

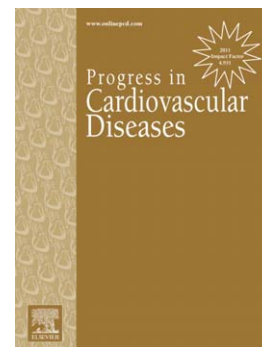
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Clinical Characteristics, Treatment Patterns and Outcomes of Hispanic Hypertensive Patients

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Abstract

Hispanics are the largest and fastest-growing minority population in the United States, currently comprising about 16.3% (52 million) of the total population. With an increased prevalence of metabolic risk factors in this population, the rate of uncontrolled hypertension (HTN) in Hispanics significantly exceeds the rates observed among non-Hispanic blacks and whites. Unfortunately, data on HTN in Hispanics remains limited due to the under-representation of Hispanics in clinical trials; with most of the data primarily restricted to observational and retrospective subgroup analyses. This article aims to review the available data on prevalence, awareness and control of HTN, risk factors and some of the challenges unique to the Hispanics population. We also discuss treatment strategies derived from large HTN trials that included Hispanics.

Abbreviations:

ACE – angiotensin-converting enzyme

ALLHAT – Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack

ARB - angiotensin receptor blocker

BP – blood pressure

CAD – coronary artery disease

CV – cardiovascular

CVD – cardiovascular disease

DBP – diastolic blood pressure

DM – Diabetes Mellitus

HCTZ – hydrochlorothiazide

hsCRP – highly sensitive C-reactive protein

HTN – hypertension

JNC – Joint National Council

MetS – Metabolic syndrome

MI – Myocardial infarction

SBP – systolic blood pressure

SR – sustained release

T2DM – Type 2 Diabetes Mellitus

US – United States

Introduction

Hispanics, with an estimated population of 52 million, represent the largest minority group in the United States (US) and by 2050 are predicted to become the country's majority population with 1 in 3 US residents being of Hispanic descent. (1)

Epidemiological and population based data suggests that the rate of uncontrolled hypertension (HTN) in Hispanics significantly exceeds the rates observed among non-Hispanic blacks and whites. (2) Approximately 29% of the adult US population carries the diagnosis of HTN (3) and with estimates suggesting that this number will continue to increase, HTN and its consequences will remain a major public health issue especially in Hispanics. In addition, Hispanics are more likely to be affected by obesity and type 2 diabetes (T2D) when compared to non-Hispanic whites. (4) The higher prevalence of these cardiovascular (CV) risk factors further contributes to the increase morbidity and mortality associated with HTN in this population. Unfortunately, data on HTN in Hispanics still remains limited due to their under-representation in clinical trials; with most of the data primarily restricted to observational and retrospective subgroup analyses. This article aims to review the epidemiology and prevalence of HTN in Hispanics, clinical characteristics, treatment strategies and specific challenges such as lack of access to health care, low socioeconomic status, language barriers and degree of acculturation.

Demographics

Unlike other ethnic groups, Hispanics represent the only ethnic group defined not by geographic origin but rather by common language, (5,6) which explains the heterogeneity and diversity of this group. In 2010 Mexican-Americans were by a large margin the most

numerous Hispanic sub-group (63%), compared to Puerto-Ricans (9.2%), Cubans (3.5%), Salvadorans (3.3%) and Dominicans (2.8%), and the remaining 18.2% self-defined as other-Hispanic or Latino origin. According to the 2010 Census, 308.7 million people resided in the US of which 50.5 million (or 16 percent) were self-described Hispanic or Latino. Additionally, more than half of the population growth in the US over the last decade was attributable to the increase in the Hispanic population. (1) In the last decade, the Hispanic population grew by 43 percent, which was four times the growth in the total population. Population growth between 2000 and 2010 varied by Hispanic sub-group; the population of people of Mexican descent increased by 54 percent from 20.6 million to 31.8 million. Mexican-Americans accounted for about three-quarters of the total growth (15.2 million) in the Hispanic population during the last decade. Puerto Ricans grew by 36 percent, increasing from 3.4 million to 4.6 million, Cubans increased by 44 percent, growing from 1.2 million in 2000 to 1.8 million in 2010 and Hispanics who reported other origins increased by 22 percent, from 10.0 million to 12.3 million.

