and inconsistent[34]. Figure 9.3 presents age-standardized (age 30-64 years) gender ratios for the prevalence of diabetes in U.S. adults of different ethnic backgrounds. Of the 14 comparisons made, only one (female excess in non-Hispanic whites from the 1976-80 NHANES II) was significant at p<0.05, which could be expected to occur by chance.

GENETIC RISK FACTORS

The general observation that NIDDM has a genetic component is undisputed[32,38-46]. The simplest evidence

factors. However, even meticulous adjustment for known demographic and behavioral risk factors leaves a significant part of the ethnic differences unexplained, pointing to the existence of important genetic or unknown nongenetic NIDDM risk factors that differ by ethnicity. For example, in the San Luis Valley Diabetes Study in Colorado, Hispanics were twice as likely as non-Hispanic whites to have NIDDM, after adjusting for age, gender, obesity, family history of diabetes, education, and income[35]. A similar 2.7-fold excess of NIDDM in Hispanics compared with non-Hispanic whites, adjusting for age, gender, body mass index (BMI), and education, was found in the prospective followup of the San Antonio Heart Study population[36] in Texas. In the 1976-80 Second National Health and Nutrition Examination Survey (NHANES II), the excess of NIDDM in blacks compared with whites could not be explained by differences in age, gender, obesity, fat distribution, family history of diabetes, or education and was greatest
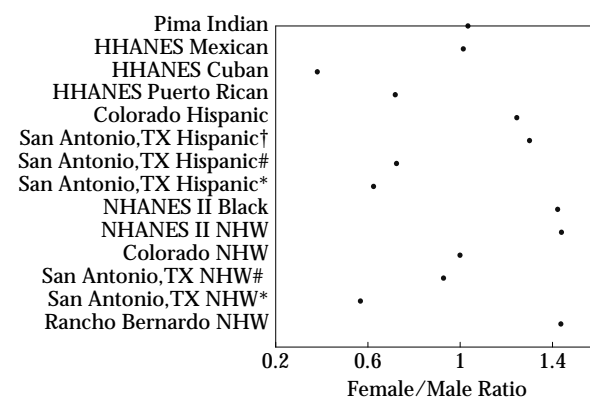
is that NIDDM is more frequent in certain ethnic groups and in certain families. This ethnic and familial clustering is likely to result from both shared genes and shared behavioral and environmental risk factors.

RACIAL ADMIXTURE

Studies of populations that derive from ethnic groups differing in NIDDM risk provide indirect evidence for the genetic factors in NIDDM. For instance, Hispanics in the southwestern United States share genes of Native Americans, who have one of the highest diabetes rates in the world[47,48], and genes of Caucasians, who are at a much lower risk. Studies of admixture are pertinent to NIDDM in American populations[49-53]. When these ecologic studies are plotted across an admixture gradient, a nearly linear association is evident. Similar findings were seen in South Pacific populations[54,55] and in Australian Aborigines with Caucasian-Aboriginal admixture[56]. At the population level, these studies provide support for the hypothesis that genes present in high-risk populations are associated with NIDDM risk. However, attempts to determine individual rather than group admixture have been less successful. Because of difficulties in calculating individual admixture percentages that show reasonable dispersion, these studies have shown either no association with NIDDM[57] or a weak and inconsistent association[58]. This may be due, at least in part, to a lack of linkage of putative NIDDM genes with the specific markers used to make these estimates of individual admixture as well as to methodological problems arising from a limited number of loci available for the calculations.

FAMILY HISTORY

Presence of NIDDM in a family member is an established risk factor for NIDDM. Pima Indians[59] and Caucasians[60,61] with at least one diabetic parent have a much higher incidence of NIDDM than those who are equally obese but do not have a diabetic parent. Information on family history of diabetes in subjects with and without diabetes in national surveys is provided in Appendices 9.1-9.4. Rates of NIDDM according to family history of diabetes in national surveys are shown in Appendices 9.5-9.8. Numerous family studies were reviewed in the first edition of *Diabetes in America*[62] with the conclusion that they were limited in value for differentiating the genetic and environmental factors shared by family members. This chapter emphasizes studies that more directly define the genes involved in NIDDM.

TWIN STUDIES

Studies of twins are shown in Table 9.1[63-70]. These studies suggest that NIDDM is highly concordant among monozygous (MZ) twins and less so among dizygous (DZ) twins. A twins study of U.S. veterans[68], with potentially little ascertainment bias, reported concordance rates of 58% for MZ twins and 17% for DZ twins. In addition, 65% of the discordant nondiabetic MZ twin brothers had elevated (although not diagnostic) 1-hour postchallenge glucose levels. Similar rates were observed in a Danish study[64]. Much lower rates were reported from the Finnish Twin Register[70], probably due to omission of some undiagnosed diabetes cases; nevertheless, the MZ concordance was approximately twofold higher than for DZ twins.

Table 9.1
Summary of Twin Studies and NIDDM

Ref.	Type of twins	No. of pairs	Concordance (%)	Comments
63	MZ	35	100	Ascertainment uncertain, criteria for diabetes diagnosis not current
64	MZ	47	55	Ascertainment from the Danish twin register; diabetes defined as "maturity onset"
65	MZ	10	70	Diabetes diagnosed at age >40 years in one twin; ascertainment possibly biased
63, 66, 67	MZ	113	69	Ascertainment biased by referral of one twin with NIDDM
68	MZ	34	58	Ascertained unbiased, from Veterans Twin Study after two examinations; diabetes defined with
	DZ	42	17	50-g glucose load and 1 hour glucose ≥250 mg/dl; discordant MZ twins had higher glucose levels than controls. Maximum proband concordance rate for MZ twins = 65%
69	MZ	46	80	Ascertainment biased by referral of one or more twins with diabetes; diagnosis using WHO
	DZ	10	40	criteria
70	MZ	140	34	Ascertainment unbiased, from the Finnish Twin Registry; diabetes diagnosed only from hospital
	DZ	303	16	discharge registry, drug registry, and death certificates; likely to underestimate prevalence

MZ, monozygotic; DZ, dizygotic; WHO, World Health Organization.

Source: References are listed within the table

These twin studies indicate that genetic factors play a major role in the etiology of NIDDM. These studies also support a role for nongenetic factors, since the concordance is much less than 100%. In addition, the estimates of concordance include some unknown component due to shared environments.

ASSOCIATION AND LINKAGE STUDIES

Specific assumptions about the mode of inheritance and other limitations need to be considered when interpreting genetic studies of various designs[71,72]. Most association studies compare the prevalence of a genetic marker in an unrelated series of persons with NIDDM with the prevalence in controls. Limitations of this approach include the limited length of the genome explored and the inclusion of diabetic persons who may have varying genetic defects, which diminish the power to discern true associations[39]. On the other hand, association studies do not require any assumption concerning the mode of inheritance. Population association studies relevant to NIDDM are summarized in Table 9.2[25,39,54,73-120]. Although there are isolated positive findings, most of these were not replicated on repeated analysis in other or larger populations. It appears unlikely that the genes for insulin, insulin receptor, glucose transporters, or islet amyloid polypeptide are associated with a substantial proportion of NIDDM in the general population. Exceptions to these negative results include findings of an association of NIDDM with the GCK gene in Mauritian Creoles[120] and U.S. blacks[119] and with the glycogen synthase gene in Finns[116].

A large number of studies using other markers that could be in linkage disequilibrium with diabetes gene(s) have been conducted. These include ABO and Rh blood groups, HLA serologies, and serum proteins[32,39]. Some results may simply reflect racial admixture, where the putative marker is associated with ancestry in a population at high risk for NIDDM. It is possible that this is the case for HLA-Bw22 reported in Micronesians[39], for haptoglobin in Mexican Americans[121] (which was not confirmed in another study[122]), and for Gm type in Pima Indians[52]. Since substantial progress has been made in studying candidate genes more closely related to carbohydrate and lipid metabolism, association studies appear useful now only as indicators of particular chromosomal loci. When weak associations are found in populations with possible racial heterogeneity, these studies should be followed by pedigree analysis or at least by analysis of another highly polymorphic locus to show that the association is not due simply to mismatching[39,123].

Table 9.2
Summary of Association Studies for Candidate Genes and NIDDM

Candidate gene and ref. no.	Population	Results[a]
Insulin		
73	U.S. white	+
74	U.S. white	+
75	British white	-
76	Welsh white	-
77	Danish white	-
78	U.S. Pima Indian	-
73	U.S. black	+
79	U.S. black	-
80	U.S. Chinese	-
81	Japanese; no family history	-
	Family history	+
82	Japanese	-
83	Japanese	-
84	Japanese	-
85	Japanese	-
54	Nauruan (Micronesian)	-
75	Punjabi Sikh	-
Insulin receptor		
86	U.S. white	+
87	U.S. white	-
88, 89	Scandinavian white	-
90	British white	-[b]
75	British white	-
76	Welsh white	-[c]
91	German white	+
86	U.S. Hispanic	+
92	U.S. Mexican American	+
80	U.S. Chinese	+[d]
93	Micronesian	-
94	Japanese	-
95	Japanese	-
96	U.S. white MODY families	-
97	U.S. white, black, Pima Indian	-[e]
75	Punjabi Sikh	-
98	Gestational diabetes	
	U.S. black	+
	U.S. white	+
	U.S. Hispanic	-
Glucose transporter 1 (restriction enzyme)		
99 (XbaI)	British white	+
	Italian white	+
100 (StuI)	British white	-
101 (XbaI)	British white	-
102 (BglII, XbaI)	U.S. white	-
103 (XbaI)	Italian white	+
103 (StuI)	Italian white	-
102 (BglII, XbaI)	U.S. Hispanic	+
102 (BglII, XbaI)	U.S. black	+
104 (XbaI TaqI PstI BglII)	U.S. black	-
99 (XbaI)	Japanese	+
102 (BglII, XbaI)	U.S. Japanese	-
80	U.S. Chinese	-
39 (BglII, XbaI)	Micronesian	-
100 (StuI)	West Indian	-

Table 9.2—Continued next page

Table 9.2—Continued

Candidate gene and ref. no.	Population	Results[a]
Glucose transporter 2		
105	British white	+[f]
106 (EcoRI-1 TaqI BclI)	British white	-
107 (BglI TaqI)	British white	-
108 (TaqI)	Italian white	-
107 (BglI TaqI)	West Indian	-
109 (EcoRI HaeIII)	U.S. black	-
Glucose transporter 4		
103 (KpnI)	Italian white	-
101 (KpnI)	British white	-
110 (SSCP)	Welsh white	-
111 (ASO Sty11)	Welsh white	-
109 (KpnI)	U.S. black	-
112 (SSCP)	European white	-
Amylin		
113 (PvuII)	British white	-
Lipoprotein lipase		
114	U.S. Hispanic, white	-
Apolipoprotein APOA1		
80	U.S. Chinese	-
Apolipoprotein APOA2		
80	U.S. Chinese	-
Apolipoprotein APOB		
80	U.S. Chinese	+
Apolipoprotein APOD		
115	Finnish	-
115	Nauruan	+
115	South Indian	+
Glycogen synthase		
112 (SSCP)	Danish white	-[g]
116 (XbaI)	Finnish white	+
Glucokinase		
117	British white	-
25	U.S. white	-
25	Welsh white	-
118	Pima Indian	-
119	U.S. black	+
120	Mauritius Creole	+

SSCP, single-stranded conformational polymorphisms; ASO, allele-specific oligonucleotide hybridization; MODY, maturity-onset diabetes of the young.
[a] Code for results: +, association found at the p<0.05 level; -, no association at the p<0.05 level. [b] The only association was for NIDDM subjects with a positive family history of diabetes compared with NIDDM subjects without a family history. [c] The only positive association was with RFLP haplotype combinations (B+R-X+) in NIDDM; such persons had higher insulin responses to a meal tolerance test. [d] Allele combinations Xba1(A) allele 2, Rsa1 allele 2, and Kpn1 allele 2 were less frequent in subjects with NIDDM, suggesting protection from NIDDM. [e] Sample sizes were only 10-15 in each group. [f] Significant only in persons with NIDDM and a positive family history of diabetes. [g] No polymorphisms identified.

Source: References are listed within the table

Linkage studies are particularly helpful in identifying major gene effects with high penetrance. However, the results of these studies strongly depend on the cor-

rectness of the assumptions about the mode of inheritance. Failure to find linkage does not rule out the possibility that a candidate gene plays some role in the disease, especially if small families are studied. On the other hand, it is difficult to ascertain large informative pedigrees for linkage analysis of NIDDM, since parents of the probands are usually deceased. Affected sib-pair analysis does not require assumptions about the mode of inheritance but, similar to linkage analysis, is limited when parents are not available for the analysis. Etiological heterogeneity is less likely within pedigrees than in association studies, and associations across a longer portion of the genome can be identified. However, linkage and sib-pair analyses must be paired with association studies to understand the proportion of NIDDM that may be due to a specific gene defect. Linkage and sib-pair studies of candidate NIDDM genes are reviewed in Table 9.3[25,93,108,113,124-135]. Candidate genes evaluated using this method have included, among many others, the insulin gene, insulin receptor gene, HepG2/erythrocyte glucose transporter 1 (GLUT1) and GLUT4 genes, and the islet amyloid polypeptide gene. In none of these studies was any evidence found for linkage of NIDDM and these gene loci in several racial and ethnic subgroups. Studies of linkage with the glucokinase gene are discussed below.

CANDIDATE GENES

Increased understanding of pathophysiology and molecular biology has led to identification of a number of candidate genes involved in glucose and lipid homeostasis. A list of these genes and their chromosomal localization is shown in Table 9.4. The field is evolving extremely rapidly and will encompass many more loci, making most of this review soon obsolete. A few candidate genes are discussed in more detail to illustrate some of the methodological problems, rather than to suggest that defects in these genes may be responsible for a majority of NIDDM cases.

