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VITAL and HEALTH STATISTICS

DATA FROM THE NATIONAL HEALTH SURVEY

Childbearing and Diabetes Mellitus

United States - 1960 - 1962

The relationship of the number of pregnancies to diabetes as shown in data from the Health Examination Survey, 1960-62, and data from Sudbury, Massachusetts.

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COOPERATION OF THE BUREAU OF THE CENSUS

In accordance with specifications established by the National Health Survey, the Bureau of the Census, under a contractual agreement, participated in the design and selection of the sample, and carried out the first stage of the field interviewing and certain parts of the statistical processing.

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PREFACE

The analysis of Health Examination Survey data in the body of this report is based on the sample group examined in Cycle I of the HES rather than on estimates for the target population. In simple terms reference is made to the 6,672 persons in the HES sample rather than the 111,086,000 people from which the sample was selected. For this reason the reader must be warned not to use the data as descriptive of the total population of the United States, since their probability of selection is not taken into account.

The use of uninflated data from the sample differs, of course, from ordinary usage. The sampling scheme of HES and the associated procedures for estimation and for estimating the variances of the estimates were designed to yield an unbiased representation of the civilian noninstitutionalized population of the conterminous United States at (essentially) a fixed point in time, and confidence intervals for that representation.

In this report, however, the data are treated as a manifestation of some general process. This is different from a description of the target population of the first cycle of the Health Examination Survey. Rather it concerns a defined biological or medical process (presumably of some generality), which may be manifesting itself in the persons examined by the HES. Were it repeated a large number of times (to use one conceptualization) it would, by chance, sometimes manifest itself by one set of numbers and sometimes by another. These sets of numbers are assumed to be distributed in a fashion definable by available statistical techniques.

The specific question under examination in this report is whether the stress of successive pregnancies predisposes women to develop diabetes. This is a problem that has been studied from varying viewpoints in several different populations. The data from the HES is viewed in this report as part of the total body of evidence on the subject. Additional evidence is still needed before firm answers are possible.

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CONTENTS

IN THIS REPORT data are presented on the relation of the number of pregnancies to diabetes. With increasing parity there was a rise in the probability of finding previously known diabetes among women in the Health Examination Survey. Data from the population of Sudbury, Massachusetts did not show a similar difference for women or for men. Blood glucose levels, on the contrary, were found to be unrelated to marital status or childbearing, except for an isolated finding of higher blood glucose levels in women of parity nine or more. The question of whether the higher parity of diabetes is due to a causal association between the metabolic stresses of pregnancy and the development of later diabetes remains moot.

SYMBOLS

Data not available	---
Category not applicable	...
Quantity zero	-
Quantity more than 0 but less than 0.05	0.0
Figure does not meet standards of reliability or precision	*

CHILDBEARING AND DIABETES MELLITUS

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INTRODUCTION

The hypothesis attributing the higher prevalence of diabetes among women to the recurrent metabolic stresses of pregnancy has excited attention since its first proposal several decades ago.[1] The consequent possibility that a controllable environmental factor might be playing a critical role in the etiology of this chronic disease has significant implications for preventive medicine. In fact, it has been suggested that the use of insulin treatment during the temporary hyperglycemia of pregnancy may prevent the appearance of permanent diabetes in the mother, as well as favorably alter the risk to the offspring of such a pregnancy.[2] The substantiation of this effect would have far-reaching significance for public health. Prospective studies are already underway, but they require the test of time.[3,4]

In 1933, Mosenthal and Bolduan[1] first attributed the higher prevalence of diabetes among women to the possible diabetogenic effects of pregnancy. This report was later supported by studies such as those of Joslin, Dublin, and Marks (1936);[5] Munro, Eaton, and Glen (1949);[6] Pyke (1956);[7] and Fitzgerald and others (1961).[8] These authors attributed the preponderance of diabetes among women to the associated influences of obesity and parity. However, their conclusions have been questioned, notably by Steinburg (1958)[9] and Vinke and his associates (1959).[10]

Data presented in this report concern the parity distribution for women examined by the Health Examination Survey (HES) and for the diabetics found in that group. In addition, blood glucose values obtained from each person in the HES group are analyzed for possible parity relationships. Since the evidence suggests that the metabolic stresses of pregnancy exist throughout gestation[11] the term parity in this report is used to describe all pregnancies regardless of their duration. Finally, in an effort to provide a key piece of evidence not collected by the HES, supplementary evidence is presented from a recent survey of a community in Massachusetts.

Between 1959 and 1962 the Health Examination Survey conducted a series of examinations on a probability sample of the civilian, noninstitutionalized population of the continental United States between 18 and 79 years of age.[12] A detailed description of the sample and response of the 6,672 persons who were examined has been published.[13] The survey was designed to obtain information on certain chronic diseases, on dental health, and on the distribution of some anthropometric and sensory characteristics. This was accomplished by a standardized 2-hour examination which included a medical history of glucose tolerance, a modified glucose tolerance test,[14] anthropometric measurements, and a pregnancy history for the women.

Upon entering the mobile clinic each examinee was greeted by a receptionist-interviewer. The first medical question asked was, "Do you have any reason to think you may have diabetes...?" and if the answer was "Yes" or the examinee uncertain, the interviewer asked a series of re-

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lated questions to determine whether a diagnosis of diabetes had been made by a physician, whether the examinee was under a doctor's care for the disease, how frequently he saw a doctor for diabetes, and whether any specific hypoglycemic agent was used in treatment (Appendix I).

Then the examinee was given a medical history form to complete. Included among the 74 questions in this section were several relating to diabetes—increased thirst, increased urination, recent weight loss, and relatives with diabetes—and several on pregnancy history (Appendix I).

