Published in final edited form as:

Diabetes Obes Metab. 2014 April ; 16(4): 326–333. doi:10.1111/dom.12220.

Metabolic Syndrome Components and Their Response to Lifestyle and Metformin Interventions are Associated with Differences in Diabetes Risk in Persons with Impaired Glucose Tolerance

Hermes Florez¹, Marinella G Temprosa², Trevor J Orchard³, Kieren J Mather⁴, Santica M Marcovina⁵, Elizabeth Barrett-Connor⁶, Edward Horton⁷, Christopher Saudek^{8,†}, Xavier F Pi-Sunyer⁹, Robert E Ratner¹⁰, and Ronald B Goldberg¹¹ for the Diabetes Prevention Program Research Group

¹Geriatric Research, Education, and Clinical Center, Miami Veterans Affairs Healthcare System and Divisions of Epidemiology, Geriatric Medicine & Endocrinology, University of Miami Miller School of Medicine, Miami, Florida ²The Biostatistics Center, The George Washington University, Rockville, Maryland ³Department of Epidemiology, Graduate School of Public Health, University of Pittsburgh, Pittsburgh, Pennsylvania ⁴Division of Endocrinology and Metabolism, Indiana University School of Medicine, Indianapolis, Indiana ⁵Northwest Lipid Research Labs, University of Washington, Seattle, Washington ⁶Department of Family and Preventive Medicine, University of California, San Diego, La Jolla, California ⁷Joslin Diabetes Center, Boston, Massachusetts ⁸The Johns Hopkins School of Medicine, Baltimore, Maryland ⁹Division of Endocrinology, Diabetes and Nutrition, Department of Medicine, St. Luke's Roosevelt Hospital Center, Columbia University College of Physicians and Surgeons, New York, New York ¹⁰Medstar Health Research Institute, Hyattsville, Maryland ¹¹Division of Endocrinology, Diabetes and Metabolism, University of Miami Miller School of Medicine, Miami, FL

Abstract

Aims—To determine the association of metabolic syndrome (MetS) and its components with diabetes risk in participants with impaired glucose tolerance (IGT), and whether intervention-related changes in MetS lead to differences in diabetes incidence.

Methods—We used the NCEP/ATP III revised MetS definition at baseline and intervention-related changes of its components to predict incident diabetes using Cox models in 3234 Diabetes Prevention Program (DPP) participants with IGT over an average follow-up of 3.2 years.

Results—In an intention-to-treat analysis, the demographic-adjusted hazard ratios (95%CI) for diabetes in those with MetS (versus no MetS) at baseline were 1.7(1.3-2.3), 1.7(1.2-2.3), and 2.0(1.3-3.0) for placebo, metformin, and lifestyle groups, respectively. Higher levels of fasting plasma glucose and triglycerides at baseline were independently associated with increased risk of diabetes. Greater waist circumference (WC) was associated with higher risk in placebo and

Address correspondence to: Hermes Florez, MD, PhD, Diabetes Prevention Program Coordinating Center, The Biostatistics Center, George Washington University, 6110 Executive Boulevard, Suite 750, Rockville, MD 20852, dppmail@biostat.bsc.gwu.edu; hflorez@med.miami.edu.

[†]Deceased

*Current affiliation: American Diabetes Association, Alexandria, Virginia

Trial registration: DPP is registered in www.clinicaltrials.gov (NCT00004992).

lifestyle groups, but not in the metformin group. In a multivariate model, favorable changes in WC (placebo and lifestyle) and HDLc (placebo and metformin) contributed to reduced diabetes risk.

Conclusions—MetS and some of its components are associated with increased diabetes incidence in persons with IGT in a manner that differed according to DPP intervention. After hyperglycemia, the most predictive factors for diabetes were baseline hypertriglyceridemia and both baseline and lifestyle-associated changes in waist circumference. Targeting these cardio-metabolic risk factors may help to assess the benefits of interventions that reduce diabetes incidence.

Keywords

diabetes prevention; cardio-metabolic risk; lifestyle; metformin

INTRODUCTION

Metabolic syndrome (MetS) consists of clustering risk factors that may be targeted for risk reduction of cardiovascular disease (CVD) and diabetes. MetS predicts the incidence of type 2 diabetes in population-based studies of normoglycemic individuals [1-2]. Whether MetS and its components predict diabetes in higher-risk individuals with IGT is less well studied. IGT is associated with atherosclerosis and increased arterial stiffness, which may lead to elevated pulse pressure (PP), further increasing the risk of diabetes and CVD [3-4]. In addition, the combination of elevated waist circumference and triglyceride—so called hypertriglyceridemic waist, has been demonstrated to be a superior predictor of insulin resistance and intra-abdominal fat [5], but its utility as a predictor of incident diabetes in individuals with IGT has not been assessed. It is not known whether intervention-associated changes in these cardio-metabolic risk factors will also reduce diabetes incidence.

The DPP, a multicenter, randomized controlled trial, demonstrated that the risk for developing diabetes was reduced 58% by intensive lifestyle (ILS) and 31% by metformin (MET) interventions in people with IGT, compared with placebo (PLA) [6]. The DPP data provides a unique opportunity to evaluate the associations of MetS and its components at baseline and their changes after intervention with the development of diabetes.

METHODS

Study participants

The eligibility criteria, design, and methods of the DPP have been reported elsewhere [6, 7]. Selection criteria included: age ≥ 25 years, BMI ≥ 24 kg/m² (≥ 22 kg/m² in Asian Americans), fasting plasma glucose (FPG) levels between 95 and 125 mg/dl, and IGT (2-hour post-load glucose of 140–199 mg/dl). Persons were excluded if they were taking medications known to alter glucose tolerance or if they had illnesses that could seriously reduce their life expectancy or their ability to participate in the trial. The current report includes 3234 participants, who were randomized into 3 treatment arms, namely ILS, MET, and PLA. Written informed consent was obtained from all participants before screening, consistent with the Declaration of Helsinki and the guidelines of each center's institutional review board.

Clinical and metabolic variables—Standardized interviewer-administered questionnaires were used to obtain demographic and clinical data. Blood pressure (BP), weight, and waist circumference (WC) were measured biannually using standard techniques. All analytical measurements for glucose, insulin, and lipids were performed at the Central Biochemistry Laboratory (Northwest Lipid Research Laboratories, University of

Washington, Seattle, WA) as reported previously. Insulin secretion was estimated with the corrected insulin response (CIR) = $(100 \times 30\text{-min insulin}) / (30\text{-min glucose} \times [30\text{-min glucose} - 70 \text{ mg/dl}])$ [8]. Insulin resistance was estimated using the reciprocal of fasting insulin.

Outcomes—Development of diabetes was determined by an annual oral glucose tolerance test and semiannual FPG tests, and required confirmation by a second test using the diagnostic criteria of the American Diabetes Association and the World Health Organization [9, 10].

Data Analysis

We classified participants into those with MetS, using the revised National Cholesterol Education Program/Adult Treatment Panel III (NCEP/ATP III) definition [11], if they had 3 or more of the following criteria: (a) WC ≥ 40 inches (102 cm) in men or ≥ 35 inches (88 cm) in women; (b) triglyceride ≥ 1.7 mmol/L (150 mg/dl) or use of lipid lowering medications; (c) HDL-C < 1.03 mmol/L (40 mg/dl) in men or < 1.29 mmol/L (50 mg/dl) in women or use of lipid lowering medications; (d) systolic BP (SBP) ≥ 130 mm Hg, diastolic BP (DBP) ≥ 85 mm Hg, or use of antihypertensive therapy; and (e) FPG ≥ 5.6 mmol/L (100 mg/dL). For comparison, the International Diabetes Federation (IDF) definition [12] was also used to identify those with MetS if they had a WC ≥ 94 cm in men or ≥ 80 cm in women plus any two of the following: (a) triglycerides ≥ 1.7 mmol/L or specific treatment for this lipid abnormality; (b) HDL-C < 1.03 mmol/L in men or < 1.29 mmol/L in women or specific treatment for this lipid abnormality; (c) SBP ≥ 130 mmHg or DBP ≥ 85 mmHg or treatment of previously diagnosed hypertension; and (d) FPG ≥ 5.6 mmol/L. PP was calculated from the difference between SBP and DBP measurements at baseline and in semi-annual visits. Hypertriglyceridemic waist was defined using the same MetS cutpoints for TG and WC. Participants were followed for an average of 3.2 years. Mean differences between groups were tested using the t test, within groups using the paired t test, and differences in proportions using the contingency chi-squared test. The normal errors longitudinal regression model assessed differences between groups in the mean change from baseline up to the time of diabetes onset or the last visit, adjusting for baseline values.

The Cox proportional hazards model [13] was used to assess the association between the covariates and diabetes onset, adjusted for baseline demographic variables (age at randomization, sex, and race/ethnicity). Multivariate models were used to examine individual and adjusted contributions of the MetS components. The Wald test provided p-values and R^2 values for individual covariates; and the likelihood ratio test tested those for the combined model. Madalla's partial R^2 described the proportion of variation in risk of diabetes explained by a covariate, expressed as a percentage [14]. To facilitate comparisons across variables, hazard ratios are reported for convenient increments approximating one standard deviation (SD) of measure. Models were run separately for each treatment group, and a test of heterogeneity was used to see if the association differed across treatment groups. Besides the use of MetS definition based on the dichotomization of thresholds, we examined the effect of each MetS component as a quantitative trait to obtain greater granularity on its specific contribution. In assessing the relationship between intervention-related changes in components and the risk for diabetes, the Cox models accounted for differences in age at randomization, sex, race/ethnicity, baseline FPG, and baseline level. Metabolic variables in the time-dependent proportional hazards analyses were entered as the average change from baseline up to, but not including, each visit when diabetes was diagnosed; and hazard ratios are expressed as a favorable change approximating one SD. The SAS system was used for all analyses (Cary, NC). Interactions in Cox models were used

to assess whether the association between baseline MetS and incident diabetes differed by sex, age, or race/ethnicity.

RESULTS

We previously reported that baseline MetS prevalence using the original NCEP/ATP III criteria was 53% [15]. Using the revised NCEP/ATP III definition, the observed prevalence was 69%, which was similar to a 66% prevalence based on the IDF definition. Participants who met the NCEP/ATP III MetS definition were heavier, had greater PP, more insulin resistance, and lower insulin secretion than those without MetS (Table 1); and there was a greater proportion of Caucasians and fewer African Americans in this group. Those with MetS at baseline had higher risk of developing diabetes compared to those without MetS (HR [95% CI]: ILS: 1.7[1.3-2.3]; MET: 1.7[1.2-2.3]; PLA: 2.0[1.3-3.0]) (Fig 1A). Similar results were observed using the IDF MetS definition (HR [95% CI]: ILS; 1.7[1.2-2.5], MET; 1.4[1.1-1.9], and PLA; 1.7[1.3-2.2]). The impact of MetS at baseline did not differ by treatment group ($p=0.85$), age, sex, or race/ethnicity.

As expected, participants with baseline fasting hyperglycemia (≥ 100 mg/dl) had 2-3 times higher risk of developing diabetes compared to those with normal FPG at baseline in univariate analyses. In addition, abdominal obesity at baseline was associated with higher diabetes risk in the ILS and PLA groups (PLA: 1.6 [1.1-2.2], $p=0.006$; ILS: 1.8 [1.1-2.8], $p=0.02$), but not in the MET group. Elevated triglycerides were associated with incident diabetes in the MET group only (1.4 [1.1-1.8], $p=0.02$); and low HDL-C was associated with increased diabetes risk only in the PLA group (1.4 [1.1-1.8] $p=0.003$). The baseline prevalence of hypertriglyceridemic waist was 36.5% and was associated with approximately half the excess risk for diabetes observed with the full MetS in the PLA (1.4 [1.1-1.8], $p=0.006$) and ILS (1.6; 1.1-2.2 $p=0.01$) groups, but was not significantly associated with diabetes risk in MET participants (1.28 [0.98-1.7] $p=0.07$). In multivariate analysis with demographic factors plus all MetS components in the model (Figure 1B), only high FPG (in all groups) and abdominal obesity (in ILS and PLA) remained significantly associated with an increased risk of diabetes. For each 12 mmHg increment in baseline PP diabetes incidence was increased by 17% ($p=0.013$) and 23% ($p=0.025$) in PLA and ILS participants, respectively, but not in those on MET (8%, $p=0.3$).

In order to have more power to detect the association between MetS components and incident diabetes, absolute levels were used (Figs 2A and 2B). For every 8 mg/dl (0.44 mmol/l) higher FPG at baseline, diabetes risk nearly doubled in PLA and ILS groups. For each 96 mg/dl (1.1 mmol/l) baseline triglyceride increment, diabetes incidence was increased by 13% ($p=0.01$), 24% ($p<0.001$) and 20% ($p=0.013$) for the PLA, MET and ILS groups, respectively; and for every 15 cm greater WC, diabetes incidence was 36% ($p<0.001$) and 52% ($p<0.001$) greater in the PLA and ILS groups, respectively, with no effect in the MET group. The association between WC and triglyceride on incident diabetes remained significant after adjusting for FPG (Fig 2b) with the exception of WC in the MET group. In additional models, there was no significant triglyceride by WC interaction in any of the treatment groups, and the effects of triglyceride and WC on diabetes development remained significant after accounting for baseline values of known diabetes predictors, namely weight, insulin secretion, and insulin sensitivity (data not shown). Triglyceride and WC increments per SD contributed to more of the variance in incident diabetes (for WC in the PLA and ILS respectively, $R^2=1.2\%$ and 2.8% , and for triglyceride in the PLA, ILS and MET, $R^2=0.7\%$, 0.6% and 1.2%) than that associated with the category (for PLA and ILS, $R^2=0.7\%$ and 0.6%).

Table 2 shows the changes from baseline for each MetS component during 3.2 years of intervention according to the DPP intervention group and their effect on incident diabetes. Favorable changes in each component were significantly associated with a reduction in diabetes for all treatment groups, except for BP and TG in the MET group (Figure 2C). In a multivariate model of baseline and changes in components (Fig 2D), baseline FPG remained the primary determinant of subsequent diabetes. A reduction in WC of 6 cm decreased diabetes risk by 45% in the ILS and 23% in the PLA but had no effect in the MET groups. In addition, an increase of 6 mg/dl (0.16 mmol/L) in HDL-C was independently associated with a 20% reduction in diabetes risk in the MET and PLA groups, while changes in triglyceride values had no effect on incident diabetes in any group. Unlike baseline WC and triglyceride, the association of changes in WC and HDL-C with incident diabetes disappeared after accounting for changes in weight, insulin secretion, and insulin sensitivity (data not shown). In proportional hazards model adjusted for demographic and baseline PP, a decrease of 9 mmHg of PP was associated with a reduction in diabetes risk in the MET (by 18%, $p=0.02$) and ILS (by 26%, $p=0.011$) groups but not in those in the PLA group (12%, $p=0.07$). The significant association remained only in the MET group in the model after further adjustment for changes in HDL, TG, and WC.

DISCUSSION

We found that the baseline presence of MetS, using either the revised NCEP/ATP III or IDF definitions (66-69% of the population) was associated with an increased risk of diabetes by 70-100% in DPP participants with IGT across age, sex, race, and intervention groups. Among cardio-metabolic risk factors studied, increased WC and PP in the ILS and PLA, and elevated TG in all three groups, were each associated with a higher risk of diabetes, while a change in WC but not TG predicted diabetes development in the ILS and PLA. Previous reports have demonstrated that MetS increases diabetes risk [1-2] although none assessed diabetes using repeated glucose measures (OGTT or fasting samples) as was done here. One study of Mexican Americans and non-Hispanic whites with IGT found that MetS was associated with incident diabetes in adults with IGT [2]. Our report extends these observations to a larger, multiethnic population and explores the effect of intervention-related changes in MetS components and PP on risk of progression from IGT to diabetes.

As expected, baseline FPG was the strongest component linking MetS with incident diabetes. TG levels had additional predictive properties, as has previously been reported [16], in all intervention groups. Hypertriglyceridemia, in this setting, is thought to reflect mainly the effects of insulin resistance on adipose tissue, muscle, and liver, and is likely not directly involved in the pathophysiologic pathway to diabetes development [17], which may explain why changes in TG were less effective predictors of diabetes risk. However, after adjustment for weight and surrogates of insulin resistance and secretion, baseline TG remained a significant predictor, suggesting an association with diabetes development through other pathways.

The utility of WC as a predictor of incident diabetes has been amply demonstrated [18-20]. We found that both baseline and changes in WC were independently associated with incident diabetes in the ILS and PLA groups, suggesting that WC may be directly linked to diabetes development. Since the predictive effect of baseline WC remained significant after adjusting for glycemia, insulin resistance, and secretion measures, other pathways, such as inflammation, may also be involved [21]. By contrast, neither baseline WC, nor change in WC was associated with incident diabetes in the MET group. It is possible that metformin blunts the effect of obesity on diabetes risk, because its ameliorative effect on diabetes development occurs mainly in those in the upper tertile of WC at baseline. Nevertheless,

changes in weight associated with MET treatment contributed to its ability to reduce diabetes development [22].

TG and WC were the individual cardio-metabolic risk factors that remained associated with incident diabetes after adjustment for FPG; therefore participants with both abnormalities were especially at risk. Hypertriglyceridemic waist was shown to be a simple tool to identify participants at increased cardiometabolic risk and might better quantify visceral obesity and its health hazards than WC alone [5]. Hypertriglyceridemic waist was present in 35% of DPP participants and was a useful predictor of diabetes in the ILS and PLA but not the MET group, whether the glucose level was elevated or not. However, hypertriglyceridemic waist does not account for the deleterious effects of incremental elevations of either TG or WC above categorical cut-points; therefore its predictive utility is limited. These findings serve to emphasize the advantages of evaluating specific MetS components individually and as continuous variables rather than as categories.

Although HDL-C has been demonstrated to predict diabetes [16, 23], it was only marginally associated with incident diabetes in the PLA, while an increase in HDL-C was associated with a reduction of diabetes risk only in the MET and PLA groups in the multivariate model. The basis for the inverse association between HDL-C and diabetes development is poorly understood. Low HDL-C in insulin-resistant states is thought to be due to remodeling of HDL as a consequence of hypertriglyceridemia; and HDL-C has been shown to correlate strongly with measures of insulin resistance [21]. Why increases in HDL-C in the MET group are associated with protection against diabetes development, while those accompanying ILS are not, is also unclear. It is possible that the effects of saturated fat restriction, which tends to lower HDL-C, may have confounded the relationship between HDL-C and diabetes development in the ILS, whereas MET has been shown to increase HDL-C slightly; this may be linked to its effect on diabetes prevention.

It is somewhat surprising that baseline BP was not associated with diabetes development in DPP, as has been previously reported in a population study [24]. However, baseline PP was associated with increased risk for diabetes. This is consistent with a recent report in high-risk Japanese hypertensive patients showing that PP is an independent predictor of new-onset diabetes and suggesting that increased arterial stiffness and microvascular dysfunction are associated with the development of diabetes [4]. Microvascular dysfunction may contribute to impaired insulin-mediated changes in muscle perfusion and glucose metabolism, providing a framework to understanding the association among obesity, hypertension, and impaired insulin-mediated glucose disposal [25, 26]. Changes in PP were predictive of diabetes only in the MET group in the multivariate model. It is conceivable that the effects of lifestyle on diabetes prevention do not parallel its effects on BP and PP, while in the metformin group these effects are more closely aligned [27]. Alternatively, the changes in BP as participants progressed from IGT to diabetes may be too small to be significant [28]. Others have shown an association of PP with MetS and its components, particularly in non-diabetic individuals [29] but more research would be needed to better understand these associations in the context of patients at high-risk for diabetes and CVD.

In conclusion, the DPP confirmed that the presence of MetS at baseline is associated with an increased risk of worsening to diabetes in participants with IGT, most of whom were also overweight or obese. After adjustment for fasting glucose levels at baseline, an increased diabetes risk is associated with elevated WC, PP, and TG. Our study evaluated baseline and follow-up measurement of these cardio-metabolic risk factors. Previous studies relied solely on baseline MetS data to assess diabetes risk while we were able to assess the impact that changes in MetS components resulting from DPP interventions had on the incidence of diabetes. Favorable lifestyle-associated changes in waist and HDL-C risk factors are

associated with diabetes risk reduction, whereas in those treated with MET, changes in PP are predictive of diabetes. Regardless of the various diagnostic criteria for the MetS and the concerns about its clinical value [30], our findings underscore the value of identifying cardio-metabolic abnormalities among individuals with high risk for diabetes as well as targeting them for lifestyle and other interventions. Recent data analysis suggest that both lifestyle and pharmacological interventions can reverse MetS, but the evidence is limited on whether these benefits are sustained and translate into long-term prevention of CVD and diabetes [31].

Acknowledgments

The investigators gratefully acknowledge the commitment and dedication of the participants of the DPP. The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) of the National Institutes of Health provided funding to the clinical centers and the Coordinating Center for the design and conduct of the study; and collection, management, analysis, and interpretation of the data (U01 DK048489). This work was also supported in part by the Intramural Research Program of the NIDDK and the University of Miami CTSA/1R18AE000049-01/VA-GRECC. The General Clinical Research Center Program, National Center for Research Resources, and the Department of Veterans Affairs supported data collection at many of the clinical centers. The Southwestern American Indian Centers were supported directly by the NIDDK and the Indian Health Service. The General Clinical Research Center Program, National Center for Research Resources supported data collection at many of the clinical centers. Funding for data collection and participant support was also provided by the Office of Research on Minority Health, the National Institute of Child Health and Human Development, the National Institute on Aging, the Centers for Disease Control and Prevention, the Office of Research on Women's Health, and the American Diabetes Association. Bristol-Myers Squibb and Parke-Davis provided medication. LifeScan Inc., Health O Meter, Hoechst Marion Roussel, Inc., Merck-Medco Managed Care, Inc., Merck and Co., Nike Sports Marketing, Slim Fast Foods Co., and Quaker Oats Co. donated materials, equipment, or medicines for concomitant conditions. McKesson BioServices Corp., Matthews Media Group, Inc., and the Henry M. Jackson Foundation provided support services under subcontract with the Coordinating Center. The opinions expressed are those of the investigators and do not necessarily reflect the views of the Indian Health Service or other funding agencies. A complete list of Centers, investigators, and staff can be found in the Appendix 1.

APPENDIX

Pennington Biomedical Research Center (Baton Rouge, LA)

George A. Bray, MD*

Iris W. Culbert, BSN, RN, CCRC**

Catherine M. Champagne, PhD, RD

Barbara Eberhardt, RD, LDN

Frank Greenway, MD

Fonda G. Guillory, LPN

April A. Herbert, RD

Michael L. Jeffirs, LPN

Betty M. Kennedy, MPA

Jennifer C. Lovejoy, PhD

Laura H. Morris, BS

Lee E. Melancon, BA, BS

Donna Ryan, MD

Deborah A. Sanford, LPN

Kenneth G. Smith, BS, MT

Lisa L. Smith, BS

Julia A. St.Amant, RTR

Richard T. Tulley, PhD

Paula C. Vicknair, MS, RD

Donald Williamson, PhD

Jeffery J. Zachwieja, PhD

University of Chicago(Chicago, IL)

Kenneth S. Polonsky, MD*

Janet Tobian, MD, PhD*

David Ehrmann, MD*

Margaret J. Matulik, RN, BSN**

Bart Clark, MD

Kirsten Czech, MS

Catherine DeSandre, BA

Ruthanne Hilbrich, RD

Wylie McNabb, EdD

Ann R. Semenske, MS, RD

Jefferson Medical College(Philadelphia, PA)

Jose F. Caro, MD*

Pamela G. Watson, RN, ScD*

Barry J. Goldstein, MD, PhD*

Kellie A. Smith, RN, MSN**

Jewel Mendoza, RN, BSN**

Renee Liberoni, MPH

Constance Pepe, MS, RD

John Spandorfer, MD

University of Miami(Miami, FL)

Richard P. Donahue, PhD*

Ronald B. Goldberg, MD*

Ronald Prineas, MD, PhD*

Patricia Rowe, MPA**

Jeanette Calles, MSED

Paul Casanova-Romero, MD

Sumaya Castillo-Florez, MD, MPH

Hermes J. Florez, MD, PhD

Anna Giannella, RD, MS

Lascelles Kirby, MS

Carmen Larreal

Valerie McLymont, RN

Jadell Mendez

Juliet Ojito, RN

Arlette Perry, PhD

Patrice Saab, PhD

The University of Texas Health Science Center(San Antonio, TX)

Steven M. Haffner, MD, MPH*

Maria G. Montez, RN, MSHP, CDE**

Carlos Lorenzo, MD, PhD

ArleneMartinez, RN, BSN, CDE

University of Colorado(Denver, CO)

Richard F. Hamman, MD, DrPH*

Patricia V. Nash, MS**

Lisa Testaverde, MS**

Denise R. Anderson, RN, BSN

Larry B. Ballonoff, MD

Alexis Bouffard, MA,

B. Ned Calonge, MD, MPH

Lynne Delve

Martha Farago, RN

James O. Hill, PhD

Shelley R. Hoyer, BS

Bonnie T. Jortberg, MS, RD, CDE

Dione Lenz, RN, BSN

Marsha Miller, MS, RD

David W. Price, MD

Judith G. Regensteiner, PhD

Helen Seagle, MS, RD

Carissa M. Smith, BS

Sheila C. Steinke, MS

Brent VanDorsten, PhD

Joslin Diabetes Center(Boston, MA)

Edward S. Horton, MD*

Kathleen E. Lawton, RN**

Ronald A. Arky, MD

Marybeth Bryant

Jacqueline P. Burke, BSN

Enrique Caballero, MD

Karen M. Callaphan, BA

Om P. Ganda, MD

Therese Franklin

Sharon D. Jackson, MS, RD, CDE

Alan M. Jacobsen, MD

Lyn M. Kula, RD

Margaret Kocal, RN, CDE

Maureen A. Malloy, BS

Maryanne Nicosia, MS, RD

Cathryn F. Oldmixon, RN

Jocelyn Pan, BS, MPH

Marizel Quitingon

Stacy Rubtchinsky, BS

Ellen W. Seely, MD

Dana Schweizer, BSN

Donald Simonson, MD

Fannie Smith, MD

Caren G. Solomon, MD, MPH

James Warram, MD

VA Puget Sound Health Care System and University of Washington(Seattle, WA)

Steven E. Kahn, MB, ChB*

Brenda K. Montgomery, RN, BSN,

CDE**

Wilfred Fujimoto, MD

Robert H. Knopp, MD

Edward W. Lipkin, MD

Michelle Marr, BA

Dace Trence, MD

University of Tennessee(Memphis, TN)

Abbas E. Kitabchi, PhD, MD, FACP*

Mary E. Murphy, RN, MS, CDE,

MBA**

William B. Applegate, MD, MPH

Michael Bryer-Ash, MD

Sandra L. Frieson, RN

Raed Imseis, MD

Helen Lambeth, RN, BSN

Lynne C. Lichtermann, RN, BSN

HoomanOktaei, MD

Lily M.K. Rutledge, RN, BSN

Amy R. Sherman, RD, LD

Clara M. Smith, RD, MHP, LDN

Judith E. Soberman, MD

Beverly Williams-Cleaves, MD

Northwestern University's Feinberg School of Medicine(Chicago, IL)

Boyd E. Metzger, MD*

Mariana K. Johnson, MS, RN**

Catherine Behrends

Michelle Cook, MS

Marian Fitzgibbon, PhD

Mimi M. Giles, MS, RD

Deloris Heard, MA

Cheryl K.H. Johnson, MS, RN

Diane Larsen, BS

Anne Lowe, BS

Megan Lyman, BS

David McPherson, MD

Mark E. Molitch, MD

Thomas Pitts, MD

Renee Reinhart, RN, MS

Susan Roston, RN, RD

Pamela A. Schinleber, RN, MS

Massachusetts General Hospital(Boston, MA)

David M. Nathan, MD*

Charles McKittrick, BSN**

Heather Turgeon, BSN**

Kathy Abbott

Ellen Anderson, MS, RD

Laurie Bissett, MS, RD

Enrico Cagliero, MD

Linda Delahanty, MS, RD

Valerie Goldman, MS, RD

Alexandra Poulos

University of California-San Diego(San Diego, CA)

Jerrold M. Olefsky, MD*

Mary Lou Carrion-Petersen, RN, BSN**

Elizabeth Barrett-Connor, MD

Steven V. Edelman, MD

Robert R. Henry, MD

Javiva Horne, RD

Simona SzerdiJanesch, BA

Diana Leos, RN, BSN

Sundar Mudaliar, MD

William Polonsky, PhD

Jean Smith, RN

Karen Vejvoda, RN, BSN, CDE, CCRC

St. Luke's-Roosevelt Hospital(New York, NY)

F. Xavier Pi-Sunyer, MD*

Jane E. Lee, MS**

David B. Allison, PhD

Nancy J. Aronoff, MS, RD

Jill P. Crandall, MD

Sandra T. Foo, MD

Carmen Pal, MD

Kathy Parkes, RN

Mary Beth Pena, RN

Ellen S. Rooney, BA

Gretchen E.H. Van Wye, MA

Kristine A. Viscovich, ANP

Indiana University(Indianapolis, IN)

David G. Marrero, PhD*

Melvin J. Prince, MD*

Susie M. Kelly, RN, CDE**

Yolanda F. Dotson, BS

Edwin S. Fineberg, MD

John C. Guare, PhD

Angela M. Hadden

James M. Ignaut, MA

Marcia L. Jackson

Marion S. Kirkman, MD

Kieren J. Mather, MD

Beverly D. Porter, MSN

Paris J. Roach, MD

Nancy D. Rowland, BS, MS

Madelyn L. Wheeler, RD

Medstar Research Institute(Washington, DC)

Robert E. Ratner, MD*

Gretchen Youssef, RD, CDE**

Sue Shapiro, RN, BSN, CCRC**

Catherine Bavido-Arrage, MS, RD, LD

Geraldine Boggs, MSN, RN

Marjorie Bronsord, MS, RD, CDE

Ernestine Brown

Wayman W. Cheatham, MD

Susan Cola
Cindy Evans
Peggy Gibbs
Tracy Kellum, MS, RD, CDE
Claresalevatan, MD
Asha K. Nair, BS
MaureenPassaro, MD
Gabriel Uwaifo, MD
University of Southern California/UCLA Research Center(Alhambra, CA)
Mohammed F. Saad, MD*
Maria Budget**
SujataJinagouda, MD**
KhanAkbar, MD
Claudia Conzues
PerpetuaMagpuri
Kathy Ngo
AmerRassam, MD
Debra Waters
Kathy Xaphthalamous
Washington University(St. Louis, MO)
Julio V. Santiago, MD* (deceased)
Samuel Dagogo-Jack, MD, MSc, FRCP, FACP*
Neil H. White, MD, CDE*
Samia Das, MS, MBA, RD, LD**
Ana Santiago, RD**
Angela Brown, MD
Edwin Fisher, PhD
Emma Hurt, RN
Tracy Jones, RN

Michelle Kerr, RD

Lucy Ryder, RN

Cormarie Wernimont, MS, RD

Johns Hopkins School of Medicine (Baltimore, MD)

Christopher D. Saudek, MD*

Vanessa Bradley, BA**

Emily Sullivan, MEd, RN**

Tracy Whittington, BS**

Caroline Abbas

Frederick L. Brancati, MD, MHS

Jeanne M. Clark, MD

Jeanne B. Charleston, RN, MSN

Janice Freel

Katherine Horak, RD

Dawn Jiggetts

Deloris Johnson

Hope Joseph

Kimberly Loman

Henry Mosley

Richard R. Rubin, PhD

Alafia Samuels, MD

Kerry J. Stewart, EdD

Paula Williamson

University of New Mexico (Albuquerque, NM)

David S. Schade, MD*

Karwyn S. Adams, RN, MSN**

Carolyn Johannes, RN, CDE**

Leslie F. Adler, PhD

Patrick J. Boyle, MD

Mark R. Burge, MD

Janene L. Canady, RN, CDE

Lisa Chai, RN

Ysela Gonzales, RN, MSN

Doris A. Hernandez-McGinnis

Patricia Katz, LPN

Carolyn King

AmerRassam, MD

SofyaRubinchik, MD

WilletteSenter, RD

Debra Waters, PhD

Albert Einstein College of Medicine(Bronx, NY)

Harry Shamoon, MD*

Janet O. Brown, RN, MPH, MSN**

Elsie Adorno, BS

Liane Cox, MS, RD

Jill Crandall, MD

Helena Duffy, MS, C-ANP

Samuel Engel, MD

Allison Friedler, BS

Crystal J. Howard-Century, MA

Stacey Kloiber, RN

NadegeLongchamp, LPN

Helen Martinez, RN, MSN, FNP-C

Dorothy Pompei, BA

Jonathan Scheindlin, MD

ElissaViolino, RD, MS

Elizabeth Walker, RN, DNSc, CDE

Judith Wylie-Rosett, EdD, RD

Elise Zimmerman, RD, MS

Joel Zonszein, MD

University of Pittsburgh(Pittsburgh, PA)

Trevor Orchard, MD*

Rena R. Wing, PhD*

Gaye Koenning, MS, RD**

M. Kaye Kramer, BSN, MPH**

Susan Barr, BS

Miriam Boraz

Lisa Clifford, BS

Rebecca Culyba, BS

Marlene Frazier

Ryan Gilligan, BS

Susan Harrier, MLT

Louann Harris, RN

Susan Jeffries, RN, MSN

Andrea Kriska, PhD

QurashiaManjoo, MD

Monica Mullen, MHP, RD

Alicia Noel, BS

Amy Otto, PhD

Linda Semler, MS, RD

Cheryl F. Smith, PhD

Marie Smith, RN, BSN

Elizabeth Venditti, PhD

Valarie Weinzierl, BS

Katherine V. Williams, MD, MPH

Tara Wilson, BA

University of Hawaii(Honolulu, HI)

Richard F. Arakaki, MD*

Renee W. Latimer, BSN, MPH**

Narleen K. Baker-Ladao, BS

Ralph Beddow, MD

LornaDias, AA

JillianInouye, RN, PhD

Marjorie K. Mau, MD

Kathy Mikami, BS, RD

PharisMohideen, MD

Sharon K. Odom, RD, MPH

Raynette U. Perry, AA

Southwest American Indian Centers(Phoenix, AZ; Shiprock, NM; Zuni, NM)

William C. Knowler, MD, DrPH*+

Norman Coeeyate**

Mary A. Hoskin, RD, MS**

Carol A. Percy, RN, MS**

Kelly J. Acton, MD, MPH

Vickie L. Andre, RN, FNP

Rosalyn Barber

ShandiinBegay, MPH

Peter H. Bennett, MB, FRCP

Mary Beth Benson, RN, BSN

Evelyn C. Bird, RD, MPH

Brenda A. Broussard, RD, MPH, MBA, CDE

MarcellaChavez, RN, AS

Tara Dacawyma

Matthew S. Doughty, MD

Roberta Duncan, RD

Cyndy Edgerton, RD

Jacqueline M. Ghahate
Justin Glass, MD
Martia Glass, MD
Dorothy Gohdes, MD
Wendy Grant, MD
Robert L. Hanson, MD, MPH
Ellie Horse
Louise E. Ingraham, MS, RD, LN
Merry Jackson
Priscilla Jay
Roylen S. Kaskalla
David Kessler, MD
Kathleen M. Kobus, RNC-ANP
Jonathan Krakoff, MD
Catherine Manus, LPN
Sara Michaels, MD
Tina Morgan
Yolanda Nashboo (deceased)
Julie A. Nelson, RD
Steven Poirier, MD
Evette Polczynski, MD
Mike Reidy, MD
Jeanine Roumain, MD, MPH
Debra Rowse, MD
Sandra Sangster
Janet Sewenemewa
Darryl Tonemah, PhD
Charlton Wilson, MD
Michelle Yazzie

George Washington University Biostatistics Center (DPP Coordinating CenterRockville, MD)

Raymond Bain, PhD*

Sarah Fowler, PhD*

Tina Brenneman**

Solome Abebe

Julie Bamdad, MS

Jackie Callaghan

Sharon L. Edelstein, ScM

Yuping Gao

Kristina L. Grimes

Nisha Grover

LoriHaffner, MS

Steve Jones

Tara L. Jones

Richard Katz, MD

John M. Lachin, ScD

Pamela Mucik

Robert Orlosky

James Rochon, PhD

Alla Sapozhnikova

Hanna Sherif, MS

Charlotte Stimpson

Marinella Temporsa, MS

Fredricka Walker-Murray

Central Biochemistry Laboratory(Seattle, WA)

Santica Marcovina, PhD, ScD*

Greg Strlewicz, PhD**

F. Alan Aldrich

Epidemiological Cardiology Research Center-Epicare(Winston-Salem, NC)

PenttiRautaharju, MD, PhD*

Ronald J. Prineas, MD, PhD*/*

Teresa Alexander

Charles Campbell, MS

Sharon Hall

Yabing Li, MD

Margaret Mills

Nancy Pemberton, MS

Farida Rautaharju, PhD

Zhuming Zhang, MD

NIH/NIDDK(Bethesda, MD)

R. Eastman, MD

Judith Fradkin, MD

Sanford Garfield, PhD

Nutrition Coding Center(Columbia, SC)

Elizabeth Mayer-Davis, PhD*

Robert R. Moran, PhD**

Quality of Well-Being Center(La Jolla, CA)

Ted Ganiats, MD*

Kristin David, MHP*

Andrew J. Sarkin, PhD*

Centers for Disease Control & Prevention(Atlanta, GA)

Edward Gregg, PhD

Ping Zhang, PhD

University of Michigan(Ann Arbor, MI)

William H. Herman, MD, MPH

Miami VAHS GRECC (Miami, FL)

Hermes Florez, MD, PhD

Neurocognitive Assessment Group

Jose A. Luchsinger, MD, MPH

+Genetics Working Group

Jose C. Florez, MD, PhD^{1, 2}

David Altshuler, MD, PhD^{1, 2}

Paul I.W. de Bakker, PhD²

Paul Franks, PhD, Mphil, MS^{3, 6}

Robert L. Hanson, MD, MPH³

Kathleen Jablonski, PhD⁵

William C. Knowler, MD, DrPH³

Jarred McAteer, AB^{1, 2}

Toni I. Pollin, PhD⁴

Alan R. Shuldiner, MD⁴

1=Massachusetts General Hospital

2=Broad Institute

3=NIDDK

4=University of Maryland

5=Coordinating Center

6=Umeå University, Sweden

* denotes Principal Investigator

** denotes Program Coordinator

+ denotes Genetics Group members

Abbreviations and Acronyms

DPP	Diabetes Prevention Program
MetS	metabolic syndrome
PP	Pulse pressure
SBP	systolic blood pressure
DBP	diastolic blood pressure
HDL	high-density lipoprotein
TG	triglycerides

WC	waist circumference
CVD	cardiovascular disease
IGT	impaired glucose tolerance

REFERENCES

1. Lorenzo C, Okoloise M, Williams K, et al. San Antonio Heart Study. The metabolic syndrome as predictor of type 2 diabetes: the San Antonio heart study. *Diabetes Care*. 2003; 26:3153–9. [PubMed: 14578254]
2. Wilson PW, D'Agostino RB, Parise H, et al. Metabolic syndrome as a precursor of cardiovascular disease and type 2 diabetes mellitus. *Circulation*. 2005; 112:3066–72. [PubMed: 16275870]
3. Henry RM, Kostense PJ, Spijkerman AM, et al. Arterial stiffness increases with deteriorating glucose tolerance status: the Hoorn Study. *Circulation*. 2003; 107:2089–95. [PubMed: 12695300]
4. Yasuno S, Ueshima K, Oba K, et al. Is pulse pressure a predictor of new-onset diabetes in high-risk hypertensive patients? A subanalysis of the Candesartan Antihypertensive Survival Evaluation in Japan (CASE-J) trial. *Diabetes Care*. 2010; 33:1122–7. [PubMed: 20185746]
5. Després JP, Lemieux I, Bergeron J, Pibarot P, Mathieu P, Larose E, Rodés-Cabau J, Bertrand OF, Poirier P. Abdominal obesity and the metabolic syndrome: contribution to global cardiometabolic risk. *Arterioscler Thromb Vasc Biol*. 2008; 28:1039–49. [PubMed: 18356555]
6. Diabetes Prevention Program Research Group. Knowler WC, Barrett-Connor E, Fowler SE, et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med*. 2002; 346:393–403. [PubMed: 11832527]
7. Diabetes Prevention Program Research Group. The Diabetes Prevention Program: design and methods for a clinical trial in the prevention of type 2 diabetes. *Diabetes Care*. 1999; 22:623–34. [PubMed: 10189543]
8. Phillips DI, Clark PM, Hales CN, Osmond C. Understanding oral glucose tolerance: comparison of glucose or insulin measurements during the oral glucose tolerance test with specific measurements of insulin resistance and insulin secretion. *Diabet Med*. 1994; 11:286–292. [PubMed: 8033528]
9. The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Report on the Expert Committee on Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care*. 1997; 20:1183–1197. [PubMed: 9203460]
10. World Health Organization. Diabetes Mellitus: report of a WHO study group. World Health Organization; Geneva, Switzerland: 1985. Technical Report Series No. 727
11. Grundy SM, Brewer HB Jr, Cleeman JI, et al. American Heart Association; National Heart, Lung, and Blood Institute. Definition of metabolic syndrome: Report of the National Heart, Lung, and Blood Institute/American Heart Association conference on scientific issues related to definition. *Circulation*. 2004; 109:433–8. [PubMed: 14744958]
12. Alberti KG, Zimmet P, Shaw J. The metabolic syndrome: a new worldwide definition. *Lancet*. 2005; 366:1059–1062. [PubMed: 16182882]
13. Cox DR. Regression models and life-tables. *JRSS (B)*. 1972; 34:187–220.
14. Lachin, JM. Biostatistical Methods: The Assessment of Relative Risks. John Wiley and Sons; New York: 2000.
15. Orchard TJ, Temprosa M, Goldberg R, et al. Diabetes Prevention Program Research Group. The effect of metformin and intensive lifestyle intervention on the metabolic syndrome: the Diabetes Prevention Program randomized trial. *Ann Intern Med*. 2005; 142:611–9. [PubMed: 15838067]
16. Wilson PW, Meigs JB, Sullivan L, et al. Prediction of incident diabetes mellitus in middle-aged adults: the Framingham Offspring Study. *Arch Intern Med*. 2007; 167:1068–74. [PubMed: 17533210]
17. Kelley DE, Goodpaster BH, Storlien L. Muscle triglyceride and insulin resistance. *Annu Rev Nut*. 2002; 22:325–46.

18. Janiszewski PM, Janssen I, Ross R. Does waist circumference predict diabetes and cardiovascular disease beyond commonly evaluated cardio-metabolic risk factors? *Diabetes Care*. 2007; 30:3105–9. [PubMed: 17712026]
19. Freemantle N, Holmes J, Hockey A, Kumar S. How strong is the association between abdominal obesity and the incidence of type 2 diabetes? *Int J Clin Pract*. 2008; 62:1391–6.
20. The Diabetes Prevention Program Research Group. Relationship of body size and shape to the development of diabetes in the Diabetes Prevention Program. *Obesity*. 2006; 14:2107–17. [PubMed: 17135629]
21. The Diabetes Prevention Program Research Group. Lipid, lipoproteins, C-reactive protein, and hemostatic factors at baseline in the diabetes prevention program. *Diabetes Care*. 2005; 28:2472–9. [PubMed: 16186282]
22. Lachin JM, Christophi CA, Edelstein SL, et al. for the Diabetes Prevention Program Research Group. Factors associated with diabetes onset during metformin versus placebo therapy in the Diabetes Prevention Program. *Diabetes*. 2007; 56:1153–59. [PubMed: 17395752]
23. Fagot-Campagna A, Knowler WC, et al. HDL cholesterol subfractions and risk of developing type 2 diabetes among Pima Indians. *Diabetes Care*. 1999; 22:271–4. [PubMed: 10333944]
24. Gress TW, Nieto FJ, Shahar E, et al. Hypertension and antihypertensive therapy as risk factors for type 2 diabetes mellitus. Atherosclerosis Risk in Communities Study. *N Engl J Med*. 2000; 342:905–12. [PubMed: 10738048]
25. Serné EH, de Jongh RT, Eringa EC, et al. Microvascular dysfunction: a potential pathophysiological role in the metabolic syndrome. *Hypertension*. 2007; 50:204–211. [PubMed: 17470716]
26. Levy BI, Schiffrin EL, Mourad JJ, et al. Impaired tissue perfusion: a pathology common to hypertension, obesity, and diabetes mellitus. *Circulation*. 2008; 118:968–976. [PubMed: 18725503]
27. Fontbonne A, Diouf I, Baccara-Dinet M, et al. Effects of 1-year treatment with metformin on metabolic and cardiovascular risk factors in non-diabetic upper-body obese participants with mild glucose anomalies: A post-hoc analysis of the BIGPRO1 trial. *Diabetes Metab*. 2009; 35:385–91. [PubMed: 19665415]
28. Goldberg RB, Temprosa M, Haffner S, et al. Effect of progression from impaired glucose tolerance to diabetes on cardiovascular risk factors and its amelioration by lifestyle and metformin intervention: the Diabetes Prevention Program randomized trial by the Diabetes Prevention Program Research Group. *Diabetes Care*. 2009; 32:726–732. [PubMed: 19171717]
29. Mannucci E, Monami M, Bardini G, Sposato I, Ungar A, Pepe G, Masotti G, Marchionni N, Rotella CM. Metabolic syndrome and pulse pressure. *Diabetes Obes Metab*. 2007; 9:600–2. [PubMed: 17587404]
30. Alberti KG, Eckel RH, Grundy SM, et al. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. *Circulation*. 2009; 120:1640–5. [PubMed: 19805654]
31. Dunkley AJ, Charles K, Gray LJ, et al. Effectiveness of interventions for reducing diabetes and cardiovascular disease risk in people with metabolic syndrome: systematic review and mixed treatment comparison meta-analysis. *Diabetes Obes Metab*. 2012; 14:616–25. [PubMed: 22284386]

A. Model adjusted for demographic factors

B. Multivariate model

Figure 1. Demographically adjusted hazard ratio (95%CI) for developing diabetes associated with baseline metabolic syndrome and components

All hazard ratios are adjusted for age randomized, sex, and race/ethnicity. Components with an asterisk (*) denote significant heterogeneity among the treatment groups. Metabolic syndrome components are defined as: **High FPG**, fasting plasma glucose ≥ 100 mg/dl; **abdominal obesity**, waist ≥ 102 cm in men and ≥ 88 cm in women; **High TG**, triglycerides ≥ 150 mg/dl or use of TG lowering medications; **High BP**, systolic/diastolic blood pressure $\geq 130/85$ mmHg or use of antihypertensive medications; **Low HDL-c**, high density lipoprotein cholesterol <40 mg/dl in men and <50 in women or use of lipid lowering

medications. High TG and abdominal obesity is defined as TG ≥ 150 mg/dl and waist ≥ 102 cm in men (waist ≥ 88 cm in women).

A. Baseline components adjusted for demographic factors **B. Multivariate analysis of baseline components** **C. Changes in components adjusted for demographic factors** **D. Multivariate analysis of changes in components**

Figure 2. Hazard ratio (95% CI) for developing diabetes associated with cardio-metabolic risk factors as continuous variables

All hazard ratios are adjusted for age randomized, sex, and race/ethnicity and computed in increments to approximate 1 SD of the baseline component and of the changes from baseline. Components with an asterisk (*) denote significant heterogeneity among the treatment groups. Changes in components are computed as the average change from baseline up to, but not including, each visit when diabetes was diagnosed. To facilitate comparison across variables, hazard ratios

Table 1

Baseline characteristics by metabolic syndrome status*

	Overall (n=3234)	Without MetS (n=1006)	With MetS (n=2228)	p-value
Age (years)	50.6 ± 10.7	50.9 ± 11.2	50.5 ± 10.4	0.360
Female	2191 (67.7%)	669 (66.5%)	1522 (68.3%)	0.308
Race				0.001
Caucasian (n [%])	1768 (54.7%)	498 (49.5%)	1270 (57.0%)	
African American (n [%])	645 (19.9%)	228 (22.7%)	417 (18.7%)	
Hispanic (n [%])	508 (15.7%)	165 (16.4%)	343 (15.4%)	
American Indian (n [%])	171 (5.3%)	65 (6.5%)	106 (4.8%)	
Asian (n [%])	142 (4.4%)	50 (5.0%)	92 (4.1%)	
Weight (kg)	94.2 ± 20.3	86.2 ± 18.2	97.8 ± 20.1	<0.001
Waist circumference (cm)	105.1 ± 14.5	98.2 ± 13.5	108.2 ± 13.9	<0.001
Systolic BP (mm Hg)	123.7 ± 14.7	118.1 ± 12.7	126.3 ± 14.8	<0.001
Diastolic BP (mm Hg)	78.3 ± 9.3	75.0 ± 7.9	79.8 ± 9.5	<0.001
Pulse pressure (mm Hg)	45.4 ± 11.8	43.1 ± 10.3	46.5 ± 12.2	<0.001
Triglyceride (mmol/l)	1.6 (1.1, 2.3)	1.2 (0.9,1.5)	1.9 (1.3, 2.5)	<0.001
HDL-C (mmol/l)	1.18 ± 0.31	1.38 ± 0.31	1.09 ± 0.26	<0.001
Fasting glucose (mmol/l)	5.9 ± 0.5	5.8 ± 0.5	6.0 ± 0.4	<0.001
1/fasting insulin	0.04 (0.03, 0.06)	0.05 (0.04, 0.08)	0.04 (0.03,0.06)	<0.001
CIR	0.54 (0.35, 0.80)	0.50 (0.31, 0.74)	0.56 (0.37, 0.82)	<0.001

Data are expressed as n (%), mean ± SD, percentage, or median (IQR), as appropriate; MetS, metabolic syndrome; BP, blood pressure; HDL-C, high density lipoprotein cholesterol; CIR, corrected insulin response

* Metabolic syndrome status is defined using the revised NCEP/ATP III definition.

Table 2

Mean changes (95% CI) in cardio-metabolic risk factors over 3.2 years of follow-up by treatment group

MetS Component	Placebo	Metformin	Intensive Lifestyle
Fasting glucose (mmol/l)	0.21 (0.17, 0.24)	−0.03 (−0.06, 0.0005)*	−0.053 (−0.089, −0.017)*
Waist circumference (cm)	−0.22 (−0.53, 0.094)	−1.69 (−2.06, −1.32)*	−5.18 (−5.59, −4.77)*†
Systolic BP (mmHg)	−0.68 (−1.21, −0.15)	−0.84 (−1.39, −0.29)	−3.37 (−3.94, −2.80)*†
Diastolic BP (mmHg)	−1.04 (−1.39, −0.69)	−1.21 (−1.56, −0.86)	−3.40 (−3.77, −3.03)*†
Pulse pressure (mmHg)	0.41 (−0.03, 0.84)	0.44 (−0.01, 0.90)	0.14 (−0.30, 0.58)
HDL-c (mmol/l)	−0.01 (−0.02, 0)	0.01 (0.003, 0.02)*	0.03 (0.02, 0.04)*†
Triglyceride (mmol/l)	−0.01 (−0.19, 0.18)	−0.004 (−0.19, 0.18)	−0.18 (−0.37, 0.01)*†

* P < 0.05 compared to placebo

† P < 0.05 compared to Metformin; all means are adjusted for the baseline value. BP, blood pressure; HDL-c, high density lipoprotein cholesterol