■ Glucokinase gene

GCK, an enzyme that catalyzes the formation of glucose-6-phosphate from glucose, is the major rate limiting step in glycolysis and acts as a primary part of the glucose sensor in the β-cell[22]. Its gene spans a region of >12 kb on chromosome 7 made up of 12 exons[24], 10 of which are shared by both the β-cell and the liver forms of the enzyme. Following initial reports of linkage of the GCK gene with MODY[19,21], several groups evaluated the potential contribution of this gene to development of late-onset NIDDM. At least 17 different mutations have been identified in the GCK gene,

including a nonsense mutation in exon 7 identified only in MODY families[124] and a missense mutation in exon 8 described in both MODY and later-onset families[135]. A missense mutation is a point mutation that causes one amino acid to be replaced by another, whereas a nonsense mutation causes premature termination of protein synthesis.

The exon 7 GCK gene polymorphism was investigated in a population association study of late-onset NIDDM in U.S. blacks[119]. In subjects with the Z+4 allele, the odds of NIDDM were 2.9, adjusted for age, sex, and BMI. In addition, the age at onset was shifted to ~10 years younger among Z+4 subjects. In Mauritius Creoles, who share African heritage with U.S. blacks, the odds of NIDDM were 2.9 in those with the Z+2 allele, adjusted for age, sex, BMI, and waist-to-hip ratio. However, no association or linkage with this polymorphism or other GCK mutations was found in Pima Indians or in U.S.[119,136], U.K.[117], and French[20,137] Caucasians. No structural mutations in the GCK gene were detected in black subjects[25,119], unlike that seen in French MODY subjects[23].

Table 9.3

Summary of Linkage and Sib Pair Studies Between Candidate Gene Loci and NIDDM

Genetic locus and ref. no.	Genetic model	Gene frequency	Population parameters	Results
Insulin				
124	AD, AR, IBD	Constrained on prevalence of 3.6%	23 Utah white Mormon pedigrees; age-dependent prevalence with sporadics	No linkage
125	AD, AR, sib pair	0.015-0.35	20 black pedigrees; age- and sex-dependent penetrance	No linkage
126			White gestational diabetic proband and offspring for insulin sensitivity and beta-cell function; no penetrance or sporadic functions	No linkage
Insulin receptor				
127	AD	0.10	3 British families with NIDDM, 1 with MODY; age-dependent penetrance	No linkage
126			Gestational diabetic proband and offspring for insulin sensitivity and beta-cell function; no penetrance or sporadic functions	No linkage
125	AD, AR, sib pair	0.015-0.35	20 black pedigrees; age- and sex-dependent penetrance	No linkage
128,129	AD, AR, IBD, sib pair	0.05 (AD), 0.25 (AR)	18 Utah white pedigrees; age-dependent prevalence with sporadics	No linkage
93	AD, AR		8 Nauruan families; complete penetrance (AD) or 90% penetrance (AR)	No linkage
Islet amyloid polypeptide (amylin)				
113	AD	0.10	British whites; age-dependent penetrance	No linkage
Glucose transporter 1				
130 (XbaI)	AD	0.01, 0.001	British white pedigree; age-dependent penetrance	No linkage
131 (Xba1 Msp1)	Sib pair		55 Italian and British white sib sets	No association
132 (Xba1, Stu1)	AD, AR	Multiple	18 Utah white pedigrees	No linkage
Glucose transporter 2				
108 (Taq1)			22 Italian diabetic pedigrees; affected pedigree members method	No linkage
132 (EcoR1)	AD, AR	Multiple	18 Utah white pedigrees	No linkage
Adenosine deaminase				
133 (Alu VpA)	Sib pair		21 Italian white and 29 British white pedigrees	No association
Glucokinase				
134	AD, AR	0.05 (AD), 0.25 (AR)	12 British white NIDDM pedigrees; age-related penetrance, exon 7 mutation	No linkage
25	AD, AR		U.S. white NIDDM pedigrees, exon 7 mutation	No linkage
135	AD	0.10	British white NIDDM pedigree (AX), exon 8 mutation	Linkage

AR, autosomal recessive; AD, autosomal dominant; IBD, identical by descent; MODY, maturity-onset diabetes of the young.

Source: References are listed within the table

Table 9.4
Chromosome Locations of Selected Candidate Genes for NIDDM

Candidate gene	Chromosome location
Insulin/insulin-like growth factor cluster	11p15.5
LIM/homeodomain Isl-1	5q
Insulin receptor	19p13.3-13.2
Insulin receptor substrate-1	2q35-36.1
Glucagon receptor	17q25
Glucagon-like-peptide-1 receptor	6p
Glucokinase	7p13
Hexokinase II	2p13.1
Glucokinase regulatory protein	?
Adenosine deaminase	20q
Phospholipase C	20q12-13.1
Islet amyloid polypeptide (amylin)	12p
Glucose transporters	
GLUT1 (HepG2) erythrocyte	1p35-31.3
GLUT2 liver, pancreas	3q26.1-26.3
GLUT3 brain	12p13.3
GLUT4 skeletal muscle, fat	17p13
GLUT5 small intestine/kidney	1p
Glycogen synthase	19
Type-1 protein phosphatase (PP-1)	?
Lipoprotein lipase	8p22
Apolipoprotein A-I, C-III, A-IV cluster	11q23
Apolipoprotein A-II	1q21-23
Apolipoprotein B	2p24-23
Apolipoprotein D	3q
Lipoprotein(a) (Lpa)	6
Haptoglobin (Hp)	16
Gc	4
Rhesus	1p36-34
t-RNA(Leu)	mitochondrial DNA

Using the exon 8 missense mutation described in a MODY pedigree, 50 "classical" NIDDM patients from the United Kingdom and 50 controls were screened[135]. The mutation was found in one person with NIDDM and in none of the controls. The pedigree of the person was investigated and 10 diabetic relatives had the same mutation, with age at diagnosis ranging from 31 to 70 years. Five diabetic relatives did not carry the mutation, indicating further heterogeneity.

The GCK mutations are associated with MODY, diabetes in families with younger onset, and persons who are relatively hypoinsulinemic. The GCK gene mutations appear to be an unlikely cause of typical NIDDM in Caucasians, Pima Indians, or U.S. Hispanics[138], but they may be relevant in black subjects.

The GCK findings also suggest analytic strategies for investigating other candidate genes in high-risk populations. Stratification of study populations by age of onset, presence of a family history, and insulin levels may be necessary to adequately explore the role of other loci, but it will significantly increase sample size requirements. In addition to the presence or absence of a functional polymorphism, regulation of gene expression controlled by a number of additional factors needs to be investigated. For instance, several mutations were identified in the promoter and 3'-untranslated regions of the GCK gene, but only one appears to cosegregate with diabetes in one family[137]. It will be critical to determine the population frequency of the candidate markers and the population attributable fraction for proposed etiological pathways. Finally, interactions of such candidate genes with behavioral risk factors, such as diet and physical activity, must be characterized so preventive measures may be explored.

■ Glucose transporter system

The glucose transporter system[139,140] has also been considered a place to explore candidate gene defects that may be responsible for hyperinsulinemia. The most likely members of this family include the liver/pancreas form (GLUT2) and the insulin-sensitive glucose transporter in adipocytes and muscle (GLUT4). Only one positive association has been reported between GLUT2 and NIDDM[104] among several association[105-108] and linkage studies[108,132]. One study in Pima Indians[141] found a weak linkage between GLUT2 and acute insulin response but not NIDDM. Levels of GLUT4 mRNA in muscle are related to whole body glucose disposal in subjects with normal glucose tolerance but not in subjects with diabetes[91]. In insulin-resistant relatives of NIDDM patients, the expression of GLUT4 and its protein were normal, suggesting that this gene is not responsible for the insulin resistance. These and other data[110,111,142,143] make it unlikely that GLUT2 or GLUT4 abnormalities account for any large proportion of NIDDM.

■ Glycogen synthase

Glycogen synthase, a key enzyme in carbohydrate storage[112,144,145], is a plausible candidate gene. Studies of Pima Indians[146] suggested that impaired nonoxidative glucose storage may be the site of a genetic defect in NIDDM. Early attempts to explore polymorphisms in this enzyme were unsuccessful[112,147]. A Finnish group reported that relatives of persons with NIDDM had impaired activation of this enzyme[148] and were 4.5 times (95% confidence interval (CI) 2.4-8.7) more likely than controls to carry an A2 allele defined by an intron polymorphism of the glycogen synthase gene[116]. In addition, hypertension and reported family history of diabetes were more common among both diabetic subjects and controls with the A2 allele.

Whole body glucose disposal and glycogen synthesis, but not oxidative glucose metabolism, were significantly decreased in NIDDM persons with at least one A2 allele. There were no differences in either diabetic subjects or controls in levels of fasting insulin by allele markers. To date, these findings have not been confirmed in other populations[149-151].

■ Insulin signal transduction pathway genes

The Rad gene, a member of the Ras-guanosine triphosphatase gene superfamily, is selectively overexpressed in skeletal muscle of NIDDM patients, compared with muscle of nondiabetic or IDDM subjects[152]. The molecular basis and significance of Rad overexpression in NIDDM is unclear; however, it points to the post-receptor action of insulin in the pathophysiology of NIDDM as being important. Two groups reported an association between a subset of NIDDM and a polymorphism in the gene for the insulin receptor substrate-1 (IRS-1), another downstream element responsible for insulin action[153,154]. This association could not be confirmed in a sib-pair study in Mexican Americans[155] or in an association study in Pima Indians[156].

■ Phosphoenol pyruvate carboxykinase

Phosphoenol pyruvate carboxykinase (PEPCK) is the rate-limiting enzyme in gluconeogenesis, entirely regulated at the level of gene expression. Insulin negatively regulates the PEPCK gene through insulin response sequences in the gene promoter. Faulty regulation of PEPCK is a strong candidate mechanism for insulin resistance and NIDDM[45].

GENETIC FACTORS ASSOCIATED WITH INSULIN RESISTANCE AND HYPERINSULINEMIA

Familial aggregation of hyperinsulinemia and/or insulin resistance was demonstrated in several populations[157-160] and in clinical studies[161-164]. In Mexican Americans in San Antonio, TX, fasting insulin levels were highest in the offspring of two parents with NIDDM, intermediate in offspring with one diabetic parent, and lowest in persons with no diabetic parents[160]. Nondiabetic siblings of diabetic subjects also had higher insulin levels than persons without a diabetic sibling. In 105 families examined at the Joslin Clinic in Boston, MA using the minimal model[165], significant familial clustering of insulin sensitivity was present even after adjustment for obesity, age, and fasting insulin[162]. A subset of families with the lowest

insulin sensitivity had a wider range of insulin sensitivity, suggesting an autosomal dominant mode of inheritance in these families.

In 16 U.S. white pedigrees with at least two NIDDM siblings, a major gene appeared to determine insulin levels, with the best fit being an autosomal recessive inheritance of fasting levels and codominant inheritance of 1-hour stimulated insulin levels[158]. Of the variance in fasting insulin levels, 33% was due to the major gene effect, 11% to polygenic effects, and 56% to unmeasured environmental effects. Importantly, the major gene effect was not evident without adjustment for obesity. These data, suggesting a mixture of two distributions, differ from the trimodal insulin and insulin sensitivity distribution in Pima Indians[157]. Population differences, such as less obesity and lower insulin levels in the Utah population compared with Pima Indians, and small sample size may be reasons for these discrepancies. These results in populations as varied as Mexican Americans[160], Chinese[163], whites[158], and Pima Indians[159] clearly indicate that insulin levels have familial clustering independent of obesity and may well have a major gene determining them. In addition, it is likely that heterogeneity exists across families[162].

The search for candidate genes that may be related to insulin resistance has taken two approaches: 1) studying rare syndromes in which insulin resistance is a major component (polycystic ovary syndrome, acanthosis nigricans, Type A insulin resistance)[1,166-168], and 2) examining clinical and population subsets for association with either hyperinsulinemia or insulin resistance[78,126]. Excellent reviews on rare insulin resistance syndromes are available[1,166,168,169]. These studies provide strong support that insulin resistance can be caused by multiple specific mutations, especially mutations of the insulin and insulin receptor genes. Limited numbers of studies in more typical NIDDM subjects have found no association between insulin or insulin receptor genes and insulin levels or insulin sensitivity[78,87-89,91,126,169]. In Pima Indians[170] and in six white NIDDM subjects[171], the insulin receptor gene sequence was normal, making it unlikely that this gene is responsible for NIDDM in most subjects.

In nondiabetic Hispanic and non-Hispanic white subjects in San Luis Valley, CO, insulin resistance syndrome (upper tertile of triglycerides and fasting insulin and lower tertile of high-density lipoprotein (HDL) cholesterol) was significantly associated with a polymorphism in the lipoprotein lipase gene (odds ratio 4.1, 95% CI 1.0-18.3)[114]. A sib-pair analysis suggested a linkage between 2-hour post-load insulin levels and a chromosome 1p36-34 locus close to the

Rhesus blood group gene in Mexican Americans[172], consistent with earlier population association findings[121].

Siblings of diabetic Pima Indians from 45 families were examined using the euglycemic-hyperinsulinemic clamp[159]. After adjusting for age, sex, and obesity, significant family aggregation of insulin sensitivity in siblings explained ~34% of the variance in insulin action. A genetic component was supported by the finding that insulin sensitivity was distributed in this population as a mixture of three normal distributions[157]. Such a mixture of distributions is consistent with a single gene codominant mode of inheritance, although it might be due to nongenetic factors as well. A sib-pair linkage analysis of 46 nuclear Pima families has linked a locus involved in regulation of insulin sensitivity in Pima Indians to the region near the fatty acid-binding protein 2 (FABP2) gene on chromosome 4q[173]. However, the study did not report any linkage between the FABP2 locus and NIDDM. A sib-pair analysis in Mexican-American families confirmed the linkage[174], but association studies in Finnish and U.K. populations[175] did not detect any convincing association between polymorphism in this region and NIDDM, insulin levels, or insulin sensitivity. Further studies of candidate genes with quantitative markers of hyperinsulinemia, probably in population subsets stratified by obesity, family history, and perhaps age of onset of NIDDM, are needed.