HTN Prevalence, Awareness and Control

The prevalence of HTN varies among racial/ethnic groups, with the highest rate seen among blacks (40.4%) when compared with whites (27.4%) and Mexican-Americans (26.1%). (1,5) However with the continued growth of the Hispanic population in the US, the number of Hispanic patients at risk for HTN and its CV consequences is rapidly going to overshadow both blacks and whites. Moreover data from the National Health and Nutrition Examination Survey for the period 2003–2010 demonstrate disparities in blood pressure (BP) control for whites (48.6%), blacks (43.0%), and Mexican-Americans

(35.5%) (Figure 1). Additionally, among those with HTN, the proportion with previously defined stage 2 HTN was greater for Mexican-Americans (19.2%) and blacks (17.7%) compared with whites (12.3%). (1)

Risk Factors for HTN

The significant risk factors for the development of HTN in the general population have been well established including age, tobacco use, obesity, T2D, sedentary lifestyle, poor nutritional status (low intake of fruits and vegetables), decreased potassium intake and excessive sodium and alcohol consumption. (7) However, in the Hispanic population as in other minority immigrant populations, a unique risk factor has been identified; acculturation and duration of time in the US. (8) While much of the epidemiological data in the Hispanic population assumes a homogenous population, it has been obtained from a predominantly Mexican-American cohort, and does not consider the heterogeneous diversity of Hispanics in the US. Interestingly, recent data suggests that while the major risk factors for the development of HTN exist within the Hispanic population, there are subtle yet important differences between various ethnic and cultural Hispanic groups. (8) (Figure 2)

T2D and Metabolic Syndrome(MetS)

T2D is almost twice as prevalent among Hispanics and carries significantly higher mortality compared to Non-Hispanic whites. (9) However Daviglius et al. recently reported a difference in the prevalence of T2D within Hispanic sub-groups, Mexican-Americans and Dominican have the highest rates (19% and 18%, respectively) followed

closely by those of Central American descent (17%), then Cubans (13%) and the lowest prevalence in Hispanics of South American heritage (10%). (8) The increased prevalence of T2D in Hispanics is not limited to adults and is much more prevalent in Hispanic adolescences (age 10-19) compared to whites. Furthermore the incidence of newly diagnosed T2D is highest among Hispanics. (10) With the increasing obesity epidemic risk for CV diseases (CVD) is not limited to T2D, the prevalence of MetS is high in the Hispanic population as well. Hispanic adolescents have more than twice the risk of developing MetS compared to non-Hispanic whites (7.6% vs. 3.1%, respectively). (11) In Hispanic adults there exists disparity in the prevalence of MetS between sexes. Hispanic women have a 22% higher age-adjusted risk for MetS compared to their male counterparts. Mexican-American men have a similar risk of MetS as non-Hispanic whites, but higher than non-Hispanic blacks. However, Mexican-American women have the highest prevalence of MetS (41%) compared to 32% and 39% for non-Hispanic whites and non-Hispanic blacks, respectively. (11) In a recent meta-analysis (12), MetS carried twice the risk (RR:2.35) for all- cause mortality and CVD (including CVD death, myocardial infarction and stroke). Finally estimates from the National Health Instrument Survey data (1984-2000), US Census bureau data (2000) and an epidemiological study of T2D-associated mortality (13) demonstrated that Hispanic children born in 2000 had almost twice the residual life-time risk of developing T2D compared to non-Hispanic whites, and it was slightly higher than non-Hispanic blacks.

Obesity

Obesity, a major risk factor for HTN and CVD, continues to be a pervasive epidemic in the US. The prevalence of over-weight / obesity in the US has risen to a staggering 64% of children and 31% in adults. (13) However Hispanics are 20% more likely to be obese compared to non-Hispanic whites, the prevalence of obesity is even greater in Mexican-American women, who are 40% more likely to be obese compared with non-Hispanic white women. This disparity is even greater in children, with Mexican-American children having 60% increased risk of being overweight compared to non-Hispanic whites. (9) Within Hispanic sub-groups, there are subtle differences in the prevalence of obesity, with Hispanics of Puerto Rican and Dominican descent having greater prevalence of obesity, with the lowest rates in those of South American descent. (8) The obesity epidemic is the driving force behind the increased incidence of T2D, (14) is associated with higher CV risk (HTN, dyslipidemia), lower school performance, increased tobacco use and less healthy life-styles. (15)

Nutrition and Physical Activity

Nutrition and exercise are both significant risk factors for HTN and also contribute to the growing obesity epidemic. Researchers have found that the quality of nutritional intake is as important as the total calories consumed to obesity. Foods such as nuts, whole grains, fruits and vegetables are associated with weight loss, while sugar, refined grains, sweets and deserts are related to weight gain. (16) Data consistently show that Hispanics have greater intake of fruits and vegetables, (17) with little difference in total caloric consumption compared to Non-Hispanics Whites, (18) yet have higher rates of obesity. (11) [Table 1] One possible explanation for the disparity between nutrition and obesity

among Hispanics may be a lack of physical activity and exercise. Hispanics are less likely to meet guideline recommended levels of daily physical activity. (19) Hispanic children spend a higher percentage of time using electronic devices or watching television, activities that have been shown to have significant impact on physical activity, nutritional intake and obesity. (11) Data obtained from The Hispanic Community Health Study/ Study of Latinos demonstrated that level of physical activity did not differ significantly by sub-group, which agrees with data from Daviglius ML et al. (8). However acculturation resulted in a shift in the type of physical activity in Hispanics. While acculturation resulted in greater Leisure Time Physical Activity, there was a decline in Travel and Occupational related physical activity, resulting in no significant change in overall physical activity. (20) Furthermore data that suggests that physical activity and exercise has less effect on HTN for Hispanics than Non-Hispanic whites and Non-Hispanic blacks. In this study the frequency of exercise directly correlated with significantly lower prevalence of HTN, however, this correlation was not as strong (or significant) in the Hispanic population. (21)

