REDUCED RATE OF ENERGY EXPENDITURE AS A RISK FACTOR FOR BODY-WEIGHT GAIN

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Abstract The contribution of reduced energy expenditure to the development of obesity has been a point of controversy. We measured 24-hour energy expenditure (adjusted for body composition, age, and sex), in a respiratory chamber, in 95 southwestern American Indians. Energy expenditure correlated with the rate of change in body weight over a two-year follow-up period (r = −0.39, P < 0.001). The estimated risk of gaining more than 7.5 kg in body weight was increased fourfold in persons with a low adjusted 24-hour energy expenditure (200 kcal per day below predicted values) as compared with persons with a high 24-hour energy expenditure (200 kcal per day above predicted values; P < 0.01). In another 126 subjects, the adjusted metabolic rate at rest at the initial visit was also found to predict the gain in body weight over a four-year follow-up period. When the 15 subjects who gained more than 10 kg were compared with the remaining 111 subjects, the initial mean (± SD) adjusted metabolic rate at rest was lower in those who gained weight (1694 ± 103 vs. 1764 ± 109 kcal per day; P < 0.02) and increased to 1813 ± 134 kcal per day (P < 0.01) after a mean weight gain of 15.7 ± 5.7 kg. In a group of 94 siblings from 36 families, values for adjusted 24-hour energy expenditure aggregated in families (intra-class correlation = 0.48). We conclude that a low rate of energy expenditure may contribute to the aggregation of obesity in families. (N Engl J Med 1988; 318:467-72.)

OBESITY is a familial disorder that may be genetically determined. The familial occurrence of obesity could result from a similarity among siblings in either an excessive caloric intake, a deficit in energy expenditure, or both. Because of limitations in current methods of quantifying energy intake in humans, it is not known whether caloric intake is a familial characteristic. Most available studies of energy intake have shown that obese subjects do not eat more than their thin counterparts. In contrast, measurements of energy expenditure show increased rates of caloric expenditure in obese persons, suggesting that excess food intake is the cause of obesity. It has recently been shown that metabolic rates at rest are similar within families and that the rate is, to some extent, genetically determined. Whether values for 24-hour energy expenditure, which includes the metabolic rate at rest, the thermic effect of food, and the caloric cost of physical activity, aggregate in families has not been studied.

The familial effect on energy expenditure may not necessarily be relevant to the familial effect on human obesity, since it is not known whether persons with low metabolic rates are more predisposed to gain weight than those with higher metabolic rates, although such a relation has been suggested. Therefore, in this study, we determined the extent of the familial aggregation of values for 24-hour energy expenditure among southwestern American Indians, a population prone to obesity. We also conducted prospective studies to determine the relative rates of weight gain in persons with low metabolic rates and those with high rates.

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Methods

Subjects

Between September 1982 and May 1987, 286 southwestern American Indians were admitted to the metabolic ward of the Clinical Diabetes and Nutrition Section, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, in Phoenix, Arizona, as part of an ongoing, longitudinal study of carbohydrate and energy metabolism. Volunteers have been restudied approximately yearly. On admission, it was determined that each subject was in good health (apart from having diabetes and obesity) on the basis of a medical history and physical examination. The subjects were not taking any medications and had no clinical evidence of hypothyroidism or hyperthyroidism. After the nature and possible consequences of the studies had been fully explained, written informed consent was obtained. Electrocardiography was performed, and blood was drawn for routine laboratory testing. All subjects began to follow a weight-maintenance diet composed of 50 percent carbohydrate, 30 percent fat, and 20 percent protein. The percentage of body fat in each subject was determined by underwater weighing, and the fat-free body mass was then calculated. Two to four days later, all subjects underwent an oral glucose-tolerance test (75 g), and the results were classified according to the criteria of the National Diabetes Data Group. Only the subjects who did not have diabetes mellitus on entry and had a normal electrocardiogram and normal results on blood and urine tests were included in the present analyses, although diabetes subsequently developed in 14 subjects.

