

Inflammation and the Incidence of Type 2 Diabetes: the Multi-Ethnic Study of Atherosclerosis (MESA)

Running title: Inflammation and the Incidence of Type 2 Diabetes

Alain G. Bertoni MD MPH¹, Gregory L. Burke MD MSc^{1,2}, James A. Owusu MD¹, Mercedes R Carnethon PhD³, Dhananjay Vaidya PhD⁴, R. Graham Barr MD DrPH⁵, Nancy S. Jenny PhD⁶, Pamela Ouyang MBBS⁴, Jerome I. Rotter MD⁷

(1) Division of Public Health Sciences, (2); Department of Epidemiology and Prevention, Wake Forest University Health Sciences, Winston-Salem, NC;

(3) Northwestern University, Chicago I (4); Dept. of Medicine Johns Hopkins University, Baltimore MD (5); Columbia University Medical Center, Departments of Medicine and Epidemiology, New York NY

(6) Dept. of Pathology, University of Vermont College of Medicine, Burlington, VT

(7) Cedars Sinai Medical Center, Los Angeles CA

Corresponding Author:

AG Bertoni

Email: abertoni@wfubmc.edu

Additional information for this article can be found in an online appendix at <http://care.diabetesjournals.org>

Submitted 8 September 2009 and accepted 16 January 2010.

This is an uncopyedited electronic version of an article accepted for publication in *Diabetes Care*. The American Diabetes Association, publisher of *Diabetes Care*, is not responsible for any errors or omissions in this version of the manuscript or any version derived from it by third parties. The definitive publisher-authenticated version will be available in a future issue of *Diabetes Care* in print and online at <http://care.diabetesjournals.org>.

Objective: Many studies have documented associations between inflammation and type 2 diabetes incidence; we assessed potential variability in this association in the major U.S. race/ethnic groups.

Research Design and Methods: Incident type 2 diabetes was assessed among men and women aged 45-84 without prior clinical cardiovascular disease or diabetes in the prospective Multi-Ethnic Study of Atherosclerosis. Interleukin 6 (IL-6), fibrinogen, and C-reactive protein (CRP) were measured at baseline (2000-2002); fasting glucose and diabetes medication use was assessed at baseline and three subsequent in-person exams through 2007. Type 2 diabetes was defined as use of diabetes drugs or glucose \geq 126 mg/dl. Covariates included baseline demographics, clinic, smoking, alcohol, exercise, hypertension medication, systolic blood pressure, insulin resistance, and BMI. Cox proportional hazards regression was used to calculate hazard ratios (HR) by quartiles of CRP, IL-6, and fibrinogen.

Results: Among 5,571 participants (mean age 61.6 years, 53% female, 42.1% white, 11.5% Chinese, 25.7% black, 20.7% Hispanic) 410 developed incident diabetes during a median follow-up time of 4.7 years (incidence 16.8 per 1000-person years). CRP, IL6 and fibrinogen levels were associated with incident diabetes in the entire sample. After adjustment, the associations were attenuated; however quartile 4 (vs. quartile 1) of IL-6 (HR 1.5, 95%CI 1.1-2.2) and CRP (HR 1.7, 95%CI 1.3-2.4) remained associated with incident diabetes. In stratified analyses, similar associations were observed among white, black, and Hispanic participants.

Conclusions: Higher levels of inflammation predict short-term incidence of type 2 diabetes in a multi-ethnic American sample.

A number of prospective studies have demonstrated an association between high levels of inflammation and the development of type 2 diabetes. (1-8) In this report we assess three inflammatory markers: C-reactive protein (CRP), interleukin-6 (IL-6), and fibrinogen. CRP is an acute phase reactant mainly produced in the liver. Recent studies have shown that CRP can also be produced by fat cells (9), which raises the possibility that CRP may simply be a marker of obesity in persons who go on to develop diabetes. Fibrinogen is involved in clotting, but is also an acute phase reactant and has been previously linked to incident diabetes (8). IL-6 is made by leukocytes and other tissues that play a role in glucose homeostasis, including pancreatic islet cells, hepatocytes, adipocytes, and skeletal muscle cells and is associated with incident diabetes. (10) The graded positive association between most inflammatory markers and diabetes incidence remains significant following adjustment for established diabetes risk factors. However, a study in the Pima population showed no association between inflammatory markers and the risk of diabetes after adjusting for established risk factors for diabetes. (11) Although a sizable number of studies have documented the inflammatory marker-diabetes association, studies on ethnic/racial variations in this association are limited, despite the well documented increased prevalence of diabetes in non-white populations in the United States (12). The aims of this analysis are: 1) to explore the ability of CRP, IL-6, and fibrinogen to predict the incidence of diabetes in a prospective, multi-ethnic cohort; and 2) to determine the extent to which observed associations are similar across race/ethnic groups. We also consider whether observed associations are independent of the major known risk factors for diabetes (obesity, family history, insulin

resistance, hypertension, age, physical inactivity)(13).

