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DIABETES INCIDENCE IN PIMA INDIANS: CONTRIBUTIONS OF OBESITY AND PARENTAL DIABETES[1]

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The incidence of diabetes mellitus was determined in 3137 Pima Indians during periodic examinations that included measurement of weight, height, and glucose tolerance. Incidence was strongly related to preceding obesity, increasing steadily from 0.8 ± 0.8 cases/1000 person-years in subjects with body mass index <20 kg/m² to 72.2 ± 14.5 cases/1000 person-years (rate ± standard error) in those with body mass index ≥40 kg/m², when age-sex adjusted to the 1970 US white population. There was little relationship between diabetes prevalence and concurrent obesity, illustrating the importance of longitudinal studies in estimating the effect of obesity on the occurrence of a disease for which weight loss is a manifestation. The association of diabetes incidence with obesity remained within each group when subjects were classified by the diabetic status of their parents, another important risk factor for diabetes. Adjusted for age and obesity, incidence was 2.3 times as high (*p* = 0.039) in subjects with one diabetic parent and 3.9 times as high (*p* = 0.0003) in those with two diabetic parents as in those with two nondiabetic parents. In the Pimas, both obesity and diabetes have become more common during this century, perhaps as a result of rapid cultural and dietary changes in a population genetically susceptible to diabetes. Similar increases in obesity and diabetes appear to be occurring in many other parts of the world.

diabetes mellitus; heredity; Indians, American; obesity

Obesity is associated with type II (or non-insulin-dependent) diabetes mellitus, although the magnitude of the association and the extent to which it might be influenced by family history of diabetes are not well known. Obesity was a predictor of diabetes in residents of Oxford, Massachusetts (1), in Israeli men (2), in middle-aged Norwegian men (3), and in earlier analyses in Pima Indians in Arizona (4, 5). The Whitehall Survey in England found only a very small association of obesity and diabetes incidence which the authors interpreted as supporting a lack of obesity effect in most people (6). These observations are extended in the present study of the development of diabetes in the Pima Indians, who have

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the highest reported diabetes incidence rate (7).

Diabetes in the Pimas is probably exclusively type II, in that it is not characterized by ketoacidosis, insulin dependence, or islet cell antibodies (8, 9). The Pimas have been under continuing observation for 15 years, and in many cases, both parents and children of the same family have been examined, so that the joint effects of obesity and parental diabetes can be evaluated. The findings of a strong association of obesity with diabetes incidence and the increased degree of obesity that has developed in Pimas during this century suggest that obesity plays a major role in the high prevalence of diabetes now found in this population.

Methods

A long-term follow-up study of diabetes has been conducted among Pima Indian residents of the Gila River Indian Community of Arizona since 1965 (10). Subjects of the present study, at least five years old and of at least half Pima ancestry, were examined approximately every two years. Examinations included measurement of height and weight (with light clothing but without shoes) and determination of venous plasma glucose concentration two hours after the ingestion of 75 g of carbohydrate (Glucola, Ames Co., Elkhart, IN, or Dexcola, Custom Laboratories, Baltimore, MD). Diabetes was diagnosed when the two-hour post-load plasma glucose concentration was 200 mg/dl (11.1 mmol/l) or greater (11), either at a survey examination or in the course of routine medical care as previously described (7).

Diabetes incidence was computed for the 3137 subjects examined at least twice. Incidence rates (as number of new cases divided by person-years at risk of diabetes since the initial examination) were stratified by age and sex. Estimates of age-sex adjusted incidence and prevalence rates with 95 per cent confidence intervals (7) were computed using the 1970 Census of the US white population, including armed forces, as the reference population. Incidence rates were also stratified by the body mass index (12), a measure of obesity defined as weight/height^2. Because subjects were examined at intervals of approximately two years, several measurements of body mass index were made for most subjects during their period at risk for diabetes. Incidence rates were computed by summing new cases and person-years at risk of diabetes over all inter-examination intervals, and stratifying by the body mass index determined at the beginning of each interval for each subject at risk. Thus, incidence rates were stratified by the body mass index determined prior to, rather than at the time of, the diabetes diagnosis. Person-years and diagnoses were also stratified by age, with time at risk accumulated in each decade counted separately.

