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Dietary Fiber Consumption and Insulin Resistance: The Role of Body Fat and Physical Activity

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and Physical Activity

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ABSTRACT

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Background: This study was conducted to determine the association between fiber intake and insulin resistance in 264 women using a cross-sectional design. **Methods**: Insulin resistance was indexed using HOMA-IR (fasting insulin (μU/mL)×fasting glucose (mg/dL)/405). HOMA-IR values were log transformed. Fiber and energy consumption were assessed using 7-day weighed food records. Fiber was expressed as grams per 1000 kilocalories. Body fat percentage (BF%) was measured using the BOD POD and physical activity (PA) was ascertained using Actigraph accelerometers worn for 7 consecutive days. **Results**: (Mean±SD) age: 40.1±3.0 years, glucose: 86.7±5.9 mg/dL; insulin: 7.1±4.3 μU/mL; HOMA-IR: 1.5±1.0; fiber intake (g/1000 kcal), total: 9.3±2.9; soluble: 1.7±0.9; insoluble: 3.8±1.9; physical activity: 2.7044 ±0.7842 million counts; BF%: 31.7±6.9; weight (kg): 66.1±10.1; total caloric intake per day (kcal): 2054.1±320.9; and dietary fat intake (% of total kcal): 30.5±0.5. Women with high total fiber intakes had significantly less insulin resistance than their counterparts (F=4.58, p=0.0332), and women with high soluble fiber intakes had significantly lower levels of insulin resistance than other women (F=7.97, p=0.0051). Participants with high insoluble fiber intakes did not differ from their counterparts (F=0.7, p=0.6875). Adjusting for either PA or BF% weakened the relationships significantly. Controlling for BF% nullified the total fiber─HOMA-IR link (F=1.96, p=0.1631), and attenuated the association between soluble fiber and HOMA-IR by 32% (F = 6.86, p=0.0094). To facilitate interpretation of the results, odds ratios were calculated to determine the association between fiber intake and HOMA-IR with both variables treated as categorical. To create dichotomous variables, fiber intake and HOMA-IR were each divided into two categories using the median (Low and High). In women who had high soluble fiber intake (upper 50%), the odds of having an elevated HOMA-IR level was 0.58 (95% CI: 0.36-0.94) times that of women with low soluble fiber intake (lower 50%). And after controlling for all of the potential confounding factors simultaneously, the odds ratio was 0.52 (95% CI: 0.29-0.93). **Conclusion**: High fiber intake, particularly soluble fiber, is strongly related to lower levels of insulin resistance in women. Part of this association is a function of differences in PA and BF%.

Keywords: Insulin sensitivity, complex carbohydrate, metabolic disorder, type 2 diabetes, diet

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Introduction

The prevalence of obesity throughout the United States has increased significantly over the past 25 years.[1] National Health and Nutrition Examination Survey (NHANES) results indicate that over one-third of the adult population in the United States is obese, encompassing 35.5% of women and 32.2% of men.[1] This upward trend is not without consequences. A review of the health consequences of obesity shows that as the body mass index (BMI) increases so does the risk of many health problems, including some forms of cancer, cardiovascular disease, type 2 diabetes, and other life threatening disorders.[2]

One of the key health problems associated with obesity is insulin resistance, a common metabolic condition that can lead to a host of serious chronic diseases.[3] Because insulin resistance is a precursor of several diseases, it has received considerable attention. Some of the diseases closely connected to insulin resistance are hypertension, type 2 diabetes, and cardiovascular disease.[4-6] Facchini et al.[4] examined prospectively over 4 to 11 years the extent to which insulin resistance predicts age-related diseases, including: hypertension, coronary heart disease, stroke, cancer, and type 2 diabetes. Results showed that approximately 1 out of 3 of the initially healthy subjects in the upper tertile of insulin resistance developed an age-related disease.[4] Whereas, among the individuals who were more insulin sensitive, no age-related events were observed.[4] Clearly, insulin resistance is a serious health risk. Consequently, additional research is warranted to determine strategies that will reduce insulin resistance in adults and curb the risk of many life-threatening diseases.

Fortunately, insulin resistance can be improved through lifestyle changes, particularly weight loss and regular physical activity.[7] Moreover, the literature shows that diets high in carbohydrates and fiber and low in fat are associated with increases in insulin sensitivity.[7-10]

Consuming a healthy diet may reduce the pathogenesis of insulin resistance and thus decrease the risk for type 2 diabetes and cardiovascular disease.

Fiber intake has been one of the main focuses of studies examining dietary approaches to reducing the risk of insulin resistance. To date, many investigations have examined the link between fiber intake and insulin sensitivity.[11-27] Comparison of these studies is difficult, given the many different methods used for detecting insulin resistance and the limitations of some dietary assessment methods. No doubt, research methods in this area can be improved due to the inconsistencies and limitations of some measurement methods.

Studies focusing on dietary fiber consumption and insulin resistance have displayed several consistent weaknesses. First, most studies have used BMI when controlling for obesity.[11-16, 26] BMI is not a high quality index of percent body fat.[28] Very few studies have used percent body fat to index obesity, and the few investigations that have assessed body fat have used weak measurement methods,[25] like bioelectrical impedance analysis (BIA).[29-30] Additionally, physical activity has a strong influence on insulin sensitivity, and the predominant assessment form in epidemiological studies has been questionnaires.[31-32] This measurement method relies on self-report and thus contains significant error, since memory and a desire to appear favorably are key factors associated with such self-reported data.[33] Lastly, most studies which have examined the relationship between fiber intake and insulin resistance have focused on total fiber consumption.[11-13, 15-17, 19-20, 22, 26-27] However, since dietary fiber consists of two main categories: soluble and insoluble, the independent influence of each should be considered, given these fibers have vastly different effects on food absorption and digestion. Few studies have examined the relationship between fiber consumption and insulin resistance using more valid and reliable objective measurement methods with fiber separated into the categories of total, soluble, and insoluble.[14]

The weaknesses of previous studies examining the relationship between fiber intake and insulin resistance were modified in the present study. These improvements included measuring objectively and reliably physical activity and body fat percentage. Moreover, total fiber consumption was separated into total, soluble, and insoluble fiber intakes to ascertain the individual influence of each fiber type.

The purpose of the present study was to examine the relationship between total, soluble, and insoluble fiber and insulin resistance, as estimated by the homeostasis model assessment of insulin resistance (HOMA-IR), in pre-menopausal, non-diabetic women. Additionally, the influence of age, body fat percentage, body weight, total physical activity, intensity of physical activity, dietary fat intake, and total caloric consumption were measured and controlled while examining the fiber and insulin resistance relationship.

Methods and Procedures

A cross-sectional design was employed in the current study to examine the relationship between fiber intake, including total, soluble, and insoluble, and insulin resistance (HOMA-IR). A total of 264 women were included in the analysis and were recruited through the use of newspaper advertisements, flyers, and emails. Distribution included two metropolitan areas in the Mountain West. Telephone interviews were used to screen applicants according to the study requirements. All of the qualified subjects were healthy, nonsmoking, pre-menopausal women. The mean age of the subjects was 40.1±3.0 years. Before the collection of data, each participant signed an Institutional Review Board approved letter of informed consent.

Insulin Resistance

Qualified hospital personnel obtained blood samples from subjects who fasted at least 12 hours before their appointment. The antecubetal vein served as the location where blood samples were taken and the sample was then centrifuged at 2000g for 15 minutes at a temperature of 4°C. Final storage of samples was in aliquots at temperatures of -20°C. The hospital laboratory determined fasting insulin levels (μU/L) and glucose levels (mg/dL) utilizing two separate methods: Access® Ultrasensitive Insulin assay (Beckman Coulter, Inc, Brea, CA) and Dimension Vista System® and the Flex reagent cartridge (Siemens, Deerfield, IL) respectively. Insulin resistance was indexed using HOMA-IR, which was estimated using fasting glucose and insulin concentrations in the following equation: HOMA-IR = [fasting glucose (mg/dL) x fasting insulin (μU/ml)]/405.[34]

HOMA-IR provides comparable assessment of insulin resistance to other validated methods. Matthews et al.[34] demonstrated that HOMA-IR produced estimates of insulin resistance similar to measurements obtained by the hyperinsulinemic euglycaemic clamp (R_s = 0.88, $p < 0.0001$), which is considered one of the “gold standard” tests. A review article revealed that when the HOMA-IR model is used in epidemiological investigations, valuable data can be obtained.[35]

Dietary Intake

Total calorie, fat, and fiber intakes were measured using seven-day diet records in which subjects weighed and recorded all food and drink consumed within a consecutive seven-day time frame. A digital food scale was issued to each subject along with an explanation of how to properly weigh and record all food and drink consumed, including water. Food description and food weight were recorded daily on the records provided. During the seven days, research personnel contacted each woman at least twice to provide support and to ensure that accurate records were being kept. Following completion of the seven days, assessment of dietary intake was accomplished using the ESHA Research software, version 7.6, (ESHA Research Inc., Salem, OR) to provide objective dietary results. If energy intake was not at least 130% of resting metabolic rate estimated through the Ravussin metabolism formula,[36] the women were required to redo their weighed food records for an additional 7 days.

