The Relationship of Diet Quality and Blood Serum Lipid Levels in a Population at High Risk for Diabetes: The Strong Heart Family Study

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Abstract

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Background: Blood serum lipid levels are often used as indicators of cardiovascular disease (CVD) risk, while diet quality has an established impact on blood serum lipid levels, including low- and high-density lipoproteins (LDL and HDL) and their corresponding apoproteins, apoB and apoA1 respectively, as well as triglycerides (TGs) and total cholesterol (TC). Diabetes mellitus (DM) is also an established risk factor for CVD, and dyslipidemia is a hallmark of accompanying metabolic disturbances, manifesting as hypertriglyceridemia, high serum levels of LDL, and lowered HDL. This study seeks to investigate the relation of diet quality, diabetes, and blood lipid levels, amongst American Indians (AIs) who participated in the Strong Heart Family Study (SHFS)—a longitudinal study of CVD and its risk factors in 12 AI communities in Arizona, North Dakota, South Dakota, and Oklahoma. To date no published studies have examined the relation of global diet quality, lipids, and diabetes in AIs.

Methods: This investigation included all SHFS participants who completed a baseline exam in 2001-2003 with available and plausible diet, lipids, and diabetes data. Block Food Frequency Questionnaires (FFQ) were used to estimate usual past-year dietary intake, and the Alternative Healthy Eating Index (AHEI) and Nettleton index were used to evaluate quality. Primary outcomes for analysis included TC (mg/dL), TG (mg/dL), HDL (mg/dL), LDL (mg/dL), and lipoproteins ApoA and ApoB. Covariates of interest included age, sex, site, BMI, waist circumference, energy intake, physical activity, systolic blood pressure, diastolic blood pressure, cigarette smoking, alcohol use, and prevalent diabetes. Generalized estimated equations (GEE) with an independence working correlation and robust standard errors and were used to estimate the cross-sectional associations of diet quality (as determined by both AHEI and the alternate index) with blood lipid level outcomes in the form of TC, TG, LDL, HDL, ApoA, and ApoB. For all analyses, potential modification of the association of diet quality with blood lipid levels by diabetes status was examined. Additional secondary analyses also examined the longitudinal association of diet quality in 2001-2003 with blood lipid levels in 2006-2009.

Results: Participants with diabetes had higher diet scores than those without diabetes (i.e., on average, participants with diabetes had scores 2.8 points higher for AHEI scoring and 2.3 points higher for Nettleton scoring when compared to participants without diabetes). Negative interactions with significance of diabetes and diet score on blood lipid outcomes were observed for TC ($p < 0.01$), LDL ($p = 0.01$), and ApoB ($p < 0.01$) for AHEI scores assessed, and TC ($p < 0.01$), LDL ($p = 0.03$}, and ApoB ($p = 0.01$) in Nettleton diet scoring. For longitudinal analyses, significant interactions of diabetes

and diet scores on blood lipid outcomes occurred in TC only for both Nettleton ($p = 0.03$) and AHEI ($p = 0.01$) indices.

Conclusions: The interaction of diet quality and blood lipid status by diabetes status is significant in this cohort for TC, LDL, and ApoB outcomes. Given the disproportionate and increasing burden of T2DM, CVD, and associated mortality in AI populations, enabling resources that reduce population T2DM incidence while promoting greater glycemic control within individuals currently living with T2DM may reduce CVD risk and improve overall mortality within this population.

Introduction

Blood serum lipid levels are often used as indicators of cardiovascular health status. Diet quality, however, has an established impact on blood serum lipid levels, particularly low- and high-density lipoproteins (LDL and HDL), their corresponding apoproteins, apoB and apoA respectively, as well as triglycerides (TGs) and total cholesterol (TC) (*1-3*). Consequently, measures of diet quality and resultant blood serum lipid level outcomes may be useful in assessing CVD risk. Higher quality diets—defined in previous study by low saturated fat and high complex carbohydrate content (*4*)—are associated with greater levels of HDL cholesterol, the primary player in reverse cholesterol transport, or the removal of unesterified cholesterol from the peripheral tissues to the liver (*5-7*). By contrast, poor diet quality is associated with greater levels of LDL and ApoB lipoprotein, the presence of which within arterial walls is the primary contributor to atherosclerosis (*3*). Poor diet quality is also associated with higher levels of triglycerides, another contributor to CVD risk, and diets with minimal saturated fats and sucrose have been found to be protective against increases in triglyceride levels nearing levels considered to be indicative of possible CVD risk (*8*).

Diabetes mellitus (DM) is also an established risk factor for CVD as it is often accompanied by hyperlipidemia with elevated levels of TGs, increased serum levels of LDL, and reduced levels of HDL (*9, 10*). Insulin resistance, the driver of hyperglycemia in T2DM, results in reduced suppression of hormone sensitive lipase (HSL) within adipocytes. The suppression in HSL allows increased free-fatty acids (FFAs) to be released into the circulation, where they are routed to the liver and then esterified into TGs and packaged into very low density lipoproteins (VLDLs). As VLDL circulates,

lipoprotein lipase (LPL) hydrolyzes the TGs within the VLDLs, thus reducing the VLDL into an intermediate density lipoprotein, or IDL. While some IDLs are cleared, others return to the general circulation (*11*).

With increased TG in VLDLs as a result of insulin resistance, there is also increased exchange between VLDLs and LDLs via cholesterol ester transfer protein (CETP); cholesterol esters are exchanged for TGs. This interaction converts VLDLs into IDLs, while the LDLs become TG-enriched. Processing of these TG-rich LDLs in the liver results in small dense LDLs. These particles are not only poor hepatic binders, meaning they are more likely to enter back into circulation, but have greater endothelial barrier permeability within arteries, contributing greatly to atherosclerosis, and resultant CVD. CETP is also involved in the exchange of cholesterol esters for TGs between HDL and apoB-containing lipoproteins, resulting in TG-enriched HDL particles. TG-enriched HDL particles are more likely to be removed from circulation as a result of hepatic lipase. These metabolic disturbances in lipid pathways as a result of insulin resistance consequently compound on one another to contribute to CVD risk over time (*11*).

As a result of this impaired lipid metabolism, numerous clinical and epidemiological studies have identified that patients with diabetes, and in particular those diagnosed with type 2 diabetes mellitus (T2DM), are more susceptible to CVD than non-diabetics (*12, 13*). Current nutrition recommendations highlight tight lipid control through dietary intervention as a key component of successful T2DM management in an effort to reduce overall CVD risk (*14, 15*). Increased adiposity, also related to poor diet quality, is similarly associated with increased serum lipid levels as well as metabolic syndrome and

resultant T2DM, however increased adiposity alone does not account for dyslipidemia presence, and it is the nature of impaired lipid pathways in T2DM that contributes most readily to CVD risk (*16-19*).

