

Obesity, Diabetes and the Thrifty Gene

The Case of the Pima

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What is diabetes? Diabetes is a disease. According to WHO:

Diabetes is a chronic disease that occurs either when the pancreas does not produce enough insulin or when the body cannot effectively use the insulin it produces. Insulin is a hormone that regulates blood sugar. Hyperglycaemia, or raised blood sugar, is a common effect of uncontrolled diabetes and over time leads to serious damage to many of the body's systems, especially the nerves and blood vessels¹.

The CDC's National Diabetes Fact Sheet (2007) defines diabetes in this way:

Diabetes is a group of diseases marked by high levels of blood glucose resulting from defects in insulin production, insulin action, or both. Diabetes can lead to serious complications and premature death, but people with diabetes can take steps to control the disease and lower the risk of complications².

The scientific community recognizes three types of diabetes. The first type of diabetes, Type 1 diabetes, previously known as insulin-dependent diabetes mellitus (IDDM) or juvenile-onset or childhood diabetes, is characterized by defects in insulin production and requires daily insulin injections. Type 1 diabetes accounts for 5 to 10 % of all diagnosed cases of diabetes among the adults. The type two diabetes, Type 2 diabetes, previously also called non-insulin-dependent diabetes mellitus (NIDDM) or adult-onset diabetes, results from the inability of the body to use insulin effectively. In adults Type 2 diabetes account for about 90 to 95% The third type is gestational, a form of glucose

intolerance diagnosed during pregnancy. Other types of diabetes result from specific genetic conditions, surgery, infections and other illness.

Type 2 Diabetes Mellitus is increasing worldwide, especially in population transitioning from traditional to modern lifestyle such as South India³ and Taiwan⁴. Prevalence and incidence of Type 2 Diabetes Mellitus are highest among the adults, but it is increasingly affecting also young people.

The impact of diabetes on a person's lifestyle is progressive over time, beginning with the body's cells being resistant to insulin-mediated glucose uptake. Eventually, the pancreas cannot sustain the high insulin production level needed for glucose uptake and insulin levels drop.

In November 2009 WHO declared that in 2005, an estimated 1.1 million people died from diabetes, more than 220 million people worldwide have diabetes, almost 80% of diabetes deaths occur in low- and middle-income countries, Almost half of diabetes deaths occur in people under the age of seventy years; 55% of diabetes deaths are in women and projections of diabetes deaths will double between 2005 and 2030.⁵

On 20 December 2006 the United Nations General Assembly designated 14 November, the current World Diabetes Day, as United Nations Day,

Recognizing also that diabetes is a chronic, debilitating and costly disease associated with severe complications, which poses severe risks for families, Member States and the entire world and serious challenges to the achievement of internationally agreed development goals including the Millennium Development Goals.⁶

In the US the Center for Disease Control (CDC) classified diabetes as an epidemic and identified the prediabetes conditions, such as a condition in which individuals have blood glucose levels higher than the normal but not high enough to be classified as diabetes. Those prediabetes conditions are classified as Impaired Fasting Glucose (IFG) and Impaired glucose tolerance (IGT). Usually people with prediabetes have an increased risk to develop Type 2 diabetes. A person's risk for developing Type 2 Diabetes Mellitus has been shown to be highly linked to obesity and any family history of diabetes.⁷

At the end of 2007, diabetes affected 23.6 million people in the United States, the 7.8% of the population. The majority of these people are diagnosed with Type 2 Diabetes Mellitus (T2DM). This variety makes up 95% of those twenty-four million. Complications

linked to diabetes is the sixth leading cause of death in the US. The Centers for Disease Control estimated the total cost of diabetes in the United States of 174 billion of dollars⁸. Since 1995 various epidemiological studies related with the data systems of the Centers for Disease Control and Prevention (CDC), the user population database of the Indian Health Service (IHS), the U.S. Renal Data System of the National Institutes of Health (NIH), the U.S. Census Bureau, community surveys and published studies, have brought to light that the susceptibility to Type 2 diabetes presented marked differences according to ethnic groups.

As with prevalence, incidence rates for blacks, Hispanics, and Native Americans are higher than for whites. It has been hypothesized that the high rates of diabetes for Native Americans are associated with a genetic predisposition to insulin resistance and obesity that evolved as a survival strategy in response to fluctuating food supplies. About 31% of the Hispanic gene pool is derived from Native American genes, and this genetic admixture has been associated with increased rates of diabetes in the U.S. Hispanic population⁹. Lifestyle factors such as decreased physical activity, change in diet including increased caloric intake, and rapid modernization into Western society are strong contributors to increased diabetes in these populations.¹⁰

The San Antonio Heart Study¹¹, the San Luis Valley Diabetes Study¹², the Starr County Study¹³ and the Hispanic Health and Nutrition Examination Survey¹⁴ provided most of the very basic information on diabetes among Hispanic Americans. HHANES, moreover, also included information on Cuban Americans in the Miami area and Puerto Ricans in the New York City Area. These studies demonstrated that the prevalence of NIDDM is two to three times higher in Mexican Americans than in non Hispanic whites. Even if NIDDM among Cuban Americans is lower than that of Mexican Americans, it is still thirty to fifty percent higher than in non Hispanic whites.

The prevalence of diabetes among American Indians is 2.8 times the overall rate. The highest prevalence rates are known among Pima, fifty percent of adults between the ages of thirty and sixty-four having NIDDM¹⁵ and other Native Americans, followed by Nauruans¹⁶ who are among the most obese people in the world: ninety percent of adults have a BMI higher than the world average.

The toll of NIDDM is much greater for minority populations than the white population:

10.8 percent of non-Hispanic blacks, 10.6 percent of Mexican Americans, and 9.0 percent of American Indians have diabetes, compared with 6.2 percent of whites.¹⁷

In 1963, laboratory equipped mobile trailer units of the National Institute of Diabetes and Digestive and Kidney Diseases, NIDDK, (then called National Institute of Arthritis, Diabetes and Digestive and Kidneys Diseases) started an epidemiological survey on the incidence of rheumatoid arthritis among the Blackfeet of Montana and the Pima of Arizona and discovered that the Pima showed unusually high rates of diabetes¹⁸.