Using seven-day dietary records where all food and drink are weighed prior to eating provides many benefits. Subjects' ability to recall foods eaten and also portion sizes are not a problem with food records. Also, with the occurrence of day to day variations in eating habits, recording foods for seven consecutive days documents habitual dietary intake when compared to other dietary assessments.[37]

Total Physical Activity

ActiGraph accelerometers (formerly called CSA; Health One Technology, Fort Walton Beach, FL) provided a means to objectively assess physical activity during the same seven consecutive days that dietary intake was measured. Instructions on how to appropriately use this device were provided during the initial appointment. The accelerometer was worn constantly throughout the day and night with the exception of water activities, during which subjects were required to remove the activity monitor. The accelerometer was attached to a nylon belt that was worn comfortably around the subjects' waist and positioned over the left hip.

Objective and reliable measurements can be obtained through the use of Actigraph accelerometers to evaluate levels of physical activity. These activity monitors were compared to doubly labeled water in a study conducted by Liu et al.[38] The monitors provided a close representation of physical activity level in free living subjects. A significant relationship was found between physical activity measured through Actigraph accelerometers and total energy expenditure (r = 0.31, $p < 0.01$), activity related energy expenditure (r = 0.30, $p < 0.05$) and physical activity level (r = 0.26, $p < 0.05$).[38] Additionally, a comparison of four accelerometers, including the one used in this study, was examined by Basset et al.[39] The only accelerometer not differing significantly from a portable metabolic system was the Actigraph device.

In the present study, total physical activity was indexed using the sum of all the activity counts acquired over the seven days of assessment. Concurrent validity for this measure has been shown by several investigations linking total physical activity with television viewing habits,[40] body fat percentage,[41] bone mineral density,[42] C-reactive protein,[43] and abdominal circumference.[44]

Intensity of Physical Activity

Intensity of physical activity was measured using Actigraph accelerometers in which participant movement was recorded in 10-minute segments for a total of 144 bouts (epochs) each day, 1008 per week. The reason for choosing 10 minutes as the length for assessing intensity of physical activity was based on the American College of Sports Medicine guidelines indicating that multiple 10-minute bouts are sufficient for accumulating physical activity.[45]

The following categories for physical activity intensity were utilized based on previous research.[46] Each category included the activity counts associated with the three levels of intensity (Low, Moderate, and Vigorous) and corresponding speeds (mph) on a treadmill: Low intensity, 0-29,999 counts in one 10-minute bout (<3 mph); Moderate intensity, 30,000-49,999 counts in one 10-minute epoch (3-4 mph); and Vigorous intensity, 50,000 counts or greater in one 10-minute bout (>4 mph).[46]

Each participant had a total of 1008 10-minute bouts of monitored activity distributed over the three intensity categories over the course of the week. The amount of time subjects engaged in physical activity within each intensity category was used to differentiate among participants. For example, one subject might have 0 bouts of Vigorous activity across the seven days of recording, whereas another subject might have 20 minutes, and another might have 120 minutes of Vigorous activity over the week. Many investigations have employed these guidelines when using the Actigraph accelerometer to assess intensity of physical activity.[40, 42, 46]

Body Fat Percentage

Body fat percentage was measured through the use of air displacement plethysmography, the BOD POD. Thoracic lung volume was also evaluated directly via the BOD POD. Before performing any measurements, the BOD POD was calibrated in order to minimize measurement error. Subjects were asked to fast for three hours prior to their appointment. A university-issued, one-piece swimsuit was worn by each woman as well as a swim cap. Subjects were instructed to use the restroom immediately prior to the measurements. Two measurements were obtained for each subject to ensure accuracy. A maximum difference of one percentage point was allowed between the two results. If a difference of more than one percentage point resulted, a third measurement was obtained. An average of the two measurements within one percentage point of each other was then used.

The BOD POD provides a valid and reliable measurement of body fat percentage as concluded by several studies. For the current study, reliability was established by performing a test-retest on 100 women from the study sample. An intraclass correlation of 0.999 ($p < 0.0001$) was found after comparing the two BOD POD tests.[47] On the same 100 women, validity of the BOD POD was also examined. Results obtained from the BOD POD were compared to body composition findings obtained from dual energy X-ray absorptiometry (DEXA) (Hologic, Inc., Bedford, MA). A Pearson correlation of 0.94 ($p < 0.001$) and an intraclass correlation of 0.97 ($p < 0.001$) were determined after comparison of the two measurements.[48] Ballard et al.[49] concluded after comparing the BOD POD to the DEXA that the BOD POD was a valid and reliable method of evaluating percent body fat in female athletes and nonathletes.

Body Weight

Each subject was weighed on an electrical scale (Tanita, Tokyo, Japan) which measured body weight to the nearest 0.005 kg. Calibration of the scale occurred daily before any measurements were obtained. Subjects refrained from eating anything for three hours before their appointment. The same one-piece swimsuit used for the BOD POD was also worn during the weigh in. The data for weight was an average of two measurements taken a week apart.

Procedures

At the first appointment, measurements of dietary intake, total physical activity, intensity of physical activity, body weight, percent body fat, homeostasis model assessment of insulin resistance (HOMA-IR), and age were obtained. The Human Performance Research Center at the university served as the location where all laboratory measurements were made. Subjects were informed at the start of their first appointment of any potential risks, as well as the benefits, from participating in the study.

During the first appointment, height, weight, and body fat percentage were measured while wearing a one-piece swimsuit in bare feet. Subjects also received a digital food scale (Ohaus 2000, Florham Park, NJ), seven-day dietary records, and an ActiGraph accelerometer all of which were explained so that each subject had knowledge of proper weighing and logging methods and appropriate use of the activity monitor. Recording of dietary intake and continuous wear of the accelerometer occurred simultaneously during the seven consecutive days.

Statistical Analyses

Dietary fiber intake (total, soluble, and insoluble) was expressed as grams of fiber per 1000 calories. HOMA-IR values were log transformed because the values were not normally distributed, but to facilitate interpretation of the findings, HOMA-IR data in the results section and tables were reported in common clinical units. Regression analysis using the General Linear Model (GLM) procedure was employed to determine the bivariate relationships between each of the three key fiber variables, total, soluble, and insoluble, and insulin resistance, specifically HOMA-IR. Partial correlation, using the GLM framework, was used to determine the extent to which each of the potential confounding variables, age, body weight, body fat percentage, dietary fat intake, total calorie consumption, total physical activity, and intensity of physical activity, influenced the fiber and HOMA-IR associations, considered individually and collectively. Alpha was set at the 0.05 level. Additionally, to assist with interpretation of the data, fiber intake and HOMA-IR scores were each divided into two categories using the median: Low and High. Specifically, the median value for HOMA-IR was 1.3 and for total, soluble, and insoluble fiber intake (grams) per 1000 calories was 8.9, 1.6, and 3.5, respectively. Odds ratios were calculated to determine the relationships between the two dichotomous variables. To determine the statistical significance of the odds ratios, 95% confidence intervals were used. Logistic regression was employed to determine the effect of each of the potential confounding variables on the odds ratios, considered individually and in combination. The SAS (Cary, NC) software program (version 9.1) was utilized for all of the statistical analysis.

Results

This cross-sectional investigation had 264 participants. The majority of the women were Caucasian (~90%), married (~80%), and employed either part- or full-time (~60%). Approximately half had received some college education (~50%). Additional characteristics for the key variables of the study are displayed in Table 1 including: age, weight, body fat percentage, physical activity, fasting insulin, fasting glucose, HOMA-IR, total caloric intake, total fiber weight, total fiber intake per 1000 calories, soluble and insoluble fiber weight, and soluble and insoluble fiber intake per 1000 calories. Average HOMA-IR for these women was 1.5 ± 1.0 and average total, soluble, and insoluble fiber intake (grams) per 1000 calories was 9.3 ± 2.9, 1.7 ± 0.9, and 3.8 ± 1.9 respectively.

Soluble Fiber and HOMA-IR

When both soluble fiber intake and HOMA-IR were treated as continuous variables, there was a 0.112 decrease in HOMA-IR for every one gram increase in soluble fiber intake when no variables were controlled statistically (F = 7.97, $p = 0.0051$) (Table 2). Table 2 shows that after controlling for the individual confounding variables, the relationship remained statistically significant. Further analysis showed that the relationship was weakened slightly, but remained statistically significant, after controlling the following variables individually: body weight (F = 7.62, $p = 0.0062$), percent body fat (F = 6.86, $p = 0.0094$), total caloric intake (F = 6.82, $p = 0.0095$), dietary fat intake (F = 6.78, $p = 0.0098$), total physical activity (F = 6.86, $p = 0.0093$), time in sedentary activity (F = 5.91. $p = 0.0157$), time in moderate activity (F = 5.98, $p = 0.0151$), and lastly, time in vigorous activity (F = 6.69, $p = 0.0102$). Controlling for age was the only confounding variable that strengthened the relationship (F = 8.44, $p = 0.0040$). With all of the potential confounders controlled simultaneously, the association between soluble fiber intake and HOMA-IR changed minimally and remained statistically significant (F = 8.00, p = 0.0051)

When the relationship between soluble fiber intake and HOMA-IR was analyzed with both variables treated as categorical, odds ratios were calculated. Both soluble fiber intake and HOMA-IR were divided into two categories using the median. The odds ratio was 0.58 and statistically significant (95% confidence interval (CI) = 0.36-0.94) with no variables controlled statistically (Table 3). The relationship remained significant, even after controlling for several potential confounding variables individually, including age, percent body fat, body weight, total caloric intake, dietary fat intake, and total physical activity. After controlling for each of the intensity of physical activity measures individually, the relationship between soluble fiber intake and HOMA-IR no longer remained significant. As shown in Table 3, after adjusting for all of the potential confounding variables simultaneously, the odds of having insulin resistance among those with High soluble fiber intake was about one-half that of the women with Low soluble fiber intake (OR = 0.52, 95% CI = 0.29-0.93).

