Diabetes Research and Resources

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What is Diabetes?

Diabetes mellitus is a class of diseases that characterized by high glucose levels in the blood. The pancreas, an organ involved in digestion, releases a hormone called insulin that affects the blood's glucose content by allowing glucose to enter the body's cells. In diabetes, the glucose in the blood cannot get into the body's cells to provide the energy needed to function. There are three major types of diabetes:[1]

Type 1 diabetes is an autoimmune disease that occurs when the body does not make enough insulin. The body's own immune system malfunctions, and attacks and kills the insulin producing beta cells in the pancreas. Type 1 diabetes can develop at any age, often in childhood, and there is no known way to prevent the disease.[2] Over 18,000 youth are diagnosed with type 1 diabetes each year in the U.S., accounting for about 5% of all diagnosed diabetes cases.[3]

Type 2 diabetes occurs when the body cannot use insulin properly due to the development of insulin resistance. Insulin resistance occurs when the body's cells do not allow insulin to enter the cells, despite the presence of insulin in the blood. Insulin resistance can eventually lead to failure by the pancreas to keep up with the insulin demands. Most cases occur in middle aged and older individuals, but type 2 diabetes is now also appearing in children.[4] Risk factors for type 2 diabetes include:[5]

- Being overweight/physical inactivity
    - However, 20% of cases occur among lean individuals and the mechanism is not well understood[6]
- Having a family history
- Having diabetes while pregnant (gestational diabetes)

Gestational Diabetes is a type of diabetes that can developed while a woman is pregnant. Overweight and obese women are at the highest risk for developing gestational diabetes. While gestational diabetes normally goes away after birth, both the mother and baby are at increased risk of developing type 2 diabetes later in life.[7]

Prediabetes refers to high blood glucose levels, but not high enough to be classified as diabetes.[8] 86 million people in the U.S. have prediabetes, and 9 out of 10 people with prediabetes do not know they have it. Without weight loss and moderate physical activity, 15-30% of individuals with prediabetes will develop type 2 diabetes within five years.[9]

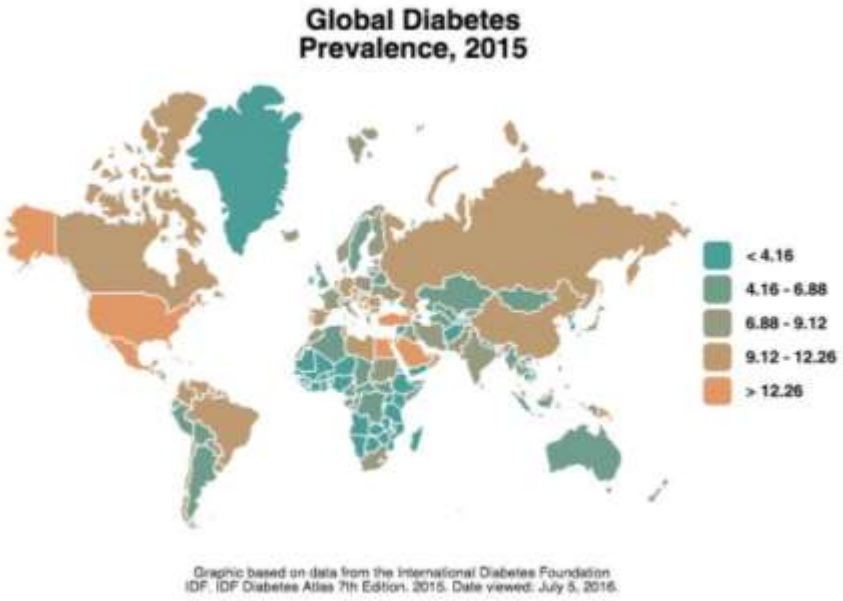
Those living with diabetes are at increased risk for:[10]

- Blindness/retinopathy
- Kidney failure/nephropathy
- Heart disease/cardiovascular disease
- Stroke
- Nerve damage/neuropathy
- Amputation of toes, feet, or legs
- If type 1, then other autoimmune diseases (thyroid disease, celiac disease, autoimmune gastritis, and Addison's disease)[11]

- Metabolic syndrome (a set of risk factors for heart disease that includes high blood glucose, abdominal obesity, high blood pressure, and high cholesterol/triglyceride levels)[12]