In 1965 the World Health Organization (WHO) and the American Diabetes Association decided that the glycosuria was a poor method in order to detect and diagnose diabetes and recommended the use of blood glucose for diabetes diagnosis. The Oral Glucose Tolerance Test (OGTT) soon became the standard procedure.

A statistical projection of the incidence and the trend of NIDDM among the Native Americans (U.S. and Canada) and Native Alaskans for the years before 1990 is rather difficult both for the U.S. and Canada difference in the collection of statistics on ethnic affiliation, and for the differences of their health services. In the 1990 U.S. Census 1.9 million individuals identified themselves as American Indians and Alaskans, and only 1.3 million of them resided in the thirty-three reservations served by the Indian Health Service (IHA)¹⁹. Since American Indians living in the reservations were not included in U.S. national health surveys, diabetes data among Native Americans are limited. Moreover until the late 1990s the health of urban Native Americans in U.S. and Canada was covered by the few data. Using the U.S. IHS data and those of the Canadian Medical Service Branch of the Department of National Health and Welfare were obtained the raw data shown in Figure 1²⁰.

That diabetes rates were higher in full-blooded Native Americans was observed in Choctaw Indians in 1965²¹ and in the early Pima surveys. Moreover the Pima community showed (and shows) the highest rates among individuals with full Native American heritage²².

The dramatic rate of presence of Type 2 Diabetes Mellitus that afflicted and still afflicts the Pima as well as their relative genetic “isolation” were among the determining factors in their choice as possible partners in the study on eventual genetic causes of Type 2 Diabetes Mellitus.

The hope was that the Pima could help, like the Mormon families in Salt Lake City helped the researchers find a gene for colon cancer, or like blood and skin samples from

Figure 1
Prevalence of Diabetes in North America Native Populations by Region

Reservation/Location	Tribe	Age	Date	Rate/1,000	Adjustment	Method	Reference
Southwest							
Tohono O'odham, AZ	Tohono O'odham	≥18	1985-86	183	None	Case registry w/record review	6
Gila River, AZ	Pima	30-64	1982-87	500	Age World pop	Biennial community screening	7
New Mexico	Pueblo (Rio Grande)	≥35	1985	213	None	Case registry w/record review	8
Zuni, NM	Zuni	≥35	1985	282	None	Case registry w/record review	8
Jicarilla Apache, NM	Apache	≥35	1985	98	None	Case registry w/record review	8
Mescalero Apache, NM	Apache	≥35	1985	164	None	Case registry w/record review	8
Navajo, NM	Navajo	≥35	1985	165	None	Case registry w/record review	8
Arizona and New Mexico reservations	Apache	≥15	1987	101	Age U S 1980	Outpatient records not verified	9
Navajo, AZ and NM	Navajo	≥15	1987	72	Age U S 1980	Outpatient records not verified	9
Navajo, AZ	Navajo	20-74	1989	165	Age/sex U S 1980	Case registry community screening	10
Navajo, AZ	Navajo	≥20	1988	124	Age U S 1980	Community sample w/screening	11
Rocky Mountain West							
Fort Hall, ID	Shoshone/Bannock	All	1987	95	Age/sex U S 1980	Case registry w/chart review	12
Nez Perce, ID	Nez Perce	All	1987	105	Age/sex U S 1980	Case registry w/chart review	12
Blackfeet, MT	Blackfeet	≥15	1986	168	Age ≥15 U S 1980	Case registry w/chart review	13
Crow, MT	Crow	≥15	1986	85	Age ≥15 U S 1980	Case registry w/chart review	13
Fort Belknap, MT	Assiniboine/ Gros Ventre	≥15	1986	118	Age ≥15 U S 1980	Case registry w/chart review	13
Fort Peck, MT	Assiniboine/Sioux	≥15	1986	173	Age ≥15 U S 1980	Case registry w/chart review	13
Northern Cheyenne, MT	Northern Cheyenne	≥15	1986	59	Age ≥15 U S 1980	Case registry w/chart review	13
Wind River, WY	Shoshone/Arapaho	≥15	1986	125	Age ≥15 U S 1980	Case registry w/chart review	13
Utah and Colorado	Ute	≥15	1987	124	Age U S 1980	Outpatient records not verified	9
Northern Plains							
Cheyenne River, SD	Sioux	All	1987	106	Age U S 1980	Outpatient records not verified	14
Crow Creek, Lower Brule, SD	Sioux	All	1987	83	Age U S 1980	Outpatient records not verified	14
Devils Lake, ND	Sioux	All	1987	111	Age U S 1980	Outpatient records not verified	14
Pine Ridge, SD	Sioux	All	1987	70	Age U S 1980	Outpatient records not verified	14
Rosebud, SD	Sioux	All	1987	82	Age U S 1980	Outpatient records not verified	14
Sisseton/Wahpeton, SD	Sioux	All	1987	64	Age U S 1980	Outpatient records not verified	14
Turtle Mountain, ND	Chippewa	All	1987	105	Age U S 1980	Outpatient records not verified	14
Standing Rock, ND/SD	Sioux	All	1987	125	Age U S 1980	Outpatient records not verified	14

