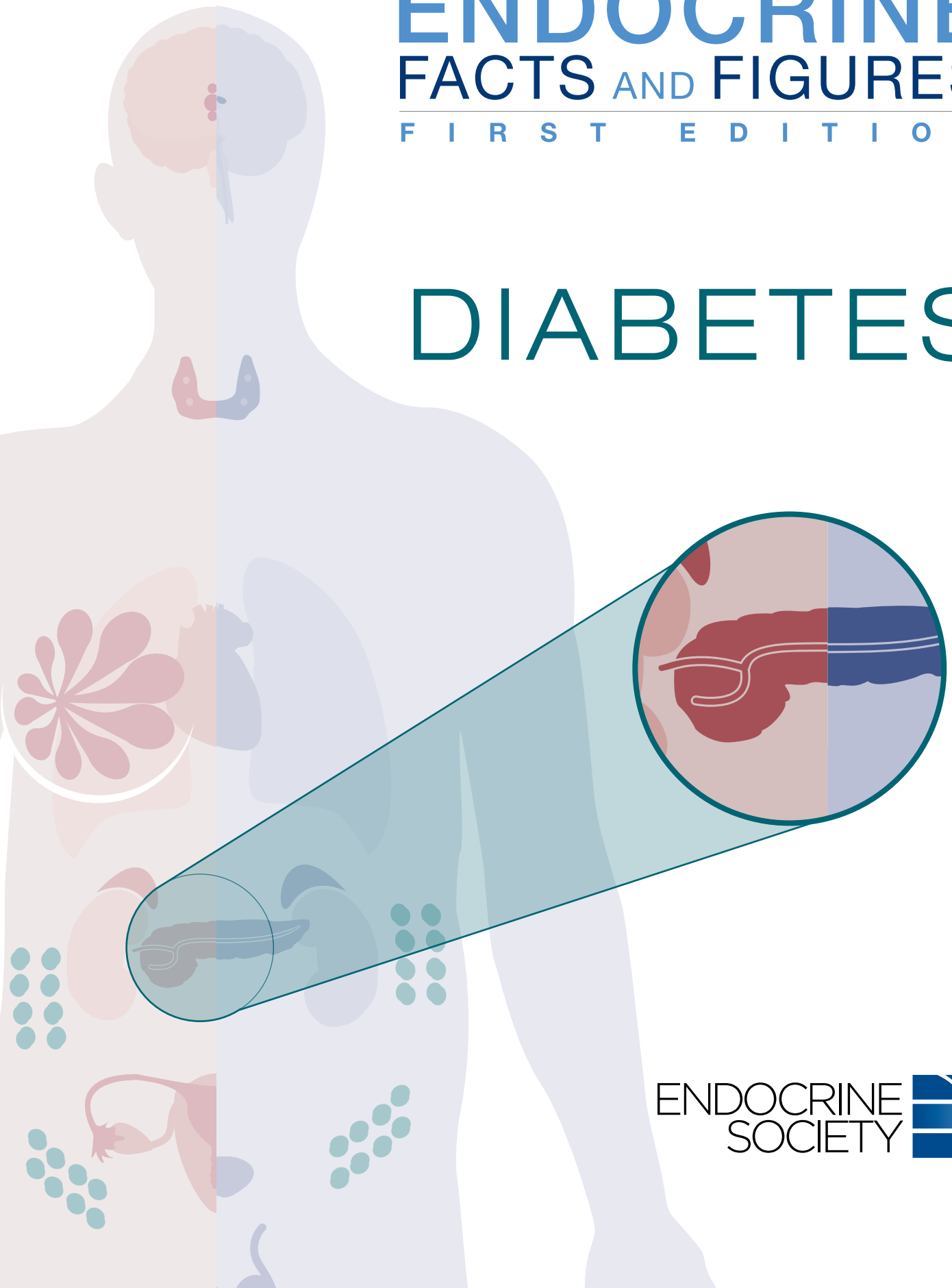
ENDOCRINE FACTS AND FIGURES

FIRST EDITION

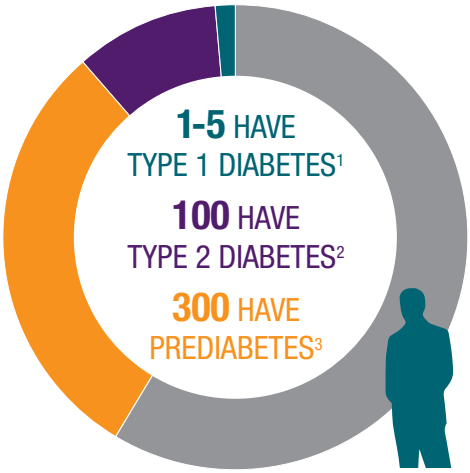
DIABETES



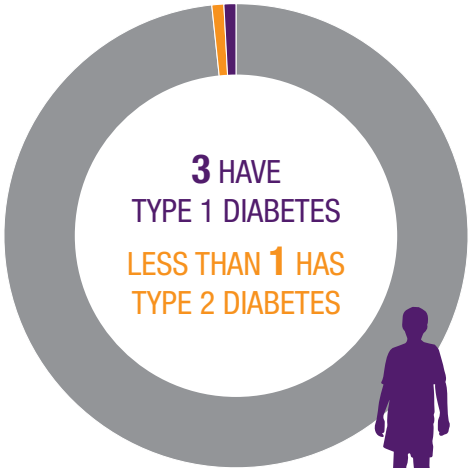
ENDOCRINE SOCIETY

OVER **29 MILLION AMERICANS** HAVE DIABETES

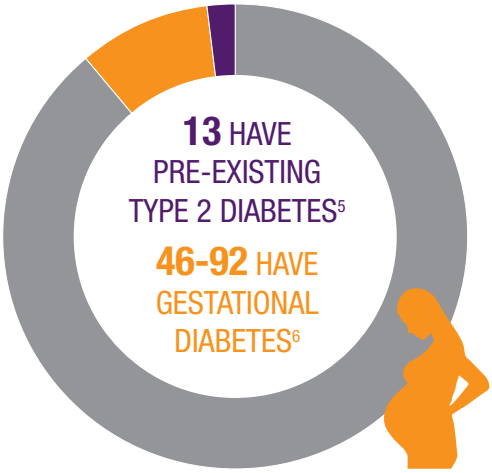
FOR EVERY **1,000 AMERICAN ADULTS** (20+ YEARS)



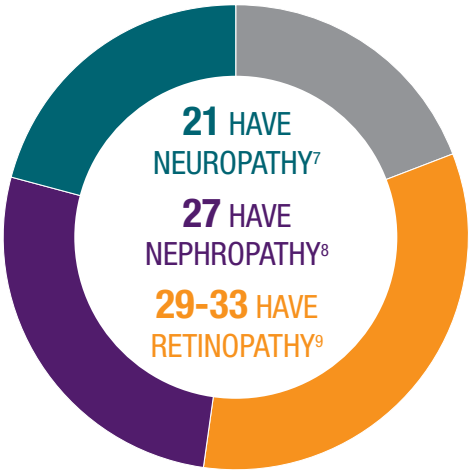
FOR EVERY **1,000 AMERICAN YOUTH** (10-19 YEARS)[4]



FOR EVERY **1,000 AMERICAN FEMALES WHO ARE PREGNANT**



FOR EVERY **100 AMERICANS** WITH DIAGNOSED DIABETES



COST BURDEN

IN 2012, DIABETES COST THE US HEALTHCARE SYSTEM
$245 BILLION[10]

BY 2021, IT IS ESTIMATED TO COST AS MUCH AS
$512 BILLION[11]

TOTAL ANNUAL HEALTHCARE COSTS (PER CAPITA)

$11,700 ADULT WITH DIAGNOSED DIABETES vs. $4,400[11] ADULT WITHOUT DIABETES

$9,061 YOUTH WITH DIAGNOSED DIABETES vs. $1,468[12] YOUTH WITHOUT DIABETES

HAVE DIABETES[3]

TYPE 2 DIABETES ACCOUNTS FOR **90-95%** OF ALL DIABETES CASES.

Source:

1 Menke et al. *Epidemiology.* 2013;24(5):773-774.
2 Selvin et al. *Annals of Internal Medicine.* 2014;160(8):517-525.
3 National Diabetes Statistics Report. Centers for Disease Control and Prevention. 2014
4 Dabelea et al. *The Journal of the American Medical Association.* 2014;311(17):1778-1786.
5 Lawrence et al. *Diabetes Care.* 2008;31(5): 899-904.
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9 Zhang et al. *The Journal of the American Medical Association.* 2010;304(6):649-656; Wong et al. *American Journal of Ophthalmology.* 2006;141(3): 446-455.
10 American Diabetes Association. *Diabetes Care.* 2013;36(4):1033-1046.
11 Vojta et al. *Health Affairs* (*Project Hope*). 2012;31(1):20-26.
12 Shrestha et al. *Diabetes Care.* 2011;34(5): 1097-1101.

Endocrine Society
2055 L Street NW, Suite 600
Washington, DC 20036 USA
Phone: 202.971.3636
Fax: 202.736.9705
endocrine.org

Mission Statement of the Endocrine Society

The mission of the Endocrine Society is to advance excellence in endocrinology and promote its essential and integrative role in scientific discovery, medical practice, and human health.

About Endocrine Facts and Figures

Endocrine Facts and Figures is a compendium of epidemiological data and trends related to a spectrum of endocrine diseases. The data is organized into nine chapters covering the breadth of endocrinology: Adrenal, Bone and Calcium, Cancers and Neoplasias, Cardiovascular and Lipids, Diabetes, Hypothalamic-Pituitary, Obesity, Thyroid, and Reproduction and Development.