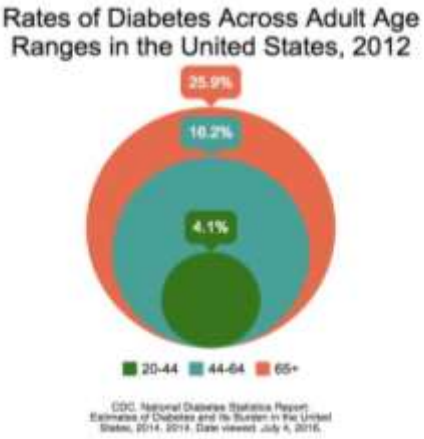
Diabetes - Current Condition

According to the most recent report from the U.S. Centers for Disease Control and Prevention (CDC), in 2014, there were 29.1 million people living with diabetes in the U.S.[13] Among the 29.1 million, an estimated 8.1 million people are undiagnosed and living with diabetes.



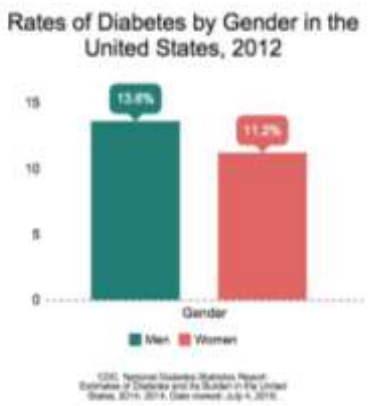
According to a 2015 report from the International Diabetes Foundation, 415 million adults are living with diabetes globally. Of those living with diabetes, 80% live in low- or middle-income countries.[14]

Of those aged 65 years or older in the United States, 25.9% have diabetes, followed by 16.2% of individuals aged 45-64 and 4.1% of those aged 20-44.[15]

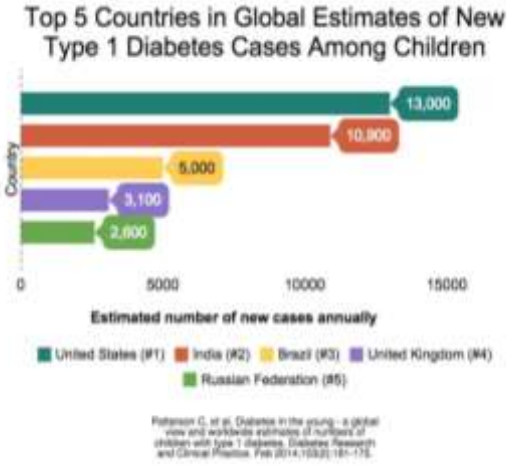


Growing Concerns

A study published in the Journal of the American Medical Association (JAMA) found the prevalence of type 1 and type 2 diabetes doubled among U.S. adults between 1990 and 2008.[16] The same study also identified a plateau, or leveling off of diabetes cases from 2008 to 2012. Researchers suggest this could be from the slowing rate of obesity cases (a major risk factor for type 2 diabetes) and better diagnostic testing.



However, the rates of diabetes continued to grow in Hispanic individuals, non-Hispanic black individuals, and populations that received a high school education or less.[17]



Among U.S. children, type 2 diabetes prevalence increased

by 30.5% and type 1 diabetes increased by 21.1% between 2001 and 2009.[18] With 13,000 cases each year, the U.S. leads all other countries in new cases of type 1 diabetes among children.[19]

Diabetes affects men and women somewhat equally, men experiencing a rate of about 13.6% while women experience a rate of about 11.2%.[20] Overall, both genders tend to be at comparable risks for diabetes.

Environmental Contributors

A variety of environmental factors may contribute to the development of various types of diabetes.

Chemical Exposures

There are numerous studies that examine the effect chemicals have on diabetes risk. Many studies have significant findings that show the strong role chemicals have in acting as diabetes triggers. These studies continue as new chemicals are found to have possible diabetic consequences.

Information in the first table below comes from following source unless otherwise indicated: Bodin J, et al. Can exposure to environmental chemicals increase the risk of diabetes type 1 development? BioMed Research International. 2015, ID 208947, 1-19.[21] The "strong", "good", and "limited" categories are taken from the CHE Toxic and Disease Database structure.

