Changing Patterns of Type 2 Diabetes Incidence Among Pima Indians

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OBJECTIVE — The rising prevalence of obesity and high prevalence of diabetes among Pima Indians suggest that the incidence of diabetes has risen over time. We examined trends in the incidence rate of type 2 diabetes among Pima Indians between 1965 and 2003.

RESEARCH DESIGN AND METHODS — Incidence rates were computed independently in three 13-year time periods in Pima Indians aged ≥5 years. Diabetes was defined by the presence of at least one of two criteria: *1)* 2-h plasma glucose concentration ≥200 mg/dl (11.1 mmol/l) or *2)* hypoglycemic treatment.

RESULTS — Among 8,236 subjects without diabetes at baseline, 1,005 incident cases occurred during follow-up. Age- and sex-adjusted incidence rates of diabetes were 25.3 cases/1,000 patient-years (95% CI 22.5–28.0) in 1965–1977, 22.9 cases/1,000 patient years (20.0–25.8) in 1978–1990, and 23.5 cases/1,000 patient years (20.5–26.5) in 1991–2003 ($P = 0.3$). The incidence rate in subjects aged 5–14 years was 5.7 (1.9–17.4) times as high in the last as in the first period, but the rate declined in those aged 25–34 years (incidence rate ratio 0.6 [0.4–0.8]). Sex-adjusted prevalence increased significantly over time only in those aged 5–24 years ($P_{trend} < 0.0001$).

CONCLUSIONS — The overall incidence of diabetes among Pima Indians remained stable over the past four decades, with a significant rise occurring only in the youth.

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Diabetes prevalence is increasing worldwide, especially in populations transitioning from traditional to modern lifestyles (1,2). While prevalence and incidence of type 2 diabetes are highest among adults, youth are increasingly affected (3,4). Whether the rising prevalence of type 2 diabetes is due to increasing incidence, declining mortality, or both is unclear (5–7). Projections based on increasing life expectancy, population growth, and progressive urbanization predict substantial increases in the prevalence of diabetes for decades to come (5). These estimates may be too low, however, since they do not account for the increasing frequency and magnitude of obesity and other major risk factors for diabetes.

We examined secular trends in the incidence rate of type 2 diabetes over the past 40 years in Pima Indians, a population with a very high prevalence and incidence of diabetes (8). Previous observations (9,10) suggest that diabetes was either rare or largely unrecognized among Pimas around the 1900s. At that time, increasing settlement of the area by people of European derivation led to diversion of the Pimas' water supply and disruption of their agriculture (10). The loss of water resulted in curtailment of subsistence farming and led to fundamental changes in their way of life (11). In the late 1930s, a review of medical records from the hospitals serving the population identified 21 Pima Indians with diabetes. The author concluded that the prevalence of diabetes was similar to that in the U.S. population (12). By the 1950s, many more Pimas were known to have diabetes, (13) and since then, a rising prevalence of obesity (14) suggests that the incidence of diabetes might continue to rise. Since 1965, systematic testing for diabetes was performed as part of a longitudinal study, using the same methods for diagnosing diabetes throughout the study.

RESEARCH DESIGN AND METHODS

Pima and the closely related Tohono O'odham (Papago) Indians, who live in a part of the Gila River Indian Community in Arizona and are ≥5 years of age, participate in a research examination approximately every 2 years regardless of health. These biennial examinations include an oral glucose tolerance test (OGTT), measurement of height and weight, and assessment for diabetes complications. Venous blood is collected in NaF 2 h after ingestion of 75 g carbohydrate. Plasma is separated and stored at −20°C until glucose measurement by the alkaline potassium ferricyanide method (AutoAnalyzer; Technicon, Tarrytown, NY) through October 1991 and by the hexokinase method (Ciba-Corning, Palo Alto, CA) thereafter. Glucose concentrations were 3.6 mg/dl higher, on average, by the latter method in 194 samples measured simultaneously by both methods. Because this difference was small and quarterly external proficiency testing confirmed the accuracy of both methods over time, no adjustment was made between the methods. The 75-g load was used throughout the study, regardless of age and body size. Since 1975, all subjects were asked to fast overnight before the OGTT. BMI was defined as weight in kilograms divided by the square of height in meters. The study population included subjects aged ≥5 years who were of at least one-half Pima or Tohono O'odham heritage, attended research examinations, and resided in the community at any time during follow-up.

