Adherence to the Mediterranean dietary pattern is positively associated with plasma adiponectin concentrations in diabetic women

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ABSTRACT
Background: Although the typical diet of the Mediterranean region has received much recognition over the past several years for its association with substantial health benefits, it remains unknown whether its favorable effects are mediated through changes in adiponectin concentrations.

Objective: The objective was to determine whether adherence to a Mediterranean-type diet is associated with higher plasma adiponectin concentrations.

Design: This study was a prospective and cross-sectional evaluation of plasma adiponectin concentrations and dietary data from 987 diabetic women from the Nurses’ Health Study who had no history of cardiovascular disease at the time blood was drawn in 1990.

Results: Women who scored highest on a 9-point scale that measures adherence to a Mediterranean-type dietary pattern tended to be older, were less likely to be current smokers, had lower body mass indexes and waist circumferences, and had higher total energy intakes, physical activities, and plasma adiponectin concentrations than did women with the lowest scores. Median plasma adiponectin concentrations were 23% higher in women who most closely followed a Mediterranean-type diet than in low adherers after adjustment for age and energy intake ($P < 0.01$). Body composition, lifestyle, and medical history explained some, but not all, of the observed association between diet and adiponectin concentrations because high adherers tended to have greater adiponectin concentrations than did moderate or low adherers, even after adjustment for these variables.

Conclusions: Our data suggest that, of the several components of the Mediterranean dietary pattern score, alcohol, nuts, and whole grains show the strongest association with adiponectin concentrations. Close adherence to a Mediterranean-type diet is associated with higher adiponectin concentrations. Am J Clin Nutr 2006;84:328–35.

KEY WORDS Mediterranean diet, adiponectin, cardiovascular disease risk

INTRODUCTION
Adiponectin, an adipose tissue–secreted cytokine, has been shown to improve insulin sensitivity, to regulate glucose and lipid metabolism, and to have pronounced antiatherosclerotic effects (1–4). It has also been associated with the favorable profile of lower fasting glucose, triacylglycerol, and total and LDL cholesterol concentrations and higher HDL-cholesterol concentrations (5, 6). Plasma adiponectin concentrations have been shown to be independently negatively correlated with the prevalence of coronary artery disease in men (7), and prospective studies of both men and women have shown an inverse relation between adiponectin and progression of coronary artery calcification (8) and with the risk of diabetes mellitus (9). Similarly, prospective studies have also shown that lower plasma adiponectin concentrations are associated with insulin resistance and cardiovascular disease (10, 11). Thus, because of the potential beneficial effect of adiponectin on cardiovascular- and endocrine-related disease, identification of modifiable predictors of adiponectin concentrations would be of major interest.

Long-term weight loss, caloric restriction, moderate alcohol intake, and a diet with a low glycemic load have been shown to be associated with higher adiponectin concentrations in men (12–14). Weight loss due to prolonged reductions in energy intake and increased physical activity were previously shown to increase adiponectin concentrations in women (15), but associations of dietary factors with adiponectin have not been thoroughly studied. Moreover, although the typical diet of the Mediterranean region has received much recognition over the past several years for its association with substantial health benefits, including decreased mortality and risk of cardiovascular disease...
We also used 2002 Institute of Medicine criteria (23) to predict predicted BMR less than the Goldberg cutoff for sedentary phys-
equation for women to predict the participants’ basal metabolic
exposure and to reduce within-person variability. Because self-
dietary measures as an average of values obtained from the 1980,
different, and women were asked how often over the
questionnaire, a commonly used unit or portion size was speci-
factors and health outcomes. Blood samples were ob-
tained from 32 826 study participants from 1989 to 1990. Of the
participants who returned their blood samples, 1188 women had
confirmed diagnosis of type 2 diabetes. Diagnosis of diabetes
was made and validated as previously reported (6). The current
analysis included 987 diabetic women with measures of plasma
adiponectin concentration and who were free of coronary heart
disease, myocardial infarction, coronary artery bypass grafting,
percutaneous transluminal coronary angioplasty, and stroke at
the time of the blood draw in 1990.

Assessment of dietary factors

Nutrient intakes in the NHS were assessed by using a semi-
quantitative food-frequency questionnaire (SFFQ). The validity
and reliability of the food-frequency questionnaires used in the
NHS were previously described (18–20). For each food in the
questionnaire, a commonly used unit or portion size was speci-
fied, and women were asked how often on average over the
previous year they had consumed that amount of each food. The
9 response categories ranged from “never” to “6 or more times
day.” Nutrient intake was computed by multiplying the fre-
quency response by the nutrient content of the specified portion
sizes. We used data from 1990 to examine the relation between
diet and adiponectin cross-sectionally. We also calculated di-
etary measures as an average of values obtained from the 1980,
1984, 1986, and 1990 SFFQs to account for long-term dietary
exposure and to reduce within-person variability. Because self-
reports of dietary intake tend to underestimate actual consump-
tion, and the extent of underreporting has been shown to correlate
directly with increasing BMI (21), we used the Harris-Benedict
equation for women to predict the participants’ basal metabolic
rate (BMR). We used the ratio of reported energy intake to
predicted BMR less than the Goldberg cutoff for sedentary phys-
ical activity level of 1.2 (22) to determine underreporter status.
We also used 2002 Institute of Medicine criteria (23) to predict
resting metabolic rate; a ratio of intake to resting metabolic rate
< 1.0 indicated underreporting.