All data is sourced from peer-reviewed publications, with an additional round of review by a group of world-renowned experts in the field. Additional oversight from the Endocrine Facts and Figures Advisory Panel ensured fair and balanced coverage of data across the therapeutic areas.

The first edition of **Endocrine Facts and Figures** emphasizes data on the United States. Future updates to the report will include additional data for other countries.

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Advisory Panel
Robert A. Vigersky, MD (Chair)
Walter Reed National Military Medical Center

Ursula B. Kaiser, MD
Brigham and Women's Hospital

Sherita H. Golden, MD, MHS
Johns Hopkins University

Joanna L. Spencer-Segal, MD, PhD
University of Michigan

R. Michael Tuttle, MD
Memorial Sloan Kettering Cancer Center

William F. Young, Jr., MD, MSc
Mayo Clinic

Diabetes Expert Reviewers
Marie McDonnell, MD
Rita Kalyani, MD, MHS
Alvin Powers, MD

Endocrine Society Staff
Lucia D. Tejada, PhD

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For More Information

For more information, updates, and the online version of this report, visit: endocrinefacts.org

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Disclaimer

This publication summarizes current scientific information about epidemiology and trends data related to a spectrum of endocrine diseases. It is not a practice guideline or systematic review. Except when specified, this publication does not represent the official policy of the Endocrine Society.

I OVERVIEW

Diabetes is a group of metabolic diseases characterized by chronic hyperglycemia resulting from defects in insulin secretion, resistance to insulin action, or both. The chronic hyperglycemia of diabetes is associated with long-term damage, dysfunction, and failure of different organs, especially the eyes, kidneys, nerves, heart, and blood vessels.[1,2]

This chapter covers facts and epidemiology data of the most common types of diabetes and related conditions including prediabetes, diabetes mellitus types 1 and 2, monogenic diabetes, diabetes in pregnancy (including gestational diabetes), and complications of diabetes.

1.1 EPIDEMIOLOGY

According to the latest estimates from the Centers for Disease Control and Prevention (CDC), the prevalence of diabetes among all ages in 2012 was 29.1 million, or 9.3% of the United States (US) population. This included 21 million diagnosed and 8.1 million undiagnosed people. Among the adult population 20 years of age or older, 1.9 million were newly diagnosed with diabetes in the US in 2010.[3] In addition, among all diagnosed and undiagnosed patients aged 20 years or older, 15.5 million were males and 13.4 million were females.[3] Tables 1 and 2 present data on the prevalence of diabetes in the US.

Diabetes in pregnancy, either pre-existing or developing during gestation, involves risks for the mother and fetus, as well as increased medical expenses. Table 3 summarizes the prevalence of diabetes in pregnancy in the US, based on a retrospective claims analysis from the Truven Health MarketScan database.[5] While this study analyzed a large population, no data specific to race/ethnicity was provided and only included individuals with insurance. Therefore, it is important to note that the prevalence of diabetes in pregnancy can vary based on an individual's racial or ethnic background.

Monogenic diabetes results from one of several genetic aberrations and is sometimes termed as Maturity-Onset Diabetes of the Young (MODY). Despite this name, it can appear at any point in the life cycle. The estimated prevalence of monogenic diabetes is derived from studies completed in European registries and health systems; two such estimates are presented in Table 4.

Table 1

Prevalence of prediabetes and diabetes in adults in the United States.

CONDITION	DATA SOURCE	POPULATION	PREVALENCE	REFERENCE
Diabetes *	NHANES 1999-2010	Age 20+ years	9.9-10.9%	Selvin et al. 2014[4]
	NHANES 2009-2012	Age 20-44 years	4.1%	Centers for Disease Control and Prevention 2014[3]
		Age 45-64 years	16.2%	
		Age 65+ years	25.9%	
Prediabetes	NHANES 2009-2012	Age 20+ years	37%	Centers for Disease Control and Prevention. 2014[3]

Note: *, prevalence of diabetes includes all types of diabetes combined.

Table 2

Prevalence of diabetes in children and adolescents in the United States.

CONDITION	DATA SOURCE	POPULATION	PREVALENCE	REFERENCE
Type 1 Diabetes	SEARCH for Diabetes in Youth 2001-2009	Age 0-19 years	0.193%	Dabelea et al. 2014[1]
Type 2 Diabetes	SEARCH for Diabetes in Youth, 2001-2009	Age 10-19 years	0.046%	Dabelea et al. 2014[1]

Table 3

Prevalence of diabetes in pregnancy in the United States.				
CONDITION	DATA SOURCE	POPULATION	PREVALENCE	
Diabetes in pregnancy	Truven Health MarketScan database (2004-2011), retrospective claims analysis	Pregnant females, age 18-45 years	Gestational diabetes	6.29%
			Gestational diabetes progressing to type 2 diabetes	0.23%
			Pre-existing type 1 diabetes	0.13%
			Pre-existing type 2 diabetes	1.21%
		Source: Jovanovic et al. 2015[5]		

Table 4

Estimated prevalence of monogenic diabetes in children.				
CONDITION	DATA SOURCE	POPULATION	PREVALENCE	REFERENCE
Monogenic Diabetes	Norwegian Childhood Diabetes Registry, 2002-2012	Age 0-14 years	3.1:100,000	Irgens et al. 2013[6]
	Molecular Genetics Laboratory at the Royal Devon and Exeter Hospital (United Kingdom), 1996-2009	Age 1+ years	10.8:100,000	Shields et al. 2010[7]

Table 5

Prevalence of complications of diabetes in the United States.		
COMPLICATION OF DIABETES	PREVALENCE	REFERENCE
Diabetic neuropathy	21.2% (among diagnosed with diabetes)	Cheng et al. 2006[8]
	21.5% (among undiagnosed)	Koopman et al. 2006[9]
Diabetic retinopathy	28.5%-33.2% (diabetic retinopathy)	Zhang et al. 2010[10]; Wong et al. 2006[11]
	4.4% (vision-threatening diabetic retinopathy)	Zhang et al. 2010[10]
	9.0% (macular edema)	Wong et al. 2006[11]
Diabetic nephropathy	34.5% (any diabetic kidney disease)	de Boer et al. 2011[12]
	26.5% (diabetic nephropathy)	Koopman et al. 2006[9]
	17.7% (prediabetes) -39.6% (diagnosed diabetes) (chronic kidney disease)	Plantinga et al. 2010[13]
Acute myocardial infarction	0.46%	Gregg et al. 2014[14]
Stroke	0.53%	Gregg et al. 2014[14]
Lower-limb amputation	0.28%	Gregg et al. 2014[14]
End-stage renal disease	0.20%	Gregg et al. 2014[14]
Death from hyperglycemic crisis	0.015%	Gregg et al. 2014[14]
Lower-limb amputation	0.28%	Gregg et al. 2014[14]
End-stage renal disease	0.20%	Gregg et al. 2014[14]
Death from hyperglycemic crisis	0.015%	Gregg et al. 2014[14]

Table 5 presents a summary of the prevalence of diabetes-related complications.

1.2

COST BURDEN OF DISEASE

The total cost burden of diabetes to the US healthcare system was estimated to be $245 billion in 2012. The American Diabetes Association estimates that the majority of annual spending related to diabetes is hospital inpatient costs (43% of total spending), followed by prescription medications (18%) (Table 6).[15]

These costs represent a 41% increase from 2007, when the total cost was $174 billion. In 2007, the cost of undiagnosed diabetes was estimated to be an additional $18 billion.[15] Given recent increasing trends in diabetes incidence, it has been estimated that health costs attributable to diabetes could rise to $512 billion in 2021.[16]

Average annual medical expenditures for people with diabetes are higher than for people without diabetes (Table 7-8).[15-17] More than 10% of healthcare spending in the US is spent on diabetes and its complications. In most cases, the highest percentage of spending is for people 65 years and older.[15]

It is estimated that the greatest burden of cost is on government programs, which account for 62.4% of all diabetes-related healthcare spending.[15] Private insurers account for 34.4%, while uninsured individuals account for 3.2% of diabetes-related healthcare costs. Uninsured patients with diabetes are far less likely to visit physicians' offices or take prescription medication for their conditions, but have up to 55% more emergency department visits than those covered by private or government-based insurance programs.[15]

Table 6

Healthcare spending attributable to diagnosed diabetes in the United States, 2012.		
CATEGORY	SUB-CATEGORY	ESTIMATED ANNUAL COST
Total costs	Direct costs, i.e., hospital and emergency care, office visits, medications	$176 billion
	Indirect costs, i.e., absenteeism, reduced productivity	$69 billion
Sex-based cost differences	Females with diabetes	$8,331 per capita
	Males with diabetes	$7,458 per capita
Source: American Diabetes Association. 2013[15]		