Tobacco Use

Current evidence supports lower prevalence of tobacco use among Hispanics compared to non-Hispanic whites and non-Hispanic blacks, particularly comparing Hispanic women with non-Hispanic whites or blacks. (22) However, as with previously discussed risk factors, there are differences in Hispanic sub-groups. Tobacco use is highest among Hispanics of Cuban and Puerto Rican descent and lowest among Dominican men and Central American Women. (12)

Acculturation

While the traditional risk factors for HTN contribute to the disease burden in the Hispanic population, the disparities noted in nutritional intake, effect of PA/exercise and lower prevalence of tobacco use, suggest that there are environmental and genetic factors associated with ethnicity that must also contribute to the development of HTN. In a recent publication from Daviglius et al., the prevalence of HTN and CV risk factors (TDM, obesity and smoking) varied between Hispanic sub-groups living in the US. The same study shows the negative effect of acculturation on CV risk factors in the Hispanic population, as well as an increased number of CV risk factors directly correlated with lower socio-economic status, acculturation, decreased physical activity and poor nutrition. (8) While acculturation was shown to have a negative effect on the rates of HTN in the Hispanic Health and Nutrition Examination Survey (23), it has also been shown to have positive effects on the rates of awareness, treatment and control of HTN (24). Interestingly while Hispanics with higher self-reported rates of acculturation report higher health self-ratings, unfortunately it did not translate into higher rates of control of HTN (25).

Genetics

With relatively little data on genetic factors of HTN, there is sufficient evidence to support the belief that there exist differences in the epidemiology of HTN between Hispanics and Non-Hispanics. Data from the Viva La Familia Study found genetic links between CV risk (26) and fasting plasma glucose (27). A meta-analysis has shown a genetic association between HTN and angiotensin-converting enzyme (ACE) activity (28,29). Data published from Mexican-Americans have linked HTN with genetic loci

associated with several risk factors for HTN, (30) including MetS (31), high serum uric acid (32) and environmental lead exposure (33).

Socioeconomic Status

Understanding of the risk factors and epidemiological data provides only part of the information necessary to understand the complexities of HTN in the Hispanic population. Socioeconomic factors such as education, income and access to regular health care have significant impact on the awareness, treatment and control of HTN in Hispanics. The most recent data from the US Census Bureau indicates a significant disparity in health care insurance for Hispanics in the US. Hispanics are more likely to be uninsured compared to Non-Hispanic whites and blacks, 29% (15.5 million), 19% (13 million) and 11% (22 million), respectively. (34) The same data demonstrated that lack of insurance is higher in non-citizens and foreign-born Hispanics. The US Census Bureau has consistently shown that income is directly related to lack of health insurance and that Hispanics traditionally have the lowest median income. (34) Beyond ethnic/racial disparity, other factors, such as income, education, foreign born and non-citizens, that often affect Hispanic Americans have been linked to lack of health care. (35) This data demonstrates some of the many factors that contribute to the overall poor awareness and control of HTN in Hispanics compared to non-Hispanic whites. (36) Furthermore data from the National Health and Nutrition Examination Survey has linked lack of regular medical care to the risk of developing HTN. (37) It has been shown that Hispanics with uncontrolled HTN are less likely to have insurance coverage compared to non-Hispanic white and black patients. (38) Disparities in health insurance coverage can be seen

among Hispanic sub-groups, Hispanics of Mexican-American and Central American descent are less likely to have health insurance compared to those of Puerto Rican and Cuban descent. (39) Socioeconomic status has been linked to sedentary life-style, childhood obesity, prevalence of CVD, delayed medical care, tobacco use and decreased life expectancy. (40)

The lack of access to healthcare is exacerbated by the lower quality of care provided to minorities and those of lower socioeconomic status. The National Center for Health Statistics project has reported that quality of care obtained is associated with lower income and minority status. (41) The same data has shown that language barriers between patients and healthcare providers contribute to decreased quality of care, patient satisfaction, physician satisfaction and safety. (41) Language barriers have been linked to decreased adherence to medical therapy, (42) decrease the discussion of medication side effects, (43) lower utilization of preventive screening, (42) and contribute to negative health outcomes (44) and higher provider mistrust. (45)