Total Fiber and HOMA-IR

Table 4 displays the relationship between total fiber intake and HOMA-IR, both treated as continuous variables, without and with control of the potential confounding variables. With no variables controlled statistically, the association was statistically significant (F = 4.58, p = 0.0332). For every one gram increase in total fiber consumption, there was a 0.026 decrease in HOMA-IR. The relationship was weakened slightly, but remained statistically significant, after controlling for body weight (F = 3.91, p = 0.0490), total physical activity (F = 3.97, p = 0.0473), and time in vigorous activity (F = 3.90, p = 0.0493). The following confounding variables, however, weakened the relationship to the point that it no longer was significant: percent body fat (F = 1.96, *p* = 0.1631), total caloric intake (F = 3.53, *p* = 0.0613), dietary fat intake (F = 3.41, *p* = 0.0659), time in sedentary activity (F = 3.37, *p* = 0.0676), and time in moderate activity (F = 3.36, *p* = 0.0680), with the last four potential confounders resulting in borderline significance. Age strengthen the relationship after being controlled (F = 4.81, *p* = 0.0291).

Treating total fiber and HOMA-IR as categorical variables resulted in the relationship failing to reach statistical significance (Table 5). The relationship remained insignificant even after controlling for the various confounding variables. However, borderline significance was seen after controlling for total caloric intake (OR = 0.75; 95% CI = 0.46 – 1.00).

Insoluble Fiber and HOMA-IR

None of the relationships between insoluble fiber and HOMA-IR were statistically significant when treated as continuous variables. After controlling for each of the potential confounding variables, the relationships remained insignificant. Similarly, with insoluble fiber and HOMA-IR treated as categorical variables, none of the odds ratios were statistically significant, without and with control of the potential confounders.

Discussion

Insulin resistance is a major cause of Type 2 diabetes and many other metabolic disorders.[4-5, 50] Several studies have determined that dietary fiber reduces insulin resistance and risk of Type 2 diabetes.[12, 14, 16] However, the vast majority of these investigations have focused on total fiber intake. Greater detail and more valuable information can be derived from studying the contributions of soluble and insoluble fiber consumption on insulin resistance, in addition to total fiber intake.

The present investigation uncovered a significant inverse association between soluble fiber intake and insulin resistance in non-diabetic, middle-aged women. However, insoluble fiber consumption was not a significant predictor of insulin resistance. Total fiber intake was also inversely associated with insulin resistance, but the relationship was much weaker than the link between soluble fiber and HOMA-IR. In fact, the relationship between total fiber intake and insulin resistance was completely nullified when differences in soluble fiber intake were controlled statistically ($F = 0.01$, $p = 0.9409$).

Important to the fiber intake and insulin resistance relationship is the fact that obesity and insulin resistance are strongly related. As obesity increases, risk of insulin resistance and Type 2 diabetes increases dramatically.[51-52] Moreover, fiber intake is inversely related to weight gain and obesity.[53-54] Consequently, to isolate the relationship between dietary fiber and insulin resistance, obesity must be controlled. To date, almost all studies have achieved this adjustment by controlling for differences in BMI, yet BMI is not a good index of body composition. Hence, in the present study, body fat percentage was controlled statistically instead of BMI. Controlling for differences in body fat percentage weakened the relationship between soluble fiber and HOMA-IR by 32%, but the association remained significant ($p = 0.0094$). The weaker link between total fiber intake and HOMA-IR was also attenuated substantially by adjusting for differences in body fat percentage (-66%), causing this relationship to become non-significant ($p = 0.1631$).

From these findings, it can be argued that part of the association between fiber intake and insulin resistance is a function of differences in body fat percentage. Although a meaningful relationship remains between soluble fiber and insulin resistance after removing the influence of body fat, the significant relationship between total fiber intake and HOMA-IR is nullified when differences in body fat are taken into account. In short, if all women had the same body fat percentage, the relationship between soluble fiber and insulin resistance would be weaker and the total fiber─HOMA-IR relationship would not exist.

Physical activity (PA) also has a strong effect on insulin sensitivity.[55] Those who exercise or engage in PA regularly have much lower risk of insulin resistance and Type 2 diabetes.[56-57] However, few investigations that have studied the relationship between fiber intake and insulin resistance have controlled for differences in PA, and those which have,[11, 13-14, 26-27] have relied on activity questionnaires, which harbor significant measurement error. To overcome this problem, the present study assessed PA objectively using accelerometry over a 7-day period. Moreover, not only was total PA evaluated, but the mediating roles of PA intensity at the sedentary, moderate, and vigorous levels were also ascertained.

The soluble fiber and HOMA-IR relationship was weakened by controlling for PA intensity, as shown in Table 2, but remained statistically significant. However, when the relationships between soluble fiber intake and HOMA-IR were expressed using odds ratios, and PA intensity was controlled, the results were weakened to the point of non-significance (Table 3). Further, most of the associations between Total fiber intake and insulin resistance were weakened to the point of non-significance when the various levels of PA intensity were controlled. Apparently, a significant portion of the relationship between fiber intake and insulin resistance is a function of differences in PA, particularly PA intensity. To date, this has not been shown in the literature.

To better understand how PA intensity influences the relationship between fiber intake and insulin resistance, post hoc analyses were conducted. Results showed that time spent in sedentary pursuits was related directly to HOMA-IR ($r = 0.153$, $p = 0.0128$). Moderate-intensity PA was inversely associated with insulin resistance ($r = -0.144$, $p = 0.0191$), and time spent in vigorous PA was also inversely related to HOMA-IR ($r = -155$, $p = 0.0114$).

Post hoc analyses showed that PA intensity was also predictive of fiber intake. Specifically, time spent in sedentary behaviors was inversely related to total fiber (r = -0.214, p = 0.0005), soluble fiber (r = -0.208, p = 0.0007), and insoluble fiber consumption (r = -0.178, p = 0.0037). Time spent in moderate intensity activities was a significant predictor of each of the fiber variables: total fiber (r = 0.223, p = 0.0003), soluble fiber (r = 0.221, p = 0.0003), and insoluble fiber (r = 0.188, p = 0.0022). Lastly, time spent in vigorous PA was predictive of total fiber (r = 0.145, p = 0.0185) and soluble fiber intake (r = 0.149, p = 0.0157), and the insoluble fiber relationship was borderline significant (r = 0.104, p = 0.0913). Overall, it appears that physically active women tend to eat more fiber than sedentary women, which partly explains why women who eat more fiber tend to have less insulin resistance.

The relationship between fiber intake and insulin resistance was influenced by several mediating factors other than body fat and physical activity. For example, adjusting for differences in body weight weakened the association because of the strong correlation between body weight and body fat percentage (r = 0.69, $p < 0.001$). Controlling for dietary fat intake also weakened the fiber─HOMA-IR relationship. Post hoc analyses revealed that this was because of the inverse association between dietary fat consumption and total fiber (r = -0.42, $p < 0.0001$), soluble fiber (r = -0.29, $p < 0.0001$), and insoluble fiber (r = -0.35, $p < 0.0001$). Total energy (kcal) intake was not related significantly to any of the fiber variables because each fiber variable was corrected for differences in energy intake (i.e., grams per 1000 kcal). However, kcal intake was predictive of fiber intake, not expressed per 1000 kcal, as shown by post hoc analyses: grams of total fiber (r = 0.37, $p < 0.0001$), soluble fiber (r = 0.23, p = 0.0002), and insoluble fiber consumed (r = 0.22, p = 0.0004).

The relationship between fiber intake and HOMA-IR was also evaluated using odds ratios. In women who had high soluble fiber intake (upper 50%), the odds of having an elevated HOMA-IR level was 0.58 (95% CI: 0.36-0.94) times that of women with low soluble fiber intake (lower 50%). And after controlling for all of the potential confounding factors simultaneously, the odds ratio was 0.52 (95% CI: 0.29-0.93). In other words, women with high fiber intake had only one-half the likelihood of insulin resistance compared to those with low fiber consumption, a substantially lower probability.

The relationship between fiber intake and insulin resistance has been researched before. However, there are many differences among previous studies, especially regarding the confounding variables that were measured and accounted for when examining this relationship. In a cross-sectional study of non-diabetic male and female adults with a family history of type 2 diabetes, the observed inverse association between total, insoluble, and soluble fiber and insulin resistance was independent of sex, age, physical activity assessed through questionnaire, BMI, and several other factors.[14] Cross-sectional analyses of the Framingham Offspring study controlled for several variables when examining this relationship, including sex, age, BMI, percentage of saturated and polyunsaturated fat, total energy intake, physical activity score obtained through questionnaire, and others.[13] Among non-diabetic Danish men and women in a cross-sectional study, the relationship was adjusted for age, sex, physical activity obtained from a self-administered questionnaire, total energy intake, BMI, and waist circumference.[11]

In addition to the cross-sectional studies examining this relationship, prospective studies like the San Luis Valley Diabetes Study included in their analysis: age, gender, ethnicity, BMI, waist circumference, total energy, and vigorous activity as determined by a questionnaire.[26] A 10-year cohort study of healthy black and white adults controlled for several covariates including sex, age, BMI, energy intake, total physical activity (questionnaire), and others.[27] Collectively, these studies demonstrate the large variation among the confounding variables adjusted for in the examination of this relationship. Of the five studies listed, all controlled for BMI and questionnaire measured physical activity, one accounted for percentage of saturated and polyunsaturated fat, four adjusted for total energy intake, and only one accounted for all four mediating variables. The present study also accounted for these variables, but used higher quality measurement methods. Specifically, physical activity was measured objectively, and instead of BMI, percent body fat was controlled statistically. These improvements make this study unique when compared to previous research examining this relationship.