MODE OF INHERITANCE

Several problems have plagued studies of the genetics of NIDDM. These include, among others, genotypic and phenotypic heterogeneity, ascertainment bias, misclassification of type of diabetes, premature mortality, late age at onset, age-dependent penetrance of the NIDDM phenotype, and multiple polymorphisms not all in linkage disequilibrium. As a consequence of these limitations, the mode of inheritance of NIDDM remains uncertain[38,46]. Studies in high-risk populations, shown in Table 9.5[39,50,158,176-178], all found evidence of a major gene influencing the distribution of NIDDM-associated traits, but the mode of inheritance varied from autosomal dominant to autosomal recessive to co-dominant on a polygenic background. A single major locus does not explain the inheritance of NIDDM. In addition, there appears to be significant polygenic and environmental components[42]. This is consistent with the common perception that multiple modes of inheritance may exist for the heterogenous NIDDM phenotype.

BEHAVIORAL AND LIFESTYLE RISK FACTORS

Numerous ecological data and observational studies reviewed below support the role of environmental/lifestyle factors in NIDDM etiology. Nonetheless, some have questioned that a role for environmental factors has been established because of the paucity of controlled experimental studies in this area. The human experimental studies are reviewed in the section "Implications for Prevention."

There are substantial methodological problems in measuring exposure to behavioral factors such as physical inactivity and diet[179-181]. Most studies have used a single recording of activity or diet as a measure of exposure. While it is assumed that such point estimates are correlated with habitual exercise or intake, it is uncertain what period of time is necessary to obtain the most valid estimates[181]. In retrospective studies, recall may be too imprecise or biased by diagnosis of diabetes and by symptoms. For adequate diet assessments, numerous repeat 24-hour diet recalls ap-

Table 9.5
Results of Genetic Modeling of NIDDM Phenotypes

Ref.	Characteristic	Population	Genetic model	Mode of inheritance	Gene frequency
50	Fasting serum glucose	Seminole Indians			
		Oklahoma	Major gene	AD=AR	0.41 (AR)
		Florida	Major gene	AD=AR	0.09 (AD)
176	Family history of NIDDM	Hispanics, Mexico City, Mexico	Major gene	AR	
177	2-hour glucose ≥200 mg/dl	Pima Indians	Major gene	Co-dominant alleles	
39	Glucose score	Micronesians, Nauru	Major gene	AD or co-dominant	0.14
178	NIDDM by OGTT	Dravidian South Indians	Major gene	Polygenic > co-dominant	0.20
158	Fasting insulin levels	Mixed Caucasian, Utah	Major gene	AR	0.25

AD, autosomal dominant; AR, autosomal recessive; OGTT, oral glucose tolerance test.

Source: References are listed within the table

pear to be required to capture the variability of diet[180], but this is rarely feasible and may induce unintended change in this risk factor. Such measurement problems have likely led to some underestimation of the effect of behavioral factors on NIDDM risk. Improvement of the validity and precision of behavioral exposure assessment is essential for etiologic studies of NIDDM.

DIET

Diet has been considered a possible cause of diabetes for centuries[182]. Total caloric intake as well as several components of diet have been considered, including carbohydrates and fats. Studies of severe food shortages during wars[183-185] provide ecological evidence that diabetes mortality and morbidity declined abruptly with decreased caloric intake.

■ Dietary carbohydrate and fiber

Studies of dietary carbohydrate intake have given extremely variable results[184]. Older studies used rather crude assessment methods, were often ecologic in design[186], or compared persons with established diabetes. An ecologic study in Mexico City, Mexico and San Antonio, TX suggested that dietary carbohydrate intake alone was unlikely to explain the interpopulation differences in NIDDM prevalence[187]. In a small sample of Pima Indian women, higher total and complex carbohydrate intake were associated with higher NIDDM incidence, but comparisons were not adjusted for higher total calorie intake, weight gain, obesity, and other factors[188]. A 12-year prospective study of diet and NIDDM in 1,247 women in Gothenberg, Sweden found no relationships to any dietary variables, including the main sources of carbohydrates and fiber[189]. No relationships with dietary factors were seen in three other prospective studies of NIDDM: the Israeli Heart Disease Study[190-192], the Zutphen Study[193], and the Nurses' Health Study[194] (Table 9.6). These prospective studies were weakened by having only a single measurement of diet, up to 25 years prior to NIDDM onset[193]. A 4-year followup of elderly subjects[195] did find a positive association between development of glucose intolerance and carbohydrate intake, adjusted for obesity and other potential confounding factors. Thus, prospective studies have reported mixed results concerning dietary carbohydrate or fiber and the risk of NIDDM. In San Luis Valley, CO, a retrospective population-based study showed no association between dietary intake of various fiber fractions and NIDDM, although a higher fiber intake was associated with lower fasting insulin levels[196].

■ Dietary fat

Studies exploring the role of high-fat/low-carbohydrate intake are summarized in Table 9.6[183,187-189,193,194,197-205]. High-fat diets have been associated with obesity[206] and altered fat distribution[207]. A higher dietary fat intake was associated with previously undiagnosed NIDDM and IGT in a random sample of Hispanics and non-Hispanic whites screened for glucose intolerance[202]. This effect was present only among sedentary persons. Among 134 persons with IGT followed for 2 years, a 40 g per day higher dietary fat intake increased diabetes risk sevenfold (95% CI 1.3-39), after adjusting for age, sex, ethnicity, obesity, fat patterning, and fasting insulin levels[205]. Consistent results were reported from a study of Japanese Americans[204].

Omega-3 fatty acids appear to reduce serum lipids and

Table 9.6
Summary of Selected Studies of High-Fat, Low-Carbohydrate Diet and Occurrence of NIDDM

Ref.	Population	Result
Ecologic studies		
183	Diabetes mortality over time, including periods of war and rationing in Europe	+
197	Prevalence of diabetes in nine populations	+
198	Japanese in Hiroshima, Japan, compared with migrants in Hawaii, U.S.	+
199	Urban vs. rural Fiji Islanders	+
187	Urban low-income subjects in Mexico City, Mexico and San Antonio, TX	+
Retrospective and cross-sectional studies		
200	Recently diagnosed diabetic and control subjects	+
201	Previously undiagnosed diabetic and nondiabetic Japanese Americans	+
202	Previously undiagnosed IGT and NIDDM Hispanic and non-Hispanic whites in Colorado	+
Prospective studies		
203	Israeli Ischemic Heart Disease Study, 5-year followup of 10,000 men	0
188	5-year followup of 187 Pima Indian women	-
189	12-year followup of 1,462 women in Gothenburg, Sweden	0
193	25-year followup of men in Zutphen, Netherlands	0
204	5-year followup of 66 Japanese Americans with IGT in Seattle, WA	+
205	2-year followup of 134 Hispanic and non-Hispanic whites with IGT in Colorado	+
194	6-year followup of 84,360 U.S. white female nurses	0

IGT, impaired glucose tolerance; +, positive association; –, negative association; 0, no association.

Source: References are listed within the table

lipoproteins, platelet aggregation, blood pressure, and insulin resistance[208-211]. Such properties and preliminary human data[212] suggest that higher intake of omega-3 fatty acids might protect people from developing NIDDM.

■ Alcohol

Alcohol consumption has been suggested as a possible independent NIDDM risk factor, either because of its effects on the liver and pancreas, or simply because additional calories result in increased weight[213,214] and abdominal adipose tissue[215]. Diabetic French men have a 7- to 13-fold excess mortality due to alcohol and cirrhosis[216], and a proportion of glucose intolerance may be due to alcohol intake and liver disease[217]. California men who reported high use of alcohol (≥176 g per week) had twice the incidence of NIDDM, compared with men who drank less alcohol, although the latter had lower rates of NIDDM than men who reported drinking no alcohol[218]. Among women, nondrinkers had the highest rates of NIDDM, and no gradient with alcohol intake was seen. An inverse association of alcohol and NIDDM, consistent with findings from the California study, was seen in the Nurses' Health Study cohort[219]. In the Kaiser-Permanente study of female twins[220], alcohol intake significantly predicted fasting glucose levels. It would be premature to conclude that the association between alcohol and NIDDM differs by gender. This area requires further investigation, since alcohol consumption would constitute a reversible risk factor for diabetes.

PHYSICAL INACTIVITY

Observational studies that have explored the relationship of NIDDM to physical activity are summarized in Table 9.7[187,221-239]. Ecologic studies[187,221-223] suggest that NIDDM prevalence is consistently lower in populations with higher levels of habitual physical activity. Lower prevalence of NIDDM at higher levels of physical activity has also been consistently found in cross-sectional and retrospective studies. In the HANES studies[236], physical activity was related to NIDDM only in Mexican Americans and not in U.S. whites or blacks. However, data from the 1971-75 NHANES I[229] were consistent with other studies.

In the above studies, lower physical activity was reported after diagnosis of NIDDM, and this could have been the result of the diabetes rather than its cause. In contrast, three prospective studies measured physical activity levels prior to NIDDM onset. In the Nurses' Health Study[237], women who reported at least weekly

physical activity had, over the next 8 years, a relative risk of self-reported NIDDM of 0.8 (95% CI 0.7-0.9), compared with those with less activity. There was no dose-response relationship beyond weekly exercise. Five-year followup of a large cohort of male physicians[239] yielded a similar estimate of the protective effect of at least weekly activity (RR = 0.7). In these men, there was evidence of dose-response, and the greatest effect was seen in men who were more overweight. The results of a 15-year followup of male college alumni[238] are consistent with these results. In this group, each 500 kcal of increased energy expenditure in leisure-time activity per week lowered the risk of NIDDM by 10%. This effect was also greatest in more obese men.

It has been postulated that this protective effect of physical activity on development of NIDDM is due to the prevention of insulin resistance. While this appears to be generally true[240,241], some studies of the acute effects of physical training suggest a more complex picture. Subjects who start an exercise program with high insulin levels respond with a drop in insulin levels[242,243]. However, persons who have lower baseline insulin levels increase their insulin levels with exercise. In addition, in some subjects undergoing physical training, there were no changes in insulin levels, but C-peptide levels (insulin secretion) and insulin sensitivity decreased[242]. Among subjects with glucose intolerance, both positive and negative results were seen in subjects placed on similar activity regimens[241]. Thus, training has variable effects depending on the endpoint and the degree of glucose tolerance. For normoglycemic persons of similar physical activity and weight, those with a family history of diabetes have lower maximal oxygen uptake than those without a family history of diabetes[244]. This is consistent with the speculation that low spontaneous physical activity is a familial trait associated with obesity and NIDDM due to genetic differences in muscle structure[245]. The exact type of structural defect in muscle is controversial, however, with studies suggesting that both decreased[246,247] and increased[248] skeletal muscle capillary density are associated with insulin resistance, hypertension, and progression from IGT to NIDDM.

Whereas numerous small short-term clinical studies show that increases in physical activity result in increases in insulin sensitivity, population studies are few. The heterogeneity of responses in insulin sensitivity with physical activity, suggested by the clinical studies, has not been explored in a larger population. In 931 nondiabetic subjects from San Luis Valley, CO, those with higher levels of habitual activity had lower fasting insulin levels (a marker for insulin sensitiv-

Table 9.7
Summary of Studies of Physical Activity and NIDDM

Ref.	Population	Results*	Comments
Ecologic Studies			
221	Western Samoa	+; rural males had lower NIDDM prevalence than urban males	Adjusted for age and obesity; physical activity higher in rural areas
222-224	Funafuti, Tuvalu, Polynesia	+; males had lower NIDDM prevalence and higher physical activity than females	No direct measures of physical activity used; women said to be completely sedentary; adjustment for obesity did not remove female excess NIDDM prevalence
187	Mexico City, Mexico, and San Antonio, TX	+; greater physical activity in Mexico City, with lower NIDDM prevalence, than in San Antonio	Similar levels of Native American admixture; obesity adjustment removed 50% of NIDDM excess in San Antonio; obesity may be related to both greater physical activity and lower caloric intake (in women); physical activity not analyzed directly in models across populations
Cross-Sectional/Retrospective Studies			
225	579 Polynesian Wallis Islanders	+;NIDDM prevalence ratio 0.37 in males, 0.45 in women with heavy physical activity vs. sedentary-moderate, not statistically significant	Four-level physical activity scale used; adjusted only for age; no multivariate analyses
226	1,235 Fiji Island male Melanesians and Indians	+; NIDDM prevalence ratio ~ 0.4-0.5 for those doing moderate or heavy exercise; no effect in females	Four-level physical activity scale used; prevalence adjusted for age, triceps skinfold thickness, and urban/rural residence
227	5,519 Melanesian and Indian Fiji Islanders; Micronesians on Kiribati	+/-; NIDDM prevalence lower in active Melanesians, Indian males, and Micronesian females compared with inactive persons	Four-level physical activity scale used; results not consistent in all gender/ethnic groups
228	133 newly diagnosed NIDDM subjects in Finland, 144 controls	+; male NIDDM: OR=0.4 (0.2-0.8) for work activity, 0.7 (0.4-1.4) for leisure-time activity compared with sedentary; female NIDDM: OR=1.2 (0.6-2.4) for work activity, 0.5 (0.3-0.9) for leisure-time activity	Results not adjusted for confounding of age and obesity since these were not included in multivariate analyses; data presented only in text
229	8,305 subjects in U.S. NHANES I	+; OR=0.33 (0.26-0.42) for active vs. not active subjects with NIDDM and controls adjusted for obesity	Prevalent cases of NIDDM with current activity by questionnaire after onset of NIDDM, no separation into work or leisure-time; not analyzed using weighting to reflect sampling; results differ from NHANES II analysis in Reference 236
230	5,398 female college alumnae: 2,622 college athletes, 2,776 nonathletes	+; athletes had RR = 0.29 (0.11-0.75) vs. non-athletes for reported lifetime NIDDM prevalence	Female athletes had longer precollege history of athletics and were more likely to be currently exercising regularly; a higher percent of athletes were also restricting diet and had lower estimated percent body fat; no multiple adjustment used
231	2,000 Rancho Bernardo, CA whites; prevalent cases of NIDDM at 1984-87 examination	+; exercise as only means of weight control associated with RR=0.5	Retrospective study of reported exercise to control weight as adult; no current measures of activity
232	157 Japanese-American men in Seattle, WA	+; rural vs. urban birthplace OR=0.5; more active-lean as youth OR=0.6 (p<0.02)	Recall of early life variables; no control for current levels of physical activity
233	807 Swedish middle-aged males and females	+; OR=0.45 (p=n.s.) for high vs. low leisure-time activity for persons with IGT	Effect weaker when family history of diabetes was positive
234	5,080 Mauritius Islanders: Indian, Chinese, and Creole	+, high vs. low physical activity had OR=0.23 (female), 0.59 (male) for NIDDM	Recall assessment of work and leisure-time activity in past 1 year; decreased OR for high physical activity similar for IGT and newly diagnosed NIDDM; also for high vs. moderate physical activity; effect not seen in Chinese subjects
235	1,147 Hindu Indian migrants to Tanzania	+; higher levels of physical activity associated with less NIDDM, prevalence ratio 0.35 for males, 0.20 for females	Independent of age and obesity
236	6,581 U.S. Hispanics (HHANES), 15,364 blacks and whites (NHANES II) in cross-sectional U.S. surveys	+/-; higher level of work activity associated with lower NIDDM prevalence in Mexican Americans, not in blacks or whites; no association with leisure-time physical activity	NIDDM included both previously diagnosed and those detected by 2-hour OGTT; results controlled for age and obesity
Prospective Studies			
237	87,253 U.S. white women nurses; 8 years followup	+; adjusted RR=0.83 (0.74-0.93) for at least weekly physical activity vs. less than weekly	Effect stronger within first 2 years of followup for symptomatic NIDDM as outcome; no dose-response seen with increasing exercise; no modifying effect of family history of diabetes, alcohol intake, or obesity
238	5,990 U.S. male university alumni; 15 years followup	+; age-adjusted RR=0.94 (0.90-0.98) for each 500 kcal increase in leisure-time activity per week	Association weaker when obesity included; dose response seen with increasing activity in middle age; greatest effect seen in most obese men, not in low-risk, nonobese, nonhypertensive men
239	21,271 U.S. male physicians; 5 years followup	+; adjusted RR=0.7 for at least weekly physical activity vs. less than weekly	Effect greatest among men who were more overweight; significant trend of greater effect with increasing amount of exercise

IGT, impaired glucose tolerance; RR, relative risk; OR, odds ratio; HHANES, 1982-84 Hispanic Health and Nutrition Examination Survey; NHANES II, 1976-80 Second National Health and Nutrition Examination Survey. *Code for Results: +, less NIDDM with more physical activity; +/–, inconsistent results for the population under study; –, no relationship between physical activity and NIDDM.