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Figure 1—Continued

Reservation/Location	Tribe	Age	Date	Rate/1,000	Adjustment	Method	Reference
Yankton/Santee, SD	Sioux	All	1987	196	Age U S 1980	Outpatient records not verified	14
Winnebago/Omaha, NE	Winnebago/Omaha	All	1987	218	Age U S 1980	Outpatient records not verified	14
North and South Dakota reservations	Sioux	≥15	1987	117	Age U S 1980	Outpatient records not verified	9
Upper Midwest							
Red Lake, MN	Chippewa	All	1987	148	Age/sex U S 1980	Case registry verified/screening	15
MN and ND reservations combined	Chippewa	≥15	1987	144	Age U S 1980	Outpatient visits not verified	9
Ontario and Manitoba, Canada	Cree/Ojibwa	All	1983	28	None	Case registry w/chart review	16
SW Ontario, Canada	Oneida/Chippewa	≥5	1985	147	Age Canada 1985	Case registry w/chart review	17
Northeast							
St Regis, NY	Mohawk	All	1989	49	Age U S 1980	Case registry w/chart review	18
River Desert/Lac Simon, Quebec, Canada	Algonquin	≥15	1989	150	None	Community survey	19
Nova Scotia, Canada	Micmac	All	1989	53	None	Case registry	20
South							
Choctaw, MS	Choctaw	All	1989	163	Age U S 1980	Case registry w/chart review	21
Cherokee, NC	Cherokee	All	1988	106	Age U S 1980	Case registry	22
Pacific Northwest							
Lummi, WA	Lummi	All	1987	40	Age/sex U S 1980	Case registry w/chart review	12
Tahola, WA	Quinalt	All	1987	50	Age/sex U S 1980	Case registry w/chart review	12
Makah, WA	Makah	All	1987	53	Age/sex U S 1980	Case registry w/chart review	12
Colville, WA	Colville	All	1987	52	Age/sex U S 1980	Case registry w/chart review	12
Spokane, WA	Spokane	All	1987	56	Age/sex U S 1980	Case registry w/chart review	12
Yakima, WA	Yakima	All	1987	75	Age/sex U S 1980	Case registry w/chart review	12
Umatilla, OR	Umatilla	All	1987	65	Age/sex U S 1980	Case registry w/chart review	12
Warm Springs, OR	Warm Springs	All	1987	75	Age/sex U S 1980	Case registry w/chart review	12
Far North							
Alaska	All native	All	1987	17	Age U S 1980	Case registry w/chart review	23
Alaska	Eskimo	All	1987	10	Age U S 1980	Registry verified w/chart audit	23
Alaska	Indian	All	1987	24	Age U S 1980	Case registry w/chart review	23
Alaska	Aleut	All	1987	29	Age U S 1980	Case registry w/chart review	23
Yukon Indian	Indian	All	1987	9	Age World pop	Case registry not verified	24
NW Territories Indian	Indian	All	1987	7	Age World pop.	Case registry not verified	24
NW Territories Inuit	Inuit	All	1987	4	Age World pop	Case registry not verified	24

Source: References are listed within the table

Source: Goldes Dorothy, "Diabetes in North American Indians and Alaska Natives," in *Diabetes In America, 2nd edition*, National Diabetes Data Group, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases NIH Publication 95.1468, Bethesda MD, (1995): 685--686.

a large group of related families in Venezuela helped the researchers identify the gene for Huntington's disease.

Pima families from the Gila River Indian Community were and are making it possible for NIDDK researchers to search for diabetes and obesity genes.

The ancestors of the Gila River Indian Community, called Pima by the Spaniards, lived in the Sonora Desert near the Gila River in what is now southern Arizona for at least 2,000 years. Archaeological finds suggest that the Pima descended from the prehistoric *Hohokam*. The Hohokam settled the land up to where the Gila River and the Salt River meet. They established a sophisticated system of irrigation that made the desert fruitful with corn, beans, tepari beans, mesquite beans, squash, the fruits of the saguaro cactus and cotton. Hunting was minor and limited to rabbits, mountain goats and deer.

The Pima, an ethnic group of Uto-Aztecan language, are divided into two groups: the Pima-Papago of Arizona and Sonora and the Tepehuan of the Sierra Madre of southern Chihuahua, Mexico. The Pima-Papago, in turn, are subdivided into Upper Pima living in Arizona and northwestern Sonora, and Lower Pima living in south-eastern Sonora. The Upper Pima are divided into the "proper" Pima Indians that call themselves "*O'Odham*," the River people, and the Papago, with whom they intermarried, whose tribal name is "*Tohono O'Odham*", the Desert people.

During the XVIII century they sheltered the *Pee Posh* (or Maricopa Indians) who fled attack by hostile tribes, and who also became part of the Gila River community.

The introduction of wheat by the Spaniards doubled the capacity of Pima fields who managed to produce three crops. The harvest of winter wheat in May was added to the two traditional crops of corn in July and October. The food surplus and the introduction of the plow and agriculture equipment in iron led to an increase in population and the extent of cultivated land. They became so successful farmers that they sold their wheat surplus to Spanish garrisons and then to American settlers in transit to California.

By 1877, however, the population had doubled but the mesquite trees had been largely burned down to provide steam for the mills, the market provided by the settlers was at the end and the cattle was in competition for water. Several years of drought between 1877 and 1904 contributed to worsen the situation. In 1895, for the first time the Pima were forced to ask the government for money to buy flour. Supplied by the missionaries of flour and lard, the Indians, who knew neither making bread nor baking ovens, invented the "Indian fried bread" frying flour dough with fat. The Great Depression gave the

final blow and in the years 1940-50 the Pima were among the poorest communities in the U.S.

Currently, enrolled Pima tribal members are about 12,000 and the Papago are around 14,000. The number of those who reside in Chihuahua and Sonora is unknown but the figures may be similar.

The Gila River Indian Community has a land area of about 1,500 sq km and a population of about 11,000 (2000 Census). It is made up of seven districts along the Gila River and its largest communities are Sacaton, Komatke, Santan and Blackwater.

It is assumed that about 2000 others are living elsewhere in the U.S., although most don't go as far as Phoenix because being born in the reserve is the condition to be an enrolled Pima and thus enjoy the welfare.

Once trusted scouts for the U.S. Cavalry, the Pima Indians are pathfinders for health, helping scientists from the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), a part of the National Institutes of Health (NIH), learn the secrets of diabetes, obesity, and their complications²³.

For nearly 30 years the population of the Gila River Indian Reservation have taken part in medical and genetic research to defeat diabetes, and diseases associated with it.

According to Dr. Peter Bennett, Chief of the Phoenix Epidemiology and Clinical Research Branch of the NIDDK, the Pima Indians are giving a great gift to the world by continuing to volunteer for research studies and the world is in their debt²⁴.

Scholars examined the incidence of Type 2 Diabetes Mellitus over the past forty years among the Pima, looking for secular trends. Early observations²⁵ suggested that diabetes was either rare or (maybe) unrecognized at the beginning of the past century (1900s). During the 1930s, hospital records identified twenty-one diabetic Pima individuals, a figure similar to that of the US trend²⁶. Obesity and Type 2 Diabetes Mellitus figures started rising dramatically during the 1950s and since then diabetes and obesity's incidence have continued to rise²⁷.

Since 1965, systematic testing for diabetes have been performed as part of a longitudinal study that would allow to locate which genes contribute to the disease, and identify which individuals are at high risk for the NIDDM and ways to intervene.