Strengths of the present study include its large sample size (n=264), measurement of soluble and insoluble fiber in addition to total fiber intake, statistical control of percent body fat instead of BMI, objective assessment and statistical control of total physical activity as well as physical activity intensity, and statistical adjustment for differences in total energy intake and dietary fat intake.

The present study was not without weaknesses, however. The cross-sectional design prevents cause-and-effects conclusions to be drawn because of the issue of temporality. Also, because the investigation focused on non-diabetic, middle-aged, non-smokers, and the sample included mostly White, non-Hispanic women, in the strictest sense, generalization should be limited to women with similar characteristics.

The observed results for soluble fiber support the proposed mechanisms by which soluble fiber influences the digestion of carbohydrates. Consumption of higher amounts of soluble fiber, especially those with high viscosity, slows gastric emptying time.[58-59] This delay results in a gradual release of glucose which corresponds to a lower insulin response.[58-59]

Several other mechanisms have been proposed as well. Because fiber is found only in plant foods, there is also the possibility that other plant constituents affect the process by which fiber influences insulin resistance. Magnesium is one example which has been researched and is suspected to influence insulin resistance.[7, 60] As observed in the present study, another factor, body fat, attenuated the relationship between soluble fiber and insulin resistance. In short, a portion of the fiber and insulin resistance relationship can be explained by differences in body fat percentage. Moreover, fiber intake is inversely related to weight gain and obesity.[53-54] Fiber rich foods promote satiation and satiety and may reduce calorie consumption which over time leads to weight loss or prevention of further weight gain.[61] Additional research is needed regarding the mechanisms by which fiber, particularly soluble fiber, reduces the risk of insulin resistance.

In summary, the relationship between fiber intake, particularly soluble fiber, and insulin resistance appears meaningful. However, the insoluble fiber and HOMA-IR association is weak. Total fiber also appears to be a good predictor of insulin sensitivity, but the association appears to be mostly a function of soluble fiber intake. A moderate portion of the soluble fiber and insulin resistance relationship appears to be a result of differences in body fat and physical activity intensity, as well as energy intake and dietary fat consumption. However, independent from these factors, soluble fiber remains a good predictor of lower levels of insulin resistance.

In conclusion, the literature contains dozens of investigations showing that dietary fiber tends to reduce insulin resistance. The vast majority of these studies, however, have not used high quality measurement methods when accounting for potential mediating factors. Future research will need to be careful to isolate the effects of fiber intake on insulin sensitivity, since body fat, intensity of physical activity, and other dietary factors can influence the relationship between fiber intake and insulin resistance.

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Table 1 Descriptive Statistics (n = 264)

Variables	Mean	SD	Minimum	25th percentile	Median	75th percentile	Maximum
Ages (years)	40.1	3.0	34.0	38.0	40.0	43.0	46.0
Weight (kg)	66.1	10.1	42.1	58.9	65.2	72.2	95.5
Body Fat (%)	31.7	6.9	14.6	27.1	32.2	36.9	44.8
Physical Activity (counts)*	2704.4	784.2	827.8	2096.9	2674.0	3173.6	4945.9
Fasting Insulin (μU/mL)	7.1	4.3	1.2	4.3	6.1	8.5	34.8
Fasting Glucose (mg/dL)	86.7	5.9	73.0	82.0	87.0	90.0	111.0
HOMA-IR	1.5	1.0	0.2	0.9	1.3	1.9	8.3
Total Kcal	2054.1	320.9	1504.0	1822.1	2009.1	2230.4	3495.1
Total Fiber Weight (g)	19.1	6.4	7.6	14.6	18.0	22.6	42.4
Total Fiber Intake per 1000 kcal (g)	9.3	2.9	3.5	7.4	8.9	10.8	19.9
Soluble Fiber Weight (g)	3.5	1.8	0.4	2.2	3.2	4.3	13.0
Soluble Fiber per 1000 kcal (g)	1.7	0.9	0.2	1.1	1.6	2.1	6.5
Insoluble Fiber Weight (g)	7.8	3.9	1.1	5.1	7.1	9.9	26.1
Insoluble Fiber per 1000 kcal (g)	3.8	1.9	0.5	2.5	3.5	4.8	12.0

SD = standard deviation

Minimum and Maximum represent the lowest and highest values within the entire sample

*Actual counts were measured objectively through accelerometers and are averages of weekly activity counts divided by 1000

Table 2 Differences in insulin resistance (HOMA-IR) corresponding to a one gram difference in soluble fiber intake, independent of key potential confounding variables

Differences in HOMA-IR	***b*[a]**	**F**	**P**
Variable Controlled:			
None	-0.112	7.97	0.0051
Age	-0.120	8.44	0.0040
Body Weight	-0.097	7.62	0.0062
Percent Body Fat	-0.085	6.86	0.0094
Total Caloric Intake	-0.096	6.82	0.0095
Dietary Fat Intake	-0.107	6.78	0.0098
Total Physical Activity	-0.092	6.86	0.0093
Time in Sedentary Activity	-0.086	5.91	0.0157
Time in Moderate Activity	-0.086	5.98	0.0151
Time in Vigorous Activity	-0.096	6.69	0.0102
All Confounders*	-0.094	7.82	0.0055

[a] *b* = regression coefficient

*In the full model, the following variables were controlled statistically: age, percent body fat, body weight, total caloric intake, dietary fat intake, total physical activity, and physical activity intensity.

Table 3 Odds of insulin resistance in women with low soluble fiber intake compared to high soluble fiber intake in women.

	Outcome: Insulin Resistance Soluble Fiber Intake Low vs High	
Odds of Insulin Resistance	**OR**	**95% CI**
Variable Controlled:		
None	0.58	0.36-0.94
Age	0.57	0.35-0.94
Percent Body Fat	0.51	0.30-0.87
Body Weight	0.52	0.31-0.89
Total Caloric Intake	0.59	0.36-0.97
Dietary Fat Intake	0.60	0.36-0.98
Total Physical Activity	0.60	0.37-0.97
Time in Sedentary Activity	0.64	0.39-1.04
Time in Moderate Activity	0.63	0.39-1.04
Time in Vigorous Activity	0.62	0.38-1.01
All covariates*	0.52	0.29-0.93

OR = odds ratio.

95% CI = 95% confidence interval.

*In the full model, the following variables were controlled statistically: age, percent body fat, body weight, total caloric intake, dietary fat intake, total physical activity, and physical activity intensity.

Table 4 Differences in insulin resistance (HOMA-IR) corresponding to a one gram difference in Total fiber intake, independent of key potential confounding variables

Differences in HOMA-IR	***b*[a]**	**F**	**P**
Variable Controlled:			
None	-0.026	4.58	0.0332
Age	-0.028	4.81	0.0291
Percent Body Fat	-0.012	1.96	0.1631
Body Weight	-0.021	3.91	0.0490
Total Caloric Intake	-0.021	3.53	0.0613
Dietary Fat Intake	-0.025	3.41	0.0659
Total Physical Activity	-0.022	3.97	0.0473
Time in Sedentary Activity	-0.020	3.37	0.0676
Time in Moderate Activity	-0.020	3.36	0.0680
Time in Vigorous Activity	-0.023	3.90	0.0493
All covariates*	-0.017	2.87	0.0914

[a] *b* = regression coefficient

*In the full model, the following variables were controlled statistically: age, percent body fat, body weight, total caloric intake, dietary fat intake, total physical activity, and physical activity intensity.

Table 5 Odds of insulin resistance in women with low Total fiber intake compared to high Total fiber intake

	Outcome: Insulin Resistance Total Fiber Intake Low vs High	
Odds of Insulin Resistance	**OR**	**95% CI**
Variable Controlled:		
None	0.74	0.46-1.20
Age	0.74	0.45-1.21
Body Weight (kg)	0.67	0.40-1.13
Percent Body Fat (%)	0.80	0.48-1.36
Total Caloric Intake	0.75	0.46-1.00
Dietary Fat Intake	0.79	0.47-1.33
Total Physical Activity	0.76	0.47-1.23
Time in Sedentary Activity	0.83	0.50-1.36
Time in Moderate Activity	0.82	0.50-1.35
Time in Vigorous Activity	0.80	0.49-1.31
All Covariates*	0.79	0.43-1.45

OR = odds ratio.

95% CI = 95% confidence interval.

*In the full model, the following variables were controlled statistically: age, percent body fat, body weight, total caloric intake, dietary fat intake, total physical activity, and physical activity intensity.

Prospectus

Dietary Fiber Consumption and Insulin Resistance: The Role of Body Fat and Physical Activity

Charity Breneman

Chapter 1

Introduction

The prevalence of obesity throughout the United States has increased dramatically over the past 25 years. National Health and Nutrition Examination Survey (NHANES) results indicate that over one-third of the adult population in the United States is obese, encompassing 35.5% of women and 32.2% of men.[1] This upward trend is not without consequences. A review of the health consequences of obesity shows that as the body mass index (BMI) increases so does the risk of many health problems, including some forms of cancer, cardiovascular disease, type 2 diabetes, and other life threatening disorders.[2]

One of the key health problems associated with obesity is insulin resistance, a common metabolic condition that can lead to a host of serious chronic diseases.[3] Because insulin resistance is a precursor of several diseases, it has received considerable attention. Some of the diseases closely connected to insulin resistance in individuals are hypertension, type 2 diabetes, and cardiovascular disease.[4-6] Facchini et al.[4] examined prospectively the extent to which insulin resistance predicts age-related diseases, including: hypertension, coronary heart disease, stroke, cancer, and type 2 diabetes. Results showed that approximately 1 out of 3 of the initially healthy subjects in the upper tertile of insulin resistance developed an age-related disease.[4] Clearly, insulin resistance is a serious health risk. Consequently, additional research is warranted to determine strategies that will reduce insulin resistance in adults and curb the risk of many life-threatening diseases.