Incidence rates were stratified by the presence or absence of diabetes in parents for the 1413 subjects whose parents both had been examined. This analysis was restricted to subjects less than 45 years of age because few people over this age had both parents examined. Incidence rates were age adjusted using the age distribution of these 1413 subjects as the reference population. The magnitude of the association of diabetes incidence with parental diabetes was estimated after stratifying by age and obesity simultaneously (13). Statistical significance was tested with the Mantel-Haenszel procedure (14).

We estimated the prevalence of diabetes in 4126 subjects as of July 1, 1972, approximately the midpoint of this study (1965 through 1979), by using the results of each subject's examination which was closest in time to that date (midpoint examination). A person was considered a prevalent case if diabetes was diagnosed on or before that examination by the

TABLE 1

Incidence of diabetes mellitus in Pima Indians according to age, sex, and body mass index

Age (years)	Sex	Body mass index*								
		<20			20–25			25–30		
		Cases	Person-years	Rate†	Cases	Person-years	Rate	Cases	Person-years	Rate
5–14	M	0	2181	0	0	662	0	0	337	0
	F	0	1989	0	1	989	1	3	382	8
15–24	M	0	400	0	3	798	4	5	524	10
	F	0	271	0	1	1165	1	3	1004	3
25–34	M	0	16	0	2	130	15	2	224	9
	F	0	24	0	0	215	0	7	413	17
35–44	M	0	11	0	3	96	31	4	192	21
	F	0	2	0	2	78	26	10	251	40
45–54	M	0	10	0	1	92	11	7	203	35
	F	0	0		2	53	38	3	126	24
55–64	M	0	5	0	2	102	20	6	167	36
	F	0	0		2	49	41	2	104	19
65–94	M	1	31	32	2	203	10	6	199	30
	F	0	19	0	0	80	0	4	96	42
Age-sex adjusted:										
Incidence rate				0.8			10.9			17.3
Standard error				0.8			2.9			2.5

criteria described above. Prevalence rates were stratified by age, sex, and obesity as determined at the midpoint examination. Means and distributions of body mass indices are also presented as of the midpoint examination.

RESULTS

Diabetes incidence was strongly related to obesity, as estimated by the body mass index (table 1). The age- and sex-specific incidence rates (figure 1) were consistently higher with increasing body mass index in all age and sex categories (except for males less than 15 years old, in whom no incident cases occurred). With 4959 person-years of follow-up in the thinnest subjects (body mass index <20 kg/m^2), only one incident case of diabetes was found. In contrast, in men aged 25 through 44 years with body mass indices ≥ 35 kg/m^2 the incidence rate was 34 cases in 234 person-years at risk, or 145 cases/1000 person-years. The age-sex adjusted diabetes incidence rates (figure 2) increased steadily from 0.8 ± 0.8 cases/1000 person-years in the least obese to 72.2 ± 14.5 cases/1000 person-years (rate $\pm$ standard error) in the most obese group.

The relationship of diabetes prevalence to obesity was less pronounced. Age- and sex-specific prevalence rates (table 2) and the age-sex adjusted prevalence rates (figure 3) showed little relationship to obesity at body mass indices over 20 kg/m^2, although subjects with body mass indices <20 kg/m^2 had a lower diabetes

TABLE 1—*Continued*

Body mass index*											
30–35			35–40			≥40			Total‡		
Cases	Person-years	Rate	Cases	Person-years	Rate	Cases	Person-years	Rate	Cases	Person-years	Rate
0	107	0	0	25	0	0	5	0	0	3330	0
0	141	0	0	50	0	1	10	100	5	3573	1
5	332	15	4	137	29	4	60	66	21	2253	9
11	567	19	4	230	17	11	151	73	30	3414	9
9	200	45	10	89	112	10	51	196	33	713	46
20	403	50	8	206	39	16	155	103	51	1431	36
13	202	64	11	69	160	3	25	119	35	598	59
19	380	50	14	219	64	12	138	87	57	1068	53
4	115	35	3	33	92	1	19	52	16	472	34
7	198	86	13	118	110	7	87	81	42	582	72
2	40	50	1	13	80	0	10	0	11	337	33
6	83	72	2	51	39	2	11	183	15	300	50
4	50	81	1	9	109	0	0		14	494	28
3	78	39	2	33	61	0	15	0	10	344	29
		32.6			48.5			72.2			27.1
		3.6			7.2			14.5			1.9