Metabolic Rate at Rest

The metabolic rate at rest was measured with a ventilated hood indirect calorimeter at least seven days after the subject was admitted to the metabolic ward and after a 12-hour overnight fast. The subjects were supine and were asked to remain motionless and awake during the test. Energy expenditure was calculated from the rates of oxygen consumption and carbon dioxide production, with use of the equations of Lusk. The metabolic rate at rest was the mean energy expenditure during a period of 40 minutes starting at least 15 minutes after the placement of the ventilated hood. The coefficient of variation of the indirect calorimetry method (2 percent) was determined by repeated measures of acetone combustion and represented a large proportion (~52 percent) of the intrapersonal variation assessed by repeated measurements of the metabolic rate at rest in 26 subjects.
Respiratory Chamber

Since June 1985, a respiratory chamber has been used to measure the rate of 24-hour energy expenditure in 95 subjects. The respiratory chamber forms an open-circuit, indirect calorimeter in which the rates of oxygen consumption, carbon dioxide production, and energy expenditure of a subject can be continuously measured over a period of 24 hours. In this study, no vigorous exercise was allowed in the chamber, and spontaneous physical activity was monitored by a radar system. The intrapersonal coefficient of variation for 24-hour energy expenditure was 2.4 percent.

Familial Effect on 24-Hour Energy Expenditure

Familial aggregation of values for 24-hour energy expenditure was determined for subjects who had at least one other sibling for whom data were also available. A total of 94 siblings from 36 different families met these criteria; 22 of the families had two siblings, 9 had three, 2 had four, and 3 had five. The subjects' characteristics are shown in Table 1. Familial aggregation was tested with the general linear-models program of the Statistical Analysis System (SAS, Cary, N.C.). Each person in a family was assigned the same value of an indicator (class) variable to denote family membership, as previously described in detail. The statistical significance of the familial effect was determined by comparing the variance among families with that within families. The similarity in values for 24-hour energy expenditure among siblings was expressed by the intraclass correlation coefficient, which is the proportion of the variance in an observation, after adjustment for covariates, that occurs among groups — in this study, different families.

Metabolic Rate at Rest as a Predictor of Weight Gain

The second analysis was designed to determine whether the metabolic rate at rest, adjusted for fat-free body mass, fat mass, age, and sex, predicted subsequent weight gain in 126 subjects in whom the metabolic rate and body composition were measured at least twice (Table 1). For each subject, the adjusted metabolic rate at rest (in kilocalories per day) before and after changes in weight was calculated as (the group mean metabolic rate at rest) + (measured metabolic rate at rest) - (predicted metabolic rate at rest), where the group mean metabolic rate at rest is the mean absolute measured rate (in kilocalories per day), the measured metabolic rate at rest is the rate (in kilocalories per day) measured in each subject, and the predicted metabolic rate at rest is the calculated rate (in kilocalories per day) obtained by using the individual fat-free body mass, fat mass, age, and sex in the linear regression equation generated from the initial examinations of the 126 subjects.

The effect of the adjusted metabolic rate at rest on the initial examination on subsequent weight gain (arbitrarily defined as a weight gain of more than 10 kg) was examined with Kaplan–Meier survival analysis in three groups of subjects defined according to tertiles of initial adjusted metabolic rate at rest (Fig. 1). The effect of the metabolic rate on weight gain was also quantified with use of the repeated measurements of body composition and metabolic rate at rest. In this analysis, the unit of observation was the interexamination interval, of which there were 267 among the 126 subjects. The metabolic rate at rest at the beginning of each interval was related to the rate of change in weight (in kilograms per year) until the next examination. One examination of one subject was deleted from our analysis, since it represented an extreme outlier, with a weight gain of more than 5 SD from the mean rate for all intervals.