Table 7

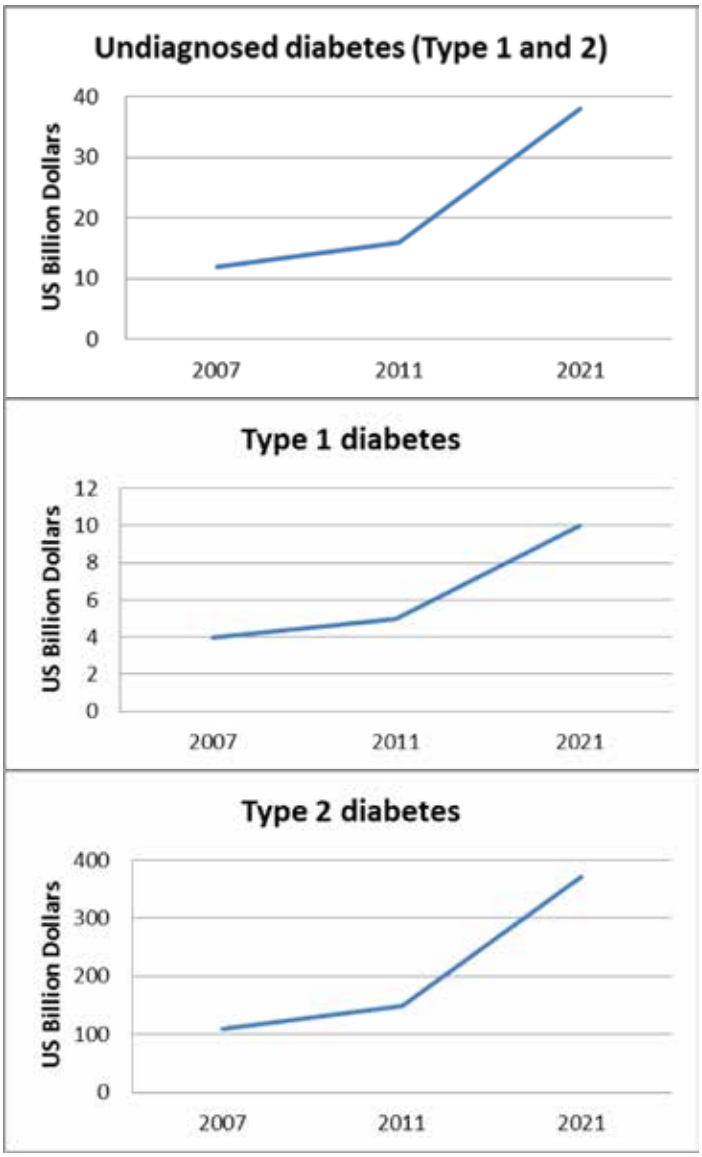
Comparison of annual total costs for adults with and without diabetes in the United States.		
DATA SOURCE	POPULATION	ANNUAL HEALTHCARE SPENDING PER CAPITA
United Healthcare, 2009	Adults with diagnosed diabetes	$11,700
	Adults without diabetes	$4,400
Source: Vojta et al. 2012[16]		

Table 8

Comparison of annual total costs for children and adolescents with and without diabetes in the United States.		
DATA SOURCE	POPULATION	ANNUAL HEALTHCARE SPENDING PER CAPITA
Commercial insurance claims data (MarketScan), 2007	Youth with diagnosed diabetes	$9,061
	Youth without diabetes	$1,468
Source: Shrestha et al. 2011[17]		

Additional factors contribute to the overall economic burden of diabetes. For example, the estimated total cost of prediabetes increased from $27 billion in 2007 to $38 billion in 2011, and could rise to $93 billion by 2021.[16] Dall et al. estimated that the annual cost per patient of prediabetes was $443.18. Furthermore, the estimated cost of undiagnosed diabetes (types 1 and 2) increased from $12 billion in 2007 to $16 billion in 2011, and could grow to as much as $38 billion by 2021.[16] These trends are summarized in Figure 1 (total cost) and Figure 2 (cost per patient).

Figure 1. Total estimated cost of diabetes (in US Billion Dollars).



Source: Vojta et al. 2012[16]

Retrospective analysis of insurance claims data shows that mean medical costs are higher among pregnant females with some form of diabetes than females without diabetes (Table 9).

Microvascular complications of diabetes, including nephropathy, neuropathy, and retinopathy, not only impact a patient's quality of life but also involve costly interventions. One-year treatment costs for these complications are summarized in Table 10.

Macrovascular complications of diabetes, including heart disease and stroke, pose some of the greatest cost burdens to the US healthcare system. Direct medical costs of these complications among patients with type 2 diabetes (in 2012 US dollars) are summarized in Table 11.

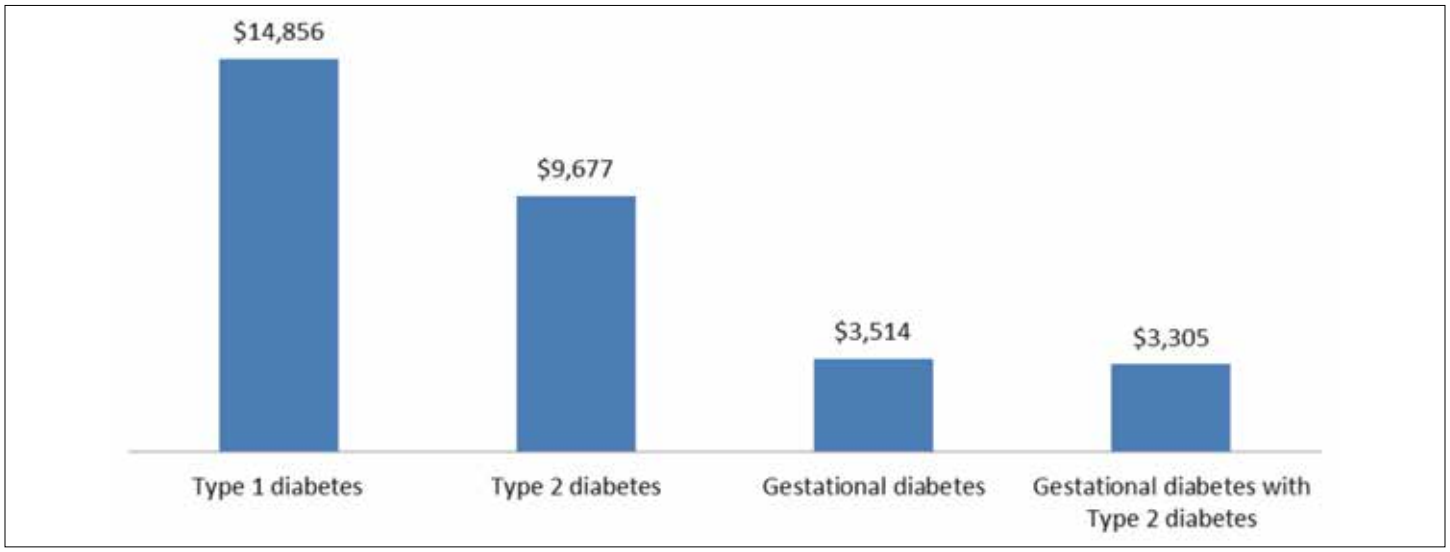
II PREDIABETES

Prediabetes describes blood glucose levels that are above normal but lower than those required for a diagnosis of overt diabetes. In the prediabetes that leads to type 2 diabetes, the body becomes resistant to insulin's actions and with time the pancreatic islets do not produce enough insulin to compensate, leading to elevated blood glucose levels.[4] The primary risk associated with prediabetes is the possible progression to type 2 diabetes. The concept of prediabetes emphasizes that type 2 diabetes is potentially preventable at this stage.[23] Without intervention, however, prediabetes usually progresses to overt type 2 diabetes within 10 years of diagnosis. In a 1994-2003 study of HMO members with at least two elevated fasting plasma glucose tests (100-125 mg/dL) but no prior history of diabetes, a higher impaired fasting glucose indicated a higher risk of developing type 2 diabetes. In the study, 8.1% of subjects with fasting glucose of 100-109 mg/DL and 24.3% of those in the higher range (110-125 mg/dL) developed diabetes. A steeper rate of increasing fasting glucose; higher BMI, blood pressure, and triglycerides; and lower HDL cholesterol predicted diabetes development.[24]

2.1 PREVALENCE AND INCIDENCE

Numerous sources have published prevalence data for prediabetes, with estimates ranging from a low of 5.8%

Figure 2. Cost of diabetes per patient per year.



Source: Dall et al. 2010[18]

Note: For gestational diabetes, costs associated to newborn's first year of life add up to $209.

Table 9

Total medical cost for pregnant patients with diabetes compared to non-diabetes patients.	
DIABETES TYPE	MEAN TOTAL MEDICAL COST (PER PATIENT)*
Type 1 diabetes	$27,531
Type 2 diabetes	$22,739
Gestational diabetes	$17,778
Gestational diabetes progressing to type 2 diabetes	$23,055
Non-diabetes	$14,355
Source: Jovanovic et al. 2015[5]	

Note: *, data reported for pregnancies that did not end in miscarriages; total cost includes pharmacy, inpatient and outpatient costs, from estimated pregnancy start date to 3 months after delivery

Table 10

Annual costs association with microvascular complications of diabetes in the United States.			
COMPLICATION TYPE	POPULATION	ANNUAL COST	REFERENCES
Diabetic nephropathy	Patients with type 1 diabetes	$1.9 billion	Gordois et al. 2004[19]
	Patients with type 2 diabetes	$15.0 billion	
Diabetic neuropathy	Patients with type 1 diabetes	$0.3-1.0 billion	Gordois et al. 2003[20]
	Patients with type 2 diabetes	$4.3-12.7 billion	
Diabetic retinopathy	Patients with diabetes over age 40 years	$0.5 billion	Centers for Disease Control and Prevention. 2011[21]

to a high of 35% among adults 20 years and older (Table 12). Reported prevalence varies depending on the criteria used to define prediabetes.

Prediabetes prevalence has increased over the last few decades. Comparison of NHANES data from 1988-1994 and 1999-2010 showed that the prevalence of prediabetes increased from 5.8% to 12.4% over the two time periods.[4] Without intervention, it is estimated that 15% to 30% of people with prediabetes will develop type 2 diabetes within five years.[26]

2.2 DEMOGRAPHIC DIFFERENCES

An evaluation of 2005 to 2008 NHANES data found similar prevalence for non-Hispanic whites (35%), non-Hispanic blacks (35%) and Mexican Americans (36%).[27] Using NHANES data from 2010, another study reported gender differences by ethnicity: prevalence was consistent across ethnic groups among females, but lower among non-Hispanic black males compared to non-Hispanic white or Mexican American males. These results are summarized in Table 13.

Table 11

Event-year* direct medical costs of macrovascular complications of diabetes.