Statistical analysis

Incidence rates of diabetes were computed independently in three 13-year time periods (January 1965–December 1977, January 1978–December 1990, and January 1991–December 2003). Dia-

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Abbreviations: OGTT, oral glucose tolerance test.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Table 1—*Baseline clinical and demographic characteristics of nondiabetic Pima Indians included in the three time periods*

	Period			
	1965–1977	1978–1990	1991–2003	*P*
n				
Total	2,859	2,583	2,794	
Men	1,337	1,085	1,199	
Women	1,522	1,498	1,595	
Follow-up (years)	6.6 (0.6–12.8)	6.3 (1.4–12.8)	6.1 (1.5–12.9)	
New cases (%)	351 (35)	297 (30)	357 (35)	
Mean age (years)*	20.8 ± 0.3	20.7 ± 0.3	22.6 ± 0.3	<0.0001
BMI (kg/m^2)†				
Men	22.8 ± 0.2	26.1 ± 0.2	27.7 ± 0.2	<0.0001
Women	25.2 ± 0.2	27.6 ± 0.2	30.1 ± 0.2	<0.0001
2-h plasma glucose (mg/dl)‡	105.8 ± 0.5	107.4 ± 0.5	107.7 ± 0.5	0.003

Data are median (range), means ± SE, or *n* (%) unless otherwise indicated. *Sex adjusted. †Age adjusted. ‡Mean baseline values, age and sex adjusted.

betes was defined by at least one of the following: *1*) 2-h plasma glucose concentration ≥200 mg/dl (11.1 mmol/l) during an OGTT or 2) self-reported treatment with hypoglycemic medicines (insulin or oral medicines).

New cases of diabetes were defined at the first time these criteria were met in subjects with at least one previous examination during the same period in which neither criterion was met. For each period, the risk extended from the date of the first examination to the examination when diabetes was diagnosed or, in those who did not develop diabetes, to the last examination within the same period. Incidence rates were computed as the number of new cases of diabetes per 1,000 person-years at risk. Subjects were included in each period in which they had at least two examinations. Accordingly, 1,163 subjects from the first period were included in the second period, and 617 subjects from the first and 1,117 from the second period were included in the third. Since the diagnostic criteria were considered independently at each examination, a subject could be considered a case in more than one period. Of the 1,005 subjects who developed diabetes, 11 met the diagnostic criteria in both the first and second periods, 2 in the first and third periods, and 9 in the second and third periods.

Prevalence of diabetes was computed independently in three 13-year time periods using data from the research examination closest to the end of each period. All-cause mortality in nondiabetic and diabetic subjects was computed in the same periods. Age-and sex-adjusted incidence, incidence rate ratios (IRRs), death rates, and prevalence were standardized to the 1985 Pima Indian population ≥5 years old. Tests for general association were computed by the Mantel-Haenszel test (15) and for linear association by the Mantel extension test (16), modified for person-time denominators (17).

Cox proportional hazards analysis was used to estimate the rate of diabetes in the second and third periods relative to the first, after adjusting for age, sex, and BMI. Age violated the proportionality assumption, so models were stratified by this covariate. Differences in normally distributed baseline variables between time periods were analyzed with general linear models, adjusted for age and sex. Data are presented as means ± SE or median (range).

RESULTS— Among 8,236 nondiabetic subjects (3,621 men and 4,615 women), 1,005 incident cases of diabetes developed during follow-up. Table 1 shows baseline characteristics of the subjects included in each time period. BMI increased throughout the study by 12% in men and 19% in women. The increase was noted in all age-groups (Fig. 1).

Age- and sex-adjusted incidence rates of diabetes were 25.3 cases/1,000 person-years (95% CI 22.5–28.0) in 1965–1977,