Source: References are listed within the table

ity), adjusted for BMI, age, and ethnicity[249].

Age-related decline in insulin sensitivity is likely caused, in part, by declining physical activity[250]. Since, at any age, higher levels of physical activity are associated with higher insulin sensitivity, it appears plausible that physical activity plays a major role in the interpopulation differences in insulin sensitivity[251]. Taken together, there is substantial consistency in the published information on physical activity and NIDDM, and it seems reasonable to conclude that increased levels of physical activity decrease the risk of NIDDM.

OBESITY

Total body adiposity has been recognized as being associated with diabetes for a very long time[47]. Nonetheless, there is substantial controversy about the meaning of the relationship, since nonobese persons develop NIDDM and many obese persons never develop NIDDM. Several explanations are possible: 1) obesity is the etiologic pathway of a distinct subtype of NIDDM, 2) a similar genetic predisposition leads independently to both obesity and NIDDM, and 3) a similar genetic defect predisposes to both, but different additional genetic and/or environmental factors complete the sufficient causes for NIDDM and obesity.

Obesity itself is unlikely to completely explain interpopulation differences in NIDDM frequency[35,37,198,252]. For example, Hispanics in San Luis Valley, CO have a twofold higher NIDDM prevalence[35] and incidence[253], compared with non-Hispanic whites after adjustment for obesity, fat patterning, age, sex, and family history of diabetes. A higher prevalence of NIDDM was also found in U.S. blacks compared with whites after adjustment for obesity and other risk factors[37]. This racial disparity was present particularly at higher levels of obesity and the adverse effect of obesity was greatest in black women. Numerous cross-sectional and retrospective studies show that obesity is associated with NIDDM prevalence[182]. Also, more rigorous prospective studies show consistently higher incidence of NIDDM in obese persons than in thinner persons in diverse populations, such as U.S. non-Hispanic[254] and Hispanic whites[255,256], Israelis[257], Swedes[258], Nauruans[259], and Pima Indians[59].

Information on the prevalence of diagnosed and undiagnosed NIDDM in national surveys, according to obesity level, is shown in Appendices 9.9-9.11. Time trends in the prevalence of overweight in the U.S. population are shown in Appendices 9.12 and 9.13.

■ Duration of obesity

In addition to the level of obesity, duration is also an important NIDDM risk factor. Maximum lifetime BMI was associated cross-sectionally with NIDDM, independent of current BMI[260]. In Pima Indians who attained a BMI ≥30, the risk of NIDDM increased from 24.8 per 1,000 person-years in those who were obese for <5 years, to 35.2 per 1,000 for obesity of 5-10 years, to 59.8 per 1,000 for >10 years of obesity, adjusted for age, sex, and current BMI[261]. Unexpectedly, in the majority of normoglycemic subjects in that study, longer obesity duration was associated with lower fasting and post-load insulin concentrations. This could have occurred if decreased insulin secretion followed prolonged obesity. It could also be due to a "survivor" effect, since persons who converted to IGT or NIDDM were excluded from these analyses.

■ Body fat distribution

The location of body fat is a strong risk factor for NIDDM, independent of the presence of obesity[182,262]. Upper body (central, abdominal) obesity, measured as waist-to-hip ratio or subscapular-triceps ratio, increased the risk of diabetes in both cross-sectional[37,263,264] and prospective studies[255,265]. Even stronger associations were demonstrated with better measures of intra-abdominal fat, such as CT scans[266-268]. Longitudinal studies have shown that, as persons age, both weight gain and increased waist circumference occur; even in older persons who lose weight, waist circumference continues to increase[269]. Such trends may partially account for the increased incidence of NIDDM with aging.

■ Shared genetic background between obesity and NIDDM

Obesity appears to interact with family history of diabetes in promoting NIDDM risk. Nondiabetic Mexican Americans with a family history of diabetes had more total and abdominal obesity (and other cardiovascular risk factors) compared with those without a family history[270]. Adjustment for serum insulin levels removed the relationships with obesity, suggesting that the association was mediated through hyperinsulinemia. In contrast, in Japanese Americans[215] and Swedes with IGT[233], the relationship between NIDDM and obesity was most apparent in subjects without a family history of diabetes. The odds of NIDDM among physically inactive and obese Swedes (compared with physically active and lean Swedes) were higher for those without than for those with a first-degree diabetic relative (9.6 versus 3.1). This does not necessarily mean that obesity is less of a risk

factor in persons with a genetic susceptibility to NIDDM; it may merely reflect a lower prevalence of obesity in subjects without a family history of diabetes in lower-risk populations.

■ Risk factors for obesity

There is evidence that obesity has a strong genetic component, based on familial studies[271-273], twins raised apart[274], and adoption studies[275]. A single major recessive gene accounting for 20%-35% of the total variance of obesity may exist[276]. Several factors have been proposed as the link between obesity and NIDDM, among which is the tumor necrosis factor α[277]. Behavioral factors, such as increased calories or decreased caloric expenditure, obviously increase the risk of obesity[182,262,272,278,279]. No effect of physical activity or dietary factors on the incidence of obesity was seen in Mexican Americans in San Antonio, TX[280]. This was not the case in a Finnish study, which found that decreased physical activity was associated with greater weight gain in both men and women[214]. While it is clear that obesity has both genetic and behavioral components, the interaction between these factors remains unclear.

■ Parity and pregnancy effects

It has been suggested that increasing parity increases the risk of NIDDM in women. Retrospective studies have found both positive[182,281] and no[222,282] associations. It has been argued that the effect of pregnancy operates through weight gain that accompanies pregnancy and that the number of births have no independent effect themselves. As expected, parity predicts weight gain[214]. A positive association between increased parity and NIDDM, adjusted for current BMI, was found in Rancho Bernardo, CA[283], suggesting that parity may have an effect beyond that of obesity. In contrast, a prospective study of 113,606 U.S. female nurses is consistent with the view that increased risk of NIDDM is secondary to obesity[284]. In this study, there was a relative risk of 1.6 (95% CI 1.3-1.9) for women with ≥6 births compared with nulliparous women; however, adjustment for age and BMI completely removed any effect of parity. Thus, it appears from this very large prospective study that parity has no independent effect beyond its effect on weight gain.

Studies of Pima Indians found an association of maternal diabetes during pregnancy with childhood obesity[285] and later NIDDM[286] in the offspring. It was hypothesized that the maternal intrauterine environment may affect the incidence of obesity and diabetes. A higher rate of maternal than paternal history of diabetes was reported by persons with NIDDM in a family study[287]. If confirmed, these results have important public health implications for the prevention of obesity and NIDDM, since higher rates of obesity and diabetes in women of reproductive age may result in a vicious cycle of obesity and diabetes in the offspring.

THINNESS AT BIRTH

It has been proposed that persons who are thin at birth or at age 1 year are at an increased lifetime risk of NIDDM[288]. This association was extended to IGT[289] and to insulin resistance with normal glucose tolerance[290]. These associations appeared to be quite strong and independent of gestational age, gender, adult BMI, waist-to-hip ratio, and social class at birth and in adulthood. Associations between low birth weight and traits related to insulin resistance were also reported for Mexican Americans in San Antonio, TX[291]. However, the initial interpretation that poor fetal nutrition leads to poor development of β-cells and their dysfunction later in life[288-290] is not widely accepted. The main argument to the contrary comes from the observations that children in high-NIDDM-risk populations, such as Pima Indians[292] or Nauruans[293], are generally hyperinsulinemic and that higher baseline insulin levels (not compatible with β-cell dysfunction) are predictive in these[293] and low-risk populations[197]. An alternative explanation is that low birth weight and low ponderal index at birth reflect an intrauterine infection affecting pancreatic β-cells. It is plausible that the increased incidence of IGT and NIDDM in persons with low birth weight reflects a latent β-cell defect (see below). It remains to be elucidated, however, how a latent β-cell defect could lead to insulin resistance or hyperinsulinemia.

SOCIOECONOMIC STATUS

In early studies, populations with greater affluence, education, and social standing (and usually greater access to food) had higher diabetes prevalence[47]. Some of this may have been an artifact of access to medical care. More recent studies have found that lower income, education, and social class are associated with increased prevalence of NIDDM[294]. In the 1976-80 NHANES II, college education (≥1 year) was associated with a 30% reduction in risk of NIDDM compared with less than a high school education, adjusted for the effects of obesity, family history of diabetes, and other factors related to NIDDM[37]. In rural San Luis Valley, CO, there was an interaction between the effects of education and ethnicity: Hispanics with less

than a high school education had 3.6 times the diabetes prevalence of non-Hispanic whites, whereas Hispanics with a high school education or greater had no excess risk compared with non-Hispanic whites, when adjusted for obesity and other relevant risk factors[35].

URBANIZATION

Urban residents have NIDDM rates higher than rural dwellers[182]. A number of lifestyle factors implicated in the etiology of NIDDM (e.g., sedentary lifestyle, obesity, and greater level of stress) are associated with urban life. The role of stress as a possible NIDDM risk factor has some support in studies of the neuroendocrine system, especially the sympathetic nervous system[295,296]. An effect of stress might be mediated through abdominal obesity[262] or directly on glucose and/or insulin levels[296]. However, little epidemiologic evidence bears directly on this hypothesis.

ACCULTURATION

A lower prevalence of NIDDM was found in Mexican Americans in San Antonio, TX who were more acculturated to non-Hispanic white culture, even after controlling for social class[297,298]. An exploration of social and dietary factors thought to represent more westernized lifestyles yielded inconsistent results, but some evidence, especially in women[298], supported the association with social class. It has been postulated[297] that as persons from a very traditional society become westernized, NIDDM risk increases, as seen in data from a poor area of Mexico City, Mexico, compared with San Antonio, TX[187]. However, with further cultural assimilation, increased leisure-time physical activity and less dietary fat intake begin to be adopted, leading to inversion of the relationship between westernization and NIDDM.

An alternative hypothesis is that acculturation occurs more easily among persons with less admixture (e.g., in the United States, those with lighter skin) and that genetic factors are responsible for the relationship with NIDDM. The most acculturated San Antonio, TX Hispanics also have the lowest Native American admixture[51,297] and the lowest NIDDM risk. The least-acculturated San Antonio barrio Hispanic men (but not women) have Native American admixture similar to the residents of Mexico City, Mexico but a 36% higher NIDDM prevalence[187]. Without precise individual estimates of genetic admixture, it is virtually impossible to disentangle the likely confounding between the effects of acculturation and genetic admixture. This

controversy needs greater emphasis in future studies, since elucidation of the interaction between ethnicity, acculturation, and genetic susceptibility may be critical for designing optimal NIDDM prevention in minority populations.

One of the major epidemiologic arguments for the role of environmental factors in the etiology of NIDDM has been the rapid increase in prevalence and incidence of NIDDM in populations undergoing rapid westernization[48,299,300]. Table 9.8 summarizes information on the prevalence of diabetes and IGT in migrant Chinese and Asian Indian groups (age 30-64 years)[34]. Although genetic comparability cannot be ensured for these comparisons, the consistently high relative prevalence for the migrant populations suggest powerful environmental influences of the migrant settings. Such changes were also documented in Native Americans[301], including Eskimoes[302], who were once thought to be largely immune to NIDDM[47]. The westernization transition is usually accompanied by increases in obesity, decreases in physical activity, and alterations in dietary intake toward more calories and fat and less complex carbohydrates. Studies of persons who have migrated from Japan to Hawaii[198] and from Yemen to Israel[303] found excess diabetes in the migrants compared with persons of the same genetic stock in the homeland.

Table 9.8
Relative Prevalence of Abnormal Glucose Tolerance in Migrant Populations, Age 30-64 Years

	Diabetes		IGT	
Population	Men	Women	Men	Women
Chinese				
China*	1.0	1.0	1.0	1.0
Singapore	4.3	4.9	0.9	0.4
Mauritius	10.0	6.4	18.3	27.1
Asian Indians				
Rural India*	1.0	1.0	1.0	1.0
Urban India	3.2	6.6	1.3	1.2
South Africa	3.9	12.2	1.4	1.0
Tanzania (Hindu)	3.2	5.8	2.1	2.9
Tanzania (Muslim)	2.6	5.8	2.7	4.5
Mauritius (Hindu)	4.8	7.8	1.7	3.1
Mauritius (Muslim)	4.9	9.8	1.1	2.7
Singapore	6.1	6.1	0.6	0.3
Rural Fiji	6.2	9.4	1.3	2.3
Urban Fiji	6.4	11.9	1.3	2.3

*Reference population; data for other groups are the ratios of their prevalence relative to prevalence in China or rural India; IGT, impaired glucose tolerance.