POPULATION	COMPLICATION TYPE	ANNUAL COST
Patients with type 2 diabetes	Myocardial infarction	$56,445
	Ischemic stroke	$42,119
	Congestive heart failure	$23,758
	Ischemic heart disease	$21,406
	Transient ischemic heart attack	$7,388

Source: Ward et al. 2014[22]

Note: *, event-year costs include resource use during initial inpatient/outpatient management, followed by subsequent care provided in the first year

Table 12

Prevalence of prediabetes in the United States by age.

DATA SOURCE	POPULATION	DEFINITION	PREVALENCE	REFERENCE
NHANES 1988-1994 and 1999-2010	US adults, age 20 + years	Calibrated A1C, 5.7%-6.4% Fasting glucose, 5.6-6.9 mmol/L	5.8%-12.4% 25.2%-28.7%	Selvin et al. 2014[4]
IDF Diabetes Atlas (2013)	Adults in North America and the Caribbean region, age 20-79 years	Impaired glucose tolerance (100-125 mg/dL)	13.2%	International Diabetes Federation. 2013[25]
2009-2012 NHANES	US adults, age 20+ years	Impaired glucose tolerance (100-125 mg/dL) or A1c, 5.7%-6.4%	37%	Centers for Disease Control and Prevention. 2014[3]

Abbreviations: A1C, Hemoglobin A1c; IDF, International Diabetes Federation; NHANES, National Health and Nutrition Examination Survey

2.3

LIFE EXPECTANCY AND MORTALITY

A review of 26 prospective cohort studies that include data on prediabetes and mortality found that the risk of all-cause and cardiovascular mortality was increased in people with prediabetes defined as impaired fasting glucose (IFG) of 110-125 mg/dL or with impaired glucose tolerance (IGT) or combined IFG 110 and/or IGT.[113]

An examination of 832 deaths among a cohort of 17,044 participants with prediabetes found that normal-weight individuals with low cardiorespiratory fitness levels had a higher risk of all-cause mortality than those who were normal weight and fit.[29]

2.4

KEY TRENDS AND HEALTH OUTCOMES

Preventing the progression of prediabetes to type 2 diabetes has been identified as a strategy to address the growing prevalence of diabetes. According to a 2006 study published by the CDC, most adult prediabetes patients who are aware of their condition try to adopt lifestyle changes to reduce their risk of progression. In a study that used data from the National Health Interview Survey (NHIS), 68% of patients with self-reported prediabetes said that during the previous year they had been trying to lose or control their weight, 60% had reduced dietary fat and/or calories, and 55% had increased physical activity. Despite the importance of risk reduction, 24% reported not engaging in any lifestyle changes.[30]

The landmark Diabetes Prevention Program (DPP)[31] further demonstrated the efficacy of weight loss, dietary modification and exercise for preventing or delaying the onset of diabetes in individuals with prediabetes. Patients in this study who were randomized to lifestyle treatment lost an average of 15 pounds and reduced their risk of developing type 2 diabetes by 58% over 3 years. The efficacy of the common first-line oral agent metformin was also established in the DPP study, where the risk of progression to diabetes was 31% lower in subjects randomized to the drug as compared to those given placebo. Metformin is only effective for as long as it is taken.

Beyond the DPP, additional studies have identified interventions that are effective in the treatment of prediabetes, toward preventing or delaying progression to type 2 diabetes. The effectiveness of lifestyle interventions in preventing type 2 diabetes, as found in the DPP, has been corroborated by international studies such as the Finnish Diabetes Prevention Study[32] and the Da Qing IGT and Diabetes Study.[33] Pharmacotherapies have also been tested as adjuncts to lifestyle modification for diabetes prevention. For example, the STOP-NIDDM trial showed that acarbose can delay development of type 2 diabetes when compared to placebo.[34] In Hispanic females with a history of gestational diabetes and high-risk for type 2 diabetes, troglitazone (an insulin-sensitizing drug) delayed or prevented its onset.[35]

III TYPE 1 DIABETES

Type 1 diabetes is an autoimmune disease in which the immune system destroys the insulin-producing beta cells of the pancreas. This results in a deficiency of insulin, causing chronic hyperglycemia.

3.1

PREVALENCE AND INCIDENCE

A report from the SEARCH for Diabetes in Youth study, a national multicenter study sponsored by the CDC and the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), found that between 2002 and 2005, 15,600 new cases of type 1 diabetes were diagnosed in the US[36]. The incidence and prevalence of type 1 diabetes are summarized in Tables 14-15.

Table 13

Prediabetes: Prevalence by sex and race/ethnicity in the United States.		
RACE/ETHNICITY	MALES	FEMALES
Non-Hispanic White	47.7%	30.0%
Non-Hispanic Black	35.7%	29.0%
Mexican American	47.0%	31.9%
Source: Go et al. 2014[28]		

Table 14

Incidence of type 1 diabetes, United States youth.		
DATA SOURCE	POPULATION	INCIDENCE
SEARCH for Diabetes in Youth, 2002-2005	US children under 10 years	19.7 per 100,000
	US children 10-20 years	18.6 per 100,000
Source: Mayer-Davis et al. 2009[36]		

Type 1 diabetes incidence rates appear to be rising; assuming increases over time, the prevalence of type 1 diabetes may increase by as much as 144% by the year 2050 (Table 16).

Most recent studies place the prevalence of type 1 diabetes among US youth between 0.15% and 0.2%. Data from the SEARCH study indicated that the prevalence of type 1 diabetes among youth increased 21.1% between 2001 and 2009, with similar increases for boys and girls and in most racial/ethnic and age groups.1 The increase in prevalence in Scenario 2 was expected to occur especially among youths of minority race/ethnicity.[38]

3.2

DEMOGRAPHIC DIFFERENCES

In the SEARCH for Diabetes in Youth Study (2009), where the population was drawn from five geographic areas of the US, the prevalence of type 1 diabetes differed somewhat from a study that represented nearly 253,000 school children in Philadelphia, Pennsylvania.[39] In the SEARCH study, the prevalence was based on youths younger than 20 years; the Philadelphia study (2005) found that the prevalence of type 1 diabetes varied only slightly by ethnicity (Table 17).

Table 15

Prevalence of type 1 diabetes, United States by age.

DATA SOURCE	POPULATION	PREVALENCE	REFERENCE
SEARCH for Diabetes in Youth	Age <20 years	0.148% (2001) 0.193% (2009)	Dabelea et al. 2014[1]
NHANES 1999-2000	Age 20-39 years Age 40-59 years Age 60+ years	0.34-0.42% 0.31-0.49% 0.08-0.12%	Menke et al. 2013[37]

Table 16

Projected increases in type 1 diabetes prevalence among youth from 2010 to 2050.

SEARCH DATA MODEL SCENARIOS	PREVALENCE PROJECTION FOR 2010-2050
Scenario 1: constant incidence over time	0.197% to 0.18% decrease/stable
Scenario 2: increases over time by age group	144% increase

Source: Imperatore et al. 2012[38]

3.3

LIFE EXPECTANCY AND MORTALITY

In a US study that compared two cohorts of type 1 diabetes patients based on year of diagnosis, the life expectancy at birth for those diagnosed between 1965 and 1980 was 15 years greater than participants diagnosed between 1950 and 1985 (68.8 years vs 53.4 years). The reasons for this increase in life expectancy was presumed to be due to earlier recognition and improved treatment; better glucose monitoring and insulin administration; reduction of renal disease resulting from improved diabetes care; and possibly, the increase in statin use.[40] In addition, mortality of adult diabetes patients due to hyperglycemic crisis (including diabetic ketoacidosis and hyperglycemic hyperosmolar state) decreased by 64% between 1990-2010[14], in part due to the near-universal adoption of protocols to treat these conditions.

Overall, life expectancy is decreased among individuals living with type 1 diabetes compared to those living without. In a recent study of Scottish type 1 diabetes patients, males lost 11.1 years of life expectancy, and females lost 12.9 years when compared to persons living without type 1 diabetes. Even among patients with preserved renal function, males lost 8.3 years of life expectancy and females lost 7.9 years. The overall largest percentage of loss in life expectancy resulted from

Table 17

Prevalence of type 1 diabetes in children by ethnicity, United States.

RACE/ETHNICITY	PREVALENCE OF TYPE 1 DIABETES	
	SEARCH FOR DIABETES IN YOUTH (0-19 YEARS)	LIPMAN ET AL. 2013 (4-18 YEARS)
White	1.93%	0.073%
African American	1.62%	0.056%
Hispanic	1.29%	0.05%
Asian/Pacific Islander	0.60%	ND
Native American	0.60%	ND

Source: 0-19 years, Dabelea et al. 2014[1]; 4-18 years, Lipman et al. 2013[39]

ischemic heart disease: males lost 36% and females lost 31% of life expectancy compared with persons without type 1 diabetes. Death from diabetic coma or ketoacidosis was associated with the largest percentage of estimated life expectancy loss occurring before age 50 (29.4% in males, 21.7% in females).[41]

Intensive therapy and glycemic control appears to lower the mortality rate among type 1 diabetes patients. In the multisite Diabetes Control and Complications Trial/ Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) study, after a mean of 27 years' follow-up of patients with type 1 diabetes, 6.5 years of initial intensive diabetes therapy was associated with a modestly lower all-cause mortality rate when compared with conventional therapy (64 versus 43 deaths).[42]

3.4
KEY TRENDS AND HEALTH OUTCOMES

Insulin is an integral part of the treatment for type 1 diabetes. Insulin (regular) or modified versions of insulin (analogs) are given subcutaneously either by injection or an infusion device. An analysis of 2007 MarketScan commercial claims data found that among youth aged 19 and younger with diabetes, 92% took insulin.[17] This likely reflects the relatively higher prevalence of type 1 diabetes in the younger age groups, as insulin is required for survival in type 1 diabetes. However, insulin therapy is sometimes used in youth with type 2 diabetes.