Mediterranean dietary pattern scores were determined by us-
ing dietary data from the SFFQ on a 9-point scale (16). Previous
validation studies within the NHS cohort have reported strong
 correlations between nutrients assessed with the SFFQ and with
multiple weeks of food records completed over the previous year
(18, 20). Median intakes of food groups associated with a tradi-
tional Mediterranean diet were calculated, and the participants
received a point on the scale if they measured above the median
consumption for fish, fruit, legumes, nuts, ratio of polysaturated
saturated fat, vegetables, and whole grains. Because most
monounsaturated fats in the diet of the study population were
derived from animal sources, as opposed to from plant sources as
in a traditional Mediterranean diet, they were not included in the
ratio of unsaturated to saturated fat. They also received a point if
intake of red and processed meats was below the median value.
Finally, a point was added to the score if alcohol consumption
was between 5 and 15 g/d. Thus, Mediterranean dietary pattern
scores ranged from 0 to 9; higher scores indicated closer adher-
ence to a Mediterranean-type diet.

Assessment of plasma adiponectin concentrations

Blood samples were collected in 1989 or 1990. Participants
were sent a blood set kit that included supplies (blood tubes,
tourniquet, needles, bandage, coolant pack), and instructions.
The participants arranged for their blood to be drawn and then
sent the samples back by prepaid overnight courier. Most sam-
plies arrived within 24 h of being collected. After arrival in the
laboratory, the samples were centrifuged (2500 × g, 20 min,
21 °C) and portioned into cryotubes as plasma, buffy coat, and
red blood cells. Cryotubes were stored in liquid-nitrogen freezers
at −130 °C or lower. Adiponectin was assayed with a radioimmu-
unoassay from Linco Research, St Charles, MO, which has a
sensitivity of 2 μg/mL and an intraassay CV of 1.78–6.21%, as
was previously described (24).

Assessment of covariates

Data on covariates were collected from NHS questionnaires.
Body mass index (BMI) was calculated from self-reported
weight (kg) in 1990 divided by height squared (m) measured in
1976. Reported measurements of waist and hip circumferences
were obtained in 1986 and used to calculate waist-to-hip ratio
(WHR). Central obesity has been cited as an important predictor
of insulin resistance (25, 26) and adiponectin (27), potentially
independent of BMI. Because of substantial nonignorable missing
data on waist and hip measures in our sample (39% missing,
n = 383 of 987 women), we used a previously used technique
(28) to estimate missing measures of waist circumference and
WHR from age and BMI. For those subjects with available waist
and hip data, this method produced predicted measures that cor-
related reasonably with actual waist circumference (r = 0.77)
and WHR (r = 0.33). Physical activity in metabolic equivalent
tasks (METs) per week was computed from 1986 data on the
duration and intensity of exercise performed (29). Smoking sta-
tus (defined as never, former, or current smoker), socioeconomic
variables, and status of self-reported hypertension, hypercholes-
terolemia, family history of diabetes (defined as the number of
diabetic first-degree relatives), and medication use were ob-
tained from the biennial questionnaires (6). Total, HDL, and
LDL cholesterol, triacylglycerols, and glycated hemoglobin A1c concentrations were determined by using the aforementioned assay techniques (21).