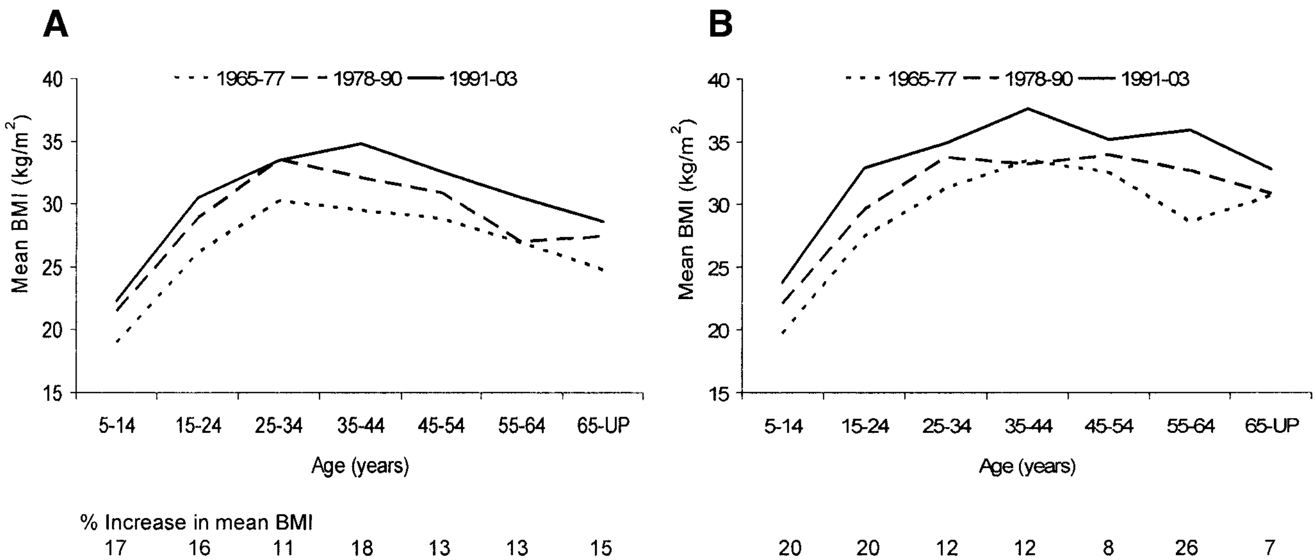


Figure 1—*Mean BMI in nondiabetic male (A) and female (B) Pima Indians by age, sex, and time period. The numbers below each graph represent the percentage of increase in mean BMI between the third and first time periods according to age-group.*

Table 2—*Sex-adjusted prevalence (%), number of incident cases of diabetes per person-years (pyrs) of follow-up, sex-adjusted incidence rates of type 2 diabetes in the three time periods, and sex-adjusted incidence rate ratios in the second (IRR2) and third (IRR3) periods relative to the first*

Age	1965–1977			1978–1990				1991–2003			
	Prevalence	Cases/pyrs	Incidence rate*	Prevalence	Cases/pyrs	Incidence rate*	IRR2	Prevalence	Cases/pyrs	Incidence rate*	IRR3
5–14	0.3	4/6,833	0.5 (0–1.2)	0.5	7/4,247	1.6 (0.4–2.8)	2.8 (0.8–9.6)	3.3	14/4,217	3.3 (1.6–5.1)	5.7 (1.9–17.4)
15–24	3.3	43/5,484	8.1 (5.6–10.7)	4.4	51/5,855	8.6 (6.1–11.0)	1.1 (0.7–1.6)	6.4	49/5,259	9.4 (6.7–12.1)	1.1 (0.7–1.7)
25–34	18.9	88/2,352	37.7 (29.5–46.0)	19.4	88/3,306	25.1 (19.5–30.7)	0.7 (0.5–0.9)	22.2	94/4,159	22.6 (18.0–27.3)	0.6 (0.4–0.8)
35–44	45.2	101/1,796	56.8 (45.4–68.2)	44.0	66/1,437	46.7 (34.9–58.4)	0.8 (0.6–1.1)	31.9	118/2,610	43.4 (35.2–51.5)	0.7 (0.6–1.01)
45–54	55.4	61/1,109	54.4 (40.7–68.1)	65.7	43/843	49.8 (34.4–65.3)	0.9 (0.6–1.4)	48.0	49/982	49.8 (35.9–63.7)	0.9 (0.6–1.3)
55–64	56.4	33/639	54.2 (35.6–73.0)	70.0	28/495	55.6 (45.0–76.2)	1.0 (0.6–1.7)	57.7	25/352	70.8 (42.6–98.9)	1.3 (0.8–2.2)
≥65	49.2	21/912	23.5 (12.7–34.4)	54.6	14/308	45.4 (21.6–69.2)	1.9 (0.9–3.9)	33.3	8/179	43.4 (13.3–73.5)	1.8 (0.8–4.2)

Data are percentages, incidence rates (95% CIs), or IRRs (95% CIs) unless otherwise indicated. *Cases/1,000 pyrs.