An analysis of over 3,000 children and adolescents (6-17 years of age) enrolled in the type 1 diabetes Exchange Clinic Registry showed that those with "excellent" glycemic control (A1C < 7%) tended to use insulin pumps and performed self-monitoring of blood glucose more frequently than those who had "poor" glycemic control (A1C ≥ 9%).[43] Similar results were found in a study of the type 1 diabetes Exchange registry's adult cohort (greater than 26 years of age), in which the "excellent" control group was more likely to be using an insulin pump than those in the "poor" control group.[44]

Among patients with type 1 diabetes, levels of glucose control have been linked to mortality. One study reported 2- to 3-fold greater risks of all-cause and cardiovascular mortality in the highest compared to the lowest quartiles of glycosylated hemoglobin.[45]

In a recent Cochrane review of 12 studies, intensive glucose control was more effective than conventional glucose control at reducing microvascular complications of diabetes such as retinopathy, nephropathy, and neuropathy, as shown in Table 18.[46]

Overall, the incidence of major diabetes complications appears to be declining. The Pittsburgh Epidemiology of Diabetes Complications (EDC) Study showed that the estimated incidence of coronary artery disease, end-stage renal disease, and blindness among type 1 diabetes patients was lower among the cohort of patients diagnosed in the 1970s compared to those diagnosed in the 1960s. The authors of this study noted a concurrent decline in microalbuminuria, which may explain the improvements between the two cohorts.[40]

IV TYPE 2 DIABETES

Classical type 2 diabetes is characterized by chronic hyperglycemia due to insulin resistance, reduced insulin secretion, and increased hepatic glucose production. The molecular reasons for these defects are unknown. Type 2 diabetes has a genetic component with more than 75 genes being identified as increasing the risk of type 2 diabetes; current research is exploring the contribution of specific genes.

4.1
PREVALENCE AND INCIDENCE

Type 2 diabetes accounts for about 90% to 95% of all diabetes cases (Table 19).[3] In addition, the prevalence of type 2 diabetes in US children and adolescents under the age of 20 years has been estimated at 0.046%.[1]

A comparative analysis of NHANES data between 1988-1994 and 2005-2010 showed a 51.2% (14.9 vs. 29.9 million) increase in the prevalence of type 2 diabetes across all ages of the US population.[47] In addition, data from the SEARCH for Diabetes in Youth study reported

Table 18

Intensive versus conventional glucose control, complications per 1000 patients.

COMPLICATION	INTENSIVE GLUCOSE CONTROL	CONVENTIONAL GLUCOSE CONTROL
Retinopathy	63 per 1000	232 per 1000
Nephropathy	159 per 1000	284 per 1000
Neuropathy	49 per 1000	139 per 1000

Source: Fullerton. 2014[46]

an incidence of 3,600 cases per year between 2002-2005 (0.4/100,000 cases at age <10 years, and 8.5/100,000 cases at age ≥ 10 years), and a prevalence of 30.5% between 2001-2009.[1]

4.2

DEMOGRAPHIC DIFFERENCES

The prevalence of type 2 diabetes is markedly higher in Native American/Alaska Native, African American, and Hispanic adults than their non-Hispanic white or Asian counterparts (Table 20). A similar trend holds for US adolescents.

Table 19

Prevalence of type 2 diabetes in the United States.

POPULATION	PREVALENCE	
	DIABETES (ALL TYPES)	TYPE 2 DIABETES (ESTIMATED)*
Total	9.3% (29.1 million)	8.4-8.8% (26.19-27.64 million)
diagnosed	72.2% (21.0 million)	64.9-68.6 (18.9-19.95 million)
undiagnosed	27.8% (8.1 million)	25.0-26.4 (7.3-7.7 million)

Source: Centers for Disease Control and Prevention. 2014[3]

Note: *, prevalence of type 2 diabetes was calculated as the 90-95% of the overall diabetes prevalence reported by the Centers for Disease Control and Prevention.

Table 20

Age-adjusted prevalence of type 2 diabetes by ethnicity.

RACE/ETHNICITY	PREVALENCE	
	ADULTS, AGE 19 YEARS AND OLDER	ADOLESCENTS, AGE 10-19 YEARS
Non-Hispanic white	7.6%	0.017%
Asian Americans	9.0%	0.034%
Hispanic	12.8%	0.079%
Non-Hispanic blacks	13.2%	0.106%
Native Americans/ Alaska Natives	15.9%	0.120%

Source: Adults, Centers for Disease Control and Prevention. 2014[3]; adolescents, Dabalea et al. 2014[1]

Compared to the national rate, some geographic areas appear to have higher rates than others. For example, a study of 510 schools representing 252,896 schoolchildren in Philadelphia, Pennsylvania found that the prevalence of type 2 diabetes was higher among African American children (2.8%) compared with white (0.3%) and Hispanic children (0.5%). Mean age at diagnoses of type 2 diabetes was 11.9 years.[39]

4.3

LIFE EXPECTANCY AND MORTALITY

Treated by conventional glycemic control, young adults with newly diagnosed type 2 diabetes lose about 15 years of their remaining life expectancy compared with a young adult without diabetes. Intensive treatment led to lower lifetime cumulative incidence and lower mortality from microvascular complications such as end-stage renal disease, 19.4% versus 25.2%.[48]

While the parallel rise in incidence of type 2 diabetes with the prevalence of obesity is clear, the relationship between BMI and all-cause mortality in type 2 diabetes patients is more difficult to pinpoint.

In a retrospective study of 106,640 Scottish patients, there were 9,631 deaths. Patients categorized as normal weight (BMI 20 to <25) or obese (BMI ≥35) with type 2 diabetes within a year of diagnosis of type 2 diabetes exhibited variably higher mortality outcomes compared with the overweight group, confirming a U-shaped association of BMI with mortality. The U-shaped relationship persisted for vascular disease. There is a possible explanation for this "obesity paradox": People who have a lower body mass at the time of diagnosis may have a different, potentially more aggressive, pathophysiology from those who develop it when obese: an increased sensitivity to visceral fat accumulation, a stronger genetic tendency to insulin resistance, or early pancreatic islet failure, all factors potentially giving a different disease phenotype associated with higher mortality.[49] However, this concept is controversial, and the findings could well be due to methodology.

A study of 11,427 health professionals diagnosed with type 2 diabetes who were free of cardiovascular disease and cancer at time of diagnosis found different results. There were 3083 deaths over 15.8 years of follow-up. The authors observed a J-shaped association between BMI and mortality among all participants and among those who had ever smoked and a direct linear relationship among those who had never smoked. They found no

evidence of lower mortality among patients with diabetes who were overweight or obese at diagnosis, as compared with their normal-weight counterparts, or of an obesity paradox.[50]

4.4

KEY TRENDS AND HEALTH OUTCOMES

Although a number of treatment options are available for the treatment of type 2 diabetes, only 53% of patients with diabetes achieve A1C targets of < 7.0%.[51] Medication adherence is one of the challenges that patients face in achieving glycemic control. Analysis of retrospective studies using large bases found that adherence to oral hypoglycemic agents ranged from 36-93%; a similar rate was estimated by observational (noncomparative) studies, which found 79-85% adherence during 6-36 months of observation.[52] These data also indicated that the less frequently a patient had to take their medication, the higher the adherence rate: for example, once-daily regimens had higher adherence than twice-daily, and monotherapy regimens had higher adherence than polytherapy.[52]

Metformin is considered to be the first-line therapy for newly diagnosed type 2 diabetes patients. A number of additional pharmacotherapies are available to those adult patients that are inadequately treated by metformin alone. Over the past decade, four new oral medication classes and 10 injectable agents and insulin products have been approved by the FDA for type 2 diabetes treatment.[53,54] Overall, the number of adult patients using antidiabetic medications increased by 42.9% between 2003-2012.[55] A total of 154.5 million prescriptions were dispensed for antidiabetic drugs in 2012, of which 78.4% were for noninsulin medications.[55] Trends for specific drug classes are provided in Table 21; please note that SGLT-2 inhibitors were still new to the market at the time of this study and not included in the overall analysis.

Weighted data from NHANES indicated a 7.4% increase in A1C levels among patients with diabetes from NHANES 2007-2008 to NHANES 2009-2010.[56] 40% to 60% of middle-aged US adults with type 2 diabetes have poor glycemic control, and type 2 diabetes patients age 51-64 years had worse glycemic control than those over age 65 years.[57] Overall, 44.3% of people with diabetes had A1C above 7.0%.[58] Of those over 65, 25.6% had A1C above 7.0%, compared with 47.9% of patients under age 65.59

A1C is used as a measure of glycemic control and improved glycemic control lowers the risk of diabetic complications.[60] Cardiovascular disease is a major cause of morbidity and mortality in type 2 diabetes, leading to a 2- to 4-fold increase risk of cardiovascular events and a 3-fold risk in cardiovascular mortality. Large studies have demonstrated reduced cardiovascular events after improved glycemic control with long-term follow-up.[61]

V DIABETES IN PREGNANCY

Diabetes in pregnancy includes two categories of patients: those who have type 1 or type 2 diabetes prior to pregnancy and those who develop gestational diabetes during a pregnancy. Gestational diabetes may progress to type 2 diabetes after pregnancy in some females.

5.1

PREVALENCE AND INCIDENCE

The prevalence of gestational diabetes can vary depending on the data source, diagnostic criteria, and the demographics of the population studied. The most recent data, taken from a retrospective insurance claims analysis, has estimated the prevalence at 6.29%. The range of data available is provided in Table 22.