This was and is the main aim of a research that actually started in 1963 and still going on studying samples drawn from every member of the Pima community who comes

into the NIH clinic at *Hu Hu Kam Memorial Hospital* for an examination.

The Pima Gila River Indian Community families who since 1965 have consented to the search of any gene/es responsible for diabetes and the complications related to this disease, have helped to provide the definition of diabetes and establish the parameters necessary to identify, treat and prevent diabetes.

First, the genetic research on the Pima allowed to discover that diabetes and obesity are related. In fact about 95% of people with diabetes are overweight. They also discovered that diabetes, obesity and insulin resistance, roll through the family trees, but these are not monogenic.

In 1962 Neel proposed that there are some individuals who responded to the ingestion of food by producing insulin at a “greater than normal availability”²⁸. At that time it was not known that this type of diabetes was a specific one, later identified as Type 2 Diabetes, but Neel himself stated that the ‘thrifty genotype’ model involved a distinct type of diabetes mellitus, different in etiology from the IDDM (Insulin Dependent Diabetes Mellitus). In fact diabetes was once described as benign in American minorities, especially among American Indians, and IDDM is rare in Native Americans and in most cases is found in individuals with significant non-Native American ancestry. It was the dramatic rising of this new type of diabetes among the ethnic minorities during the 1950s, especially the full-blooded Native Americans, that led to the recognition of the Type 2 Diabetes, NIDDM. Neel suggested that the quick insulin trigger in NIDDM was an asset to tribal hunter-gatherers on feast-or-famine regimes²⁹ but changing dietary patterns had compromised this mechanism. The environmental trigger would be the change from traditional lifestyle to the modern one, leading to inactivity and in diet leading to over alimentation, especially more carbohydrates and fats. This genetic adaptation was termed the ‘thrifty genotype’.” The theory suggested a mechanism similar to that of sickle cell anaemia gene, which confers a survival advantage in areas with endemic malaria.

The insulin trigger was supposed under genetic control, a statement that seemed consistent with the genetic trait frequent in specific groups or tribes. At that time the thrifty genotype theory seemed to explain the higher prevalence seen in genetically related groups. Diabetes death rates vary considerably across race and ethnic groups. In 1988 in a sample of 4,920 Native Americans of the Pima and Papago tribes, Knowler et al., discovered that

there is a very strong negative associations between the Gm haplotype $Gm^{3;5,13,14}$ and type 2 type 2-or non-insulin-dependent-diabetes mellitus. [...] One might conclude from this observation that the absence of this haplotype- or the presence of a closely linked gene-is a causal risk factor for the disease. It is shown that $Gm^{3;5,13,14}$ is a marker for Caucasian admixture, and it is most likely the presence of Caucasian alleles and the concomitant decrease of Indian alleles that lowers the risk for diabetes, rather than the direct action of the haplotype or of a closely linked locus.³⁰

This and other related studies gave a more genetic explanation to the results of 1965 Drevets's research on the Oklahoma Choctaw³¹.

In 1999 Hegele³² estimated that diabetes affects six percent of Aboriginal adults compared with two percent of all Canadian adults. There is a wide range in the prevalence of diabetes among aboriginal groups. In Canada the parallel of latitude and the language phylum helps explain those prevalence.

Research on diabetes in minorities published from 1976-1994 revealed that all minorities, except Alaska Natives, have a prevalence of NIDDM that is two to six times greater than that of the white population.

The thrifty genotype theory looked also consistent with the fact that diabetes tends to aggregate in families.

The NIDDM, however, is not just a single entity and is not monogenic. There are several forms of late onset, Type 2 diabetes. For instance in the Oji-Cree (*Anishinini*) population in Ontario was found a genetic mutation that has recently been associated with a form of NIDDM, maturity-onset diabetes of the young (MODY) ⁽³²⁾. But this mutation is only known from this single population and only accounts for a portion of their incidence of NIDDM.

One of the major problems of thrifty genotype theory was that its "expression" manifested itself very quickly while it is known that genetic change is not a rapid process. The dramatic changes in lifestyle of the Pima, Nauruans and Aborigines in recent decades (the hypothesized environmental trigger of the thrifty genotype theory) were not sufficient to justify a genetic "change".

Moreover if a genetic cause is at work, then the prevalence in genetic groups should be relatively predictable. This is not the case.

In 1999 a study compared 984 Arizona Pima with 226 Mexican Pima and a group of 198

non-Pima individuals living in the same environment as the Mexican Pima. The results showed the following rates of diabetes: AP= 38.2%, MP= 6.4% and NP= 3.4% respectively³³. The evidence supporting the genetic relatedness of the two Pima groups was based on linguistic similarities leading to assume that the Pima groups separated 700 to 1000 years ago.

The vast prevalence of differences in the genetically allied Pima argues very strongly for an environmental causation. A further comparison of a variety of Native American groups reveals a broad range of NIDDM prevalence³⁴.

Therefore, despite the general agreement of scholars on the theory of the *thrifty gene*, not only the gene or genes responsible of NIDDM remained to be elusive but research conducted for years on genetically “isolated” groups belied the theory.

In 1999 Neel admitted “it is now clear that the original thrifty genotype hypothesis, with its emphasis on feast or famine, presented an overly simplistic view”³⁵.

The frenetic search of the *thrifty gene*, the human genome sequence, the constant progress of genetics and analytical techniques led to the *thrifty phenotype* hypothesis³⁶.

As Jacobs³⁷ points out:

“The concept underlying this new hypothesis is that poor fetal and early post-natal nutrition imposes mechanisms of nutritional thrift upon the growing individual. The resultant long-term consequences are impaired development of the endocrine pancreas and a far greater susceptibility to NIDDM. Genes do not provide an unalterable blueprint, but conditional options and gene-environment (nutrient) interaction must be described in the context of development³⁸. The interaction of genes and nutrients determine phenotype and individual development. Changes in nutrition affect heritability of variant phenotypes that are dependent on the nutrient environment for their expression³⁹. A study in 1970 showed that malnutrition may produce a permanent reduction in the capacity for insulin secretion⁴⁰.”

