

Title: The 2005 Dietary Guidelines for Americans and Insulin Resistance in the Framingham Offspring Cohort

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Running Title: Dietary Guidelines and Insulin Resistance

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Abbreviations: CVD, cardiovascular disease; DGA, Dietary Guidelines for Americans; DGAI, Dietary Guidelines for Americans Adherence Index; FFQ, food frequency questionnaire; HOMA-IR, homeostasis model assessment of insulin resistance

Abstract

Objective – The aim of this study was to examine the relationship between a diet consistent with the 2005 Dietary Guidelines for Americans (DGA), as assessed by the 2005 Dietary Guidelines for Americans Adherence Index (DGAI), and measures of insulin resistance in the Framingham Heart Study Offspring Cohort.

Research Design and Methods – We examined cross-sectional associations between DGAI score and degree of insulin resistance as measured by the homeostasis model assessment of insulin resistance (HOMA-IR) and fasting insulin in 3,082 participants in the Framingham Offspring Cohort fifth examination (January 1991-June 1995).

Results – Participants in the highest quintile category of the DGAI score had significantly lower HOMA-IR than those in the lowest quintile category after adjusting for age, gender and waist circumference (6.4 compared to 6.7, $p=0.04$). We observed a significant interaction between DGAI score and sex, and upon stratification, the association appeared to be largely confined to women (5.9 compared to 6.6, $p<0.001$). No association was apparent in men (7.2 compared to 7.1, $p=0.30$). Similar associations were evident between the DGAI score and fasting insulin.

Conclusions – Consumption of a diet consistent with the 2005 DGA may be an effective means to limit insulin resistance in women.

The “Dietary Guidelines for Americans” (DGA), dietary recommendations intended to decrease chronic disease risks among American adults, were first released in 1980 by the US Departments of Agriculture and Health and Human Services (1; 2). A limited number of studies have examined if adherence to earlier versions of the DGA was associated with lower risk of overall chronic disease, including cardiovascular disease, but findings were weak or inconclusive (3; 4). Insulin resistance is an important risk factor for cardiovascular disease (CVD) (5-7) and type 2 diabetes (8; 9) Fasting insulin, a marker of insulin resistance, was not related to the Healthy Eating Index, which measures adherence to earlier an earlier version of the DGA, although fasting glucose and C peptide levels were lower among those consuming healthier diets (10). Previous investigations have also considered associations between indices of adherence to earlier versions of the DGA and markers of inflammation (11), and components of metabolic syndrome (10). The sixth edition released In 2005 represents a significant departure from the guidelines written over the past 20 years, by focusing on energy density and obesity prevention (12; 13). No study to date has examined the relation between adherence to the 2005 DGA and CVD risk or intermediate markers of risk.

We developed the 2005 Dietary Guidelines for Americans Adherence Index (DGAI) to determine if a diet consistent with the 2005 DGA was associated with a lower risk of chronic disease (12; 14). This study assessed the relationship between adherence to the 2005 DGA and IR as measured by HOMA-IR and fasting insulin in the Framingham Offspring Cohort.

Research Design and Methods

The original Framingham Heart Study began in 1948 with 5,209 adults aged 28-62 years, residing in Framingham, Massachusetts (15). The offspring of these participants and the offspring’s spouses were invited to participate in the Framingham Heart Study Offspring Cohort, and 5,135 of the 6,838 eligible individuals participated in the first examination between 1971 and 1975 (16). A total of 3,799 participants were examined at the 5th examination of the Offspring Cohort (January 1991-June 1995). Usable FFQ data were available for 3,418 (90%) of the participants at this examination. In addition, individuals were excluded if they were missing covariates essential to determine the DGAI score including height, weight, age, physical activity score (n=95); if they had diagnosed diabetes based on use of insulin or oral hypoglycemic medication (n=110) or if they were missing information about their diabetes status (n=131). The final sample included 3,082 participants.