Statistical analyses

Comparisons of descriptive measures were conducted by using linear regression to test for trend across Mediterranean diet pattern score groups for continuous variables and appropriate chi-square tests for categorical variables. Reported correlations were calculated by using Spearman’s nonparametric analysis. Associations between a Mediterranean-type diet and plasma adiponectin concentration were evaluated by using simple linear regression models for crude analysis and multiple linear regression for adjusted analyses, with logarithmic transformation of plasma adiponectin concentration values to achieve normal distribution. Dietary variables were examined both cross-sectionally with the use of 1990 data (year of blood draw) and also prospectively as a cumulative average of nutrient data from 1980, 1984, 1986, and 1990. Participants were divided into groups of low (scores of 0 to 3), middle (4 to 5), and high (6 to 9) adherence to a Mediterranean-type eating pattern based on their diet scores for analysis. The association of a Mediterranean-type diet on log-transformed adiponectin was also examined continuously and in quintiles by using multiple linear regression models. We adjusted for potential confounders in multivariate analyses, and these included age, BMI, waist circumference, physical activity, smoking, hypertension status, hypercholesterolemia, triacylglycerol concentration, glycated hemoglobin A1c concentration, family history of diabetes, insulin and oral diabetic medication use, and fiber intake from cereal, fruit, and vegetable sources. Components used to determine the diet score, as well as macronutrient intake, were examined in quintiles by using multivariate regression models of log-transformed adiponectin by each component and tested for linear trends for all dietary variables except alcohol, for which a quadratic trend was tested. We also examined the interaction of diet score and several lifestyle factors (age, BMI, activity level, energy intake, and smoking status) for a differential effect on plasma adiponectin concentration. To determine whether underreporting may have influenced our results, we repeated the analyses after exclusion of underreporters (as defined above) and also included the ratio of reported energy intake to predicted BMR as a covariate in multivariate models. All analyses were conducted by using the SAS statistical package (version 8.2 for UNIX; SAS Institute, Cary, NC). The reported $P$ values are 2-sided.

RESULTS

The characteristics of the study population (diabetic women free of heart disease), by level of adherence to a pattern of eating consistent with the Mediterranean diet, are presented in Table 1. Women with the highest scores (values of 6 to 9) tended to be older; tended to have lower BMI, waist circumference, and triacylglycerols; tended to have higher total energy intake, physical activity levels, and HDL-cholesterol and plasma adiponectin concentrations; and were less likely to currently smoke than were the women who scored ≤3 points on the scale. There were no significant differences among the Mediterranean diet groups with respect to WHR, socioeconomic variables, hypertensive status, total and LDL cholesterol, glycated hemoglobin A1c, number of diabetic first-degree relatives, or use of reported medications. In Table 2, mean intakes of the individual components of the Mediterranean dietary pattern score are reported, as are fiber intakes from several sources. Compared with the low adherers, those with higher adherence to a Mediterranean-type diet consumed more alcohol, fish, fruit, legumes, nuts, vegetables, and whole grains; had a higher ratio of polyunsaturated to saturated fat; ate less red and processed meats; and had higher total, cereal, fruit, and vegetable fiber intakes. In correlational analyses, adiponectin concentration was significantly positively associated with age ($r = 0.08$, $P = 0.02$) and physical activity ($r = 0.12$, $P < 0.01$) and negatively correlated with BMI ($r = -0.31$, $P < 0.01$), waist circumference ($r = -0.37$, $P < 0.01$), and WHR ($r = -0.36$, $P < 0.01$). Adiponectin was also directly associated with the Mediterranean dietary pattern score ($r = 0.11$, $P < 0.01$), servings per day of fruit ($r = 0.08$, $P < 0.01$), and whole grains ($r = 0.14$, $P < 0.01$) and was marginally associated with servings per day of nuts ($r = 0.06$, $P = 0.07$).

We then examined plasma adiponectin according to low (diet scores of 0 to 3), middle (4 to 5), or high (6 to 9) adherence to a Mediterranean-style diet in the study population on the basis of data collected from 1980 to 1990. Increasing concentrations of plasma adiponectin were significantly associated with higher adherence to a Mediterranean-type diet in this population before and after adjustment for age and energy intake. As shown in Table 3, women with high adherence to a Mediterranean-type diet had concentrations of plasma adiponectin that were 23% higher than those with low adherence after control for age and energy intake; the difference was 1.4 µg/mL between the groups (6.9 compared with 5.5 µg/mL). High adherers had significantly higher adiponectin concentrations than did low or moderate adherers, even after further adjustment for BMI, waist circumference, activity level, and smoking status. Additional adjustment for hypertension status, HDL cholesterol, triacylglycerols, glycated hemoglobin A1c, family history of diabetes, and insulin and oral diabetic medication use indicated that anthropometric, lifestyle, and medical history explained some, but not all, of the observed increase in adiponectin concentrations in the high adherers (7.4 compared with 6.5 and 6.7 µg/mL). Modeled median adiponectin for high, middle, and low adherers, respectively). Additional adjustment for fiber intake from cereal, fruit, and vegetables did not alter the relation between adiponectin and diet score (data not shown).

The positive association between consumption of a Mediterranean-type diet and adiponectin concentration was also apparent when examined continuously and in quintiles (data not shown) rather than in low, middle, and high groupings. When we considered nutrient data from 1990 separately in a cross-sectional analysis, the obtained measures were consistent with reported results, although somewhat less precise because of greater random variation (data not shown). Overall, the participants’ diets showed consistency over follow-up, with a correlation coefficient ($r$) of 0.75 for the 1990 diet score with the cumulative average of scores from 1980 to 1990.

