1. a. Full Title: Diet instability among individuals with diabetes in the Atherosclerosis Risk in Communities (ARIC) Study

b. Abbreviated Title: Diet Instability in Diabetics

2. Writing Group:
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3. Timeline: Analyses planned to be completed by August 2000

4. Rationale:
   There is a need to understand relationships between diet and diabetic complications among persons with diabetes, the numbers of which increase as the population ages. Individuals with diabetes suffer from microvascular complications, such as nephropathy and retinopathy, in addition to chronic macrovascular disease and neuropathy. Few nutritional epidemiological studies exist investigating the role of diet in preventing diabetic complications.

   In past studies of diet and disease, persons with diabetes have been removed from analyses (1,2,3). Since dietary modification is essential in achieving blood glucose control, diets among persons with diabetes may not be stable over long periods of time (4). Additionally, individuals with diabetes may not have as consistent a dietary intake over time due to the American Diabetes Association’s (ADA) ever-changing dietary recommendations and their approach of individualized Medical Nutrition Therapy (4). Persons with diabetes suffer from many complications: heart disease, stroke, high blood pressure, blindness, kidney disease, nervous system disease, amputations, dental disease, and complications of pregnancy (5). Therefore, individuals with diabetes could likely have additional complications other than the disease of interest being studied. As a result, these additional complications and the potential for dietary change can make analyses complicated. Unfortunately, the exclusion of persons with diabetes from studies prevents further investigation of relationships between diet and disease among these individuals.
Dietary Instability:
Instability of dietary intake as measured over time, could be due to a number of different reasons; increased random error, conscious dietary change, or unconscious dietary change. If persons with diabetics truly have less stable dietary intakes over time, one must investigate alternative methods for better analyzing diet and disease relationships among persons with diabetes. For example, one could identify persons with diabetes who have unstable diets and exclude them from analyses. We assume that the measurement of an unstable diet is mostly due to a change in dietary intake over time rather than random error. Therefore, not excluding these identified dietary changers could bias the diet and disease relationships being measured, especially if the dietary change was made after the measurement of diet. Exclusion of diabetic changers from analyses could occur without eliminating all persons with diabetes from the analyses. Then, the relationships of diet and disease among persons with diabetes could be analyzed with more clarity.

Some studies have shown that individuals are likely to change their diets after diagnosis with diabetes. Niewind et al. showed that 84 newly diagnosed individuals with insulin dependent diabetes mellitus (IDDM) were more likely to change their diets to reduce high sugar and fat containing foods, while incorporating low fat foods into their meals (6). In a study comparing the diets of women with and without diabetes, both groups of women consumed similar diets in 1980, when neither group had diabetes. By 1984, the women diagnosed with noninsulin dependent diabetes mellitus (NIDDM) were more likely to consume lower intakes of sucrose and higher intakes of fat and protein. The diagnosis of diabetes may have cause the observed dietary changes (7).

The severity of diabetes or its complications could be systematically related to dietary change. For example, individuals with diabetic complications might be more likely to increase their carbohydrate intake. Awareness of this potential bias, when studying relationships between diet and diabetic complications could aid in the development of analytical steps to remove the bias. Decision making processes based on when to best measure dietary intake in diabetics could be based on the probability and type of dietary change among diabetics.

5. Main Hypotheses/Study Questions:
Hypothesis 1:
Diets of persons with diabetes are less stable over time compared to persons without diabetes.

Persons with Type 2 diabetes in the Atherosclerosis Risk in Communities Study (ARIC), who reported estimates of diet at Visit 1 (1987-89) and Visit 3 (1993-95) will be analyzed. Individuals with diabetes are hypothesized to have lower correlations of dietary estimates, comparing reported intake at Visit 1 to Visit 3, than persons without diabetes. The dietary estimates of intake at Visits 1 and 3 were assessed by the Willett food frequency questionnaire.