Unless there was a clear history of diabetes under medical care, the examinee was offered a drink containing 50 grams of glucose with lemon flavoring ("Dextol") which was diluted in 250 cc. of water. The drink was administered without regard to the time or content of the previous meal (Appendix II). An hour after the glucose drink was given, a blood specimen was obtained by venipuncture, and about 30 minutes later a urine specimen was collected. The blood specimen was shipped to the laboratory of the Diabetes Field Research Unit in Boston, where blood glucose determinations were done by the Somogyi-Nelson method[15] (Appendix III).

The use of oral hypoglycemics or insulin was accepted as documentation of stated diabetes. If a person diagnosed by a physician was not on medication, the diagnosis was accepted unless the blood glucose level was less than 138 mg. per 100 ml. without challenge or 148 mg. per 100 ml. with challenge. In most instances the levels were substantially higher (Appendix IV). Most of the stated diabetics met these arbitrary criteria for definite diabetes. If a stated diabetic did not satisfy the criteria for a definite diagnosis but had consulted a physician about diabetes within the last 6 months and had a followup medical appointment scheduled within the next 6 months, he was considered a questionable case. Otherwise a diagnosis was not accepted. Less than 9 percent of the examinees reporting diabetes failed to meet the criteria for a definite or questionable diagnosis.

Data from the population of Sudbury, Massachusetts were obtained during a comprehensive epidemiologic study initiated there in 1964.[16] Seventy-seven percent of the total population, aged 15 years and over, had medical examinations. Stated diabetics were verified in detail and new diabetics were accepted if two postprandial blood sugars were above the 92d and 98th percentile levels for the whole population respectively *and* a glucose tolerance test was abnormal.[17] Blood glucose determinations were performed on venous whole blood samples using the Auto Analyzer. This method was found to give results comparable with the Somogyi-Nelson method when a random subsample of the population's samples were tested by both methods.[18]

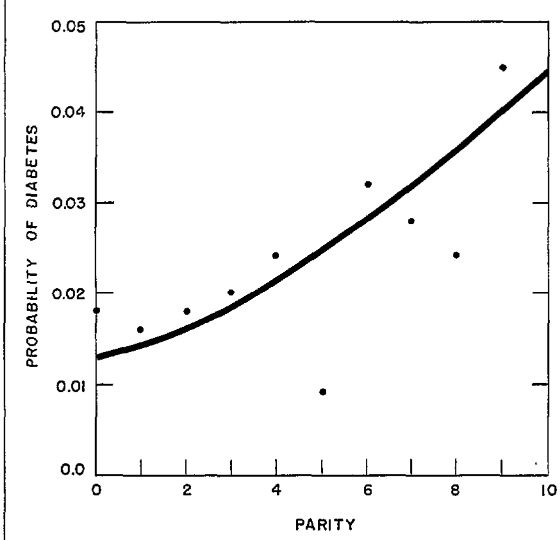

Figure 1. Age-adjusted probability of having diabetes, by parity.

RESULTS

Diabetes

Figure 1 displays the age-adjusted probability of definite or possible diabetes for women in the Health Examination Survey according to the number of pregnancies. Despite the irregular distribution of these points, it is clear that the probability of diabetes is increased with parity.

The relationship of parity to diabetes may be considered in different terms: Are diabetic women more likely to have a higher parity than nondiabetic women? Table 1 shows the mean number of pregnancies by age for definite or possible diabetics and nondiabetics. In the three age groups with sizable numbers of diabetics—45-54, 55-64, and 65-74 years—mean parity was higher for diabetics than for nondiabetics. While it is difficult to draw any conclusions about the other age groups due to small sample sizes and a consequently high sampling variability of the data, there is a suggestion that diabetic women under 45 years of age reported fewer pregnancies than nondiabetic women. Overall, however, the mean parity for diabetic women ages 18-79 years was higher than the mean parity for nondiabetic women. This difference is statistically significant at a level of 5 percent, although, as has already been indicated, the level, and indeed the direction of the differences, was not consistent among the various age groups. Even if the parity count is restricted to live births, mean parity was elevated in diabetic women (table 2).

Blood Glucose Level

Table 3 presents the distribution by age and parity of women examined by the Health Examination Survey who had a blood glucose determination 1 hour following the ingestion of 50 grams of glucose; pregnant women and previously known diabetics were excluded. Their mean blood glucose levels are given by parity for specific age groups (table 4), and summarized for all ages (table 5). The results indicate that these levels did not rise with increasing parity. The correlation of parity with blood glucose level was also seen to be very low when all parities were considered together (table 6). The high parity groups, however, were seen to have significantly higher blood glucose levels.

A closer examination of parity nine or more is provided in table 7. Here the mean blood glucose level, adjusted for obesity as measured in skinfold thickness, was seen to be higher than for women of lower parity. This difference is statistically significant at a 5-percent level. While the difference is not clearly manifest in every age group, this variation could have arisen by chance. A similar analysis for parity eight did not yield the same result—the higher than expected blood glucose level for this group was not statistically significant. Since the glucose levels for white and Negro populations did not appear to differ,[14] racial differences in the percent of high-parity women did not have to be taken into account.

Data exhibiting mean blood glucose levels for both men and women are given in table 8. Analyses with respect to marital status or childbearing confirm that having children is not, in general, associated with higher blood glucose levels.

Diabetes for Men

The absence of parity data on men in the Health Examination Survey precluded an analysis for men of parity in relation to the prevalence of diabetes or blood glucose level. For this reason recourse was made to the data from the Sudbury Study (table 9).