Dietary Data

Dietary intake was assessed using a semi-quantitative food frequency questionnaire, version 1988-GP (FFQ) developed by Willett, et al (17; 18). The questionnaires were mailed to the participants before the examination and the participants were asked to bring the completed questionnaire with them to their appointment. The FFQ consisted of 126 items, including a list of foods with a standard serving size and a selection of 9 frequency categories ranging from “never or <1 serving/month” to “≥ 6 servings/day”. Participants were asked to report their frequency of consumption of

each food item during the last year. There were also separate questions about vitamin and mineral supplements, and type of breakfast cereal most commonly consumed, and an area to write in foods commonly consumed that were not listed on the FFQ. Dietary information was judged as unreliable and excluded from further analysis if reported energy intakes were <2.51 MJ/d (600 kcal) for all, or >16.74MJ/d (4000 kcal/d) for women and >17.57 (4200 kcal/d) for men, or if ≥12 food items were left blank. Participants who met the energy intake criteria and had fewer than 12 blank items were included in analyses and were considered to be non-consumers of the missing items.

Dietary Guidelines for Americans Index

The DGAI was developed to assess adherence to sixteen of the twenty-three key recommendations in the 2005 DGA, including all the recommendations that pertain specifically to dietary intake (12; 14). Because the DGAI was developed to assess dietary recommendations for the general population, the recommendations for vulnerable populations (e.g., pregnant women) and for non-dietary intake behaviors (e.g., oral hygiene, physical activity, and food safety) were excluded from the index. Specifics concerning the scoring the DGAI are described elsewhere (14), and are summarized briefly below.

There are a total of 20 items on the DGAI. Eleven index items assessed the *food intake* recommendations (assessed at one of the ten calorie-specific adult food intake patterns from the USDA food guide) (12). Each participant's calorie level was based on the "estimated energy requirement" equation, which included: height, weight, age, gender, and physical

activity (19). Physical activity was determined using the "walking equivalents method" as described in the energy section of the DRI (19).

Nine items assessed the *healthy choice* (nutrient intake) recommendations which are given in absolute amounts, or as percent of total kilocalories of intake, and are the same for each calorie level and therefore all individuals. Each item has a maximum value of 1.0, and most have an intermediate value of 0.5 (for partial adherence), while zero points were awarded for non-adherence. To limit the likelihood that one could receive a higher score solely by consuming more food, a major shortcomings of previous indices, a penalty for over-consuming energy dense foods was included (20). The maximum possible DGAI score is 20 points.

Laboratory Determinations

Fasting plasma glucose levels were measured in fresh plasma with a hexokinase reagent kit (A-gene glucose test, Abbott, South Pasadena, CA) and glucose assays were run in duplicate. The intra-assay coefficient of variation for this method at the 5th examination cycle was less than 3% (21). Fasting insulin was measured in EDTA plasma as total immunoreactive insulin (Coat-A-Count Insulin, Diagnostic Products Corporation, Los Angeles, CA) and run in duplicate. The intra- and inter-assay CVs ranged from 5% to 10%, and the lower limit of sensitivity was 8 pmol/L(21).

Determination of Insulin Resistance

The homeostasis model assessment of insulin resistance (HOMA-IR) was used to assess the degree of insulin resistance. HOMA-IR was assessed as:

$$\frac{\text{fasting plasma insulin } (\mu\text{U/mL}) \times \text{fasting plasma glucose (mmol/L)}}{22.5}$$

This method has been shown in studies to correlate well with results obtained using euglycemic clamps ($R=0.88$, $p<0.001$) (22). In addition, fasting insulin concentrations were used to estimate the degree of insulin resistance.

Lifestyle variables

Height (to the nearest 0.25 inch) and weight (to the nearest 0.25 lb) were measured with the participants standing, with shoes off, wearing only a hospital gown. Body mass index (BMI) was calculated as weight in kg divided by height in m^2 . Waist circumference was measured at the umbilicus while the participant was standing, with the tape measure parallel to the floor. The use of any medications, including hypoglycemic medication (insulin or oral agents) was determined during the physical exam. Information on age (years), current smoking (yes/no), current multivitamin use (yes/no) and physical activity (assessed as a weighted average of the proportion of a typical day spent sleeping and performing sedentary, slight, moderate, or heavy physical activities, expressed in METs) were also assessed at the same time (16; 23).