Fortunately, insulin resistance can be improved through lifestyle changes, particularly weight loss and regular physical activity.[7] Moreover, the literature shows that diets high in carbohydrates and fiber as well as low in fat are associated with increases in insulin sensitivity.[7-

[10] Consuming a healthy diet may reduce the pathogenesis of insulin resistance and thus decrease the risk for type 2 diabetes and cardiovascular disease.

One of the main focuses of studies examining dietary approaches to reducing the risk of insulin resistance is fiber intake. To date, many investigations have examined the link between fiber intake and insulin sensitivity.[18-34] Comparison of these studies is difficult, given the many different methods used for detecting insulin resistance and the limitations of some dietary assessment methods. No doubt, research methods in this area can be improved due to the inconsistencies and limitations of some measurement methods.

Studies focusing on dietary fiber consumption and insulin resistance have displayed several consistent weaknesses. For example, most studies have used BMI when controlling for obesity.[18-25, 33] BMI is not a high quality index of percent body fat.[11] Very few studies have used percent body fat to index obesity, and the few investigations that have assessed body fat have used weak measurement methods,[25] like bioelectrical impedance analysis (BIA).[12-13] Since obesity strongly influences insulin concentrations, percent body fat, measured using reliable methods, should be part of investigations designed to establish a more valid association between dietary fiber intake and insulin resistance.

Additionally, physical activity has a strong influence on insulin sensitivity and the predominant assessment form in epidemiological studies has been questionnaires.[14-15] This measurement method relies on self-report and thus contains significant error, since memory and a desire to appear favorably are key factors associated with such self-reported data.[16] Objective methods, such as pedometers or accelerometers, would provide a better approach to evaluating physical activity among subjects, and would also serve as a better potential confounding variable than has been used in past studies.

To date, most studies which have examined the relationship between fiber intake and insulin resistance have focused on total fiber consumption.[18-20, 22-24, 26-27, 29, 33-34] However, the association can be studied in more detail by dividing dietary fiber into two categories: soluble and insoluble. Given these fibers have vastly different effects on food absorption and digestion, the independent effect of total, soluble, and insoluble fibers on insulin sensitivity deserves further research.

Overall, additional research employing more valid and reliable measurement methods to evaluate the relationship between fiber intake and insulin resistance is needed. These methods include using percent body fat over BMI, and an objective measure of physical activity, rather than a self-reported questionnaire. Additionally, fiber intake broken down into total, soluble, and insoluble categories would provide more detailed results that would establish the extent to which these three types of fiber differ in their influence on insulin. Together, these methodological differences would result in a high-quality investigation that should afford more information about the true association between fiber intake and insulin resistance in women.

Statement of the Problem

This study will focus on determining the association between total dietary fiber intake and insulin resistance in approximately 275 women. The extent to which soluble and insoluble fiber consumption predict insulin resistance will be examined as well. Additionally, the influence of age, body fat percentage, body weight, total physical activity, intensity of physical activity, dietary fat intake, and total caloric consumption on the fiber and insulin resistance relationships will also be investigated.

Research Questions

1. To what extent is total dietary fiber intake (grams per 1000 kcal) related to insulin resistance in middle-aged women?
2. To what extent is soluble fiber intake (grams per 1000 kcal) associated with insulin resistance levels in middle-aged women?
3. To what extent is insoluble fiber intake (grams per 1000 kcal) associated with insulin resistance in middle-aged women?
4. To what extent is fiber intake, total, soluble, and insoluble (grams per 1000 kcal) associated with insulin resistance levels in middle-aged women after controlling statistically for differences in age, body fat percentage, body weight, objectively measured physical activity, intensity of physical activity, dietary fat intake, and total energy consumption, individually and in combination?

Delimitations

The data that will be used in this proposed study was collected as part of the Brigham Young University (BYU) Lifestyle Project. Several factors determined whether individuals were included in the Lifestyle Project sample, including age, gender, tobacco use, BMI, and health. Pre-menopausal women between the ages 35 and 45 who had a BMI of less than 30 kg/m^2 were potential subjects. Telephone interviews limited the sample to only healthy, nonsmoking women who had no plans of becoming pregnant in the course of the study. Data on dietary intake was collected through seven-day food diaries. Physical activity was measured objectively using accelerometers. The BOD POD was used to measure percent body fat, and the homeostasis model assessment of insulin resistance (HOMA-IR) was used to index insulin resistance in all participants.

Limitations

There is potential error when using self-reported methods to assess food intake over a period of time. Unconscious changes in habitual diet as well as inaccurate usage of the digital food scale could potentially influence the data collected. Also, the accelerometer could have been incorrectly worn during the course of physical activity assessment which could influence results when controlling for this confounding factor. Other limitations include those associated with a cross-sectional study design and the inclusion of only middle-aged women as subjects in the study.

Definitions

<u>Insulin resistance</u>: Decreased ability of the muscle and fat tissues to respond to the hormone insulin, as a result, the body produces abnormally high amounts of insulin to compensate. Insulin resistance will be estimated through the HOMA-IR as calculated by the following equation: fasting insulin (μU/ml) x fasting glucose (mg/dL)/405.[17]

<u>Body Fat Percentage</u>: The amount of adipose tissue found within an individual's body, expressed as a percentage of body weight. Body fat percentage will be estimated using the BOD POD.

<u>Physical Activity</u>: Any bodily movement produced by skeletal muscle, objectively measured using accelerometers worn for seven consecutive days in the present study.

<u>Dietary Fiber</u>: The non-digestible portion of plant cell walls that is classified into soluble and insoluble fiber and will be measured in grams of fiber per 1000 calories consumed.

<u>Soluble Dietary Fiber</u>: The type of dietary fiber that is soluble in water and will be expressed in grams per 1000 calories eaten.

<u>Insoluble Dietary Fiber</u>: This type of dietary fiber is insoluble in water and will be expressed in grams per 1000 calories consumed.

Chapter 2

Review of Literature

Insulin resistance is often found in association with obesity and physical inactivity and has been observed as a risk factor for type 2 diabetes and atherosclerotic diseases.[2-3] These diseases and disorders are becoming more common today because of the upward trend in the prevalence of obesity.[3] Consequently, many researchers are focusing on developing strategies that promote weight loss and reduce the occurrence of insulin resistance to curtail the growing epidemic of type 2 diabetes and its consequences.

Several lifestyle interventions have been employed to assist adults, particularly those who are overweight or obese, in their quest to increase insulin sensitivity and to reduce the risk of developing type 2 diabetes. Research shows that changing dietary intake is one of the best strategies to reduce insulin resistance. [7-10] The authors of numerous reviews have presented similar conclusions indicating that a high-carbohydrate, high-fiber, and low-fat diet is associated with increased insulin sensitivity.[7-10] Several of these reviews have mentioned difficulty when interpreting the related studies due to the different methods used in detecting insulin sensitivity and the limitations of dietary assessments. However, the authors of the reviews have drawn similar conclusions regardless of the varied study designs and techniques of obtaining data.

The purpose of this current review is to provide an overview of the literature that discusses dietary fiber intake and its relationship with the occurrence of insulin resistance, whether decreasing the risk or increasing insulin sensitivity. Since very few studies have examined soluble and insoluble fiber separately, this review will examine dietary fiber and the effect whole grains have on insulin sensitivity, as well as the few studies on the types of fiber.

This review will categorize the related studies according to research design and will follow the respective order: cross-sectional, experimental, and prospective.

Cross-Sectional

Studies that use a cross-sectional design provide a way to determine the extent to which two or more variables are related. The following studies found an inverse relationship between insulin resistance and dietary fiber or whole grain intake. Most of these studies, however, used body mass index (BMI) as a means to control for the influence that obesity has on the prevalence of insulin resistance. Particular attention should be given to the studies that utilized BMI because of the limitations associated with this method.

Lau et al.[18] examined the relationship between insulin resistance and daily values of simple sugars, dietary fiber, glycemic load, and glycemic index. Data from an intervention study called Inter99 was used in which the nationality of the population was Danish. After excluding some participants, the authors included a total of 5,675 individuals in the study. A food frequency questionnaire (FFQ) was self-administered to the participants in which they reported their dietary intake for the month prior. Other data collected was waist circumference, BMI, physical activity, smoking status, and homeostasis model assessment of insulin resistance (HOMA-IR). The data collected on physical activity and smoking status was obtained from a self-administered questionnaire. An inverse relationship was seen between increases in daily consumption of glucose, fructose, dietary fiber, vegetables, and fruit with HOMA-IR. This inverse relationship between HOMA-IR and carbohydrate and glycemic load was no longer significant after adjusting for dietary fiber intake. A dietary fiber intake of 10 grams per day had a HOMA-IR ratio of 0.97, thus showing an inverse association that was statistically significant (95% confidence interval [CI]: 0.96-0.99). This relationship remained statistically significant after adjusting for potentially confounding factors (95% CI: 0.96-0.99). The authors concluded that dietary fiber intake may play a role in preventing insulin resistance after controlling for obesity.