* Body mass index = weight/height² (kg/m²).
† Incidence rate in new cases/1000 person-years.
‡ Total includes subjects with missing body mass index representing 3 cases in 104 person-years.

prevalence rate. The total prevalence rate was very high, with 599 (50 per cent) of the 1210 people aged at least 35 years having the disease.

The obesity association with incidence persisted when subjects were stratified by parental diabetes, which was also an important risk factor for diabetes (table 3). Simultaneous stratification by parental diabetes, body mass index, and age showed that incidence rates increased with each of these variables. Adjusting simultaneously for age and obesity (see Methods), we estimated the incidence rate to be 2.3 times as high (p = 0.039) in subjects with one diabetic parent and 3.9 times as high (p = 0.0003) in subjects with two diabetic parents as in subjects with both parents nondiabetic. Among subjects with only one diabetic parent, there was little difference in diabetes incidence between those whose mother and those whose father had diabetes (incidence rate ratio = 1.8, mother diabetic compared with father diabetic, p = 0.15), and so these groups were pooled. Similar effects of parental diabetes and obesity occurred in the younger and older subjects. Age adjusted rates (figure 4) show that the obesity effect was much greater in those with at least one diabetic parent than in those with neither parent diabetic, illustrating synergism between parental diabetes and obesity. However, in