Type 1 Diabetes		
Chemical	**Sources**	**Effects**
Vacor (strong evidence)	Rodenticide, banned in the U.S.	Destroys pancreatic beta cells; causes type 1 diabetes in humans
Air Pollution (good evidence)	Traffic-related air pollution, from cars, trucks, and diesel exhaust	Some studies find associations between various air pollutants and type 1 diabetes.

Chemicals with limited evidence for type 1 diabetes:

Arsenic

- Contaminates drinking water
- Impairs the immune system, alters the gut microbiome diversity, lowers insulin secretion, and destroys beta cells[22]

Persistent organic pollutants

- Widespread environmental contaminants that all humans are exposed to; includes PCBs, dioxins/furans, and organochlorine pesticides like DDT

- Some studies find associations with type 1 diabetes or autoimmunity[23]

Nitrate/nitrite/N-nitroso compounds

- Nitrite can be found in processed meats; nitrate can be found in groundwater
- Associated with type 1 diabetes in numerous, but not all, human and animal studies[24]

BPA

- Animal studies show that can affect beta cells, promote autoimmunity, and exacerbate diabetes development in a mouse model of type 1 diabetes[25, 26]
- BPA has not been studied in relation to human type 1 diabetes

PFOS

- One human study found an association with type 1 diabetes[27]

Pesticides

- One human study found associations with type 1 diabetes[28]

Type 2 Diabetes		
Chemical	**Sources**	**Effects**
Air Pollution[29] (strong evidence)	Traffic-related air pollution, from cars, trucks, and diesel exhaust	Enhanced insulin resistance and inflammation around major organs, promoting diabetes
Arsenic[30] (strong evidence)	contaminates drinking water	Impairs the immune system, alters the gut microbiome diversity, impairs insulin secretion, destroys beta cells
Dioxin[31] (strong evidence)	Found in the herbicide Agent Orange used during the Vietnam War, also a persistent organic pollutant	Linked to type 2 diabetes in exposed veterans
Persistent organic pollutants[32, 33] (strong evidence)	Widespread environmental contaminants that all humans are exposed to; includes PCBs, dioxins/furans, and organochlorine pesticides like DDT.	DDE, heptachlor, HCB, DDT, trans-nonachlor, and chlordane most strongly linked to type 2
Pesticides[34] (good evidence)	Used for pest and weed control	Odds of diabetes incidence increased with both ever use and cumulative days of use

Cadmium[35] (good evidence)	Batteries; pigments; coatings and platings; stabilizers for plastics; cigarettes[36]	Impairs insulin release and disrupts glucose homeostasis
Selenium[37] (good evidence)	Soil; dietary supplements	Interferes with insulin signaling, which is critical to the regulation of glucose levels
Bisphenol A (BPA) (good evidence)	Production of plastic and epoxy resins coating the inside of metal cans and can leach from the plastic into food	BPA causes insulin resistance in animal studies and is associated with type 2 diabetes in humans

Chemicals with limited evidence to type 2 diabetes:

Radiation[38]

- High doses of radiation (nuclear accidents) have shown some indication of being linked to diabetes

Perfluorinated compounds (PFCs), also known as perfluoroalkyl substances (PFAS)

- used in fire-fighting foam, textiles, kitchen ware, and food packaging materials; Human exposure to PFAS is mainly through diet via marine food and game
- Some studies find associations with type 2 diabetes

Phthalates

- Used as plasticizers in a variety of consumer products, like paint and cosmetics. Exposure is mainly through diet via contamination from plastic into food, but also through phthalates in dust from indoor air and via the skin from cosmetic products
- Promotes insulin resistance through sustained oxidative stress and inflammation

Mercury and other metals

- Limited but conflicting evidence

Gestational Diabetes

There is also very preliminary (limited) evidence linking the development of gestational diabetes to environmental chemical exposures. These chemicals include: arsenic and other metals;[39, 40] air pollution;[41, 42, 43] pesticides[44]; PFOA[45]; and flame retardants[46]. Most of these associations have not been studied in additional cohorts or in the laboratory.