Lutsey et al.[19] looked at whole grain intake and its association with insulin resistance and other factors by using data from the MESA prospective cohort study. Total number of participants was 6,814 men and women who ranged in age from 45 to 84 years. This particular study collected data on BMI, current smoking status, alcohol use, self-reported physical activity, and dietary intake from a self-administered FFQ. This FFQ was only administered once and as a result the dietary assessment was based solely on a single measurement. In order to evaluate the different relationships with whole grain, three models were developed in which Model 1 was adjusted for age, race, gender, education, and energy intake. There was an inverse relationship between whole grain consumption and BMI, HOMA-IR, and serum insulin along with other factors. Comparing the lowest quintile to the highest quintile in Model 1, a HOMA-IR score of 1.70 versus 1.50 mU/l*mmol/l showed that as whole grain intake increased, HOMA-IR decreased ($p < 0.0001$ across all quintiles), indicating a strong inverse association between whole grain consumption and HOMA-IR.

McKeown et al.[20] (2004) used data collected from the Framingham Offspring Study on 2,834 subjects. The relationship between carbohydrate intake, insulin resistance, and prevalence of metabolic syndrome was examined using the HOMA-IR method to determine insulin resistance. BMI, waist to hip ratio, and dietary data through a semi-quantitative FFQ were collected. Lower values of insulin resistance were associated with higher consumption of whole grain and dietary fiber, including fruit and cereal fiber. The inverse relationship between whole grains and HOMA-IR was attenuated and became insignificant after adjusting for cereal ($p =$

0.34) and fruit (*p* = 0.09) fiber. When examining the inverse relationship between cereal fiber and HOMA-IR, the association remained significant after controlling for whole grains (P = 0.003). Another observation made from the data was how the inverse relationship between HOMA-IR and the intake of whole grain, dietary fiber, and cereal fiber became stronger as the subjects' BMI increased.

Ylonen et al.[21] examined the relationship between total, soluble, and insoluble fiber with insulin resistance, insulin secretion, and glucose concentrations among 552 subjects with relatives diagnosed with type 2 diabetes. Data from the Botnia Dietary Study was used in this cross-sectional study. Two 3-day estimated food records were used to examine dietary intake in which six months separated the two records. Blood samples, BMI, waist circumference, waist-to-hip ratio, and blood pressure were collected. Physical activity during the past twelve months was assessed through questionnaire. An inverse association was found between total, soluble, and insoluble fiber with insulin resistance which was estimated through HOMA-IR, and this relationship was independent of gender, age, physical activity, BMI, waist to hip ration, systolic blood pressure, serum triglyceride, HDL cholesterol, and NEFA concentrations. When gender was examined separately, insulin resistance was no longer significantly related to total, soluble, and insoluble fibers.

Taiwanese vegetarians were the target population in a study conducted by Hung et al.[22] in which the relationship between habitual vegetarian diet and hormone levels and glycemic and lipid control was examined. The study used 98 non-smoking and non-alcoholic drinking females between the ages of 31 and 45 in which half were vegetarians and the other half were omnivores. The subjects' dietary intake was collected using the 24-hour recall method, along with HOMA-IR and blood levels of hormones, glucose, and glucagon. Dietary analysis showed that a

Taiwanese vegetarian diet typically consisted of mainly grains, rice, vegetables, fruits, and large amounts of soyabeans and soya products, which resulted in containing high amounts of fiber and a low fat content. When comparing the two groups, the vegetarian group was found to have significantly lower insulin resistance than the omnivores. After performing a multiple regression analysis, both BMI and diet were observed to be independent predictors of HOMA-IR, where BMI explained 18% of the variation in insulin resistance and diet only 15%. After controlling for BMI, the Taiwanese vegetarians were 30% lower in insulin resistance than the omnivores, which was concluded to be a result of both the vegetarian diet and the lower BMI among vegetarians; both of which may play a role in increasing insulin sensitivity. Further investigation into the components of whole grain revealed that only fiber and magnesium were found to explain a significant portion of the relationship.

In a study conducted by Liese et al.[23], the relationship between whole grain intake and insulin resistance was examined among 1,625 subjects of differing ethnicities. The data on the subjects was obtained from the Insulin Resistance Atherosclerosis Study in which the dietary assessment was measured through an interview that used a semi-quantitative FFQ and physical activity was assessed through a one year recall. BMI, waist circumference, and insulin sensitivity through an intravenous-glucose-tolerance test were also collected. The authors found that an increased consumption of whole grains was associated with increased insulin sensitivity, independent of sex, age, race, and total caloric intake. This relationship was weakened slightly after adjusting for BMI and waist circumference. The average insulin sensitivity was 2.16 ± 1.96 $min^{-1} \bullet \mu U^{-1} \bullet mL^{-1} \bullet 10^{-4}$ which improved by 0.075 ± 0.024 ($p = 0.001$) for every increase in whole grain servings per day. The fiber and magnesium portions of whole grain were concluded to be the explanation for the association between whole grain and insulin sensitivity.

Lovejoy and DiGirolamo[24] examined the relationship between habitual dietary intake and insulin sensitivity in twenty-two lean and twenty-three obese subjects. BMI, waist-to-hip ratio, blood samples, and dietary intake were collected on each subject. The Health Habits and History Questionnaire was utilized to assess dietary intake. Initial comparison of subjects revealed that the obese subjects had statistically significant higher fasting glucose and insulin levels as well as reduced insulin sensitivity. Dietary analysis showed that the obese subjects consumed significantly lower amounts of fiber ($p = 0.006$) and carbohydrates ($p = 0.007$) and higher amounts of fat ($p = 0.001$). Insulin sensitivity (log of the insulin sensitivity index) was positively and significantly associated with total dietary fiber ($r = 0.43$; $p = 0.01$). Dietary fiber intake explained 18% of the variation in insulin sensitivity. Consumption of low amounts of fiber and high amounts of fat were associated with increased insulin resistance.

In conclusion, most of the above studies found an inverse relationship between insulin resistance and whole grains/fiber. Some of the authors made the conclusion that when examining the association between whole grain and insulin resistance, dietary fiber was the reason for the observed inverse relationship. A higher intake of dietary fiber was also shown to have lower levels of insulin resistance in the subjects. Several limitations can be seen when examining these cross-sectional studies, including the utilization of BMI as a measurement of obesity and FFQ as a dietary assessment tool.

Experimental

Experimental research studies the effects of a treatment or intervention in order to determine whether a cause and effect relationship exists. The investigations reviewed examine many different aspects of insulin resistance, such as insulin sensitivity, insulin response, or the reduction of insulin resistance. Also, some studies focused on the effect that supplementing fiber into a diet would have on insulin resistance, whereas others changed some aspect of the participants' diet. Again, attention should be given to the measurement methods used to examine obesity, dietary intake, and physical activity.

Weickert et al.[25] investigated whether insoluble cereal fiber would have an effect on insulin sensitivity. The study design was a controlled randomized cross-over in which seventeen overweight/obese female subjects were included. The intervention diet lasted for three days and consisted of three specific portions of oat fiber-enriched bread or the control white bread, with the rest of the caloric intake coming from liquid meals. Fiber intake was within the recommended daily requirement. Euglycemic-hyperinsulinemic clamp was used to assess whole-body insulin sensitivity among the subjects. Lean mass was found using bioelectrical impedance analysis along with the measurement of BMI, resting energy expenditure (REE), respiratory quotient, weight, and blood samples. Results show significant improvements of 13% in insulin sensitivity among the subjects within a 72-hour period of consuming a diet containing the recommended range of insoluble fiber.

The relationship between diets containing high amounts of carbohydrate and fiber and insulin sensitivity was examined by Fukagawa et al.[26] The subjects consisted of twelve healthy young and old individuals, six within each age group. The intervention diet lasted from 21 to 28 days and consisted of carbohydrates that comprised 68% of their dietary intake, which contained fiber from whole grains, vegetables, and fruits. This diet was found to decrease fasting insulin by 24% in both young and old subjects ($p < 0.01$). Insulin sensitivity increased significantly among healthy adults as a result of the high carbohydrate/high fiber diet.

Pereira et al.[27] examined whether whole grains would increase insulin sensitivity among overweight/obese hyperinsulinemic adults using a randomized, controlled cross-over design.

The participants consisted of six women and five men who were selected through strict criteria. Habitual dietary intake was assessed before the baseline examination by administering the Health Habits and History Questionnaire to the subjects. Examination of the subjects' habitual diet revealed a low intake of vegetables, carbohydrates, fruit, and fiber. Each participant was assigned to receive either the whole-grain or refined-grain diet for two six-week periods. After each period, a euglycemic-hyperinsulinemic clamp test was administered to each subject. The diet containing whole grain improved insulin sensitivity (mean difference: 0.07×10^{-4} mmol · kg^{-1} · min^{-1} per pmol/L; 95% CI: 0.003×10^{-4}, 0.144×10^{-4}; $p < 0.05$) over the 6-week period when compared to the refined grain diet. There was lower levels of insulin resistance after consumption of whole grains (5.4 ± 0.18 U) compared to the refined grain diet (6.2 ± 0.18 U) as shown by the homeostasis model. Whole grains may effectively improve insulin sensitivity in overweight, hyperinsulinemic adults within a 6 week period.