24-Hour Energy Expenditure as a Predictor of Weight Gain

The third analysis was designed to determine whether the rate of 24-hour energy expenditure, adjusted for fat-free body mass, fat mass, age, and sex, as described above for metabolic rate at rest, predicted a subsequent gain in body weight. We used data from 95 subjects in whom body-composition studies were repeated at least three months after they had been studied in the respiratory chamber (Table 1). In contrast to our analysis of the longitudinal data on metabolic rate at rest, we used only an initial measure of 24-hour energy expenditure in this analysis, but it was related to repeated measurements of body weight. The rate of change in body weight was calculated from the highest measured subsequent weight and correlated with the adjusted 24-hour energy expenditure. Weight gain was also analyzed by survival analysis — i.e., in terms of the time until "failure," defined as the first occurrence of a weight gain of at least 7.5 kg after the initial examination — with use of the proportional-hazards linear model (this model was not used in the analysis of metabolic rate at rest because of the lack of proportionality of hazard rates over time). A smaller weight gain was used in this analysis (as compared with the 10 kg used in the analysis of the metabolic rate at rest) because of the shorter follow-up period after the measurement of 24-hour energy expenditure. Tests for the adequacy of the model (described by Harrell) indicated that the hazard rates for low and high initial energy expenditure were approximately proportional at all follow-up times.

In addition to testing the effects of the initial 24-hour energy expenditure on weight gain, we tested the effects of sex, age, and fat-free body mass at base line and the inter-

Table 1. Physical Characteristics of Subjects in Three Studies.

<table>
<thead>
<tr>
<th>Factor Studied</th>
<th>FAMILIAL AGGREGATION OF VALUES FOR 24-HR ENERGY EXPENDITURE</th>
<th>FAMILIAL AGGREGATION OF VALUES FOR 24-HR ENERGY EXPENDITURE</th>
<th>FAMILIAL AGGREGATION OF VALUES FOR 24-HR ENERGY EXPENDITURE</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of subjects (M/F)</td>
<td>52/42</td>
<td>60/66</td>
<td>53/42</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>26±5 (18–38)</td>
<td>26±5 (18–41)</td>
<td>27±6 (18–49)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>165±7 (148–182)</td>
<td>165±8 (148–185)</td>
<td>166±7 (148–185)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>92±23.3 (49.0–178.1)</td>
<td>98±19.6 (70.5–164.6)</td>
<td>97±25.1 (53.1–178.1)</td>
</tr>
<tr>
<td>Body fat (%)</td>
<td>22±9 (9–47)</td>
<td>36±7 (16–51)</td>
<td>33±9 (7–47)</td>
</tr>
<tr>
<td>Fat-free mass (kg)</td>
<td>61±11.7 (36.8–96.2)</td>
<td>62±11.3 (41.0–95.3)</td>
<td>63±12.8 (40.3–105.9)</td>
</tr>
<tr>
<td>Fat mass (kg)</td>
<td>31±4.6 (16.4–81.9)</td>
<td>35±12.2 (13.4–78.3)</td>
<td>33±15.3 (3.9–81.9)</td>
</tr>
</tbody>
</table>

*Fifty subjects in this study are also included in the study of the metabolic rate.
actions of all these variables with one another and with the initial energy expenditure. Since none of the interactions were significant or substantially changed the estimated effects of the initial 24-hour energy expenditure, the model was reduced to one containing only the main effects of the variables.

RESULTS

Familial Effect on 24-Hour Energy Expenditure

The values for 24-hour energy expenditure, adjusted for body composition, age, and sex, aggregated in families. In the linear model in which 24-hour energy expenditure was a function of family membership, such membership was a significant determinant of 24-hour energy expenditure (P<0.001), and the intraclass correlation coefficient for the familial effect was 0.48. To determine whether the familial effect on 24-hour energy expenditure was independent of the familial effect on body size, age, and sex, a linear model was used that included family membership, fat-free body mass, fat mass, age, and sex. Family membership was a significant determinant of 24-hour energy expenditure (P<0.02; Fig. 2), and the intraclass correlation coefficient for the familial effect was 0.26.