Research has demonstrated that diet quality has a predictive impact in both future CVD and T2DM risk and outcomes (*8, 20*). Components of healthy eating known to reduce atherogenicity and improve overall heart health include consumption of fruits, vegetables, whole grains, and fats primarily from monounsaturated fatty acids (MUFAs) and polyunsaturated fatty acids (PUFAs) containing food sources. These healthy components should coincide with reduced consumption of sugar-sweetened beverages, red and processed meats, and sodium, with occasional to moderate consumption of alcohol if consumed at all (*8, 21, 22*).

Additional studies have also identified diet-related interaction of total fat and saturated fat intake with blood lipid outcomes (*23-26*). In one study, the substitution of complex carbohydrate for saturated fat intake decreased LDL without similarly decreasing HDL or elevating VLDL and TG. In that study, TC, VLDL, and TG concentrations were also inversely related to rates of insulin-mediated glucose management, while HDL concentrations were positively related to glucose disposal. These associations were independent of adiposity and insulin, thus again linking insulin resistance (IR) and overall diabetes-induced changes in metabolism to VLDL—resultant LDL—and HDL status (*27*). Improved diet quality, particularly where carbohydrate content and saturated fat is concerned, is also associated with greater glycemic control amongst those with diabetes, thus further contributing to an improved CVD profile (*20, 21*). As

such, diet quality can be a marker of reduced risk for population level health outcomes as they relate to T2DM, CVD, and associated metabolic disturbances.

Though T2DM and CVD are major health concerns that influence mortality for all Americans, the burden of both T2DM and CVD in American Indian (AI) populations is particularly problematic, with AI individuals having 2.3 times greater likelihood of living with diabetes than non-Hispanic whites of the same age (*28-30*). Between 1994 and 2009, the prevalence of T2DM amongst AI and Alaska Native adults (age 25-34) increased by 110%, and the overall death rate due to diabetes for AI and Alaska Natives compared to the general U.S. population is 1.6 times higher (*31*). Previous studies amongst AI communities demonstrate that normal glucose tolerance is associated with improved lipid levels—most notably lower VLDLs and TGs, and enhanced HDL counts—in AIs with well-managed diabetes demonstrating better lipid profiles than non-diabetics with impaired glucose tolerance, or participants with less well-managed diabetes (*23*).

To date, no published studies have examined the interaction of global/overall diet quality, lipids, and diabetes in AIs. Given the robust natures of the SHFS dataset and large sample size, better understanding the relation of diet quality, lipids, and diabetes will provide interesting insight into potential pathways for diabetes intervention within this specific population.

Methods

Setting & Study Population

The SHFS is a population-based longitudinal study of the risk factors and genetics for CVD among AIs. It was conducted in 12 communities in Arizona, North Dakota, South Dakota, and Oklahoma. Two examinations were including as a part of this study—a baseline examination in 2001-2003 (Phase Four exam), and a follow-up examination in 2006-2009. Specifics of Strong Heart Family Study design have been previously described (*32, 33*). In total, 1,468 men and 2,197 women from 94 large families participated in the baseline exam and 91% of participants then went on to participate in the follow-up exam. Both examinations included a personal interview, laboratory work-up, physical examination, and medication review. Written informed consent was obtained from all participants at each exam. The institutional review board from each Indian Health Service region for all of the 12 participating communities approved the study.

This investigation included all SHFS participants from Phase Four with available diet, lipids, and diabetes data. Participants with missing, incomplete, or implausible diet, lipids, body composition, or diabetes data at the Phase Four exam were excluded. This included individuals with caloric intakes less than 600 kilocalories for women and men, or greater than 6,000 kilocalories for women and 8,000 kilocalories for men. The final sample size included 2,200 individuals from all four sites, or approximately 60% the initial sample size. The longitudinal analysis included 1,899 participants.

Primary Exposures: Dietary Quality, Total Fat, and Saturated Fat Intakes

A Block 119-item FFQ was administered at the Phase Four examination to measure usual dietary intake during the previous year. The Block FFQ is a well-established and widely used food questionnaire, demonstrating both reliability and validity in previous studies (*34, 35*). Each participant was asked on average how often a specific food item was consumed during the year prior. Frequency was assessed using verbal measures of regularity—i.e. seasonally, never, a few times per year, once per month, 2-3 times per month, once per week, twice per week, 2-3 times per week, 5-6 times per week, or daily—with quantity measured via portion size as small, medium, or large. SHFS participants were also administered an additional set of questions regarding the frequency and quantity of consumption of various foods commonly consumed by the AI population. These items included Spam, flour and corn tortillas, fry bread, Indian taco, red and green chili, menudo, pozole, and guysava. These additional questions regarding ethnic food consumption can contribute to better understanding of overall nutrient content, as well as diet quality in this population (*36*).

The primary exposure of interest was diet quality. This was assessed using two eating indices that were designed to assess diet quality as predictive of chronic disease risk; (a) the Alternative Healthy Eating Index (AHEI) and (b) a diet index designed specifically to measure the influence of diet on risk of cardio-metabolic diseases. The USDA's Healthy Eating Index (HEI) measures diet quality based upon adherence to current USDA dietary guidelines. However, it does not take into account food and nutrient contributions to chronic disease risk in particular, and thus alternative measures were used (*21*).

The AHEI is based on 11 components that are divided into categories by whether high, low, or moderate consumption is ideal. Foods ideally consumed in high quantities include vegetables, fruit, whole grains, nuts and legumes, long chain omega-3 fats, and polyunsaturated fatty acids. Alcohol is the one category for which moderate consumption is deemed to be ideal, whereas foods to be ideally consumed in the lowest amounts include sugar sweetened beverages (SSBs) and fruit juice, red and processed meat, trans fat, and sodium. Each category has the potential to contribute zero (worst) to 10 (best) points with the total score ranging from zero (no adherence) to 110 (perfect adherence) (*21, 37*). More favorable foods score higher, and thus contribute to an overall higher score, indicating higher quality of diet (*38*).