Pharmacology Therapy

Data on anti-HTN therapy in Hispanics remains limited [Table 2]. Their underrepresentation in large HTN trials and the absence of specific recommendations in the recently published (Joint National Committee) JNC 8 (46) underscore the need for further studies focusing on this population. The Antihypertensive and Lipid-lowering Treatment to Prevent Heart Attack (ALLHAT) Trial (47,48) was the first study to include a large number of Hispanics. In brief, the ALLHAT trial aimed to investigate whether an ACE inhibitor (lisinopril) to a calcium channel blocker (amlodipine) was superior to a thiazide diuretic (chlorthalidone) in preventing CV complications of HTN in high-risk

individuals. (47,48) In this study, 15.7% (n = 5246) Hispanics were enrolled. Despite a lower rate of HTN control at enrollment, Hispanics had higher control rates than non-Hispanic whites and blacks after 6 months of treatment, and significantly higher odds of achieving HTN control than non-Hispanic whites within 24 months of follow-up. (47,48) Similarly, investigators from the INVEST trial (49) compared the efficacy of a verapamil sustained-release (SR) strategy to that of an atenolol strategy in 8045 Hispanic HTN patients with respect to adverse CV outcomes and BP control. The major finding of this study was that a better BP control was achieved in Hispanic patients when compared with non-Hispanic patients. Moreover, this better BP control in Hispanic patients was accomplished with fewer drugs compared with the non-Hispanic patients. In addition to lower CV adverse outcomes in the Hispanic patients, BP management with either the verapamil SR or the atenolol strategies resulted in similar BP reduction, and with the exception of lower risk of new-onset T2D in the verapamil SR strategy. (49) With an increased risk of adverse metabolic outcomes like MetS and T2D, beta-blockers may not be ideal agents for the treatment of HTN in Hispanics. (50,51) In contrast, ACE inhibitors and angiotensin receptor blockers could particularly be attractive agents for the treatment of HTN in the Hispanic population, as they have been associated with a 25% reduction in the risk of T2D when used in the general hypertensive population. (52) In this regard, a single-arm trial (53) designed to examine the efficacy and safety of fixed-dose combinations of irbesartan and hydrochlorothiazide in a multiethnic group of patients with uncontrolled systolic HTN (total population 844 patients, 14% Hispanics) treatment with hydrochlorothiazide (HCTZ) 12.5 mg/d for 2 weeks followed by a combination of irbesartan 150 mg and HCTZ 12.5 mg/d for 8 weeks followed by an

additional 8 weeks of irbesartan 300 mg and HCTZ 25 mg/d resulted in mean reductions of 22.9 ± 13.2 mm Hg in systolic BP ($P < .001$) and 10.6 ± 8.1 mm Hg in diastolic BP ($P < .001$) from baseline. These reductions were similar to the BP reductions achieved in blacks and whites. (53) Similar results were shown in the Valsartan-Managing Blood Pressure Aggressively and Evaluating Reductions in hsCRP (Val-MARC) study (54, 55) where valsartan/HCTZ was more effective than valsartan alone in lowering BP among Hispanics. (54, 55) In summary, the available data suggest that the rennin angiotensin aldosterone system antagonists agents alone or in combination with diuretics, seem to be an effective treatment strategy for Hispanics HTN patients.

Conclusions / Future Directions

As demonstrated by the limited data available from clinical trials, the pressing problem for the management of HTN in the Hispanic population is not finding adequate and effective therapy, but identifying HTN and providing access to care for the Hispanic population. The higher prevalence of uncontrolled HTN is directly related to lack of access to healthcare, which is partially due to lower socio-economic status, language barriers and education. With limited data on medication class effect on HTN control and CV outcomes in Hispanics, we cannot make treatment recommendations. However, as shown previously, presence of comorbidities such as obesity, MetS, dyslipidemia (56), and T2D in Hispanics may aid in the choice of a specific anti-HTN therapy.

While future clinical trials should endeavor to separate the heterogeneous Hispanic population into sub-groups, this may not be feasible for recruitment purposes. However, practitioners should keep in mind the differences in risk factor profiles among the Hispanic sub-groups when evaluating and treating HTN.

Drug therapy cannot be the sole treatment strategy to deal with the inevitable increase in disease burden over the next decades. Efforts to improve patient education about the importance of physical activity and risk factor modification and access to regular medical care in the Hispanic population must be the cornerstone of any treatment strategy. As the Hispanic population continues to grow in the US, the health and well-being of this heterogeneous group of people will be ultimately reflected on the health of the nation.