A randomized cross-over study was conducted by Juntunen et al.[28] in which the relationship between high fiber rye bread and insulin secretion/sensitivity was investigated. The study design consisted of an eight week test period followed by an eight week washout period. The subjects for this study consisted of 20 postmenopausal women (age: 59 ± 6.0 y; BMI: 27.5 ± 2.9). The test breads used in the study were high-fiber rye bread, and white bread, which made up around 20% of the daily caloric intake. A frequently sampled intravenous-glucose-tolerance test (FSIGTT) was administered to the subjects in the morning after fasting overnight. The results showed that the rye bread significantly increased acute insulin response (9.9 ± 24.2%) compared to the wheat bread (2.8 ± 36.3%; $p = 0.047$). No significant changes occurred in insulin sensitivity.

Rave et al.[29] used a randomized two-way cross-over study to examine the effect of a hypo-energetic diet with whole grains on insulin resistance within 31 obese male and female subjects (BMI > 29 and < 40) who had elevated fasting glucose. Body weight, waist to hip ratio, blood pressure, and blood samples were obtained from each subject. The subjects were randomly assigned to consume either a whole grain-based diet or a meal replacement diet for a four-week period; after a two week washout period, the subjects were crossed over to the other diet for another four-weeks. Both diets contained similar contents of dietary fiber; however, the whole grain diet contained mostly insoluble fiber whereas the fiber content of the meal replacement was mostly soluble fiber. Both hypo-energetic diets resulted in a decrease in insulin resistance, fasting blood glucose, and serum insulin in which there were no significant differences between treatments. Independent of the amount of weight lost, HOMA-IR score ($p = 0.049$) improved more after the completion of the whole grain diet as compared to the meal replacement.

Vuksan et al.[30] examined the effects of soluble fiber from Konjac-mannan (KJM) on a diet high in carbohydrates in eleven subjects with insulin resistance. Subjects were randomly assigned to either the control diet containing wheat bran fiber or the KJM fiber-enriched diet for a three week treatment period. The subjects then were crossed over to the other diet for another three week period after a two week washout period. Analysis revealed that metabolic control improved with the addition of the KJM fiber to the diet of subjects with insulin resistance. Significant reductions occurred in hyperglycemia and hyperlipidemia; however, no significant differences were seen for insulin concentrations between the two treatments (a treatment difference of $3.9 \pm 8.9\%$; $p = 0.9683$). The authors concluded that KJM along with other viscous fibers may improve diets already high in carbohydrates and thus help with reducing insulin resistance.

Kim et al.[31] researched the relationship between glucose and insulin responses with whole grains containing soluble fiber in which seventeen obese women with an increased risk of developing insulin resistance were included in the sample. The study used a random cross-over design. Each subject consumed a two-day controlled diet followed by the intervention diet containing varying amounts of soluble fiber. The insulin response was significantly reduced at 30 minutes ($p < 0.05$) and 60 minutes ($p < 0.05$) after consuming barley that contained 10 grams of β-glucan as compared to the lower amounts of β-glucan. Obese women with an increased risk for insulin resistance may benefit from consuming products high in β-glucan whole grain.

Hallfrisch et al.[32] conducted a controlled cross-over experiment to determine whether soluble oat extracts have a beneficial effect on risk factors of both heart disease and diabetes mellitus. A total of 23 hypercholesterolemic subjects were included, seven men and sixteen women. The study began with a one week equilibration period in which subjects were required to consume a provided standard diet. The subjects were divided into two groups with one group consuming initially a diet containing 1% β – glucan for five weeks and the other group initially consuming a diet containing 10% β – glucan during the same five weeks. Meals were prepared by researchers and subjects were instructed to consume all the food. No other food was allowed to be consumed except coffee, tea, or water. Subjects were weighed daily and blood samples were collected with plasma radioimmunoassay. Significant declines were observed in glucose ($p < 0.05$), insulin ($p < 0.05$), and glucagon ($p < 0.05$) responses as a result of consuming carbohydrate loads containing either 1% or 10% of β – glucans. Analysis revealed that insulin responses declined in both men and women as increasing amounts of soluble fiber were consumed.

Even though different aspects of insulin sensitivity were examined using studies employing experimental designs, most of the studies came to similar conclusions. Several studies examined the relationship between insulin sensitivity and some form of a fiber rich diet, of which three of the four studies observed insulin sensitivity to improve after the intervention period. Whole grains, a high fiber food, were also found to decrease insulin resistance and may benefit those at risk for developing insulin resistance.

Prospective

Prospective research allows for data to be collected over a longer period of time compared to cross-sectional or experimental research. Moreover, risk of developing insulin resistance over time can be ascertained using prospective cohort research. Very few prospective studies have researched the association between fiber intake and insulin resistance.

Marshall et al.[33] studied the association of fat, carbohydrates, and fiber with hyperinsulinemia among a non-diabetic population. The sample size was 1,069 Hispanic and non-Hispanic individuals ranging from 20-74 years old (53.2% were female). Data was collected during three visits between the years 1984 and 1992 and during each of these visits fasting insulin concentrations and a 24-hour dietary recall by trained interviewers were obtained. BMI, alcohol consumption, and frequency/duration of vigorous activity were also measured. High saturated fat consumption ($p = 0.02$) and low intake of starch ($p = 0.0007$) and fiber ($p = 0.008$) were associated with higher concentrations of fasting insulin independent of age, race, sex, activity, BMI, waist circumference, gender and total caloric intake. Analysis showed that diets high in fat and low in carbohydrates were related significantly with fasting hyperinsulinemia.

Ludwig et al.[34] examined the association between dietary fiber intake and weight gain, insulin levels, and other risk factors of cardiovascular disease. The sample consisted of 2,909 healthy adults between the ages of 18 to 30 years and subjects were either Caucasian or African American. The data collected at year 10 consisted of body weight, insulin levels, and other CVD risk factors. The diet assessment consisted of a quantitative FFQ administered by an interviewer in which around 700 foods were included. This diet history survey was validated against 7 random 24 hour diet recalls collected on the participants. In only the Caucasian participants, comparison of the lowest and highest quintiles of fasting insulin levels showed a mean difference of -5.6 pmol/L in dietary fiber ($p = 0.07$) and +4.2 pmol/L in saturated fat ($p = 0.05$), independent of BMI and other confounding factors. In African Americans, only fiber was associated with fasting insulin level (-9.7 pmol/L, $p = 0.01$). Dietary fiber was concluded to reduce the risk of hyperinsulinemia by lowering insulin levels and also by decreasing obesity.

The above prospective studies looked at the relationship between carbohydrate/fiber intake and hyperinsulinemia. A diet low in carbohydrate/fiber was found to be associated with higher levels of insulin or hyperinsulinemia, whereas a diet that contained high fiber was inversely associated with insulin levels and also hyperinsulinemia. BMI was collected on the subjects in both studies in order to control for the presence of obesity.

Conclusion

Most of the studies presented in this review support the relationship between high consumption of dietary fiber/whole grains and increased insulin sensitivity. Cross-sectional studies included in this review mostly observed an inverse relationship between insulin resistance and whole grains/fiber. The experimental studies reported that supplementing fiber or increasing whole grain/fiber consumption in a diet may help reduce insulin resistance. Both of the prospective studies saw higher levels of insulin/hyperinsulinemia with diets low in carbohydrates/fiber. Even though most of the research presented showed this relationship, there are still areas for further research within this topic.

A significant limitation of most of the studies reviewed is that BMI, but not body fat, was controlled when evaluating the relationship between fiber intake and insulin resistance. Percent body fat provides a more accurate measurement of obesity because it takes into account fat free mass and fat mass, whereas BMI is calculated from height and weight. BMI is not an accurate measurement of body composition.[11] Very few studies have measured percent body fat and when measured, the main method employed has been bioelectrical impedance analysis, which is only slightly more accurate than BMI.[12-13] Percent body fat, obtained through more reliable methods, could show a stronger association between dietary fiber intake and insulin resistance. Since obesity has a strong influence on insulin concentrations, percent body fat would make a better covariate over BMI and may provide a different perspective into how a diet high in fiber influences insulin resistance.

Another limitation common among many of the studies is that physical activity, which has a strong influence on insulin sensitivity, was rarely measured. In studies that measured physical activity, questionnaires were used. Self-reported physical activity is typically a weak measurement and often contains significant error.[14] A better approach would be to assess physical activity using objective methods, such as pedometers or accelerometers. This would provide a better control than has been employed in previous research.

Lastly, dietary fiber can be divided into two categories: soluble and insoluble. Some of the experimental studies have examined one of the two types of fiber. One cross-sectional study[15] did examine the relationship between total, soluble, and insoluble fiber with insulin resistance; however, this study did not determine the extent to which soluble and insoluble fibers differ in their association with insulin resistance. Further research is needed to examine this.

Overall, most of the studies examining the relationship between fiber consumption and insulin resistance contain similar weaknesses in their measurement methods, including using BMI and questionnaires as a measure of obesity and physical activity, respectively. Since insulin sensitivity is influenced significantly by obesity and physical activity, using unreliable methods to measure these variables can potentially reduce or even negate the relationship observed. Hence, the purpose of this particular investigation will be to examine the relationship between total, soluble, and insoluble fiber intakes and insulin resistance while taking into account body composition and physical activity using high quality assessment methods.

Chapter 3

Methods

Design

Cross-sectional associations between fiber intake, including total, soluble, and insoluble, and insulin resistance (HOMA-IR) will be examined. Data will be pre-existing and will be provided by the BYU Lifestyle Project.

Subjects

Data was collected on approximately 275 women between the ages of 35-45 years. Subjects were recruited through the use of newspaper advertisements, flyers, and emails. Distribution included the two metropolitan areas of Salt Lake City and Provo, Utah as well as the cities neighboring each. Telephone interviews were used to screen applicants according to the study requirements.