Source: Reference 34

GENETIC-ENVIRONMENTAL INTERACTIONS

While it has been postulated for some time that diet, physical activity, and other environmental factors operate on a susceptible genotype, few studies have explored this arena directly. The limiting factors include the paucity of candidate genetic markers, inaccurate family histories of diabetes, and the need for large samples to adequately stratify or model interactions. Nonetheless, it appears that such approaches should be taken whenever sufficient data are available. Some studies that have examined such interactions are summarized below.

Diet and physical activity are the two major risk factors for both obesity and insulin resistance[272,304], which also have genetic component(s)[271,274,275,305,306]. Stratification of analyses by the presence of family history of diabetes did not reveal any differences in the effect of physical activity on the incidence of NIDDM between subjects with and without a family history[237]. Possible interactions of a high-fat diet with family history of diabetes were explored in the San Luis Valley Diabetes Study in Colorado[202], but no difference was found in the effect of fat intake among persons with and without a family history of diabetes. In a large cross-sectional study of 32,662 white women, obesity and family history of diabetes had a positive synergistic (multiplicative) effect[307].

Twin studies have explored an interaction between dietary or alcohol intake and familial factors. In male twins discordant for NIDDM, no differences were found in diet composition or alcohol intake[68]. In a similar study of female twins, alcohol intake was significantly associated with fasting plasma glucose in both matched and unmatched analyses, suggesting it was unlikely to have a genetic component[220].

Given the heterogeneity in NIDDM that is increasingly evident, studies of candidate gene markers should be done in the context of environmental data. While it can be postulated that obesity, physical inactivity, and diet act in the same way in hypoinsulinemic and hyperinsulinemic NIDDM, there are as yet no data to confirm or refute such a hypothesis. Definition of the interface between genetic susceptibility for NIDDM and the environment should be of highest priority for epidemiologists using molecular tools in the next few years. With the increasing body of information concerning genetic factors in NIDDM and their interactions with nongenetic factors, more sophisticated modeling of the pathogenesis of the NIDDM phenotype will become feasible[308-310].

METABOLIC FACTORS ASSOCIATED WITH NIDDM RISK

METABOLIC FACTORS PROMOTING PROGRESSION TO DIABETES

■ Insulin resistance and hyperinsulinemia

The central role of insulin resistance in the pathogenesis of the main form of NIDDM is widely accepted[311-315]. Insulin resistance is defined as the subnormal biologic response to a given concentration of insulin[316]. Given the pleiotropic actions of insulin on glucose, lipid, and protein metabolism, multiple defects could result in hyperinsulinemia or insulin resistance. Insulinemia, especially levels of fasting insulin, correlate surprisingly well (at the level of 0.6-0.8) with more sophisticated measures of insulin resistance such as the euglycemic clamp[157] or the minimal model[165,317], at least among persons with relative euglycemia.

Studies of Pima Indians[318,319], Hispanics[320], and non-Hispanic whites[320,321] who developed IGT from normal glucose tolerance demonstrated that insulin resistance precedes a defect in insulin secretion. Such studies strongly argue for a two-step process[318], the first being insulin resistance and the second being β-cell failure. Loss of pulsatile insulin secretion has also been suggested as the first lesion leading to NIDDM[322]. However, this observation was made in glucose-intolerant subjects and not in subjects with normal glucose tolerance, making the primacy of this defect uncertain. Suppression of hepatic glucose output was normal in insulin-resistant relatives of NIDDM subjects, suggesting that the liver is not the primary site of the defect[323].

■ Hyperglycemia

Numerous epidemiologic studies have examined the role of elevated glucose levels as a risk factor for the development of NIDDM[62,311]. *In vitro* and animal studies suggest that chronic hyperglycemia is detrimental to insulin secretion and may also induce insulin resistance[324]. This gluco-toxicity may perpetuate the diabetic state and eventually lead to a permanent loss of β-cell function.

FACTORS PROMOTING ATHEROSCLEROSIS BUT PROBABLY NOT PROGRESSION TO DIABETES

NIDDM, atherosclerosis, and hypertension share several critical risk factors, including dietary fat, physical

inactivity, and upper body obesity. Dietary and metabolic factors related to this so-called "syndrome X"[325] are probably linked by insulin resistance and possibly by a common genetic defect. Therefore, it is not unexpected that decreased HDL cholesterol and increased triglyceride concentrations, elevated blood pressure levels, and albuminuria all precede and, to some degree, predict the onset of NIDDM[326]. However, there is little evidence that these metabolic abnormalities may independently accelerate progression from normal glucose tolerance or IGT to NIDDM. In the most informative prospective study of syndrome X to date[327], elevated insulin levels preceded other components of the syndrome.

■ Dyslipidemia

Increased triglycerides and decreased HDL levels have been consistently associated with NIDDM, IGT, and syndrome X. Increased triglyceride levels might possibly induce insulin resistance through interference with peripheral insulin binding and action[328,329] or through increased availability and oxidation of free fatty acids[330]. Reduction of elevated triglyceride levels, however, does not normalize insulin levels or insulin sensitivity in subjects with syndrome X[331], suggesting that increases in triglyceride levels are the result of insulin resistance rather than its cause.

Very low-density lipoprotein concentration was an independent predictor of glucose intolerance in a 14-year followup of the Framingham Study in Massachusetts[332]; however, insulin levels were not measured. The Paris Prospective Study found no association between triglyceride levels and the incidence of NIDDM[333]. A 10-year followup of subjects with familial hypertriglyceridemia demonstrated that the baseline triglyceride level was a significant predictor of NIDDM and IGT incidence, independent of insulin levels[331]. This independence was not, however, interpreted as evidence for the primary role of an increase in triglyceride concentration in the origin of syndrome X and progression to NIDDM.

■ Hyperdynamic circulation

Elevated blood pressure levels[197,334] and heart rate[335] precede the development of NIDDM in many patients. Hyperdynamic circulation (pulse pressure and heart rate in the upper quartile of the population distribution) was associated with a fourfold increased risk of NIDDM in an 8-year follow-up study[335]. As with the association between triglycerides and NIDDM, the chronology of changes is not totally clear. However, there is more evidence for a primary role of insulin levels and insulin sensitivity in the etiology of

NIDDM than for hyperdynamic circulation.

■ Albuminuria

Elevated urinary albumin excretion occurs early in the course of NIDDM, in persons with IGT, and in nondiabetic offspring of NIDDM subjects[334]. In 891 Finnish nondiabetic subjects followed for 3.5 years, albuminuria predicted the development of NIDDM independently of blood pressure levels, but not after adjustment for plasma glucose and insulin levels. This observation highlights albuminuria as a plausible component of syndrome X. However, more data are needed to determine the chronology of events and the importance of this phenomenon in the etiology of NIDDM.

■ Sex hormones

Levels of some sex hormones and low levels of sex hormone binding globulin predict the development of NIDDM in women but not in men[336]. Although sex hormones do not appear to play a primary role in the etiology of NIDDM, they may be related to factors such as central adiposity and insulin action, warranting further studies.

METABOLIC EPIPHENOMENA

■ Proinsulin

The association between hyperinsulinemia and NIDDM risk may theoretically be secondary to an association with proinsulin. Insulin cross-reacts with proinsulin in conventional assays. Several studies have reported disproportionately elevated proinsulin levels in subjects with NIDDM[337]. In nondiabetic subjects, proinsulin levels appear to be more strongly related to increased triglycerides than insulin, despite its weaker relationship to obesity[338]. Even studies with proinsulin measured using highly specific assays may be inconclusive, given the collinearity of insulin and proinsulin levels. The current evidence is insufficient to include proinsulin levels among the primary risk factors for NIDDM.

■ Islet associated polypeptide (amylin)

A high proportion of NIDDM patients have pancreatic amyloid deposits made up of islet amyloid polypeptide (IAPP)[339], also called amylin[340]. IAPP was identified at autopsy in the pancreata of 77% of diabetic Pima Indians but in only 7% of controls[341], comparable to other ethnic groups. The sequences of IAPP predicted from cDNA probes appear to be the same in

diabetic and nondiabetic subjects[342] and the precursor DNA sequence is normal[343]. Thus, it is unlikely that a mutation is responsible for the accumulation seen in the pancreas.

IAPP has attracted substantial attention as a possible cause of insulin resistance and NIDDM. The protein is co-secreted with insulin[344]. It has been proposed[340] that IAPP can act in concert with insulin to switch the site of carbohydrate disposal from skeletal muscle to adipose tissue. This could occur if IAPP made peripheral skeletal muscle insulin resistant, while maintaining relative adipose sensitivity to insulin-mediated glucose disposal. Although substantial evidence for such a mechanism exists[339,345], it has been obtained only at pharmacologic levels of IAPP infusion, calling its relevance into question. IAPP levels do not differ among persons with varying degrees of glucose intolerance[346], nor do they differ between first-degree relatives of persons with NIDDM and controls, unless the relatives were also glucose intolerant[347]. In insulin-resistant Pima Indians with IGT or obesity but without NIDDM, no deposits of IAPP were found[340]. No genetic linkage or association was detected between the IAPP gene and NIDDM in Caucasians[113]. Although formation of IAPP deposits may occur concurrently with progression from IGT to NIDDM, it is unlikely that IAPP could be a precursor of insulin resistance.

INTEGRATION OF GENETIC, BEHAVIORAL, AND METABOLIC FACTORS IN A MODEL OF NIDDM CAUSATION

INTERMEDIATE RISK CATEGORIES

■ Impaired glucose tolerance

IGT is defined as a glycemic response to the standard 75-g oral glucose challenge that is intermediate between normal and diabetic, i.e., venous plasma or capillary whole blood glucose concentration 140-199 mg/dl at 2 hours after a glucose load. The incidence of IGT was reported to be 17.6 per 1,000 person-years in non-Hispanic whites and 32.6 per 1,000 person-years in Hispanics[348]. The importance of IGT as a prognostic category for development of NIDDM is generally accepted, but some aspects remain controversial[349-351]. In Colorado, Hispanics with IGT have nine times higher risk of developing NIDDM than Hispanics with normal glucose tolerance, whereas in non-Hispanic whites, IGT increases the risk of NIDDM 23 times[348]. The average annual incidence of NIDDM among persons with IGT in the San Luis Valley Diabetes Study in Colorado was 8.7% for Hispanics and 5.3% for non-

Table 9.9
Incidence of Diabetes in Persons with Impaired Glucose Tolerance

Ref.	Population	Mean age (years)	No. of subjects	Duration of followup (years)	Average annual incidence (%)
352	Nauruans	38	51	6.2	4.0
353	Pima Indians	32	384	3.3	6.1
354	Maltese	35-74	75	6.0	5.1
355	French	44-55	486	2.5	2.1
348	Colorado Hispanics	20-74		4.0	8.7
	Non-Hispanic whites	20-74		4.0	5.3
356	South African Indians	49	128	4.0	12.6
357	San Antonio, TX Hispanics and non-Hispanic whites	25-64	211	8.0	2.7

Source: References are listed within the table

Hispanic whites. Studies in other populations have reported a wide range of diabetes incidence for persons with IGT followed for 2-17 years, from 1.5% to 14% per year[350]. More stringent estimates, derived from studies using the WHO classification, range from 2.1% to 12.6% per year (Table 9.9)[348,352-357]. Between 20% and 45% of subjects studied remained IGT at the end of these intervals, and another 30%-50% showed normal glucose tolerance on subsequent oral glucose tolerance tests (OGTTs)[350,355,358-361]. IGT is obviously a heterogeneous category including many persons who will never develop NIDDM. On the other hand, up to 30% of persons developing NIDDM may not exhibit IGT at all or only for a short time (<4 years), and this phenomenon is relatively more frequent in high-risk populations[318,348]. This has important implications for screening and prevention programs. It has been suggested that rapid progression from normal to diabetic glucose tolerance is associated primarily with β-cell defect rather than insulin resistance[351].

■ Gestational diabetes

Glucose intolerance first detected during pregnancy is a risk factor for later development of both NIDDM[291,362] and IDDM[363]. Results of followup of patients with gestational diabetes for development of diabetes have been summarized[364]. Comparison of the reported rates is complicated by variable diagnostic and exclusion criteria, variable diabetes ascertain-

ment bias, and lack of a standardized life-table analysis. The reported cumulative diabetes incidence rates range from 6% to >60%. Pregnancy induces insulin resistance, which may precipitate overt hyperglycemia in persons with subclinical NIDDM or IDDM. However, it is unknown in what proportion of gestational diabetes the disease is truly acquired during pregnancy, rather than merely uncovered due to increased testing. The prevalence of undiagnosed diabetes meeting WHO criteria in U.S. women of childbearing age is similar to the prevalence of gestational diabetes, suggesting that gestational diabetes is simply the discovery of preexisting NIDDM[365]. No study of gestational diabetes has reported glucose tolerance status of the participants prior to the pregnancy. Further research is needed to determine the role of gestational diabetes in the natural history of NIDDM.

RISK ASSESSMENT

■ Categorization

Categorization of glucose tolerance into normal or impaired, based on glucose values at 2 hours after a 75-g oral glucose load, is frequently used for prediction of future diabetes. While the concept of IGT has been challenged as too variable or too broad a category[349,350,366], the relative simplicity of the OGTT is an appealing argument for use of IGT as a screening criterion for subjects with pre-NIDDM.

■ Risk prediction based on multiple regression equations

It has been proposed[367] that the risk of NIDDM can be predicted from multivariate regression equations that include risk factors such as BMI, fat centrality, family history of diabetes, and fasting blood glucose, as well as triglyceride and HDL concentrations, blood pressure, and heart rate. One of the objectives of this approach was to base the prediction on variables commonly measured in ordinary clinical practice, which usually do not include an OGTT. The gender- and ethnicity-specific predictive models performed at least as well as the IGT/normal categorization in predicting NIDDM over 8 years[367]. This promising approach should be further explored in other populations.