METHODS

The Multi-Ethnic Study of Atherosclerosis (MESA) is a population-based sample of 6,814 men and women from four ethnic groups (38% white, 28% African-American, 22% Hispanic, and 12% Chinese) aged 45–84 without clinical cardiovascular (CVD) prior to recruitment. Details regarding MESA's design and objectives have been published (14). Briefly, persons who reported a medical history of heart attack, angina, coronary revascularization, pacemaker or defibrillator implantation, valve replacement, heart failure, or cerebrovascular disease were excluded. During the baseline exam (2000 to 2002), standardized questionnaires and calibrated devices were utilized to obtain demographic data, tobacco usage, medical conditions, current prescription medication usage, weight, waist circumference and height. Body-mass index was calculated as weight (kilos)/ height² (meters). Resting seated blood pressure was measured three times using a Dinamap automated oscillometric sphygmomanometer (model Pro 100, Critikon, Tampa, FL); the last two measurements were averaged for analysis. Hypertension was defined based on use of an antihypertensive medication, or systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg. Education was categorized as less than high school, completed high school, some college/technical school certificate or associate degree, bachelor's degree, and graduate or professional school. We utilized MESA Typical Week Physical Activity Survey intentional exercise variable, defined as the sum of walking for exercise, sports/dancing, and conditioning MET-hours/week (14). Alcohol use was queried and coded as current/former/never.

Participants were asked about current or former cigarette smoking, age at which smoking started and ended, and number of daily cigarettes typically consumed. Pack years was calculated, defined as number years smoking times packs per day (cigarettes per day divided by 20). Family history of diabetes was assessed at exam 2 and was unavailable for those who missed that exam.

Laboratory assessment. Fasting blood samples were drawn and processed using a standardized protocol and sent for measurement of glucose and inflammatory markers to central laboratories. (15) Serum glucose was measured by the glucose oxidase method on the Vitros analyzer (Johnson & Johnson Clinical Diagnostics). Insulin was determined by a radioimmunoassay method using the Linco Human Insulin Specific RIA Kit (Linco Research). The homeostasis model assessment of insulin resistance (HOMA-IR) was calculated as $\text{insulin mU/L} * (\text{glucose mg/dl} * 0.055) / 22.5$. (16) CRP and fibrinogen were measured using the BNII nephelometer (N High Sensitivity CRP and N Antiserum to Human Fibrinogen; Dade Behring). Intra-assay CVs for CRP range from 2.3 – 4.4% and inter-assay CVs range from 2.1 – 5.7%. The intra-assay and inter-assay CVs for fibrinogen were 2.7% and 2.6%, respectively. IL-6 was measured by ultra-sensitive ELISA (Quantikine HS Human IL-6 Immunoassay; R&D Systems). The laboratory CV for the IL-6 assay was 6.3%.

Diabetes definition. Participants with diabetes at baseline, defined as using hypoglycemic drugs or if the fasting glucose was ≥ 7.0 mmol/L (126 mg/dl), were excluded from these analyses. Persons were considered to have impaired fasting glucose if they did not have diabetes by the preceding criteria and their fasting glucose was ≥ 5.6 and < 7.0 mmol/L (> 100 and < 126 mg/dl). Persons newly utilizing hypoglycemic medication or having fasting glucose ≥ 7 mmol/L at exams

2, 3, or 4 were considered to have incident type 2 diabetes.

Statistical analysis. Descriptive statistics were utilized to compare characteristics of participants who developed diabetes compared to those who did not.. We primarily analyzed these data by dividing the population into quartiles of each inflammatory variable. We also noted that the distributions of IL-6 and CRP were skewed, and differed by race (generally lower levels in Chinese and higher in black participants). Thus we also assessed the relationship between log transformed IL6 and CRP and incident diabetes separately in each race/ethnic group.

Unadjusted incidence rates were calculated using person-time analysis. Participants were censored at the last follow-up exam which they attended (exams 2, 3 or 4). Cox proportional hazards modeling was utilized to estimate hazard ratios associated across quartiles. Model 1 included the inflammation marker of interest, age, gender, race/ethnicity site, exercise, education, systolic blood pressure, antihypertensive medication use, alcohol consumption, and smoking. Model 2 included model 1 variables plus HOMA-IR. Model 3 included model 2 variables plus body-mass index. All covariates were defined as their value at the baseline visit. Potential interactions between each inflammatory variable and race/ethnicity or gender were assessed using a multivariable interaction term. We performed additional analyses, first replacing BMI with waist circumference, and second, adding family history of diabetes to model 3, which did not appreciably change our results, therefore we do not present them. Finally, we constructed a composite inflammation score by standardizing the distributions of IL6 and CRP, and averaging the two. The sample was then divided into quartiles according to the composite score. Incidence rates were calculated and hazard ratios modeled as

detailed above. All analyses were performed using Stata 8.2 (Statacorp, College Station, Texas).