Statistical Methods

All statistical analyses were conducted using SAS statistical software version 9.1 (SAS Institute, Cary, NC). HOMA-IR and fasting insulin were positively skewed and a natural logarithm transformation was applied to normalize these data. Geometric means were calculated for fasting insulin and HOMA-IR. Unless otherwise noted, statistical significance indicated a P-value <0.05 .

Participant characteristics were compared across quintile categories of

DGAI score, adjusted for gender and age, using the SAS procedure PROC GLM. P-values for linear trend between the DGAI score as a continuous variable and participant characteristics were assessed using linear regression for continuous characteristics and logistic regression for dichotomous characteristics.

Geometric mean HOMA-IR and insulin concentrations were compared across quintile categories of DGAI score using the SAS procedure PROC GLM. Potential confounding variables considered in analyses included age, gender, waist circumference, BMI, smoking, total reported energy intake, multivitamin use and physical activity. To assess linear trend, we first examined the linearity of the relationship between the DGAI score and HOMA-IR and fasting insulin levels using the SAS LOESS procedure. P-value for linear trend then was determined as the p-value for the DGAI linear regression coefficient relating the DGAI score as a continuous variable to HOMA-IR and insulin levels using SAS PROC REG. First-order interactions were tested in separate models between DGAI score and those factors that were independent predictors of either HOMA-IR or fasting insulin levels.

Results

The final sample included 3,082 participants with a mean age of 54 (± 9.8 SD, range: 26 to 82 years) and a mean BMI of 27.3 (± 4.8), 1,438 men, mean age 54.7 (± 9.9), mean BMI 28.2 (± 4.1) and 1,644 women, mean age 54.2 (± 9.7), mean BMI 26.5 (± 5.3). Age, gender and BMI were not significantly different between those included in the final sample and those excluded.

The DGAI score ranged from 2.5 to 17.0 and was associated with several

participant characteristics (Table 1). Participants in the highest DGAI quintile category were more likely to be women than men (77% vs. 27%, P-trend <0.001), were older (57 vs. 51 yrs, P-trend <0.001) and more likely to use multivitamin supplements (40% vs. 23%, P-trend <0.001). They also had lower waist circumference (89 vs. 95 cm, P-trend <0.001) and BMI (26.3 vs. 28.0, P-trend <0.001), and were less likely to be current smokers (8% vs. 35%, P-trend <0.001). There was a weak, inconsistent inverse trend across DGAI categories for physical activity (P-trend = 0.05), and no significant trends were observed between the DGAI score and total reported energy intake and fasting plasma glucose concentrations.

A higher DGAI score was inversely associated with HOMA-IR after adjustment for age and gender (Table 2). This association was attenuated but remained statistically significant after waist circumference was added to the model (P-trend = 0.04). Additional adjustment for BMI, smoking, multivitamin supplement use, physical activity, and energy intake, did not significantly affect this association (data not shown).

First-order interactions between DGAI score and age, gender, and waist circumference were tested in separate models, and a significant interaction was observed only for gender ($p < 0.001$). Therefore, the analyses of DGAI score, HOMA-IR and fasting insulin were stratified by gender (Table 2). When DGAI was controlled for age alone, there was a significant relationship seen in both men (P-trend <0.01) and women (P-trend <0.001). After adjustment for age and waist circumference, the relationship was no longer significant in men (P-trend = 0.30), but it remained highly significant in women (P-trend <0.001). As

was the case with the overall association, further adjustment for BMI, smoking, multivitamin supplement use, physical activity, and energy intake had little effect on the association in either men or women (data not shown).

The results for fasting insulin were very similar to those for HOMA-IR (Table 2) as expected in this non-diabetic sample in which elevated fasting glucose concentrations would not be common. The Spearman rank correlation coefficient between HOMA-IR score and fasting insulin was 0.94.