As with other types of diabetes, an increase in the prevalence of gestational diabetes has been observed over time. Using data from the National Hospital Discharge Survey, Getahun et al. noted a relative increase

Table 21

Trends in prescription of major antidiabetic drug classes, 2003-2012.

MEDICATION TYPE	MEDICATION CLASS	NUMBER OF PRESCRIPTIONS IN 2012 (IN MILLIONS)
Non-insulin drugs	All	121.0
	Biguanides (e.g., metformin)	60.4
	Sulfonylureas	32.3
	DPP-4 inhibitors	9.7
	Thiazolidinediones	5.8
	GLP-1 analogs	3.1
Insulins and insulin analogs	All	33.4

Source: Hampp et al. 2014[55]

of 122% between the 1989-1990 survey to the 2003-2004 survey.[64]

Analysis of records from all Kaiser Permanente hospitals in Southern California showed that the prevalence of pre-existing diabetes among pregnant females rose from 0.81% in 1999 to 1.82% in 2005.[63] An additional retrospective study of insurance claims data in the MarketScan database (for years 2004-2011) provided additional insights on the prevalence of pre-existing type 1 diabetes versus type 2 diabetes among pregnant females (Table 23). Further, this study noted that the rate of gestational diabetes progressing to type 2 diabetes in their cohort was 0.23%.[5]

Data from PRAMS collected between 2004 and 2006, indicated that prevalence increased with maternal age[65,66], as shown in Table 24.[65]

Several studies have shown an increase in gestational diabetes prevalence from the late 1980s until the early 2000s (Table 25), but prevalence levels have remained

Table 22

Prevalence of gestational diabetes: summary of selected studies published since 2008.

DATA SOURCE	POPULATION	PREVALENCE	REFERENCE
MarketScan database, 2004-2011	Pregnant females, age 18-45 years	6.29%	Jovanovic et al. 2015[5]
Pregnancy Risk Assessment Monitoring System, 2009-2010 and birth certificate records (2010)	Pregnant females, all ages	4.6%-9.2%	DeSisto et al. 2014[62]
Kaiser Permanente Southern California hospital records, 1999-2005	Pregnant females, age 13-58 years	7.6%	Lawrence et al. 2008[63]
National Hospital Discharge Survey, 2003-2004	Pregnant females, age 14 to 45 years	4.2%	Getahun et al. 2008[64]

Table 23

Pre-existing type 1 or type 2 diabetes among pregnant females aged 18-45 years, 2004-2011.

DATA SOURCE	CONDITION	PREVALENCE
Truven Health MarketScan database (2004-2011), retrospective claims analysis	Pre-existing type 1 diabetes	0.13%
	Pre-existing type 2 diabetes	1.21%

Source: Jovanovic et al. 2015[5]

Table 24

Gestational diabetes: prevalence by age.

AGE	PREVALENCE
Under 20 years	1.0%
20-34	3.6%
35+	8.4%

Source: Kim et al. 2010[65]

Table 25

Trends in gestational diabetes.

DATA SOURCE	POPULATION	CHANGE OVER TIME	REFERENCE
1989-1990 and 2003-2004 NHDS	Pregnant females with gestational diabetes	Relative increase of 122% (1.9% in 1989-90 to 4.2% in 2003-04)	Getahun et al. 2008[64]
1991, 1997 and 2000 KPNC	Pregnant females with gestational diabetes	Increased 68% from 1991-1997 (3.7% to 6.6%) then leveled off at 6.2% through 2000	Ferrara et al. 2007[67]
1999 and 2005 KPSC	Pregnant females with gestational diabetes	Remained constant from 1999 (7.5%) to 2005 (7.4%)	Lawrence et al. 2008[63]
1999 and 2005 KPSC	Pregnant females with existing diabetes	Increased from 0.81% in 1999 to 1.82% in 2005	Lawrence et al. 2008[63]

Abbreviations: KPNC, Kaiser Permanente Northern California; KPSC, Kaiser Permanent Southern California; NHDS, National Hospital Discharge Survey

fairly stable since then. In addition, new diagnostic criteria may result in a 2- to 3-fold increase in the diagnosed prevalence of gestational diabetes.[66]

5.2

DEMOGRAPHIC DIFFERENCES

Gestational diabetes in 1995-2008 was more prevalent among Hispanics and Asian/Pacific Islanders than among whites or blacks, as indicated in an analysis of hospital records from Kaiser Permanente Southern California[68] (Table 26).

NHDS data showed that between 1989-1990 and 2003-2004, among females under 25 years old, the frequency of gestational diabetes increased by 13% among whites and 260% among blacks.[64]

5.3

LIFE EXPECTANCY AND MORTALITY

Pregnancy-related mortality ratios increase with maternal age for all females and within all age groups, and non-Hispanic black females have the highest risk of dying from pregnancy complications (Table 27).

Over time, the contribution to pregnancy-related deaths of hemorrhage, hypertensive disorders of pregnancy, embolism, and anesthesia complications continued to decline, whereas the contribution of cardiovascular conditions and infection increased (Table 28).

Among the causes, cardiovascular conditions ranked first, with 14.4% of 490 maternal deaths occurring after a live birth, 11.4% after a stillbirth, 7.8% after an abortion, 20.2% with the fetus undelivered, and 12.7% unknown.[69]

5.4

KEY TRENDS AND HEALTH OUTCOMES

A retrospective analysis of insurance claims in the MarketScan Commercial Claims and Encounters database showed that between the years 2000-2011, the use of glyburide (an oral sulfonylurea medication, also known as glibenclamide) to treat gestational diabetes increased from 7.4 to 64.5%.[70] The data indicated that since 2007, glyburide surpassed insulin as the most common treatment for gestational diabetes. Its use is somewhat controversial because glyburide is not approved by the US Food and Drug Administration for treatment of gestational diabetes, though it has been recommended by the Endocrine Society[71] and the American College of Obstetrics and Gynecology[72] as a suitable alternative to insulin if necessary. A systematic review and meta-analysis of the literature found that glyburide is inferior to both insulin and metformin to treat gestational diabetes, though treatment failure was higher with metformin than with glyburide; this report recommended against using glyburide to treat gestational diabetes if insulin or metformin was available as an option.[73]

Table 26

Gestational diabetes: prevalence by ethnicity.

ETHNICITY	PREVALENCE
Asian/Pacific Islander	17.1%
Hispanic	11.1%
White	7.4%
Black	6.9%
Other	7.7%

Source: Xiang et al. 2011[68]

Table 27

Pregnancy-related mortality ratios by race/ethnicity, 2006-2010.

RACE/ETHNICITY	DEATHS PER 100,000 LIVE BIRTHS
Non-Hispanic white	12.0
Non-Hispanic black	38.9
Hispanic	11.7
Other race/ethnicity	14.2

Source: Creanga et al. 2015[69]

Table 28

Causes of pregnancy-related deaths, 2006-2010.

CAUSE OF DEATH	PERCENT OF PREGNANCY-RELATED DEATHS
Hemorrhage	11.4%
Embolism	14.9%
Hypertensive disorders	9.4%
Infection	13.6%
Anesthesia complications	0.7%
Cardiomyopathy	11.8%
Cerebrovascular accident	6.2%
Cardiovascular conditions	14.6%
Noncardiovascular conditions	12.8%
Unknown etiology	4.7%

Source: Creanga et al. 2015[69]

Among the 10% of all pregnancies in the US complicated by diabetes, 0.2% to 0.5% involve type 1 diabetes; both fetus and mother are at increased risk for adverse effects. A 2011 literature review advised a rigorous protocol of pre-conception counseling, carbohydrate counting, use of insulin analogues, continuous subcutaneous insulin infusion (insulin pump) therapy, and real-time continuous glucose monitoring with alarms for low glucose values to obtain near-normoglycemia without episodes of severe hypoglycemia.[74]

Beyond drug treatment, increasing physical activity has the effect of reducing the risk of type 2 diabetes among pregnant females. Compared with females who maintained their total physical activity levels, females who increased their total physical activity levels by 7.5 metabolic equivalent hours/week or more (equivalent to 150 minutes per week of moderate-intensity physical activity) had a 47% lower risk of type 2 diabetes. This association remained significant after additional adjustment for BMI.[75]

Immediately subsequent to pregnancy, about 5%-10% of females with gestational diabetes are diagnosed with type 2 diabetes, and females who have had gestational diabetes have a 35%-60% risk of developing type 2 diabetes in the next 10 to 20 years.27 The risk of subsequent overt type 2 diabetes accumulates over time and the same is likely for cardiovascular disease.[76] Females with previous gestational diabetes are at the risk of developing it again in subsequent pregnancies[77]. The risk of gestational diabetes in a second pregnancy among females with a history of the disease was 41.3%, compared to 4.2% in females without a prior diagnosis.[77]

Although having gestational diabetes is known to increase the risk of developing type 2 diabetes later in life, the most recent findings indicate that lifestyle interventions — specifically, increased exercise — can decrease that risk.[75]

Patients with pre-existing diabetes who become pregnant are at greater risk for maternal and fetal complications than their nondiabetic counterparts. In a study of 213 pairs of type 2 diabetes patients and control patients from 2000 to 2008, patients with diabetes had higher rates of preeclampsia, poly- and oligohydramnios, cesarean delivery, shoulder dystocia, postpartum hemorrhage, preterm delivery, large-for-gestational age infant, fetal anomaly, neonatal hypoglycemia, hyperbilirubinemia, respiratory distress syndrome, sepsis, intubation, and neonatal intensive care unit admission.[78]

The role of intrauterine hyperglycemia and future risk of type 2 diabetes in human offspring appears to be involved in the pathogenesis of type 2 diabetes/pre-diabetes in adult offspring of primarily Caucasian females with either diet-treated GDM or type 1 diabetes during pregnancy. In a study of glucose tolerance among adult offspring of females with either gestational diabetes mellitus (GDM) or type 1 diabetes, taking the impact of both intrauterine hyperglycemia and genetic predisposition to type 2 diabetes into account, the risk for type 2 diabetes or pre-diabetes was increased by 4.02 to 7.76% in offspring of mothers with type 1 diabetes and was significantly related to the mother's having elevated blood glucose in late pregnancy.[79]

VI MONOGENIC DIABETES

Monogenic diabetes is a group of rare disorders occurring as a result of single gene mutations; the mutation most commonly reduces the body's capacity for normal insulin production. More than 20 different genes have been linked to monogenic diabetes.[80] Types of monogenic diabetes include neonatal diabetes, with onset during the first year of life, and maturity onset diabetes of the young (MODY), which occurs in children and adolescents. MODY can be misdiagnosed as type 1 or type 2 diabetes.[81]

6.1 PREVALENCE AND INCIDENCE

Few studies have explored the epidemiology of monogenic diabetes (Table 29), and no thorough studies have been completed in the US.