To elucidate the specific aspects of the Mediterranean diet that might influence the association with adiponectin, intakes of the individual food components of the diet score were divided into quintiles and studied in relation to median adiponectin. Of the 9 food categories used to determine the Mediterranean diet score, alcohol, fruit, nuts, and whole grains showed significant age- and energy-adjusted trends with plasma adiponectin concentration.
food categories. A point for consuming less than the median amount of red and processed meats and a point each for consuming more than the median amount of the other listed foods was given.

Adiponectin concentrations were higher in women who consumed 0.2–5.0 g alcohol/d (6.0 μg/mL) than in those who consumed <15 g/d (4.9–5.4 μg/mL); adiponectin concentrations were lowest in those who consumed 0.2–5.0 g alcohol/d. Women in the highest quintile of nut intake had adiponectin concentrations that were 12% higher than those in the lowest quintile, and women with the highest whole-grain consumption had median adiponectin concentrations that were 22% higher.

\( \text{PLASMA ADIPONECTIN AND THE MEDITERRANEAN DIET} \)

### Table 1: Baseline characteristics of diabetic women according to Mediterranean dietary pattern score

<table>
<thead>
<tr>
<th>Mediterranean dietary pattern score ( (n = 987) )</th>
<th>Total</th>
<th>0–3 ( (n = 335) )</th>
<th>4–5 ( (n = 491) )</th>
<th>6–9 ( (n = 165) )</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adiponectin (μg/mL)(^1)</td>
<td>5.57 (1.0–42)</td>
<td>5.17 (1.0–42)</td>
<td>5.42 (1.2–40)</td>
<td>6.52 (1.2–38)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Age (y) (</td>
<td>\text{SD}</td>
<td>)</td>
<td>58.8 ± 6.9</td>
<td>57.7 ± 6.9</td>
<td>59.1 ± 6.5</td>
</tr>
<tr>
<td>BMI (kg/m(^2))</td>
<td>30.0 ± 6.3</td>
<td>30.5 ± 6.8</td>
<td>29.8 ± 5.9</td>
<td>29.1 ± 6.0</td>
<td>0.05</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>90.5 ± 14.5</td>
<td>92.6 ± 15.7</td>
<td>90.4 ± 13.7</td>
<td>87.3 ± 14.4</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>WHR</td>
<td>0.84 ± 0.09</td>
<td>0.84 ± 0.09</td>
<td>0.84 ± 0.09</td>
<td>0.82 ± 0.10</td>
<td>0.15</td>
</tr>
<tr>
<td>Total energy intake (kcal)</td>
<td>1746 ± 451</td>
<td>1564 ± 399</td>
<td>1792 ± 444</td>
<td>1978 ± 431</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Physical activity (METs/wk)</td>
<td>11.7 ± 15.3</td>
<td>8.8 ± 12.6</td>
<td>12.3 ± 16.1</td>
<td>16.0 ± 17.0</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Smoking [n (%)]</td>
<td>None</td>
<td>447 (45)</td>
<td>164 (49)</td>
<td>204 (42)</td>
<td>79 (48)</td>
</tr>
<tr>
<td>Former</td>
<td>399 (40)</td>
<td>113 (34)</td>
<td>212 (43)</td>
<td>74 (45)</td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>140 (14)</td>
<td>58 (17)</td>
<td>72 (15)</td>
<td>10 (6)</td>
<td></td>
</tr>
<tr>
<td>Socioeconomic status</td>
<td>White race [n (%)]</td>
<td>722 (76)</td>
<td>236 (75)</td>
<td>359 (76)</td>
<td>127 (79)</td>
</tr>
<tr>
<td>Currently married [n (%)]</td>
<td>771 (78)</td>
<td>251 (79)</td>
<td>397 (84)</td>
<td>123 (79)</td>
<td>0.20</td>
</tr>
<tr>
<td>Education [n (%)]</td>
<td>Registered nurse</td>