Metabolic Rate at Rest as a Predictor of Weight Gain

In the follow-up study of metabolic rate at rest (126 subjects), a linear regression analysis indicated that 76 percent of the variance in that rate was explained by differences in fat-free body mass (metabolic rate at rest [in kilocalories per day] = 525 + 19.6 fat-free mass [in kilograms]; r² = 0.76, P<0.001). When the covariates fat mass, age, and sex were also taken into account, another 5 percent of the variance in the metabolic rate at rest was explained. However, even after adjustment for differences in these covariates, the metabolic rate was still quite variable, ranging from 1453 to 2059 kcal per day (mean ± SD, 1756±109, or from 301 kcal per day below to 303 kcal per day above the expected rate).

The cumulative incidence of a 10-kg gain in body weight for the three tertiles of adjusted metabolic rate at rest is shown in Figure 1; the subjects with the lowest adjusted rates had the highest incidence of weight gain. In addition, there was a weak correlation between the adjusted metabolic rate at rest at the first visit and the change in body weight (r = -0.19, P<0.04) or the rate of change in body weight (r = -0.15, P<0.11) from the initial weight to the highest weight during follow-up. When the unit of observation was the interexamination interval, the adjusted metabolic rate at rest at the beginning of each interval correlated significantly with the subsequent weight change (267 observations among 126 subjects; r = -0.12, P<0.05). When these 267 observations were stratified into tertiles according to the adjusted metabolic rate at rest, the mean rates of weight change and the percentage of subjects who gained weight were significantly related to the metabolic rate at rest; the change in weight ranged from a gain of 2.75 kg per year in the lowest tertile to a loss of 0.07 kg per year in the highest tertile (Table 2).

When the subjects were divided into two groups — 15 subjects who gained more than 10 kg and 111 who did not — despite similar initial mean physical characteristics, the initial adjusted metabolic rate at rest was lower in those who gained weight (1694±103 as compared with 1764±109 kcal per day, P<0.02; Table 3). After a follow-up of 21±7 months and an increase in body weight of 15.7±5.7 kg (an increase in fat mass of 9.8±5.1 kg) in the subjects who gained weight, the adjusted metabolic rate at rest increased to 1813±134 kcal per day, a value similar to that for the mean metabolic rate at rest in the subjects who did not gain weight (1795±151 kcal per day; Table 3 and Fig. 3).

24-Hour Energy Expenditure as a Predictor of Weight Gain

In the 95 subjects who were studied in the respiratory chamber, 87 percent of the variance in 24-hour energy expenditure was explained by differences in fat-free body mass, fat mass, age, and sex. The adjusted 24-hour energy expenditure ranged from 1930 to

Table 2. Weight Gain Stratified According to Adjusted Metabolic Rate at Rest at the Beginning of Each Interval between Examinations.*

<table>
<thead>
<tr>
<th>TERTILE OF ADJUSTED METABOLIC RATE AT REST</th>
<th>P VALUE†</th>
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</thead>
<tbody>
<tr>
<td>LOWEST</td>
<td>MIDDLE</td>
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<tr>
<td>Mean weight change (kg/yr)</td>
<td>2.75</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>% of subjects</th>
<th>2.0</th>
<th>3.0</th>
<th>4.0</th>
<th>5.0</th>
<th>7.5</th>
<th>10.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight gain (kg/yr)</td>
<td>49</td>
<td>44</td>
<td>38</td>
<td>36</td>
<td>22</td>
<td>9</td>
</tr>
<tr>
<td>41</td>
<td>34</td>
<td>22</td>
<td>17</td>
<td>7</td>
<td>2</td>
<td></td>
</tr>
</tbody>
</table>

*There were 267 interexamination intervals among 126 subjects.
†Determined by analysis of variance for weight change and by chi-square test for linear trend for the different proportions of persons who gained weight.
<table>
<thead>
<tr>
<th>SUBJECTS WHO</th>
<th>No. of subjects (M/F)</th>
<th>SUBJECTS WHO</th>
<th>GAINED &gt;10 kg</th>
<th>DID NOT GAIN WEIGHT</th>
<th>P VALUE*</th>
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<tbody>
<tr>
<td>Initial study</td>
<td>9/6</td>
<td>51/60</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (yr)</td>
<td>25±6</td>
<td>26±5</td>
<td>NS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Height (cm)</td>
<td>167±8</td>
<td>164±8</td>
<td>NS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>104±17.9</td>
<td>97.8±19.8</td>
<td>NS</td>
<td></td>
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<tr>
<td>Body fat (%)</td>
<td>35±6</td>
<td>36±8</td>
<td>NS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metabolic rate at rest</td>
<td>1694±103</td>
<td>1764±109</td>
<td>&lt;0.03</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**At follow-up visit‡**