The average number of births at Sudbury was higher for diabetic than nondiabetic women but the difference was small. While these data are not inconsistent with the HES findings, neither are they inconsistent with the hypothesis that no difference exists in parity between diabetic and nondiabetic women. The data for men were equally inconclusive when age differences were controlled. This was true whether only confirmed "stated" diabetics were included in the analyses, or persons with previously unrecognized disease were also included.

DISCUSSION

The confirmed higher parity among female diabetics may be considered in various ways. This analysis is concerned primarily with the possibility that the stresses of recurrent pregnancies are related in a causal way to diabetes. The data in this report do not allow this question to be answered. It had been hoped that findings from the Sudbury Study would provide a clear answer. For example, a definite association between family size and diabetes for women, and the absence of such an association for men would tend to confirm a causal relationship. Alternatively, a clear association for both men and women would argue against an etiologic role. However, there was no clear association between higher parity and diabetes for either men or women in Sudbury. What is more, the hypothesis that high parity is a cause of diabetes is weakened by the failure to find any meaningful correlation between blood glucose levels and parity in the HES sample. The HES findings, however, agree with those of other studies suggesting that diabetics tend to have large families.[19, 20] The data from the HES and Sudbury studies, but especially from the HES, would be consistent with this conclusion.

The findings with respect to women of parity nine or more are difficult to fit into the picture. It is not clear from the HES data whether the higher mean glucose levels in these women represent a real relationship, a random statistical variation, or an unsuspected artifact. While figures from a large prenatal population indicated that the relationship between higher gestational blood glucose levels and increasing parity could be accounted for by the concurrent rise in maternal age,[21] such an explanation would not apply to the Health Examination Survey data. The explanation may lie, at least in part, in the higher than average glucose levels noted for women of limited education or income,[22] since two-thirds of all women of parity nine or more had only a grade school education and women of high parity also tend to have lower incomes. Available data (table 10) would argue against this explanation, suggesting, rather, that blood glucose levels at parity nine or more are high no matter what the education or income. Unfortunately, the data on this subject are too limited to be interpreted with confidence. It is conceivable that other artifacts account for this finding, since women of very high parity may be an unusual group in many respects. A further discussion of this subject is included in Appendix V.

An explanation for the presumed effects of sex and parity on the incidence of diabetes in previous studies must consider the variation in methods used to identify the diabetic, as well as the characteristics of the population studied. For example, although the Oxford, Massachusetts Study of diabetes found more female "previously known" diabetics, they were equally balanced by a male excess of newly discovered diabetics.[23] It is obvious that diagnostic habits, techniques, and local health attitudes influence the results of this type of investigation. Conflicting evidence for a male or female preponderance in the sex prevalence of diabetes[14,17] or even that the sex prevalence is changing[24] if, indeed, such prevalence measurements can be made with sufficient accuracy,[17] lead to the same conclusion. The commonly accepted majority of females among diabetics is still very much an open question.

The many relationships of pregnancy to diabetes cannot, of course, be explored by these data. It is conceivable that women who fail to cope with the temporary stress of gestation will show the effects years later. The increased risks to the pregnancy of such potentially diabetic persons are acknowledged.[4] On the other hand, whether such metabolic stresses result in an acceleration in the appearance of diabetes is questionable. The failure to demonstrate an earlier onset of diabetes in women of high parity would appear to argue against such a possibility.[6, 7, 19] While prospective evidence is still lacking, available data seem to favor the conclusion that pregnancy has no role in the causation or earlier appearance of diabetes. The Health Examination Survey, therefore, confirms the tendency toward higher parity among diabetic women without providing an explanation for it. To attribute this increase in family size to an altered fertility rate or to more subtle psychosocial factors would be purely speculative.

SUMMARY

1. Blood glucose levels of women examined by the Health Examination Survey were found to be unrelated to marital status or childbearing. The isolated finding of higher blood glucose levels in women of parity nine or more is discussed.

2. With increasing parity there was a rise in the probability of finding previously known diabetes among women in the Health Examination Survey. Age-adjusted data from the population of Sudbury, Massachusetts, did not show a similar difference either for men or women.

3. The data in this report do not resolve the question of whether the higher parity of diabetics is due to a causal association between the metabolic stresses of pregnancy and the development of later diabetes. The available evidence, however, favors a tentative conclusion that no such relationship exists.

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DETAILED TABLES

Table 1. Mean parity for diabetic and nondiabetic women, by age: Health Examination Survey, 1960-62

Age	Number of women		Mean parity		
	Diabetic	Non-diabetic	Diabetic	Non-diabetic	Difference
18-24 years	3	531	-	1.13	-1.13
25-34 years	6	740	1.67	2.87	-1.20
35-44 years	5	779	2.80	3.28	-0.48
45-54 years	22	683	4.55	3.14	1.41
55-64 years	18	425	4.22	2.83	1.39
65-74 years	20	279	5.55	3.62	1.93
75-79 years	4	66	1.50	3.71	-2.21
Mean	...	...	...	...	0.67

NOTE: If i is the specified parity (i=0,1,...,8,9; more than 9 parity being taken as 9) and N_{ik} is the number of women of parity i in age group k ($\sum_i N_{ik} = N_k$) and n_{ik} the number of women in that age and parity group with diabetes ($\sum_i n_{ik} = n_k$) and

$$d_k = \sum_i i n_{ik}/n_k - \sum_i i(N_{ik} - n_{ik})/(N_k - n_k)$$

and

$$r_k = [\sum_i i^2 N_{ik} - (\sum_i i N_{ik})^2/N_k]\left(\frac{1}{n_k} - \frac{1}{N_k - n_k}\right)\left(\frac{1}{N_k}\right)$$

then the mean difference in parity for all age groups is taken as

$$D = \left(\sum_k \frac{d_k}{r_k}\right)\Big/\left(\sum_k \frac{1}{r_k}\right) = 0.67309$$

with variance

$$V = \sum_k 1/r_k = 0.08677$$

D^2/V being distributed as chi-square with 1 d.f.