RESULTS

After excluding 857 (12.5%) participants with diabetes at baseline, 349 (5.1%) without a follow-up visit, 25 (0.4%) missing exam 1 diabetes status, and 12 (0.2%) missing all inflammatory markers at baseline, our final study sample was 5,571 individuals. Of these, 410 were classified as having incident diabetes during a median follow-up time of 4.7 years (incidence rate 16.5 per 1000-person years). Participant characteristics, stratified by race/ethnicity, are presented in Table 1. Overall, diabetes risk factors differed significantly between race/ethnic groups. Non-white participants had a greater prevalence of IFG at baseline, and higher incident diabetes rates, compared to whites. Chinese participants had on average a lower BMI and waist circumference, and less frequently reported a family history of diabetes. Levels of all three inflammation markers differed significantly by race/ethnicity ($p < 0.001$). Mean IL6, CRP, and fibrinogen were lower among Chinese, and tended to be higher among Hispanics and blacks, when compared to whites.

There was a modest level of correlation between pairs of inflammatory markers, and between each marker and BMI (table in online Appendix, available at <http://care.diabetesjournals.org>). There was little to no correlation between CRP/ IL-6/ fibrinogen and age, blood pressures, glucose, exercise, and pack-years smoking.

For each marker, rates of incident diabetes were higher for participants in higher quartiles compared to the lowest quartile (Table 2). Diabetes incidence was three-fold higher among participants whose baseline levels of CRP or IL-6 were in the 4th vs. the 1st quartile. The relationship between fibrinogen and incidence appeared different,

with only the 4th quartile being significantly elevated compared to the lower 3 quartiles. The univariate and adjusted associations between inflammation and diabetes are shown in Table 2. In general, all the observed associations remained significant after adjusting for demographic factors health behaviors, and blood pressure variables. For fibrinogen, only the 4th quartile was significantly associated with diabetes, and after adjusting for HOMA there was no longer a linear trend; with subsequent addition of BMI to the model there was no evidence for any association between level of fibrinogen and diabetes. In contrast, while addition of HOMA and BMI both attenuated the hazard ratios, there remained a significant association between both CRP and IL6 and diabetes incidence.

There was no statistical evidence of a significant interaction between inflammation level and race/ethnicity (or gender). Nonetheless, given our primary study aim, we performed stratified analyses for CRP and IL6 levels (Table 3). In each race/ethnic group participants with higher levels of IL-6 or CRP had a higher diabetes incidence than those with the lowest levels. Additionally, in a given quartile of CRP, IL-6, incidence rates tended to be higher in each non-white race/ethnic group compared to whites. CRP quartile was significantly associated with incident diabetes after adjustment for model 1 variables in whites, African-Americans, and Hispanics. Adjustment for HOMA and subsequently BMI attenuated the associations; however CRP quartile 4 remained associated with incident diabetes after full adjustment in AA and Hispanic participants. IL-6 was associated with incident diabetes after adjustment for model 1 variables in all groups except Chinese. As with CRP, the magnitude of the associations were attenuated after addition HOMA to the models; subsequent addition of BMI suggested there was no

longer an independent association between IL6 and diabetes in any group.

Similar results were obtained when repeating analyses using log-transformed inflammation levels. Specifically, the risk of diabetes per 1-unit change in log transformed CRP in the entire sample was 1.17 (95% CI 1.06-1.29) after full adjustment; for IL6 it was 1.30 (95% CI 1.09-1.55) and fibrinogen 1.10 (95% CI 0.65, 1.84). In stratified analyses, inflammation was similarly related to diabetes incidence in each race/ethnic group, again except in Chinese, in whom generally no statistically significant associations were observed (data not shown).

The composite score, constructed from the distribution of both IL6 and CRP, demonstrated similar patterns as seen above (Table 4). In the entire sample, the rate of diabetes increased with each quartile (p for trend <0.001). The hazard ratios were attenuated after adjusting for HOMA and BMI, but participants in Quartile 4 remained with a 60% higher risk of incident diabetes compared to those with the least inflammation. In the race-ethnicity stratified analyses, similar patterns were observed, although for Chinese participants none of the trends were significant.

DISCUSSION

Our results suggest that in a multi-ethnic sample of American adults aged 45-84 and free of clinical cardiovascular disease at baseline, people with higher levels CRP, IL6, and fibrinogen have a higher incidence of diabetes over a 2-5 year interval. The observed patterns of association were largely consistent among the four race/ethnic groups examined. The association between inflammation and incident diabetes was more consistent for CRP and IL-6; overall, and in each subgroup examined, rates of incident diabetes were 2-3 fold higher for participants with levels in the highest quartile of this sample. The increased risk associated with

higher levels of these two inflammatory markers was largely explained by established diabetes risk factors, and in particular BMI. Consideration of both IL6 and CRP distribution jointly showed similar patterns of association as with either marker alone. While fibrinogen level was also associated with incident diabetes, after adjustment for demographics, education, smoking, alcohol, exercise, hypertension and HOMA-IR there was no longer a significant association; further adjustment for BMI resulted in no suggestion of an independent association.