THE TWO-STEP MODEL: INSULIN RESISTANCE FOLLOWED BY β-CELL FAILURE

Figure 9.4 summarizes a two-step model for NIDDM etiology[182,318,348]. The first step from normoglycemia to IGT is largely due to insulin resistance, while the second step from IGT to NIDDM is due to a β-cell defect and declining insulin secretion. This model assumes that normoglycemic persons have intact β-cell structure and function prior to development of severe insulin resistance. The proponents of this model claim that the primary role of insulin resistance versus an insulin secretion defect in the development of NIDDM can be easily demonstrated in studies of normoglycemic subjects progressing to IGT and NIDDM[157,323,353,368]. Inclusion of subjects who already have hyperglycemia substantially confounds understanding of the defects, since hyperglycemia itself significantly alters both insulin secretion and insulin sensitivity[323]. However, a study of childhood obesity[369] appears to counter these arguments. In that small clinical study, abnormal patterns of insulin secretion preceded hyperinsulinemia and insulin resistance in obese children. The utility of the two-step model is that it focuses investigations about possible etiologic factors at easily measurable stages in the deterioration of glucose tolerance. The evidence for the two-stage model of the natural history of NIDDM is summarized below.

■ Genetic susceptibility and behavioral risk factors

Genetic susceptibility to NIDDM is likely to include separate but interrelated genes for insulin resistance, obesity, abdominal fat patterning, and other specific gene defects. Some of these have been identified, oth-

Figure 9.4
The Two-Step Model of NIDDM Etiology

Source: Reference 348
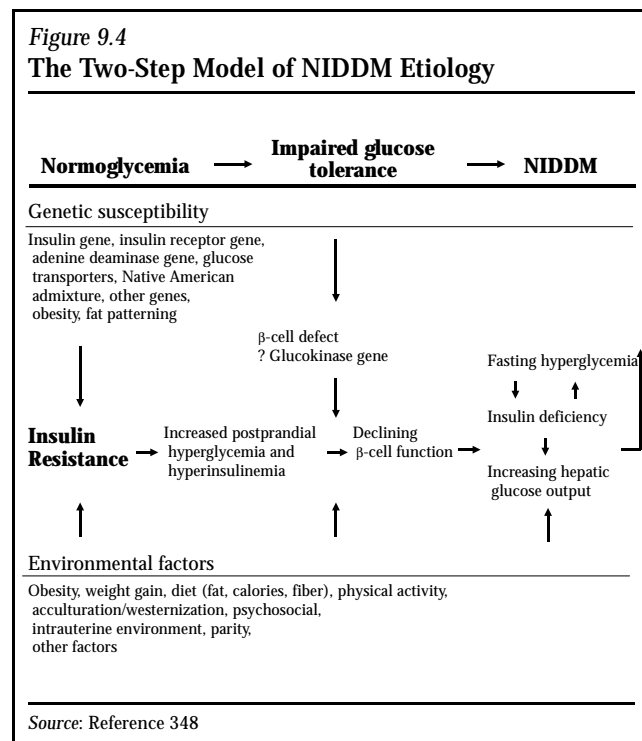
ers are still unknown. Major behavioral factors include dietary calories and fat, physical inactivity, and weight gain. Cultural and psychosocial factors may operate through diet, activity, and weight gain, and may also operate independently. It appears that these behavioral factors can operate not only to start the cascade but also as promoters during decompensation to NIDDM.

■ Insulin resistance

Weight gain is the primary mechanism causing insulin resistance. Evidence for this comes from a study of 192 Pima Indian volunteers who were examined prospectively with yearly euglycemic-hyperinsulinemic clamps[370]. After ~3.5 years of followup, subjects who were the *least* insulin resistant (most insulin sensitive) gained the *most* weight. Conversely, more insulin-resistant persons gained less weight. Insulin resistance may be a feedback mechanism to prevent further weight gain above that determined by some set point[371]. Rapid weight gain was also shown to increase insulin resistance in subjects with hyperandrogenism, insulin resistance, and acanthosis nigricans[372] and in normal women who increased their insulin resistance by 56% during pregnancy-induced weight gain[373]. On the other hand, weight loss in severely obese subjects appears to deter progression from IGT to NIDDM[374]. However, development of IGT in normoglycemic Pima Indians was not related to weight gain but rather to baseline insulin levels[375], suggesting that this feedback mechanism may be more relevant in very early stages of the pathology leading to NIDDM.

Whether such a mechanism also operates in populations not so prone to excess obesity and diabetes as Pima Indians is unclear. However, positive results were obtained using insulin levels, rather than insulin sensitivity, in a study of 789 normoglycemic Hispanics and non-Hispanic whites[376]. Lower levels of fasting insulin predicted greater weight gain over the next 4 years, adjusted for initial body weight, age, sex, and current BMI. The results were not influenced by smoking status, ethnicity, alcohol intake, or intentional weight change. Thus, it appears that in both high- and moderate-risk populations, insulin resistance develops as a result of weight gain, perhaps as a mechanism to prevent further obesity. It is of interest that obesity accounts for only ~15% of the variability of insulin sensitivity[157]. Much of the variability appears to be familial and may be due to genetic differences.

■ β-cell failure

Numerous studies have shown that insulin responses increase during the progression of glucose intolerance

from normal to impaired. However, there is a progressive fall in insulin secretion as glucose levels rise, either by unmasking a primary defect in insulin secretion, from "pancreatic exhaustion," from glucose toxicity[377], or from a combination of these defects[312]. Prospective studies of persons with IGT have identified a *decrease* in insulin levels after a glucose challenge (consistent with a secretory defect) as a predictor of the development of NIDDM in both high- and moderate-risk populations[256,318,321,378,379].

This two-stage model has been proposed principally for the hyperinsulinemic, insulin-resistant form of NIDDM. It acknowledges that hypoinsulinemic varieties of NIDDM exist, e.g., those associated with GCK enzyme defects, where a person may bypass the insulin-resistant phase of the transition and enter the model via genetic β-cell defects.

THE LATENT β-CELL DEFECT MODEL

Figure 9.5 presents an alternative model of the natural history of NIDDM. This model assumes that early β-cell injuries due to viral infections, chemical toxins, or genetic defects lead to a significant reduction of functional β-cell capacity in a large proportion of the general population. In subjects carrying certain HLA and non-HLA genes, such injury leads to β-cell autoimmunity and, in some cases, to clinical IDDM. However, in the majority of these cases, autoimmunity does not develop or is short-lived and β-cell destruction is not progressive. The same genetic and behavioral factors that cause insulin resistance in the two-step model in Figure 9.4 naturally operate in

Figure 9.5
The Latent β-Cell Defect Model of NIDDM Etiology
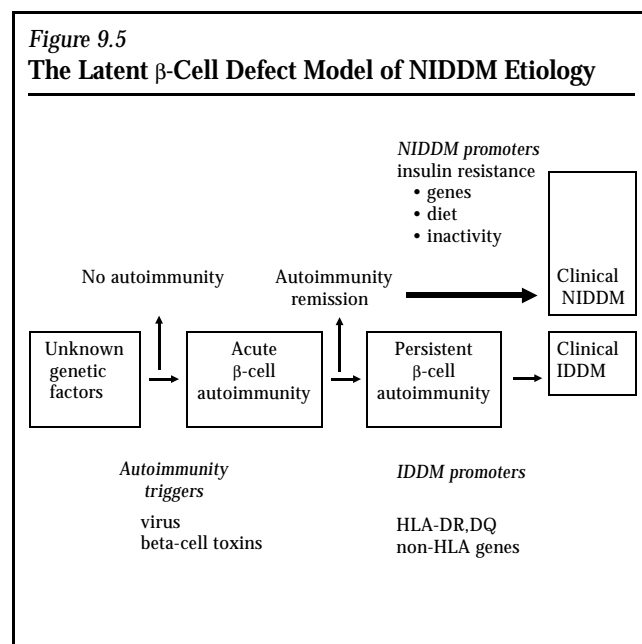
individuals with existing subclinical β-cell loss and may provide the final event precipitating diabetes in a majority of the NIDDM cases. However, an estimated 20% of individuals with subclinical β-cell loss develop hypoinsulinemic diabetes without ever being insulin resistant. The major conceptual difference between this model and the two-step model is the emphasis on environmental insults to the β-cells prior to development of insulin resistance. The evidence for this latent β-cell defect model of the natural history of NIDDM is summarized below.

■ Aborted β-cell autoimmunity

Studies of schoolchildren with no family history of IDDM[380-383] reported the prevalence of β-cell autoimmunity to be as high as 0.7%-4.1%. Over 1-2 years, autoimmunity remitted in up to 78% of these children without the occurence of diabetes or measurable impairment of β-cell function[384-386]. The cumulative risk of β-cell autoimmunity by age 20 years is likely to be ~5%-15%, given the high remission rate and the fact that the assays used (ICA by immunofluorescence) were less sensitive than antigen-specific assays now available[8]. What causes β-cell autoimmunity is currently unclear; however, a large body of evidence points to viral and early childhood dietary factors[387]. This process is sustained in only ~10%-30% of children who develop β-cell autoimmunity, resulting in IDDM after a variable preclinical period. Thus, ~5%-15% of the general population of children is likely left with a subclinical loss of β-cells due to a short bout of β-cell autoimmunity.

■ Genetic defects leading to normo- or hypoinsulinemic NIDDM

As reviewed above, in families with MODY[25] and in a subset of families with later-onset NIDDM[135], a primary GCK defect without hyperinsulinemia may be sufficient to cause hyperglycemia. It is likely that other genetic defects in glucose metabolism exist that are associated with normo- or hypoinsulinemic NIDDM.

ALTERNATIVE MODELS

In an alternative sequence, hypersecretion of the β-cells is the primary genetic defect, and hyperinsulinemia subsequently leads to development of peripheral insulin resistance. Little evidence is available to support this alternative hypothesis. A further speculation is that the multiple defects in glucose and lipid metabolism might be explained by gene defects in insulin's ability to phosphorylate proteins[323]. Such

a hypothesis would focus genetic studies toward a different set of candidate genes than have been explored to date.

MODIFICATION OF GENETIC FACTORS

The gene(s) involved in the etiology of NIDDM are likely to be identified soon. If widespread screening for such gene(s) is practical, high-risk subjects who are identified may become prime targets for the interventions detailed below. Counseling will likely focus on avoiding behavioral risk factors and preventing diabetes in the carriers, rather than on preventing NIDDM in the offspring.

MODIFICATION OF BEHAVIORAL FACTORS

Most previous NIDDM prevention studies have involved altering lifestyle to reduce body weight[388,389]. There is currently no evidence from randomized interventions that any manipulation of specific dietary components prevents progression from IGT to NIDDM. In a randomized study of newly diagnosed NIDDM patients, a low-carbohydrate diet was compared with a modified-fat diet[390]. Some of the 93 subjects would now be classified as IGT under WHO criteria. Weight decreased slightly more on the low-fat diet, but at 1 year there were no differences in fasting glucose and insulin levels. In a study of eight Pima Indians and two Caucasians with new-onset NIDDM and 10 nondiabetic controls, subjects were placed on a 500 kcal diet for at least 4 weeks to induce an average 15% loss of body weight[391]. Despite significant lowering in blood glucose levels, none of the patients achieved normality. Weight reduction can reverse insulin resistance and, theoretically, should prevent progression to NIDDM in at-risk persons. However, long-term maintenance of a reduced body weight is difficult, and most patients regain the lost body weight within 3 years.

A few studies have demonstrated the benefits of adding exercise programs to dietary interventions for enhancing long-term weight loss in nondiabetic obese individuals[392,393]. In one study, obese NIDDM subjects assigned to a 10-week diet and exercise intervention achieved significantly greater weight loss at 1 year followup than did subjects assigned to a diet intervention only[394]. While the majority of intervention studies in NIDDM patients demonstrated improvements

in blood glucose control in addition to weight loss, there are no data demonstrating the effectiveness of exercise-induced weight loss in preventing NIDDM in at-risk persons[395].

Multifactorial interventions in persons with IGT, including diet modifications, exercise, weight loss, and oral hypoglycemic agents showed no discernible effect on the incidence of NIDDM[396,397]. In one inconclusive study, subjects receiving tolbutamide in addition to a diet intervention showed somewhat lower incidence of NIDDM[398]. There was no difference in all-cause mortality between the tolbutamide and diet-only groups, but lower vascular mortality occurred for those treated with tolbutamide[399]. To date, only one long-term study has successfully attempted to prevent NIDDM using lifestyle modifications in persons with IGT[388]. In this Swedish study, 217 middle-aged men with IGT were nonrandomly assigned to a diet and exercise intervention or to a control (no intervention) group. Over a 6-year follow-up period, half as many of the treated men as the controls had developed diabetes. This study demonstrated the feasibility of a long-term intervention program in some persons with IGT and suggested that a combined behavioral intervention may reduce or delay the development of NIDDM. However, other studies were less successful[400]. Beginning in 1995, a large multicenter trial in the United States will test the effectiveness of dietary and physical activity modifications in preventing the development of NIDDM in subjects with IGT.

MODIFICATION OF METABOLIC FACTORS

NIDDM is associated with all of the metabolic components of syndrome X[325], including insulin resistance, hyperinsulinemia, hyperglycemia, decreased HDL cholesterol, increased triglyceride concentrations, elevated blood pressure levels, and albuminuria. Intervening on each of these factors separately may or may not reduce the risk of NIDDM, depending on whether the effect of such intervention is on the causal pathway leading to NIDDM, as opposed to the pathways leading to atherosclerosis or hypertension. For example, lowering blood pressure with thiazides or beta-blockers may actually worsen insulin resistance and dyslipidemia. Although hypertension may be prevented, the risk of NIDDM[197] and atherosclerosis may be increased.

Thiozolodinediones are a new class of drugs that potentiate hepatic and peripheral insulin action[401]. Limited human experience suggests improved insulin sensitivity with amelioration of hyperin-sulinemia[401,402], some weight gain[403], and no significant incidence of hypoglycemia[404]. A member of this class, troglitazone, appears to prevent NIDDM among persons with IGT[405]. More data are needed to establish the effectiveness of these agents in preventing NIDDM in the population at large.