<td>716 (76)</td>
<td>246 (78)</td>
<td>360 (76)</td>
<td>110 (71)</td>
</tr>
<tr>
<td>Bachelor’s degree</td>
<td>160 (17)</td>
<td>50 (16)</td>
<td>80 (17)</td>
<td>30 (19)</td>
<td></td>
</tr>
<tr>
<td>Graduate degree</td>
<td>69 (7)</td>
<td>20 (6)</td>
<td>34 (7)</td>
<td>15 (10)</td>
<td></td>
</tr>
<tr>
<td>Employment status [n (%)]</td>
<td>Full time</td>
<td>256 (27)</td>
<td>99 (31)</td>
<td>117 (25)</td>
<td>40 (26)</td>
</tr>
<tr>
<td>Part time</td>
<td>140 (15)</td>
<td>37 (12)</td>
<td>80 (17)</td>
<td>23 (15)</td>
<td></td>
</tr>
<tr>
<td>Retired</td>
<td>275 (29)</td>
<td>84 (27)</td>
<td>147 (31)</td>
<td>44 (29)</td>
<td></td>
</tr>
<tr>
<td>Homemaker</td>
<td>273 (29)</td>
<td>95 (30)</td>
<td>132 (28)</td>
<td>46 (30)</td>
<td></td>
</tr>
<tr>
<td>Medical history</td>
<td>Hypertension [n %]</td>
<td>410 (42)</td>
<td>138 (41)</td>
<td>203 (42)</td>
<td>69 (42)</td>
</tr>
<tr>
<td>Hypercholesterolemia [n %]</td>
<td>395 (40)</td>
<td>128 (38)</td>
<td>193 (40)</td>
<td>74 (45)</td>
<td>0.32</td>
</tr>
<tr>
<td>Total cholesterol (mg/dL)</td>
<td>226.7 ± 43.5</td>
<td>228.6 ± 45.9</td>
<td>226.1 ± 42.7</td>
<td>224.6 ± 41.2</td>
<td>0.59</td>
</tr>
<tr>
<td>HDL cholesterol (mg/dL)</td>
<td>51.0 ± 14.9</td>
<td>50.8 ± 14.3</td>
<td>50.4 ± 15.3</td>
<td>53.5 ± 14.7</td>
<td>0.03</td>
</tr>
<tr>
<td>LDL cholesterol (mg/dL)</td>
<td>138.8 ± 38.2</td>
<td>140.6 ± 38.5</td>
<td>137.6 ± 38.7</td>
<td>138.6 ± 35.7</td>
<td>0.61</td>
</tr>
<tr>
<td>Triacylglycerols (mg/dL)</td>
<td>207.4 ± 155.1</td>
<td>209.8 ± 176.9</td>
<td>213.7 ± 145.7</td>
<td>183.5 ± 131.6</td>
<td>0.04</td>
</tr>
<tr>
<td>Glycated hemoglobin (%)</td>
<td>6.9 (1.8)</td>
<td>6.9 (1.8)</td>
<td>6.9 ± 1.8</td>
<td>6.7 ± 1.7</td>
<td>0.40</td>
</tr>
<tr>
<td>Diabetic first-degree relative [n %]</td>
<td>None</td>
<td>483 (49)</td>
<td>176 (53)</td>
<td>220 (45)</td>
<td>87 (53)</td>
</tr>
<tr>
<td>1</td>
<td>341 (35)</td>
<td>104 (31)</td>
<td>185 (38)</td>
<td>52 (32)</td>
<td></td>
</tr>
<tr>
<td>≥2</td>
<td>133 (13)</td>
<td>44 (13)</td>
<td>70 (14)</td>
<td>19 (12)</td>
<td></td>
</tr>
<tr>
<td>Medication use [n (%)]</td>
<td>Insulin</td>
<td>186 (19)</td>
<td>60 (18)</td>
<td>98 (20)</td>
<td>28 (17)</td>
</tr>
<tr>
<td>Oral diabetes medication</td>
<td>214 (22)</td>
<td>76 (23)</td>
<td>103 (21)</td>
<td>35 (21)</td>
<td>0.86</td>
</tr>
<tr>
<td>Thiazide diuretics</td>
<td>316 (32)</td>
<td>108 (32)</td>
<td>153 (31)</td>
<td>55 (34)</td>
<td>0.87</td>
</tr>
<tr>
<td>Other blood pressure medication</td>
<td>97 (10)</td>
<td>33 (10)</td>
<td>51 (10)</td>
<td>13 (8)</td>
<td>0.64</td>
</tr>
<tr>
<td>β-Blocker</td>
<td>159 (16)</td>
<td>50 (15)</td>
<td>83 (17)</td>
<td>26 (16)</td>
<td>0.72</td>
</tr>
<tr>
<td>ACE inhibitor</td>
<td>88 (9)</td>
<td>27 (8)</td>
<td>47 (10)</td>
<td>14 (9)</td>
<td>0.73</td>
</tr>
<tr>
<td>Calcium-channel blocker</td>
<td>51 (5)</td>
<td>16 (5)</td>
<td>28 (6)</td>
<td>7 (4)</td>
<td>0.71</td>
</tr>
<tr>
<td>Cholesterol-lowering medication</td>
<td>44 (4)</td>
<td>9 (3)</td>
<td>28 (6)</td>
<td>7 (4)</td>
<td>0.11</td>
</tr>
</tbody>
</table>

\(^1\) WHR, waist-to-hip ratio; MET, metabolic equivalent task; ACE, angiotensin-converting enzyme.

