

Is Prehypertension a Risk Factor for the Development of Type 2 Diabetes?

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OBJECTIVE— Prehypertension is associated with cardiovascular disease and insulin resistance. However, whether subjects with prehypertension have more diabetes risk is not known. We examine whether prehypertension is a risk factor for developing type 2 diabetes.

RESEARCH DESIGN AND METHODS— Incident diabetes was examined in nondiabetic normotensive participants in the San Antonio Heart Study ($n = 2,767$; aged 25–65 years; median follow-up 7.8 years).

RESULTS— Incident diabetes was 12.4% in subjects with prehypertension and 5.6% in subjects with normal blood pressure. The odds of incident diabetes were 2.21 greater for individuals with prehypertension than for those with normal blood pressure (95% CI 1.63–2.98) after adjusting for age, sex, and ethnicity. Prehypertension was not associated with incident diabetes after additional adjustment for BMI, impaired glucose tolerance, insulin resistance and secretion, and family history of diabetes (odds ratio 1.42 [95% CI 0.99–2.02]).

CONCLUSIONS— Subjects with prehypertension are at increased risk of diabetes. Much of this risk is explained by disorders related to the insulin resistance syndrome.

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Hypertension predicts future cardiovascular disease (1,2) and type 2 diabetes (3). Prehypertension (systolic blood pressure [SBP] 120–139 mmHg and/or diastolic blood pressure [DBP] 80–89 mmHg), a novel blood pressure category of “The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report” (4), is also associated with increased cardiovascular risk (5,6) and insulin resistance (7). Furthermore, results from the Framingham Heart Study indicate that cardiovascular risk may be more relevant in individuals with SBP 130–139 mmHg and/or DBP 85–89 mmHg (8). Therefore, we investigated the relationship between prehypertension and incident type 2 diabetes in the San Antonio Heart Study (SAHS).

RESEARCH DESIGN AND METHODS

The SAHS is a longitudinal epidemiological study on cardiovascular disease and type 2 diabetes in Mexican Americans and non-Hispanic whites living in San Antonio, Texas (aged 25–65 years). Details of the study design, including blood pressure measurement protocols and laboratory details, have been published previously (9,10). Subjects were seen only at the initial encounter and at follow-up.

We used JNC 7 criteria to define normal blood pressure, prehypertension, and hypertension (4). Diabetes was defined as fasting plasma glucose ≥ 126 mg/dl, 2-h plasma glucose ≥ 200 mg/dl, and/or use of glucose-lowering agents; impaired fasting glucose (IFG) as fasting glucose 100–125 mg/dl; and impaired glucose tolerance (IGT) as 2-h plasma glucose 140–

199 mg/dl (11). The homeostasis model assessment of insulin resistance (HOMA-IR) and β -cell function (HOMA- β C) were used to quantify the level of insulin resistance and secretion (12).

After excluding individuals with baseline hypertension or diabetes ($n = 1,171$) or individuals who did not present for the follow-up exam ($n = 1,220$), there were 2,767 (69.4%) subjects eligible for analysis. Median follow-up time was 7.8 years (range 6.3–10.7 years).

The relationship between baseline characteristics and prehypertension was examined using one-way ANCOVA for continuous variables and logistic regression analysis for dichotomous variables. The relation of measures of blood pressure to metabolic variables was assessed by Pearson's partial correlation coefficients. Multivariate logistic regression analysis was used to examine the risk of future diabetes associated with prehypertension.

RESULTS— The prevalence of prehypertension at baseline was 31.3%. Prehypertension was associated with male sex and Mexican-American ethnic origin as well as with higher BMI, HOMA-IR, HOMA- β C, and levels of fasting glucose, 2-h glucose, fasting insulin, and triglycerides ($P < 0.001$ for all comparisons) (supplemental Table, available in an online appendix at <http://care.diabetesjournals.org/cgi/content/full/dc09-0328/DC1>).

After adjusting for age, sex, and ethnicity, SBP was positively related to BMI ($r = 0.32$), waist circumference ($r = 0.29$), HOMA-IR ($r = 0.17$), HOMA- β C ($r = 0.11$), as well as levels of 2-h glucose ($r = 0.14$), fasting insulin ($r = 0.17$), and triglycerides ($r = 0.18$) (all correlations, $P < 0.001$).