Strengths of our analyses include utilizing a multi-ethnic, gender balanced, and prospective cohort study to assess incident diabetes. MESA participants were carefully characterized with respect to standard diabetes risk factors, including fasting insulin. Rather than rely on self-reported diabetes at follow-up, MESA measured glucose and assessed medication use at the three follow-up examinations, furthermore all blood samples were analyzed centrally at one laboratory. There are several limitations to our analyses, however. By design MESA excluded persons with prevalent CVD, potentially limiting the generalizability of these results. We may have included some individuals with diet-controlled diabetes in the at-risk population, as we did not consider persons with a self-report of diabetes who were not taking medicine and had normal fasting glucose to have diabetes mellitus. On the other hand, we used the same definition at follow-up, which should be a conservative bias (potentially underestimating the true incidence rate). The failure to find significant interactions by race/ethnicity may reflect inadequate power. We did not have adequate sample size to present analyses stratified by race/ethnicity and gender. Biomarkers were only measured once and intra-individual variability cannot be accounted for. However, assay variability would be expected to bias findings towards

the null so the observed associations are potentially underestimations.

Our findings among Chinese participants merit some discussion. The apparently different relationships between inflammation and incident diabetes may be solely due to insufficient power, rather than any biological differences. Of note, we found few studies assessing inflammation level and diabetes in Chinese subjects; although CRP did appear associated with type 2 DM in a cross-sectional study.(17) CRP was associated with remaining glucose intolerant or progressing to diabetes among 228 Hong Kong Chinese with impaired glucose tolerance, however only 21 participants developed diabetes, precluding analyses about incident diabetes. (18) The lower-levels of inflammation present among Chinese in this sample may also explain our findings, if there is a threshold effect. At least one study including U.S. resident Chinese women also reported lower levels of CRP compared to other race/ethnic participants, even after adjusting for BMI differences (19).

The current epidemic of diabetes is projected to worsen such that up to 7% of the US population will be affected by 2050 (from 4% in 2000); up to 37% of the increased prevalence is estimated to be due to projected changes in the country's demographic composition with a decrease in whites and increase in minorities groups (20). As such, investigating diabetes incidence in a multi-ethnic sample is important. One recent analysis in a multi-ethnic cohort of postmenopausal women suggested both CRP and IL-6 predicted incident diabetes similarly in white, black, Hispanic and Asian/Pacific Islanders (21). There are several important differences between the study by Liu et al and the present one herein, including a case-control design and reliance on self-report or hospital discharge diagnoses; nevertheless, they also observed significant attenuation of the association between CRP or IL-6 and

incident diabetes when adjusting for BMI and baseline fasting glucose (21). CRP remained associated with incident diabetes in the Insulin Resistance and Atherosclerosis Study (a white, African American and Hispanic cohort) after adjustment for metabolic syndrome variables and insulin resistance, however they did not present a stratified analysis. (22) We are not aware of other studies reporting stratified results from a multi-ethnic sample including men. Our results suggest that the relationship between both CRP and IL-6 and incident diabetes is likely to be largely mediated by insulin resistance and adiposity in these race/ethnic groups. Fat cells, in particular visceral adipocytes, are known to be important producers of inflammatory proteins. There is substantial debate whether inflammation is directly playing a pathophysiologic role, or is simply a marker for underlying processes that affect both insulin sensitivity and inflammation levels (10).

Our results suggest that CRP and IL-6, or a composite score encompassing both, but not fibrinogen level, may be considered as potentially independent predictors of diabetes in a racially diverse population such as the U.S. It is plausible that inflammatory markers may be utilized to refine diabetes risk prediction, and thus better target (or motivate) individuals for lifestyle interventions. However, we note that CRP level did not appreciably improve diabetes risk prediction in the Framingham Offspring cohort or the IRAS study (22,23). One potential implication of the many studies demonstrating a relationship between inflammation and diabetes is that trials of anti-inflammatory agents be undertaken to prevent diabetes. However a recent randomized trial failed to demonstrate that chronic aspirin use prevented incident diabetes in women (24). In contrast, the Finish Diabetes Prevention Study lifestyle intervention reduced CRP and IL6 (25). Future research aimed at

understanding potential causal relationship between inflammation and diabetes may yield novel approaches to preventing diabetes. However, it remains important to focus on ways to increase adherence to lifestyle interventions of exercise and diet to reduce diabetes risk.

ACKNOWLEDGMENT:

This research was supported by contracts N01-HC-95159 through N01-HC-95165 and N01-HC-95169 from the National Heart, Lung, and Blood Institute. The authors thank the other investigators, the staff, and the participants of the MESA study for their valuable contributions. A full list of participating MESA investigators and institutions can be found at <http://www.mesa-nhlbi.org>