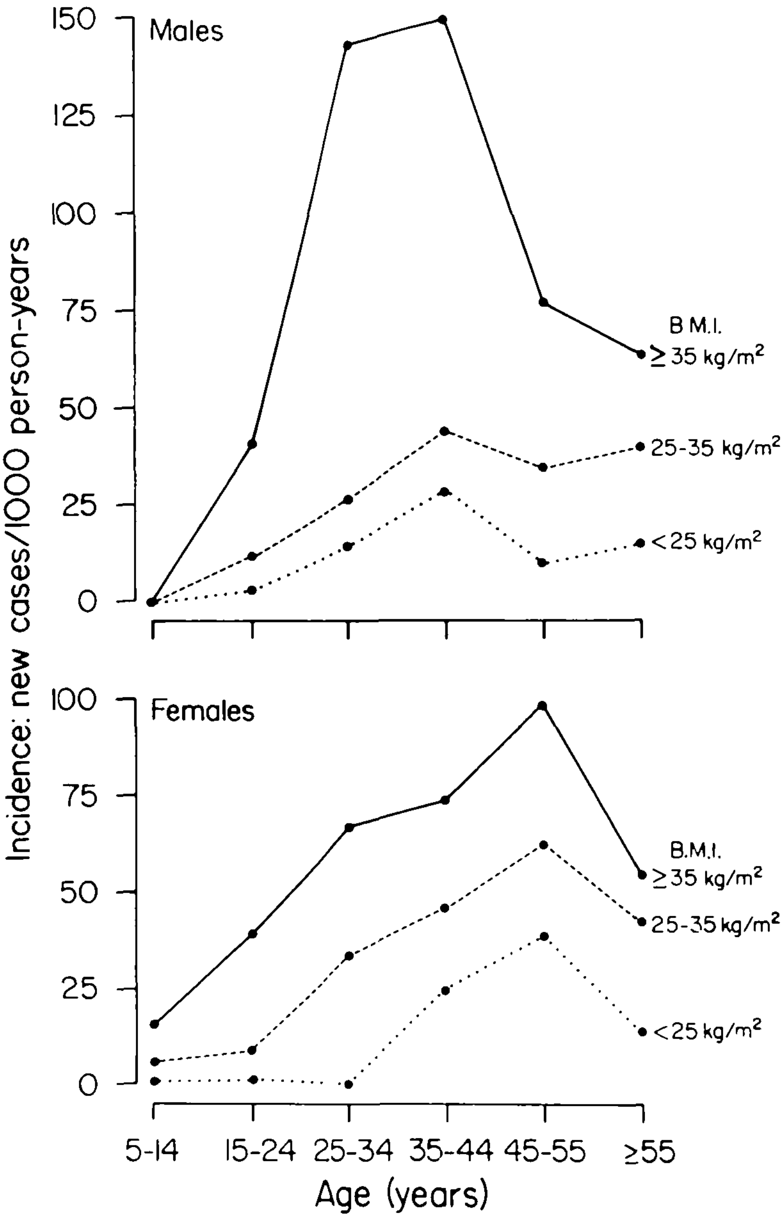

FIGURE 1. Diabetes incidence rates in Pima Indians according to age, sex and three categories of body mass index (B.M.I.) (weight/height²): <25, 25–35, and ≥35 kg/m². Diabetes was diagnosed by a two-hour post-load plasma glucose concentration of at least 200 mg/dl.

the most obese groups, those with only one diabetic parent had similar incidence rates to those with both parents diabetic.

The changes in two-hour plasma glucose concentration and body weight before and after the development of diabetes are shown in figure 5 for the 62 subjects at least 25 years of age at diagnosis, whose diabetes was first diagnosed at a survey examination and who had examinations

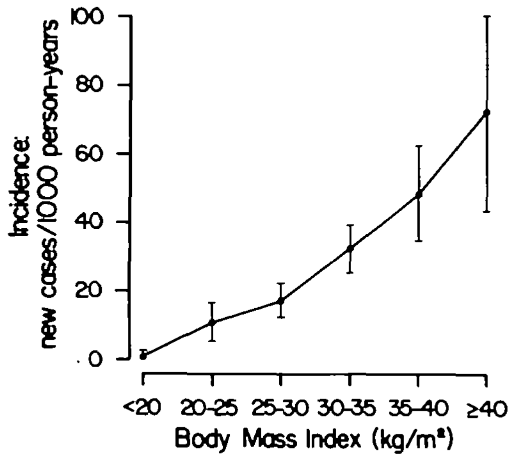

FIGURE 2. Age-sex adjusted incidence rates (with 95% confidence intervals, i.e., ± 1.96 standard errors) for diabetes in Pima Indians, by body mass index.

two years before and two years after the diagnosis. The patterns of changes in plasma glucose and body weight between the last three examinations were similar for the 28 subjects having all four examinations and the 34 subjects with only the last three examinations, and so the results of all 62 are pooled (figure 5). Average plasma glucose concentrations increased dramatically during the two years prior to diagnosis but changed little between four and two years prior to diagnosis and remained high for at least two years after diagnosis. In contrast, mean weights of subjects aged 25 to 44 years increased most during the period from four to two years preceding diagnosis, and decreased after diagnosis. Subjects aged 45 years or more did not gain weight prior to diagnosis, but lost weight during the two years afterwards.

DISCUSSION

Obesity and parental diabetes were important risk factors for diabetes in the Pimas, who have the highest reported diabetes incidence rate, yet the association with obesity does not entirely account for the greater diabetes incidence in Pimas when compared with other populations. The Pimas are very obese, with considerably higher mean body mass indices in all age and sex categories, compared with the US population according to the Health and Nutrition Examination Survey of 1971–1974 (figure 6). The distribution of body mass indices is much higher in the Pimas than in the rest of the US population (table 4). The frequency of Pimas exceeding the 90th percentile for body mass index in the US population varies from 60 per cent in males 25 through 34 years old to only 15 per cent in females 65 through 74 years old. Young Pima adults were especially obese, with 87–97 per cent of those 20 through 34 years old exceeding the US median body mass index for their age and sex. However, the high diabetes incidence rate in the Pimas cannot be attributed entirely to obesity. For body mass indices between 20 and 25 kg/m², which are lower than the means for the US population in most age groups, the age-sex adjusted incidence rate was 10.9 ± 2.9 cases/1000 person-years (rate ± standard error), eight times as high as the 1.34 ± 0.04 cases/1000 person-years (irrespective of obesity) in the predominantly white population of Rochester, Minnesota (15). Comparable height and weight data are lacking in the Rochester study, but unless the Rochester population is much less obese than the total US population, obesity could not account for the difference between the Pima and Rochester incidence rates. The strong association of obesity and diabetes incidence shown in figure 2 of the present paper is similar to that reported by Westlund and Nicolaysen (3) for Norwegian men. We cannot, however, directly compare obesity-specific diabetes incidence rates in Pimas and Norwegians, because of important differences in study design and methods of diabetes detection in these two studies. Studies of obesity