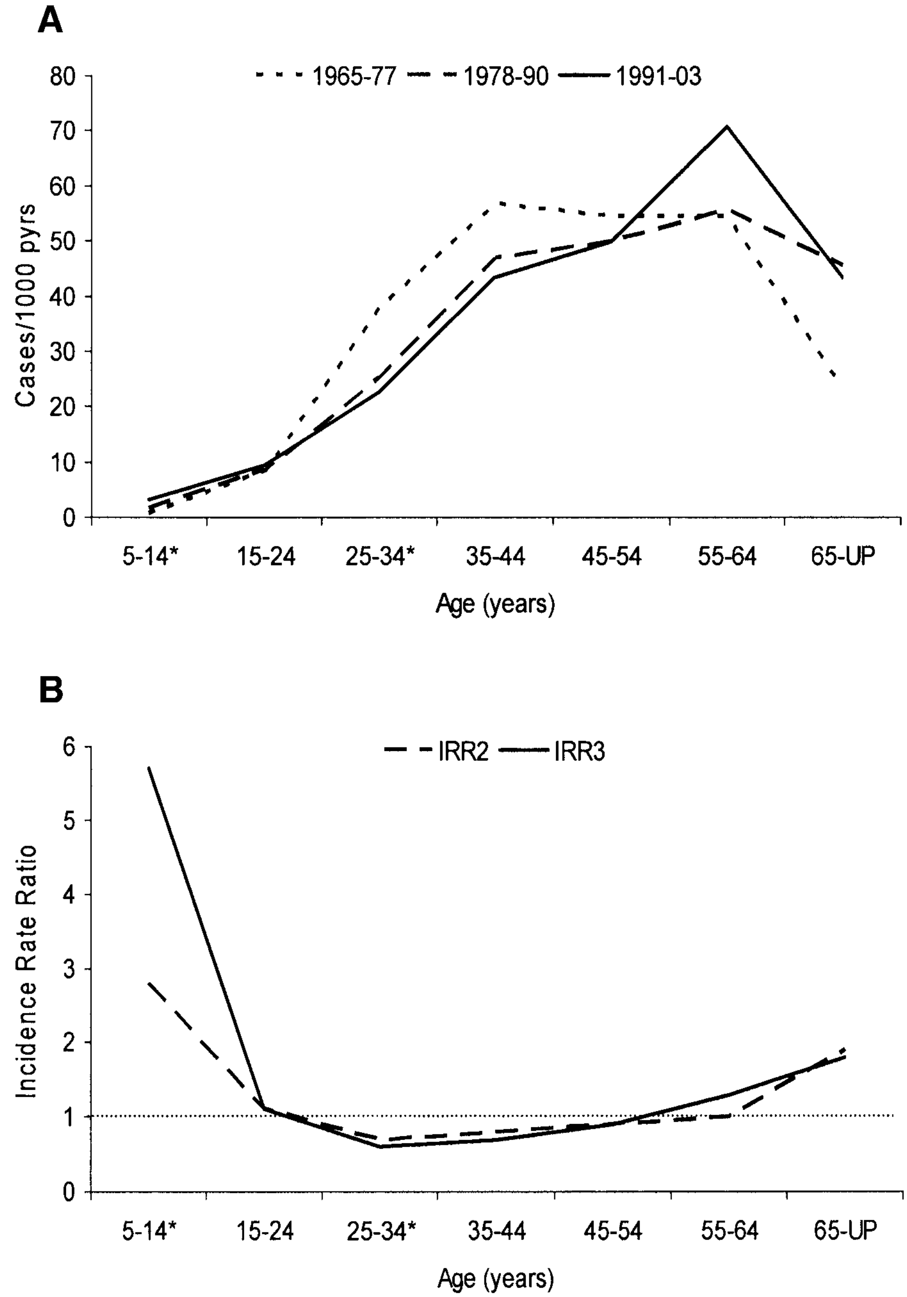
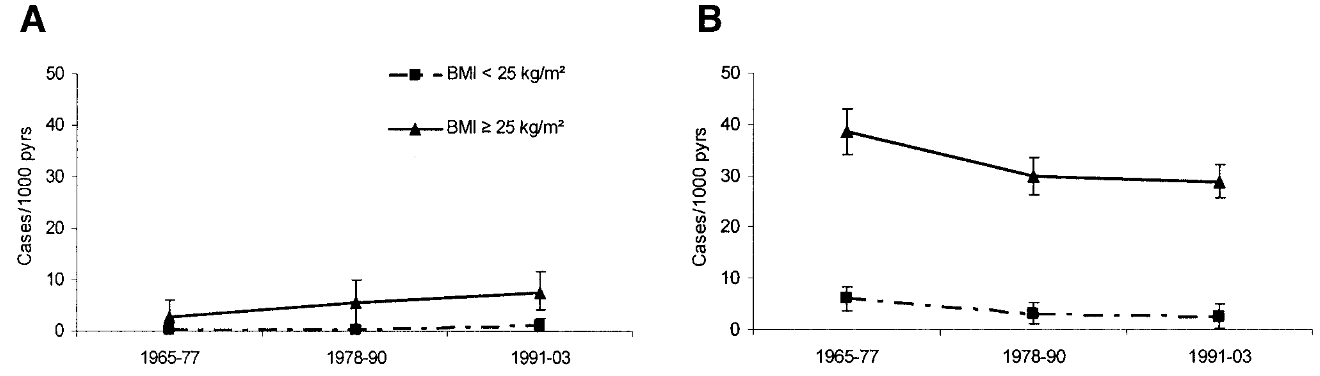