The following nutrients and foods will be investigated. These nutrients and foods are hypothesized to promote or be protective against the development of diabetic complications (refer to the Relation of Diet to Diabetic Retinopathy manuscript proposal, Mares-Perlman 1998).
Hypothesis 2:
Diet change among persons with Type 2 diabetes is systematically related to diabetic retinopathy. Dietary change is systematically associated with the severity of diabetes and its complications.

These characteristics of persons with diabetes may be related to diet change, an increase or a decrease in specific nutrient estimate intakes between Visits 1 and 3.

Age
Race
Sex
Treatment - diet, oral hypoglycemic pills, insulin use
Duration of diabetes
Body mass index (BMI)
Hypertension
Retinopathy
Cataract
Cardiovascular disease (CVD)
Nephropathy

Individuals with diabetes will be identified to have stable or unstable diets for particular nutrients. An individual will be considered to have an unstable diet for a particular nutrient if the difference between their dietary intake estimate of the nutrient at Visit 3 (1993-95) and Visit 1 (1987-1989) is 20% greater or less than the group median estimate of the nutrient at Visit 1. Comparisons of persons with unstable diets/diet changers to nonchangers, by the above characteristics, will be conducted.

Preliminary data:
Preliminary data suggests, after adjustment for age, sex, and race, that it is more common for people with, compared to without retinopathy, to have estimates at Visit 3 vs. Visit 1 than were higher for carbohydrate (%energy) (29 vs. 22%, p= 0.09), lower for fat (%energy) (31 vs. 23%, p=0.08) and lower for fiber (g/1000kcals) (28 vs. 19, p=0.005). The change in dietary intake between Visits 1 and 3 may have been caused by knowledge of incident retinopathy between Visits 1 and 3. This, of course, cannot be verified since incident retinopathy cases between Visits 1 and 3 were not recorded.
6. Data:

Population:
There are approximately 15,800 individuals who participated in the ARIC baseline study. Of these, 15,428 gave self-reported diet data at Visit 1. Only 10,268 of the 15,428 also provided dietary data at Visit 3. Of the remaining, 1,936 people were missing dietary or ocular data and 19 persons were excluded because they had Type 1 diabetics. The final sample included 850 persons with Type 2 diabetics and 9,418 persons without diabetes.

Diagnosis of Type 2 diabetes at Visit 1 (1987-89):
A participant was considered to have diabetes at Visit 1 if they met the following criteria:
(1) A participant’s fasting glucose was $\geq 126$ mg/dL or their nonfasting glucose was $\geq 200$ mg/dL
(2) And/or they had a self-reported medical history of diabetes (i.e. stated they had diabetes/sugar in the blood, or used medications in the last two weeks for diabetes or high blood sugar).

Retinal data from Visit 3 (1993-95):
Level of diabetic retinopathy
Number of microaneurisms
Number and type of retinal hemorrhage
Presence of Hemorrhages or microaneurisms
Presence of hard or soft exudates, macular edema, intraretinal microvascular abnormalities (IRMA), venous beading
Self-reported question:
1. Eye problems from diabetes?

Cataract data from Visit 3:
Self-reported question asked as to whether participant had or did not have cataracts.
1. Dr. said you had cataracts?
2. Had surgery on eyes for cataracts?

Cardiovascular Disease:
The incidence of CVD between Visits 1 and 3 will be used. CVD variable determined by the following: A positive history of intermittent claudication, angina, or myocardial infarction (MI) by the Rose questionnaire, a physician’s diagnosis of MI, a Q-wave on the electrocardiogram (ECG), a coronary revascularization, or a positive response the question Has a doctor ever told you that you had a stroke? (8).

Nephropathy:
Renal dysfunction will be determined by serum creatinine levels provided at Visits 1, 2, and 4. A change in serum creatinine of 0.4 mg/dL (after excluding people with baseline serum creatinine >1.5 mg/dL) will define incident early renal disease, as used previously in this population (9).