There were 213 (7.7%) new cases of diabetes: 12.4% (10.4–14.9) in subjects with prehypertension and 5.6% (4.7–6.8) in those with normal blood pressure. After adjusting for age, sex, and ethnicity, the odds of incident diabetes were 2.21 greater for individuals with prehypertension than for individuals with normal blood pressure (95% CI 1.63–2.98). After the additional adjustment for BMI, IGT, HOMA-IR, HOMA- β C, and family history of diabetes, diabetes risk associated

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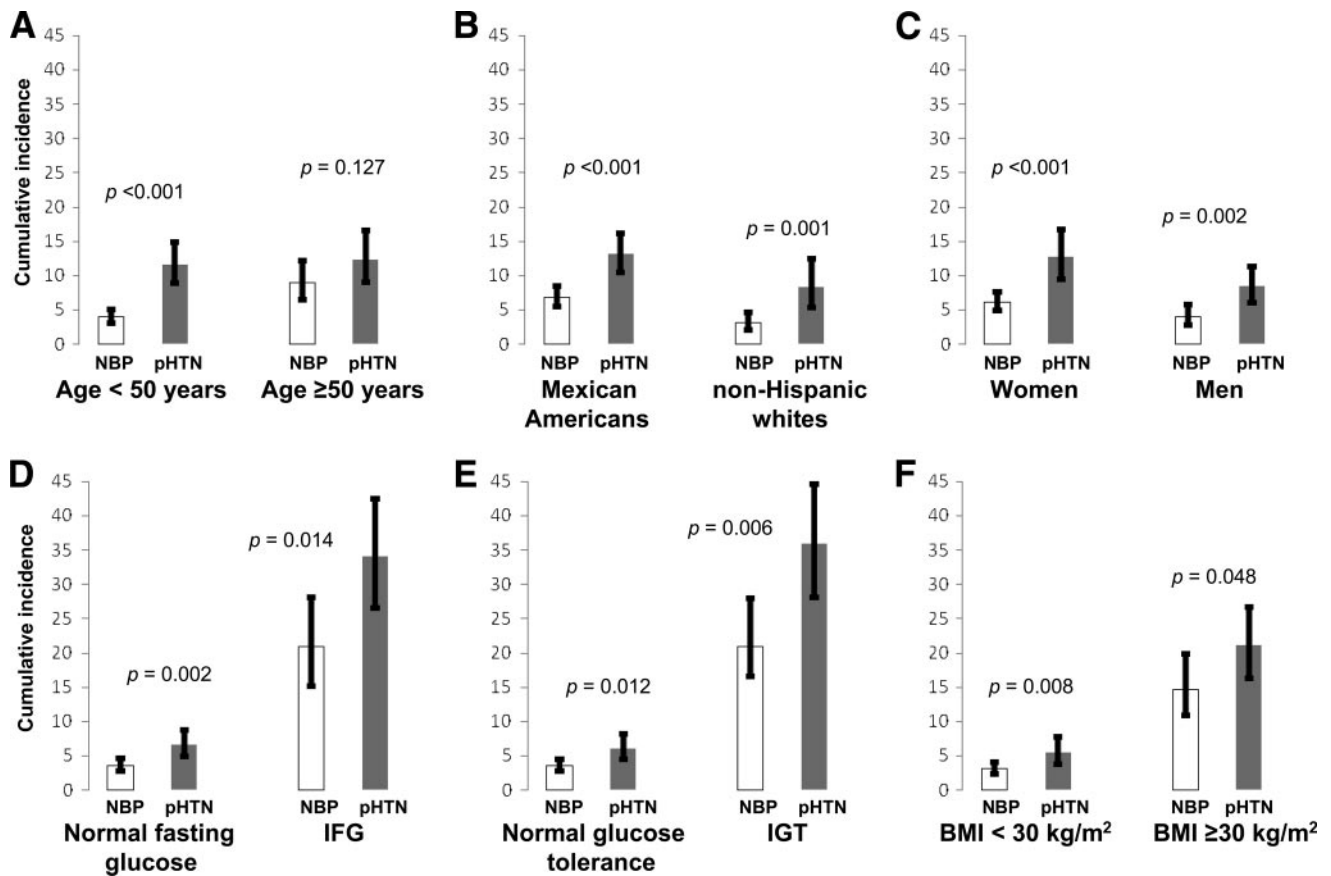


Figure 1—Shown is the 7.8-year cumulative incidence of diabetes by prehypertension status and categories of age, ethnicity, sex, fasting glucose, glucose tolerance, and BMI. A: Age, adjusted for sex and ethnicity. B: Ethnicity, adjusted for age and sex. C: Sex, adjusted for age and ethnicity. D–F: Fasting glucose (D), glucose tolerance (E), and BMI (F), adjusted for age, sex, and ethnicity. P values for test of difference in incident diabetes between subjects with prehypertension and subjects with normal blood pressure. White bars = NBP, normal blood pressure; gray bars = pHTN, prehypertension.

with prehypertension was not statistically significant (odds ratio 1.42 [95% CI 0.99–2.02]; $P = 0.052$). The risk remained significant for SBP 130–139 mmHg and/or DBP 85–89 mmHg (1.69 [1.03–2.77]) but did not remain significant for SBP 120–129 mmHg and DBP 80–84 mmHg (1.31 [0.88–1.94]).