The index items were assessed individually to determine if there was one item or group of items that was largely responsible for the relationship between the total index score and HOMA:IR. Most individual index items, when controlled for age, sex, and BMI, and WC were not significantly associated with HOMA, however a higher score on a few index items proved to be related to lower HOMA:IR. Those fully meeting the fiber, whole grain intake (>50% of grains as whole), dark green vegetables (\geq recommended servings for kcal pattern), *trans* fat (<1% of total calories) and alcohol intake recommendations had significantly lower HOMA than those who received a zero score for these items (P < 0.05).

Conclusions

This is the first examination of the relationship between a diet consistent with the 2005 DGA and insulin resistance. Our findings suggest that, in the Framingham Offspring Cohort, women who consumed a diet more consistent with the 2005 DGA had better insulin sensitivity than those who did not, whereas the 2005 DGA score was not associated with insulin sensitivity among men.

The reason for the observed gender difference is not apparent. The relationship between DGAI and both HOMA-IR (P-trend<0.01) and fasting insulin (P-trend=0.002) was attenuated by adjustment for waist circumference in men, but not in women. Previous studies have found that waist circumference is a strong predictor of insulin resistance in both men and women (24-26). This has also been shown previously in this study population (6). It is unclear whether the relationship between DGAI scores and HOMA-IR in men was confounded by waist circumference or if waist circumference may be part of the causal pathway relating dietary intake and insulin resistance. It may also be possible that the difference between the association in men and women might be a result of the differential diet patterns in men and women achieving higher scores. We observed (data not shown) that among individuals in the highest DGAI quintile category, women had a significantly higher mean DGAI score than men (P<0.001). Moreover, women in the highest DGAI quintile category were more likely to achieve a higher DGAI score by meeting the recommendations for orange and starchy vegetables, grains, variety, total fat and sodium, whereas men in the highest DGAI quintile were more likely to achieve a higher score by meeting the fiber and trans fat recommendations. There were also many differences in the diet patterns of men and women in the lowest quintile category. Such differences might be responsible, in part, for the observed differences between the DGAI score and IR in men and women.

When we assessed the index items to determine if there was one item or group of items that was largely responsible for the relationship between the total index score and HOMA:IR. We

observed that those fully meeting the fiber, whole grain intake (>50% of grains as whole), dark green vegetables (\geq recommended servings for kcal pattern), *trans* fat (<1% of total calories) and alcohol intake recommendations had significantly lower HOMA than those who received a zero score for these items. However, an overall healthy diet pattern as indicated by a higher total index score was more strongly associated with IR than any of the individual components. Moreover, the association between the overall score and IR does not appear to be a consequence of meeting any single index recommendation, but if a consequence of meeting many different recommendations.

The few published studies assessing the relations between adherence to previous versions of the DGA and disease risk have been largely inconclusive. The Healthy Eating Index (20) has been used to assess overall disease outcomes in only 2 published studies (3; 4). Both failed to show a relationship between a diet consistent with the DGA and decreased risk of overall chronic disease (CVD, cancer, and other non-traumatic death), but showed an inverse association with CVD risk in men only (4). A subsequent paper suggested that the alternate Healthy Eating Index, which was a substantial modification of the HEI, improved prediction of overall chronic disease risk and CVD risk in both men and women (27).

In 2001 Harnack and colleagues, using an index based on the 2000 DGA that included items on both weight and physical activity, showed a statistically significant (15%) lower incidence of all cancers in women (28). When the physical activity and body weight

recommendations were removed from the index, it was no longer significantly associated with a decrease in overall cancer risk. Rather than including weight and physical activity in our index, we chose to focus on the DGA dietary recommendation and to control for central adiposity, overweight and physical activity.

The Recommended Food Score (RFS), which has been proposed as another means of assessing a diet consistent with the DGA, approximates healthy eating patterns based on variety in the diet. It measures the number of different foods consumed over a one-week period that are consistent with the recommendations made in the 1990 DGA, and is heavily weighted by fruit and vegetable consumption. It does not consider any macro- or micronutrient recommendations (29). Like the HEI, this index also has the inherent problem of being positively correlated with the number of foods consumed, and therefore total calorie intake. It is, however, essential to consume a variety of foods to receive a high score, which makes the RFS an excellent measure of variety.