Table 1: The AHEI-2010 Scoring Method (*21*)

Component	Criteria for Minimum Score (0)	Criteria for Maximum Score (110)
Vegetables, *servings/d*	0	≥5
Fruit, *servings/d*	0	≥4
Whole grains, *g/d*	0	
Women		75
Men		90
Sugar-sweetened beverages and fruit juice, *servings/d*	≥1	0
Nuts and legumes, *servings/d*	0	≥1
Red/processed meat, *servings/d*	≥1.5	0
Trans fat, *% of energy*	≥4	≤0.5
Long-chain (n-3) fats (EPA & DHA), *mg/d*	0	250
PUFA, *% of energy*	≤2	≥10
Sodium, *mg/d*	Highest decile	Lowest decile
Alcohol		
Women	≥2.5	0.5 – 1.5
Men	≥3.5	0.5 – 2.0
Total	0	110

An additional eating index, devised by Nettleton et al, was also used in this analysis for comparison. This index (*39*) is based on a 27-point scale, and includes whole grains, fish, fruits, vegetables, nuts/seeds as foods ideally consumed in higher amounts, and red and processed meats, sweets, SSBs, and fried potatoes as foods ideally consumed in lower amounts. Intake of each diet component is categorized into quartiles and assigned

ascending values (0-3) for favorable foods and descending values (3-0) for unfavorable foods (*35, 39-41*). As with the AHEI, a higher score is indicative of overall higher diet quality; the highest score being 27, and representative of a three-point score in all nine food categories (*39*).

Primary Outcomes and Key Covariates

Primary outcomes for the cross-sectional analyses include TC (mg/dL), TG (mg/dL), HDL (mg/dL), LDL (mg/dL), and lipoproteins ApoA and ApoB. In the follow-up examination, ApoA and ApoB were unavailable, so outcomes for the longitudinal analyses include TC (mg/dL), HDL (mg/dL), and LDL (mg/dL) only. Covariates for this study include age, sex, site, BMI, waist circumference, energy intake, physical activity, systolic blood pressure, diastolic blood pressure, cigarette smoking, alcohol use, and prevalent diabetes.

Statistical Analysis

All analyses were performed using STATA version 14. Generalized estimated equations (GEE) with an independence working correlation and robust standard errors were used to estimate the cross-sectional associations of diet quality (as determined by both AHEI and the alternate index) with blood lipid level outcomes in the form of TC, TG, LDL, HDL, ApoA, and ApoB status using data from the 2001-2003 (Phase Four) exam (or 2006-2009 Phase Five exam for secondary analyses). GEE was used to address potential familial correlation within the data. In total, there were 96 family clusters included in the analysis, with a mean of 19 participants from each family cluster (range: 1-54

participants per family cluster). Primary outcomes were log transformed to account for skew as appropriate (HDL and TGs).

Three models were fit to examine the relation of diet quality and lipids: (1) a minimally-adjusted model that included age, sex, site, and total caloric intake; and (2) a model that additionally adjusted for education (years), smoking (never, former, current), physical activity (steps per day), and prevalent diabetes (yes/no); a model that adjusted for all model 1 and model 2 covariates, and BMI. For all analyses, diabetes was tested as a candidate for effect modification in the association of diet quality and blood lipid values, by including an interaction term (diabetes*AHEI or diabetes*nettleton) in each model 3. If diabetes was found to be an effect modifier (based on $p<0.05$ for the interaction term), results were stratified by diabetes status for that lipid outcome.

Results

Of the 2,200 SHFS participants who comprised the analytic cohort, 60.00% were women, and the mean age at baseline was 40.80 years. Mean BMI was 31.28 kg/m^2, with a mean waist circumference of 102.15cm. Mean diet scores for this analytic cohort were 44.71 and 13.60 for AHEI and Nettleton indices respectively.

Table 2: Descriptive Statistics of Key Variables Stratified by Diabetes Status

	No Diabetes (N = 1789)		Diabetes (N = 411)	
Key Variables	**mean**	**SD**	**mean**	**SD**
Age (years)	38.14	16.20	52.44	14.14
% Female	0.59	.	0.63	.
Waist Circumference (cm)	99.54	16.96	113.47	17.61
BMI (kg/m^2)	30.45	7.10	34.90	7.69
Systolic BP (mmHg)	121.39	15.57	129.28	18.36
Diastolic BP (mmHg)	76.17	10.89	76.59	11.08
Insulin (uU/mL)	14.84	14.66	29.17	32.34
Fasting Glucose (mg/dL)	93.88	10.25	175.72	72.10
Total Cholesterol (mg/dL)	181.80	35.93	187.80	35.83

HDL (mg/dL)	52.70	14.82	47.99	12.36
LDL (mg/dL)	100.24	30.19	99.02	30.56
Triglycerides (mg/dL)	147.03	88.93	214.47	131.72
ApoA1 (mg/dL)	138.91	26.43	138.60	25.24
ApoB (mg/dL)	93.00	23.95	102.17	23.47
Fibrinogen-Lt BI (mg/dL)	367.99	82.13	426.98	93.62
Years of Education	12.29	2.28	12.28	2.36
Alcohol – Never (%)	0.11	0.32	0.14	0.35
Alcohol – Former (%)	0.26	0.44	0.47	0.50
Alcohol – Current (%)	0.62	0.48	0.39	0.49
Smoking – Never (%)	0.41	0.49	0.35	0.48
Smoking – Former (%)	0.22	0.41	0.35	0.48
Smoking – Current (%)	0.38	0.48	0.30	0.46
Phys Activity (steps/day)	6231.02	3965.52	4044.06	3132.11
Kilocalories	2472.92	1358.55	2246.65	1252.16
AHEI	44.19	9.07	46.99	8.59
Nettleton	13.22	3.77	15.25	3.48
Servings of Vegetables	2.62	2.08	2.75	2.15
Servings of Fruit	1.01	0.84	1.17	0.94
Servings of Legumes	0.78	1.09	0.73	0.82
Servings of Meat	1.46	1.21	1.45	1.17
% Trans Fats	1.61	0.59	1.59	0.50
Omega-3 Fatty Acids (mg)	68.53	129.21	64.48	119.01
% PUFAs	8.45	2.35	8.95	2.30
Dietary Sodium (mg)	3281.56	2036.25	3200.84	1933.20
Whole Grains (g)	19.02	25.68	25.75	26.97
Whole Fruit (g)	106.11	133.13	133.12	135.70
Vegetables (g)	140.53	128.41	170.44	135.44
Nuts (g)	14.39	27.12	11.03	17.37
Fish (g)	8.88	16.75	8.36	15.42
Meat (g)	101.65	86.15	97.72	81.14
Dessert (g)	86.65	80.10	76.97	74.22
Sugar Sweetened Beverages (g)	718.71	614.88	458.92	487.49
Fried Potatoes (g)	26.06	32.04	18.34	24.75