Figure 2—*A: Age-specific, sex-adjusted incidence rates of type 2 diabetes in three time periods. In each period, sex-adjusted incidence rates increased up to 55–64 years and then declined.* B: *IRRs relative to the first time period. IRR2, IRRs in the second relative to the first period; IRR3, IRRs in the third relative to the first period.* $^*P_{trend} < 0.05$.

22.9 cases/1,000 person-years (20.0–25.8) in 1978–1990, and 23.5 cases/1,000 person-years (20.5–26.5) in 1991–2003. The decline from the first period was not significant (IRR for second vs. first period 0.9 [95% CI 0.8–1.1] and third vs. first period 0.9 [0.7–1.1]). Sex-adjusted incidence rates are shown in Fig. 2*A*. Age-specific incidence increased over time in subjects aged 5–14 years (IRR for third vs. first period 5.7 [1.9–17.4]) but declined in those aged 25–34 years (IRR for third vs. first period 0.6 [0.4–0.8]) (Table 2, Fig. 2*B*).

In subjects 5–14 years old, age- and sex-adjusted incidence of diabetes was positively related to BMI but not significantly so for the small number of cases (Fig. 3). Incidence, however, declined over time in older subjects ($P_{trend} <$ 0.0004 for BMI $\geq$25 kg/m^2; $P_{trend} = 0.03$ for BMI <25 kg/m^2) despite an increasing proportion of subjects in the higher BMI category. Adjustment for BMI in a propor-



No. at risk						
BMI<25kg/m²	1346	826	722	944	656	440
BMI≥25kg/m²	365	409	526	1408	1060	1329

Figure 3—*Age- and sex-adjusted incidence of type 2 diabetes and 95% CIs according to BMI in youth (aged 5–14 years)* (A) *and adults (aged ≥15 years)* (B) *in the three time periods. A significantly decreasing trend was observed only in adults* (P = *0.0004 for BMI ≥25 kg/m²;* P = *0.03 for BMI <25 kg/m²). In youth, incidence of diabetes was positively associated with BMI, but not significantly* (P = *0.1 for BMI ≥25 kg/m²;* P = *0.6 for BMI <25 kg/m²).*

tional hazards model accounted in part for the increased incidence of diabetes in those aged 5–14 years (hazard rate ratio for third vs. first period 3.6 [95% CI 1.2–11.3]).

Age-specific prevalence increased over time in subjects <25 years old ($P_{trend} < 0.0001$) but did not show a similar trend for older ages. All-cause mortality remained stable throughout the study in diabetic and nondiabetic subjects <25 years old, suggesting that the increasing prevalence of diabetes in youth was largely attributable to the increasing incidence of diabetes in this age-group.

CONCLUSIONS— 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 (18). Given the lack of systematic screening for diabetes before 1965, an epidemic rise in the incidence of diabetes in the Pimas is difficult to confirm. Nonetheless, the available evidence suggests that a rise did occur between the 1930s and the beginning of this study (12,13). Although the reasons for the high prevalence and incidence of diabetes in the Pimas are not known with certainty, genetic factors and an increasing prevalence of obesity associated with rapid lifestyle changes are likely. The low prevalence of diabetes even today among Pima Indians from Maycoba, Mexico (19,20), who share considerable genetic similarity with those in the U.S., supports the notion of an epidemic of diabetes in the Gila River Community coinciding with increased contact with European Americans and the ensuing change in lifestyle. Accordingly, we propose 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 relatively stable incidence since that time, but with a shift to 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 (18,21). The declining incidence of diabetes among Pimas aged 25–34 years may reflect, in part, a shift to a younger age at onset in those at greatest risk.

Among American Indians aged 15–19 years nationwide, the prevalence of diagnosed diabetes increased by 69% in 1990–1998 but remained unchanged in those <15 years old (22). In Japan, a 10-fold increase in the incidence of type 2 diabetes over a 20-year period was reported in children aged 6–12 years and a 2-fold increase among those aged 13–15 years, coinciding with a secular increase in the prevalence of obesity (23,24). Data on secular changes in the incidence of type 2 diabetes are sparse in other populations. The San Antonio Heart Study (25) showed an increasing incidence of type 2 diabetes among Mexican Americans and a borderline significant trend in non-Hispanic whites over 8 years, associated with higher BMI. The authors suggested that the higher prevalence of diabetes in the Mexican Americans was primarily due to its increasing incidence and, to a lesser extent, to declining cardiovascular mortality among diabetic subjects (26). The Framingham Study (27) reported a doubling in the incidence of type 2 diabetes in Caucasians aged 40–55 years over the last three decades, largely occurring in people with BMI ≥30 kg/m². By contrast, in adult Pima Indians, diabetes incidence was stable over four decades, despite increasing mean BMI. Diabetes incidence actually declined in the most obese group even as the proportion of the population in this group increased, suggesting 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.

In this study, diabetes was diagnosed independently in the three periods, different from a previously used method (11) in which person-time at risk was counted continuously to the end of the first of two periods but only to the last examination in the second. The previous approach could result in an underestimate of person-time at risk in the second compared with the first period, leading to an overestimate of the incidence rate in the second period. This problem was avoided in the present analysis by counting person-time the same way in each period. By this approach, however, 6% fewer subjects and 27% fewer cases were included than would have been if the periods had not been considered independently. By using two instead of three independent time periods, 239 more cases and 648 more subjects were included in the study, and the findings were unchanged.

We evaluated participation rates among individuals who were initially nondiabetic and remained alive in each period. Of these, 75, 71, and 67% in each period had at least one follow-up examination in the same period and were thus included in the analysis. BMI and 2-h plasma glucose concentrations were similar in subjects with only one examination and in those with more examinations, suggesting that incidence of diabetes was not biased by selection of a higher-risk population. The ratio of study participants to the midpoint census population of each period declined during the study. Since the census population does not differentiate between diabetic and nondiabetic individuals, the extent to which the decline was related to diabetes cannot be determined.

The new assay for glucose introduced in the third period measured the glucose concentration as slightly higher than that measured by the previous method. Thirty-five subjects with glucose concentrations at the low end of the diabetic range by the new method might have been nondiabetic by the initial method. After reclassification of these subjects as nondiabetic, the overall incidence of diabetes declined significantly ($P = 0.005$), but the increasing trend for ages 5–14 years remained.

In summary, over the past 40 years, average BMI in the Pima Indians has increased by 19%, yet diabetes incidence has remained unchanged or possibly declined, except in the youth, in whom the incidence increased nearly sixfold. Increasing obesity among the youth and the vicious cycle of diabetes in pregnancy begetting more diabetes in youth in successive generations appear to have shifted the onset of diabetes to younger ages. The lifestyle changes that occurred in the first half of the 20th century may have contributed to an abrupt and dramatic rise in diabetes incidence, which peaked before 1965. Lifestyle interventions are effective at reducing the incidence of diabetes among high-risk individuals in short-term clinical trials (28–30). To what extent these interventions are effective in community settings remains to be determined.

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