REFERENCES

1. Pradhan AD, Manson JE, Rifai N, Buring JE, Ridker PM: C-reactive protein, interleukin 6, and risk of developing type 2 diabetes mellitus. *JAMA*. 286:327-334, 2001
2. Spranger J, Kroke A, Mohlig M, Hoffmann K, Bergmann MM, Ristow M, Boeing H, Pfeiffer AF: Inflammatory cytokines and the risk to develop type 2 diabetes: results of the prospective population-based European Prospective Investigation into Cancer and Nutrition (EPIC)-Potsdam Study. *Diabetes*. 52:812-817, 2003
3. Thorand B, Lowel H, Schneider A, Kolb H, Meisinger C, Frohlich M, Koenig W: C-reactive protein as a predictor for incident diabetes mellitus among middle-aged men: results from the MONICA Augsburg cohort study, 1984-1998. *Arch Intern Med*. 163:93-99, 2003
4. Hu FB, Meigs JB, Li TY, Rifai N, Manson JE: Inflammatory markers and risk of developing type 2 diabetes in women. *Diabetes*. 53:693-700, 2004
5. Thorand B, Kolb H, Baumert J, Koenig W, Chambless L, Meisinger C, Illig T, Martin S, Herder C: Elevated levels of interleukin-18 predict the development of type 2 diabetes: results from the MONICA/KORA Augsburg Study, 1984-2002. *Diabetes*. 54:2932-2938, 2005
6. Doi Y, Kiyohara Y, Kubo M, Ninomiya T, Wakugawa Y, Yonemoto K, Iwase M, Iida M: Elevated C-reactive protein is a predictor of the development of diabetes in a general Japanese population: the Hisayama Study. *Diabetes Care*. 28:2497-2500, 2005
7. Rutter MK, Meigs JB, Sullivan LM, D'Agostino RB, Sr., Wilson PW: C-reactive protein, the metabolic syndrome, and prediction of cardiovascular events in the Framingham Offspring Study. *Circulation*. 110:380-385, 2004
8. Festa A, D'Agostino R, Jr., Tracy RP, Haffner SM: Elevated levels of acute-phase proteins and plasminogen activator inhibitor-1 predict the development of type 2 diabetes: the insulin resistance atherosclerosis study. *Diabetes*. 51:1131-1137, 2002
9. Calabro P, Chang DW, Willerson JT, Yeh ET: Release of C-reactive protein in response to inflammatory cytokines by human adipocytes: linking obesity to vascular inflammation. *J Am Coll Cardiol*. 46:1112-1113, 2005
10. Kristiansen OP, Mandrup-Poulsen T: Interleukin-6 and diabetes: the good, the bad, or the indifferent? *Diabetes*. 54 Suppl 2:S114-24.:S114-S124, 2005
11. Krakoff J, Funahashi T, Stehouwer CD, Schalkwijk CG, Tanaka S, Matsuzawa Y, Kobes S, Tataranni PA, Hanson RL, Knowler WC, Lindsay RS: Inflammatory markers, adiponectin, and risk of type 2 diabetes in the Pima Indian. *Diabetes Care*. 26:1745-1751, 2003
12. Cowie CC, Rust KF, Byrd-Holt DD, Eberhardt MS, Flegal KM, Engelgau MM, Saydah SH, Williams DE, Geiss LS, Gregg EW: Prevalence of Diabetes and Impaired Fasting Glucose in Adults in the U.S. Population: National Health and Nutrition Examination Survey 1999-2002. *Diabetes Care* 29:1263-1268, 2006
13. Rewers M, Hamman RF: Risk Factors for non-insulin-dependent diabetes. In *Diabetes in America*. 2nd ed. Harris MI, Cowie CC, Stern MP, Boyko EJ, Reiber GE, Bennett PH, Eds. Washington D.C., US Govt Printing Office, 1995, p. 179-220
14. Bild DE, Bluemke DA, Burke GL, Detrano R, Diez Roux AV, Folsom AR, Greenland P, Jacob DR, Jr., Kronmal R, Liu K, Nelson JC, O'Leary D, Saad MF, Shea S, Szklo M, Tracy RP: Multi-ethnic study of atherosclerosis: objectives and design. *Am.J.Epidemiol*. 156:871-881, 2002

15. Cushman M, Cornell ES, Howard PR, Bovill EG, Tracy RP: Laboratory methods and quality assurance in the Cardiovascular Health Study. *Clin Chem* 41:264-270, 1995
16. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC: Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia* 28:412-419, 1985
17. Ye X, Franco OH, Yu Z, Li H, Hu FB, Liu H, Wang X, Tang H, Liu Y, Chen Y, Lin X: Associations of inflammatory factors with glycaemic status among middle-aged and older Chinese people. *Clin Endocrinol (Oxf)*. 70:854-862, 2009
18. Tan KCB, Wat NMS, Tam SCF, Janus ED, Lam TH, Lam KSL: C-Reactive Protein Predicts the Deterioration of Glycemia in Chinese Subjects With Impaired Glucose Tolerance. *Diabetes Care* 26:2323-2328, 2003
19. Screening for high blood pressure: recommendations and rationale. *Am J Prev Med*. 25:159-164, 2003
20. Boyle JP, Honeycutt AA, Narayan KM, Hoerger TJ, Geiss LS, Chen H, Thompson TJ: Projection of diabetes burden through 2050: impact of changing demography and disease prevalence in the U.S. *Diabetes Care* 24:1936-1940, 2001
21. Liu S, Tinker L, Song Y, Rifai N, Bonds DE, Cook NR, Heiss G, Howard BV, Hotamisligil GS, Hu FB, Kuller LH, Manson JE: A prospective study of inflammatory cytokines and diabetes mellitus in a multiethnic cohort of postmenopausal women. *Arch Intern Med*. 167:1676-1685, 2007
22. Hanley AJG, Karter AJ, Williams K, Festa A, D'Agostino RB, Jr., Wagenknecht LE, Haffner SM: Prediction of Type 2 Diabetes Mellitus With Alternative Definitions of the Metabolic Syndrome: The Insulin Resistance Atherosclerosis Study. *Circulation* 112:3713-3721, 2005
23. Wilson PW, Meigs JB, Sullivan L, Fox CS, Nathan DM, D'Agostino RB, Sr.: Prediction of incident diabetes mellitus in middle-aged adults: the Framingham Offspring Study. *Arch Intern Med*. 167:1068-1074, 2007
24. Pradhan AD, Cook NR, Manson JE, Ridker PM, Buring JE: A Randomized Trial of Low-Dose Aspirin in the Prevention of Clinical Type 2 Diabetes in Women. *Diabetes Care* 32:3-8, 2009
25. Herder C, Peltonen M, Koenig W, Sutfels K, Lindstrom J, Martin S, Ilanne-Parikka P, Eriksson JG, Aunola S, Keinanen-Kiukaanniemi S, Valle TT, Uusitupa M, Kolb H, Tuomilehto J: Anti-inflammatory effect of lifestyle changes in the Finnish Diabetes Prevention Study. *Diabetologia*. 52:433-442, 2009