Baseline characteristics of study participants stratified by diabetes status may be found in Table 2. In total there were 411 diabetes diagnosed participants and 1,789 without diabetes. Women made up 59.00% of non-diabetics and 63.00% of those with diabetes, while the mean age of each group was 38.14 (SD 16.20) and 52.44 (SD 14.14) years respectively. Mean scores for both Nettleton and AHEI indices were recorded. Mean

AHEI score was 44.19 (SD 9.07) amongst those non-diabetics and 46.99 (SD 8.59) amongst those with diabetes, while Nettleton scores were similarly distributed, with mean scores of 13.22 (SD 3.77) and 15.25 (SD 3.48) when assessed amongst non-diabetics and diabetics respectively. Waist circumference was higher amongst diabetics at 113.47 cm (SD 17.61) versus 99.54 cm (SD 16.96) amongst non-diabetics, with similar disparities in BMI of 34.90 (SD 7.69) and 30.45 (SD 7.10) kg/m^2 respectively.

Table 3a. Association of AHEI, Nettleton & Blood Lipids in the Strong Heart Family Study (No Significance)

Blood Lipid Variables[a]	Total Sample		
	AHEI		
	β[b]	95% CI	p-value
Triglycerides[c]	0.00	(-0.00, 0.00)	NS
HDL[d]	0.00	(-0.00, 0.00)	NS
ApoA	0.07	(-0.05, 0.20)	NS
	Nettleton		
	β[b]	95% CI	p-value
Triglycerides	0.00	(-0.00, 0.01)	NS
HDL	0.00	(-0.00, 0.00)	NS
ApoA	0.09	(-0.21, 0.39)	NS

[a]Model displayed for each blood lipid was adjusted for education (years), smoking (never, former, current), physical activity (steps per day), prevalent diabetes, and BMI; [b]Values are per SD difference in AHEI and Nettleton scores; [c]Triglycerides were ln-transformed for analyses; [d]HDL was ln-transformed for analyses

No significant interaction was observed with either diet score when assessed in terms of TG, HDL, and ApoA (see Table 3a). Based on β values for diet and blood lipid, for every one unit change in diet score, a change of less than 0.10 units was seen for all three of these blood lipids, and was not found to interact significantly with diabetes status. Blood lipids TC, LDL, and ApoB did demonstrate interaction with diet score by diabetes status (see Table 3b) and were found to be significant. The direction of this relation across all significant blood lipids for diet interaction by diabetes status was negative. Reference direction and slop of this interaction as determined by β for interaction can be observed

in Figures 1-6. For every one-point increase in diet quality by AHEI, change in TC, LDL and ApoB was -0.87, -0.68, and -0.47 respectively. Similarly, by Nettleton's index, each one-point increase in diet quality demonstrated negative directional change in TC, LDL, and ApoB as -2.02, -1.23 and -1.09 respectively.

Table 3b. Association of AHEI, Nettleton & Blood Lipids in the Strong Heart Family Study by Diabetes Status (Significant Findings)

Blood Lipid Variables[a]	Total Sample		
	AHEI		
	β[b]	95% CI	*p*-interaction (AHEI* diabetes)
Total Chol	0.00	(-0.16, 0.16)	0.00
LDL	-0.13	(-0.26, 0.00)	0.01
ApoB	-0.01	(-0.11, 0.08)	0.00
	Nettleton		
	β[b]	95% CI	*p*-interaction (AHEI* diabetes)
Total Chol	-0.13	(-0.58, 0.32)	0.00
LDL	-0.27	(-0.64, 0.10)	0.03
ApoB	-0.05	(-0.32, 0.22)	0.01

[a]Model displayed for each blood lipid was adjusted for education (years), smoking (never, former, current), physical activity (steps per day), prevalent diabetes, and BMI; [b]Values are per SD difference in AHEI and Nettleton scores.

A comparable negative interaction was also found at the 2006-2009 follow-up exam, though with fewer covariates available for analysis, and more limited results. There were 301 participants lost to follow-up at the 2006-2009 exam, thus total participants for the follow-up diet quality-blood lipid interaction by diabetes interaction were reduced to 1,899, or 86.30% of the initial sample. Follow-up exam results of diet index score by diabetes interaction are displayed in Tables 4a and b, with graphical representation of β in Figures 7-8. Both ApoA and ApoB were unavailable at follow-up exam for analysis. Of blood lipids available for assessment at follow-up (TC, TG, LDL, and HDL only), TC was significant by both AHEI and Nettleton for diabetes interaction.

Table 4a. Association of AHEI, Nettleton & Blood Lipids in the Strong Heart Family Study 2006-2009 (No Significance)

Blood Lipid Variables[a]	Total Sample		
	AHEI		
	β[b]	95% CI	p-value
Triglycerides[c]	0.00	(-0.00, 0.00)	NS
LDL	0.11	(-0.00, 0.22)	NS
HDL[d]	0.00	(0.00, 0.00)	NS
	Nettleton		
	β[b]	95% CI	p-value
Triglycerides	0.00	(0.03, 0.88)	NS
LDL	0.10	(-0.25, 0.46)	NS
HDL	0	(0.00, 0.01)	NS

[a]Model displayed for each blood lipid was adjusted for education (years), smoking (never, former, current), physical activity (steps per day), prevalent diabetes, and BMI; [b]Values are per SD difference in AHEI and Nettleton scores; [c]Triglycerides were ln-transformed for analyses; [d]HDL was ln-transformed for analyses

Table 4b. Association of AHEI, Nettleton & Blood Lipids in the Strong Heart Family Study by Diabetes Status 2006-2009 (Significant Findings)

Blood Lipid Variables[a]	Total Sample		
	AHEI		
	β[b]	95% CI	*p*-interaction (AHEI* diabetes)
Total Chol	0.22	(0.07, 0.36)	0.03
	Nettleton		
	β[b]	95% CI	*p*-interaction (AHEI* diabetes)
Total Chol	0.45	(0.03, 0.88)	0.01

[a]Model displayed for each blood lipid was adjusted for education (years), smoking (never, former, current), physical activity (steps per day), prevalent diabetes, and BMI; [b]Values are per SD difference in AHEI and Nettleton scores.

Discussion

The interaction of diet quality and blood lipid status by diabetes status is significant in this cohort for TC, LDL, and ApoB outcomes, and the directionality of the relation is negative. There was no significant interaction for blood lipid outcomes TG, HDL, or ApoA. At follow-up exam (2006-2009), only TC demonstrated significant interaction by diabetes status, again with negative directionality.

