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Author Manuscript

*Diabetes Obes Metab.* Author manuscript; available in PMC 2015 April 01.

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

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### 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

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Trial registration: DPP is registered in [www.clinicaltrials.gov](http://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  $\geq$  25 years, BMI  $\geq$  24 kg/m<sup>2</sup> ( $\geq$  22 kg/m<sup>2</sup> 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  $\geq 40$  inches (102 cm) in men or  $\geq 35$  inches (88cm) in women; (b) triglyceride  $\geq 1.7$  mmol/L (150 mg/dl) or use of lipid lowering medications; (c) HDL-C  $<1.03$  mmol/L (40 mg/day) in men or  $<1.29$  mmol/L (50 mg/dl) in women or use of lipid lowering medications; (d) systolic BP (SBP)  $\geq 130$  mm Hg, diastolic BP (DBP)  $\geq 85$  mm Hg, or use of antihypertensive therapy; and (e) FPG  $\geq 5.6$  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  $\geq 94$  cm in men or  $\geq 80$  cm in women plus any two of the following: (a) triglycerides  $\geq 1.7$  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  $\geq 130$  mmHg or DBP  $\geq 85$  mmHg or treatment of previously diagnosed hypertension; and (d) FPG  $\geq 5.6$  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.

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**Abbreviations and Acronyms**

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

<b>WC</b>	waist circumference
<b>CVD</b>	cardiovascular disease
<b>IGT</b>	impaired glucose tolerance

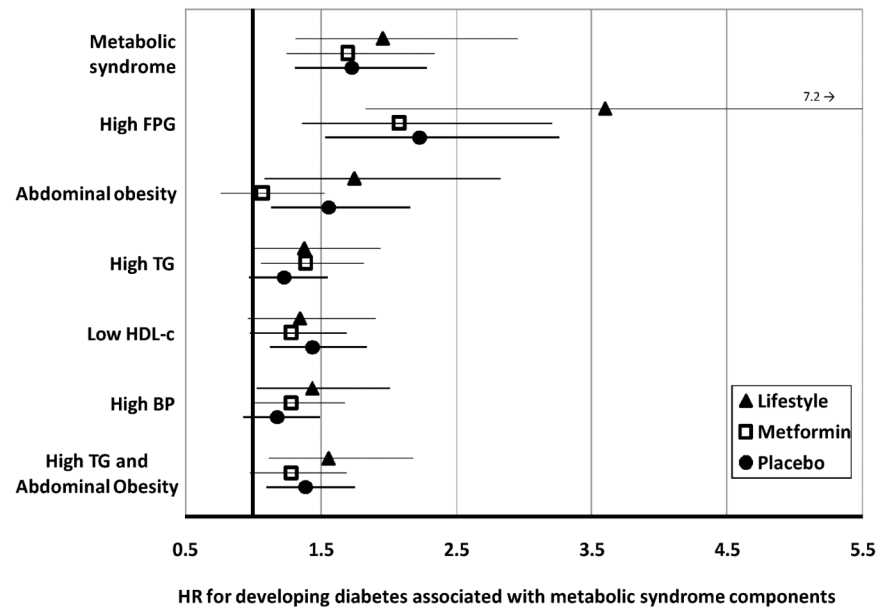
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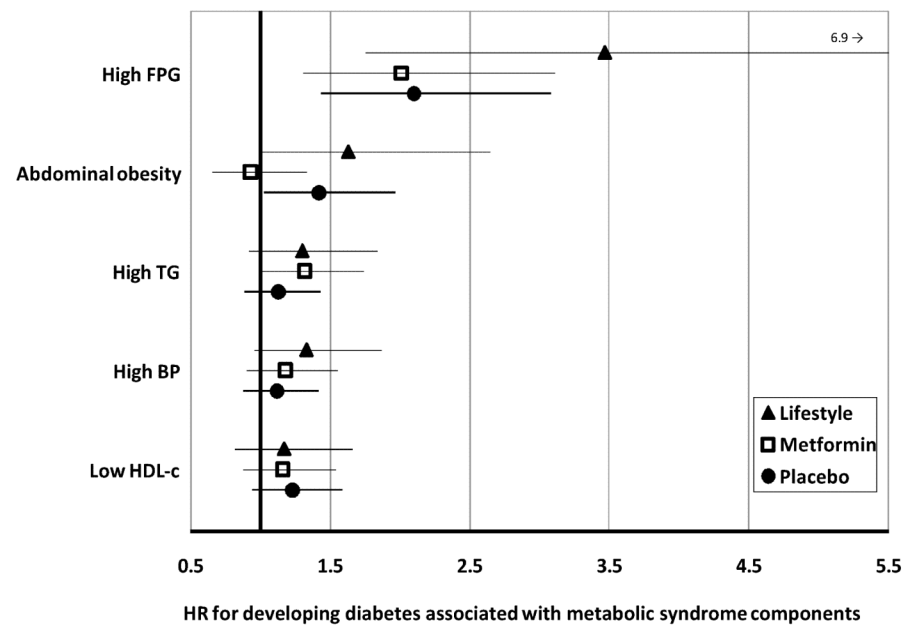