$\sum_k (d_k - D)^2/r_k = 29.06$. This statistic, which is distributed as chi-square with 6 d.f., indicates that the variation of the d_k was too large to be attributed to chance at a 5 percent level.

Table 2. Mean number of births, by age of woman and diabetic status: Health Examination Survey, 1960-62

Age	Diabetic	Non-diabetic	Difference
	Mean number of births		
18-24 years	-	0.93	-0.93
25-34 years	1.50	2.48	-0.98
35-44 years	2.20	2.82	-0.62
45-54 years	3.82	2.65	1.17
55-64 years	4.00	2.48	1.52
65-74 years	4.65	3.25	1.40
75-79 years	1.50	3.32	-1.82

Table 3. Number of women, by age and parity: Health Examination Survey, 1960-62

Age	Parity										
	Total	0	1	2	3	4	5	6	7	8	9+
	Number of women										
All ages----	3,267	651	454	616	509	358	228	132	91	71	157
18-24 years-------	441	220	83	74	32	16	11	2	2	1	-
25-34 years-------	665	97	88	124	142	95	56	27	21	8	7
35-44 years-------	751	99	68	155	143	108	68	35	17	17	41
45-54 years-------	663	90	103	126	114	75	49	29	23	14	40
55-64 years-------	410	91	65	75	51	33	25	19	9	9	33
65-74 years-------	276	42	42	47	23	25	17	18	18	18	26
75-79 years-------	61	12	5	15	4	6	2	2	1	4	10

NOTE: Includes only women with blood glucose determination after challenge. Excludes pregnant women and women with diagnosed diabetes.

Table 4. Mean blood glucose levels of women, by age and parity: Health Examination Survey, 1960-62

Age	Parity										
	Total	0	1	2	3	4	5	6	7	8	9+
	Mean glucose in mg.%										
All ages----	125.5	121.4	128.3	123.0	121.2	124.3	125.7	129.6	131.6	141.4	146.5
18-24 years-------	103.9	103.8	103.9	106.6	106.5	92.3	105.1	81.0	99.0	79.0	-
25-34 years-------	110.5	112.4	112.4	111.2	109.8	110.5	109.4	105.5	104.2	103.9	112.1
35-44 years-------	119.5	122.6	120.3	114.1	116.1	119.7	118.5	124.0	126.5	124.5	134.5
45-54 years-------	132.3	129.6	138.8	128.6	125.8	131.1	133.9	131.2	121.9	155.2	151.3
55-64 years-------	144.0	137.9	147.3	140.7	139.8	157.2	153.7	144.1	164.3	137.7	144.2
65-74 years-------	158.4	160.6	159.8	153.7	166.6	142.3	155.2	159.9	169.5	162.1	160.3
75-79 years-------	172.0	184.5	193.4	160.4	192.0	170.0	138.5	164.5	105.0	171.0	172.4

NOTE: Includes only women with blood glucose determination after challenge. Excludes pregnant women and women with diagnosed diabetes.

Table 5. Excess of actual over expected mean glucose values for women 18-79 years of age, by parity: Health Examination Survey, 1960-62

Parity	Number of women	Excess of actual over expected mean glucose level in mg.%	
		Unadjusted[1]	Adjusted[2]
0	651	-0.1	-
1	454	2.8	3.0
2	616	-2.7	-2.6
3	509	-2.3	-2.2
4	358	-0.6	-0.9
5	228	0.4	-
6	132	-0.3	-0.3
7	91	0.6	0.4
8	71	4.7	4.4
9 and over	157	9.2	8.5

[1]If d_i is the difference in mean glucose levels between the specified parity class and all parities in the i^{th} age group and n_i is the number of women in that age-parity group then $\sum_i n_i d_i / \Sigma n_i$ is the unadjusted excess of actual over expected.

[2]Adjusted for skinfold thickness. If b_i is the slope of the linear regression of skinfold thickness on blood glucose level in the i^{th} age group and s_i is the i^{th} difference in skinfold thickness between the 2 parity classes, then $b_i s_i$ is the adjustment for skinfold thickness in the i^{th} age group.

NOTE: Includes only women with blood glucose determination after challenge. Excludes pregnant women and women with diagnosed diabetes.

Table 6. Correlation of parity and blood glucose levels in women, by age: Health Examination Survey, 1960-62

Age	Parity	
	All parities	0-8
18-24 years	-0.024	-0.024
25-34 years	-0.040	-0.045
35-44 years	0.066	0.012
45-54 years	0.071	0.005
55-64 years	0.058	0.080
65-74 years	0.032	0.018
75-79 years	-0.095	-0.153

NOTE: Includes only women with blood glucose determination after challenge. Excludes pregnant women and women with diagnosed diabetes. Parity greater than 9 is scored as 9.

Table 7. Mean blood glucose levels for women with parity less than nine and parity nine and over, by age: Health Examination Survey, 1960-62

Age	Parity: 0-8	Parity: 9 and over	Difference: Actual	Difference: Adjusted for skinfold thickness[1]
	Mean glucose in mg.%			
18-24 years	...	---	---	---
25-34 years	110.4	115.0	4.6	4.3
35-44 years	118.6	134.5	15.9	14.3
45-54 years	131.1	151.3	20.2	19.6
55-64 years	144.0	144.2	0.3	-0.7
65-74 years	158.0	163.0	5.0	5.0
75-79 years	172.3	170.4	-1.9	-1.0
Mean[2]	...	...	11.3	10.4

[1]If b_i is the slope of the linear regression of skinfold thickness on blood glucose level in the i^{th} age group and s_i is the i^{th} difference in skinfold thickness between the 2 parity classes, then $b_i s_i$ is the adjustment for skinfold thickness in the i^{th} age group.