- Weight gain (kg) 15.7±5.7 0.1±5.6 —
- Fat-free mass increase (kg) 5.9±4.0 1.2±4.1 —
- Fat mass increase (kg) 9.8±5.1 −1.0±5.2 —
- Interval since initial study (mo) 21.7 38±6 —
- Metabolic rate at rest (kcal/day) 1813±134 1795±131 NS

*NS denotes not significant.
†Adjusted for fat-free mass, fat mass, age, and sex.
‡First follow-up visit when weight gain was >10 kg in subjects who gained weight and last visit in subjects who did not gain weight. Weight change, fat-free mass, and fat mass are different in the two groups of subjects by experimental design.

2625 kcal per day (mean, 2335±146) and correlated with the change in body weight (r = −0.33, P<0.001) and with the rate of change in body weight (r = −0.39, P<0.001; Fig. 4). A proportional-hazards model was used to predict the probability of gaining at least 7.5 kg, as a function of the interval since the initial measurement. This weight gain occurred in 15 of the 95 subjects who were followed for 3 to 23 months. In this model, which contained both covariates and fat-free body mass, fat mass, age, and sex, the adjusted 24-hour energy expenditure was a significant predictor of weight gain (P<0.02). According to the model, a person with a low adjusted 24-hour energy expenditure (200 kcal per day below the mean) had a 59 percent probability of gaining more than 7.5 kg in 21 months — a value more than four times the 13 percent probability of weight gain in a person with a high adjusted 24-hour energy expenditure (200 kcal per day above the mean). Similar results were obtained with models using weight gains of 5.0, 10.0, or 12.5 kg as the end points (data not shown). The 15 subjects who gained more than 7.5 kg had lower adjusted values for 24-hour energy expenditure than the 80 who did not (2262±194 as compared with 2349±133 kcal per day, P = 0.12 by t-test with unequal variance), even though age and initial body composition were similar in the two groups.

**DISCUSSION**

Obesity is a familial disorder that is probably partly determined genetically.1-3 Many investigators who have studied the different components of energy expenditure in lean and obese persons have suggested that in the absence of a clear defect in energy expenditure in obese subjects, obesity is the result of excessive energy intake.11,12,25 However, only prospective stud-

![Figure 3. Deviation from Predicted Metabolic Rate at Rest (RMR), Adjusted for Fat-Free Body Mass, Fat Mass, Age, and Sex, in 15 Subjects Whose Body Weight Increased by More Than 10 Kg between the Initial and a Subsequent Measurement.](image-url)

The thick lines represent the mean (±SD) change in metabolic rate at rest (P<0.01) between the initial visit and the visit at which the body weight had increased by more than 10 kg. The broken line represents the mean change in the remaining 111 subjects (P not significant). The mean initial adjusted metabolic rate at rest was lower in those who gained weight than in those who did not (P<0.02).
per day, a deficit that would increase the risk of gaining 7.5 kg over 21 months by four or five times.

Energy expenditure at rest and over a period of 24 hours are both known to vary considerably from person to person and are directly related to body size.10,13 However, even after adjustment for differences in body size and composition, age, and sex, the variability in energy expenditure is larger than can be accounted for by methodologic errors or day-by-day intraindividual biologic variations.10,13 This implies that subjects with similar physical characteristics can require more or less energy to maintain their body weights and can therefore be more or less "energy efficient." Selective breeding of rodents,28 cattle,29 and pigs30 has produced breeds with different "efficiencies" in energy use during growth and with different energy requirements for maintenance of their adult weights. Thus, there is reason to believe that there may be similar differences among humans and to hypothesize that people with lower rates of energy expenditure have a higher risk of weight gain.