Dietary Data:
Estimates of dietary intake were assessed at Visit 1 (1987-89) and Visit 3 (1993-95) from self-report using the Willett food frequency questionnaire and updated databases. The total nutrient intake (dietary intake plus supplement intake) of vitamins C, E, the mineral magnesium, and beta-carotene were extrapolated using the reported Visit 3 supplement data estimates of supplement use, type, duration and dose (see ARIC Supplement Project Documentation). The following nutrients and foods will be analyzed.

- Energy (kcals)
- Dietary fiber (g/1000 kcals)
- Carbohydrate (% kcal)
- Dietary Vitamin C (mg/1000 kcals)
- Protein (% kcal)
- Total (diet + supplements) Vitamin C (mg/1000 kcals)
- Total fat (% kcal)
- Dietary Vitamin E (IU/1000 kcals)
- Saturated fat (% kcal)
- Total Vitamin E (IU/1000 kcals)
- Monounsaturated fat (% kcals)
- Dietary Magnesium (mg/1000 kcals)
- Polyunsaturated fat (% kcals)
- Total Magnesium (mg/1000 kcals)
- Fruits and Vegetables (servings/day)
- Grains, Cereals, and nuts (servings/day)

**Other Variables:**

Hypertension definition: - diagnosis of hypertension at Visit 1 will be used. An individual is considered hypertensive if their diastolic blood pressure _ 90 mm Hg and their systolic blood pressure is _ 140 mm Hg and or they are on anti-hypertensive pills.

Duration of diabetes will be calculated by subtracting the reported age at diagnosis from the age at Visit 1.

Persons determined to be diabetic as described above, but diagnosed at Visit 1, will be assigned their age at Visit as their age at diagnosis.

The reported Visit 1 variables for Body Mass Index (BMI) in kg/m2 as well as sex, age and race will be used.

7. **Statistical Analyses and Power Calculations:**

Individuals with diabetes will be considered to have unstable diets for a particular nutrient if their estimates of dietary intake at Visit 3 (1993-95) are 20% greater or less than the median estimate of that nutrient at Visit 1 (1987-89).

Correlation coefficients will be calculated between nutrient estimates at Visit 1 and Visit 3. Preliminary data suggest lower consistency in diets of persons with diabetes. We can detect a significant difference (at a 95% confidence interval) between dietary intake of carbohydrate, and total fat between persons with and without diabetes (Table 1). Race and sex did not confound these relationships.
Table 1:

<table>
<thead>
<tr>
<th></th>
<th>Diabetic (n=850)</th>
<th>Nondiabetic (n=9,418)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total energy (kcals)</td>
<td>0.51</td>
<td>0.56</td>
</tr>
<tr>
<td></td>
<td>(0.46,0.56)</td>
<td>(0.55,0.57)</td>
</tr>
<tr>
<td>Carbohydrate (%kcals)</td>
<td>0.36*</td>
<td>0.44</td>
</tr>
<tr>
<td></td>
<td>(0.30,0.42)</td>
<td>(0.42,0.46)</td>
</tr>
<tr>
<td>Protein (% kcals)</td>
<td>0.40</td>
<td>0.45</td>
</tr>
<tr>
<td></td>
<td>(0.34,0.42)</td>
<td>(0.43,0.47)</td>
</tr>
<tr>
<td>Total fat (%kcals)</td>
<td>0.36*</td>
<td>0.44</td>
</tr>
<tr>
<td></td>
<td>(0.30,0.42)</td>
<td>(0.42,0.46)</td>
</tr>
</tbody>
</table>

*Significantly different Spearman correlation coefficients.

Chi-square tests adjusted for age, race, and sex will be calculated to compare the percent of individuals who fall into each category of dietary stability, for a specific nutrient estimate, by the particular characteristic of interest (treatment type, duration, BMI, hypertension, retinopathy, cataract, CVD, neuropathy). This will enable us to detect whether possible systematic error, by category of dietary stability and different characteristics of individuals with diabetes exists.