[2]If d_i is the difference in mean blood glucose levels for the 2 parity classes in the i^{th} age group and $1/w_i$ is the variance of that difference, then $\Sigma w_i d_i / \Sigma w_i$ is the mean difference shown, with a variance of $1/\Sigma w_i$. For computational convenience the same value of w_i was used for the actual and adjusted differences although they should have been slightly less for the adjusted differences. $\sum_i (d_i - D)^2 w_i = 5.16$ (not significant at a 5 percent level).

NOTE: Includes only women with blood glucose determination after challenge. Excludes pregnant women and women with diagnosed diabetes.

Table 8. Mean blood glucose in adults, never married and married, with or without children, by sex and age: Health Examination Survey, 1960-62

Sex and age	Never married	Married: Total	Married: No children	Married: Children	Never married	Married: Total	Married: No children	Married: Children
	Number of persons				Mean glucose in mg.%			
Men								
18-24 years	243	157	52	105	92.6	96.5	98.2	95.6
25-34 years	96	569	87	481	105.9	101.2	102.3	101.1
35-44 years	39	646	78	567	128.7	113.5	111.9	113.8
45-54 years	30	502	79	422	120.0	118.8	118.3	119.0
55-64 years	30	368	79	289	135.4	131.8	135.5	130.8
65-74 years	16	233	41	192	171.0	137.9	142.0	136.9
75-79 years	2	65	12	53	179.0	151.6	151.7	151.6
Women								
18-24 years	198	243	43	197	103.1	104.6	111.0	103.2
25-34 years	60	605	64	540	115.1	110.0	108.4	110.1
35-44 years	33	718	78	638	110.2	119.9	125.4	119.2
45-54 years	29	634	94	536	124.7	132.7	138.6	131.6
55-64 years	26	384	75	306	133.1	144.8	138.6	146.5
65-74 years	13	263	37	224	170.2	157.8	160.4	157.2
75-79 years	3	58	12	46	147.3	173.3	192.5	168.3

NOTE: Includes only persons with blood glucose determinations after challenge. Excludes persons with diagnosed diabetes and pregnant women. For a few persons it is not known whether or not they had children.

Table 9. Parity and diabetes, by age and sex: Sudbury, Massachusetts[1]

Age	Men		Women		Men		Women	
	Diabetic[1]	Nondiabetic	Diabetic[1]	Nondiabetic	Diabetic	Nondiabetic	Diabetic	Nondiabetic
	Number of persons				Mean number of children ever born			
All ages	53	[3]2,154	31	[2]2,385	2.7	2.1	2.6	2.3
15-24 years	-	371	-	391	-	0.1	-	0.3
25-34 years	5	526	2	706	2.4	2.2	1.5	2.6
35-44 years	8	741	2	701	2.6	2.8	4.0	3.0
45-54 years	18	305	4	298	2.9	2.6	2.0	2.5
55-64 years	6	[2]130	9	162	2.3	2.0	1.2	2.1
65-74 years	14	65	6	85	2.6	2.4	3.0	2.5
75 years and over	2	[2]16	8	[2]42	3.5	3.6	4.2	2.3

[1]Includes the stated, confirmed, and newly discovered diabetics in the Sudbury population.

[2]Excludes 1 person with number of children not stated.

[3]Excludes 2 persons with number of children not stated.

Table 10. Mean glucose level at parity nine and at lower parities for women with low income or education, by selected ages: Health Examination Survey, 1960-62

Family income, education, and age	Number of women		Mean glucose in mg.%		
	Parity 0-8	Parity 9	Parity 0-8	Parity 9	Difference
FAMILY INCOME					
Under $2,000					
35-44 years	60	11	129.8	116.6	-13.2
45-54 years	96	16	134.0	155.3	21.3
$2,000-$3,999					
35-44 years	113	10	127.0	162.3	35.3
45-54 years	129	8	130.0	165.5	35.5
EDUCATION					
Under 5 years					
35-44 years	26	10	136.3	131.6	-4.7
45-54 years	33	8	147.5	165.0	17.5
5-8 years					
35-44 years	131	13	123.9	126.4	2.5
45-54 years	182	22	132.5	149.6	17.1
9-12 years					
35-44 years	430	18	117.2	142.1	24.9
45-54 years	303	7	127.9	151.4	23.5

APPENDIX I

ITEMS ON THE MEDICAL HISTORY RELATING TO GLUCOSE TOLERANCE

1. a. Do you have any reason to think that you may have diabetes, sometimes called sugar diabetes or sugar disease? YES NO ?
   (IF YES or ?)
   b. Did a doctor tell you that you had diabetes? YES NO
   c. How long ago did you start having it?
   1 year | 1-5 years | over 5 years
   d. Do you take insulin? YES NO.
   e. (IF TAKE INSULIN:) How many units a day? ____________
   f. Do you take any medicine by mouth for diabetes? YES NO
   g. Do you know the name of the medicine?
   (Name)____________
   h. When did you last visit your doctor for diabetes?
   (date)____________
   i. When is your next appointment to visit your doctor for your diabetes?
   (date)____________ ☐ No appointment

2. a. When did you have your last meal? Time ____________ AM TODAY / PM YESTERDAY

	YES	NO
b. Did you have meat or fish	☐	☐
c. Eggs or cheese	☐	☐
d. Bread, cereal, potatoes	☐	☐
e. Cake, pie, sweet rolls, ice cream	☐	☐

	YES	NO
3. a. Have you had anything to eat or drink since that meal?	☐	☐
(IF YES) What was it? b. Coffee?	☐	☐
With cream?	☐	☐
With sugar?	☐	☐
c. Other (Specify)	☐	☐

____

7. a. Have you ever had any children of your own (not including adopted children)? YES NO
   (IF YES)
   b. Did any of your children weigh more than 10 lbs at birth? YES NO ?

69. Have you had any recent increase in being thirsty (drink a lot of water)? [YES] [NO] [?]

70. Have you had any recent increase in urination (pass a lot of water)? [YES] [NO] [?]

71. a. Have you lost any weight recently (without trying to)? [YES] [NO] [?]

IF YES:

b. How much weight have you lost?_______lbs.

c. Over what period of time have you lost this weight?_______________

72. a. Has any of your relatives ever had diabetes? [YES] [NO] [?]

IF YES:

b. Please give relationship of this person or these persons to you: _______________________________

74. WOMEN ONLY

a. Age when periods started_______________

b. Have periods stopped? (not counting pregnancy) [YES] [NO]

IF YES:

c. Age when periods stopped ____________

d. Was this due to an operation? [YES] [NO]

IF NO:

e. Have they begun to stop? [YES] [NO]

f. Date of last period ______________

g. How many babies have you ever had who were born alive? ________

h. Have you ever had any pregnancies that did not result in a live birth? [YES] [NO]

j. IF YES, how many? _______

k. Are you pregnant now? [YES] [NO] [?]

m. IF YES, how many months? _______

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APPENDIX II

CASUAL ASPECTS OF THE GLUCOSE TOLERANCE TEST

The glucose tolerance test used in the Health Examination Survey required that the examinee be given a challenge of 50 grams of glucose shortly after beginning the examination and that 1 hour later a venous blood specimen be taken. In that sense the glucose tolerance test was standardized. There were a number of respects, however, in which the glucose tolerance test was not standardized. For example, an examinee might appear for examination at any time of the day, from early morning until late in the evening. Or, he might arrive either just after eating or many hours after his last meal. And the content of his last meal, as well as his usual diet, was entirely uncontrolled by the survey. Given all these

Table I. Mean blood glucose levels, by time of day challenge was given, specified intervals between last meal and challenge, sex, and age: Health Examination Survey, 1960-62

Interval between last meal and challenge, sex, and age	Time of day challenge was given		
	8-11 a.m.	12-5 p.m.	6 p.m. or later
60-119 minutes	in mg.%		
Men			
18-39 years	87.4	95.8	98.1
40-54 years	108.5	127.3	110.0
55 years and over	130.6	155.1	106.5
Women			
18-39 years	92.7	105.7	100.5
40-54 years	107.7	125.1	116.1
55 years and over	118.1	148.5	131.3
120-179 minutes			
Men			
18-39 years	103.3	101.0	97.4
40-54 years	115.1	116.5	113.6
55 years and over	129.1	135.0	117.3
Women			
18-39 years	102.1	108.8	98.8
40-54 years	121.0	118.7	119.7
55 years and over	146.6	153.5	135.4
180-239 minutes			
Men			
18-39 years	107.7	99.0	94.5
40-54 years	119.5	113.6	110.7
55 years and over	130.5	142.8	137.8
Women			
18-39 years	110.1	114.0	100.0
40-54 years	144.2	131.5	101.8
55 years and over	150.3	148.8	124.8

NOTE: Values in this table do not constitute estimates for the population of the United States.

variables it might well be asked, "How standardized was the glucose tolerance test used by the Health Examination Survey?"

To answer this question, at least in part, the Health Examination Survey, with the help of staff members of the Tecumseh Community Health Study, instituted a special study to investigate the effect on blood glucose levels of differences in the size of the glucose challenge, time of day, and time since last meal.[25] The study was undertaken with a group of 24 prisoners who were given a series of glucose tolerance tests under a variety of conditions, extending over a period of 16 weeks. It was found that with a challenge of 50 grams of glucose the blood glucose level 1 hour after challenge was affected to no discernible extent by the time between the last meal and challenge, but that levels after the midday meal were higher than levels after the morning meal. It was also found that any standard test procedure yielded results comparable to any other standard procedure. Response to any given procedure, as with most biological behavior, tended to vary from one time to the next.

In part, the same factors can be examined on the basis of the examination findings themselves. All examinees were asked when they had last eaten. The time of challenge was noted. Mean blood glucose levels are presented in table I by sex, in broad age groups, according to the time of day that the examinee was given the glucose drink, and according to the interval between his last meal and the glucose drink. These data are for examined persons only and do not constitute estimates for the population of the United States. The data are restricted to persons who came in for examination 1 to 4 hours after the meal, since such persons account for the majority of all examinees. When differences in blood glucose level associated with time of challenge and interval since last meal are measured against differences between people, the following conclusions are reached:

1. Persons given 50 grams of glucose 2 to 3 hours or 3 to 4 hours after the morning meal had higher blood glucose levels after challenge than persons given the same glucose challenge between 1 and 2 hours after the same meal.
2. So far as can be judged from the data, no similar effect is discernible for the midday or evening meals.
3. The blood glucose level after challenge also varied with time of day. Levels were higher after the midday meal than after the morning or evening meals.

Except for the effect of time on blood glucose levels after the morning meal, these findings are consistent with those from the special study[25] and may be considered extensions from the very restricted and special group of 24 male prisoners to the population as a whole.

It is of interest to examine table I for age and sex differentials on the possibility that differences between the various age-sex groups in time of appearance for the examination may somehow introduce an artifact when the data are consolidated. This is not the case. Even in data specific for time of day and time since last meal there is strong gradient by age and a definite, though weaker, sex differential, just as there is in the consolidated data.