TABLE 2

Prevalence of diabetes mellitus in Pima Indians according to age, sex, and body mass index

Age (years)	Sex	Body mass index*								
		<20			20–25			25–30		
		Cases	Total	Rate†	Cases	Total	Rate	Cases	Total	Rate
5–14	M	0	441	0	0	161	0	0	92	0
	F	0	353	0	0	226	0	1	103	1
15–24	M	0	38	0	1	136	1	2	132	2
	F	0	19	0	1	168	1	3	154	2
25–34	M	0	0		5	28	18	11	47	23
	F	0	3	0	0	17	0	9	66	14
35–44	M	0	4	0	13	20	65	25	65	39
	F	0	0		0	7	0	24	52	46
45–54	M	0	2	0	6	19	32	33	68	49
	F	0	0		7	12	58	25	36	70
55–64	M	0	1	0	14	29	48	17	47	36
	F	1	2	50	12	17	71	23	33	70
65–94	M	4	14	29	19	63	30	33	52	64
	F	2	7	29	22	36	61	33	47	70
Age-sex adjusted:										
Prevalence rate				5.4			20.5			26.0
Standard error				2.3			1.5			1.2

and diabetes incidence in other populations using similar methods would be valuable.

Obesity was strongly related to diabetes incidence over the entire range of body mass indices shown in figure 2, but there was little change in prevalence rates with changes in body mass index above 20 kg/m^2 (figure 3). The association of obesity and diabetes prevalence was complicated by the well-known fact that many subjects lose weight after diabetes diagnosis (figure 5). Comparison of prevalence rates between people with different degrees of obesity did not reflect the magnitude of the obesity and diabetes association which was seen clearly in the incidence rates. Incidence, rather than prevalence, studies are thus preferable in population comparisons of the effect of obesity on the occurrence of a disease such as diabetes for which weight loss is a manifestation.

Considered in historical perspective, these findings help explain the Pimas' present high frequency of diabetes. The Pimas and their ancestors are thought to have lived in their present desert location for at least 2000 years, subsisting on gathering and on irrigation farming until recently (16). Disruption of their traditional agricultural lifestyle and introduction of new foods by whites have changed their diet and pattern of exercise considerably. Their diet composition is now similar to that of the general US population (17).

Although measurement data are sparse,

TABLE 2—*Continued*

Body mass index*											
30–35			35–40			≥40			Total‡		
Cases	Total	Rate	Cases	Total	Rate	Cases	Total	Rate	Cases	Total	Rate
0	42	0	0	9	0	0	3	0	0	751	0
0	41	0	0	16	0	0	4	0	1	747	0
4	87	5	2	31	7	2	22	9	11	448	2
3	100	3	2	48	4	5	31	16	14	523	3
19	71	27	7	29	24	14	34	41	56	209	27
11	77	14	8	36	22	15	39	39	43	238	18
24	59	41	9	22	41	6	12	50	77	183	42
39	75	52	21	53	40	12	32	38	96	220	43
13	28	46	9	17	53	0	6	0	62	143	43
26	45	58	21	40	53	8	20	40	88	154	57
10	17	59	4	9	44	0	2	0	45	105	43
14	24	58	11	19	58	3	4	75	69	104	66
10	19	53	2	3	67	0	0		73	161	45
14	25	56	8	10	80	2	2	100	89	140	64
		24.9			26.3			23.3			24.8
		1.4			1.9			2.0			0.7

* Body mass index = weight/height² (kg/m²).