Studying the “Changing Patterns of Type 2 Diabetes Incidence Among Pima Indians” Pankov, Hanson et al.⁴¹, discovered that

“Incidence rates of type 2 diabetes increased among Pima Indians aged 5-14 years, decreased in those aged 25-34 years, and did not change significantly

in other ages over the past four decades. The rising incidence was confined to the youth, suggesting that increasing obesity over time shifted the onset of diabetes to younger ages.” [...]

Accordingly, we proposed that the Pima Indians from the Gila River underwent an abrupt rise in the incidence of type 2 diabetes following the transition to a nontraditional lifestyle and before the initiation of the present longitudinal study. This rapid rise was followed by a relatively stable incidence since that time, but with a shift to a younger age at onset of diabetes as a consequence of increasing obesity in children and young adults and increasing frequency of exposure to diabetes in utero. The declining incidence of diabetes among Pima aged 25-34 years may reflect, in part, a shift to a younger age at onset in those at greatest risk.”⁴²

The shift to a younger age of diagnosed type 2 diabetes and the correlated obesity is a worldwide phenomenon. Among the American Indians aged 15-19 the diagnosed NIDDM increased by 69% in 1990-98. Among non-Hispanic white youth aged 10-19 years, the rate of new cases of type 1 diabetes was higher than for Type 2 diabetes. For Asian/Pacific Islander and American Indian youth aged 10-19 years, the opposite was true: the rate of new cases of type 2 was greater than the rate for type 1 diabetes. Among African American and Hispanic youth aged 10–19 years, the rates of new cases of type 1 and type 2 diabetes were similar⁴³.

In Japan a 10 fold increase of NIDDM and obesity among children (6-12 years old) is reported during the last 20 years span. The fact that adult Pima had stable incidence in the last 4 decades suggest that “changes in the age at which obesity develops, the rate of weight gain, or both may influence the effect of obesity on diabetes incidence”⁴⁴.

Under this hypothesis there exist multiple mechanisms through which diabetes can function.

These differences have been shown to exist by *Genome-Wide Association Studies* (GWAS) performed on assays of genetic markers called *Single-Nucleotide Polymorphisms* (SNPs). It is possible through a GWAS to link certain alleles of these SNPs to the presence of versions of a gene that can cause observable disease in a person. Multiple GWAS studies have been performed using thousands of SNPs on Caucasian, Asian, and African

populations. This has led to the identification of several genes such as CDKAL1, SLC30A8, HHEX, EXT2, IGF2BP2, LOC387761, and others as being statistically correlated with a person's susceptibility towards developing type 2 diabetes. However, when these same genes are tested for statistical significance in a population that is non-Caucasian (such as Africans, Asians, or Native Americans) many of these genes are not shown to be significantly associated with diabetes.

Therefore, it is highly probable that the disease known as type 2 diabetes develops differently among different populations”⁴⁵.

In 2007 Robert L. Hanson⁴⁶ was in charge of a project to identify SNPs associated with T2DM among 300 full heritage Pima diagnosed diabetics.

Regarding SNPs identified in other GWA Studies of Type 2 Diabetes Mellitus involving several European populations, Hanson points out that “None of the SNPs most strongly associated in the present study was in any of these regions”⁴⁷. Unfortunately the most significant SNP is located in a non-coding region, and therefore functional analysis was impossible.

In 2007 the Diabetes Molecular Genetics Section, Phoenix Epidemiology and Clinical Research Branch, National Institutes of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Phoenix, Arizona, published a report on their research whether variation in TCF7L2 has a major role in Type 2 diabetes susceptibility in Pima Indians⁴⁸. This investigation was originated by the discovery that a microsatellite marker (DG10S478) within intron 3 of the transcription factor 7-like 2 (TCF7L2) gene and five intronic single nucleotide polymorphisms (SNPs) were reported to be highly associated to NIDDM in subjects from Icelandic, Danish, and U.S. populations. Subsequently scholars studied associations with these specific variants in subjects of European origin: Japanese and Indi⁴⁹. The subjects of the study were Pima Indians participants of the ongoing longitudinal study of NIDDM among the Gila River Indian Community and at the end the study involved 3,501 full heritage Pima Indians for whom there was DNA and information on diabetes status and BMI. The conclusions of this study were that variation within TCF7L2 gene does not confer major risk for NIDDM among the Pima Indian population.

Full heritage Pima Indians, thanks to their decades of documented clinical history, are

an important subject for the study of these SNPs. Recent studies suggest that a different set of genes yet to be identified is responsible for causing the genetic susceptibility among the Pima.

They also suggest that if any progress is made in linking the Caucasian GWAS genes to a Type 2 Diabetes Mellitus mechanism, this will not benefit the Pima Indians since their version of Type 2 Diabetes Mellitus is not statistically associated with those genes. That is true for the Pima but also for other minority populations.

That means that, because GWA Studies require a large number of subjects and controls to produce meaningful results, smaller minority populations with distinct genetic characteristics will suffer from low-power SNP statistical analyses.

The great tenacity and perseverance with which the Gila River Pima fight diabetes has uncovered much about the disease. Thank you to Gila River Pima a most significant discovery has made that is genetic discoveries made on samples from Caucasian are not useful for the cure of the disease among the Pima or other minorities.

Several anthropologic studies⁵⁰ have documented the interpretations of Native Americans affected by diabetes regarding the etiology of the disease, the experience of illness, and the efficacy of treatment. Many Native American communities perceive diabetes as a new disease that has come from the outside. Moreover many native and indigenous peoples are convinced or are persuaded to refuse the taking of samples of genetic material for purposes of study.

The motivation is the possible exploitation by multinational drug companies. We assume that this exploitation exists and / or is possible, we are not naive to the point.

But the most important question is: do those communities know that the genetic discoveries made on other segments of the human race cannot be effective for them? Do they know that refusing the genetic research they may also refuse treatment and continue to be victims of the disease? Is it theirs an informed choice?

The Pima have not followed the sirens of politicized antisecientism and are trying to improve their health. This is the great lesson that the Pima are giving us.