In these longitudinal studies, we showed that a low rate of energy expenditure at rest or over a period of 24 hours is a predictor of a marked gain in body weight in a population prone to obesity.17 Two important studies have previously suggested that persons who gain weight may have enhanced metabolic efficiency.31,32 Leibel and Hirsch showed that formerly obese subjects needed 24 percent fewer calo-

ries per unit of body-surface area to maintain their new weights than control subjects.31 More recently, Geissler et al. observed that 16 formerly obese subjects had 24-hour metabolic rates that were about 15 percent lower than those of 16 matched lean controls.32 Other studies have also demonstrated the effect of differences in energy expenditure on body weight. Higher rates of weight loss are found in people with higher metabolic rates at rest.33 In addition, a 10 percent increase in 24-hour energy expenditure from smoking 20 cigarettes a day34,35 can at least partly account for the difference in body weight observed between smokers and nonsmokers,36 whether or not food intake is influenced by smoking.

It is interesting to estimate how much of the increase in body energy stores in the persons who gained weight may be attributable to their deficit in energy expenditure. If one assumes an energy cost of 2 kcal per gram of lean tissue deposition and 12 kcal per gram of fat deposition,17-39 the positive energy balance necessary to deposit 15.7 kg (9.8 kg of fat and 5.9 kg of fat-free mass) would amount to ~129,000 kcal. The mean adjusted metabolic rate at rest in the 15 subjects who gained weight was 71 kcal per day lower than that in those who did not. This would amount to 44,000 kcal over 622 days (the mean duration of follow-up for a weight gain of >10 kg) and thus represent 34 percent of the energy imbalance. Similar calculations show that only 40 percent of the increase in body energy stores can be accounted for by the 87-kcal deficit in daily energy expenditure observed in the 15 subjects who gained weight. These calculations, which are of course only gross estimates, and the fact that not all the subjects with low rates of energy expenditure gained weight, suggest that not all the increase in body energy stores is attributable to a deficit in energy expenditure. Other important factors, such as caloric intake and the energy cost of physical activity in persons following their normal routine, have an important role in the regulation of body weight.

After the weight gain, the new adjusted metabolic rate at rest in the 15 subjects who gained weight was similar to that measured in the subjects who did not. Therefore, weight gain may be a compensatory mechanism that results in an increased rate of energy expenditure; this can occur through such mechanisms as increased sympathetic nervous system activity, increased rates of protein turnover, gluconeogenesis, substrate cycling, ion pumping, and so forth. Furthermore, because of the increased workload associated with a gain in weight, the energy cost of physical activity also increases in proportion to weight gain, as long as there is no change in the pattern of physical activity. This increase in energy expenditure will ultimately match the energy intake.

The hypothesis that obesity results from overeating is difficult to test because of the lack of good methods for assessing energy intake. Most studies of food intake show that obese subjects do not eat more than nonobese subjects.46 On the other hand, most studies
investigating the different components of energy expenditure have failed to find a defect in obese subjects. This has led Garrow to conclude that “it is difficult to accept the hypothesis that the primary problem might be a greater than normal metabolic efficiency.” It is difficult to select subjects for studies of weight gain, because it is difficult to know who will gain weight. By making longitudinal measurements in a population with a high prevalence of obesity, we have demonstrated the importance of energy expenditure with respect to the magnitude of changes in body weight. In a recent study in subjects who had been adopted, Stunkard et al. showed that genetic influences play an important part in human fattiness. We have also observed a familial effect on energy expenditure at rest and over a 24-hour period. Considered together, the data suggest that a reduced rate of energy expenditure may contribute to the familial aggregation of human obesity.

We are indebted to Ms. Carol Lamkin and the nursing staff of the Clinical Research Unit, to the dietary staff, to Susan Elson for help in the preparation of the manuscript, to Dr. Peter Bennett for his continued support and advice, to Dr. Hannele Yki-Jarvinen and Thomas E. Anderson for their help in conducting these studies, and to all the residents and leaders of the Gila River Indian Community who made this study possible.

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