Table 1. Characteristics of participants, by race/ethnicity, in the Multi-Ethnic Study of Atherosclerosis 2000-2007.

Characteristic	White N=2348	Chinese N=644	African American N=1427	Hispanic N=1152
Age	62.3 (10.2)	61.3 (10.2)	61.5(10.2)	60.5 (10.3)
Female †	52.4%	51.7%	55.6%	52.6%
Current Smoking	11.1%	5.4%	18.1%	13.7%
Pack-years Tobacco	14.6 (27.3)	4.3 (12.7)	11.4 (18.9)	7.4 (16.0)
Former Alcohol use	17.1%	15.5%	31.0%	24.3%
Current Alcohol use	73.6%	32.2%	52.3%	51.1%
Education \geq Bachelors	51.4	40.9	36.3	11.0
Exercise (MET-hrs/wk)	28.4 (37.3)	19.7 (26.5)	29.9 (48.4)	22.8 (35.5)
Weight (lbs)	173.7 (36.4)	138.3 (24.3)	186.6 (37.4)	168.7 (32.1)
BMI (kilo/m2)	27.5 (4.9)	23.9 (3.3)	29.8 (5.8)	29.1 (4.8)
Waist (cm)	97.2 (14.1)	86.6 (10.1)	99.8 (14.2)	99.5 (12.7)
Hypertension medication	30.7%	24.5%	44.6%	28.0%
Hypertension	36.6%	34.2%	54.7%	37.3%
SBP (mmHg)	122.6 (19.9)	122.8 (21.1)	130.6 (21.2)	125.2 (21.3)
DBP (mmHg)	70.2 (9.9)	71.9 (10.3)	74.6 (10.1)	71.7 (10.1)
Glucose (mg/dl)	87.8 (10.0)	91.5 (10.1)	90.2 (10.7)	91.0 (10.8)
Impaired Fasting Glucose	10.4%	17.2%	15.9%	17.3%
HOMA-IR	1.3 (1.0)	1.4 (1.0)	1.5 (1.1)	1.7 (1.3)
Family History*	29.1%	25.6%	42.3%	41.0%
C-reactive protein (mg/l)	3.3 (5.0)	1.9 (5.2)	4.5 (6.9)	3.7 (4.7)
CRP \geq 3.0 mg/l	32.6%	12.3%	43.2%	40.9%
Interleukin 6 (pg/ml)	1.4 (1.2)	1.1 (1.0)	1.6 (1.2)	1.6 (1.1)
Fibrinogen (mg/dl)	332.4 (68.7)	327.6 (60.2)	357.3 (77.4)	354.0 (70.5)
Incident Diabetes‡	11.1/1000	16.2/1000	21.6/1000	21.9/1000

Data presented are means (standard deviations) except where noted to be percentages.

* Family history data available for 5404, ‡ Rate per 1000 person-years.

All differences across race/ethnicity are significant at $p < 0.001$ except † $p = 0.2$

Table 2. Hazard Ratios for incident diabetes associated with inflammatory markers in the Multi-Ethnic Study of Atherosclerosis 2002-2007