Participants in this cohort had overall lower mean AHEI and Nettleton scores when compared to the Nurses' Health Study and other previous large-cohort assessments of diet quality, indicating overall poor diet quality when compared to larger, more diverse cohorts (*37, 38, 40-42*). These scores align with previous research demonstrating poor diet quality within this cohort. Changes in lifestyle, including the adoption of largely Western diets, including increased consumption of saturated fat and SSBs have contributed to an overall poor diet quality, with resultant impact on blood lipid levels in SHFS participants. This, along with other changes in lifestyle such as smoking status and physical activity, has contributed to CVD risk (*42*).

The findings of the present study indicate that participants with diabetes report consuming diets of higher quality than those without diabetes. Moreover, participants with higher quality diet have lower TC, HDL, LDL, and ApoB although the magnitude of these associations is influenced by diabetes status. Our results compliment the findings from studies in non-AI populations that indicate that diet quality as assessed by AHEI or Nettleton indices was associated with CVD risk factors (*20, 43, 44*). Previous research assessing diet quality amongst AIs is lacking, and no published studies have examined the interaction of overall diet quality by index with lipids among AIs. However, one previous study evaluated the impact of high-quality high-carbohydrate, low-saturated fat diets on blood lipid levels amongst diabetics and non-diabetics in a Southwest AI population with comparable results. In that study, significant differences in blood lipid levels could be seen in LDL and ApoB amongst diabetics and non-diabetics when dietary quality was high—defined by the high-carbohydrate, low-saturated fat diet—compared to low diet quality, or one of higher saturated fat content. VLDL TG content, however,

did not show significant change between diet types when stratified by diabetes status, nor when left unstratified, which is consistent with lack of significant impact on the relation between diet index and TG status in this cohort (*1*).

Given the interaction of poor diet quality and diabetes status on TG levels, it was hypothesized that there would be significant change in TG status by diet quality, with potential for amplifying effect based on diabetes diagnosis. Previous research has demonstrated an interaction of diet quality and TG, influenced by individual dietary components—such as quality of carbohydrate, as well as ratio of saturated to unsaturated fatty acid content—and that poor quality carbohydrate compared to high quality carbohydrate may result in meaningful TG movement (*1, 23*). However, the lack of significant impact on overall TG status reported herein could be a result of limited power in the SHFS. Larger studies may be necessary to better understand the interactions of diet, TG, and diabetes. No assessment has been done with a more comprehensive dietary measure such as the dietary indices used in this research. Similar to the findings reported herein, previous study in AI populations has demonstrated that TG levels do differ according to diabetes status—with diabetes diagnosis associated with significantly greater TG levels (*23*).

It is interesting to note that participants with a diabetes diagnosis had overall higher diet scores when compared to non-diabetics (see Table1b). Given Indian Health Services standardization of diabetes care, and the likelihood that intervention has taken place in a cohort with high prevalence of T2DM, this difference—though slight—is likely explained by education and outreach efforts following T2DM diagnosis (*45, 46*). This

difference in diet pattern between participants with diabetes and those without diabetes, however, is likely too small to have a large impact on blood lipid level outcomes when comparing diabetics to non-diabetics.

It is assuring that the interaction of diet quality with TC is similar in both cross-sectional and longitudinal analyses. This consistency highlights the importance of continuation of public health programming targeting reduction in CVD risk factors, particularly lipids, through diet programs that promote healthy patterns of eating, and dietary resources that improve overall metabolic health.

Strengths of this study include the relatively large, population-based sample, validated dietary instruments, and standardized indices for assessing diet quality. Limitations include limited power to stratify by diabetes status. While prevalence of diabetes is overall high in this cohort, the number of participants in the cohort was insufficient to provide a large enough stratified sample. Furthermore, the Block FFQ—while a validated and reliable tool to better understand dietary content (*34-36*)—is subject to bias and lacks the true precision to fully elucidate complex dietary and metabolic interactions. When it comes to overall diet, foods consumed by participants may differ in nutrient content from reference foods used in nutritional computations.

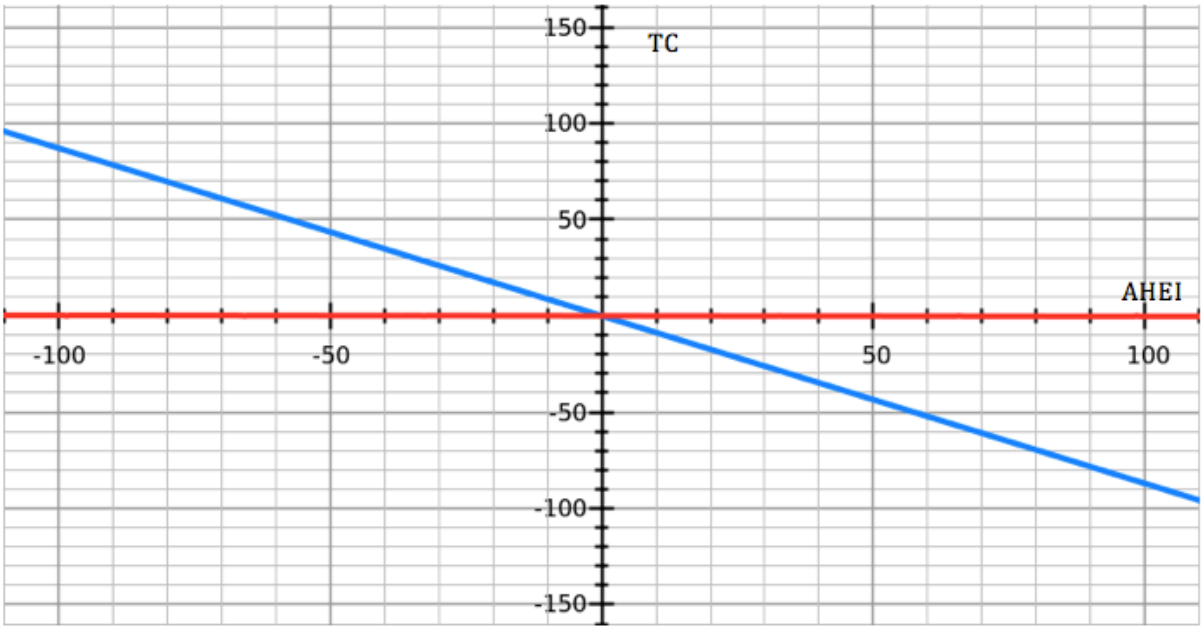
In summary, dietary patterns have an impact on serum lipid levels, particularly in the presence of diabetes, and the disproportionate and increasing burden of T2DM, CVD, and associated mortality in AI populations should drive additional public health conversations surrounding how to reduce incidence of diabetes while also providing

resources for greater glycemic control. Though it is heartening that individuals with diabetes in this cohort demonstrate improved dietary choices, albeit slight, promotion of and opportunity for access to healthy dietary components that allow for improved blood lipid outcomes and glycemic control will be paramount to reduction in overall risk and increase in metabolic success.