APPENDIX III

QUALITY OF BLOOD GLUCOSE DETERMINATIONS

During the period between January and May 1962, in the course of conducting a special study of glucose tolerance tests, the Health Examination Survey instituted a series of quality checks on the work of the laboratory responsible for the blood glucose determinations of the survey—the laboratory of the Field Research Unit, Diabetes and Arthritis Branch, Division of Chronic Diseases, Bureau of State Services, U.S. Public Health Service, at Brighton, Massachusetts. The results of these checks were highly favorable. Full details are available in the report of that study.[25]

Both before and after this period, quality checks of the laboratory determinations at Brighton had been undertaken in connection with the routine field collection of specimens. The first series of checks occurred during the period between February 9 and March 3, 1961. Aliquots were obtained of 272 specimens collected routinely during the field work at San Jose and San Francisco, California. One aliquot was treated as a regular specimen and shipped to the Brighton laboratory for determination. The other was sent to a special laboratory of the Metabolic Unit of the University of California by special arrangement with Dr. Peter Forsham. The technicians at the Brighton laboratory were unaware that a comparison study was in progress, arrangements having been made through Dr. Hugh Wilkerson for this undertaking. As a subsidiary inquiry, 60 specimens were obtained in triplicate, one aliquot going to the Brighton laboratory, the second going promptly to the San Francisco laboratory, and the third being held and sent to the San Francisco laboratory 6 to 9 days later. The conclusions from these comparisons were as follows:

1. There was no definite evidence that any artifacts were introduced in the measurement of blood glucose by HES methods of transporting the specimens or by the delay between drawing the blood and measuring it.
2. Blood determinations by a single technician on a single run were highly consistent, in a sense to be specified later.
3. There were differences in the levels between technicians, runs, and laboratories; in other words, the measurement of blood glucose on the 272 specimens in this comparison was not fully standardized.
4. No change in glucose concentration was demonstrated even when the specimen was kept as long as 6 to 9 days before being measured.

There was a distinct difference in levels between the two laboratories. The mean glucose concentrations for the 272 specimens were 117.0 mg.% at the Brighton laboratory and 109.2 mg.% at the San Francisco laboratory. During this period, two technicians were working on these specimens at the Brighton laboratory. One tended to measure close to the level of the San Francisco laboratory, whereas the other tended to be distinctly higher; the apparent difference between the levels for the two technicians was about 5 mg.%.

The first 104 measurements by one of the technicians at the Brighton laboratory were compared with measurements on the same specimens by the San Francisco laboratory. These determinations represented six runs at the Brighton laboratory and nine runs at the San Francisco laboratory. If every measurement at San Francisco were increased by 6.3 percent, 9 out of 10 of the Brighton measurements would come within 5 mg.% of the San Francisco measurement; that is, if a fixed difference in measurement level is assumed, there is a remarkably high consistency between (and consequently within) the measurements at the two laboratories.

The basis for the difference in laboratory levels was never satisfactorily elucidated. Both laboratories used essentially the same laboratory techniques. Both were well controlled. There were no obvious criteria for choosing between them. Control specimens were sent the two laboratories and for these the determinations made by the Brighton laboratory were closer to the alleged glucose concentrations. On the other hand, the levels obtained by the San Francisco laboratory on these specimens tended to be slightly higher than those obtained by the Brighton laboratory. In other words, the comparisons between the laboratories were in the opposite direction from those that were obtained during the rest of the series and only confuse the issue.

Interlaboratory comparison is a harsh test of any laboratory. The general conclusion was that blood glucose determinations are not so well standardized as is commonly thought and that additional work in standardization is highly desirable. Although the results of this series were in some respects equivocal, by any realistic standards the laboratory work being done on specimens from the Health Examination Survey was quite reliable.

Between June 1961 and May 1962, a series of aliquots from specimens collected in the field were sent at regular intervals to the laboratory of the Framingham Heart Study, by arrangements with Dr. Thomas R. Dawber, Director. Except for one aberrant set of comparisons the Brighton laboratory averaged slightly higher than the Framingham. Of more interest, perhaps, is the variability of measurement. This may be represented by the statistic $s = \sqrt{w}$, where $w = \frac{\sum d_i^2}{2n}$

d_i being the difference between determinations by the Boston and Framingham laboratories on the same specimen, and n being the number of specimens. The overall value of s was 8.0 mg.%, or 5.9 mg.% if the one aberrant set were omitted. When it is considered that this figure includes variability arising from differences between laboratories, between technicians within laboratories, and between laboratory runs over a period of 1 year, the results are very encouraging.

APPENDIX IV

DIABETES—DOCUMENTATION

Of the 6,672 sample persons examined, 114 were diagnosed as having definite known diabetes and 11 as having questionable known diabetes. The persons with questionable known diabetes gave a history of disease and reported that the diagnosis had been made by a physician. Furthermore, all reported having seen a physician for the disease within the previous 6 months. None, however, were taking any hypoglycemic medication. Because they reported they were under close medical supervision, none were given a glucose challenge. Their blood glucose levels ranged from 74 mg.% to 122 mg.%. Only one was found to have urine glucose and his blood glucose level was 74 mg.%.

The 114 persons diagnosed as having definite known diabetes either reported they were on medication or were found to have elevated blood glucose levels. Of the total, 82 were using hypoglycemic agents of some sort, 33 using insulin alone, 5 using both insulin and an oral hypoglycemic, and 44 using only an oral hypoglycemic. Of the 32 persons not on hypoglycemic medication, 24 received a challenge and 8 did not. Blood glucose levels for these 32 persons ranged from 148 to 412 mg.% with challenge and from 138 to 364 mg.% without challenge. Five cases of definite known diabetes were persons who gave a history of diabetes but denied that it had been diagnosed by a physician. Since their blood glucose levels ranged from 218 to 412 mg.% it was assumed that these cases had, in fact, been medically diagnosed.