NOTE

- 1 World Health Organization (WHO), Fact Sheet 312 (November 2009), <http://www.who.int/mediacentre/factsheets/fs312/en/print.html>.
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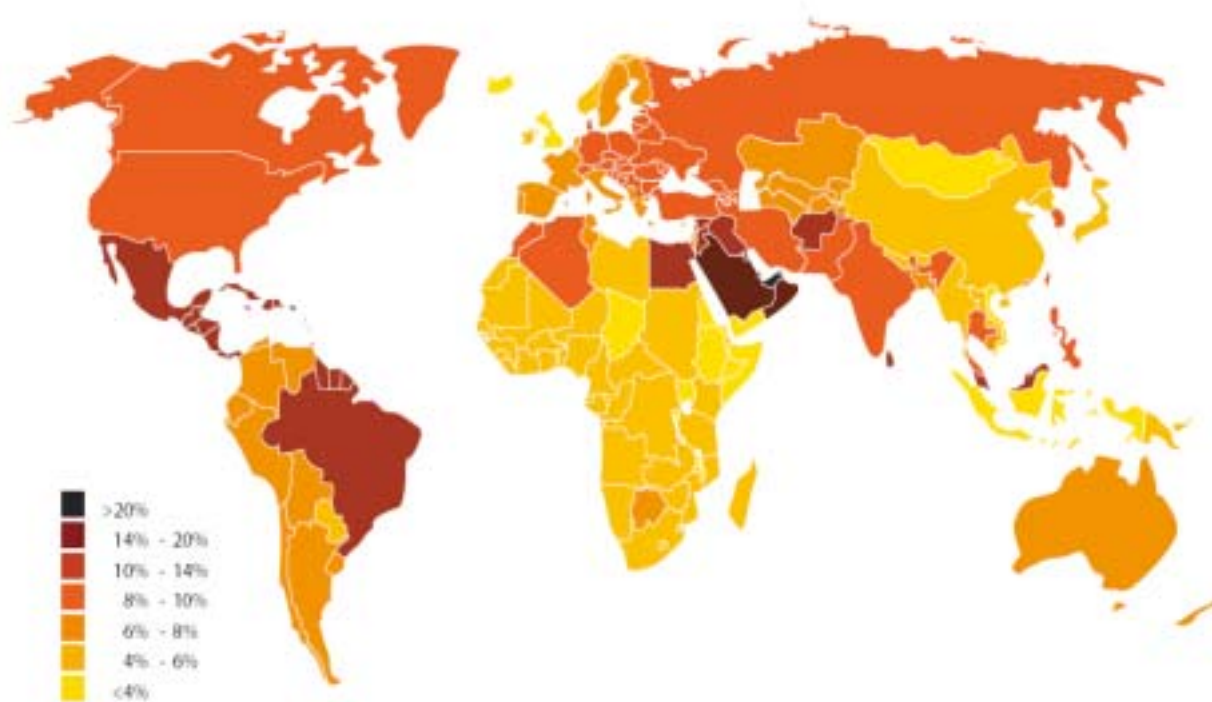
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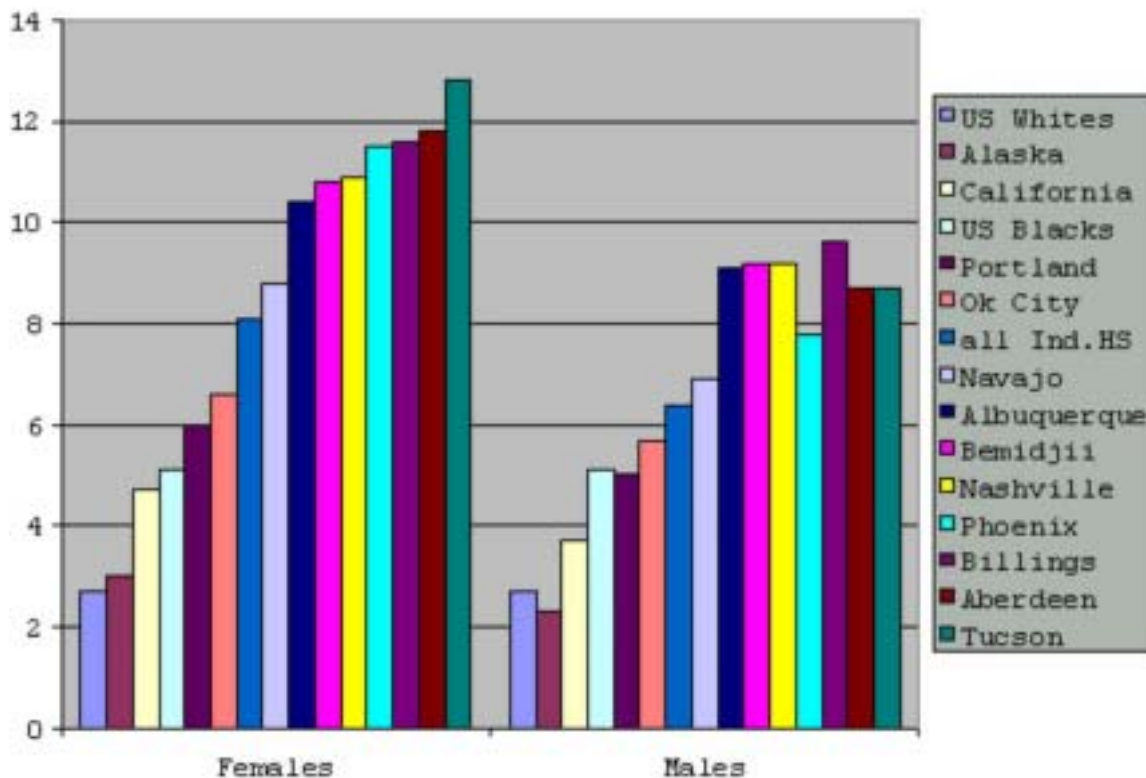
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Appendix