Subjects with prehypertension had more diabetes risk than those with normal blood pressure regardless of sex, ethnic origin, and categories of obesity and glucose tolerance (Fig. 1). Prehypertension was also associated with increased diabetes risk in individuals aged 25–49 years but not in those aged 50–65 years ($n = 752$; $P = 0.127$).

CONCLUSIONS— Our study confirms previous reports on the relation of prehypertension to obesity (13) and insulin resistance (7) and demonstrates that individuals with prehypertension have higher rates of conversion to diabetes than those with normal blood pressure.

Much of the diabetes risk associated with prehypertension is explained by disorders related to the insulin resistance syndrome.

Subjects with prehypertension have more diabetes risk than those with normal blood pressure regardless of sex, ethnicity, and categories of obesity and glucose tolerance. However, prehypertension is not associated with incident diabetes in subjects aged ≥ 50 years. Potential explanations may be a lack of statistical power ($n = 752$) or a lesser relationship between blood pressure and insulin resistance in individuals aged ≥ 50 years.

A significant limitation in our study is the lack of information on waist circumference, chronic inflammation, and physical activity for all participants. These confounders could be relevant for explaining the relationship between prehypertension and incident diabetes.

In summary, our study shows that subjects with prehypertension had greater risk of converting to diabetes than those with

normal blood pressure. Further study is needed regarding mechanisms of this phenomenon and treatment options for participants with prehypertension.

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References

1. Prospective Studies Collaboration. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet* 2002;360:1903–1913
2. Wolf PA, D’Agostino RB, Belanger AJ, Kannel WB. Probability of stroke: a risk

- profile from the Framingham Study. *Stroke* 1991;22:312–318
3. Gress TW, Nieto FJ, Shahar E, Wofford MR, Brancati FL. Hypertension and anti-hypertensive therapy as risk factors for type 2 diabetes mellitus. *N Engl J Med* 2000;342:905–912
 4. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr, Jones DW, Materson BJ, Oparil S, Wright JT Jr, Roccella EJ. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. *JAMA* 2003;289:2560–2572
 5. Qureshi AI, Suri FK, Kirmani JF, Divani AA, Mohammed Y. Is prehypertension a risk factor for cardiovascular diseases? *Stroke* 2005;36:1859–1863
 6. Hsia J, Margolis KL, Eaton CB, Wenger NK, Allison M, Wu L, LaCroix AZ, Black HR. Prehypertension and cardiovascular disease risk in the Women's Health Initiative. *Circulation* 2007;115:855–860
 7. Player MS, Mainous AG, Diaz VA, Everett CJ. Prehypertension and insulin resistance in a nationally representative adult population. *J Clin Hypertens* 2007;9:424–429
 8. Vasani RS, Larson MG, Leip EP, Evans JC, O'Donnell CJ, Kannel WB, Levy D. Impact of high-normal blood pressure on the risk of cardiovascular disease. *N Engl J Med* 2001;345:1291–1297
 9. Burke JP, Williams K, Gaskill SP, Hazuda HP, Haffner SM, Stern MP. Rapid rise in the incidence of type 2 diabetes from 1987 to 1996: results from the San Antonio Heart Study. *Arch Intern Med* 1999;159:1450–1456
 10. Stern MP, Fatehi P, Williams K, Haffner SM. Predicting future cardiovascular disease: do we need the oral glucose tolerance test? *Diabetes Care* 2002;25:1851–1856
 11. The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Follow-up report on the diagnosis of diabetes mellitus. *Diabetes Care* 2003;26:3160–3167
 12. Haffner SM, Mykkanen L, Festa A, Burke JP, Stern MP. Insulin-resistant prediabetic subjects have more atherogenic risk factors than insulin-sensitive prediabetic subjects. *Circulation* 2000;101:975–980
 13. Pang W, Sun Z, Zheng L, Li J, Zhang X, Liu S, Xu C, Li J, Hu D, Sun Y. Body mass index and the prevalence of prehypertension and hypertension in a Chinese rural population. *Intern Med* 2008;47:893–897