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**A. Model adjusted for demographic factors**



**B. Multivariate model**

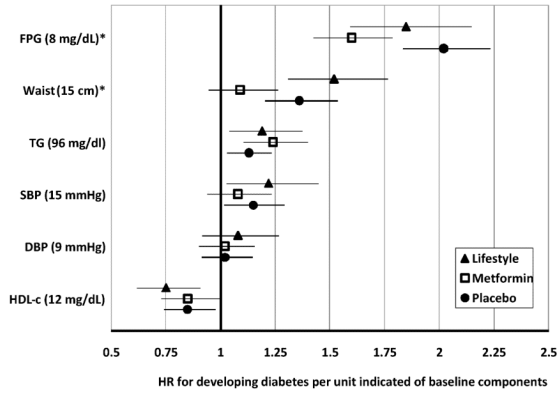


**Figure 1. Demographically adjusted hazard ratio (95%CI) for developing diabetes associated with baseline metabolic syndrome and components**

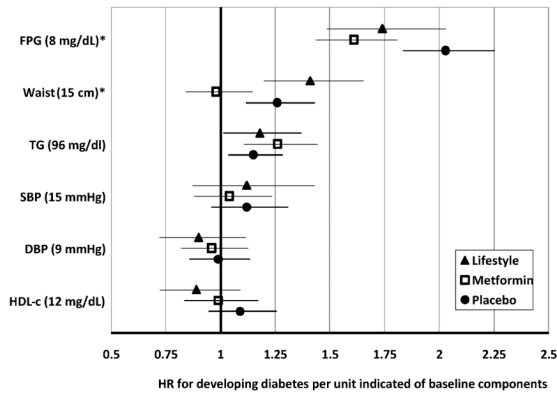
All hazard ratios are adjusted for age randomized, sex, and race/ethnicity. Components with an asterisk (\*) denote significant heterogeneity among the treatment groups. Metabolic syndrome components are defined as: **High FPG**, fasting plasma glucose  $\geq 100$  mg/dl; **abdominal obesity**, waist  $\geq 102$  cm in men and  $\geq 88$  cm in women; **High TG**, triglycerides  $\geq 150$  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  $\geq$  150 mg/dl and waist  $\geq$  102 cm in men (waist  $\geq$  88 cm in women).

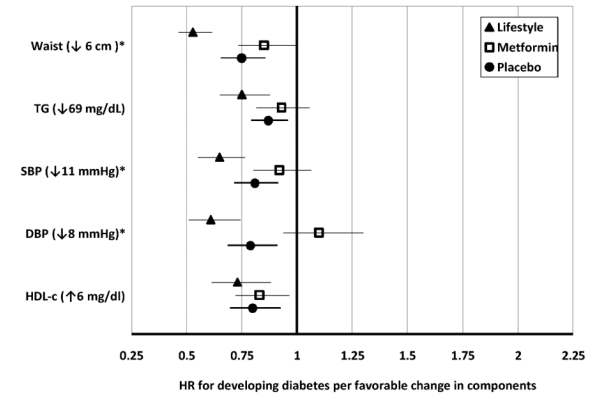
**A. Baseline components adjusted for demographic factors**



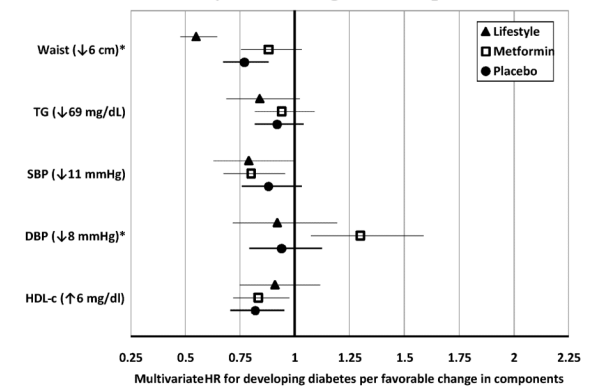
**B. Multivariate analysis of baseline components**



**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\*

	<b>Overall (n=3234)</b>	<b>Without MetS (n=1006)</b>	<b>With MetS (n=2228)</b>	<b>p-value</b>
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 &lt; 0.05 compared to placebo

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