† Prevalence rate in cases/100 people.

‡ Total includes 46 subjects with missing body mass index, of whom 20 (43%) had diabetes.

obesity was reportedly rare as recently as a few decades ago. Mean weights, adjusted for height by linear regression (18), were compared in Pima children aged 5 through 18 years at their midpoint examination with measurements of 250 Pima children judged to be aged 18 years or younger by Hrdlicka (19) in 1908. Pima children now average 6 kg heavier than Pima children of comparable height at the beginning of this century, indicating that their obesity may be a recent phenomenon. Thus, it appears that the older Pimas may never have been so obese as the younger ones are now. If so, the declining obesity with age seen at one point in time (figure 6 and table 4)

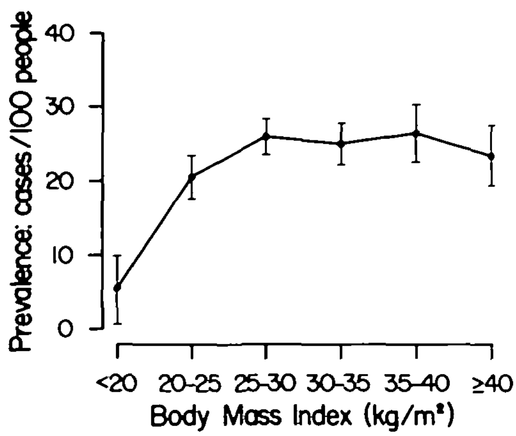

FIGURE 3. Age-sex adjusted prevalence rates (with 95% confidence intervals, i.e., ± 1.96 standard errors) for diabetes in Pima Indians, by body mass index.

TABLE 3

Incidence of diabetes mellitus in Pima Indians, according to age, body mass index, and parental diabetes status in subjects aged 5–44, with both parents examined. Both sexes are combined

Age (years)	Diabetic parents	Body mass index* <20 Cases	Person-years	Rate†	20–25 Cases	Person-years	Rate	25–30 Cases	Person-years	Rate
5–24	Neither	0	1144	0	0	715	0	0	335	0
	One	0	1322	0	1	1101	1	3	679	4
	Both	0	676	0	2	576	4	6	434	14
25–44	Neither	0	15	0	0	51	0	2	76	27
	One	0	5	0	1	103	10	5	257	20
	Both	0	1	0	1	84	12	4	114	35
Age adjusted incidence rate ± SE	Neither			0.0			0.0			4.3 ± 3.1
	One			0.0			2.4 ± 1.8			6.9 ± 2.6
	Both			0 0			4.9 ± 2.9			17.4 ± 5 5

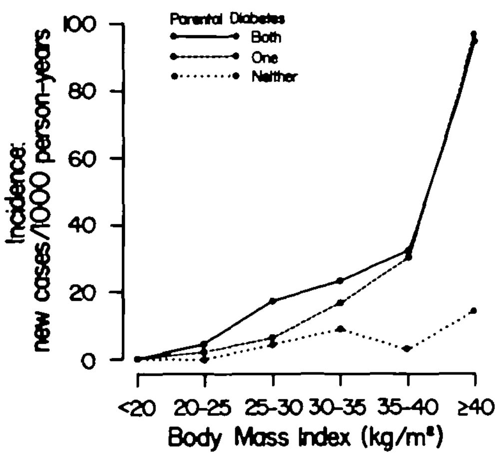

FIGURE 4. Age adjusted incidence of diabetes in Pima Indians according to body mass index. Rates are shown for subjects aged five through 44 years with two nondiabetic parents, parents discordant for diabetes, and two diabetic parents. Parents' diabetic status was determined by glucose tolerance testing.