Figures

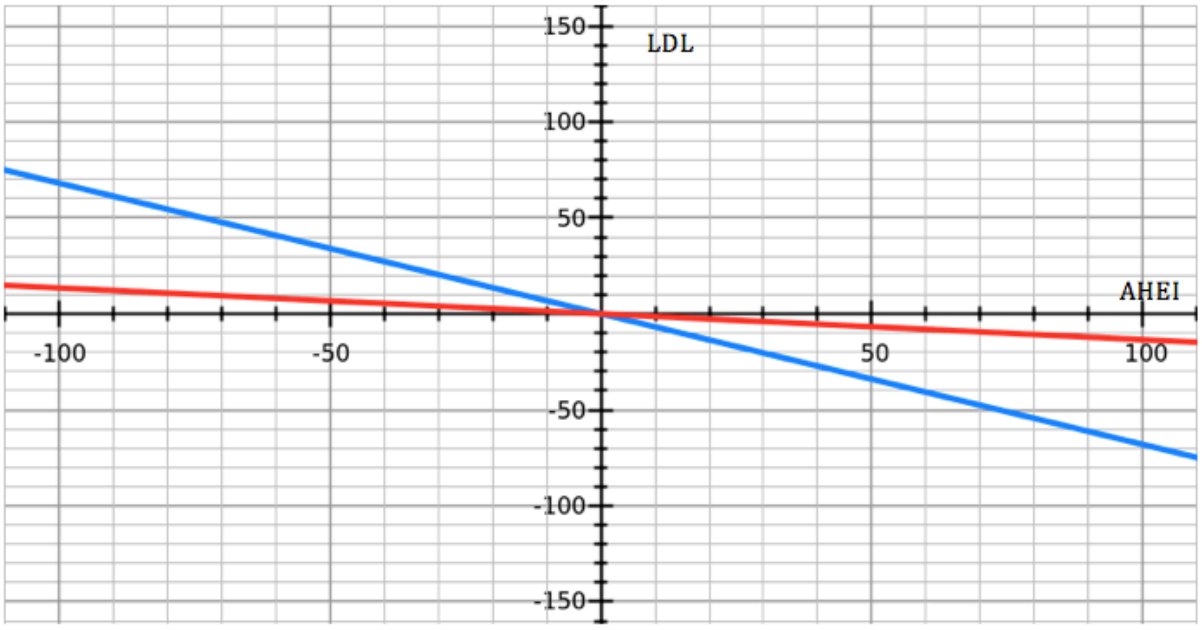
Model displayed for each blood lipid was adjusted for education (years), smoking (never, former, current), physical activity (steps per day), prevalent diabetes, and BMI; Values are per SD difference in AHEI and Nettleton scores.

Figure 1: Association of AHEI with TC by Diabetes Status Relative to Reference



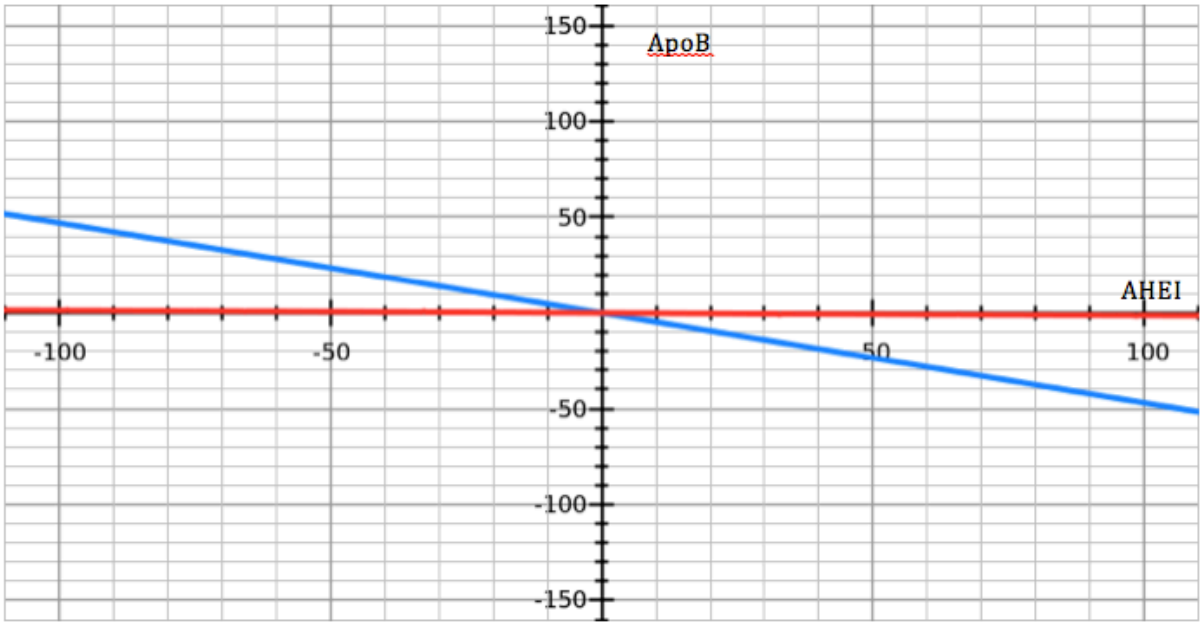
Diabetes (Slope = -0.87); No Diabetes (Slope < 0.01)