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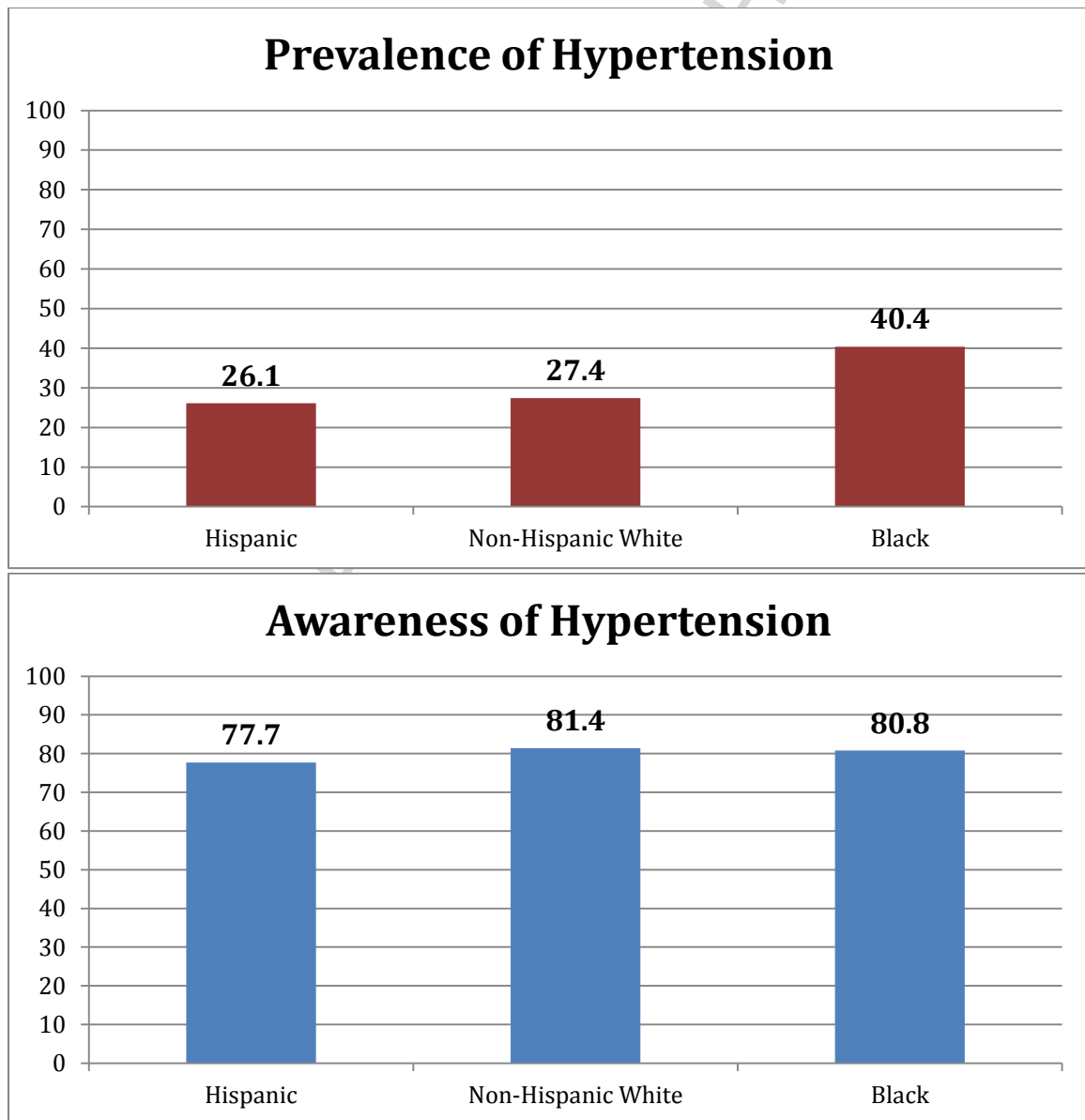
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Figures

Figure 1: Ethnic disparity in prevalence, awareness, treatment and control of hypertension among adults in the US, adjusted by age. (Adapted from CDC/NCHS, National Health and Nutrition Examination Survey, NCHS Data Brief Number 107, October 2012)