	Quartile 1	Quartile 2	Quartile 3	Quartile4	p trend
N=5554					
CRP, mg/l	0.15-0.80	0.81-1.80	1.81-4.08	4.09-97.4	
Rate	9.0	13.4	16.7	27.4	<0.001
Univariate	1 (ref)	1.5 (1.1-2.1)	1.9 (1.3,2.6)	3.1 (2.3,4.1)	<0.001
Model 1	1 (ref)	1.5 (1.3, 2.0)	1.8 (1.3, 2.4)	2.8 (2.1, 3.9)	<0.001
Model 2	1 (ref)	1.3 (0.9, 1.8)	1.5 (1.0, 2.0)	2.1 (1.5, 2.9)	<0.001
Model 3	1 (ref)	1.2 (0.9, 1.7)	1.3 (0.9, 1.8)	1.7 (1.3, 2.4)	<0.01
N=5445					
Il6, pg/ml	0.12-0.73	0.74-1.14	1.15-1.792	1.793-12.9	
Rate	8.2	14.9	15.7	28.2	<0.001
Univariate	1 (ref)	1.8 (1.3,3.5)	1.9 (1.4,2.7)	3.4 (2.5,4.6)	<0.001
Model 1	1 (ref)	1.7 (1.2, 2.4)	1.7 (1.2, 2.4)	3.0 (2.2, 4.2)	<0.001
Model 2	1 (ref)	1.5 (1.1, 2.1)	1.3 (0.9, 1.8)	2.0 (1.4, 2.8)	<0.001
Model 3	1 (ref)	1.4 (1.0, 2.0)	1.1 (0.8, 1.6)	1.5 (1.1, 2.2)	0.02
N=5557					
Fibrinogen, mg/l	144-293	294-334	335-384	385-701	
Rate	13.9	13.3	16.4	22.5	<0.001
Univariate	1 (ref)	1.0 (0.7,1.3)	1.2 (0.9, 1.6)	1.6 (1.2, 2.1)	<0.001
Model 1	1 (ref)	1.0 (0.7, 1.3)	1.1 (0.8, 1.5)	1.5 (1.1, 2.0)	0.01
Model 2	1 (ref)	0.9 (0.7,1.2)	1.1 (0.8, 1.4)	1.2 (0.9, 1.6)	ns
Model 3	1 (ref)	0.8 (0.6,1.1)	1.0 (0.7,1.3)	1.0 (0.8, 1.3)	ns

Rate =Rate of incident diabetes per 1000 person-years. Other data presented are hazard ratios (95% confidence intervals). Model 1 adjusted for age, gender, race, education, site, alcohol, smoking, exercise, systolic blood pressure, and anti-hypertensive medication use. Model 2=Model 1 plus Homeostasis model of insulin resistance (HOMA) Model 3= Model 2 plus body-mass index P value for trend across quartiles is noted; ns = not significant.

Table 3. Hazard Ratios for incident diabetes associated with inflammatory marker quartiles , stratified by race/ethnicity, in the Multi-Ethnic Study of Atherosclerosis 2002-2007

CRP		Quartile 1	Quartile 2	Quartile 3	Quartile4	p trend
White	Rate	5.5	10.4	10.5	18.8	<0.001
	Model 1	1 (ref)	1.8 (0.9, 3.3)	1.8 (1.0, 3.5)	3.2 (1.8, 5.8)	<0.01
	Model 2	1 (ref)	1.4 (0.8, 2.6)	1.3 (0.7, 2.4)	2.0 (1.1, 3.6)	ns
	Model 3	1 (ref)	1.3 (0.7, 2.4)	1.0 (0.5, 2.0)	1.5 (0.8, 2.9)	ns
Chinese	Rate	12.9	14	24.3	28.6	ns
	Model 1	1 (ref)	1.0 (0.5, 2.0)	1.6 (0.8, 3.3)	2.0 (0.7, 5.8)	ns
	Model 2	1 (ref)	0.8 (0.4, 1.8)	1.4 (0.6, 2.9)	1.0 (0.3, 3.6)	ns
	Model 3	1 (ref)	0.7 (0.3, 1.5)	1.0 (0.5, 2.2)	0.9 (0.3, 3.0)	ns
African American	Rate	12.8	14.7	20.1	33.2	<0.001
	Model 1	1 (ref)	1.3(0.6, 2.5)	1.7 (0.9, 3.1)	2.6 (1.5, 4.7)	<0.01
	Model 2	1 (ref)	1.2 (0.6, 2.3)	1.6 (0.8, 2.9)	2.2 (1.2, 4.0)	<0.05
	Model 3	1 (ref)	1.1 (0.6, 2.2)	1.5 (0.8, 2.7)	1.9 (1.0, 3.5)	ns
Hispanic	Rate	9.8	17.5	21.2	34.4	<0.001
	Model 1	1 (ref)	1.8 (0.9, 4.0)	2.1 (1.0, 4.5)	3.5 (1.7, 7.2)	<0.01
	Model 2	1 (ref)	1.7 (0.8, 3.7)	1.7 (0.8, 3.6)	2.7 (1.3, 5.5)	<0.05
	Model 3	1 (ref)	1.7 (0.8, 3.8)	1.7 (0.8, 3.5)	2.5 (1.2, 5.1)	ns
Interleukin 6		Quartile1	Quartile 2	Quartile 3	Quartile4	p trend
White	Rate	5.1	9.1	12.2	20.5	<0.001
	Model 1	1 (ref)	1.7 (0.9, 3.4)	2.2 (1.2, 4.2)	3.6 (1.9, 6.7)	<0.001
	Model 2	1 (ref)	1.2 (0.6, 2.3)	1.4 (0.7,2.7)	1.8 (0.6, 3.5)	ns
	Model 3	1 (ref)	1.0 (0.5, 2.0)	1.1 (0.6,2.2)	1.3 (0.7,2.6)	ns
Chinese	Rate	9.7	23.4	18.2	22.3	ns
	Model 1	1 (ref)	2.3 (1.1, 4.7)	1.6 (0.7, 4.1)	2.4 (0.9, 5.8)	ns
	Model 2	1 (ref)	2.1 (1.0, 4.3)	1.0 (0.4, 2.7)	1.9 (0.8, 4.9)	ns
	Model 3	1 (ref)	1.8 (0.9, 3.7)	0.8 (0.3, 2.1)	1.4 (0.5,3.7)	ns
African American	Rate	11.0	18.0	18.6	34.8	<0.001
	Model 1	1 (ref)	1.5 (0.8, 3.2)	1.6 (0.8, 3.1)	3.0 (1.6, 5.6)	<0.001
	Model 2	1 (ref)	1.4 (0.7, 2.7)	1.4 (0.7, 2.7)	2.3 (1.2, 4.4)	0.01
	Model 3	1 (ref)	1.3 (0.7, 2.6)	1.2 (0.6, 2.4)	1.9 (1.0, 3.7)	ns
Hispanic	Rate	12.8	18.8	17.9	34.1	<0.01
	Model 1	1 (ref)	1.4 (0.7, 2.9)	1.3 (0.6, 2.6)	2.4 (1.2, 4.6)	0.02
	Model 2	1 (ref)	1.2 (0.6, 2.5)	0.7 (0.4, 1.5)	1.2 (0.6, 2.4)	ns
	Model 3	1 (ref)	1.2 (0.6, 2.5)	0.7 (0.3, 1.4)	1.1 (0.5, 2.2)	ns