Table 29

Prevalence of monogenic diabetes.

DATA SOURCE	POPULATION	PREVALENCE	REFERENCE
Norwegian Childhood Diabetes Registry, 2002-2012	Children 0-14 years of age with newly diagnosed diabetes in Norway	3.1 per 100,000	Dabelea et al. 2014[1]
Referral data for genetic testing, 1996-2009	UK children	10.8 per 100,000	Shields et al. 2010[7]

The UK study found that fewer than 20% of MODY cases are diagnosed by molecular testing.[7]

Given these numbers, and the similarity in ethnic backgrounds between the US and UK populations, monogenic diabetes prevalence in the US is likely approximately 50 to 100 cases per year. Monogenic diabetes can be accurately diagnosed by DNA sequencing, but monogenic diabetes often remains undiagnoseds.[82]

6.2
DEMOGRAPHIC DIFFERENCES

Rates of diagnosis of monogenic diabetes are increasing among those with clinical features of type 1 or type 2 diabetes as genetic studies become available, but population-based data on incidence and prevalence show wide variation due to lack of standardisation in the studies.[83]

Two international studies show results ranging from 2.5%-4.2% of children with diabetes (Table 30).

6.3
LIFE EXPECTANCY AND MORTALITY

There is little information available on life expectancy and mortality in individuals with monogenic diabetes. However, an increased risk of cardiovascular mortality at younger ages was found among family members with *HNF1A* mutations in comparison with familial control subjects. 66% of mutation carriers died from a cardiovascular-related illness compared with 43% of control subjects.[85]

6.4
KEY TRENDS AND HEALTH OUTCOMES

Extended genetic testing of young adult-onset diabetes patients revealed that about 0.8% of those diagnosed with type 1 diabetes had *HNF1A* mutations and 4% of those diagnosed with type 2 diabetes had *HNF1A*, *HNF4A*, or *GCK* mutations. This genetic testing approach identified twice the number of MODY cases than that of current clinical practice, suggesting a possible need to incorporate molecular testing into existing diagnosis protocols.[86]

In neonates with monogenic diabetes, early sulfonylurea therapy can improve glycemic control and potentially improve neurodevelopmental outcomes. In an observational study of 154 subjects with neonatal diabetes within the University of Chicago Monogenic Diabetes Registry, 73 (47%) had a mutation in *KCNJ11* or *ABCC8*. In 9 of the children in the trial, an empiric sulfonylurea trial was initiated within 28 days of diabetes diagnosis. A genetic cause was subsequently found in 8 cases, and insulin was discontinued within 14 days of sulfonylurea initiation in all of these cases.[87] A subsequent study found that earlier age at initiation of sulfonylurea therapy was associated with improved therapeutic response.[88] Sulfonylurea therapy appears to be safe and often successful in neonatal diabetes patients before genetic testing results are available; however, larger numbers of cases must be studied. In a case study of a Chinese girl whose treatment of persistent hyperglycemia with insulin was not effective, long-term glycemic control was achieved with sulfonylurea therapy initiated at the age of 3 years. Fewer episodes of hypoglycemia occurred on sulfonylurea than on insulin therapy.[89] Furthermore, in adults with monogenic diabetes who were misdiagnosed and treated with insulin for decades, sulfonylureas have been shown to restore endogenous insulin secretion.[90]

Table 30

Prevalence of childhood monogenic diabetes by nationwide genetic tests.		
NATION	PREVALENCE	REFERENCE
Poland	4.2-4.6/100,000, or 3.1%-4.2% of children with diabetes	Fendler et al. 2012[81]
New Zealand	~2.5% of children with diabetes	Wheeler et al. 2013[84]

VII COMPLICATIONS OF DIABETES

The acute complications of diabetes include diabetic ketoacidosis, and severe glycemic crisis (hypoglycemia and hyperglycemia). The chronic complications of diabetes are divided into microvascular complications, which occur exclusively in individuals with diabetes and include neuropathy, retinopathy, and nephropathy; and macrovascular complications which occur more commonly in individuals with diabetes and include atherosclerotic vascular disease, stroke, and lower-limb amputations adverse cardiovascular outcomes.

An evaluation of data from NHANES and the Behavioral Risk Factor Surveillance System (BRFSS) reported that most diagnosed persons with diabetes undergo annual examinations to check for common complications of diabetes. For example, data from 1999-2010 indicate that 71.4% of persons with diagnosed diabetes undergo an annual foot exam.[58] In addition, according to the National Hospital Discharge Survey (NHDS), diabetes-related lower extremity amputation rates decreased by 0.8 per 1,000 per year nationwide between 1996 and 2002.[91] Table 31 presents data on changes in the prevalence of some macrovascular complications of diabetes between 1990 and 2010. The remainder of this section will focus on the microvascular complications of diabetes.

7.1

DIABETIC NEUROPATHY

Diabetic neuropathy is a group of nerve disorders caused by diabetes.[92,93] These include peripheral neuropathy, autonomic neuropathy, proximal neuropathy, and focal neuropathy. The risk of developing diabetic neuropathy increases with age, longer duration of diabetes, and poorer control of blood glucose.

7.1.1

Prevalence and Incidence

The prevalence of diabetic peripheral neuropathy (DPN) has been extensively studied. However, data are incomplete for the prevalence of other types of neuropathies. The prevalence of diabetic neuropathy is higher among older diabetes patients and may vary depending on the type of diabetes (Table 32).

7.1.2

Demographic Differences

No differences have been reported in risk of neuropathy among whites, blacks, and Hispanics in the US.[96-98] There are no known sex differences in the risk of developing diabetic neuropathy.

7.1.3

Life Expectancy and Mortality

A meta-analysis of 15 studies[99], published between 1966-2001, revealed an association between cardiovascular autonomic neuropathy and increased relative risk for mortality (1.20) in people with diabetes, though not as strong as previously reported by others.

Table 31

Prevalence of macrovascular complications of diabetes among United States adults, 1990-2010.

COMPLICATION	DATA SOURCE	POPULATION	PREVALENCE	
			1990	2010
Acute myocardial infarction	National Hospital Discharge Survey	US adults, age 20+ years	1.41%	0.46%
Stroke	National Hospital Discharge Survey	US adults, age 20+ years	1.12%	0.53%
Lower-limb amputation	National Hospital Discharge Survey	US adults, age 20+ years	0.58%	0.28%

Source: Gregg et al. 2014[14]

Table 32

Prevalence of diabetic peripheral neuropathy.

DATA SOURCE	POPULATION	PREVALENCE	REFERENCE
1999-2002 NHANES	Persons diagnosed with diabetes, age 40+ years	21.2%	Cheng et al. 2006[8]
1999-2002 NHANES	Persons diagnosed with diabetes, age 40+ years	21.5%	Koopman et al. 2006[9]
1999-2000 NHANES	Persons diagnosed with diabetes, age 40+ years	28.5%	Gregg et al. 2004[94]
SEARCH for Diabetes in Youth	Type 2 diabetes patients, age <20 years	25.7%	Jaiswal et al. 2013[95]
SEARCH for Diabetes in Youth	Type 1 diabetes patients, age <20 years	8.2%	Jaiswal et al. 2013[95]

Abbreviation: NHANES, National Health and Nutrition Examination Survey

Table 33

DPN patients: treatment adherence and opinions.	
FREQUENCY OF PROFESSIONAL CONSULTATIONS FOR DPN	
2 or more in preceding 3 months	59.6%
4 or more in preceding 3 months	41.2%
PRESCRIPTION MEDICATION BEHAVIOR AND ATTITUDES	
Mean prescription medication types in preceding week	3.8
Used at least 1 medication	79.2%
Used at least 2 medications	52.2%
Used prescription NSAIDs	46.7%
Satisfied with medications	22.4%
Considered medications effective	23.1%
OVER-THE-COUNTER (OTC) MEDICATION: BEHAVIOR AND ATTITUDES	
Mean OTC medication types in preceding week	2.1
Used acetaminophen	36.1%
Satisfied with medications	7.8%
Considered medications effective	6.7%

Source: Gore et al. 2006[101]

7.1.4

Key Trends and Health Outcomes

Diabetic peripheral neuropathy (DPN) is an underdiagnosed condition. In one cross-sectional study of patients with type 2 diabetes from rural Arkansas, 9.6% had a diabetic peripheral neuropathy diagnosis and 43% reported symptoms of peripheral neuropathy; 79% of those with symptoms had not been diagnosed with DPN.[100]

The drugs duloxetine and pregabalin are approved by the Food and Drug Administration for the treatment of diabetic neuropathic pain. However, a study of diagnosed DPN patients seeing community-based practitioners throughout the US indicated that NSAIDs were the class most commonly prescribed to treat neuropathy patients. The study identified treatment practices and approaches, summarized in Table 33.[101]