Figure 2: Association of AHEI with LDL by Diabetes Status Relative to Reference



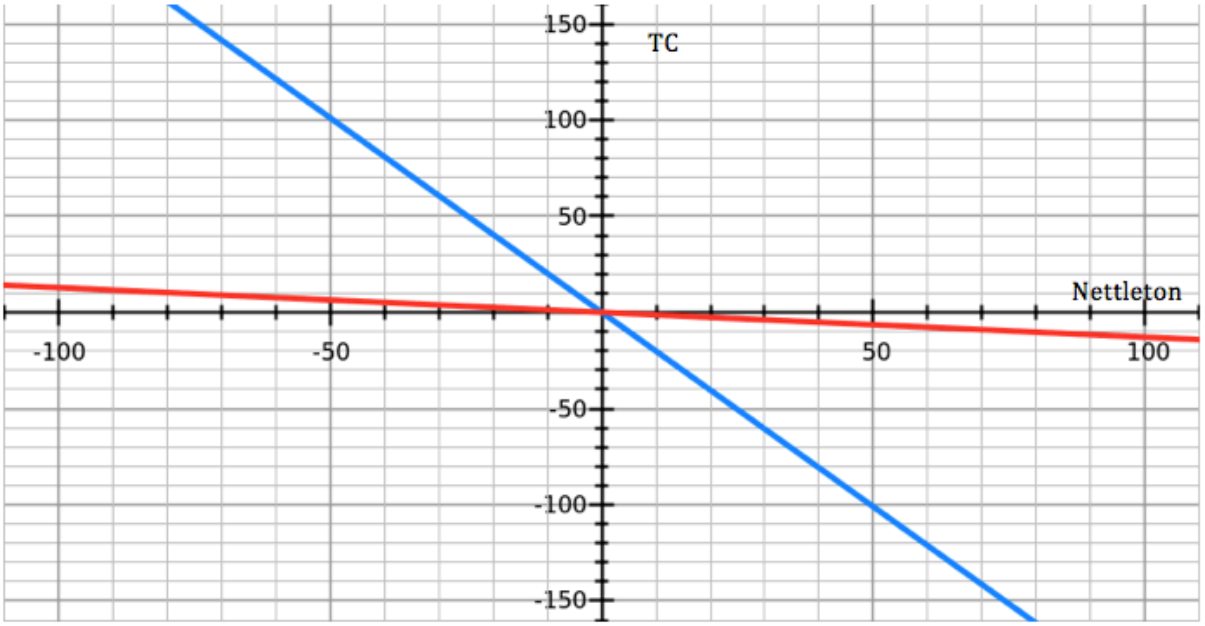
Diabetes (Slope = -0.68); No Diabetes (Slope = -0.13)

Figure 3: Association of AHEI with ApoB by Diabetes Status Relative to Reference



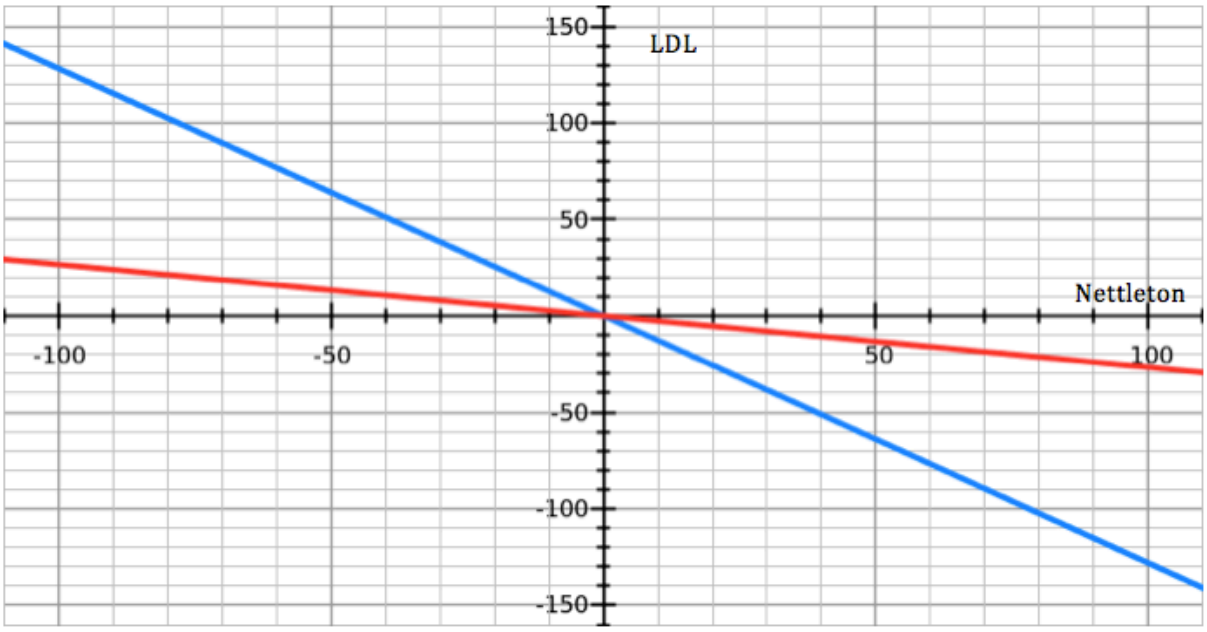
Diabetes (Slope = -0.47); No Diabetes (Slope = -0.01)

Figure 4: Association of Nettleton and TC by Diabetes Status Relative to Reference



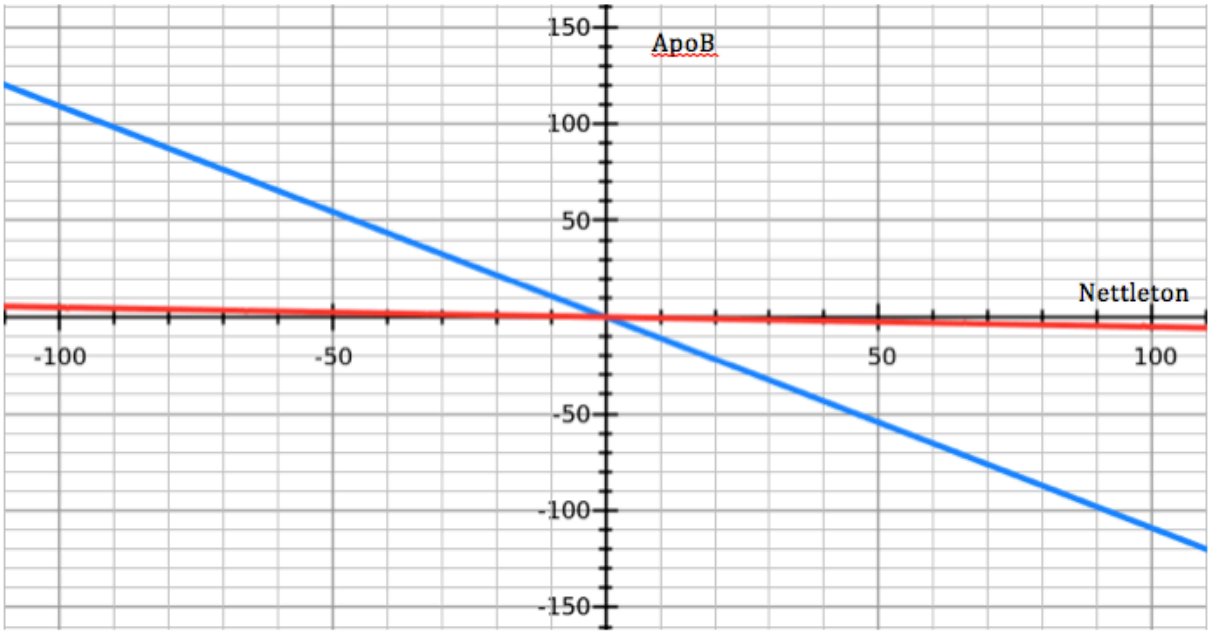
Diabetes (Slope = -2.02); No Diabetes (Slope = -0.13)