We hypothesize that the individuals who change their diets are more likely to have more severe diabetes and/or diabetic complications. For example, say we hypothesize the following:

**Null Hypothesis:** The proportion of persons who increase their carbohydrate intake among diabetics with retinopathy is equal to the proportion of persons who increase their carbohydrate intake among diabetics without retinopathy.

**Alternative Hypothesis:** The proportions of people who decrease their intake of carbohydrate are not identical in the two populations.
Table 2: Sample Size Calculations Using a 5% Significance Level (two-sided) and an 80 or 90% Power

<table>
<thead>
<tr>
<th>% of individuals whose intake of carbohydrate at Visits 3 &gt; Visit 1</th>
<th>% of individuals whose intake of carbohydrate at Visits 3 &gt; Visit 1</th>
<th>% Increase</th>
<th>Sample / Group Power = 0.80</th>
<th>0.90</th>
</tr>
</thead>
<tbody>
<tr>
<td>Among individuals without retinopathy</td>
<td>Among individuals with retinopathy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.10</td>
<td>0.20</td>
<td>100%</td>
<td>201</td>
<td>268</td>
</tr>
<tr>
<td>0.25</td>
<td>150%</td>
<td>101</td>
<td>135</td>
<td></td>
</tr>
<tr>
<td>0.20</td>
<td>0.35</td>
<td>75%</td>
<td>139</td>
<td>186</td>
</tr>
<tr>
<td>0.38</td>
<td>90%</td>
<td>100</td>
<td>134</td>
<td></td>
</tr>
<tr>
<td>0.40</td>
<td>100%</td>
<td>83</td>
<td>110</td>
<td></td>
</tr>
<tr>
<td>0.30</td>
<td>0.45</td>
<td>50%</td>
<td>164</td>
<td>219</td>
</tr>
<tr>
<td>0.48</td>
<td>60%</td>
<td>116</td>
<td>154</td>
<td></td>
</tr>
<tr>
<td>0.50</td>
<td>67%</td>
<td>94</td>
<td>126</td>
<td></td>
</tr>
<tr>
<td>0.40</td>
<td>0.55</td>
<td>38%</td>
<td>174</td>
<td>233</td>
</tr>
<tr>
<td>0.58</td>
<td>45%</td>
<td>121</td>
<td>162</td>
<td></td>
</tr>
<tr>
<td>0.60</td>
<td>50%</td>
<td>98</td>
<td>131</td>
<td></td>
</tr>
</tbody>
</table>

We hypothesize that the percent of persons without retinopathy who increase their intake of carbohydrate to be 40%. If we wish to detect a difference of 50%, with 80% power, between persons without retinopathy who increase their intake of carbohydrate and persons with retinopathy who increase their intake of carbohydrate, we would need approximately 98 individuals in each group (Table 2). We have 850 individuals with diabetes. Preliminary studies show that there are 549 participants who do not have retinopathy among participants who either increase their carbohydrate intake or do not change their intake of carbohydrate between Visits 1 and 3. There are 199 participants who do have retinopathy. We believe our study to be large enough to find differences between diet stability categories and the severity of diabetes and/or its complications if they do exist.

8.a. Will the data be used for non-CVD analysis in this manuscript? __X___Yes
_____No

b. If Yes, is the author aware that the file ICTDER01 must be used to exclude persons with a value RES_OTH = ACVD Research@ for non-DNA analysis, and for DNA analysis RES_DNA = ACVD Research@ would be use? __X___Yes
9.a. Will the DNA data be used in this manuscript? ______Yes __X__No

b. If yes, is the author aware that either DNA data distributed by the Coordinating Center must be used, or the file ICTDER01 must be used to exclude those with value RES_DNA = No use/storage DNA?
_______Yes ________No

References: