Cardiology Research and Practice

The Growing Problem of Cardiometabolic Disorders in an Ever-Shrinking World

Guest Editors: Bobby Varkey Khan, Martin Thoenes, Anjali Arora, and Donna Murnaghan

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Research Article

Novel Neurovascular Protective Agents: Effects of INV-155, INV-157, INV-159, and INV-161 versus Lipoic Acid and Captopril in a Rat Stroke Model

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Background. Lipoic acid (LA), which has significant antioxidant properties, may also function as a potent neuroprotectant. The synthetic compounds INV-155, INV-157, INV-159, and INV-161 are physiochemical combinations of lipoic acid and captopril. We sought to determine if these compounds have neuroprotective potential following middle cerebral artery occlusion (MCAO) in rats. *Methods*. Male Sprague-Dawley rats were injected intravenously with captopril (1–50 mg/kg) 30 minutes prior to MCAO. Blood pressure, heart rate, baroreceptor reflex sensitivity, and infarct size were measured. In addition, dose response effect on infarct size and cardiovascular parameters was determined using INV-155, INV-157, INV-159, and INV-161 and compared to captopril and LA. *Results*. Pretreatment with captopril and LA at all doses tested was neuroprotective. The compounds INV-159 (0.5–10 mg/kg) and INV-161 (1–10 mg/kg) produced a significant,dose-dependent decrease in infarct size. In contrast, INV-155 and INV-157 had no effect on infarct size. *Conclusions*. Combined pretreatment with captopril potentiated the neuroprotective benefit observed following LA alone. Both INV-159 and INV-161 were also neuroprotective. These results suggest that patients taking combinations of captopril and LA, either as combination therapy or in the form of INV-159 or INV-161, may also benefit from significant protection against cerebral infarction.

1. Introduction

Hypertension prevalence is highly variable among populations worldwide. In the United States there is a disproportionate burden of this disease and its complications in African Americans [1]. African Americans have the highest prevalence of hypertension in the world, significantly higher than people of African origin living outside the United States [2]. According to the 2003-2004 National Health and Nutrition Examination Survey (NHANES) hypertension prevalence is 39.1% in African Americans and 28.5% in White Americans [3]. The increased prevalence of hypertension in African-Americans has been attributed to both genetic and environmental factors [4]. Additionally, hypertension is usually observed at a younger age in African-Americans and it results in more severe disease complications. This results in a significantly higher hypertension related mortality rate for African Americans, 49.9% and 40.6% for African American men and women, respectively, compared to 17.9% for the overall US population in 2004 [1].

Cardiometabolic syndrome, a constellation of common cardiovascular risk factors (obesity/overweight, atherogenic dyslipidemia, glucose intolerance, and elevated blood pressure) has been shown to directly increase atherosclerotic cardiovascular disease [5]. Of particular interest is the important role of the endothelium in vascular homeostasis. Endothelial changes are considered precursors to early changes in the atherosclerotic endothelium leading to chronic diseases including cardiometabolic syndrome. Patients are often prescribed antihypertensive drugs such as captopril in an attempt to lower their risk for cardiovascular disease [6]. In addition, patients diagnosed with this syndrome would

have a high probability of endothelial dysfunction and/or biomarkers associated with these disorders. Anti-inflammatory and antioxidant therapies have been shown to reduce the biomarkers associated with this endothelial dysfunction [7]. In fact, in a cross-over, double-blinded study in patients diagnosed with cardiometabolic syndrome, our group has recently demonstrated that one such naturally occurring product α-lipoic acid (LA) improves endothelial function. This effect was potentiated in patients taking an angiotensin converting enzyme (ACE) inhibitor similar to captopril [7]. Since both captopril [8, 9] and LA [10] have been shown to provide neuroprotective effects, we designed the current study to determine if this combination therapy would also provide neuroprotection. The results provide support for our hypothesis that the combination of ACE inhibition and LA may provide additional cerebrovascular protection in patients with cardiometabolic syndrome.

2. Methods

All experiments were carried out in accordance with the guidelines of the Canadian Council on Animal Care and were approved by the University of Prince Edward Island's Animal Care Committee.

2.1. General Surgical Procedures. All experiments were conducted on male Sprague-Dawley rats (200–350 g; Charles River; Montreal, PQ, Canada). For all animals, food and tap water were available *ad libitum*. Rats were anaesthetized with sodium thiobutabarbital (Inactin; Sigma-Aldridge; St. Louis, MO, USA; 100 mg/kg; i.p.) which provided a stable plane of anesthesia for the full duration of the experimental time periods (no animals required anesthetic supplementation). To monitor blood pressure and heart rate, a polyethylene catheter (PE-50; Clay Adams, Parsippany, NJ, USA) was inserted into the right femoral artery. For intravenous administration of drugs a second polyethylene catheter (PE-10; Clay Adams, Parsippany, NJ, USA) was inserted into the right femoral vein. Arterial blood pressure was measured with a pressure transducer (Gould P23 ID, Cleveland, OH) connected to a Gould model 2200S polygraph. Heart rate was determined from the pulse pressure using a Gould tachograph (Biotach). These parameters were displayed and analyzed using PolyviewPro/32 data-acquisition and analysis software (Grass; Warwick, RI, USA). An endotracheal tube was inserted to facilitate breathing. Body temperature was monitored and maintained at 37 ± 1EC using a Physitemp feedback system (Physitemp Instruments; Clifton, NJ, USA).

2.2. Middle Cerebral Artery Occlusions. Our research group had previously published the detailed methodology for transient occlusion of the middle cerebral artery [11]. Briefly, animals were placed in a David Kopf stereotaxic frame (Tujunga, CA, USA) and the right middle cerebral artery (MCA) approached through a rostra-caudal incision of the skin and frontalis muscle at the approximate level of bregma. Blood flow through the MCA was impeded by the placement of surgical suture behind the MCA at 3 designated positions along the exposed vessel. The ends of the sutures were positioned so that the middle of each suture applied pressure to the MCA and completely impeded blood flow as confirmed using laser Doppler flowmetry (OxyFlo, Oxford-Optronix, Oxford, UK). This 3-point placement of surgical sutures produced a highly reproducible and consistent focal ischemic lesion restricted to the ipsilateral cerebral cortex. To facilitate removal of the sutures at the end of the occlusion period (30 minutes), a few drops of warm physiological saline (37EC) was first applied to the areas where the MCA was in contact with the sutures. Following removal of the sutures, blood was allowed to reperfuse the area for an additional 5.5 hours (I/R).

2.3. Cardiac Baroreflex Testing. To determine the effect of drug administration on the reflex bradycardia following baroreceptor activation, the baroreceptor reflex was evoked using a bolus intravenous injection of the α-adrenergic receptor agonist, phenylephrine-hydrochloride (Sigma-Aldridge; St.Louis, MO, USA; 0.1 mL; 2.5 μg/mL; i.v.). The ratio of the peak change in the magnitude of the reflex bradycardia to the magnitude of the phenylephrine-induced pressor response (ΔHR/ΔMAP) was used as a measure of baroreceptor sensitivity [12] (BRS). BRS was tested 10 minutes and immediately prior to drug administration. BRS was then tested 15 minutes following drug administration (15 minutes prior to MCAO), and then 5, 10, and 20 minutes following MCAO, as well as immediately prior to suture removal at 30 minutes. The BRS was also tested 30, 60, 90, 150, 210, 270, and 330 minutes following suture removal.

2.4. Drug Development. The synthetic drugs INV-155, INV-157, INV-159, and INV-161 were obtained from InVasc Therapeutics Inc. (Atlanta, Georgia, USA). These are patented, proprietary drugs commercially available from InVasc Therapeutics Inc., and are sold for the treatment of cardiometabolic syndrome in humans. All of these compounds are based on the physiochemical synthetic combination of captopril and α-lipoic acid (LA) in a 1 : 1 ratio, but differ in their configuration (derivatives of the parent compounds).

2.5. Effect of Drug Administration on Infarct Volume, Blood Pressure, Heart Rate, and BRS. In the first experiment, to examine the effect of captopril on ischemic and reperfusion-induced cell death, administration of captopril (Sigma-Aldridge; St. Louis, MO, USA; 1, 5, 10, or 50 mg/kg; 1 mL/kg; i.v.; $n = 4$ to 7/group) or physiological saline (0.9% sodium chloride; 1 mL/kg; i.v.; $n = 5$) was made 30 minutes prior to the onset of MCAO. Thirty minutes following drug injection, the sutures were put in place for 30 minutes, followed by 5.5 hours of reperfusion. Infarct volume was measured following 5.5 hours of reperfusion and BRS was measured at the intervals described above.

In the second experiment, a concentration of captopril of 5 mg/kg was chosen as it did not produce a significant change in blood pressure or heart rate, and was coadministered in combination with various doses of lipoic acid (0.0005, 0.05 and 0.5 mg/kg, 1 mL/kg; i.v.; $n = 6$/group) which have

been previously reported to have no significant effect on infarct volume in the same MCAO model developed in our laboratory [10]. This coadministration was done 30 minutes prior to MCAO. Following 5.5 hours of reperfusion, BRS were measured at the intervals described above and infarct volume was determined.

In the third experiment, we aimed to determine if administration of the combined drugs would result in a reduction in infarct volume. Therefore, captopril (5 mg/kg) and lipoic acid (0.5 mg/kg; 1 mL/kg; i.v.) were coadministered immediately prior to the removal of the sutures (30 minutes after MCAO) and infarct volume was measured following 5.5 hours of reperfusion.

In the fourth experiment, we compared the efficacy of the physiochemical combination of captopril-lipoic acid compounds (INV-155, INV-157, INV-159, and INV-161; 10 mg/kg; 1 mL/kg; i.v.; $n = 4$ or 5 per group) or vehicle (2% sodium bicarbonate; 1 mL/kg; i.v.; $n = 4$) administered 30 minutes prior to MCAO followed by 5.5 hours of reperfusion. INV-159 and INV-161 produced significant neuroprotection and were further studied to determine if the neuroprotection was dose dependent. In addition to 10 mg/kg, 0.1, 0.5, and 1 mg/kg (1 mL/kg; i.v.; $n = 4$/group) of INV-159 were administered and 0.1 and 1 mg/kg (1 mL/kg; i.v.; $n = 4$/group) of INV-161 were administered. Infarct volume and BRS was determined as described above.

2.6. Effect of Drug Administration on Blood Flow through the MCA. To examine the effect of systemic captopril, lipoic acid, captopril-lipoic acid combinations, INV-159, and INV-161 administration on cerebral blood flow, we used laser Doppler flowmetry to measure blood flow before, during and following MCAO. Laser Doppler signals from the MCA were recorded as relative values in blood perfusion units (bpu). The tip of a 0.5 mm probe (OxyFlo, Oxford-Optronix, Oxford, UK) was placed directly over the MCA just ventral to the bifurcation of the MCA to the frontal and parietal cortices. Warm physiological saline was applied to the area so that the probe was measuring blood flow through the saline. Blood flow through the MCA was measured at 10 and 5 minutes prior to drug administration, and then 5, 10, 15, 20, 30, and 60 minutes following drug administration.

2.7. Histological Procedures. At the end of each experiment (total of 6 hours for each rat), all animals were perfused transcardially with phosphate buffered saline (PBS; 0.1 M; 200 mls), the brains were removed and sliced into 1 mm coronal sections using a rat brain matrix (Harvard Apparatus; Holliston, MA, USA). Sections were incubated in a 2% solution of 2,3,5-triphenol tetrazolium chloride (TTC; Sigma-Aldrich; St. Louis; MO, USA) for 5 minutes. Infarct volumes for both sides of each brain section were calculated with the use of scanned digital images of each brain section and using a computer-assisted imaging system (Scion Corporation; Frederick, MD, USA). The sum total of all the individual infarct volumes provided the total infarct volume for each rat.

2.8. Statistical Analysis. Data were analyzed using a statistical software package (SigmaStat and SigmaPlot; Jandel Scientific, Tujunga, CA). All data are presented as a mean ± standard error of the mean (S.E.M.). Differences were considered statistically significant if $P \leq 0.05$ by a one-way analysis of variance (ANOVA) followed by a Bonferroni post hoc analysis. When only two groups were being compared, Student's *t*-test was used.

3. Results

3.1. The Effect of Preadministration of Captopril on Infarct Volume. The following experiment was designed to determine the effect of captopril pretreatment on MCAO-induced ischemia/reperfusion (I/R) injury. Captopril was administered 30 minutes prior to suture placement and infarct volume was measured following 5.5 hours of reperfusion. Captopril pre-treatment did not result in significant neuroprotection compared to saline with any of the doses tested ($P \geq 0.05$; Figures 1(a) and 1(b)).

3.2. The Effect of Preadministration of the Combination of Captopril and Lipoic Acid on Infarct Volume. The following experiment was designed to determine the effect of coadministration of captopril with previously reported nonneuroprotective doses of lipoic acid on MCAO-induced ischemia/reperfusion (I/R) injury. The drug combinations were administered 30 minutes prior to suture placement and infarct volume was measured following 5.5 hours of reperfusion. Combining captopril (5 mg/kg) with each dose of lipoic acid (0.005, 0.05, and 0.5 mg/kg) resulted in significant neuroprotection compared to saline ($P \geq 0.05$; Figure 2).

3.3. The Effect of Postadministration of the Drug Combination of Captopril and Lipoic Acid on Infarct Volume. The following experiment was designed to determine the effect of the co-administration of captopril and lipoic acid on MCAO-induced ischemia/reperfusion (I/R) injury. Co-administration of the drug combination immediately prior to suture removal (30 minutes post-MCAO) did not result in a significant change in infarct volume compared to the administration of saline ($P \geq 0.05$; Figure 3).

3.4. The Effect of Preadministration of the Compounds INV-155, INV-157, INV-159, and INV-161 on Infarct Volume. The following experiment was designed to determine the neuroprotective capacity of the designer drugs INV-155, INV-157, INV-159, and INV-161 on MCAO-induced ischemia/reperfusion (I/R) injury. Each drug was administered 30 minutes prior to suture placement and infarct volume was measured following 5.5 hours of reperfusion. INV-155 (10 mg/kg) and INV-157 (10 mg/kg) did not result in significant neuroprotection compared to sodium bicarbonate vehicle ($P \geq 0.05$; data not shown). However, INV-159 (10 mg/kg) and INV-161 (10 mg/kg) did result in significant neuroprotection compared to sodium bicarbonate vehicle and therefore complete dose-response curves were generated for each drug. INV-159 produced significant neuroprotection using doses

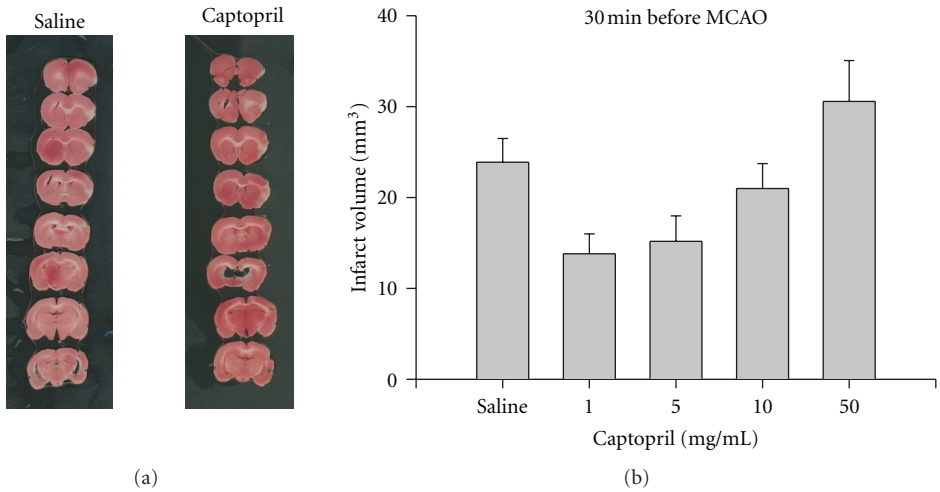

Figure 1: (a) Representative photomicrographs of TTC stained, 1 mm thick coronal slices illustrating the extent of the infarct within the prefrontal cortex following 30 minutes pretreatment (i.v.) with either saline or captopril (5.0 mg/kg) and ischemia/reperfusion (I/R). (b) Effect of pretreatment with either saline or captopril on infarct volume (mm^3) calculated from TTC-stained 1 mm thick coronal sections throughout the extent of the infarct following I/R and pretreatment (i.v.; 30 minutes) with either saline or captopril. Each bar represents the mean ± S.E.M (n = 4–7/group).

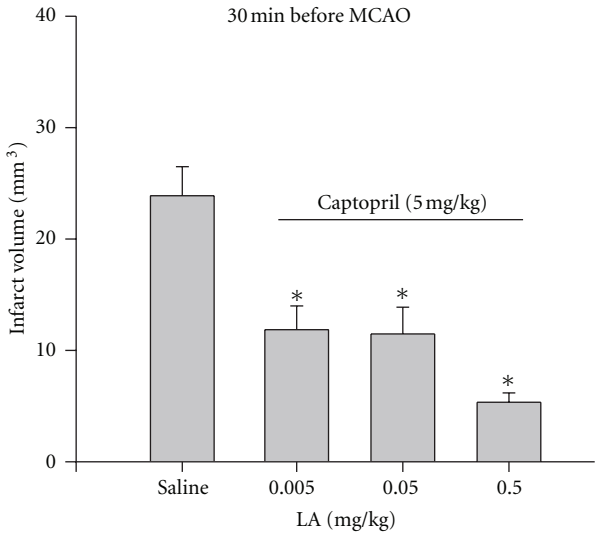

Figure 2: Effect of pretreatment (30 minutes before MCAO) with either saline (n = 5) or co-administration of captopril and lipoic acid (n = 6/group) on infarct volume (mm^3) calculated from TTC-stained I mm thick coronal sections throughout the extent of the infarct following I/R. Each bar represents the mean ± S.E.M. and *indicates significance ($P \leq 0.05$) from the saline control group (n = 4–7/group).

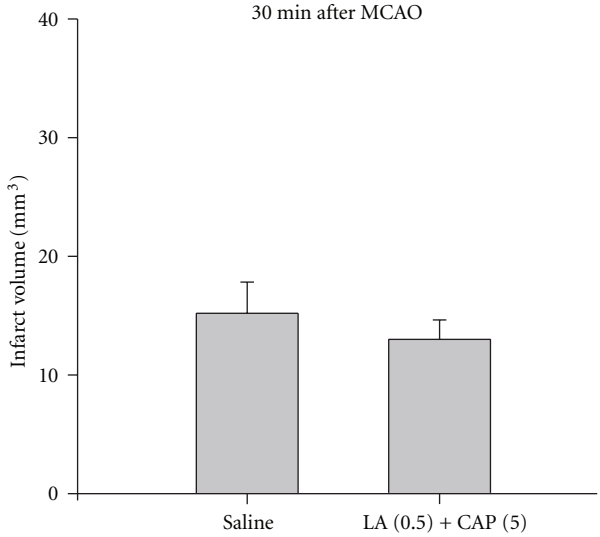

Figure 3: Average infarct volume (mm^3) following either saline (n = 6) or a combination of captopril (5 mg/kg) and lipoic acid (0.5 mg/kg; n = 4) administration (i.v.) immediately prior to suture removal and the beginning of reperfusion (30 minutes after MCAO) calculated from TTC-stained coronal sections throughout the extent of the infarct. Each bar represents the mean ± S.E.M.

of 0.5, 1.0, and 10 mg/kg (Figure 4(a); $P \leq 0.05$ for each dose) and INV-161 produced significant neuroprotection using doses of 1.0, and 10 mg/kg (Figure 4(b); $P \leq 0.05$ for each dose).

3.5. The Effect of Drug Preadministration on Cardiovascular Parameters. The following experiments were designed to determine the effect of drug preadministration on blood pressure, heart rate, and BRS before and following 30 minutes of MCA occlusion. Preadministration of captopril (1.0 mg/kg and 5 mg/kg) or saline did not significantly alter mean blood pressure or mean heart rate prior to, during, or following occlusion ($P > 0.05$; n = 4-5/dose; data not shown). However, the administration of captopril (10 and 50 mg/kg) resulted in a transient decrease in mean arterial

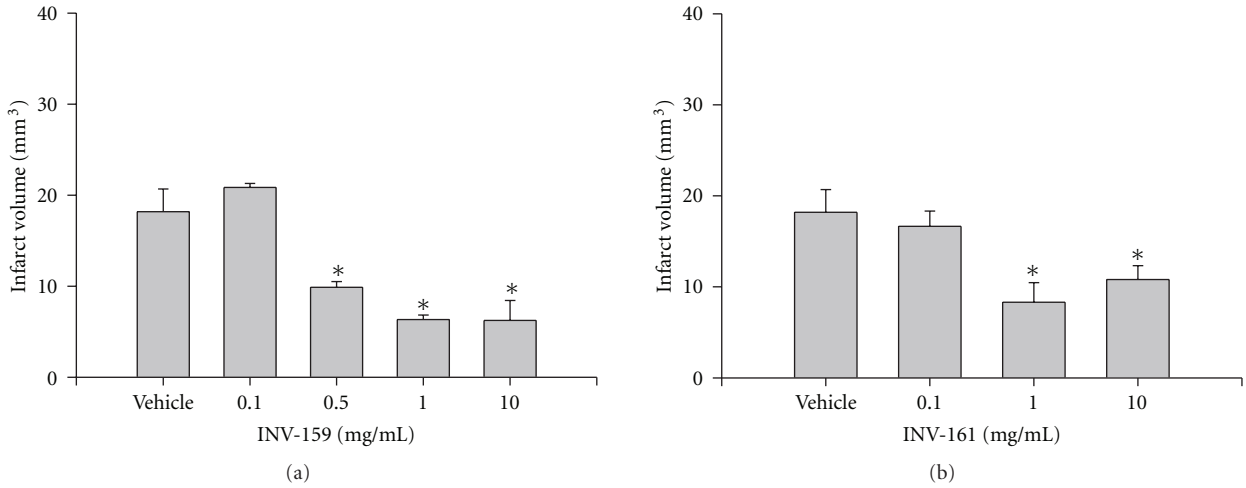

Figure 4: (a) Effect of pretreatment with either 2% sodium bicarbonate (vehicle), INV-159, or INV-161 (b) on infarct volume (mm^3) calculated from TTC-stained 1 mm thick coronal sections throughout the extent of the infarct following I/R. Each bar represents the mean ± S.E.M. and * indicates significance ($P \leq 0.05$) from the vehicle control group (n = 4-5/group).

pressure by 19 ± 5 and 34 ± 11 mmHg, respectively, (from an average baseline of 113 ± 9 mmHg) for ~5 minutes. This hypotensive effect was accompanied by a reflex tachycardia of 9 ± 2 and 19 ± 6 beats/min (from an average baseline heart rate of 412 ± 23 beats/min. When the BRS was tested following return of the cardiovascular parameters to baseline values 5 minutes after captopril injection, there was no significant difference compared to the preinjection value (0.55 ± 0.1 versus 0.5 ± 0.2).

Co-administration of captopril (5 mg/kg) with lipoic acid (doses 0.005, 0.05, and 0.5 mg/kg) 30 minutes prior to MCAO did not significantly alter mean arterial pressure, mean heart rate, or BRS prior to, during, or following occlusion compared to saline vehicle ($P > 0.05$; $n = 5$; data not shown). Administration of INV-159 (10 mg/kg) or INV-161 (10 mg/kg) did not significantly alter mean arterial pressure, mean heart rate, or BRS prior to, during, or following occlusion compared to vehicle (2% sodium bicarbonate; $P > 0.05$; $n = 4$/group; data not shown).

3.6. Effect of Drug Administration on Blood Flow through the MCA. To quantify blood flow through the MCA before, during, and following occlusion, we used laser Doppler flowmetry (Figure 4(b)). Administration of captopril (5 mg/kg), INV-159 (10 mg/kg) or INV-161 (10 mg/kg) 30 minutes prior to MCA occlusion did not result in significant changes in blood flow compared to preadministration values ($P > 0.05$; n = 4-5/drug; data not shown).

4. Discussion

The present investigation was conducted to determine if combination therapy using two known compounds, captopril and lipoic acid (LA) already prescribed and used by humans for the treatment of symptoms associated with cardiometabolic syndrome, could provide beneficial effects against cerebrovascular disease. The results of the present study supported our hypothesis that these drugs, in combination or synthetically combined, provide significant neuroprotection in a rat stroke model. In addition, no adverse cardiovascular complications were observed following pretreatment with any of these drugs, nor did they reverse the autonomic dysfunction observed following MCAO.

Cardiovascular and metabolic diseases (including atherosclerosis, stroke, and diabetes mellitus) represent the single largest global pharmaceutical opportunity within the pharmaceutical industry. The annual prescription drug revenue in this cardiometabolic space now exceed $400 billion annually. The advancing age of baby boomers, increased worldwide incidence of obesity, and a transition to a Western diet in much of the developing world clearly suggests that these chronic diseases will continue to be a primary driver within the industry. Cardiovascular and metabolic diseases represent huge product opportunities. However, the FDA have been driven by safety concerns and responding to congressional pressures associated with drug safety and efficacy benefit and the rising impact of healthcare on the gross domestic product. As a result, the agencies have become more restrictive in defining acceptable clinical endpoints. Furthermore, they are reducing the acceptance on surrogate endpoints in phase III trials designed for product approval. We believe that combining known nutraceuticals, such as LA, with approved prescription drugs (such as captopril) to magnify clinical benefits offer a significant development advantage and expedites the regulatory process for novel drug discovery.

In terms of the advantage of combination therapy, our results show that captopril significantly potentiated the neuroprotective effects of LA. Since captopril did not affect infarct volume or cerebral blood flow alone, it may not have facilitated access of LA to the brain. Therefore, the exact mechanism of this synergistic interaction requires further investigation.

In conclusion, our results support a role for the combination of captopril and LA to provide potential neuroprotection, and that this strategy of combination therapy for novel drug discovery should be further exploited.

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Clinical Study

Hypertension Control and Cardiometabolic Risk: A Regional Perspective

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Background. We investigated the association between blood pressure control and common cardiometabolic risk factors from a global and regional perspective. *Methods*. In the present analysis of a large cross-sectional i-SEARCH study, 17.092 outpatients receiving antihypertensive treatment were included in 26 countries. According to clinical guidelines for the management of arterial hypertension, patients were classified based on the level of seated systolic/diastolic blood pressure (SBP/DBP). Uncontrolled hypertension was defined as SBP/DBP ≥ 140/90 mmHg for non-diabetics, and ≥ 130/80 mmHg for diabetics. *Results*. Overall, mean age was 63.1 years, 52.8% were male, and mean BMI was 28.9 kg/m^2. Mean SBP/DBP was 148.9/87.0 mmHg, and 76.3% of patients had uncontrolled hypertension. Diabetes was present in 29.1% with mean HbA1c of 6.8%. Mean LDL-cholesterol was 3.2 mmol/L, HDL-cholesterol 1.3 mmol/L, and triglycerides 1.8 mmol/L; 49.0% had hyperlipidemia. Patients with uncontrolled hypertension had a higher BMI (29.4 versus 28.6 kg/m^2), LDL-cholesterol (3.4 versus 3.0 mmol/L), triglycerides (1.9 versus 1.7 mmol/L), and HbA1c (6.8 versus 6.7%) than those with controlled blood pressure ($P < 0.0001$ for all parameters). *Conclusions*. Among outpatients treated for arterial hypertension, three quarters had uncontrolled blood pressure. Elevated SBP/DBP and uncontrolled hypertension were associated with increasing BMI, LDL-cholesterol, triglycerides, and HbA1c, both globally and regionally.

1. Introduction

Arterial hypertension represents a major cause of cardiovascular morbidity and mortality, and affects approximately 1 billion individuals worldwide [1, 2]. Despite the availability of efficient nonpharmacological and pharmacological therapies, blood pressure control rates are largely unsatisfactory, mostly due to underdiagnosis and undertreatment [3]. Furthermore, arterial hypertension is frequently clustered with other metabolic disorders, such as an elevated body mass index (BMI), waist circumference (WC), fasting glucose, triglycerides (TG), and HDL-cholesterol—all of which are associated with adverse cardiovascular outcomes [4–7]. Therefore, international guidelines mandate not only an assessment of the global cardiovascular risk, but also a risk-based approach to antihypertensive therapy [8]. Apart from the impact of the association of an elevated blood pressure with metabolic disorders on patient's cardiovascular risk, there are also implications from a therapeutic perspective. Recent data have shown independent antihypertensive effects of statins in patients with hypertension and hypercholesterolemia, and an association of blood pressure lowering with a decrease in the antioxidative activity of HDL-cholesterol [9, 10]. These data illustrate not only a potential cross-talk between

different biochemical pathways, involved in the pathogenesis of atherosclerotic disease, but also the ability of pharmacological treatments to act on several risk factors at the same time. Especially in light of the low blood pressure control rates worldwide, it appears to be important to have a deeper understanding of the association of blood pressure with relevant metabolic risk factors and cardiovascular risk markers. The present analysis aims to investigate the association of blood pressure control with several metabolic risk factors/cardiovascular risk indicators, and to gain insights into regional/ethnical differences of these associations from a large international survey, conducted in more than 20.000 patients with arterial hypertension.

2. Methods

A large cross-sectional International Survey Evaluating microAlbuminuria Routinely by Cardiologists in patients with Hypertension (i-SEARCH) study was conducted in 2005-2006 in cardiology outpatient clinics in 26 countries world-wide as described previously [11]. 21.794 patients, aged ≥18 years with currently treated or newly diagnosed arterial hypertension, were enrolled into the study. In all patients, urinary dipstick screening was performed and the prevalence of microalbuminuria (MAU) was determined. Furthermore, information on patient demographics, anthropometric measures, cardiovascular risk factors, metabolic parameters, comorbid conditions, and cardiovascular drug therapy was collected. The present analysis was performed in 17.092 patients receiving antihypertensive treatment. According to contemporary clinical guidelines for the management of arterial hypertension [8], patients were classified based on the level of seated systolic/diastolic blood pressure (SBP/DBP) measured at rest on day of study visit. For each level of SBP (<120, 120-139, 140-159, 160-179, ≥180 mmHg) and DBP (<90, 90-99, 100-109, ≥110 mmHg), the association with the following indicators of cardiometabolic risk was determined: BMI (kg/m^2), WC (cm), diabetes mellitus (%), HbA1c (%), LDL/HDL-cholesterol (mg/dL), triglycerides (mg/dL), and C-reactive protein (CRP, mg/dL). Furthermore, cardiometabolic risk was determined according to blood pressure control. Uncontrolled hypertension was defined as SBP/DBP ≥140/90 mmHg for nondiabetic and ≥130/80 mmHg for diabetic patients.

All analyses were performed both globally and separately for the following 5 geographical regions: Northern Europe (Belgium, Germany, Sweden, Switzerland), Southern Europe (Greece, Italy, Spain, Turkey), North America (Canada), Middle East (Kuwait, Lebanon, Qatar, Saudi Arabia, United Arab Emirates) and Asia (Hong Kong, Indonesia, Korea, Singapore, Taiwan, Thailand, Vietnam). The analysis population comprised patients with no missing data for SBP/DBP and the respective metabolic parameter. A linear model was used to estimate the least square means of BMI, WC, HbA1c, LDL-cholesterol, HDL-cholesterol, triglycerides, and CRP for each level of SBP/DBP and by region. The model was adjusted for age and gender (BMI, WC, and CRP); for age, gender, and antidiabetic treatment (HbA1c); and for age, gender, and the presence of diabetes (LDL- and HDL-cholesterol, triglycerides). A logistic regression analysis was conducted to estimate the prevalence of diabetes for each level of SBP/DBP and region, adjusted for age and gender (predictive marginal probabilities). Continuous variables are depicted as adjusted means (least square means) ± standard deviations and categorical variables as percentages (95% confidence intervals).

3. Results

3.1. Cardiometabolic Risk Profile. Overall, mean patient age was 63.1 years out of which 52.8% were male. Mean SBP/DBP was 148.9/87.0 mmHg, and 76.3% of patients had uncontrolled blood pressure. Diabetes was present in 29.1% of patients with mean HbA1c of 6.8%. Mean LDL-cholesterol was 3.2 mmol/L, mean HDL-cholesterol 1.3 mmol/L, and mean triglycerides 1.8 mmol/L, and 49.0% of patients had hypercholesterolemia. MAU was present in 58.8% of patients, and mean CRP was 0.92 mg/dL. 38.8% of patients were present or past smokers, and 28.6% had a family history of a myocardial infarction. For concomitant cardiovascular disease and regional distribution of individual parameters, see Table 1.

3.2. Blood Pressure and BMI/WC. Globally, the mean BMI was higher in patients with SBP ≥180 versus <120 mmHg (29.5 versus 28.2 kg/m^2), in patients with DBP ≥110 versus <90 mmHg (30.3 versus 28.5 kg/m^2), and in patients with uncontrolled versus controlled blood pressure (29.4 versus 28.6 kg/m^2) ($P < 0.0001$ for all parameters). Mean WC was higher in patients with SBP ≥180 versus <120 mmHg (101.2 versus 97.5 cm), in patients with DBP ≥110 versus <90 mmHg (103.2 versus 98.8 cm), and in patients with uncontrolled versus controlled blood pressure (100.7 versus 98.8 cm) ($P < 0.0001$ for all parameters). By comparing the association of BMI and WC across the regions, an increase in BMI with increasing SBP/DBP could be observed for Northern, Southern Europe and the Middle East region, whereas in North America and Asia, BMI decreased with increasing SBP, and increased with DBP ($P < 0.05$ for all comparisons). Only in Northern and Southern Europe, uncontrolled versus controlled blood pressure was associated with an increase in BMI ($P < 0.0001$). With increasing SBP/DBP an increase in WC could be observed for Northern Europe, Southern Europe, North America, and Middle East (in the latter only for DBP, $P < 0.0001$), whereas an inverse relationship between SBP/DBP and WC was observed for Asia ($P < 0.0001$). For details see Tables 2 and 3.

3.3. Blood Pressure and Diabetes/HbA1c. The prevalence of diabetes was 28.4% in patients with an SBP <120 mmHg and 32.6% in patients with an SBP ≥180 mmHg ($P < 0.0001$). Diabetes was present in 30.9% of patients with a DBP <90 mmHg and 28.1% of patients with a DBP ≥110 mmHg ($P < 0.0001$). There was no difference in the prevalence of diabetes in patients with uncontrolled versus controlled hypertension in the overall population (27.7% versus 30.4%; $P = 0.18$). Mean HbA1c increased from 6.7% in patients

Table 1: Patient characteristics.

	Total ($N = 17,092$)	Northern Europe ($N = 5,655$)	Southern Europe ($N = 6,655$)	North America ($N = 1,455$)	Middle East ($N = 570$)	Asia ($N = 2,757$)
Age	63.1	64.9	62.5	65.7	57.1	60.5
Gender (male, %)	52.8	53.0	52.9	56.3	61.0	48.5
BMI (kg/m^2)	28.9	29.7	29.2	30.2	29.8	25.9
Waist circumference (cm)	99.7	102.5	100.9	102.6	102.5	89.5
Systolic blood pressure (mmHg)	148.9	151.5	148.6	144.3	156.6	145.1
Diastolic blood pressure (mmHg)	87.0	87.7	87.7	81.4	92.0	85.6
Uncontrolled blood pressure (%)*	76.3	82.1	75.6	64.9	87.9	69.5
Diabetes mellitus (%)	29.1	33.9	27.4	30.9	33.8	21.7
HbA1c (%)	6.8	6.7	6.7	6.7	7.9	7.1
LDL cholesterol (mmol/L)	3.2	3.2	3.3	2.6	3.4	3.1
HDL cholesterol (mmol/L)	1.3	1.5	1.3	1.3	1.1	1.3
Triglycerides (mmol/L)	1.8	1.9	1.7	1.7	2.0	1.8
Hyperlipidemia (%)	49.0	53.0	43.3	64.4	56.1	46.1
Smoking (current/past; %)	38.8	36.4	41.8	55.7	44.9	28.5
Family history of MI (%)	28.6	22.0	29.6	40.0	25.5	36.3
Microalbuminuria (%)	58.6	54.3	59.6	53.8	71.6	64.7
CRP (mg/dL)	0.92	1.02	0.91	0.54	0.91	0.49
Coronary artery disease (%)	25.1	21.5	23.7	40.5	30.4	26.4
Congestive heart failure (%)	6.4	6.3	6.7	5.5	8.3	6.0
Atrial fibrillation (%)	9.3	9.5	11.1	11.7	4.7	4.0
Myocardial infarction (%)	31.6	24.4	34.1	41.7	27.9	37.1
Ischemic stroke (%)	5.1	24.7	5.5	5.6	4.4	14.6
Peripheral artery disease (%)	4.6	6.1	5.0	5.7	4.7	0.5
Betablockers (%)	48.7	59.7	40.2	44.8	52.5	48.1
Calcium Antagonists (%)	36.0	30.3	31.9	43.4	36.7	53.6
ACE-Inhibitors (%)	42.3	45.8	42.8	49.5	31.9	32.1
AT1-Rezeptorantagonists (%)	35.8	30.1	41.3	31.1	47.9	34.4
Diuretics (%)	9.9	10.9	10.5	8.0	10.7	7.4

* Uncontrolled blood pressure was defined as SBP/DBP ≥140/90 in non-diabetic and ≥130/80 in diabetic patients.

with an SBP of <120 mmHg to 7.0% in patients with an SBP of ≥180 mmHg ($P < 0.0001$), from 6.8% in patients with a DBP <90 mmHg to 6.9% in patients with a DBP ≥110 mmHg ($P < 0.0027$), and from 6.7% in patients with controlled to 6.8% in patients with uncontrolled blood pressure ($P < 0.0001$). A significant increase in HbA1c with SBP and DBP was observed in Northern and Southern Europe, but not in Northern America, Middle East, and Asia. For details, see Tables 4 and 5.

3.4. Blood Pressure and Lipids. The mean LDL-cholesterol was higher in patients with SBP ≥180 versus <120 mmHg (3.4 versus 2.9 mmol/L), in patients with DBP ≥110 versus <90 mmHg (3.5 versus 3.0 mmol/L), and in patients with uncontrolled versus controlled blood pressure (3.4 versus 3.0 mmoL) ($P < 0.0001$ for all parameters). Mean HDL-cholesterol was 1.3 mmol/L, and there was no association between HDL in patients with uncontrolled versus controlled hypertension ($P = 0.13$). Triglycerides increased from 1.5 mmol/L in patients with an SBP <120 mmHg to 1.9 mmol/L in patients with an SBP ≥180 mmHg, and from 1.7 mmol/L in patients with a DBP <90 mmHg to 1.9 mmol/L in patients with a DBP ≥110 mmHg ($P < 0.0001$ for both parameters). Triglycerides were also higher in patients with uncontrolled versus controlled blood pressure (1.9 versus 1.7 mmol/L, $P < 0.0001$). The regional comparison revealed an increase in LDL-cholesterol as well as triglycerides with increasing SBP and DBP for all 5 regions, whereas no association between HDL-cholesterol and blood pressure levels was observed. For details see Tables 6, 7, and 8.

3.5. Blood Pressure and CRP. The mean CRP was higher in patients with SBP ≥180 versus <120 mmHg (1.1 versus

Table 2: Blood pressure and BMI (kg/m^2; mean ± SE; adjusted for age, gender).

	Total ($N = 16,945$)	Northern Europe ($N = 5,621$)	Southern Europe ($N = 6583$)	North America ($N = 1,423$)	Midde East ($N = 567$)	Asia ($N = 2,751$)	P value
SBP (mmHg)							
<120	28.2 (0.249)	29.1 (0.487)	28.4 (0.453)	30.1 (0.601)	28.3 (1.467)	26.2 (0.474)	<0.0001
120–139	28.5 (0.086)	29.1 (0.168)	28.6 (0.132)	30.4 (0.253)	31.0 (0.647)	26.4 (0.187)	<0.0001
140–159	28.8 (0.066)	29.6 (0.108)	29.0 (0.102)	30.2 (0.222)	29.7 (0.370)	25.7 (0.158)	<0.0001
160–179	29.5 (0.105)	30.2 (0.169)	29.9 (0.165)	30.2 (0.403)	29.6 (0.474)	25.7 (0.287)	<0.0001
≥180	29.5 (0.163)	30.2 (0.249)	30.2 (0.264)	29.1 (0.763)	30.0 (0.629)	25.5 (0.445)	<0.0001
P value	<0.0001	<0.0001	<0.0001	<0.0001	0.0126	<0.0001	
DBP (mmHg)							
<90	28.5 (0.063)	29.3 (0.110)	28.6 (0.102)	29.9 (0.176)	29.7 (0.440)	26.0 (0.144)	<0.0001
90–99	29.2 (0.082)	30.1 (0.134)	29.4 (0.124)	30.5 (0.342)	29.5 (0.395)	25.7 (0.207)	<0.0001
100–109	29.5 (0.113)	30.0 (0.187)	30.2 (0.169)	31.5 (0.548)	30.4 (0.471)	25.9 (0.276)	<0.0001
≥110	30.3 (0.227)	30.8 (0.362)	31.0 (0.350)	31.9 (1.286)	30.6 (0.793)	26.3 (0.642)	<0.0001
P value	<0.0001	<0.0001	<0.0001	<0.0001	0.0157	<0.0001	
RR (mmHg)							
uncontrolled*	29.4 (0.066)	29.9 (0.085)	29.5 (0.082)	30.1 (0.190)	29.8 (0.259)	25.7 (0.132)	<0.0001
controlled**	28.6 (0.061)	28.9 (0.170)	28.4 (0.134)	30.3 (0.239)	30.6 (0.650)	26.2 (0.184)	<0.0001
P value	<0.0001	<0.0001	<0.0001	<0.0001	0.0080	<0.0001	

* SBP/DBP ≥140/90 in non-diabetic and ≥130/80 in diabetic patients, **<140/90 in non-diabetic and <130/80 in diabetic patients.

Table 3: Blood pressure and WC (cm ± SD, adjusted for age, gender).

	Total ($N = 16,808$)	Northern Europe ($N = 5,568$)	Southern Europe ($N = 6,505$)	North America ($N = 1,435$)	Middle East ($N = 553$)	Asia ($N = 2,747$)	P value
SBP (mmHg)							
<120	97.5 (0.557)	100.2 (1.028)	98.5 (0.948)	100.9 (1.254)	96.9 (3.078)	89.9 (0.994)	<0.0001
120–139	98.5 (0.218)	100.3 (0.400)	99.2 (0.314)	102.1 (0.600)	100.8 (1.536)	90.6 (0.445)	<0.0001
140–159	99.6 (0.171)	102.2 (0.268)	100.3 (0.255)	102.5 (0.548)	101.0 (0.923)	89.0 (0.392)	<0.0001
160–179	100.9 (0.244)	103.4 (0.373)	102.0 (0.364)	102.4 (0.880)	102.4 (1.070)	89.0 (0.634)	<0.0001
≥180	101.2 (0.414)	103.3 (0.603)	103.4 (0.642)	101.3 (1.816)	104.6 (1.528)	89.2 (1.067)	<0.0001
P value	<0.0001	<0.0001	<0.0001	<0.0001	0.1275	<0.0001	
DBP (mmHg)							
<90	98.8 (0.154)	101.1 (0.256)	99.5 (0.237)	101.7 (0.405)	100.1 (1.024)	89.9 (0.334)	<0.0001
90–99	100.1 (0.198)	103.1 (0.309)	100.5 (0.287)	102.5 (0.782)	100.4 (0.924)	89.0 (0.476)	<0.0001
100–109	101.3 (0.305)	102.8 (0.485)	103.4 (0.441)	105.1 (1.417)	105.6 (1.230)	89.5 (0.716)	<0.0001
≥110	103.2 (0.607)	105.1 (0.916)	104.1 (0.891)	107.4 (3.250)	105.0 (2.041)	89.7 (1.611)	<0.0001
P value	<0.0001	<0.0001	<0.0001	<0.0001	0.0012	<0.0001	
RR (mmHg)							
uncontrolled*	100.7 (0.167)	102.7 (0.201)	101.2 (0.195)	102.2 (0.445)	102.1 (0.619)	89.2 (0.311)	<0.0001
controlled**	98.8 (0.149)	100.1 (0.400)	99.0 (0.315)	102.1 (0.559)	100.0 (1.523)	90.2 (0.430)	<0.0001
P value	<0.0001	<0.0001	<0.0001	<0.0001	0.0882	<0.0001	

* SBP/DBP ≥140/90 in non-diabetic and ≥130/80 in diabetic patients, **<140/90 in non-diabetic and <130/80 in diabetic patients.

0.7 mmol/L), in patients with DBP ≥110 versus <90 mmHg (1.0 versus 0.8 mmol/L), and in patients with uncontrolled versus controlled blood pressure (1.0 versus 0.8 mmol/L) ($P < 0.0001$ for all parameters). An increase in CRP with SBP and DBP was observed in Northern Europe and Northern America only. For details see Table 9.

4. Discussion

In the present analysis of a large international study of patients treated for arterial hypertension, both an elevated SBP and DBP, and uncontrolled hypertension were associated with increasing BMI, WC, LDL-cholesterol, triglycerides,

Table 4: Blood pressure and diabetes (% (95% CI), adjusted for age, and gender).

	Total ($N = 16,325$)	Northern Europe ($N = 5,415$)	Southern Europe ($N = 6,238$)	North America ($N = 1,406$)	Middle East ($N = 519$)	Asia ($N = 2,747$)	P value
SBP (mmHg)							
<120	28.4 (24.78; 31.94)	28.3 (21.79; 35.96)	33.2 (26.56; 40.53)	36.5 (27.70; 46.41)	32.3 (14.11; 58.00)	21.4 (15.72; 28.48)	<0.0001
120–139	27.3 (25.86; 28.65)	33.7 (30.86; 36.77)	25.7 (23.65; 27.94)	33.6 (29.39; 38.16)	33.9 (23.15; 46.63)	22.7 (19.92; 25.83)	<0.0001
140–159	28.8 (27.69; 29.83)	33.6 (31.77; 35.57)	29.8 (28.12; 31.63)	28.8 (25.21; 32.59)	40.0 (33.26; 47.09)	22.5 (20.07; 25.07)	<0.0001
160–179	30.4 (28.98; 31.89)	37.4 (34.96; 33.96)	31.4 (29.16; 33.84)	32.7 (27.24; 38.59)	32.1 (25.62; 39.44)	21.0 (17.62; 24.84)	<0.0001
≥180	32.6 (30.12; 35.00)	34.8 (31.08; 38.77)	36.5 (32.50; 40.66)	16.4 (9.30; 27.44)	49.5 (38.68; 60.35)	26.8 (20.84; 33.64)	<0.0001
P value	<0.0001	0.1571	0.0009	0.0491	0.1353	0.6222	
DBP (mmHg)							
<90	30.9 (29.95; 31.95)	37.6 (35.77; 39.53)	29.6 (27.97; 31.25)	34.3 (31.51; 37.31)	38.8 (31.44; 46.82)	25.8 (23.58; 28.08)	<0.0001
90–99	27.9 (26.76; 29.14)	34.2 (32.11; 36.36)	29.2 (27.32; 31.08)	25.3 (20.77; 30.55)	34.4 (28.23; 41.10)	21.2 (18.53; 24.24)	<0.0001
100–109	25.5 (23.70; 27.26)	26.9 (23.92; 30.13)	31.0 (28.16; 34.07)	22.2 (14.84; 31.73)	38.7 (30.21; 47.89)	13.6 (10.43; 17.64)	<0.0001
≥110	28.1 (24.68; 31.55)	31.3 (26.06; 37.12)	33.3 (28.08; 38.99)	18.4 (7.02; 40.17)	42.7 (29.81; 56.68)	16.7 (9.95; 26.69)	<0.0001
P value	<0.0001	<0.0001	0.3635	0.0002	0.8877	<0.0001	
RR (mmHg)							
uncontrolled*	27.7 (26.73; 28.71)	34.7 (33.30; 36.06)	30.8 (29.48; 32.07)	28.6 (25.81; 31.56)	38.0 (33.68; 42.54)	22.4 (20.55; 24.34)	<0.0001
controlled**	30.4 (29.42; 31.34)	34.3 (31.37; 37.33)	27.1 (27.98; 29.40)	35.4 (31.36; 39.70)	37.1 (25.98; 49.82)	22.9 (20.18; 25.96)	<0.0001
P value	0.1783	0.8316	0.0497	0.0106	0.6824	0.6820	

* SBP/DBP ≥ 140/90 in non-diabetic and ≥ 130/80 in diabetic patients, ** <140/90 in non-diabetic and <130/80 in diabetic patients.

Table 5: Blood pressure and HbA1c (%± SD, adjusted for age, gender, and diabetes treatment).

	Total ($N = 3,582$)	Northern Europe ($N = 1,640$)	Southern Europe ($N = 1,058$)	North America ($N = 358$)	Middle East ($N = 149$)	Asia ($N = 377$)	P value
SBP (mmHg)							
<120	6.7 (0.115)	6.2 (0.202)	6.4 (0.199)	6.6 (0.214)	6.4 (0.725)	6.8 (0.257)	0.4127
120–139	6.6 (0.047)	6.4 (0.072)	6.3 (0.081)	6.4 (0.113)	7.3 (0.348)	6.7 (0.114)	0.0073
140–159	6.8 (0.037)	6.5 (0.049)	6.5 (0.062)	6.6 (0.111)	7.3 (0.168)	6.8 (0.102)	<0.0001
160–179	6.9 (0.052)	6.6 (0.063)	6.7 (0.084)	6.6 (0.167)	7.6 (0.187)	6.9 (0.179)	<0.0001
≥180	7.0 (0.084)	6.7 (0.102)	6.9 (0.135)	6.4 (0.402)	8.0 (0.243)	6.9 (0.292)	<0.0001
P value	<0.0001	0.0003	0.0012	0.4751	0.6808	0.7181	
DBP (mmHg)							
<90	6.8 (0.031)	6.5 (0.043)	6.4 (0.055)	6.5 (0.074)	7.2 (0.172)	6.8 (0.080)	<0.0001
90–99	6.8 (0.045)	6.5 (0.056)	6.5 (0.069)	6.6 (0.175)	7.6 (0.180)	6.7 (0.128)	<0.0001
100–109	6.9 (0.076)	6.6 (0.096)	6.8 (0.111)	6.4 (0.312)	8.0 (0.226)	6.4 (0.243)	<0.0001
≥110	6.9 (0.172)	6.7 (0.211)	6.6 (0.288)	7.7 (0.934)	7.2 (0.489)	7.2 (0.921)	0.6603
P value	0.0027	0.1605	0.0136	0.3190	0.3332	0.4885	
RR (mmHg)							
uncontrolled*	6.8 (0.039)	6.5 (0.035)	6.6 (0.046)	6.6 (0.088)	7.6 (0.111)	6.8 (0.082)	<0.0001
controlled**	6.7 (0.030)	6.3 (0.073)	6.3 (0.079)	6.5 (0.104)	7.1 (0.316)	6.7 (0.110)	0.0075
P value	<0.0001	0.0004	0.0091	0.2444	0.3367	0.3114	

* SBP/DBP ≥ 140/90 in non-diabetic and ≥ 130/80 in diabetic patients, ** <140/90 in non-diabetic and <130/80 in diabetic patients.

Table 6: Blood pressure and LDL-Cholesterol (mmol/L ± SD, adjusted for age, gender, and diabetes).

	Total ($N = 11{,}529$)	Northern Europe ($N = 3{,}723$)	Southern Europe ($N = 4{,}679$)	North America ($N = 904$)	Middle East ($N = 485$)	Asia ($N = 1{,}738$)	P value
SBP (mmHg)							
<120	2.9 (0.044)	3.0 (0.088)	3.0 (0.076)	2.5 (0.109)	2.8 (0.231)	2.8 (0.093)	0.0003
120–139	3.0 (0.048)	3.1 (0.035)	3.0 (0.028)	2.4 (0.054)	2.9 (0.121)	2.9 (0.042)	<0.0001
140–159	3.2 (0.015)	3.2 (0.025)	3.2 (0.024)	2.6 (0.053)	3.4 (0.075)	3.0 (0.038)	<0.0001
160–179	3.3 (0.020)	3.3 (0.033)	3.3 (0.032)	2.7 (0.081)	3.5 (0.080)	3.3 (0.057)	<0.0001
≥180	3.4 (0.034)	3.4 (0.055)	3.5 (0.058)	3.0 (0.153)	3.9 (0.131)	3.5 (0.096)	<0.0001
P value	<0.0001	<0.0001	<0.0001	<0.0001	0.0005	<0.0001	
DBP (mmHg)							
<90	3.0 (0.013)	3.1 (0.022)	3.1 (0.021)	2.4 (0.037)	3.0 (0.081)	2.9 (0.031)	<0.0001
90–99	3.3 (0.016)	3.3 (0.028)	3.3 (0.027)	2.8 (0.074)	3.4 (0.073)	3.1 (0.045)	<0.0001
100–109	3.4 (0.026)	3.4 (0.047)	3.4 (0.041)	2.9 (0.141)	3.9 (0.098)	3.4 (0.069)	<0.0001
≥110	3.5 (0.049)	3.5 (0.086)	3.6 (0.080)	3.9 (0.311)	3.5 (0.169)	3.6 (0.151)	0.5736
P value	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	
RR (mmHg)							
uncontrolled*	3.4 (0.014)	3.3 (0.019)	3.3 (0.018)	2.7 (0.042)	3.5 (0.050)	3.1 (0.029)	<0.0001
controlled**	3.0 (0.012)	3.0 (0.034)	3.0 (0.027)	2.4 (0.050)	2.9 (0.115)	2.9 (0.040)	<0.0001
P value	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	

* SBP/DBP ≥140/90 in non-diabetic and ≥130/80 in diabetic patients, ** <140/90 in non-diabetic and <130/80 in diabetic patients.

Table 7: Blood pressure and HDL-Cholesterol (mmol/L ± SD, adjusted for age, gender, and diabetes).

	Total ($N = 11{,}849$)	Northern Europe ($N = 3{,}787$)	Southern Europe ($N = 4{,}924$)	North America ($N = 909$)	Middle East ($N = 477$)	Asia ($N = 1{,}752$)	P value
SBP (mmHg)							
<120	1.3 (0.025)	1.4 (0.051)	1.2 (0.044)	1.4 (0.065)	1.1 (0.135)	1.3 (0.053)	0.0498
120–139	1.3 (0.008)	1.4 (0.015)	1.3 (0.012)	1.3 (0.024)	1.1 (0.054)	1.3 (0.018)	<0.0001
140–159	1.3 (0.007)	1.5 (0.011)	1.3 (0.010)	1.3 (0.024)	1.2 (0.034)	1.3 (0.017)	<0.0001
160–179	1.3 (0.009)	1.4 (0.014)	1.3 (0.014)	1.3 (0.035)	1.1 (0.035)	1.3 (0.025)	<0.0001
≥180	1.3 (0.016)	1.5 (0.025)	1.2 (0.026)	1.3 (0.070)	1.0 (0.059)	1.3 (0.045)	<0.0001
P value	0.3309	0.0558	0.1317	0.3366	0.6608	0.7711	
DBP (mmHg)							
<90	1.3 (0.005)	1.4 (0.010)	1.3 (0.009)	1.3 (0.017)	1.2 (0.038)	1.3 (0.014)	<0.0001
90–99	1.3 (0.007)	1.4 (0.012)	1.3 (0.011)	1.3 (0.033)	1.2 (0.033)	1.3 (0.020)	<0.0001
100–109	1.3 (0.011)	1.4 (0.016)	1.2 (0.014)	1.3 (0.047)	1.1 (0.034)	1.2 (0.024)	<0.0001
≥110	1.3 (0.033)	1.6 (0.057)	1.2 (0.052)	1.4 (0.208)	1.0 (0.114)	1.2 (0.102)	<0.0001
P value	0.0222	0.0013	0.0904	0.7721	0.0188	0.6265	
RR (mmHg)							
uncontrolled*	1.3 (0.006)	1.5 (0.008)	1.3 (0.008)	1.3 (0.019)	1.1 (0.022)	1.3 (0.013)	<0.0001
controlled**	1.3 (0.006)	1.4 (0.016)	1.3 (0.013)	1.3 (0.023)	1.1 (0.054)	1.3 (0.019)	<0.0001
P value	0.1340	0.0916	0.1632	0.9361	0.8361	0.8030	

* SBP/DBP ≥140/90 in non-diabetic and ≥130/80 in diabetic patients, ** <140/90 in non-diabetic and <130/80 in diabetic patients.

HbA1c, and CRP, whereas there was no association between HDL-cholesterol and blood pressure levels. Furthermore, the presence of diabetes was associated with an elevated SBP only. The observed associations between blood pressure levels and metabolic parameters were consistent across all 5 geographic regions, even though some associations were not significant, especially in regions with a low sample size for individual parameters, such as the Middle East, Asia, and—partly—North America. Based on the data presented herein, it appears difficult to draw any firm conclusions on stronger and weaker associations of individual cardiometabolic parameters with blood pressure for some regions as compared to the overall population or the European region. Furthermore, regional samples cannot be necessarily considered as

Table 8: Blood pressure and triglycerides (mmol/L ± SD, adjusted for age, gender, and diabetes).

	Total ($N = 12,601$)	Northern Europe ($N = 4,049$)	Southern Europe ($N = 5,095$)	North America ($N = 910$)	Middle East ($N = 504$)	Asia ($N = 2043$)	P value
SBP (mmHg)							
<120	1.5 (0.037)	1.6 (0.078)	1.6 (0.068)	1.5 (0.102)	1.3 (0.206)	1.7 (0.076)	0.4212
120–139	1.7 (0.017)	1.8 (0.033)	1.6 (0.027)	1.8 (0.054)	1.7 (0.120)	1.8 (0.038)	<0.0001
140–159	1.8 (0.014)	1.9 (0.025)	1.7 (0.023)	1.7 (0.054)	2.1 (0.075)	1.9 (0.036)	<0.0001
160–179	1.9 (0.020)	2.0 (0.033)	1.8 (0.033)	1.7 (0.085)	2.2 (0.082)	2.0 (0.055)	<0.0001
≥180	1.9 (0.034)	2.0 (0.055)	1.8 (0.057)	1.9 (0.157)	2.3 (0.134)	2.2 (0.097)	0.0054
P value	<0.0001	<0.0001	<0.0001	0.1658	0.0039	0.0008	
DBP (mmHg)							
<90	1.7 (0.012)	1.8 (0.021)	1.6 (0.020)	1.7 (0.037)	1.7 (0.078)	1.8 (0.028)	<0.0001
90–99	1.9 (0.016)	2.0 (0.028)	1.8 (0.026)	1.9 (0.074)	2.2 (0.073)	1.9 (0.042)	<0.0001
100–109	1.9 (0.027)	2.0 (0.050)	1.8 (0.044)	2.0 (0.154)	2.3 (0.108)	2.1 (0.073)	<0.0001
≥110	1.9 (0.053)	1.8 (0.089)	1.9 (0.084)	1.9 (0.342)	2.4 (0.180)	2.3 (0.161)	0.0073
P value	<0.0001	<0.0001	<0.0001	0.0469	0.0012	<0.0001	
RR (mmHg)							
uncontrolled*	1.9 (0.014)	2.0 (0.018)	1.7 (0.017)	1.8 (0.043)	2.1 (0.050)	1.9 (0.028)	<0.0001
controlled**	1.7 (0.011)	1.7 (0.033)	1.6 (0.027)	1.7 (0.050)	1.7 (0.115)	1.8 (0.037)	0.0024
P value	<0.0001	<0.0001	<0.0001	0.4255	0.0025	0.0081	

* SBP/DBP ≥140/90 in non-diabetic and ≥130/80 in diabetic patients, **<140/90 in non-diabetic and <130/80 in diabetic patients.

Table 9: Blood pressure and CRP (mg/dL ± SD, adjusted for age, and gender).

	Total ($N = 2,493$)	Northern Europe ($N = 1,207$)	Southern Europe ($N = 943$)	North America ($N = 109$)	Middle East ($N = 112$)	Asia ($N = 122$)	P value
SBP (mmHg)							
<120	0.7 (0.090)	0.8 (0.131)	0.8 (0.160)	0.6 (0.284)	0.6 (0.576)	0.1 (0.304)	0.3399
120–139	0.7 (0.037)	0.7 (0.062)	0.8 (0.053)	0.4 (0.154)	0.4 (0.286)	0.4 (0.139)	0.0141
140–159	0.9 (0.030)	1.0 (0.043)	0.9 (0.050)	0.5 (0.146)	1.1 (0.145)	0.5 (0.133)	0.0009
160–179	1.1 (0.041)	1.1 (0.055)	1.1 (0.070)	0.5 (0.250)	0.9 (0.168)	0.6 (0.219)	0.0196
≥180	1.1 (0.066)	1.3 (0.087)	0.8 (0.117)	1.1 (0.301)	0.8 (0.230)	0.3 (0.500)	0.0097
P value	<0.0001	<0.0001	0.0520	0.0356	0.4130	0.3783	
DBP (mmHg)							
<90	0.8 (0.027)	0.8 (0.038)	0.8 (0.043)	0.4 (0.112)	0.9 (0.164)	0.4 (0.114)	<0.0001
90–99	1.0 (0.035)	1.1 (0.049)	0.9 (0.058)	0.6 (0.187)	1.1 (0.150)	0.6 (0.155)	0.0022
100–109	1.1 (0.050)	1.3 (0.072)	1.0 (0.078)	1.0 (0.293)	0.8 (0.193)	0.4 (0.253)	0.0013
≥110	1.0 (0.091)	1.2 (0.130)	0.8 (0.158)	0.6 (0.424)	0.9 (0.338)	0.9 (0.456)	0.3130
P value	<0.0001	<0.0001	0.4665	0.0056	0.5488	0.1511	
RR (mmHg)							
uncontrolled*	1.0 (0.028)	1.1 (0.031)	0.9 (0.037)	0.6 (0.114)	0.9 (0.096)	0.5 (0.106)	<0.0001
controlled**	0.8 (0.026)	0.7 (0.061)	0.8 (0.054)	0.4 (0.143)	0.6 (0.348)	0.4 (0.140)	0.0057
P value	<0.0001	<0.0001	0.1596	0.2786	0.4071	0.1582	

* SBP/DBP ≥140/90 in non-diabetic and ≥130/80 in diabetic patients, **<140/90 in non-diabetic and <130/80 in diabetic patients.

ethnically/culturally homogenous and any regional analysis might be confounded by differences in the genetics or dietary habits of study participants.

Overall, our data are consistent with findings from other investigations, where the prevalence of additional cardiometabolic risk factors among hypertensive patients was as high as 82% and was associated with poor blood control in the United States [12]. Of interest, data from the large European Global Cardiometabolic Risk Profile in Patients with Hypertension Disease (GOOD) survey in 3280 outpatients treated

for or newly diagnosed with hypertension indicate that the prevalence of cardiometabolic risk factors is higher in Central Europe (Hungary) and Atlantic European Mainland (Belgium, Germany, and the Netherlands) compared with the Northwest (Norway, Sweden, and the United Kingdom) and Mediterranean (Italy, Portugal, Slovenia, Spain, and Turkey) regions [13]. Similarly to the GOOD Survey, only one quarter of patients had controlled blood pressure in our study [14].

Our results confirm the significant association between systemic hypertension and other cardiometabolic risk factors, including visceral obesity, diabetes, and hyperlipidemia. Obviously, the vast majority of patients with arterial hypertension are at multiple risk of cardiovascular disease. Therefore, our data emphasize the statement of current joint guidelines of the European Society of Hypertension and European Society of Cardiology concerning an intensified diagnostic and therapeutic measures in patients with an elevated SBP and DBP [8].

Reasons for the observed association between increasing blood pressure and the presence of cardiometabolic risk factors remain to be determined. It is a subject of an ongoing debate, whether patients with an elevated SBP and DBP simply more frequently have an unfavorable cardiometabolic risk profile with poorly treated cardiovascular parameters or whether there is a causal relationship between a high systemic blood pressure and the deterioration of multiple cardiometabolic markers. The intra-abdominal obesity and recently discovered endogenous gland activity of adipose tissue producing various hormones and cytokines, such as angiotensinogen, insulin, resistin, lipoprotein lipase, leptin, lactate, plasminogen activator inhibitor, adipsin, and interleukin, seem to play a central role in the development of disadvantageous cardiometabolic profile and may represent the causal link between arterial hypertension, atherogenic dyslipidemia, diabetes, thrombosis, and inflammation [15]. This hypothesis is further supported by the mandatory presence of abdominal obesity in the definition of potentially detrimental metabolic syndrome [16, 17]. Other possible reasons include organ damage as a consequence of hypertension which may lead to potentiation of other cardiometabolic risk factors. In addition, visceral obesity, hypertriglyceridemia, and low HDL-cholesterol levels were associated with resistance to antihypertensive therapy in the GOOD survey [18].

Proinflammatory mechanisms are thought to be a hallmark of the cardiovascular disease process, notably in disease states such as hypertension. These findings are often exacerbated by the increasing prevalence of obesity worldwide. Obesity is often accompanied by high plasma levels of nonesterified fatty acids that cause insulin resistance in skeletal muscle and overload the liver with lipids, producing fatty liver and atherogenic dyslipidemia [19]. Fat accumulation in the liver may also stimulate hepatic cytokine production and lead to higher levels of proinflammatory markers. Taken together, the abnormal proinflammatory state leads to a worsening of metabolic control, abnormal vascular function, and eventually cardiovascular and renal diseases [20].

Lifestyle changes, including an increased prevalence of obesity and the metabolic syndrome contribute to the incidence of hypertension [21, 22]. At the environmental level, barriers to healthy lifestyles include lack of access to exercise facilities at work or in the community, lack of bicycle and walking paths, and high traffic and crime in urban settings which prevent access to safe walking areas. Seasonal variation, market availability, and affordability of fresh fruits and vegetables in small urban stores are issues, thus multilevel approaches incorporating both individual and policy level changes are advocated. These variations are magnified within certain ethnic and geographical situations. Nevertheless, despite the uncertainty about the causal relationship between an elevated SBP and DBP and the presence of cardiometabolic risk factors, the association appeared to be significant and consistent across various continents and ethnicities in our study. The benefits of a multidimensional approach influencing antioxidative, antiinflammatory, or antithrombotic pathway on cardiovascular outcomes were repeatedly demonstrated in the context of hypertension management [23]. Consequently, a systematic assessment of the global cardiovascular risk and a risk-based approach to antihypertensive therapy shall be mandated in all patients with arterial hypertension.

4.1. Strengths and Limitations of Our Study. The strengths of our study include the prospective enrollment of a large sample of treated hypertensive patients and the collection of detailed information on systemic blood pressure and cardiometabolic parameters.

One study limitation is the fact that the numbers of enrolled patients differ substantially between the 5 regions. Therefore, the regional comparisons and *P*-values should be interpreted with caution. Neither a uniform methodology nor a central laboratory was used for measurements of blood pressure and cardiometabolic parameters. Thus, differences in region-specific techniques and measurements may have influenced the comparability of results. Another study limitation is the fact that the present analysis of lipid measurements was not adjusted for statin use. However, the analysis was adjusted for age and, therefore, for age-dependent rise of LDL-cholesterol and triglycerides, and indirectly also for statin use because the elderly more often receive statin treatment. Finally, our study was not designed to explore reasons for the observed association between an elevated blood pressure and cardiometabolic risk factors.

5. Conclusions

An elevated SBP and DBP, but also uncontrolled hypertension, are associated with an increase in cardiometabolic risk, independently of the geographic region. These findings not only highlight the importance of a thorough risk-stratification of patients with arterial hypertension, but also the necessity of treating concomitant cardiometabolic risk factors in order to decrease the overall cardiovascular risk of patients with arterial hypertension.

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Review Article

Lifestyle Risk Factors and Cardiovascular Disease in Cubans and Cuban Americans

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Cardiovascular disease is the leading cause of mortality in Cuba. Lifestyle risk factors for coronary heart disease (CHD) in Cubans have not been compared to risk factors in Cuban Americans. Articles spanning the last 20 years were reviewed. The data on Cuban Americans are largely based on the Hispanic Health and Nutrition Examination Survey (HHANES), 1982–1984, while more recent data on epidemiological trends in Cuba are available. The prevalence of obesity and type 2 diabetes mellitus remains greater in Cuban Americans than in Cubans. However, dietary preferences, low physical activity, and tobacco use are contributing to the rising rates of obesity, type 2 diabetes mellitus, and CHD in Cuba, putting Cubans at increased cardiovascular risk. Comprehensive national strategies for cardiovascular prevention that address these modifiable lifestyle risk factors are necessary to address the increasing threat to public health in Cuba.

1. Introduction

According to the World Health Organization, cardiovascular disease (CVD) is the leading cause of death worldwide. Sixty percent of the global burden of coronary heart disease (CHD) occurs in developing countries [1]. While access to health care remains a barrier to prevention and treatment of CHD in many developing countries, Cuba is different. Cuba has had a system of socialized medicine and universal access to health care for over 40 years. In creating strategies to address the rising tide of CHD in Latin America and the Caribbean, it is useful to examine the Cuban experience to inform which approaches may be the most useful in resource-poor settings. While improving medical treatment for illnesses such as hypertension, dyslipidemia, and CHD will help to lower CHD mortality, prevention is a key component of turning the tide of the rising epidemic. Comprehensive CHD prevention includes examining the contribution of lifestyle risk factors to cardiovascular disease and creating strategies to modify diet, physical activity, and tobacco use in the population.

Beyond comparing Cuba to other developing countries, it is interesting to compare Cubans living in Cuba to those living in the United States. Several waves of immigration to the United States from Cuban have occurred since the Cuban Revolution in 1959. Although the majority of Cuban Americans tend to be white Cubans of higher socioeconomic background compared to the Cubans who remain in Cuba, comparing lifestyle factors such as diet, physical activity, and tobacco use provides an interesting perspective on the effect of immigration to the United States on cardiovascular disease risk. While it is assumed that acculturation to the American lifestyle conveys an increased risk for cardiovascular disease, one might posit that many Cubans have unhealthy lifestyle behaviors that are further amplified upon moving to the United States and improving their economic status. While

the published data on CHD and CHD risk factors in Cubans and Cuban Americans are limited, the available literature will be reviewed in this paper.

2. Methods

Original articles, review articles, and reports that examine CHD and CHD risk factors in Cubans and Cuban Americans were searched and reviewed. Using PubMed, we searched the following terms: Cuba, Cubans, coronary heart disease, cardiovascular disease, hypertension, diabetes, tobacco, metabolic syndrome, obesity, diet, and physical inactivity. The bibliography of review articles were also searched for sources not found in PubMed. References suggested by colleagues in Cuba were also included in this paper. These references include articles published in Cuban journals and reports from the Cuban Ministry of Public Health which were found on their website (www.infomed.sld.cu). A total of 38 references were retrieved and included in this paper.

3. Diet

The fall of the Soviet Union in 1989 precipitated an economic crisis in the 1990's known as the Special Period. During the Special Period, patterns of nutrition and physical activity changed as food and energy resources became scarce. Vitamin and mineral deficiencies became more common and contributed to increased rates of anemia and optic neuropathy [2–4]. According to surveys conducted in Havana and Cienfuegos from 1980 to 2005, caloric intake decreased from 2899 kcal in 1988 to 1863 kcal in 1993. This change coincided with a rapid decline in type 2 diabetes mellitus and CHD mortality in the time period between 1997 and 2002, although morbidity was not impacted and continued to rise during this period [2, 3, 5].

Since the modest economic recovery, the increasing availability of inexpensive fast-food vendors in addition to the inconsistent accessibility and affordability of fresh fruits and vegetables is affecting the quality of the Cuban diet. However, in addition to food availability, food preferences should also be considered. In a recent survey of Cuban food preferences, red meat, ham, white bread, soft drinks, and processed food were identified as preferred food items. Ham and red meat were considered healthy by 85% and 90% of participants. This survey also reproduced earlier findings that the fruit and vegetable intake of most Cubans was inadequate [6, 7]. While cost was identified as a major factor in dietary choices, this survey demonstrates that if the barrier of cost was removed, food preferences would remain a barrier to healthy eating in Cuba.

Data on Cuban American dietary preferences are less available. While there are no recent surveys of Cuban American dietary patterns, the 1982–84 HHANES survey describes dietary trends at that time. Seventy-three percent of Cuban American men and 75.7% of Cuban American women reported high "junk food" consumption [8]. While these data are based on self-reporting, they suggest that food preferences in Cuban Americans may not be that different than in Cubans.

4. Physical Inactivity

Physical inactivity is associated with a 19% increased risk of CHD when compared to individuals who regularly engage in vigorous physical exercise [9]. Physical inactivity in the elderly has been the subject of several studies in Havana. In a 2008 study of elderly patients in a polyclinic in Havana, physical inactivity was the most prevalent risk factor present in 74% of the sample [10]. Eighty-two percent of elderly women in another Havana study in 2011 reported low physical activity, a much greater percentage when compared to elderly women in Bridgetown, Barbados [11]. Another study of 1,905 elderly people in Havana found that decreased physical activity was a significant risk factor for overweight [12]. Some sources have estimated that presently 53–69% of all Cubans are sedentary [13]. Not only are adults inactive, but children are also becoming increasingly inactive with television and video games cited as the primary causes [14]. In a 2002 study of preschool children, only boys in rural areas and small towns met the minimum recommended daily physical activity as recommended by the Center for Disease Control (CDC) [15].

Physical inactivity is also common among Cuban Americans. The Miami Community Health Study examined CAD risk factors in African Americans, Cuban Americans, and white Americans living in Dade County, Florida, from 1991–1995. Self-reported physical activity varied according to sex. Forty-seven percent of Cuban American men reported physical activity less than 1000 kcal a week, which was greater than that reported in African American and White American men. However, Cuban American women reported less physical inactivity than African American and white American women with 51.6% undergoing less than 1000 kcal of physical activity per week [16].

5. Obesity

The global trends of poor dietary habits and low physical activity have resulted in the rising prevalence of obesity worldwide. Similar to the rest of the world, obesity has become a public health concern in Cuba. A 2001 national survey of a representative sample found that 29.7% of men and 31.5% of women were overweight and 7.9% of men and 15.4% of women were obese [17]. Other studies have suggested that 24.6% of women and 14.9% of men are obese [14]. These data suggest that obesity more greatly affects Cuban women than Cuban men. In examining obesity in rural Cuba, a 2008 study in the Isla de la Juventud province found that 31.3% of the adult population was estimated to be overweight and 13.4% was obese [18]. These data are similar to other studies done in rural Cuba, suggesting that while obesity is less prevalent in rural Cuba, it remains a public health concern throughout the island.

Obesity in elderly Cubans has been compared to that in elderly populations in Latin America and the Caribbean. A 2003 study of the elderly population in the rural Cuban province of Pinar del Rio Cubans showed that they had lower body mass index (BMI), lower measurement of skin folds, lower waist circumference, and higher physical activity

levels compared to elderly people in rural Chile and Mexico [19]. The average waist circumference in this small sample of elderly Cuban men was 81.3 cm and 80.5 cm in elderly Cuban women. This contrasts greatly to rural elderly Mexican men and women who had an average waist circumference 88.3 cm and 93.1 cm. In 2000, another study examined obesity in a larger sample of elderly Cubans in Havana and elderly Barbadians in Bridgetown [11]. The elderly Cubans had lower prevalence of obesity compared to elderly Barbadians affecting 12.7% of men and 30.7% of women. This comparison suggests that although obesity remains a public health concern throughout Cuba, urban and rural elderly Cubans are less obese than their counterparts in Latin America and the Caribbean.

Obesity is increasingly affecting young adults and children. Cuba was among the four Latin American countries with the highest rates of obesity among 20–29-year olds in 1994, which of note was during the most difficult years of the Special Period [20]. In examining contemporary childhood obesity, the Comprehensive Childhood Study of 2004-2005 found that 10.2% of children are overweight and 8.8% are obese [14]. In 2005, the prevalence of excess weight in children <19 years of age in Havana was similar to that of 1972. However, there was a significant increase in high adiposity in children, many of whom had a normal BMI [21].

In the 1982–84 HHANES survey, nearly 30% of Cuban American men and 34% of Cuban American women were classified as overweight [22]. These data are similar to those seen in Mexican American men and women (30% and 39% resp.) and Puerto Rican American men and women (25% and 37%) [22]. Nine percent of Cuban American men and 15% of Cuban American women were obese, also comparable to other Latinos [23]. Overweight prevalence was higher among hypertensive Cuban Americans [24]. Of note, increased BMI in Cuban Americans was not associated with income, education, acculturation, or socioeconomic status [25]. However, this may be a limitation of the population sample in the HHANES study which underrepresented the poor. There are no available recent data on obesity in Cuban Americans.

6. Tobacco

Similar to other countries, tobacco use in Cuba is greater among men than among women. It is estimated that 40% of all men smoke tobacco every day, with a higher rate of 60% in middle age men. Moreover, 25% of women and 32% of men age greater than 60 smoke tobacco, a figure much greater than other Caribbean and Latin American countries [7]. Elderly Cubans smoke at higher rates than the rest of the population. A large study in Havana from 2011 estimated that 46.5% of elderly men and 21.5% of elderly women smoked tobacco [11]. Moreover, in the same study, an additional 31% of men and 15% of women were former smokers. The prevalence of tobacco use in Havana in this study was much greater than in Bridgetown, Barbados. In a 2003 case control study of patients with acute MI in Cuba, smoking was responsible for a third of the burden of acute myocardial infarction in Cuba [26].

In the HHANES 1982–1984 survey, smoking was reported in 23.9% of Cuban American women and 45.1% of Cuban American men [8, 24]. Within this cohort, 27.3% of Cuban American men were heavy smokers (greater than 20 cigarettes a day) compared to 11.9% of Cuban American women [8]. Birth cohort analysis of HHANES (1982–1984) data revealed that smoking rates among successive birth-cohorts increased substantially in Cuban American women [27]. Subsequent studies from the early 1990's reported a lower prevalence of tobacco use. Smoking rates among men ranged from 21.4 to 30.3% and in women 11.6–25.9% [16, 28, 29]. Among smokers, Cuban American men had the highest mean daily cigarette use (17.8 cigarettes a day) compared to other Latino ethnic groups [29].

7. Type 2 Diabetes and the Metabolic Syndrome

With poor dietary habits increasing and physical activity declining, more Cubans are at risk for developing type 2 diabetes mellitus and the metabolic syndrome. The metabolic syndrome, which consists of hypertension, glucose intolerance, dyslipidemia, and abdominal obesity, is increasingly being recognized as an independent risk factor for CHD beyond the sum of the risk conveyed by its individual components [30]. There are few studies that have examined the prevalence of the metabolic syndrome in Cuba. A cross-sectional study in the city of Cienfuegos found the prevalence of the metabolic syndrome according to the NCEP ATP III definition in adults to be 22% (95% confidence interval 14.5–28.8) [31]. However, in adults greater than 40 years old, the prevalence of the metabolic syndrome is 44% [31]. The prevalence of the metabolic syndrome in rural areas of Cuba is unknown.

Moreover, there are little data on the epidemic of type 2 diabetes mellitus in Cuba. In one survey of individuals age 60 and older, 15% of participants reported having type 2 diabetes mellitus [7]. Another study of elderly individuals in Havana reported type 2 diabetes mellitus was more prevalent in women compared to men [11]. While 19.9% of elderly women had type 2 diabetes mellitus, only 7.3% of men were diabetic. Other studies have estimated a national prevalence of type 2 diabetes ranging from 4.6 to 17% [6, 13, 31].

A few small observational studies have been done in order to gain insight into the impact of the metabolic syndrome on the health of Cubans. A 2005 observational study of patients in a Havana hospital examined the comorbidities of patients that died in the intensive care unit. Of the 149 patients that died during the study, 88 patients (32.9%) had the metabolic syndrome as defined by NCEP ATP III. The metabolic syndrome was a comorbidity in all deaths attributed to cardiogenic shock, myocardial infarction, and mesenteric thrombosis and was present in greater than 60% of individuals that died from ischemic and hemorrhagic stroke [32].

Data from the 1982–84 HHANES reveal that 16% of Cuban Americans aged 45–74 had type 2 diabetes mellitus, which was slightly greater than non-Latino Whites (12%), but significantly less than Mexican Americans (24%) and Puerto Rican Americans (26%) [33]. From 1996 to 1997,

diabetes-related mortality was twice as high for Mexican and Puerto Rican Americans than Cuban Americans in persons aged greater than 35 [34].

When combining HHANES data with the National Health and Nutrition Examination Survey (NHANES), age-standardized prevalence of diabetes in Cuban Americans is only 9.3% [35].

A recent observational study demonstrated that among 161 nondiabetic Cuban Americans in South Florida, 41% met criteria for the metabolic syndrome as defined by NCEP ATP III [36]. Moreover, Cuban Americans with the metabolic syndrome had elevated high-sensitivity CRP levels that may also indicated an increased risk for type 2 diabetes mellitus and cardiovascular diseases [36]. This observation has yet to be further explored.

8. Coronary Heart Disease

The increasing prevalence of obesity, type 2 diabetes mellitus, and the metabolic syndrome is putting more Cubans at risk for CHD. Obesity is not only associated with an increased risk of hypertension, type 2 diabetes mellitus, and hyperlipidemia, but also earlier age at which first non-ST elevation myocardial infarction occurs [37]. Twenty-six percent of all deaths in 2002 were attributed to heart disease [7]. In a 2001 study conducted in a polyclinic in Havana, CHD was one of the most prevalent chronic diseases in patients age 60 and older, third to hypertension and type 2 diabetes mellitus [10]. Of all of the heart transplants done in Cuba from 1985 to 2005, 57.5% of the cases were due to CHD [38]. While the prevalence of CHD has continued to rise over the last four decades, mortality related to ischemic heart disease has been declining since the 1990's [39]. From 1991 to 2000, the percentage of deaths from ischemic heart disease secondary to MI decreased from 73% to 54% [39]. Public health initiatives and advances in care for patients with acute myocardial infarction have contributed to this decline. However, when Cuba was compared to 9 other Latin American countries, the United States, and Canada in 2000, Cuban women had the highest CHD mortality rates and Cuban men ranked third behind that of Venezuela and the United States [7].

Similar to the distribution of CHD risk factors, CHD affects urban areas more than rural areas. The rate of cardiovascular disease is 40% higher in urban areas when compared to rural areas [7]. In the year 2008, the city of Havana had the largest cardiovascular-related mortality at 256.6 deaths per 100,000 compared to the Isla de la Juventud whose cardiovascular-related mortality was the lowest at 105.0 per 100,000 [40].

Like many Latino ethnic groups, there is very little data on the prevalence and incidence of CHD in Cuban Americans. Data from the National Health Interview Survey-Multiple Causes of Death (NHIS-MCD), 1986–1995, reveal that cardiovascular disease is the leading cause of death for Cuban Americans [41]. Rates of cardiovascular-related mortality are similar to that of white Americans but less than that of Mexican Americans, Central Americans, and South Americans [41].

9. Conclusion

The Cuban dietary and physical activity patterns convey an increased risk for CHD even before immigrating to the United States. While pharmacological treatment of CHD and CHD risk factors such as hypertension and dyslipidemia is essential in confronting this epidemic, Cuba has already achieved much success in this area. In a 2008 study conducted in Cienfuegos, 40% of the participants with hypertension were at or below goal blood pressure of 140/80 mmHg, which was greater than national rates in the United States (34%) [42, 43]. Yet despite achieving rates of hypertension control greater than that of developed countries, Cuba has to confront to challenge of modifying the lifestyle of its population in order to provide more comprehensive cardiovascular prevention. This includes creating more programs and space for physical activity and recreation in addition to making healthy foods like fresh fruits and vegetables affordable and available. These changes extend much further than the Ministry of Public Health, but also include education, urban planning, and agriculture. Cuba is not alone in facing this challenge, but as Cuba creates solutions in the setting of limited resources, it can serve as a model for the rest of the developing world.

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Review Article

Premature Coronary Artery Disease and Familial Hypercholesterolemia: Need for Early Diagnosis and Cascade Screening in the Indian Population

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Cardiovascular disease (CVD) is the leading cause of death in India, accounting for 28% of mortality. The average age of onset of CVD is younger (below 55 years) among Indians than in other populations. This may be due to bad lifestyle, genetic factors, or both. Hypertension, smoking, diabetes, and physical inactivity have been identified as modifiable risk factors for heart disease. Hypercholesterolemia is the most common and treatable cause of heart disease. Genetic factors that lead to hypercholesterolemia have not been fully studied in India. Familial Hypercholesterolemia results from mutations in the LDL receptor, ApoB, PCSK9, and ApoE genes. There is an urgent need to screen subjects with premature CAD and their relatives in India for the presence of FH, identify the mutations that lead to high cholesterol, and carry out cascade screening in the at-risk relatives. Those harbouring mutations in the above genes can be treated to lower the cholesterol levels, prevent early CVD, and avoid death. A programme based on these lines has been initiated in Delhi.

1. Introduction

Cardiovascular disease (CVD) is the leading cause of death in India, accounting for 28% of mortality [1]. Deaths from CVD have increased from 2,266,000 in 1990 to 2,669,100 in 2004, which is a 17.8% increase in less than two decades [2]. Prevalence of CVD in the urban Indian population is between 6.5 to 13.2% and in the rural population between 1.6 to 7.4%. The prevalence in the rural areas is growing rapidly possibly due to changing life styles [3].

The average age of onset of CVD is younger (below 55 years) among Indians than in other populations around the world [4]. The case fatality rate for coronary heart disease and other CVDs is higher in India than in the developed countries. This is because effective mechanisms for management and control of CVD are not been fully established and also due to cost of interventions. The heavy burden of CVD in Indians is generally considered to be due to increased incidence of metabolic syndrome and an unhealthy lifestyle. Investigations of the genetic causes for this increased trend have been largely unexplored and the contribution of Familial Hypercholesterolemia (FH) is unknown.

The Framingham Heart Study (FHS) was started in 1950s when there was growing burden of CVD in the United States. It led to the recognition of risk factors for CVD such as smoking, high blood pressure, an abnormal lipid profile, obesity, diabetes, physical inactivity, and psychosocial factors. This has been shown to be true in all ethnic groups [5]. Asian Indians have been shown to manifest CVD at lower levels of these risk factors, as compared to other populations.

Epidemiological studies have been conducted in India to determine the prevalence and age-specific trends in cardiovascular risk factors among adolescents and young Asian Indians. Major risk factors identified were smoking or tobacco use, obesity, hypertension, dysglycemia, and dyslipidemia. It was observed that the prevalence of multiple cardiovascular risk factors was low in adolescents, but rapid

escalation of these risk factors occurred by the age 30–39 years [6].

Arora and Trehan [7] investigated 3020 cases of Indians having Coronary Artery Bypass Graft (CABG) for three or more vessel disease in comparison with those having two or less vessel disease. Risk factors differed in the cases with early as compared with those having late onset of CAD. Cigarette smoking and positive family history of CAD was observed more frequently in those with early onset of the disease, whereas hypertension and diabetes mellitus occurred more frequently in those with late onset of disease.

Goel and colleagues [8] documented that in Indians the risk factors for CAD occur at much lower levels of total cholesterol and low-density lipoprotein cholesterol than other populations. High triglyceride and low high-density lipoprotein levels were observed in the Indian subjects. Younger patients had a more atherogenic lipid profile than the older subgroup with CAD. Smoking and family history of premature CAD were the most common associated risk factors.

High cholesterol level, the major modifiable risk factor for heart disease, has both an environmental as well as a genetic component. Premature CAD in the Indian population might be due to an unhealthy lifestyle alone or due to genetic factors in combination with an unhealthy lifestyle. The genetic component has been largely ignored in India although it has the highest number of deaths due to heart disease. It would be interesting to determine what fraction of deaths due to CVD are due to genetic factors especially FH. Many countries in the west have introduced MEDPED (Make Early Diagnosis to Prevent Early Death) programs. An index case with FH is identified, and the responsible molecular mutation is determined. Then using a combination of cholesterol levels and mutation studies, the extended family members are screened. The programme has been highly successful in reducing mortality due to CVD in these subjects [9].

Reports are available from the Indian subcontinent of cases with Homozygous FH that have been identified on dermatological and cardiological features [10–12]. In all these cases, the patients had a very characteristic distribution of planar xanthomas in interdigital spaces of fingers along with tendinous and some tuberous xanthomas at other places. It was observed that most of these patients had a family history of xanthomas, premature deaths, and deranged plasma cholesterol levels in siblings or the parents. The treatment options available are lipid lowering drugs, LDL apheresis, and liver transplantation [13–15]. Genetic characterization in such families would enable early diagnosis and provision of therapy at a younger age. Guidelines have been developed in UK for diagnosis and treatment of patients of FH and cascade testing among family members [16].

Hypercholesterolemia (monogenic and multifactorial) affects 1 in 20 subjects in the general population. On the other hand, frequency of FH is 1 in 500 for heterozygotes. Homozygotes are rare with a frequency of 1 in a million. FH is characterized by isolated elevation of plasma low-density lipoprotein cholesterol and is associated with high risk of premature cardiovascular disease. The affected families can be segregated in three clear groups on the basis of their plasma LDL cholesterol concentrations: presumed homozygotes with levels four times higher than in normal individuals (>800 mg/dL), heterozygotes with levels two times higher than the normal (200–800 mg/dL), and unaffected individuals (100 mg/dL). This is due to the gene dosage effect [17]. It is estimated that there are about 10,000,000 people with FH worldwide [18]. Of these affected subjects, less than 10% are treated with LDL-lowering drugs. If undiagnosed and untreated, the cumulative risk of CAD by age 60 years is more than 60% among men and 30% among women with heterozygous FH [19]. This risk ratio could be much higher in Indians due to the early occurrence of CAD.

2. The Genetic Equation in FH

Familial Hypercholesterolemia results from defects in hepatic uptake and degradation of LDL via the LDL-receptor pathway. The high-density lipoprotein cholesterol levels are seen to be in the normal range or low in patients with FH. The defects are generally caused by loss of function mutations in the LDL receptor gene, by mutations in gene encoding apolipoprotein B, or by gain of function mutations in PCSK9 gene.

2.1. LDL Receptor Gene. In 1985, Brown and Goldstein [20] discovered the LDL receptor, a cell surface glycoprotein that binds apolipoprotein B on the LDL particle as a part of the process of receptor mediated endocytosis. The human LDLR receptor cDNA and gene were cloned and characterized in 1984 and 1985, respectively [21]. LDL receptor gene is located on the distal short arm of chromosome 19, in the region p13.1-p13.3. LDLR gene spans 45 kb and comprises of 18 exons and 17 introns. The cellular defects of LDL-receptor function are classified into five groups: defects in ligand binding, transport, internalization, recycling, and null alleles which are the receptor negative mutations. The first molecular characterization of LDL receptor mutation was reported in 1985 by Lehrman et al. [22]. More than 900 mutations in the LDLR have been reported since its discovery [23]. Various mutations found include point mutations, large rearrangements, premature stop codons, single amino acid substitutions and insertions [24–26]. Not much work has been done in the field of molecular genetic characterization of FH in the Indian population. A study on Indians in South Africa found mutations in exons 3, 4, 9, and 14 of LDLR gene. The mutations majorly occurred in the CpG rich regions of the gene making it a mutational hotspot in South African Indians [27]. Unrelated families had different mutations. Ashavaid et al. in a study in Mumbai identified four previously known mutations and two novel insertion mutations in LDLR gene in Indian subjects [28].

2.2. ApoB. Some patients with hypercholesterolemia have no defect in LDL receptor, but have defective clearance of LDL due to mutations in ApoB gene. In such patients, cholesterol concentrations in plasma can vary from those found in heterozygous FH to only modest hypercholesterolemia [29].

The defect lies in inability of the LDL to bind to LDLR receptor due to defective ApoB, the protein moiety of LDL [30]. The defect is known as Familial Defective Apolipoprotein B-100 (FDB). Mutations are found only in the LDL binding domain of ApoB, which consists of exon 26 and 27 of ApoB gene. In a study conducted in 40 subjects with clinical features of FH in India, none of the patients or controls showed a mutation in exon 26 of ApoB. This suggests that common mutations in ApoB are not associated with hypercholesterolemia among Indians [31]. However the possibility of other unknown mutations and polymorphisms at the ApoB locus cannot be ruled out.

2.3. PCSK9. Another locus causing autosomal dominant hypercholesterolemia was identified to be a gene on chromosome 1-Proprotein Convertase Subtilisin/Kexin type IX (PCSK9) [32]. This gene encodes for a protein of 694 amino acids belonging to a family of proprotein convertase subtilase. PCSK9 is secreted by hepatocytes and appears to downregulate the density of functional LDL receptors in hepatocytes by promoting endosomal degradation rather than recycling of the receptor on the surface [33]. Hypercholesterolemia is caused by gain-of-function mutations in the PCSK9 gene [34]. Since its discovery, various missense mutations in PCSK9 have been shown to cosegregate with severe hypercholesterolemia in many families in several countries. It was observed that ApoE genotypes exerted their respective effects on LDL cholesterol in an additive manner to that of the PCSK9 variants [35].

2.4. ApoE. It is a key protein in the modulation of metabolism of highly atherogenic ApoB containing lipoproteins. ApoE is polymorphic in nature and three common alleles, that is, $\varepsilon 4$, $\varepsilon 3$, and $\varepsilon 2$ code for three major isoforms, that is, ApoE4, E3, and E2. Six different ApoE phenotypes: E3/3, E4/4, E2/2, E4/3, E3/2, and E4/2 occur in the general population with varying frequencies. It has been estimated that ApoE polymorphisms may account for 2–16% of the variability of LDL cholesterol levels [36]. In Asian Indians, these allele frequencies observed were 0.031–0.094 for $\varepsilon 2$, 0.803–0.968 for $\varepsilon 3$, and 0.000–0.133 for $\varepsilon 4$ [37]. Frequency of ApoE $\varepsilon 3$ allele was found to be high (0.913) in people of north India [38]. In another study on Asian Indians, individuals with at least one $\varepsilon 4$ allele were considered to be at risk to develop premature myocardial infarction, independent of other conventional risk factors [39].

3. Conclusions

Special efforts are required to identify individuals with FH in India as they are at high risk of premature coronary heart disease. The condition is seriously underdiagnosed and the diagnosis is often made too late, restricting the benefits of the treatments available. Since this condition is genetically determined, families must become the focus of attention. Cascade testing can identify more individuals with FH who will benefit from early treatment, result in a near-normal life expectancy. The innovative use of DNA testing allied with cholesterol assay will help to ensure that children, young people, and adults with this condition are identified and offered timely advice and treatment. A cost-effective method is being developed to screen for mutations in families with cases having premature CAD. This will help to establish a program in India similar to the MEDPED program. With this initiative many lives will be saved from premature CAD and early death.

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Review Article

The Emerging Epidemic of Obesity, Diabetes, and the Metabolic Syndrome in China

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China is one of the fastest developing countries in the world. Rapid economic progress has resulted in changes to both diet and physical activity. New found prosperity, increased urban migration, and the adoption of sedentary lifestyles by an aging Chinese population have resulted in a dramatic shift in disease burden—from infectious to chronic. Modern Chinese find themselves increasingly afflicted with the same noncommunicable chronic diseases typical of industrialized nations. Today, cardiovascular disease is the number one cause of both morbidity and mortality, affecting both rural and urban Chinese. The rising incidence of cardiovascular disease has been fueled by an epidemic of cardiometabolic risk factors. While hypertension and smoking have received considerable spotlight, little attention has been given to obesity, diabetes, and metabolic syndrome. Their increasing prevalence is the focus of this paper.

1. Introduction

China is one of the fastest developing countries in the world. Since embracing market reforms in 1979, the country has experienced unequaled economic growth and has sustained an average of GDP growth of over eight percent for nearly three decades. Meanwhile, increased global trade and advances in agriculture have led to food surpluses in a country previously plagued by severe cyclical famine. This, coupled with improvements in sanitation and immunization, has dramatically raised average life expectancy from 46.6 years in 1960 to 73.1 years in 2009 [1]. Increased longevity, urbanization, and changes in traditional diets have resulted in an epidemic of cardiovascular disease (CVD). Today, CVD is the leading cause of both morbidity and mortality in China, responsible for one-third of all annual deaths [1, 2]. The increased burden of CVD can be attributed, in part, to the rapid rise in risk factors hypertension, smoking, obesity, diabetes mellitus, and metabolic syndrome. Considerable attention has already been given to both smoking and hypertension. However, while the prevalence of smoking remains high, its incidence peaked in the mid 1990s, and currently it is expected to decline over the next three decades [3]. In the meantime, rates of obesity, diabetes, and metabolic syndrome are projected to rise considerably. These cardiometabolic risk factors will play an increasingly important role in the rising CVD epidemic in China and deserve special attention.

2. Obesity

Obesity is an excess of body fat, defined in western populations by Body Mass Index >30 kg/m^2 [14]. It is a known risk factor for the development of atherosclerotic cardiovascular disease, type 2 diabetes, dyslipidemia, and hypertension [15]. There is a growing body of evidence that demonstrate for any given BMI Asians have a greater percentage of body fat and a higher cardiovascular risk [10, 16–18]. In addition, Chinese people are more likely to develop central obesity, which has been associated with a higher risk of developing cardiovascular disease [19]. Based on these studies, the Working Group on Obesity in China recommended a BMI

Table 1: Obesity trends 1992–2002 [4].

Classification BMI Kg/m^2	Prevalence (%) 1992	2002	Percent change 1992–2002	Estimated number of overweight & obese chinese*
Overweight 24.0–27.9	16.4	22.8	39.0%	305,748,000
Obese > 28.0	3.6	7.1	97.2%	95,211,000

Adapted from [5].
*Based on a population statistics reported by the Chinese Bureau of Statistics, 2011.

Table 2: Awareness, treatment, and control of diabetes in Chinese[t].

Population	Awareness	Treatment	Control
China	23.7%	4.81%	0.40%

[t]Percentage of total diabetics.
Adapted from [6].

cutoff of 24 kg/m^2 and 28 kg/m^2, for overweight and obesity, respectively [20]. The Chinese Ministry of Health has incorporated these cutoffs in guidelines to prevent and control overweight and obesity in Chinese adults [20].

Rapid economic development and industrialization have led to changes in traditional diets and increasingly sedentary lifestyles [21, 22]. China, once considered one of the leanest populations in the world, has experienced rapidly escalating rates of overweight and obesity. A recent meta-analysis of nationally representative data by Wang [5] estimated that the prevalence of overweight and obesity rose 49.5 percent between 1992 and 2002, from 20.0 to 29.9 percent (using the WGOC cutoff for overweight and obesity) (Table 1). The rise has been greatest in urban high-income populations, such as Beijing. Similar rates have been found in other studies [4, 23], translating into an estimated 401 million overweight or obese Chinese.

In 2003, the total medical cost attributable to overweight and obesity was estimated at 2.6 billion USD, or 3.7 percent of total national medical costs [24]. The prevalence of overweight and obesity and it's economic burden on the Chinese healthcare system will only increase as greater numbers of rural Chinese move into the ranks of the urban middle class.

3. Diabetes

Changes in diet and lifestyle have also led to a tremendous increase in the number of Chinese with obesity-related type 2 diabetes mellitus (T2DM). Diabetes is a major risk factor for cardiovascular disease and its prevalence has increased dramatically in the past two decades. In 1994, the prevalence of DM and IGT among individuals between 25 and 64 years was estimated to be 2.6 percent and 3.2 percent, respectively [25]. By 2001, the prevalence of diabetes and IGT had increased to 5.49 percent and 7.33 percent, respectively [26]. In 2008, the prevalence of diabetes and IGT in Chinese >20 years old had risen to 9.7 percent and 15.5 percent, respectively [27], (Figure 1).

Alarmingly, the prevalence of diabetes in China has nearly quadrupled over the last 15 years. Although the prevalence of DM and IGT remain lower than that of other

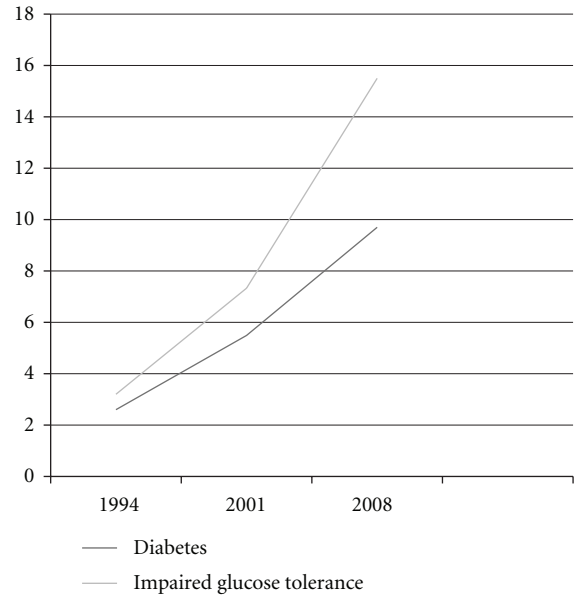

Figure 1: Prevalence of diabetes mellitus and impaired glucose tolerance in China 1994–2008. Adapted from [25–27].

industrialized nations, such as the USA, China's enormous population, estimated to be over 1.3 billion, makes it home to the largest diabetic population in the world. Today, there are 92.4 million Chinese suffering from diabetes, with an additional 148.2 million living with impaired glucose tolerance [27].

Despite the increasing prevalence of diabetes in China, rates of awareness, treatment, and control remain low. In 2000, a nationally representative study of 15,236 Chinese adults found that nearly 75 percent of diabetics were unaware of their diagnosis [6]. Of those that were aware, only 20 percent were taking prescribed medications or pursuing nonpharmacological interventions (exercise or dietary modification), of these, only 8.3 percent managed to achieve glycemic control [6] (Table 2). Similar rates of awareness were reported by Yang et al., 2010 [27]. Based on these estimates, there are currently 84.7 million Chinese with *uncontrolled* diabetes mellitus. They are at increased risk for developing long-term complications including cardiovascular disease, renal disease, peripheral neuropathy, retinopathy, and blindness. In 2007, the direct medical costs of obesity-related DM and its complication were estimated to be 26 billion USD, representing 16 percent of all Chinese medical

Table 3: NCEP ATP III diagnostic criteria for metabolic syndrome [7–9].

Criteria	Category
Elevated fasting glucose	≥110 mg/dL or use of antidiabetic medications±
Elevated triglycerides	≥150 mg/dL
Reduced HDLC	<40 mg/dL in men <50 mg/dL in women
Elevated blood pressure	≥130 mm Hg or ≥85 mm Hg DBP or use of antihypertensive medication
Elevated waist circumference	>102 cm in men >88 cm in women
WHO modified Asian waist circumference criteria [10]	
Elevated waist circumference	>90 cm in men >80 cm in women

±WHO classifies fasting blood glucose >100 mg/dL as elevated.
Adapted from [11–13].

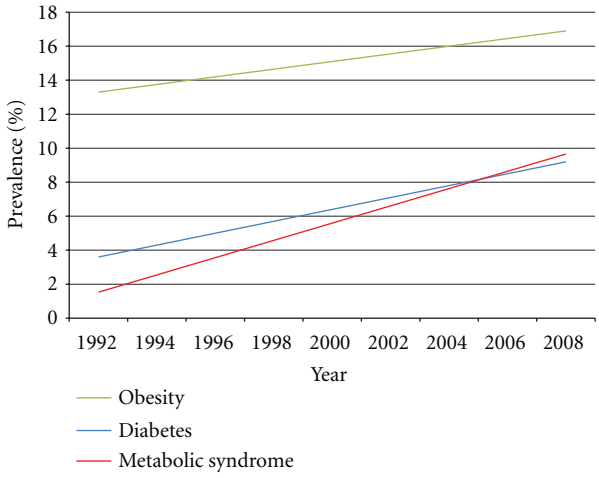

Figure 2: Prevalence of obesity, diabetes and, metabolic syndrome trends over time 1992–2008.

expenditures. If current trends continue, this cost is projected to increase to 47.2 billion USD by 2030 [28].

4. Metabolic Syndrome

The metabolic syndrome (MetS) is a combination of interconnected risk factors for obesity, insulin resistance and glucose intolerance, dyslipidemia, and hypertension. The adult treatment panel III of the National Cholesterol Education Program (NCEP) defined a group of five clinical criteria for effective classification of MetS (Table 3).

An individual that meets three or more of these criteria can be given the clinical diagnosis of MetS. The syndrome is associated with the development of diabetes, cardiovascular, and kidney disease, and an increased risk for mortality [29, 30]. Based on the NCEP classification, a rapidly growing epidemic of metabolic syndrome is taking place in China. In 1992, the prevalence of metabolic syndrome in China was 13.3 percent, 12.7 percent in males and 14.2 percent in females [31]. By 2000, the prevalence of metabolic syndrome had increased to 15.1 percent, 13.6 percent in men and 16.6 percent in women [32]. This prevalence rate was determined using the modified Asian criteria for waist circumference, based on studies which have shown that Asians suffer from the same risk of cardiovascular disease development at smaller waist circumferences, 90 cm for men and 80 cm for women [33, 34]. In 2000, 64 million Chinese had metabolic syndrome, this number increases to 71 million using the modified ATP III criteria for Asian populations [35].

Numerous studies have shown that the prevalence of metabolic syndrome increases with age [35–37]. This finding has important implications for China, whose enormous population is aging rapidly as an unintended consequence of the "one child policy" adopted by the government in 1978. The population of Chinese seniors grows by 3.3 percent annually. By 2050, 30 percent of the population will be over the age of 65 years [38]. The increasing prevalence of MetS among elderly Chinese was demonstrated in a Hong Kong-based population study by Thomas [39]. Of participants aged 25–29 years, only 3.1 percent had MetS, compared to 41.0 percent of those aged over 70 years. The age- and gender-adjusted prevalence was 21.2 percent. This approaches prevalence rates found in other industrialized nations [40, 41]. The high prevalence of MetS among Hong Kong Chinese forewarns a rapidly increasing problem in Mainland, China. Hong Kong, with its vibrant economy fostered by decades of British occupation has already gone through the rapid socioeconomic changes the rest of the country is currently experiencing. In addition, the rapid influx of rural Chinese into the country's overcrowded megacities will only accelerate the rapid rise in MetS and related complications [42], (Figure 2).

5. Conclusion

China is a middle-income country in rapid economic and epidemiologic transition. Decades of economic development have led to dramatic changes in life expectancy, lifestyle, and diet. An older more sedentary population finds itself increasingly more burdened by diseases of its newfound wealth obesity, diabetes, and metabolic syndrome, which already

approach those found in industrialized nation in both Europe and the USA. The increasing prevalence of cardiometabolic risk factors has resulted in an unprecedented rise in the incidence of cardiovascular disease. The incidence of CVD is predicted to rise by at least 50% in the next 20 years, with an additional 23 percent increase resulting from trends in cardiometabolic risk factors [43]. Perhaps even more alarming, Chinese are less likely to be diagnosed and less likely to gain control of their chronic disease [6, 44] and have limited access to quality healthcare services [45, 46]. Furthermore, the Chinese healthcare system, with its historical focus on treating infectious diseases, is ill equipped to handle the rising epidemic of cardiovascular disease [47]. The Chinese have proven themselves capable of rapid large-scale socioeconomic change. However, the ability of the government to respond and control such an epidemic will depend on whether or not it approaches the task with the same vigor it has approached economic development. While China can benefit from the rich body of existing research on cardiometabolic disease, more studies on Chinese-specific risk factors are needed.

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Research Article

The Association of Chronic Kidney Disease and Metabolic Syndrome with Incident Cardiovascular Events: Multiethnic Study of Atherosclerosis

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Background. There is an association between chronic kidney disease (CKD) and metabolic syndrome (MetS). We examined the joint association of CKD and MetS with incident cardiovascular (CVD) events in the Multiethnic Study of Atherosclerosis (MESA) cohort. *Methods*. We analyzed 2,283 Caucasians, 363 Chinese, 1,449 African-Americans, and 1,068 Hispanics in the MESA cohort. CKD was defined by cystatin C estimated glomerular filtration rate $\leq$ 60 mL/min/1.73 m^2 and MetS was defined by NCEP criteria. Cox proportional regression adjusting for age, ethnicity, gender, study site, education, income, smoking, alcohol use, physical activity, and total and LDL cholesterol was performed to assess the joint association of CKD and MetS with incident CVD events. Participants were divided into four groups by presence of CKD and/or MetS and compared to the group without CKD and MetS ($CKD^-/MetS^-$). Tests for additive and multiplicative interactions between CKD and MetS and prediction of incident CVD were performed. *Results*. During follow-up period of 5.5 years, 283 participants developed CVD. Multivariate Cox regression analysis demonstrated that CKD and MetS were independent predictors of CVD (hazard ratio, 2.02 for CKD, and 2.55 for MetS). When participants were compared to the $CKD^-/MetS^-$ group, adjusted HR for the $CKD^+/MetS^+$ group was 5.56 (95% CI 3.72–8.12). There was no multiplicative interaction between CKD and MetS ($P = 0.2$); however, there was presence of additive interaction. The relative excess risk for additive interaction (RERI) was 2.73, $P = 0.2$, and the attributable portion (AP) was 0.49 (0.24–0.74). *Conclusion*. Our findings illustrate that the combination of CKD and MetS is a strong predictor of incident clinical cardiovascular events due to presence of additive interaction between CKD and MetS.

1. Introduction

A large percentage of the US population (10%) suffers from chronic kidney disease (CKD) [1] which is associated with metabolic syndrome [2–4]. Metabolic syndrome (MetS) is a construct of physical and laboratory anomalies that confers a higher risk for diabetes mellitus, cardiovascular events and mortality. The National Cholesterol Education Program Adult Treatment Panel (ATP III) criteria define MetS as having at least three of the following: abdominal or central obesity; high triglyceride levels; low high-density lipoprotein (HDL) cholesterol; hyperglycemia; hypertension [5], which has high prevalence in the US [6].

Both CKD [7–9] and MetS [10, 11] have been shown to be independently associated with increased cardiovascular events and mortality, and studies suggest that CKD and MetS are associated with each other as well [2–4]. The increased cardiovascular risk of kidney disease is partly explained by

an increased burden of traditional cardiovascular risk factors, such as abnormalities in serum lipid concentrations and distribution (elevated triglycerides and lower high-density lipoprotein), diabetes mellitus, and hypertension [2, 12, 13] which are also part of the MetS construct. There is evidence to suggest that CKD progression and associated adverse CVD outcomes are related to severe vitamin D deficiency. The recent findings of vitamin D, being a modulator of both insulin resistance [14] and the renin-angiotensin system [15] and the implication of the renin-angiotensin system in local pancreatic islet structure and function [16, 17], suggest that perhaps renal dysfunction and MetS may share common pathological pathways. This overlap in associated risk factors combined with the potential modifying effect of impaired renal function raises the question about whether the co-occurrence of both conditions would augment or attenuate the anticipated risk based on the effect of the two risk factors individually. The purpose of this study is to understand the joint associations of the two conditions with CVD events in a multiethnic population which could lead to improvements in risk stratification and determine whether participants with both conditions should be specifically targeted for more aggressive and early risk factor interventions. Because cystatin C appears to be more sensitive in detecting mild to moderate decrease in glomerular filtration rate [18, 19], shows strong associations with incident cardiovascular events [20] and all cause mortality [20, 21], and is not affected by age, gender, ethnicity, or muscle mass, this study focused on CKD defined by reduced GFR using a cystatin C-based estimating equation [22].

2. Materials and Methods

2.1. Study Population. The Multiethnic Study of Atherosclerosis (MESA) design has been previously described [23]. Briefly, MESA is a prospective cohort study that began in July 2000 to investigate the prevalence, correlates, and progression of subclinical CVD. The study included 6814 men and women aged 45–84 years old recruited from 6 US communities (Baltimore, MD; Chicago, IL; Forsyth County, NC; Los Angeles County, CA; northern Manhattan, NY; St. Paul, MN). MESA cohort participants were 38% Caucasian ($n = 2622$), 28% African-American ($n = 1893$), 22% Hispanic ($n = 1496$), and 12% Chinese ($n = 803$). Individuals with a history of physician-diagnosed myocardial infarction, angina, heart failure, stroke, or transient ischemic attack, or who had undergone an invasive procedure for CVD (coronary artery bypass graft, angioplasty, valve replacement, pacemaker placement, or other vascular surgeries) were excluded from the study at baseline (2000–2002). After excluding participants with missing data on serum cystatin C ($n = 58$) and covariates ($n = 1143$), we had 5,613 participants at baseline with complete data on serum cystatin C, Mets, and covariates of interest. This study was approved by the Institutional Review Boards of each study site and written informed consent was obtained from all participants.

2.2. Laboratory Measures and Data Collection. Medical history, anthropometric measurements, and laboratory data for the present study were taken from the first examination of the MESA cohort (July 2000–August 2002). Information about age, sex, ethnicity, and medical history were obtained by questionnaires. Resting blood pressure was measured using the Dinamap monitor PRO 100 (Critikon, Tampa, Fla, USA) automated oscillometric device. Three measurements were obtained at 1-min intervals with the subject in the seated position with back and arm supported after 5 min of rest with an appropriate-sized cuff, with the cuff at the level of the heart, using a standardized protocol. The average of the second and third measurements was recorded as the resting blood pressure. Hypertension was defined as a systolic blood pressure ≥ 140 mm Hg, a diastolic blood pressure ≥ 90 mm Hg, or currently taking medications for blood pressure control [24]. Smoking use was defined as never, former, and current smokers. Smoking ever is defined as ≥ 100 cigarettes in one's lifetime; current is defined as having smoked a cigarette in the last 30 days. Diabetes was defined as a fasting glucose ≥ 126 mg/dL or use of insulin or hypoglycemic medications. Plasma lipids (HDL cholesterol, triglycerides, and total cholesterol) were measured from blood samples obtained after a 12-hour fast and measured using a standardized kit (Roche Diagnostics). LDL cholesterol was calculated with the Friedewald equation [25]. Cystatin C was measured from frozen sera at a central laboratory (University of Vermont, Colchester, Vt, USA) using a BNII nephelometer (Dade Behring Inc, Deerfield, Ill, USA) and a particle-enhanced immunonephelometric assay (N Latex Cystatin C; Dade-Behring) [26]. The analytical coefficient of variation for this assay is 2.5%.