Figure 5: Association of Nettleton and LDL by Diabetes Status Relative to Reference



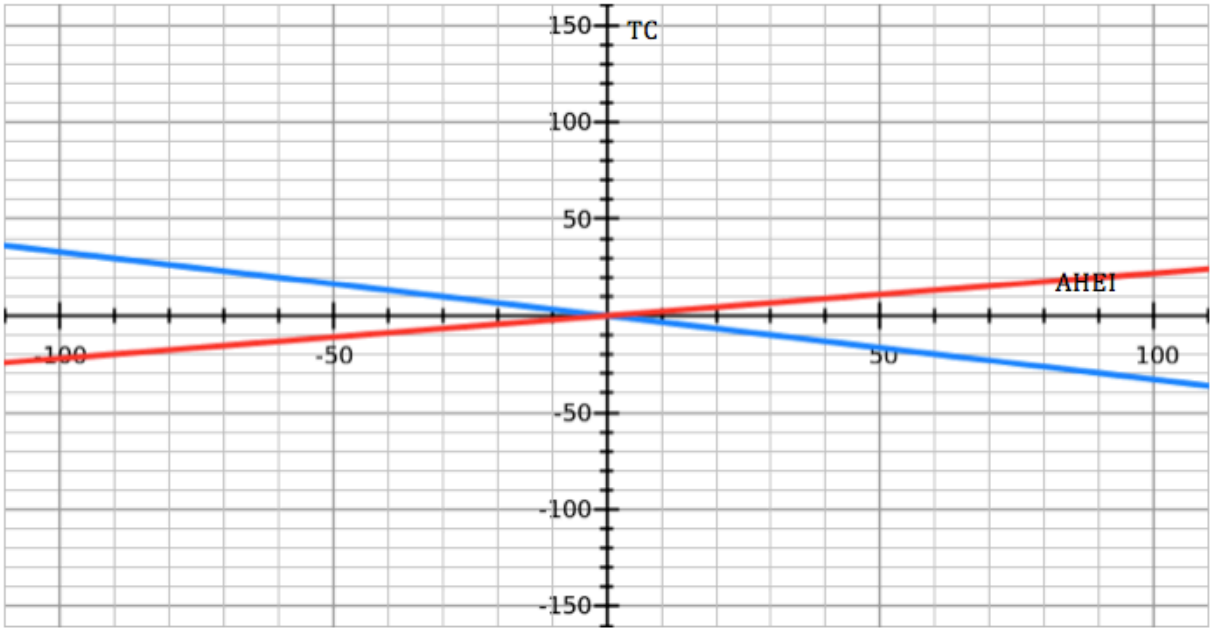
Diabetes (Slope = -1.28); No Diabetes (Slope = -0.27)

Figure 6: Association of Nettleton and ApoB by Diabetes Status Relative to Reference



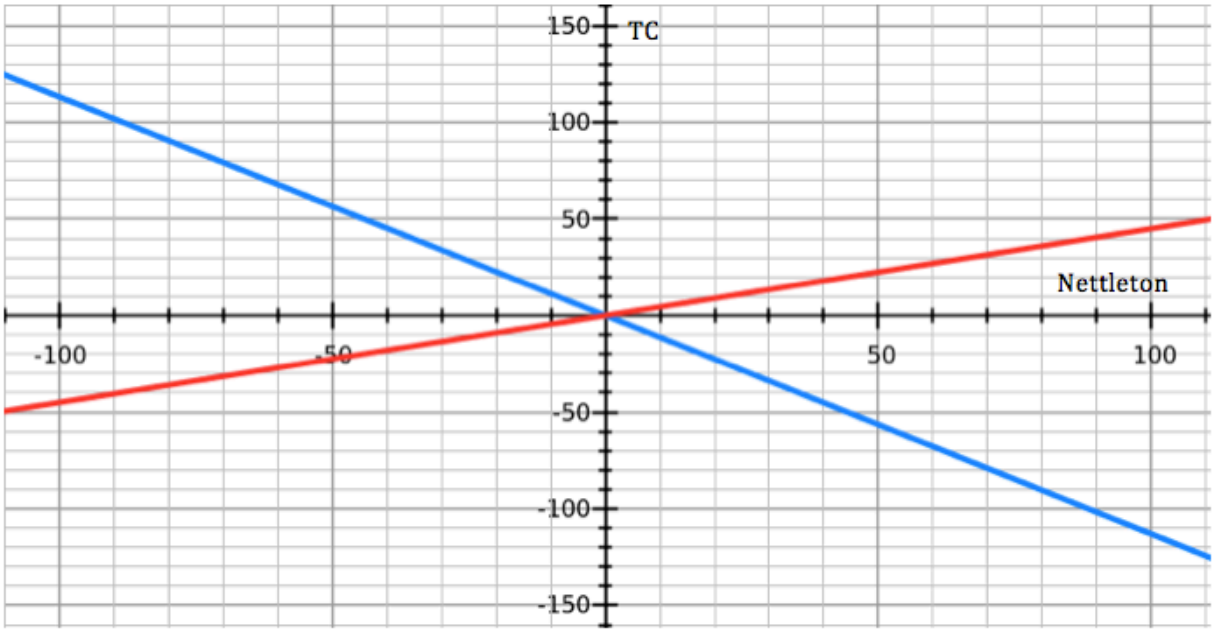
Diabetes (Slope = -1.09); No Diabetes (Slope = -0.05)

Figure 7: Association of AHEI and TC by Diabetes Status Relative to Reference (2006-2009)



Diabetes (Slope = -0.33); No Diabetes (Slope = 0.22

Figure 8: Association of Nettleton and TC by Diabetes Status Relative to Reference (2006-2009)



Diabetes (Slope = -1.13); No Diabetes (Slope = 0.45)

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