\(^2\) Calculated by using the cumulative average of dietary data from 1980, 1984, 1986, and 1990, and the score ranged from 0 to 9 points; participants scored a point for consuming less than the median amount of red and processed meats and a point each for consuming more than the median amount of the other listed food categories.

\(^3\) All values are medians; range in parentheses.

\(^4\) All such values.

(Table 4). After additional control for BMI, waist circumference, physical activity, and smoking, there was still a trend toward significance for a quadratic association with alcohol and a positive linear relation with nut intake, and the direct association of adiponectin with whole grains remained highly significant. The association of adiponectin with fruit intake was attenuated to nonsignificance. Adiponectin concentrations were higher in...
The Mediterranean dietary pattern score is a method to determine whether the diet deviates from traditional Mediterranean eating habits. The score includes several components:

- Alcohol (g/d)
- Fish (servings/d)
- Fruit (servings/d)
- Legumes (servings/d)
- Nuts (servings/d)
- PUFA:SFA
- Red and processed meats (servings/d)
- Vegetables (servings/d)
- Whole grains (servings/d)

Each component is scored on a scale of 0-6, with higher scores indicating a more Mediterranean diet. The total score is calculated for these components:

- Total fiber
- Cereal fiber
- Fruit fiber
- Vegetable fiber

Higher scores in these categories indicate a more Mediterranean diet pattern. The score is calculated by summing up the points for each food group, with a higher total score indicating a diet closer to traditional Mediterranean eating habits.

Table 2 provides the dietary intakes of diabetic women according to Mediterranean dietary pattern score:

<table>
<thead>
<tr>
<th>Mediterranean diet score components</th>
<th>Total</th>
<th>0–3</th>
<th>4–5</th>
<th>6–9</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohol (g/d)</td>
<td>3.7 ± 7.8</td>
<td>3.5 ± 8.3</td>
<td>3.5 ± 7.4</td>
<td>4.6 ± 8.0</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Fish (servings/d)</td>
<td>0.3 ± 0.2</td>
<td>0.2 ± 0.1</td>
<td>0.3 ± 0.2</td>
<td>0.5 ± 0.3</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Fruit (servings/d)</td>
<td>2.5 ± 1.2</td>
<td>1.8 ± 0.9</td>
<td>2.7 ± 1.1</td>
<td>3.4 ± 1.1</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Legumes (servings/d)</td>
<td>0.4 ± 0.2</td>
<td>0.3 ± 0.2</td>
<td>0.5 ± 0.2</td>
<td>0.6 ± 0.3</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Nuts (servings/d)</td>
<td>0.3 ± 0.4</td>
<td>0.2 ± 0.3</td>
<td>0.3 ± 0.3</td>
<td>0.4 ± 0.5</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>PUFA:SFA</td>
<td>1.1 ± 0.6</td>
<td>1.1 ± 0.5</td>
<td>1.1 ± 0.6</td>
<td>0.9 ± 0.5</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Red and processed meats (servings/d)</td>
<td>0.5 ± 0.1</td>
<td>0.4 ± 0.1</td>
<td>0.5 ± 0.1</td>
<td>0.6 ± 0.1</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Vegetables (servings/d)</td>
<td>2.9 ± 1.4</td>
<td>2.0 ± 0.9</td>
<td>3.2 ± 1.1</td>
<td>4.0 ± 1.7</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Whole grains (servings/d)</td>
<td>1.3 ± 0.9</td>
<td>0.8 ± 0.7</td>
<td>1.3 ± 0.9</td>
<td>2.1 ± 1.0</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Fiber intake (g/d)</td>
<td>19.8 ± 6.5</td>
<td>15.2 ± 4.0</td>
<td>20.8 ± 5.3</td>
<td>26.4 ± 7.0</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Cereal fiber</td>
<td>4.5 ± 2.1</td>
<td>3.5 ± 1.6</td>
<td>4.6 ± 1.9</td>
<td>6.0 ± 2.5</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Fruit fiber</td>
<td>4.7 ± 2.5</td>
<td>3.3 ± 1.8</td>
<td>5.0 ± 2.3</td>
<td>6.7 ± 2.7</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Vegetable fiber</td>
<td>6.6 ± 2.6</td>
<td>4.8 ± 1.6</td>
<td>7.1 ± 2.1</td>
<td>8.9 ± 3.1</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

Table 3 presents plasma adiponectin concentrations in diabetic women by Mediterranean dietary pattern score:

<table>
<thead>
<tr>
<th>Adiponectin</th>
<th>0–3</th>
<th>4–5</th>
<th>6–9</th>
<th>P for trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>5.54 ± 1.04</td>
<td>5.56 ± 1.03</td>
<td>6.88 ± 1.06</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Model 1</td>
<td>5.52 ± 1.04</td>
<td>5.50 ± 1.03</td>
<td>6.73 ± 1.06</td>
<td>0.01</td>
</tr>
<tr>
<td>Model 2</td>
<td>5.49 ± 1.04</td>
<td>5.57 ± 1.03</td>
<td>6.91 ± 1.06</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Model 3</td>
<td>5.64 ± 1.04</td>
<td>5.58 ± 1.03</td>
<td>6.66 ± 1.06</td>
<td>0.03</td>
</tr>
<tr>
<td>Model 4</td>
<td>5.75 ± 1.04</td>
<td>5.61 ± 1.03</td>
<td>6.38 ± 1.06</td>
<td>0.05</td>
</tr>
<tr>
<td>Model 5</td>
<td>5.53 ± 1.04</td>
<td>5.40 ± 1.04</td>
<td>6.39 ± 1.06</td>
<td>0.05</td>
</tr>
<tr>
<td>Model 6</td>
<td>6.65 ± 1.04</td>
<td>6.50 ± 1.04</td>
<td>7.39 ± 1.06</td>
<td>0.09</td>
</tr>
</tbody>
</table>

All values are means ± SE. Model 1, unadjusted; model 2, adjusted for age; model 3, adjusted for age and total energy intake; model 4, adjusted for age, total energy intake, and BMI; model 5, adjusted for age, total energy intake, BMI, and waist circumference; model 6, adjusted for age, total energy intake, BMI, waist circumference, physical activity, and smoking status; model 7, adjusted for age, total energy intake, BMI, waist circumference, physical activity, smoking status, hypertension, insulin and oral diabetic medication use, and HDL-cholesterol, triacylglycerol, and glycated hemoglobin concentrations.
with reasonable reported intakes, the results were consistent, albeit somewhat stronger than those presented (α = 0.05 for all models; data not shown). Additionally, adjustment for the ratio of reported intake to predicted energy expenditure in multivariate analyses had no substantial effect on the above associations (data not shown). Taken together, these results suggest that the under-reporting of energy intake by our study participants did not likely bias our results, but the resulting random misclassification may have attenuated the observed associations.

**DISCUSSION**

We report herein that adherence to a Mediterranean-type diet, evaluated either cross-sectionally at the time when blood samples were collected or for a period of 10 y before the blood draw, was positively associated with plasma adiponectin concentrations in diabetic women with no history of heart disease. Control for anthropometric, lifestyle, and medical history covariates did explain some of the observed association, but a trend toward increased adiponectin concentrations in high adherers to a Mediterranean dietary pattern was still apparent. Although the strength of the association was modest, these data support the hypothesis that following a Mediterranean-type diet may increase adiponectin concentrations, a potential mediator of the beneficial effects of such a diet on morbidity and mortality (16, 17), independent of variations in age, adiposity, energy intake, physical activity, and other potential confounders.

A limited number of studies to date have focused on modifiable predictors of adiponectin concentrations, and even fewer alterable risk factors of low adiponectin have been identified. We previously reported no significant association between adiponectin concentration and energy or macronutrient intakes in a cross-sectional analysis of 114 students, after multivariate adjustment (30), and found a similar lack of association between adiponectin concentration and energy or macronutrient intakes in a study population. In addition, although relatively short-term caloric restriction, alterations in carbohydrate and fat intakes for 10 wk, or both do not alter adiponectin concentrations (31), more prolonged lifestyle modification (for 6 mo) has resulted in increased adiponectin concentrations (12). Similarly, Esposito et al (15) reported in a 2-y randomized controlled trial that a Mediterranean-type diet accompanied by increased physical activity significantly increases adiponectin concentrations in obese postmenopausal women, even after accounting for the decrease in adiponectin concentrations, a potential mediator of the beneficial effects of such a diet on morbidity and mortality (16, 17), independent of variations in age, adiposity, energy intake, physical activity, and other potential confounders.
decreased body weight associated with the intervention. The findings of our study are consistent with those of the above studies and extends them by showing that adherence to a Mediterranean-type diet is associated with higher adiponectin concentrations, above and beyond variations in energy intake, exercise, body weight, and central obesity and that the relation cannot be fully explained by additional confounders. Furthermore, the findings suggest that the association of adiponectin concentrations with a Mediterranean-type diet can be attributed mainly to intakes of alcohol, nuts, and whole grains.