Prevalence estimates of diabetes, 2025



SOURCE: DIABETES ATLAS THIRD EDITION, © INTERNATIONAL DIABETES FEDERATION, 2006



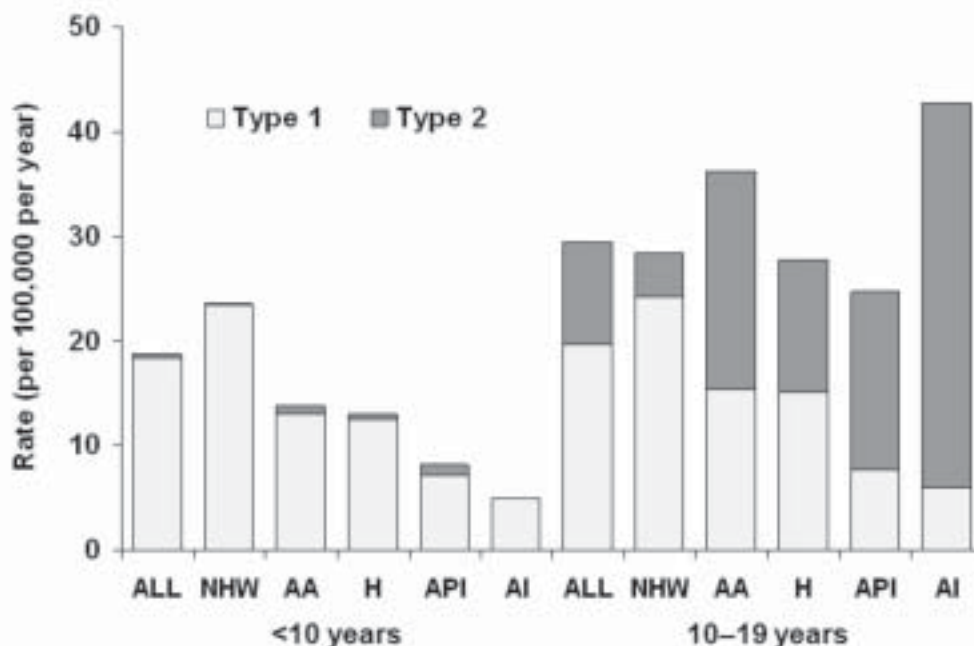
This chart shows the age-adjusted prevalence of diabetes (percent) by gender in the Indian Health Service population for 1996. Age adjustment was computed by using the 1980 U.S. population. The prevalence rates were obtained from statistical information compiled by the U.S. Centers for Disease Control and Prevention, February 14, 1998. On both charts the U.S. White and U.S. Black rates are male and female rates added together.

The chart displays noticeable differences between male and female prevalence rates in Native American rates, with female rates always being higher than male rates, except in the U.S. Blacks and the U.S. Whites rates. There are averaged female/male rates. Rates of Native Americans, except in Alaska are significantly higher than U.S. Whites.

U.S. Black rates are higher than Alaska and California Native Americans only and significantly higher than U.S. Whites.

Source: Gail King, "Type II Diabetes, the Modern Epidemic of American Indians in the United States", <http://www.as.ua.edu/ant/bindon/ant570/Papers/King/King.htm>

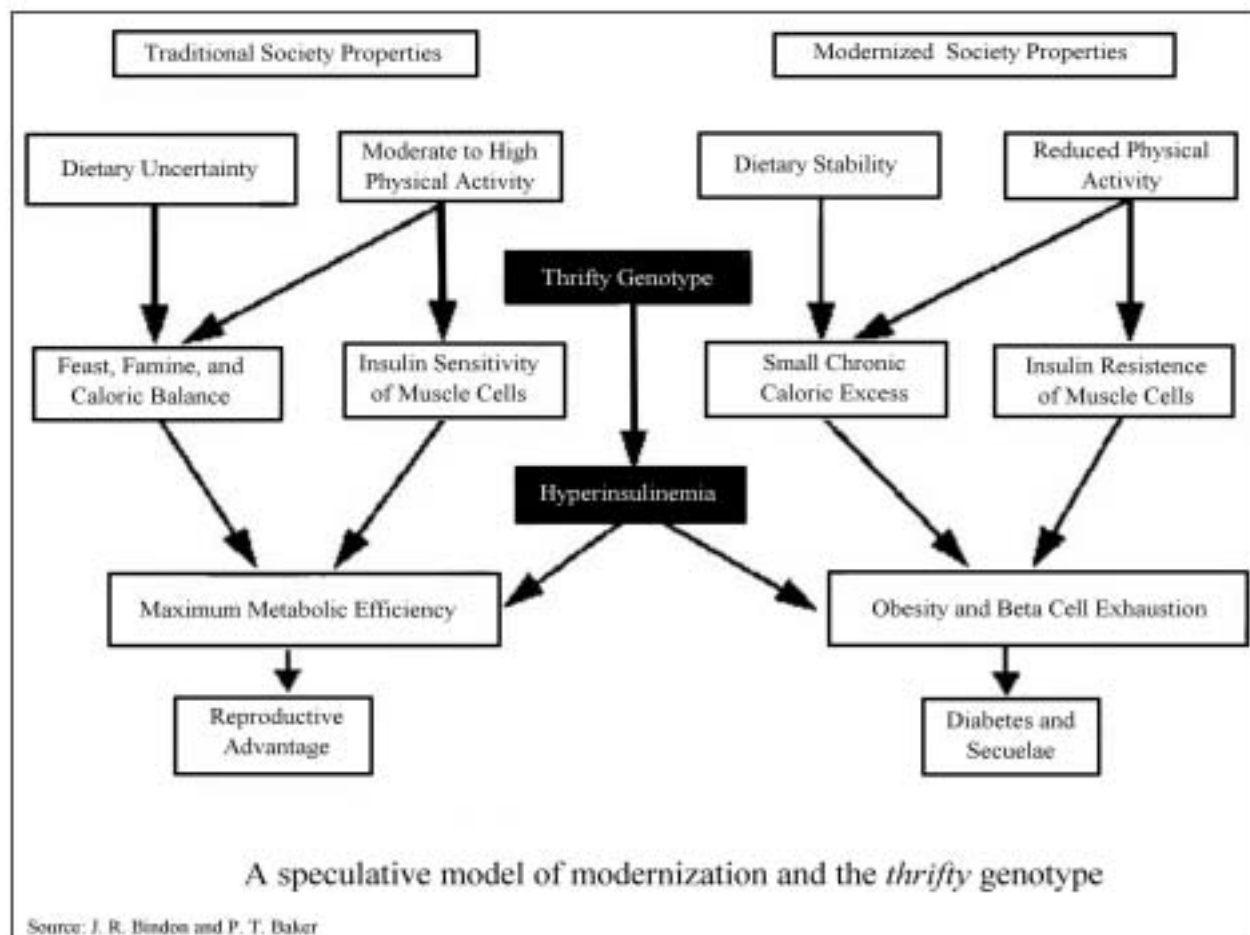
Rate of new cases of type 1 and type 2 diabetes among youth aged <20 years, by race/ethnicity, 2002–2003



CDC. National Diabetes Fact Sheet, 2007.

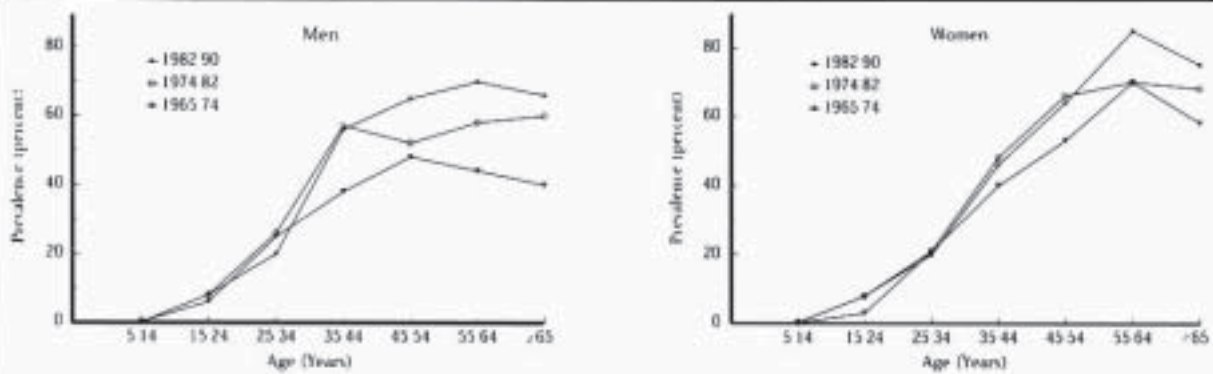
Source: SEARCH for Diabetes in Youth Study

NHW=Non-Hispanic whites; AA=African Americans; H=Hispanics; API=Asians/Pacific Islanders; AI=American Indians



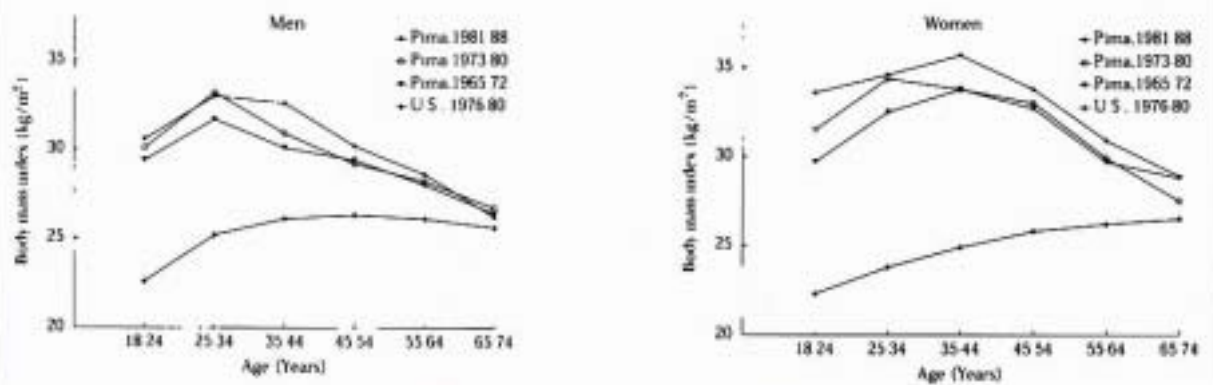
Source: J. R. Bindon and P. T. Baker

Prevalence of Diabetes in Pima Indians, by Age, Sex, and Time Period



Source: Knowler WC, Sead M.F., Pettitt D.J., Nelson R.D., Bennett P.H., "Determinants of diabetes mellitus in the Pima Indians," *Diabetes Care* 16:1 (1993):216-227

Mean Body Mass Index in Pima Indians and the U.S. White Population

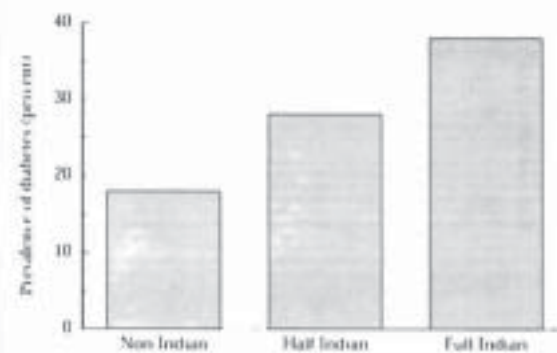


Data for US whites are from the Second National Health and Nutrition Examination Survey

Source: Knowler WC, Sead M.F., Pettitt D.J., Nelson R.D., Bennett P.H., "Determinants of diabetes mellitus in the Pima Indians," *Diabetes Care* 16:1 (1993):216-227

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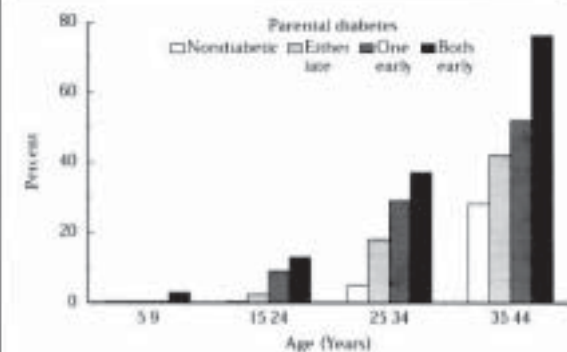
Prevalence of NIDDM in Pima Indians, by Indian Heritage



Data are age and sex adjusted.

Source: Knowler et al., "Diet, lifestyle and Type II diabetes mellitus: An association in American Indians with genetic inheritance," *Am J Human Genet* 43 (1988): 523-528

Prevalence of Diabetes in Pima Indians, by Presence and Age at Onset of Diabetes in the Parents



Persons for whom both parents had been examined were grouped into four groups according to parental diabetes: both early, one early either late, or non-diabetic; according to whether the parents had diabetes and whether the parental diabetes was diagnosed before or after age 45 years

Source: Knowler, Pettitt, Sead, Bennett, "Diabetes mellitus in the Pima Indians: Incidence, risk factors and pathogenesis," *Diabetes Metabolism Research* 4 (1992): 1-21