Lifestyle Factors

Diet

- Type 1 Diabetes: Consumption of cow's milk, infant formula, gluten, processed foods, and numerous other dietary factors in early life have been studied in relation to type 1 diabetes development, but none have been shown to unequivocally affect the risk of type 1 diabetes.[47] Probiotics, omega-3 fatty acids, and breastfeeding are being studied as possible protective factors for type 1 diabetes.[48, 49]
- Type 2 Diabetes: Sugar-sweetened beverage consumption has a strong association with increased type 2 diabetes risk.[50] Consumption of omega-3s (primarily found in fish) have shown protective effects against type 2 diabetes.[51] Human guts low in bacterial richness have been associated with higher risks of obesity and insulin resistance, both risk factors for type 2 diabetes.[52]

Weight

- Type 1 Diabetes: there are numerous studies that indicate an association with weight gain, and numerous studies that do not. One study found a middle ground, reporting a slight increased risk for type 1 diabetes in those with a higher BMI.[53]
- Type 2 Diabetes: the associations between weight gain and type 2 diabetes are much better established. The Diabetes Prevention Program has found that weight reduction and intensive lifestyle interventions reduces the incidence of diabetes by 58%.[54]

Physical Activity

- Greater physical activity has shown to lower all-cause mortality in patients with diabetes.[55]

Stress (see CHE's page on the psychosocial environment)

- Type 1 Diabetes: studies show that stress is associated with type 1 diabetes development for both children and adults.[56]
- Type 2 Diabetes: both stressful life events (such as PTSD[57]) as well as chronic stress (such as high stress jobs[58]) have been associated with increased type 2 diabetes risk.

Other Contributors

Vitamin D Deficiency

Studies have shown that areas with lower levels of ultraviolet B radiation (the main source of vitamin D in humans) had a higher incidence of type 1 diabetes.[59] Vitamin D intake in early life is associated with a lower risk of type 1 diabetes, and maternal vitamin D intake during pregnancy may decrease the risk of type 1 diabetes in the offspring, although the evidence is not yet conclusive.[60]

Healthy Gut/Microbiome

A healthy gut is full of good bacteria that promote a healthy immune system to fight off bad bacteria and other pathogens. Broad exposure to a wealth of non-pathogenic microorganisms early in life are associated with protection against allergies, type 1 diabetes, and inflammatory

bowel disease.[61] Studies have found differences in gut microbacteria from individuals that have diabetes and those that do not, and these differences may affect type 1 diabetes susceptibility.[62] Several lines of evidence suggest that the microbiome may influence the development of type 1 diabetes and increasing evidence suggests that microbiome-host interactions may be one environmental factor that influences type 2 diabetes risk as well as its progression.[63] The microbiome is modifiable through environmental circumstances, including method of birth, breast-feeding, antibiotics, diet, exposure to toxins, and hygiene.[64]

Genetic Factors

Genes alone do not explain the rising rates of diabetes seen throughout the world. Some studies even suggest that genetic predisposition to type 1 diabetes is decreasing and becoming less prevalent in children today, as compared to years past.[65] Overall, genome studies have found numerous genes associated with a higher or lower risk of type 1 and type 2 diabetes.[66]

Epigenetics

Epigenetics is a set of mechanisms that can turn on or off particular genes or sections of chromosomes. These changes are maintained as the cell divides and replicates.[67] These epigenetic effects are likely the result of both genetic and environmental factors. Nutrition and exposure to certain chemicals *in utero* have been shown to increase risk of the fetus developing type 2 diabetes later in life.[68] As the fetus develops *in utero*, nutrients from the mother's diet can influence which genes are turned on and off. When the mother is malnourished, genes involved in the baby's pancreatic development and obesity-associated genes can be affected. Maternal obesity itself also increases the risk of developing insulin resistance and has been associated with an increased risk of large gestational weight, fat accumulation, and type 2 diabetes in offspring.[69]

Mechanisms of Diabetes

There is still much to learn about how diabetes works and to complicate things further, diabetes often looks different among those affected. For example, in type 1 diabetes, some individuals' pancreas will have sections with functional insulin-producing cells while other individuals with type 1 do not.[70]

Autoimmunity

This is the primary mechanism for type 1 diabetes. It involves the body attacking its own immune system, specifically the insulin-producing beta cells in the pancreas. Type 1 diabetes is often diagnosed by testing for autoantibodies. Exposure to certain environmental factors, such as viruses, have the potential to trigger the autoimmunity involved with type 1 diabetes.[71]