Several studies have examined the relationship between these diet scores and biomarkers for chronic disease risk. The RFS was shown to be related to overall mortality in women (30), but was not significantly associated with C-Reactive protein (31). Two studies have used this index to assess men and women together, in relation to intermediate markers of disease, and both using the NHANES III population. Kant and colleagues observed an inverse association between both the HEI (P-trend <0.05) and RFS scores (<0.05), and CRP levels (10). While the other, using the same population, found the relationship with CRP was confined to women (11). Kant also found that there was no relationship between RFS or HEI

and fasting insulin or triglycerides, while there was a significant relationship for both with fasting glucose. The relationship between other intermediate markers of CVD risk, including homocysteine, CRP, and fibrinogen, were more strongly inversely related to RFS than HEI (10).

Our findings have some potential limitations. The DGAI was designed specifically for use with the Harvard semi-quantitative FFQ (17; 18). The semi-quantitative nature of this dietary assessment questionnaire limits our ability to accurately measure energy intake. Another potential limitation was the cross-sectional and historical nature of these analyses, which does not allow us to directly determine if a poor dietary pattern precedes the occurrence of reduced insulin sensitivity. Finally, our findings could be a consequence of confounding by determinants of insulin resistance or other healthy behaviors, which we have not considered. However, the fact that the association between the DGAI score and levels of insulin resistance were maintained after adjustment for important known and suspected determinants of insulin resistance, such as age, abdominal adiposity (as waist circumference) and overweight (as BMI), and correlates of a healthy lifestyle, such as physical activity, smoking and vitamin supplement use, argues against confounding as the basis for the observed association.

In the Framingham Offspring Cohort, we observed that a higher DGAI quintile score was associated with lower HOMA-IR in women, suggesting that adherence to the 2005 DGA recommendations may favorably affect insulin resistance, an important intermediate marker of CVD and type 2 diabetes risk. More definitive studies are required to document the benefit of following a diet consistent with the 2005

Dietary Guidelines for Americans. Further work should concentrate on prospective assessment of adherence to the 2005 DGA and intermediate markers of risk for CVD and diabetes, such as insulin resistance, inflammatory markers, and metabolic syndrome.

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Table 1. Participant characteristics* according to quintile category of the 2005 Dietary Guidelines for Americans Index

	2005 Dietary Guidelines for Americans Index (DGA) Quintile Category					P-trend [†]
	1	2	3	4	5	
DGAI Range	<6.75	7.00-8.50	8.75-10.25	10.50-12.00	>12.25	
Participants (n= 3082)	586	625	646	592	633	
DGAI score, median [‡] (range)	5.50 (2.50-6.75)	8.00 (7.00-8.50)	9.50 (8.75-10.25)	11.25 (10.50-12.00)	13.25 (12.25-17.0)	
Nutrient sub-score, median [§]	3.00	4.50	5.25	5.75	6.75	
Food group sub-score, median	2.50	3.00	4.50	5.50	7.00	
Female (%)	26.7	40.3	53.1	67.9	77.4	<0.001
Age (yrs)	51.1	53.9	54.3	55.9	57.0	<0.001
Waist circumference (cm)	95	94	92	91	89	<0.001
BMI (kg/m ²)	28.0	27.8	27.2	27.0	26.3	<0.001
Fasting plasma glucose (mg/dL)	97.4	98.3	98.5	99.0	96.1	0.36
Total reported calories (kcal/day)	1838	1828	1865	1909	1893	0.07
Physical activity score (METS)	35.3	34.8	34.0	35.0	34.6	0.05
Current smokers (%)	35.0	24.3	18.8	10.8	7.7	<0.001
Multivitamin users (%)	23.4	24.5	26.8	31.5	40.1	<0.001

*means and percents adjusted for gender and age. Age is adjusted for gender only and gender for age only.

†P value for test for trend: linear regression for continuous variable or logistic regression for dichotomous variables.

‡Scores range from 0-20 possible points, median and range

§Scores range from 0-11 possible points and are assessed at the same level for all participants

|| Scores range from 0-9 possible points and are assessed on a calorie specific level

Table 2. Geometric mean HOMA-IR and fasting insulin across quintile category of DGAI

	2005 Dietary Guidelines for Americans Index (DGAI) Quintile Category					P-trend*
	1	2	3	4	5	
DGAI Range	<6.75	7.00-8.50	8.75-10.25	10.50-12.00	>12.25	
All Participants (n= 3082)	586	625	646	592	633	
HOMA-IR: Model 1 [†]	7.0 (6.8-7.2) [‡]	6.9 (6.7-7.1)	6.8 (6.6-7.0)	6.5 (6.3-6.7)	6.1 (5.9 -6.3)	<0.001
HOMA-IR: Model 2 [§]	6.7 (6.5-6.9)	6.7 (6.6-6.9)	6.8 (6.6-7.0)	6.6 (6.4-6.8)	6.4 (6.3-6.6)	0.04
Women (n=1644)	164	253	344	399	484	
HOMA-IR: Model 1	6.7 (6.3-7.1)	6.6 (6.3-6.9)	6.3 (6.1-6.6)	6.1 (5.9-6.3)	5.8 (5.6-6.0)	<0.001
HOMA-IR: Model 2	6.6 (6.3-6.9)	6.3 (6.1-6.6)	6.2 (6.0-6.4)	6.1 (5.9-6.3)	5.9 (5.7-6.1)	<0.001
Men (n=1438)	422	372	302	193	149	
HOMA-IR: Model 1	7.4 (7.1-7.7)	7.3 (7.0-7.7)	7.4 (7.1-7.8)	7.1 (6.7-7.4)	6.6 (6.2-7.1)	0.005
HOMA-IR: Model 2	7.1 (6.9-7.4)	7.2 (6.9-7.5)	7.6 (7.3-7.9)	7.3 (6.9-7.6)	7.2 (6.8-7.6)	0.30
All Participants (n=3082)	586	625	646	592	633	
Fasting Insulin: Model 1	29.6 (28.9-30.5)	29.2 (28.4-29.9)	28.7 (28.0-29.5)	27.4 (26.7 -28.1)	26.4 (25.8-27.1)	<0.001
Fasting Insulin: Model 2	28.7 (28.0-29.4)	28.6 (27.9-29.2)	28.7 (28.1-29.4)	27.7 (27.1-28.4)	27.5 (26.8-28.1)	0.004
Women (n=1644)	164	253	344	399	484	
Fasting Insulin: Model 1	29.8 (28.5-31.1)	27.3 (26.4-28.4)	27.3 (26.4-28.1)	26.8 (26.0-27.6)	25.5 (24.7-26.2)	<0.001
Fasting Insulin: Model 2	28.1 (27.0-29.3)	27.6 (26.7-28.5)	27.5 (26.7-28.2)	26.5 (25.8-27.1)	26.3 (25.6-26.9)	<0.001
Men (n=1438)	422	372	302	193	149	
Fasting Insulin: Model 1	30.6 (29.7-31.6)	29.7 (28.6-30.8)	30.9 (29.7-32.1)	28.6 (27.3-30.0)	27.7 (26.3-29.1)	0.002
Fasting Insulin: Model 2	29.7 (28.9-30.6)	29.9 (29.0-30.8)	30.2 (29.3-31.3)	29.6 (28.4-30.8)	29.1 (27.8-30.6)	0.66

* P value for test for trend based on linear regression coefficient for DGAI linear as a continuous variable.

† Model 1 – adjusted for gender and age (gender strata controlled for age only)

‡ Geometric mean (95% confidence interval).

§ Model 2 – adjusted for variables in model 1 and waist circumference (gender strata controlled for age and waist circumference)