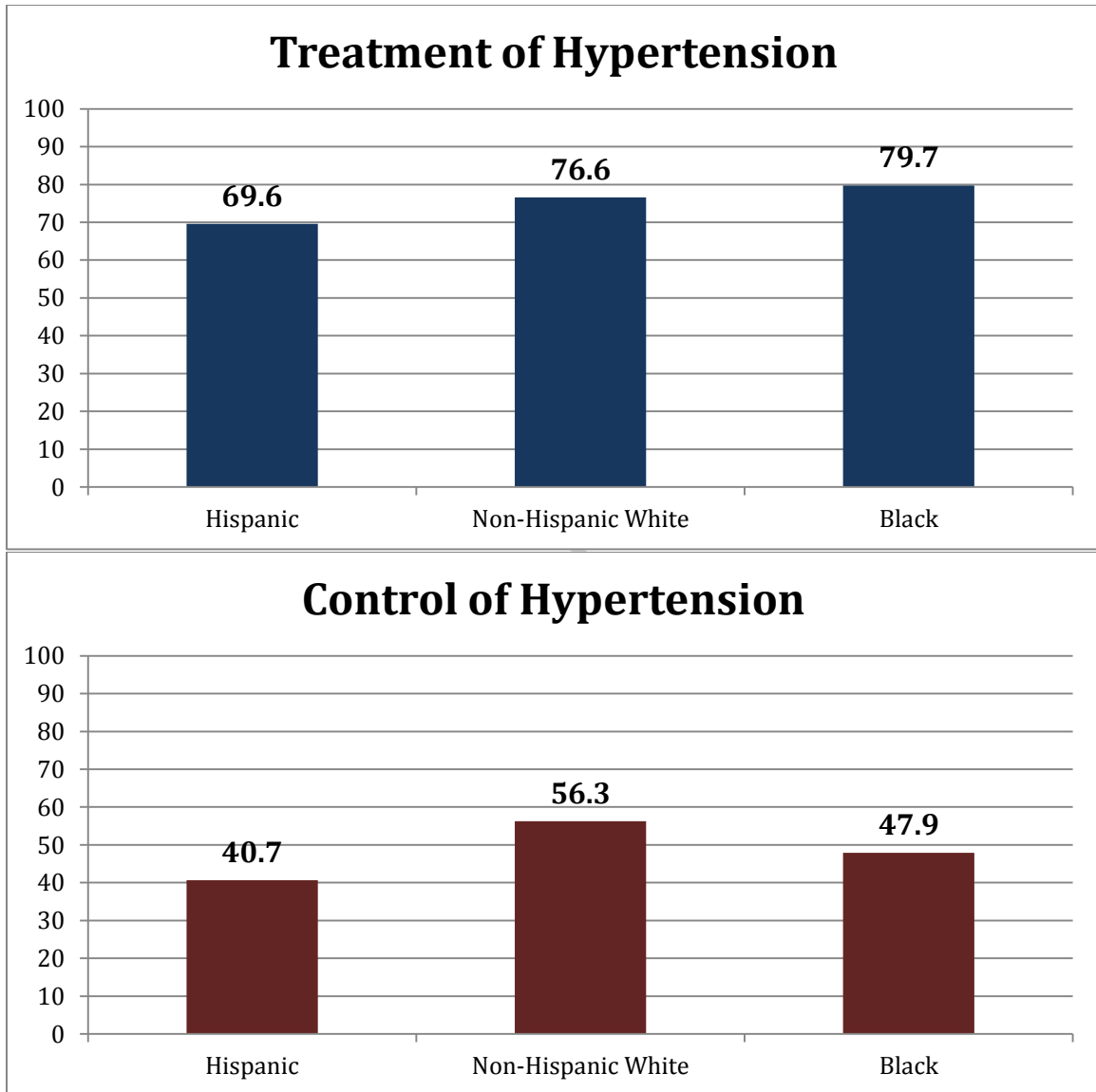
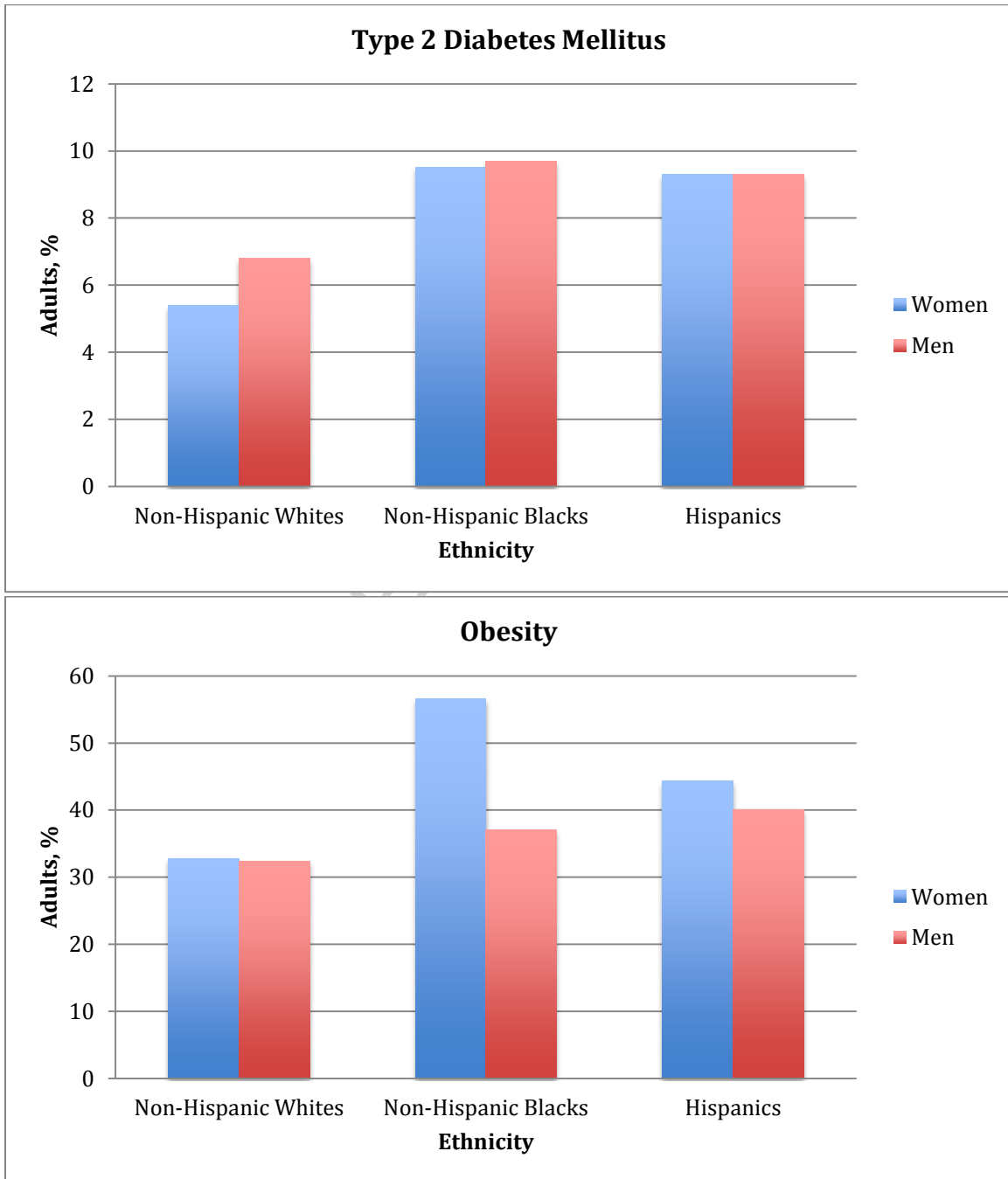