Chronic Inflammation

Inflammation is involved in the development of both type 1 and type 2 diabetes. The autoimmune reaction involved in type 1 diabetes leads to higher levels of inflammatory markers, such as cytokines,

that control the strength of the immune response.[72] For type 2 diabetes, chronic inflammation is closely linked to the high prevalence of obesity. Obesity is a major risk factor for type 2 diabetes and represents a state of chronic low-grade inflammation. The excess fat cells present in obesity promote the formation of visceral adipose tissue. This type of tissue surrounds the abdominal organs and increases the risks of insulin resistance as well as other conditions. The presence of visceral adipose tissue results in further inflammation due to activation of pro-inflammatory antibodies, leading to a cycle of chronic inflammation.[73]

Insulin Resistance

Insulin resistance is well-established as a gateway to type 2 diabetes. The major risk factors for type 2 diabetes include over-nutrition, low dietary fiber, sedentary lifestyle, sleep deprivation, and depression. These have been found to induce low-grade inflammation, which could eventually lead to insulin resistance.[74] Individuals that are insulin resistant cannot respond properly to insulin since the insulin molecules are not able to enter the cells as easily. This results in high levels of glucose, or sugar, in the blood. The initial response is for the pancreas to produce more insulin, but since the insulin is unable to enter cells and lower blood sugar levels, it also remains in the blood leading to high insulin levels. [75]

Endocrine Disruption

Insulin resistance can also be caused by endocrine disrupting chemicals (EDCs). Widespread EDCs, such as dioxins, pesticides and bisphenol A (BPA), cause insulin resistance and alter beta cell function in animal models. These EDCs are present in human blood and can accumulate in and be released from fat cells. After binding to cellular receptors and other targets, EDCs either imitate or block hormonal responses.[76]

Endocrine disrupting chemicals are thought to interfere with fetal programming by affecting gene regulation and gene expression (epigenetics) during pregnancy. When pregnant mothers are exposed to EDCs, EDCs can enter the bloodstream and alter the expression of genes in the developing fetus. The environmental exposures that the fetus encounters *in utero* have the chance of becoming persistent alterations in the individual's epigenome, leading to increased risk of diabetes across multiple generations.[77] Epigenetics and its link to diabetes remains an active area of research.

While these mechanisms were all discussed separately, it is likely they are all interconnected and act together in promoting diabetes. Also, different mechanisms may be of varying significance based on where an individual lives and their environment.[78]

Vulnerable Populations

There are major variations in diabetes prevalence among different ethnic groups in the U.S. Among adults aged 20 years or older, the Native American population experiences a disproportionately high rate of type 2 diabetes, while non-Hispanic whites have the lowest rates of type 2 diabetes.[79] Among

children, non-Hispanic whites are at highest risk for type 1 diabetes, and Native Americans are at the lowest risk. However, the reverse is true for type 2 diabetes, with Native Americans being most at risk and non-Hispanic whites being at the lowest risk.[80]