EFFECTIVENESS OF INTERVENTION

It has been argued that, to avoid major health burden from a disease such as NIDDM that develops in middle-aged and elderly persons, it may be sufficient to delay the onset of severe hyperglycemia rather than prevent the disease altogether. This approach, focusing on preventing hyperglycemia and microvascular complications, may be insufficient to reduce the primary mortality and morbidity in NIDDM patients—that caused by cardiovascular disease[406]. On the other hand, interventions that reduce insulin resistance and the associated cardiovascular risk factors are those most likely to have a significant impact on all-cause mortality and life quality in populations at risk for NIDDM.

CONCLUSIONS

NIDDM is a heterogeneous condition caused by genetic and behavioral factors. Some genes involved in NIDDM have been identified but apparently not those responsible for the main form of NIDDM, associated with obesity, hyperinsulinemia, and insulin resistance. Identification of additional genes appears imminent and may greatly help to focus future prevention programs on persons at highest risk.

The role of physical inactivity, dietary fat, and weight gain in the etiology of NIDDM is established. What remains to be elucidated is how these behavioral factors interact with the candidate genetic factors to produce diabetes on the individual and population levels. Better understanding of the genetic-environmental interactions and of the heterogeneity of NIDDM would assist in designing optimal measures to prevent the disease. It is still uncertain, as it was 10 years ago[62], whether intervention on the few established behavioral risk factors can prevent or delay development of NIDDM.

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Appendix 9.1

Percent of Persons with a Medical History of NIDDM and Normal Glucose Tolerance Who Report a Sibling or Parental History of Diabetes, U.S., 1976-80
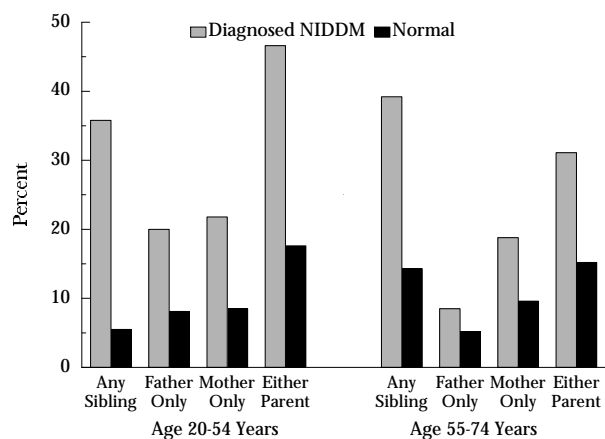
NIDDM defined by excluding all subjects who appear to have IDDM from the group of persons with self-reported history of physician-diagnosed diabetes (IDDM defined by age at onset <30 years, percent desirable weight <120, and continuous insulin use since diabetes diagnosis); nondiabetic defined by oral glucose tolerance test using World Health Organization criteria.

Source: 1976-80 Second National Health and Nutrition Examination Survey

Appendix 9.2

Percent of Persons with a Medical History of NIDDM and Percent of Nondiabetic Persons Who Report a Parental History of Diabetes, U.S., 1989
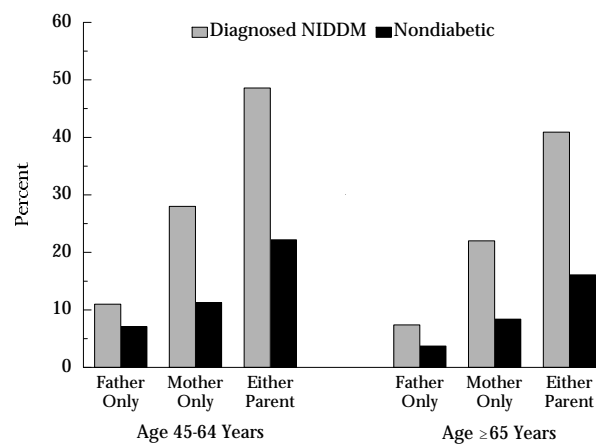
NIDDM defined by excluding all subjects who appear to have IDDM from the group of persons with self-reported history of physician-diagnosed diabetes (IDDM defined by age at onset <30 years, percent desirable weight <120, and continuous insulin use since diabetes diagnosis); nondiabetic defined as all other persons.

Source: 1989 National Health Interview Survey

Appendix 9.3
Percent of Persons Age 20-74 Years with a Family History of Diabetes by Diabetes Status, U.S., 1976-80

Race, sex, age (years), and diabetes status	Father only	Mother only	Both parents	Either parent	Neither parent	Any sibling
All persons	7.4	10.5	0.7	18.9	81.1	9.5
Age 20-54	8.2	9.9	0.8	19.2	80.8	6.5
Medical history of NIDDM	20.0	21.8	2.5	46.6	53.5	35.8
Undiagnosed NIDDM	13.7	11.0	0.0	24.7	75.4	15.0
IGT	6.1	22.0	1.5	30.1	69.9	10.1
Normal glucose tolerance	8.1	8.5	0.6	17.6	82.4	5.5
Age 55-74	5.0	12.3	0.5	18.0	82.0	17.7
Medical history of NIDDM	8.5	18.8	2.8	31.1	68.9	39.2
Undiagnosed NIDDM	4.5	21.4	0.4	26.3	73.7	26.1
IGT	3.3	15.4	0.9	19.6	80.4	17.9
Normal glucose tolerance	5.2	9.6	0.1	15.2	84.8	14.3
Men	7.2	9.5	0.7	17.5	82.5	8.9
Age 20-54	7.8	8.6	0.7	17.2	82.9	5.8
Medical history of NIDDM	15.8	21.4	2.5	41.2	58.8	36.7
Undiagnosed NIDDM	4.2	4.7	0.0	8.8	91.2	22.3
IGT	7.8	20.1	1.2	29.1	70.9	6.2
Normal glucose tolerance	7.7	7.6	0.7	16.0	84.0	5.1
Age 55-74	5.4	12.3	0.6	18.6	81.5	18.0
Medical history of NIDDM	8.4	13.9	3.7	26.9	73.1	35.4
Undiagnosed NIDDM	6.3	17.4	0.9	24.5	75.5	24.7
IGT	5.1	16.5	0.9	22.5	77.5	18.6
Normal glucose tolerance	5.1	10.4	0.2	16.0	84.0	15.5
Women	7.6	11.4	0.7	20.2	79.8	10.0
Age 20-54	8.6	11.1	0.8	21.2	78.8	7.2
Medical history of NIDDM	22.9	22.1	2.6	50.2	49.8	35.3
Undiagnosed NIDDM	20.6	15.5	0.0	36.0	64.0	9.9
IGT	5.1	23.3	1.8	30.7	69.3	12.5
Normal glucose tolerance	8.5	9.4	0.6	19.2	80.8	5.8
Age 55-74	4.8	12.3	0.4	17.6	82.4	17.5
Medical history of NIDDM	8.6	22.4	2.2	34.1	65.9	42.0
Undiagnosed NIDDM	3.4	24.0	0.0	27.4	72.6	26.9
IGT	1.7	14.5	0.9	17.0	83.0	17.3
Normal glucose tolerance	5.3	9.0	0.1	14.5	85.5	13.2
Non-Hispanic whites	7.4	10.3	0.6	18.6	81.4	8.9
Age 20-54	8.1	9.4	0.7	18.5	81.5	5.7
Medical history of NIDDM	23.6	23.4	0.0	49.1	50.9	32.1
Undiagnosed NIDDM	19.4	6.5	0.0	25.9	74.1	5.7
IGT	6.3	22.0	2.2	30.9	69.1	8.9
Normal glucose tolerance	7.9	8.2	0.6	16.9	83.1	5.0
Age 55-74	5.5	12.7	0.5	18.9	81.1	17.2
Medical history of NIDDM	7.5	19.9	3.1	31.4	68.6	38.3
Undiagnosed NIDDM	5.5	22.7	0.0	28.2	71.8	27.7
IGT	4.1	17.0	1.1	22.2	77.8	17.4
Normal glucose tolerance	5.7	9.8	0.2	15.8	84.2	13.8
Non-Hispanic blacks	5.1	10.6	1.4	18.6	81.4	12.6
Age 20-54	6.2	10.0	1.7	19.6	80.4	10.6
Medical history of NIDDM	3.1	13.2	8.1	24.4	75.6	53.9
Undiagnosed NIDDM	0.0	29.6	0.0	29.6	70.4	45.1
IGT	0.0	18.7	0.0	18.7	81.3	13.8
Normal glucose tolerance	7.5	7.9	1.8	19.3	80.7	7.7
Age 55-74	1.8	12.4	0.6	15.2	84.8	19.1
Medical history of NIDDM	10.0	16.7	2.5	31.4	68.6	43.1
Undiagnosed NIDDM	0.0	9.5	3.0	12.5	87.5	20.7
IGT	0.0	16.2	0.0	16.2	83.8	18.6
Normal glucose tolerance	1.1	11.0	0.0	12.1	87.9	13.7

IGT, impaired glucose tolerance. Diabetes status was determined from medical history and results of a 75-g 2-hour oral glucose tolerance test using World Health Organization criteria.

Source: 1976-80 Second National Health and Nutrition Examination Survey

Percent of Persons Age ≥18 Years with a Parental History of Diabetes by Diabetes Status, U.S., 1989

Race, sex, age (years), and diabetes status	Father only	Mother only	Both parents	Either parent	Neither parent	Don't know
All IDDM	9.1	3.5	1.7	16.4	83.6	2.1
18-39	7.3	4.7	2.3	16.3	83.7	1.9
≥40	14.1	0.0	0.0	16.7	83.3	2.7
Men	8.5	3.9	3.3	17.0	83.0	1.4
Women	9.6	3.1	0.0	15.7	84.3	2.9
All NIDDM	10.0	24.7	5.3	45.4	54.6	5.4
18-44	17.5	24.0	9.2	52.4	47.6	1.7
45-64	11.0	28.0	5.5	48.6	51.4	4.1
≥65	7.4	22.0	4.2	40.9	59.1	7.4
Men	8.1	23.5	4.2	41.5	58.5	5.7
Women	11.5	25.6	6.1	48.3	51.7	5.1
Non-Hispanic whites	10.8	24.2	5.1	44.7	55.3	4.6
Non-Hispanic blacks	8.1	27.2	5.2	47.9	52.1	7.4
Mexican Americans	7.4	23.9	6.7	42.5	57.5	4.6
All nondiabetic	5.9	8.2	1.0	17.3	82.7	2.1
18-44	6.0	6.8	0.9	15.5	84.5	1.7
45-64	7.1	11.3	1.6	22.2	77.8	2.3
≥65	3.7	8.4	0.4	16.1	83.9	3.6
Men	5.8	7.5	0.9	16.5	83.5	2.3
Women	6.1	8.8	1.1	18.0	82.0	2.0
Non-Hispanic whites	6.0	7.9	0.9	16.7	83.3	1.9
Non-Hispanic blacks	5.3	10.4	1.1	19.5	80.5	2.8
Mexican Americans	7.6	9.8	2.2	22.5	77.5	2.9

Source: 1989 National Health Interview Survey

Appendix 9.5
Percent of Persons Reporting a Parental History of Diabetes Who Have NIDDM, Age 20-74 Years, U.S., 1976-80 and 1989

Diagnosed NIDDM defined by excluding all subjects who appear to have IDDM from the group of persons with self-reported history of physician-diagnosed diabetes (IDDM defined by age at onset <30 years, percent desirable weight <120, and continuous insulin use since diabetes diagnosis); undiagnosed NIDDM defined by oral glucose tolerance test using World Health Organization criteria.

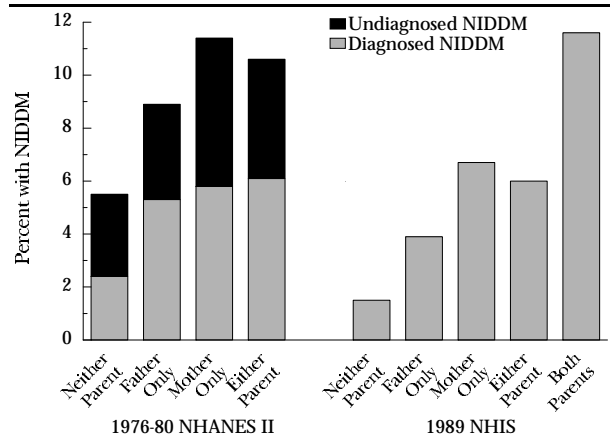*Source*: 1976-80 Second National Health and Nutrition Examination Survey and 1989 National Health Interview Survey

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Appendix 9.6
Age-Standardized Prevalence of NIDDM for Whites and Blacks Age 20-74 Years, by Family History of Diabetes, U.S., 1976-80
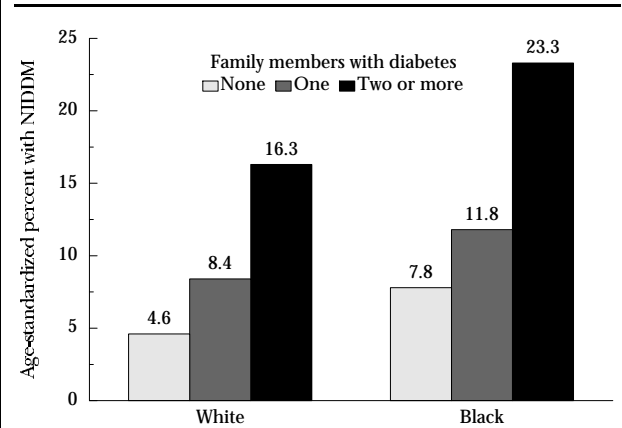

NIDDM includes both diagnosed and undiagnosed NIDDM, defined by excluding all subjects who appear to have IDDM from the group of persons with self-reported history of physician-diagnosed diabetes and by results of oral glucose tolerance test using World Health Organization criteria.