All qualified subjects were healthy, nonsmoking, premenopausal women with no plans of becoming pregnant within the study's timeframe. The mean age of the subjects was approximately 40 years. Before the collection of data, each participant signed a Brigham Young University Institutional Review Board approved letter of informed consent.

Procedures

At baseline for the BYU Lifestyle Project, measurements of dietary intake, total physical activity, intensity of physical activity, body weight, percent body fat, homeostasis model assessment of insulin resistance (HOMA-IR), and age were obtained. The Human Performance Research Center at BYU served as the location where all laboratory measurements were made. Subjects were informed at the start of any potential risks as well as the benefits from participating in the study. Written consent was signed by each subject before measurements were taken.

During the first appointment for all subjects, height and weight were measured while wearing a BYU issued one-piece swimsuit. The BOD POD (Life Measurements Instruments, Concord, CA) was used to assess percent body fat in all subjects wearing a standard one-piece swimsuit and also a swim cap. Subjects also received a digital food scale (Ohaus 2000, Florham Park, NJ), seven dietary records, and an ActiGraph accelerometer (formerly call CSA; Health One Technology, Pensacola, FL) all of which were explained so that each subject had knowledge of proper weighing and logging methods and appropriate use of the activity monitor. All food and drink intake was weighed and logged for seven consecutive days and the accelerometer was worn continuously within the same timeframe, except during water activities.

Variables

A total of ten variables will be used in this study. Insulin resistance will be indexed using HOMA-IR scores and will serve as the criterion variable. Fiber intake per 1000 calories, including total, soluble, and insoluble, will be the primary predictor variables. Potential confounding variables will include age, dietary fat intake, total caloric consumption, body weight, body fat percentage, objectively measured physical activity, and intensity of physical activity. The potential confounding variables will be controlled through statistical methods.

Instruments and Measurement Methods

The variables measured as part of the BYU Lifestyle Project that will be included in this study will be as follows: insulin resistance, dietary intake, physical activity, intensity of physical activity, percent body fat, and body weight, which will be discussed individually.

Insulin Resistance

Qualified hospital personnel obtained blood samples from subjects who fasted at least 12 hours before their appointment. The antecubetal vein served as the location where blood samples were taken and the sample was then centrifuged at 2000g for 15 minutes at a temperature of 4°C. Final storage of samples was in aliquots at temperatures around -20°C. The hospital laboratory determined fasting insulin levels (μU/L) and glucose levels (mg/dL) by utilizing two separate methods: Access® Ultrasensitive Insulin assay (Beckman Coulter, Inc, Brea, CA) and Dimension Vista System® and the Flex reagent cartridge (Siemens, Deerfield, IL) respectively. Insulin resistance was determined through the use of HOMA-IR, which was estimated using fasting glucose and insulin concentrations in the following equation: HOMA-IR = [fasting glucose (mg/dL) x fasting insulin (μU/ml)]/405.[17]

HOMA-IR provides comparable assessment of insulin resistance to other validated methods. Matthews et al.[17] demonstrated that HOMA-IR produced correlational estimates of insulin resistance as compared to measurements obtained by the hyperinsulinemic euglycaemic clamp ($R_s = 0.88$, $p < 0.0001$), which is considered one of the "gold standard" tests. A review article revealed that when the HOMA-IR model is used in appropriate situations, such as in prospective cohort and epidemiological studies, valuable data can be obtained.[35]

Dietary Intake

Total caloric, fat, and fiber intakes were measured through seven-day diet records in which the subjects weighed all food and drink consumed within a consecutive seven-day time frame. A digital food scale was issued to each subject along with an explanation of how to properly weigh and record all food and drink consumed, including water. Food description and food weight were recorded daily on the logs provided. During the seven days, research personnel contacted each woman every other day to provide support and to ensure accurate records were being kept. Following completion of the seven days, assessment of dietary intake was accomplished using the ESHA Research software, version 7.6, (ESHA Research Inc., Salem, OR) to objectively provide dietary analysis.

Using seven-day dietary records where all food and drink are weighed prior to eating provides many benefits. Subjects' ability to recall foods eaten and also portion sizes are not relied upon with food records. Also, with the occurrence of day to day variations in eating habits, recording foods for seven consecutive days documents habitual dietary intake when compared to other dietary assessments.[36]

Total Physical Activity

ActiGraph accelerometers (formerly call CSA; Health One Technology, Pensacola, FL) provided a means to objectively assess physical activity during the same seven consecutive days that dietary intake was measured. Instructions on how to appropriately use this device were provided during the initial appointment. The accelerometer was worn constantly throughout the day with the exception of during water activities in which subjects were required to remove the activity monitor. The accelerometer was attached to a nylon belt that was worn comfortably around the subjects' waist and positioned over the left hip.

Objective and reliable measurements can be obtained through the use of Actigraph accelerometers to evaluate levels of physical activity. These activity monitors were compared to doubly labeled water in a study conducted by Liu et al.[37] Based on these findings, it was demonstrated that the monitors provided a close representation of physical activity level in free living subjects. A significant relationship was found between physical activity measured through

Actigraph accelerometers and total energy expenditure (r = 0.31, $p < 0.01$), activity related energy expenditure (r = 0.30, $p < 0.05$) and physical activity level (r = 0.26, $p < 0.05$). [34]

A comparison of four accelerometers, including the one used in this study, was examined by Basset et al.[38] The results revealed that the only accelerometer not differing significantly from a portable metabolic system was the Actigraph device.

Intensity of Physical Activity

Intensity of physical activity was measured using Actigraph accelerometers in which participant movement was recorded in 10-minute segments for a total of 144 bouts (epochs) each day, 1008 per week. The reason for choosing 10 minutes as the length for assessing intensity of physical activity is based on the American College of Sports Medicine guidelines indicating that multiple 10-minute bouts are sufficient for accumulating physical activity.[39]

The following categories for physical activity intensity were utilized based on previous research.[40] Each category shows the activity counts associated with the three levels of intensity (Low, Moderate, and Vigorous) and corresponding speeds (mph) on a treadmill: Low intensity, 0-29,999 counts in one 10-min bout (<3 mph); Moderate intensity, 30,000-49,999 counts in one 10-min epoch (3-4 mph); and Vigorous intensity, 50,000 counts or greater in one 10-min bout (>4 mph).[40]

Each participant had a total of 1008 10-minute bouts of monitored activity distributed over the three intensity categories over the course of the week. The amount of time subjects were engaged in physical activity within each intensity category was used to differentiate among participants. For example, one subject might have 0 bouts of Vigorous activity across the seven days of recording, whereas another subject might have 20 minutes, and another might have 120 minutes of Vigorous activity over the week.

Body Fat Percentage

Body fat percentage was measured through the use of air displacement plethysmography, the BOD POD. Thoracic lung volume was also evaluated directly via the BOD POD. Before performing any measurements, the BOD POD was calibrated in order to minimize measurement error. Subjects were asked to fast for three hours prior to their appointment. A BYU one-piece swimsuit was worn by each woman as well as a swim cap. Subjects were instructed to use the restroom immediately prior to the measurements. Two measurements were obtained for each subject to ensure accuracy. A difference of one percentage point was allowed between the two results. If a difference of more than one percentage point resulted, a third measurement was obtained. An average of the two measurements within one percentage point of each was then used.

The BOD POD provides a valid and reliable measurement of body fat percentage as concluded by several studies. The BYU Lifestyle Project established reliability by performing a test-retest on 100 women from the study sample. An intraclass correlation of 0.999 ($p < 0.0001$) was found after comparing the two BOD POD tests.[41] On the same women, validity of the BOD POD was also examined in which measurements of the BOD POD were compared to measurements obtained from dual energy X-ray absorptiometry (DEXA) (Hologic, Inc., Bedford, MA). A Pearson correlation of 0.94 ($p < 0.001$) and an intraclass correlation of 0.97 ($p < 0.001$) were determined after comparison of the two measurements.[42] Ballard et al.[43] concluded after comparing the BOD POD to the DEXA that the BOD POD was a valid and reliable method of evaluating percent body fat in female athletes and nonathletes.

Body Weight

Each subject was weighed on an electrical scale (Tanita, Tokyo, Japan) which measured body weight to the nearest 0.005 kg. Calibration of the scale occurred daily before any measurements were obtained. Subjects refrained from eating anything three hours before their appointment. The same one-piece swim suit used for the BOD POD was also worn during the weigh in. The data for weight was an average of two measurements taken a week apart.

Data Analysis

Regression analysis using the General Linear Models (GLM) procedure will be employed to determine the bivariate relationships between each of the three key fiber variables, total, soluble, and insoluble, and insulin resistance, specifically HOMA-IR. Partial correlation, using the general linear models (GLM) framework, will be used to determine the extent to which each of the potential confounding variables, age, body weight, body fat percentage, dietary fat intake, total calorie consumption, total physical activity, and intensity of physical activity, influence the fiber and HOMA-IR associations, considered individually and collectively. Additionally, to assist with interpretation of the data, HOMA-IR scores will be divided into quartiles and the middle two quartiles will be collapsed, providing three total HOMA-IR categories: Low, Moderate, and High. GLM will be used to determine the extent to which mean dietary fiber intake (total, soluble, and insoluble), expressed as grams of fiber per 1000 calories, differ across the three HOMA-IR categories. Again, partial correlation using the GLM will be employed to evaluate the influence of each of the potential confounding variables, individually and collectively, on mean differences among the HOMA-IR categories. Alpha will be set at the 0.05 level and the SAS (Cary, NC) software program (version 9.1) will be utilized for all of the statistical analysis.

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