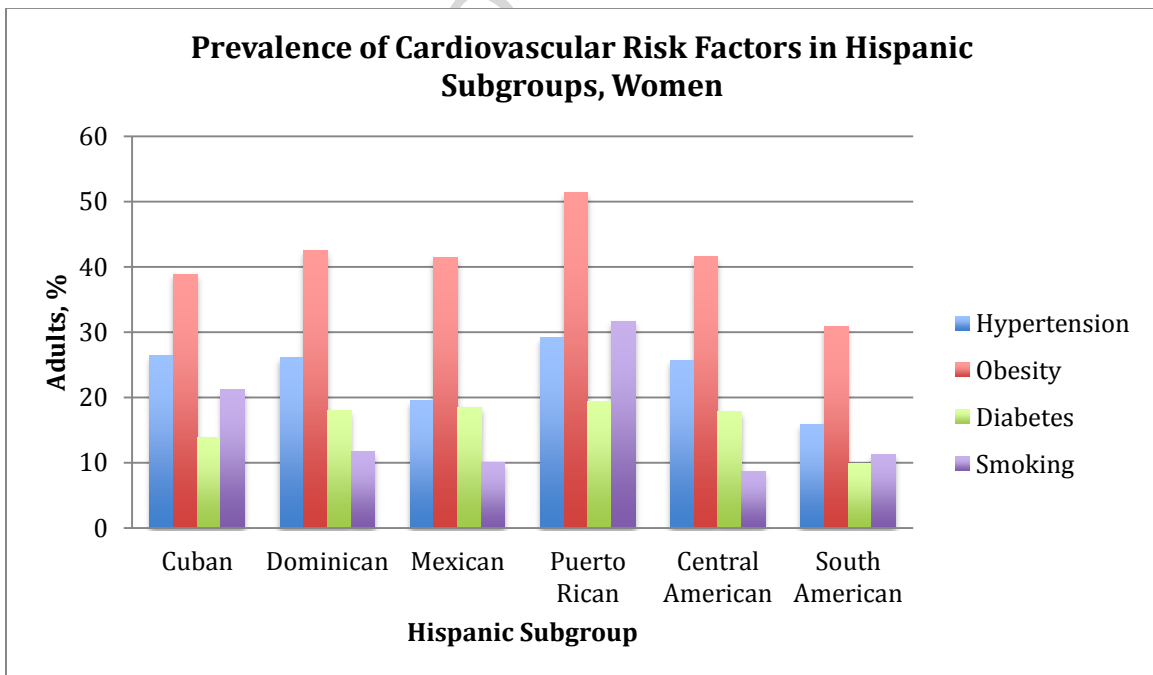
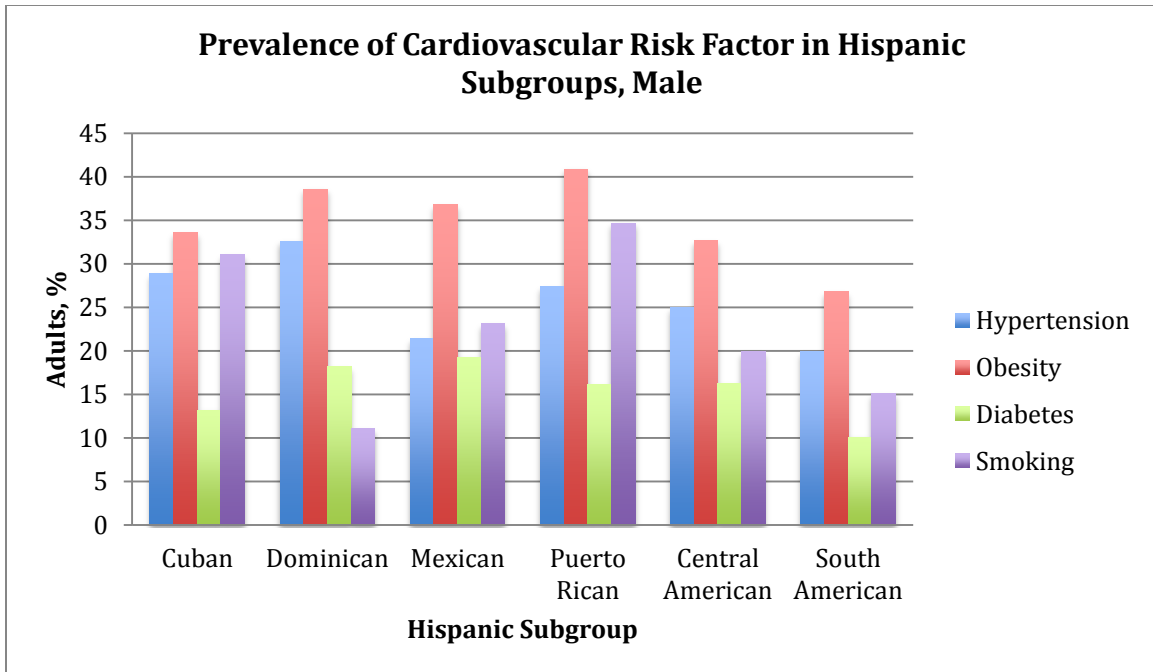