Source: 1976-80 Second National Health and Nutrition Examination Survey

Appendix 9.7
Percent of Persons in NIDDM Diagnostic Categories by Family History of Diabetes, Age 20-74 Years, U.S., 1976-80

Race, sex, age (years), and diabetes status	Family history of diabetes				
	Mother only	Father only	Either parent	Neither parent	Any sibling
All persons, age 20-74					
Medical history of NIDDM	5.8	5.3	6.1	2.4	12.6
Undiagnosed NIDDM	5.6	3.6	4.5	3.1	7.7
IGT	19.9	7.3	14.7	10.0	16.1
Normal glucose tolerance	68.8	83.8	74.7	84.5	63.6
All persons, age 20-54					
Medical history of NIDDM	3.4	3.8	3.9	1.1	8.5
Undiagnosed NIDDM	1.9	2.9	2.2	1.6	4.0
IGT	18.5	6.2	13.0	7.2	13.4
Normal glucose tolerance	76.2	87.2	81.0	90.2	74.1
All persons, age 55-74					
Medical history of NIDDM	11.1	12.3	12.7	6.2	16.7
Undiagnosed NIDDM	13.8	7.0	11.5	7.1	11.6
IGT	23.0	12.1	19.9	17.9	18.9
Normal glucose tolerance	52.1	68.6	55.9	68.8	52.8
Men, age 20-54					
Medical history of NIDDM	3.3	2.7	3.3	1.0	7.5
Undiagnosed NIDDM	0.8	0.8	0.8	1.6	5.7
IGT	15.5	6.7	11.2	5.7	7.2
Normal glucose tolerance	80.4	89.8	84.8	91.8	79.6
Men, age 55-74					
Medical history of NIDDM	7.7	10.6	10.0	6.2	13.8
Undiagnosed NIDDM	9.6	7.9	8.9	6.3	8.8
IGT	25.7	18.3	23.2	18.2	19.8
Normal glucose tolerance	57.0	63.3	57.9	69.4	57.7
Women, age 20-54					
Medical history of NIDDM	3.5	4.7	4.4	1.2	9.3
Undiagnosed NIDDM	2.7	4.6	3.3	1.6	2.7
IGT	20.7	5.8	14.3	8.7	18.1
Normal glucose tolerance	73.1	85.0	78.1	88.6	69.9
Women, age 55-74					
Medical history of NIDDM	3.5	4.0	3.8	0.9	7.8
Undiagnosed NIDDM	1.0	3.6	2.1	1.4	1.5
IGT	17.2	5.7	12.4	6.3	12.0
Normal glucose tolerance	78.3	86.7	81.7	91.5	78.7
Non-Hispanic whites, age 20-54					
Medical history of NIDDM	13.9	14.0	15.0	6.2	19.2
Undiagnosed NIDDM	17.3	6.3	13.8	7.8	13.9
IGT	20.8	6.3	17.1	17.8	18.2
Normal glucose tolerance	48.0	73.5	54.1	68.3	48.7
Non-Hispanic whites, age 55-74					
Medical history of NIDDM	10.5	9.1	11.2	5.7	15.2
Undiagnosed NIDDM	13.3	7.4	11.1	6.6	12.4
IGT	23.3	12.8	20.4	16.6	18.0
Normal glucose tolerance	52.9	70.7	57.4	71.1	54.4
Non-Hispanic blacks, age 20-54					
Medical history of NIDDM	3.9		3.5	2.7	12.1
Undiagnosed NIDDM	7.5		3.7	2.2	11.2
IGT	24.3		12.0	12.8	17.7
Normal glucose tolerance	64.4		80.7	82.3	59.0
Non-Hispanic blacks, age 55-74					
Medical history of NIDDM	15.5		24.5	9.6	29.8
Undiagnosed NIDDM	8.3		8.8	11.1	10.6
IGT	22.9		18.7	17.3	17.4
Normal glucose tolerance	53.3		47.9	62.0	42.2

IGT, impaired glucose tolerance. Undiagnosed diabetes, IGT, and nondiabetic determined by oral glucose tolerance test in persons without a medical history of diabetes using World Health Organization criteria; table excludes persons who appear to have IDDM; in cells with no entry, data are unreliable because of small sample size.

Source: 1976-80 Second National Health and Nutrition Examination Survey

Appendix 9.8
**Prevalence of NIDDM by Family History of Diabetes, Age 20-74 Years, U.S., 1989**

Race, sex, and age (years)	Mother only	Father only	Both parents	Either parent	Neither parent
All persons					
20-74	6.7	3.9	11.6	6.0	1.5
20-54	3.4	2.0	6.2	3.0	0.6
55-74	13.9	11.6	28.1	14.2	4.6
Men					
20-74	6.3	3.0	9.4	5.2	1.5
20-54	3.2	1.2	6.1	2.6	0.6
55-74	13.7	10.0		13.0	4.7
Women					
20-74	7.0	4.8	13.2	6.6	1.6
20-54	3.6	2.7	6.2	3.4	0.6
55-74	14.0	13.0	33.6	15.0	4.5
Non-Hispanic whites					
20-74	5.9	3.6	10.9	5.3	1.3
20-54	2.9	1.7	5.9	2.5	0.5
55-74	11.2	10.3	21.9	11.7	3.8
Non-Hispanic blacks					
20-74	10.8	7.0	17.4	10.2	3.0
20-54	5.7	4.7	11.3	5.9	1.1
55-74	34.2	23.0		33.2	10.1
Mexican Americans					
20-74	6.6	3.0		5.5	2.3
20-54	2.8	1.5		2.5	0.8
55-74	38.8	19.8			10.8

NIDDM defined by excluding all subjects who appear to have IDDM from the group of persons with self-reported history of physician-diagnosed diabetes (IDDM defined by age at onset <30 years, percent desirable weight <120, and continuous insulin use since diabetes diagnosis); in cells with no entry, data are unreliable because of small sample size.

Source: 1989 National Health Interview Survey

Appendix 9.9
Prevalence of NIDDM by Body Mass Index, Age 20-74 Years, U.S., 1976-80
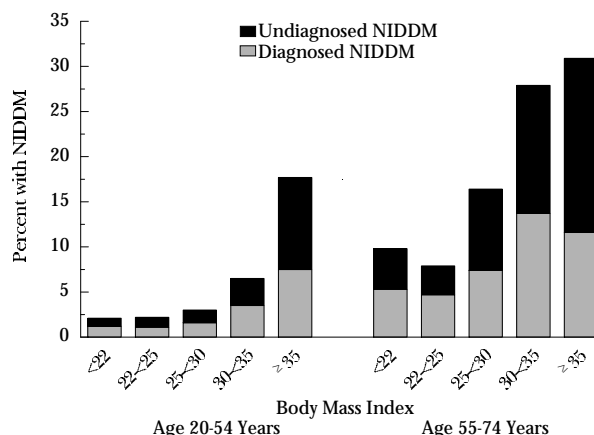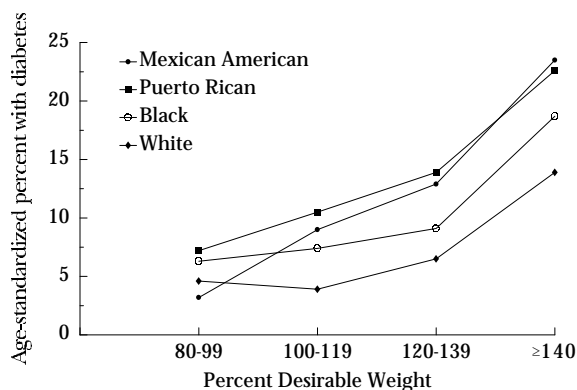

NIDDM includes both diagnosed and undiagnosed NIDDM, defined by excluding all subjects who appear to have IDDM from the group of persons with self-reported history of physician-diagnosed diabetes and by results of oral glucose tolerance test using World Health Organization criteria; body mass index, weight (kg) divided by height-squared (m^2).

Source: 1976-80 National Health and Nutrition Examination Survey

Appendix 9.10
Age-Standardized Prevalence of NIDDM for U.S. Populations, by Percent Desirable Weight, Age 20-74 Years, 1976-80 and 1982-84

NIDDM includes both diagnosed and undiagnosed NIDDM, defined by excluding all subjects who appear to have IDDM from the group of persons with self-reported history of physician-diagnosed diabetes and by results of oral glucose tolerance test using World Health Organization criteria; NHANES was a sample of the entire U.S. population; in HHANES, Mexican Americans were sampled from the southwestern U.S., Cuban Americans from the Miami, FL area, and Puerto Ricans from the New York City area.

Source: 1976-80 Second National Health and Nutrition Examination Survey and 1982-84 Hispanic Health and Nutrition Examination Survey

Appendix 9.11
## Prevalence of NIDDM by Obesity Level, Age 20-74 Years, U.S., 1976-80 and 1982-84

	\<22	Body mass index 22-24.99	25-29.99	30-34.99	≥35
Age 20-74 years					
Medical history	2.0	2.0	3.3	6.9	8.9
Undiagnosed	1.6	1.6	3.6	6.8	13.2
Total	3.5	3.6	6.9	13.8	22.0
Age 20-54 years					
Medical history	1.2	1.1	1.6	3.5	7.5
Undiagnosed	0.9	1.1	1.4	3.0	10.2
Total	2.1	2.2	3.0	6.5	17.7
Age 55-74 years					
Medical history	5.3	4.7	7.4	13.7	11.6
Undiagnosed	4.5	3.2	9.0	14.2	19.3
Total	9.8	7.8	16.4	27.9	30.9
Men, age 20-74 years					
Medical history	2.1	2.2	2.8	3.9	10.5
Undiagnosed	2.7	1.8	3.2	4.0	4.9
Total	4.8	4.0	5.9	7.9	15.4
Men, age 20-54 years					
Medical history	1.2	1.1	1.4	1.0	7.5
Undiagnosed	2.4	1.3	1.0	1.4	4.1
Total	3.5	2.4	2.4	2.4	11.6
Men, age 55-74 years					
Medical history	6.0	5.5	6.5	11.2	29.2
Undiagnosed	4.1	3.3	8.9	11.0	9.8
Total	10.1	8.8	15.3	22.3	39.0
Women, age 20-74 years					
Medical history	1.9	1.8	4.1	9.6	8.3
Undiagnosed	1.0	1.4	4.2	9.3	16.4
Total	2.9	3.3	8.4	18.9	24.6
Women, age 20-54 years					
Medical history	1.2	1.2	2.0	6.0	7.5
Undiagnosed	0.2	0.9	1.8	4.8	13.6
Total	1.5	2.0	3.8	10.8	21.1
Women, age 55-74 years					
Medical history	5.0	3.8	8.5	15.2	9.3
Undiagnosed	4.7	3.0	9.1	16.2	20.5
Total	9.6	6.8	17.7	31.4	29.8
Total NIDDM, age 20-74 years					
Non-Hispanic white men	5.0	3.1	5.5	9.1	9.2
Non-Hispanic white women	3.1	2.9	8.4	16.8	26.1
Non-Hispanic black men	3.2	8.1	8.8		
Non-Hispanic black women	1.2	7.1	7.4	23.5	21.2
Mexican-American men	2.7	3.8	8.6	19.4	
Mexican-American women	2.4	2.8	12.1	17.8	23.4
Cuban Americans	1.6	7.1	12.7	15.9	
Puerto Ricans	2.1	7.4	9.8	19.5	

Body mass index, weight (kg) divided by height-squared (m²); National Health and Nutrition Examination Survey was a sample of the entire U.S. population; in the Hispanic Health and Nutrition Examination Survey, Mexican Americans were sampled from the southwestern United States, Cuban Americans from the Miami, FL area, and Puerto Ricans from the New York City area; in cells with no entry, data are unreliable because of small sample size.

Source: 1976-80 Second National Health and Nutrition Examination Survey and 1982-84 Hispanic Health and Nutrition Examination Survey

Appendix 9.12
## Percent of Adults Who Are Overweight, Age 20-74 Years, U.S., 1960-91
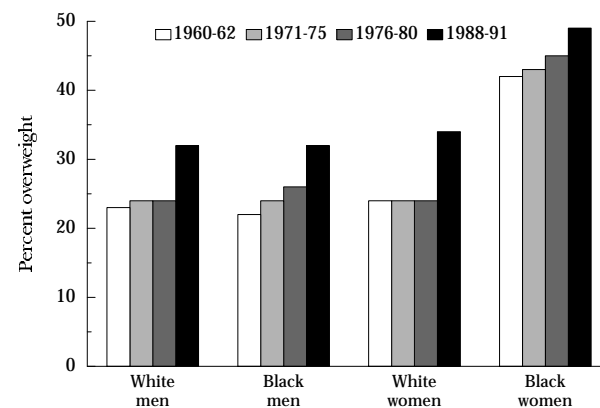
Overweight defined as BMI [body mass index, weight (kg) divided by height-squared (m²)] ≥27.8 for men and ≥27.3 for women, which are the sex-specific 85th percentile values of BMI for men and women age 20-29 years in the 1976-80 NHANES; these values represent ~124% of desirable weight for men and ~120% of desirable weight for women.

Source: Reference 407, 1960-62 National Health Examination Survey and the 1971-75, 1976-80 and 1988-91 National Health and Nutrition Examination Surveys

Appendix 9.13
Percent of Adolescents Who Are Overweight, Age 12-19 Years, U.S., 1976-80 and 1988-91
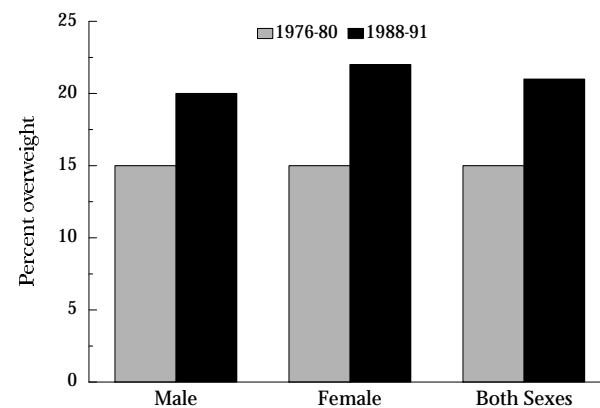
Overweight defined as BMI [body mass index, weight (kg) divided by height-squared (m²)] ≥23.0 for males age 12-14 years, ≥24.3 for males age 15-17 years, ≥25.8 for males age 18-19 years, ≥23.4 for females age 12-14 years, ≥24.8 for females age 15-17 years, and ≥25.7 for females age 18-19 years.

Source: Reference 408, 1976-80 and 1988-91 National Health and Nutrition Examination Surveys