The distribution of blood glucose levels in mg.% in persons having definite known diabetes was as follows:

	Total	Under 150	150-169	170-199	200-299	300+
Not on hypoglycemic medication						
Challenge	24	1	2	6	11	4
No challenge	8	1	2	3	1	1
On hypoglycemic medication						
Challenge	8	1	-	-	2	5
No challenge	[1]74	34	4	2	18	12

[1]For 4 persons no specimen was available.

In order to identify the sample group for the Health Examination Survey, a household interview was conducted at each sample household. This made available a large amount of information both for persons subsequently examined and for sample persons who were not examined. Included in this information were data derived from a morbidity questionnaire.

Reports of diabetes from the household interview are in close correspondence with the final diagnoses made from the health examination. Altogether 107 examined persons were reported to have diabetes on the household interview, as compared with 125 with definite or questionable known diabetes on the examination. In 96 cases the two sources agreed. There were 29 cases found on examination but not reported on household interview and 11 cases reported on the interview but not diagnosed on the examination. Of the latter, two persons gave a history of diabetes on the examination but the diagnoses could not be confirmed by the evidence available, while nine persons gave no such history on the examination. Although the two sources yield comparable information on diabetes, the household interview can be considered as providing a net understatement of the prevalence of known diabetes in the population. This is in accord with a previous study of this subject, which found 88 cases of diabetes reported by household interview for every 100 identified from medical sources.[26]

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APPENDIX V

STATISTICAL NOTES

The data from the Health Examination Survey come from 42 primary sampling units or stands (standard metropolitan statistical areas or sets of 1 to 3 contiguous counties). The possibility of variation from stand to stand is obviously of analytical concern. In this instance, it is possible that a concurrent variation of parity and blood glucose level by stand could yield a spurious correlation or a discordant variation by stand might conceal a real correlation. For example, all 9-parity women might be at places where (for entirely unrelated reasons, such as a shift in laboratory standards) blood glucose levels are unusually high or unusually low.

To explore the "stand effect," the blood glucose level for each stand has been plotted against the percentage of women of parity nine or more (fig. I). Each statistic is presented relative to the expected value for that stand—expected, that is, on the basis of the age distribution of the sample at that place and the average values for all stands combined for each age group. Thus, if the actual value is higher than the expected the statistic is presented as a positive difference.

From figure I it appears that places with an "excess" number of women of parity nine or more also tend to have higher than expected mean blood glucose levels, although the association is not very strong. Some association might have been anticipated. The HES found that women in the South had higher than average blood glucose levels and high parity is also more common in the South than in the remainder of the country. (To be precise this "effect," if, indeed, it is more than a chance phenomenon, may really not be a "stand effect" at all, but may arise at another stage of sampling, or from measurement variation. For analytical purposes, however, it is convenient to treat it as a stand effect.)

Having uncovered this association the question arises, "What is the appropriate method of allowing for it in analysis?" From table 3 it is evident that almost all of the information about parity nine or more is concentrated in the age groups between 35 and 74 years. From table 7 it appears that parity nine or more is associated with a distinct elevation of blood glucose level in the age groups 35-44 and 45-54 years but not in the age groups 55-64 and 65-74 years.

This prior information is used in allowing for the stand effect. Mean values for women 35-54, and 55-74 years are computed for parity nine and parity zero through eight in each stand. The mean value for parity nine or more at all stands was compared with a value for parity zero through eight obtained by weighting the stand-specific value for parity zero through eight

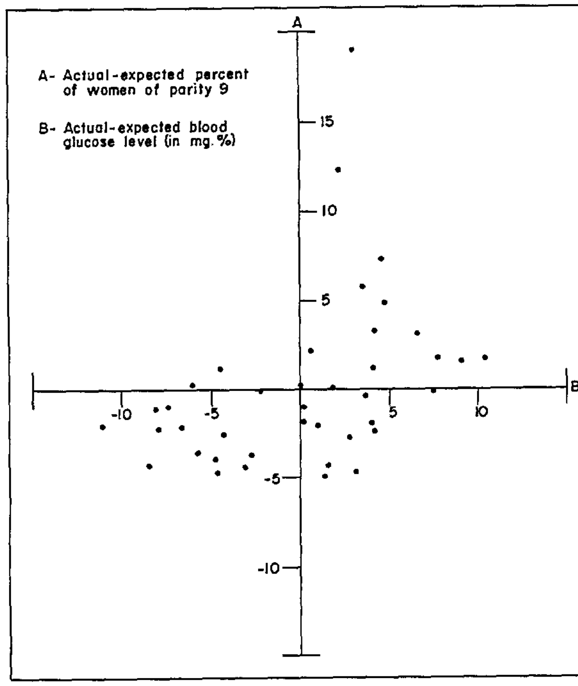

Figure I. Excess in blood glucose level and in the proportion of women of parity nine, by stand.

by the number of parity nine women in that stand and summing over all stands. Symbolically, if n_{ij} is the number of parity nine women in a specific stand in the j^{th} age group and X_{ij} is the mean blood glucose level for women of parity zero through eight, then the adjusted mean for parity zero through eight is $\sum_i n_{ij} X_{ij} / \sum_i n_{ij}$.

This leads to the following comparisons for the total HES sample:

Women	Mean blood glucose		
	Parity 9	Parity 0-8	
		Un-adjusted	Ad-justed
35-44 years--	142.8	124.5	127.4
55-74 years--	151.3	150.8	150.1

Thus, what might be described as the stand effect has only a trivial influence on the conclusions one would draw from the data.

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