Figure 2: Prevalence of CV / HTN Risk Factors in Hispanic Population – Adapted from NHANES 2013, Office of Minority Health, CDC and Daviglius ML et al. (4).





Tables**Table 1: Nutrient Intake and Physical Activity by Race / Ethnicity [17, 18]**

Risk Factor	Non-Hispanic White	Non-Hispanic Blacks	Mexican American	All Hispanics
Nutrition (13)				
Calorie, kcal.day	2150	2202	2138	2124
Protein g/day	83.3	79.7	84.8	84.2
Carbohydrate, g/day	257	254	277	273
Total Fat, g/day	81.4	78.8	73.7	73.1
Saturated Fat, g/day	26.9	25.2	23.7	23.6
Dietary Fiber, g/day	17.3	13.6	20	18.4
Sodium, g/day	3.6	3.3	3.3	3.4
Potassium, g/day	2.9	2.3	2.8	2.7
Alcohol, g/day	12.3	11.4	7.9	8.9
Fruits and Vegetable, cup equivalent/day (57)				
Men	3.04	2.49	3.26	-
Women	2.58	2.46	3.03	-
Physical Activity (PA)				
Met guideline recommended regular leisure-time PA, % (7)	22.9	16.6	-	15.7
Adults meeting both aerobic and muscle strengthening guidelines, % (14)	21	21	-	18
Leisure-Time Physical Inactivity, %(58)				
Men	18.4	27.0	-	32.5
Women	21.6	33.9	-	39.6

Table 2: Clinical Trials in Hypertension with large Hispanic Subgroup Included

(See attached separate document for Table 2 in Landscape format)

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Table 2: Clinical Trials in Hypertension with large Hispanic Subgroup Included

Trial /Paper	Title	Study Design	Ethnicity	Treatment	Outcomes	Results
			n (%)	Non-Hispanic		
Margolis et al. (48)	BP Control in Hispanics in ALLHAT	Hispanic subgroup analysis of the ALLHAT randomized active control trial. Patients with hypertension and ≥ 1 CHD risk factor (N = 33,357)	6329 (19.4)	26 313 (80.6)	Amlodipine 2.5-10mg/day Lisinopril 10-40 mg/day Doxazosin 2-8 mg/day Chlorthalidone 12.5-25 mg/day	BP control (SBP / DBP < 140/90 mm Hg)
Cooper-DeHoff et al. (49)	BP control and cardiovascular outcomes in high-risk Hispanic patients – findings from INVEST	Randomized, open-label trial in patients with CAD and hypertension. Subgroup analysis of the INVEST trial. (N = 22,576)	8045 (35.6)	14,531 (64.4)	Verapamil SR 240-360 mg/daily Atenolol 50-100 mg/day Trandolapril or HCTZ added to achieve BP goal.	Risk of adverse CV outcomes (primary); BP control (SBP/DBP <130/85 mmHg for patients with T2DM or renal impairment: <140/90 mmHg for all others).
Ofili et al. (53)	Irbesartan/HCTZ fixed combinations in patients of different racial/ethnic groups with uncontrolled systolic BP on monotherapy	Subgroup analysis of INCLUSIVE open-label, single-arm, sequential treatment trial in patients with uncontrolled BP (N=825)	119 (14.1)	725 (85.9)	HCTZ 12.5 mg/day Irbesartan/HCTZ 150/12.5 mg/day or 300/25 mg/day	Primary outcome was mean change in SBP from baseline at 18 weeks; secondary – mean change in DBP at 18 weeks. SBP/DBP control at weeks 2, 10 and 18.