Table 34

Prevalence of Diabetic Retinopathy.				
CONDITION	DATA SOURCE	POPULATION	PREVALENCE	REFERENCES
Diabetic retinopathy	2005-2008 NHIS	Patients with diabetes, age 40+ years	28.5%	Zhang et al. 2010[10]
Any retinopathy	MESA	Patients with diabetes, age 45-85 years	33.2%	Wong et al. 2006[11]
Macular edema	MESA	Patients with diabetes, age 45-85 years	9.0%	Wong et al. 2006[11]
Vision impairment	2010 NHIS	Patients with self-reported diabetes	16.7%	Centers for Disease Control and Prevention. 2011[21]
Vision-threatening diabetic retinopathy	2005-2008 NHIS	Patients with diabetes, age 40+ years	4.4%	Zhang et al. 2010[10]

Abbreviations: MESA, Multi-Ethnic Study of Atherosclerosis; NHIS, National Health Interview Survey

Table 35

Prevalence and severity of diabetic retinopathy by sex.		
SEX	DIABETIC RETINOPATHY (PREVALENCE AMONG PATIENTS WITH DIABETES)	VISION-THREATENING DIABETIC RETINOPATHY (PREVALENCE AMONG PATIENTS WITH DIABETES)
Males	31.6%	25.7%
Females	4.2%	4.7%

Source: Zhang et al. 2010[10]

7.2

DIABETIC RETINOPATHY

Diabetic retinopathy is a condition in which high blood glucose causes damage to the blood vessels in the retina.[102,103]

In nonproliferative retinopathy, blood vessels swell or become blocked. In proliferative retinopathy, damaged blood vessels deprive the retina of oxygen, causing new vessels to grow along the retina and on the surface of the gel, or vitreous, inside of the eye.[102,103]

7.2.1

Prevalence and Incidence

Diabetic retinopathy occurs in both type 1 and type 2 diabetes; the likelihood of developing the condition increases with duration of disease and is higher in people with uncontrolled blood glucose levels (Table 34).
The 2005-2008 NHIS data indicated that both retinopathy and vision-threatening retinopathy were higher among males than females[10] (Table 35).

7.2.2

Demographic Differences

Based on NHIS data from 2005 to 2008, the crude prevalence of diabetic retinopathy and vision-threatening diabetic retinopathy in patients over 40 years of age were highest among non-Hispanic blacks[10] (Table 36).

7.2.3

Life Expectancy and Mortality

A long-term epidemiological study in a Wisconsin population of type 1 diabetes patients revealed that diabetic retinopathy was associated with cardiovascular end points such as angina, stroke, and myocardial infarction.[104] The severity of retinopathy was associated with mortality from heart disease, which was consistent across all age groups examined. Sex differences in the relationship between retinopathy and cardiovascular outcomes were not apparent in this study. The hazard ratio for mortality involving heart disease, including diabetic retinopathy as a variable, was calculated to be 1.3.

7.2.4

Key Trends and Health Outcomes

Most patients with diagnosed diabetes undergo annual examinations to check for common complications of diabetes (Table 37).

NHIS data from 1997 to 2010 indicated that whereas self-reported diabetes plus visual impairment in adults

Table 36

Prevalence of diabetic retinopathy by race/ethnicity.

RACE/ETHNICITY	DIABETIC RETINOPATHY (PREVALENCE AMONG PATIENTS WITH DIABETES)	VISION-THREATENING DIABETIC RETINOPATHY (PREVALENCE AMONG PATIENTS WITH DIABETES)
Non-Hispanic Black	38.8%	9.3%
Mexican American	34.0%	7.3%
Non-Hispanic White	2.4%	3.2%

Source: Zhang et al. 2010[10]

Table 37

Diagnosis and preventive behaviors related to diabetic retinopathy.

DATA SOURCE	POPULATION AND BEHAVIOR	PREVALENCE	REFERENCE
1999-2010 NHANES and BRFSS	Diagnosed diabetes undergoing annual eye exam	73.4%	Ali et al. 2013[58]
1997-2010 NHIS	Self-reported diabetes visiting an eye-care provider annually	63% (diabetes + vision impairment) 57% (diabetes + no vision impairment	Centers for Disease Control and Prevention. 2011[21]

Abbreviations: BRFSS, Behavioral Risk Factor Surveillance System; NHANES, National Health and Nutrition Examination Survey; NHIS, National Health Interview Survey

increased, the age-adjusted prevalence of visual impairment among diagnosed persons with diabetes decreased[21] (Table 38).

The use of macular photocoagulation has reduced the risk of visual impairment by diabetic macular edema. The role of vascular endothelial growth factor (VEGF) in diabetic retinopathy and diabetic macular edema pathogenesis has been demonstrated in recent studies, and the efficacy and safety of intravitral anti-VEGF has recently been demonstrated in clinical trials.[105]

7.3 DIABETIC NEPHROPATHY

Diabetic nephropathy is a condition in which the kidney becomes damaged, resulting in the scarring of nephrons, the small units that filter the blood and remove waste from the body.[106,107]

7.3.1 Prevalence and Incidence

According to NHANES data, diabetic kidney disease affects between 24% and 40% of people with diagnosed diabetes (Table 39).

With adjustments for demographic factors, evaluation of three installments of NHANES data (1988-1994, 1999-2004 and 2005-2008) indicated no change in the prevalence of any diabetic kidney disease or albuminuria between 1988 and 2008.[12]

7.3.2 Demographic Differences

A retrospective study of over 15,000 health records of diabetes patients with no prior history of kidney disease found differing rates of diabetic kidney disease (DKD). Racial/ethnic minorities had higher rates of proteinuric DKD than non-Hispanic whites and lower rates of nonproteinuric DKD. Chinese, Filipino, Hispanic, and non-Hispanic black females exhibited significantly higher odds of proteinuric DKD than non-Hispanic whites. Conversely, Chinese, Hispanic, and non-Hispanic black females and Hispanic males had significantly lower odds of nonproteinuric DKD than NHWs[109] (Table 40).

Table 38

Prevalence of visual impairment in self-reported and diagnosed diabetes, US.

	1997	2009
Self-reported diabetes	2.7 million	3.9 million
Diagnosed diabetes*	23.7%	16.7%

Source: Centers for Disease Control and Prevention. 2011[21]

Note: *, age-adjusted prevalence

Table 39

Prevalence of diabetic kidney diseases.

Any diabetic kidney disease	2005-2008 NHANES	Patients with diagnosed diabetes, age 20+ years	34.5%	De Boer et al. 2011[12]
Albuminuria	2005-2008 NHANES	Patients with diagnosed diabetes, age 20+ years	23.7%	De Boer et al. 2013[12]
Nephropathy	1999-2002 NHANES	Patients with diagnosed diabetes, age 40+ years	26.5%	Koopman et al. 2006[9]
Chronic kidney disease	1999-2006 NHANES	Patients with diagnosed diabetes, age 20+ years	39.6%	Plantinga et al. 2010[13]
	1999-2006 NHANES	Persons with undiagnosed diabetes, age 20+ years	41.7%	Plantinga et al. 2010[13]
	1999-2006 NHANES	Patients with prediabetes, age 20+ years	17.7%	Plantinga et al. 2010[13]
Renal disease	1997-1999 Veterans Health Administration data	VA patients with diagnosed diabetes	10.4%	Young et al. 2003[108]

Abbreviation: NHANES, National Health and Nutrition Examination Survey

7.3.3

Life Expectancy and Mortality

For patients with type 2 diabetes and nephropathy, the Charlson comorbidity index (CCI), along with hemoglobin and serum albumin, is an effective predictor of mortality.[110] 533 Chinese patients with type 2 DN with comorbidity CCI score >1, 44.7% (238/533) died. Mortality increased with CCI scores: 21.0% (50/238) patients with CCI scores of 1-2, 56.7% (135/238) patients with CCI scores of 3-4, and 22.3% (53/238) patients with CCI scores >/=5.[111]

Table 40

Rates of diabetic kidney disease by race/ethnicity.

RACE/ETHNICITY	PROTEINURIC DKD	NONPROTEINURIC DKD
Non-Hispanic white	24.8%	11.7%
Asian Indian	24.8%	9.7%
Chinese	27.6%	6.3%
Filipino	37.9%	9.8%
Hispanic	32.5%	7.6%
Non-Hispanic black	35.3%	6.9%

Source: Bhalla et al. 2013[109]

7.3.4

Key Trends and Health Outcomes

In 2011, according to the United States Renal Data System, diabetes was listed as the primary cause of kidney failure in 44% of all new cases.[112] Table 41 presents data on differences in mortality rate among Medicare patients based on different disease profiles.

According to 1999-2004 data from NHANES, awareness of chronic kidney disease among adult persons with diabetes with stage 3 chronic kidney disease (CKD) rose from 12.2% in 1999-2000 to 19.1% in 2003-2004.[13] Increased systolic blood pressure variability between outpatient events is associated with increased incidence of cardiovascular end points. A post-hoc analysis of two observational trials showed that greater visit-to-visit variability of systolic blood pressure was associated independently with more rapid doubling of serum creatinine and end-stage renal disease, but not with time to cardiovascular death, myocardial infarction, stroke, hospitalization for heart failure, or revascularization.[110]

Table 41

Mortality among Medicare patients age 66 years and older by disease profile.

DISEASE PROFILE	MORTALITY
No diabetes, chronic kidney disease, or cardiovascular disease	40 per 1,000 patient-years
Diabetes	50 per 1,000 patient-years
Diabetes, chronic kidney disease, cardiovascular disease	100 per 1,000 patient-years

Source: National Institute of Diabetes and Digestive and Kidney Diseases. 2013[112]

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