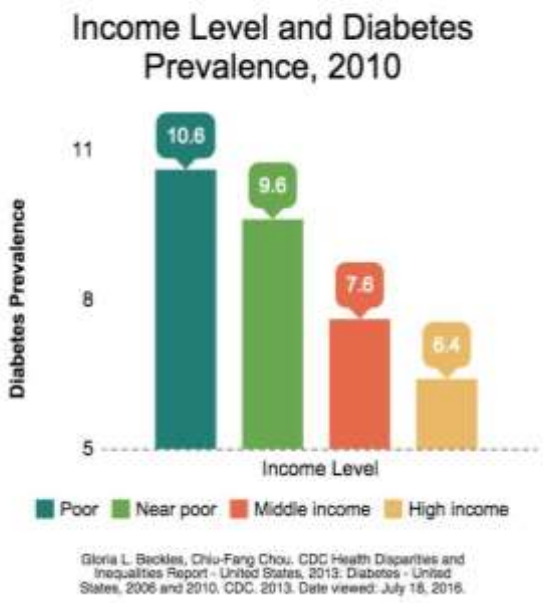
Vulnerable Periods

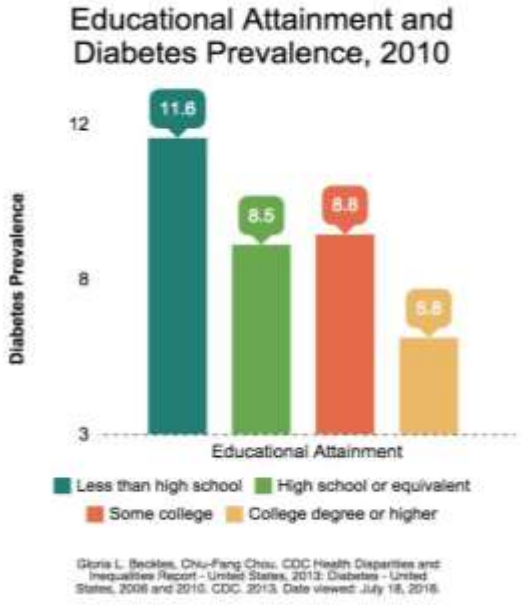
While diabetes usually develops years after birth, maternal influences during pregnancy have been shown to influence diabetes risk for the fetus later in life. Studying famines has revealed that being pregnant during times of caloric restrictions is associated with increased risk for type 2 diabetes later in life for the infant.[81] This could be the result of genes in the fetus switching on/off (epigenetics) to maximize energy conservation, and these genes become problematic in an environment with greater caloric availability. Additionally, maternal over-nutrition and insulin resistance during pregnancy has also been shown to impair fetal nutrition, predisposing the fetus to diabetes in adulthood.[82]

The ability of chemicals to cross the placenta and influence fetal development during pregnancy further illustrate that the periconception period is a vulnerable time for new individuals.[83] Many chemicals will have little effect on the mother but irreversible effects on the fetus.

Disproportionality of Diabetes

The socioeconomically disadvantaged and low-income groups experience the highest prevalence of diabetes. A report from the CDC found that those with the lowest levels of education and income experienced the highest rates of diagnosed diabetes in the United States.[84] See the results below:





Diabetes disproportionately affects the most vulnerable groups in the United States. This could be the result of a variety of factors, including high stress, high cost and limited availability of healthy food, disproportionate exposures to chemicals, and the fact that many jobs which do not require significant schooling have larger occupational hazards.[85] Contributing to type 2 diabetes risk could also be related to the cheaper cost of energy-dense foods and resulting higher levels of obesity among low-income groups. There are many societal barriers in place that help explain why these groups are most affected.

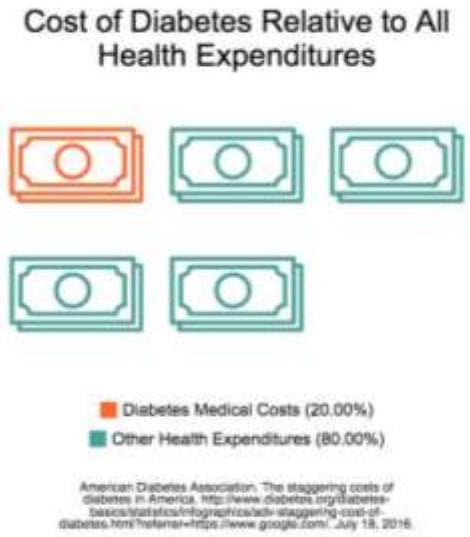
The cost of treating diabetes is high for all patients and makes low-income groups even more vulnerable to the worst effects of diabetes. One study estimated the lifetime medical costs of diabetes to be $124,600 if diagnosed at age 40, $91,200 if diagnosed at age 50, $53,800 if diagnosed at age 60, and $35,900 if diagnosed at age 65.[86]

Ethical Considerations: Diabetes-related Stigma

A diabetes diagnosis oftentimes comes with diabetes-related stigma. Due to landmark studies that have shown type 2 diabetes can be prevented by maintaining a healthy lifestyle, individual behavior is often called into question to determine why an individual may have diabetes. For example, people with diabetes often perceive the public as blaming them for self-inflicting themselves with the disease. This often leads to self-blame and lower perceived self-worth for people with type 2 diabetes. Another source of stigma is the required needle use for insulin treatment and worry of being mistaken as an illicit drug user. These sources of stigma and others have real impacts on both psychological health and physical health.[87]

National Economic Costs

According to a 2012 CDC study, the direct and indirect costs of diabetes totaled $245 billion. The medical costs associated with diabetes patients are 2.3 times the cost of those living without diabetes, totaling $196 million in 2012. Indirect costs of diabetes refers to disability, work loss, and premature death and was found to be $69 billion.[88] Altogether, $1 of every $5 dollars spent on healthcare in the United States goes to covering the costs of diabetes.[89]



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