Rate=Rate per 1000 person years. Other data presented are hazard ratios (95% confidence intervals). Model 1 adjusted for age, gender, race, education, site, alcohol, smoking, exercise, systolic blood pressure, and anti-hypertensive medication use. Model 2=Model 1 plus Homeostasis model of insulin resistance (HOMA) Model 3= Model 2 plus body-mass index P value for trend across quartiles is noted; ns = not significant.

Table 4. Association between a composite score composed of Interleukin 6 and C reactive protein and incident diabetes in the Multi-Ethnic Study of Atherosclerosis, 2002-2007

Sample		Quartile				p-trend
		1	2	3	4	
Overall N=5437	Rate	8.6	12.1	16.7	28.5	<0.001
	Model 1	1 (ref)	1.5 (1.1, 2.1)	1.8 (1.3, 2.5)	3.0 (2.2, 4.2)	<0.001
	Model 2	1 (ref)	1.3 (0.9, 1.8)	1.4 (1.0, 1.9)	2.0 (1.4, 2.8)	<0.001
	Model 3	1 (ref)	1.2 (0.8, 1.4)	1.2 (0.8, 1.7)	1.6 (1.1, 2.2)	0.03
White N=2311	Rate	5.9	7.2	11.0	22.3	
	Model 1	1 (ref)	1.2 (0.6, 2.4)	1.8 (1.0, 3.4)	3.7 (2.0, 6.6)	<0.001
	Model 2	1 (ref)	0.8 (0.4, 1.6)	1.2 (0.6, 2.2)	1.8 (1.0, 3.3)	0.02
	Model 3	1 (ref)	0.7 (0.4, 1.4)	0.9 (0.5, 1.8)	1.3 (0.7,2.5)	ns
Chinese N=633	Rate	11.1	23.8	14.2	25.6	ns
	Model 1	1 (ref)	2.1 (1.0, 4.1)	1.1 (0.4, 3.0)	2.2 (0.9, 3.0)	ns
	Model 2	1 (ref)	1.6 (0.8, 3.3)	0.9 (0.4, 2.5)	1.4 (0.5, 3.8)	ns
	Model 3	1 (ref)	1.4 (0.7, 2.8)	0.6 (0.2, 1.7)	1.1 (0.4, 3.0)	ns
African American N=1376	Rate	9.7	13.6	23.3	33.5	<0.001
	Model 1	1 (ref)	1.5 (0.7, 3.1)	2.4 (1.2, 4.8)	3.5 (1.8, 6.8)	<0.001
	Model 2	1 (ref)	1.4 (0.7, 3.0)	2.1 (1.1, 4.2)	2.7 (1.4, 5.3)	0.01
	Model 3	1 (ref)	1.3 (0.6, 2.8)	1.9 (1.0, 3.9)	2.2 (1.1, 4.5)	ns
Hispanic N=1117	Rate	12.0	18.6	19.8	32.7	<0.01
	Model 1	1 (ref)	1.5 (0.7, 3.0)	1.5 (0.7, 3.1)	2.5 (1.3, 4.9)	0.03
	Model 2	1 (ref)	1.1 (0.5, 2.2)	0.9 (0.4, 1.9)	1.4 (0.7, 2.9)	ns
	Model 3	1 (ref)	1.0 (0.5, 2.2)	0.9 (0.4, 1.8)	1.3 (0.6, 2.6)	ns

Rate= Incidence rate per 1000 person years. Other data presented are hazard ratios (95% confidence intervals). Model 1 adjusted for age, gender, race, education, site, alcohol, smoking, exercise, systolic blood pressure, and anti-hypertensive medication use. Model 2=Model 1 plus Homeostasis model of insulin resistance (HOMA) Model 3= Model 2 plus body-mass index P value for trend across quartiles is noted; ns = not significant