Consumption of ≥15 g (≈1 serving) alcohol/d was also associated with a tendency toward higher adiponectin concentrations. Despite expectations that any significant quadratic trend would indicate decreased adiponectin concentrations in nondrinkers and high consumers of alcohol, we actually found the lowest adiponectin concentrations in the women who consumed 0.2–5.0 g alcohol/d (equal to less than one-third serving per day) and the highest concentrations in those with the greatest alcohol intake. This is most likely explained by the fact that our study group did not contain a substantial proportion of heavy drinkers; >1% of the women reported intakes equivalent to ≥3 drinks/d. Thus, the beneficial effect of alcohol consumption on adiponectin concentrations is likely consistent with moderate consumption of 1 to 2 drinks/d. Because none of the participants reported an intake of ≥4 drinks/d, we could not assess the effect of heavy alcohol consumption on adiponectin concentrations, and we emphasize that nondrinkers did not have lower adiponectin concentrations than light drinkers (<1 drink/d). This finding suggests that an association between alcohol consumption and adiponectin concentrations may mediate the observed improvements in insulin sensitivity with increased alcohol consumption in numerous epidemiologic studies (32, 33). Furthermore, this finding is consistent with that of a recent randomized crossover trial of middle-aged men (34), which found an 11% increase in adiponectin and a 21% increase in insulin sensitivity with moderate alcohol consumption. In addition, it has been shown that eicosanoid acid, a fatty acid derived mainly from peanut oil, is positively associated with adiponectin in humans (35), which provides a possible explanation for the observed relation between nut consumption and increased adiponectin concentrations in our study. Finally, it has been well-documented that whole grains are associated with improved insulin resistance and have beneficial effects on markers of cardiovascular disease risk (36, 37). Our results suggest that whole-grain consumption in a Mediterranean-type diet is an important mediating factor in the relation with adiponectin because higher grain intakes corresponded to the greatest increase in circulating adiponectin concentrations. Nuts and whole grains are both good sources of fiber, which have also been associated with favorable metabolic and cardiovascular responses (14, 36, 37); however, the relation between diet score and adiponectin cannot be attributed solely to fiber consumption, because the significance of the association persisted even after adjustment for fiber intake from cereal, fruit, and vegetable sources. Because foods are not eaten in isolation, we examined models that mutually adjusted for each of the Mediterranean-type diet food groups and found slightly weaker individual component associations, which indicated the importance of the overall dietary pattern, rather than of specific food groups, to adiponectin concentrations. Thus, other factors within the Mediterranean dietary pattern, in addition to whole-grain and fiber intakes, influence the association of the Mediterranean dietary pattern score with adiponectin. Future studies are needed to identify these determinants.

Our results are strengthened by the fact that the present analysis used dietary data collected prospectively in the 10 y before the time when blood samples were taken, which allowed for examination of the cumulative effect of long-term diet on adiponectin. Previously published studies (12, 27, 38) suggest that adiponectin concentrations are most likely affected by dietary intakes over relatively long periods of time, but this remains to be confirmed by future research. We found similar results using both cross-sectional and 10-y prospective dietary data, which supports the notion that not only current intake, but also intake over several years, may influence adiponectin concentrations. However, although we established a temporal relation between diet and adiponectin, our study was associative and thus more apt for hypothesis generating than for drawing inferences about causal pathways. Another possible limitation of the study includes the potential for measurement error of adiponectin, diet, and covariates. Measurement error of adiponectin is most likely minimal given the low CVs reported, and adiponectin concentrations tend to be stable, with only a small degree of circadian variability (39) and little within-person variation over time (40). Also, the instrument used for the dietary and covariate assessments was previously validated, and possible measurement errors were shown to be small in magnitude (5, 41, 42). There was some evidence of increased underreporting in women with higher BMIs, and, when we restricted our sample to women with reasonable reported intakes, our results showed stronger statistical significance. Adjustment for the ratio of reported energy intake to predicted BMR did not materially alter our results, which suggests that underreporting did not bias our study. Additional random misclassification could have attenuated the effect estimates but could not have spuriously produced the statistical significance of our results. In our analyses, we attempted to account for variables that were likely associated with adiponectin or consumption of a Mediterranean-type diet. However, the potential for residual confounding by uncontrolled covariates was possible, and our study was also limited by the fact that direct waist and hip measures were missing for more than one-third of the participants. Finally, the sample used herein does not represent a random sample of the US population; thus, future studies should include men and nondiabetic women and should consider morbidity and mortality in relation to adiponectin concentrations and a Mediterranean-type dietary pattern.

In conclusion, adherence to a Mediterranean-type dietary pattern is associated with higher plasma adiponectin concentrations in diabetic women, and this relation cannot be fully explained by anthropometric, lifestyle, and other health-related variables. Future studies should extend these data by studying the underlying mechanism and assessing in greater detail whether the beneficial effect of a Mediterranean-type diet on morbidity and mortality is mediated through changes in adiponectin concentrations.

CSM provided the original idea for the analysis. CSM and CJW wrote the manuscript. CSM, FBH, and CJW designed and conducted the statistical analysis and produced the tables. JEM, JBM, and FBH contributed the original sample and data collection and banking and provided editorial review and comments about the article. Funding was secured by CSM, JEM, and FBH. All authors contributed to the final manuscript, and none declared any conflicts of interest.
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