reflects the recent development of obesity in the young rather than weight loss with aging. In addition to obesity, the high prevalence of diabetes is probably recent, although temporal changes in diabetes prevalence are difficult to estimate because of changing diagnostic criteria. Hrdlicka (19), during the course of physical and medical observations in Pima Indians, noted one case of diabetes in 1908. Russell (20), in the same year, did not include diabetes in a list of 28 diseases affecting the Pimas. In 1940, Joslin (21) identified 21 Pima Indians with diabetes, and concluded that diabetes prevalence was similar in American Indians and in the general population. Since the 1950s, diabetes has been recognized as a common disease in the Pimas (22, 23). Now diabetes is a major health problem for the Pimas, with one-half of the adults at least 35 years old affected. The disease is not only frequent but also serious, often requiring insulin to control hyperglycemia and accompanied by retinopathy (24, 25), nephropathy (26), and coronary heart disease (27).

The probable concurrent increases in obesity and diabetes prevalence in the Pimas during this century suggest that changing food consumption and life-style with resultant obesity have contributed importantly to the present high incidence of diabetes in the Pimas. Similar changes

TABLE 3—*Continued*

Body mass index*											
30–35			35–40			≥40			Total‡		
Cases	Person-years	Rate	Cases	Person-years	Rate	Cases	Person-years	Rate	Cases	Person-years	Rate
1	129	8	0	34	0	0	26	0	1	2388	0.4
5	364	14	3	114	26	4	42	95	16	3631	4
3	248	12	3	103	29	6	68	89	20	2112	10
1	64	16	1	56	18	2	24	86	6	285	21
8	245	33	4	81	50	5	50	101	23	739	31
13	163	80	4	56	71	4	31	129	26	452	58
		9.1 ± 7.0			3.0 ± 3.0			14.2 ± 10.1			3.9 ± 1.5
		16.9 ± 5.5			30.3 ± 13.4			96.2 ± 40.4			8.9 ± 1.4
		23.5 ± 6.9			36.1 ± 15.2			95.6 ± 32.1			17.5 ± 2.6

* Body mass index = weight/height² (kg/m²).
† Incidence rate in new cases/1000 person-years.
‡ Total includes subjects with missing body mass index, representing no incident cases in 24 person-years.

may have contributed to the high diabetes prevalence rates in several other populations which have undergone major cultural transition accompanied by increasing obesity, such as many other American Indian tribes (28), Polynesians (29), and inhabitants of several Pacific Islands, including Nauru (30). The frequency of diabetes also appears to have increased in some populations following migration. Age-sex-specific diabetes prevalence rates were much higher in Yemenites and Kurds who had lived in Israel for at least 25 years than in those who had immigrated recently (31). Diabetes prevalence was estimated to be 1.8 times as high in Japanese migrants from Hiroshima to Hawaii as in Japanese living in Hiroshima (32). All of these observations are consistent with Neel's (33) hypothesis that diabetes results from the introduction of a steady food supply to people who have evolved a "thrifty genotype" with an ability to store energy efficiently, which has permitted survival under conditions of alternating periods of feast and famine.

The mechanisms involved in the development of diabetes are poorly understood. Diabetes incidence in the Pimas was strongly related to obesity and to parental occurrence of diabetes (figure 4), yet no specific mode of inheritance has been demonstrated (34). After accounting for parental diabetes, we found that obesity was still a strong risk factor for diabetes. Hyperglycemia and many other metabolic abnormalities in Pima diabetics are at least partially reversible with caloric restriction and weight reduction (35), suggesting that obesity is causally related to diabetes. Further evidence for a causal relationship was provided by the sharp fall in death rates attributable to diabetes in food deprived areas of Europe during World War I (36), suggesting that either diabetes incidence or case fatality was decreased with food deprivation. Thus, both obesity and heredity appear to be important in the development of type II (or non-insulin-dependent) diabetes. Increasing obesity in presumed genetically susceptible people appears to have played a

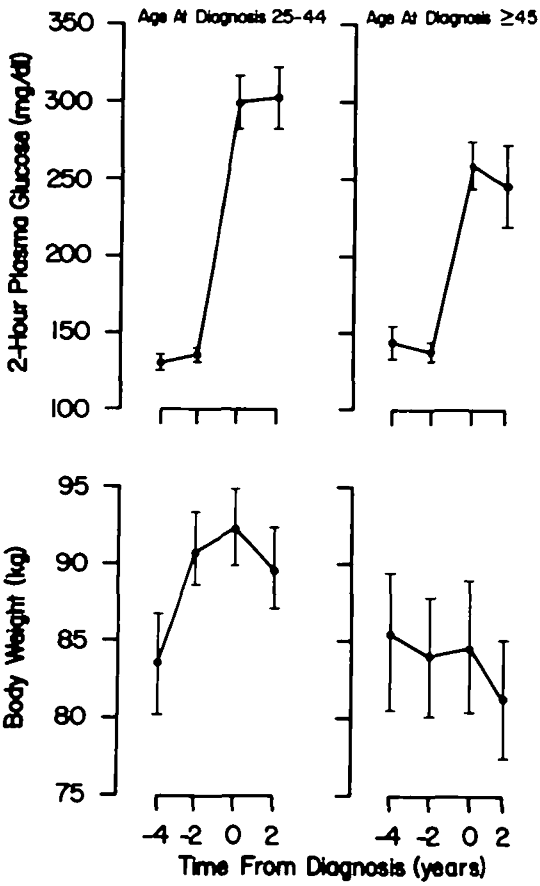

FIGURE 5. Changes in two-hour post-load plasma glucose concentrations and body weight at four years (to within one year) before diagnosis, two years before diagnosis, at diagnosis, and two years after diabetes diagnosis, in Pima Indians aged at least 25 years at diagnosis. Means ± standard errors of the means are shown for 62 subjects: 39 aged 25 through 44 years at diagnosis (of whom only 19 had measurements four years before), and 23 aged at least 45 years at diagnosis (of whom only nine had measurements four years before).

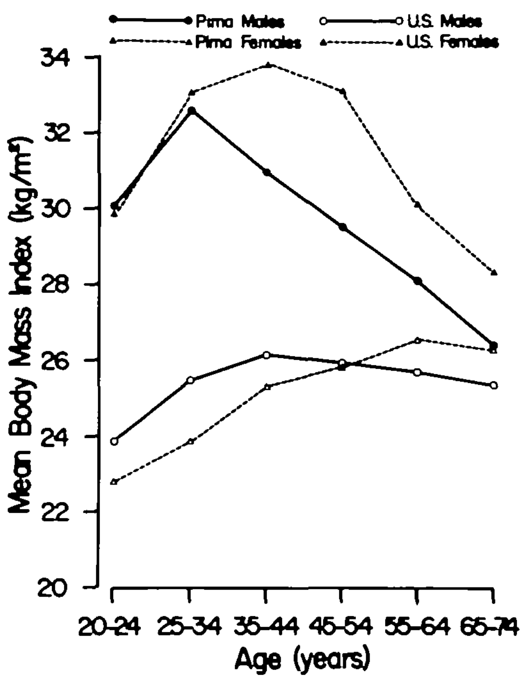

FIGURE 6. Mean body mass index, i.e., weight/height² (kg/m²), in Pima Indian adults, compared to measurements in the general US population from the Health and Nutrition Examination Survey, 1971–1974 (Sidney Abraham, National Center for Health Statistics, personal communication).

TABLE 4

Percentage of Pima Indians exceeding age-sex-specific percentiles of body mass index for the general US population derived from the Health and Nutrition Examination Survey, 1971–1974 (Sidney Abraham, National Center for Health Statistics, personal communication)

Population	Age (years)	Sex	% of people exceeding body mass index percentile		
			50th	75th	90th
US	All	Both	50	25	10
Pima	20–24	M	92	73	53
		F	94	78	57
	25–34	M	87	78	60
		F	97	88	58
	35–44	M	83	67	44
		F	98	83	53
	45–54	M	77	54	33
		F	93	77	55
	55–64	M	66	49	24
		F	76	48	29
	65–74	M	56	39	20
		F	66	38	15

major role in the high diabetes prevalence rates seen today in the Pimas and in several other populations.

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