Chronic kidney disease was defined as cystatin C derived glomerular filtration rate ≤ 60 mL/min/1.73 m^2 using the formula derived and validated by Stevens et al. [22] ($\text{eGFR}_{\text{cysC}} = 76.7 * \text{cystatin C}^{-1.19}$). The National Cholesterol Education Program/Adult Treatment Panel (NCEP ATP III) [5, 27] definition was used to classify participants having MetS in the MESA cohort. Three of five components are required for diagnosis. (1) Waist circumference ≥ 102 cm : men, ≥ 88 cm : women, (2) hypertension ≥ 130 mm Hg systolic or ≥ 85 mm Hg diastolic or use of medications for hypertension, (3) fasting blood glucose ≥ 100 mg/dL or treatment for impaired fasting glucose, (4) triglycerides ≥ 150 mg/dL or specific treatment, and (5) HDL-C ≤ 40 mg/dL in men and ≤ 50 mg/dL in women.

A dummy variable with four categories for all the possible permutations of CKD and MetS was created. The categories were as follows: (a) no CKD and no MetS ($\text{CKD}^-/\text{MetS}^-$), (b) CKD and no MetS ($\text{CKD}^+/\text{MetS}^-$), (c) no CKD and MetS ($\text{CKD}^-/\text{MetS}^+$), and (d) both CKD and MetS ($\text{CKD}^+/\text{MetS}^+$).

2.3. Cardiovascular Events. A detailed description of events and the process of adjudication can be found at the MESA website (http://www.mesa-nhlbi.org). Briefly, participants were contacted every 9–12 months to inquire about hospital admissions, cardiovascular diagnoses, and deaths. Hospital records were abstracted for possible CVD events and were sent for review and classification by an independent adjudication committee. For the purposes of this study, a

CVD event was defined as incident myocardial infarction, resuscitated cardiac arrest, definite angina, probable angina if followed by revascularization, stroke, stroke death, coronary heart disease (CHD) death, other atherosclerotic death, and other CVD death as defined by the MESA protocol.

2.4. Statistical Analysis. Descriptive analyses of all the variables utilized in the data analysis were conducted. The baseline features were compared, using ANOVA or Kruskal-Wallis tests for continuous variables and the chi-square or the Fisher exact tests for categorical variables, into four columns: Neither CKD/MetS; CKD only; MetS only; both CKD and MetS.

A Cox proportional hazards regression with and without adjustment for age, ethnicity, gender, study site, education, income, smoking, alcohol use, physical activity, total, and LDL cholesterol was performed to assess the independent association of CKD and MetS with incident CVD events with CKD and MetS in the same model.

We next divided the participants into four groups according to the presence/absence of CKD and/or MetS. Survival analysis was performed using cumulative event-free Kaplan-Meier curves according to the presence/absence of CKD or MetS, and the groups were compared by log-rank test for trend. A similar Cox proportional hazards regression was performed to investigate the relationship of the four groups (neither CKD/MetS, CKD only, MetS only, nor both CKD and MetS) with incident CVD events using two sets of models: unadjusted models and models adjusted (Table 2) for established cardiovascular risk factors (age, ethnicity, gender, study site, education, income, smoking, alcohol use, physical activity, and total and LDL cholesterol) using $CKD^-/MetS^-$ as the reference category. The potential confounders were selected based on their relationship with cardiovascular disease and the prior literature. Additionally, a similar analysis was performed after excluding participants with prevalent diabetes.

Formal tests for additive and multiplicative interactions between CKD and MetS and prediction of incident CVD were also performed. We tested additive and multiplicative interactions in the proportional hazards model. A formal interaction term CKD × MetS was introduced in the model with all covariates to test for multiplicative interaction.

Formal tests for indices of additive interaction such as relative excess risk due to interaction (RERI), attributable portion (AP), and synergy index (SI) were performed as described by Li and Chambless [28]. RERI is calculated as ((HR (both CKD and MetS) − HR (CKD alone) − HR (MetS alone) + 1)). AP is calculated as RERI divided by HR (both CKD and MetS). SI is ratio of increase in hazard due to both exposures (CKD and MetS) to the sum of the increases due to one exposure alone. Please see The appendix for formal calculations. All statistical analyses were performed using JMP Version 8 (SAS Institute Inc., Cary, NC/USA).

3. Results

3.1. Participant Characteristics. The sociodemographic characteristics of the study sample are depicted in Table 1. The mean age of the sample was 61.6 years with the mean age being much higher at 69.7 years for participants with both CKD and MetS. A larger proportion of Chinese-Americans had no CKD/MetS (81%) compared to other ethnicities, and only 1% of Chinese-Americans had both the conditions compared to 3% for all other ethnicities. Among women, 31% had MetS as compared to 26% of men. Diabetes was more prevalent in the groups with MetS and both CKD/MetS compared to those without MetS or CKD/MetS. Smoking rates were not much different between the groups, whereas alcohol consumption was significantly higher in healthy participants. Additionally, the healthy participants were significantly more physically active as compared to participants with either or both conditions.

3.2. Cardiovascular Events. During 5.5 years of followup, 283 CVD events were identified (118, $CKD^-/MetS^-$ group; 10, $CKD^+/MetS^-$ group; 120, $CKD^-/MetS^+$ group; 35, $CKD^+/MetS^+$ group). A Kaplan-Meier survival curve shows decreased survival free of CVD events across the four groups of CKD and MetS with a log test for trend which is statistically significant ($P < 0.0001$) (Figure 1). These curves show significantly poorer survival in the $CKD^+/MetS^+$ group.

When CKD and MetS were entered into the same model, the results of multivariate Cox regression analysis including age, sex, ethnicity, smoking habit, cholesterol both total and LDL-C, alcohol consumption, and physical activity found that CKD (HR 2.02, 95% CI 1.43–2.79, $P < 0.0001$) and MetS (HR 2.55, 95% CI 2.01–3.25, $P < 0.0001$) were both significantly associated with incident CVD events.

Table 2 shows the results from a series of crude and multivariate regression analysis, showing how the association of CKD and MetS with CVD risk changed as groups of CVD risk factors were added to the regression model. In the crude model, the risk for CVD was significantly higher in the $CKD^+/MetS^+$ group compared with the $MetS^-/CKD^-$ group (HR 8.46). The hazard in the $CKD^+/MetS^+$ group remained highly significant in the multivariate model (HR 5.56). It remained significant even after further adjustment for antihypertensive medications and systolic blood pressure (HR 4.55, 95% CI 3.01–6.73). Furthermore, when compared with the $CKD^+/MetS^-$ group or with the $CKD^-/MetS^+$ group, the risk of CVD events was significantly higher in the $CKD^+/MetS^+$ group in univariate Cox regression analysis (versus $CKD^+/MetS^-$ group: HR 3.14, 95% CI 1.61–6.69, $P < 0.001$; versus $CKD^-/MetS^+$ group: HR 3.38, 95% CI 2.28–4.87, $P = 0.0001$) and in multivariate Cox regression analysis (versus $CKD^+/MetS^-$ group: HR 3.89, 95% CI 1.99–8.31; versus $CKD^-/MetS^+$ group: HR 2.32, 95% CI 1.56–3.37, $P < 0.0001$, resp.).

We performed several additional analyses to address the robustness of these findings. Because patients with diabetes were more frequent in the $CKD^+/MetS^+$ group, we repeated our analysis for the 4,591 participants without previous diabetes. In this study, 210 CVD events occurred during the follow-up period. The independent predictive value of $CKD^+/MetS^+$ for CVD events was also confirmed by the Kaplan-Meier method (log rank test for trend chi-square = 60; $P < 0.0001$) and by multivariate Cox regression analysis.

Table 1: Baseline characteristics of study participants in the MESA cohort at baseline (2000).

Variables	Total	$CKD^-/MetS^-$	$CKD^+/MetS^-$	$CKD^-/MetS^+$	$CKD^+/MetS^+$	*P* value
n	5163	3444	119	1455	145	
Age, years	61.6 (10.1)	60.7 (10.1)	71.1 (9.7)	62.2 (9.6)	69.7 (9.3)	0.0001
Caucasian	2283 (44%)	1565(69%)	65 (3%)	581 (25%)	72 (3%)	0.0002
Chinese	363 (7%)	293 (81%)	5 (1%)	61 (17%)	4 (1%)	0.0001
African	1449 (28%)	953 (66%)	29 (2%)	428 (30%)	39 (3%)	0.0001
Hispanic	1068 (21%)	633 (59%)	20 (2%)	385 (36%)	30 (3%)	0.0001
Male, %	2722 (53%)	1872(69%)	74 (3%)	697 (26%)	79 (3%)	0.0001
Female, %	2441 (47%)	1572 (64%)	45 (2%)	758 (31%)	66 (3%)	0.0001
DM, %	572 (11%)	128 (4%)	2 (2%)	394 (27%)	48 (33%)	0.0001
Current smokers, %	741 (14%)	491 (14%)	19 (16%)	213 (15%)	18 (12%)	0.8
Current drinking, %	3576 (69%)	2494 (72%)	78 (66%)	919 (63%)	85 (59%)	0.0001
Physical activity, min/wk	1644 (2395)	1777 (2537)	1670 (2855)	1372 (2012)	1205 (1683)	0.0001
Total cholesterol, mg/dL	193 (35)	194 (34)	187 (38)	193 (36)	188 (39)	0.08
SBP, mmHg	126 (21)	122 (20)	130 (23)	133 (21)	137 (25)	0.0001
DBP, mmHg	72 (10)	72 (10)	71 (10)	74 (10)	72 (11)	0.0001
LDL-C, mg/dL	117 (31)	118 (31)	113 (32)	116 (33)	113 (31)	0.01
HDL-C, mg/dL	51 (15)	55 (15)	52 (14)	43 (10)	42 (11)	0.0001
TG, mg/dL	125 (65)	103 (49)	109 (43)	173 (72)	170 (67)	0.0001
Fasting glucose, mmHg	96 (27)	90 (19)	89 (9)	110 (40)	109 (33)	0.0001
$eGFR_{cysC}$, mL/min/1.73m^2	93 (22)	98 (20)	51 (9)	90 (19)	49 (10)	0.0001
MetS components, %						
HTN, %	2219 (43%)	1078 (31%)	70 (59%)	954 (66%)	117 (81%)	0.0001
Obesity, %	2763 (54%)	1319 (38%)	57 (48%)	1259 (87%)	128 (88%)	0.0001
Elevated TG, %	1457 (28%)	415 (12%)	13 (11%)	939 (66%)	90 (62%)	0.0001
Low HDL-C, %	1957 (38%)	736 (21%)	32 (27%)	1078 (74%)	111 (77%)	0.0001
Impaired Glucose, %	2062 (40%)	1037 (30%)	39 (33%)	892 (61%)	94 (65%)	0.0001
CVD events, %	283 (5%)	118 (3%)	10 (8%)	120 (8%)	35 (24%)	0.0001

P values obtained by one aay analysis of variance. Data presented in total numbers (percentages) and continuous measures presented as mean value (standard deviation). DM: diabetes mellitus; SBP: dystolic blood pressure, mmHg; DBP: diastolic blood pressure, mmHg; LDL-C: mg/dL low density lipoprotein cholesterol; HDL-C: mg/dL high density lipoprotein cholesterol; TG: mg/dL, triglyceride; $eGFR_{cysC}$: mL/min/1.73 m^2 glomerular filtration rate estimated from cystatin C; CVD: cardiovascular events; MetS: metabolic syndrome; CKD: chronic kidney disease.

Table 2: Unadjusted and multivariate-adjusted HRs of CVD events associated with CKD and MetS.

	Total participants ($n = 5,163$)		Participants without diabetes ($n = 4,591$)	
	Crude	Adjusted	Crude	Adjusted
$CKD^-/MetS^-$	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
$CKD^+/MetS^-$	2.70 (1.32−4.88)	1.43 (0.70−2.62)	2.90 (1.42−5.26)	1.41 (0.69−2.61)
$CKD^-/MetS^+$	2.51 (1.94−3.23)	2.40 (1.85−3.11)	2.17 (1.60−2.91)	2.08 (1.54−2.81)
$CKD^+/MetS^+$	8.46 (5.72−12.20)	5.56 (3.72−8.12)	7.27 (4.33−11.54)	4.43 (2.60−7.15)

Hazard ratios (95% CI) adjusted for age, ethnicity, gender, study site, education, income, smoking, alcohol use, physical activity, and total and LDL cholesterol. HR: hazard ratio; CI: confidence interval; CVD: cardiovascular events; CKD: chronic kidney disease; MetS: metabolic syndrome.

Furthermore, even when compared with the $CKD^+/MetS^-$ group or with the $CKD^-/MetS^+$ group, the risk of CVD events was significantly higher in the $CKD^+/MetS^+$ group in the multivariate model (versus $CKD^+/MetS^-$ group: HR 3.13, 95% CI 1.48–7.03, $P = 0.03$; versus $CKD^-/MetS^+$ group: HR 2.13, 95% CI 1.23–3.49, $P = 0.01$).

Finally, when interaction was tested between CKD and MetS, no multiplicative interaction was demonstrated (CKD × MetS, $P = 0.2$). When formal tests for additive interaction such as relative excess risk due to interaction (RERI), attributable portion (AP), and synergy index (SI) were performed, there was presence of significant additive interaction as shown in Table 3 and Appendix. RERI (95% CI) was estimated at 2.73 (0.57–4.85, $P = 0.02$), AP (95% CI) was estimated at 0.49 (0.24–0.74), and SI (95% CI) was estimated at 2.49 (1.24–4.98). According to the

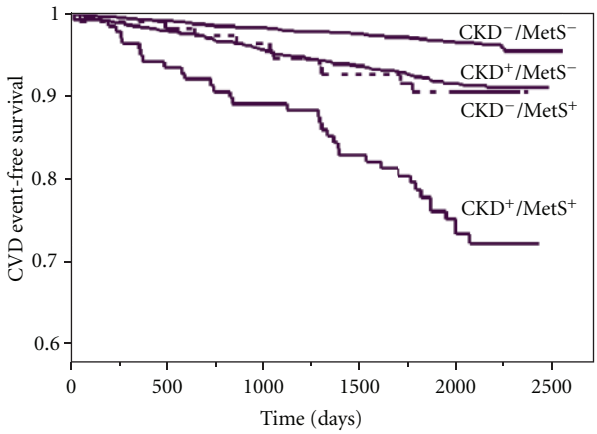

Figure 1: Kaplan-Meier plots showing cumulative CVD event-free survival in participants in four groups divided by presence or absence of CKD and presence or absence of MetS (log-rank test for trend $X^2 = 114$; $P < 0.001$); CKD: chronic kidney disease; MetS: metabolic syndrome; CVD: cardiovascular disease.

Table 3: Estimates of multiplicative and additive interaction (95% confidence interval, CI) controlling for covariates.

		CKD × MetS	
Parameters	Estimate	95% CI	*P*-value
β_3	0.48	−0.23, 1.28	0.2
RERI	2.73	0.57, 4.85	0.02
AP	0.49	0.24, 0.74	
SI	2.49	1.24, 4.98	

CKD: chronic kidney disease; MetS: metabolic syndrome; β_3: parameter estimate of CKD × MetS testing for multiplicative interaction; RERI: relative excess risk due to additive interaction; AP: attributable portion; SI: synergy index are measures testing for additive interaction.

three measures of additive interaction between CKD and MetS, there is 2.73 relative excess risk due to the additive interaction, the risk of CVD in individuals who had been exposed to both risk factors (CKD and MetS) is 2.49 times higher than the sum of risks in individuals exposed to a single risk factor alone, and 49% of the incident CVD in individuals exposed to both risk factors is attributable to the additive interaction.

4. Discussion

In this ethnically diverse population of 5,163 individuals, aged 44–84, both chronic kidney disease and metabolic syndrome are independent predictors of incident cardiovascular events. This study identified a significant positive relationship between the cooccurrence of CKD and MetS and risk for CVD events. In a multivariate model, the hazard for incident cardiovascular events was increased due to presence of significant additive interaction between CKD and MetS. However, no multiplicative interaction between CKD and MetS was demonstrated. Additionally, the presence of both CKD and MetS conferred a significantly higher hazard compared to the presence of each condition separately. From the viewpoint of prevention and clinical practice, additive interaction is more important than multiplicative interaction, as it relates to a higher absolute excess of cases.

Defined by cystatin C, CKD [7, 29] has been shown to predict cardiovascular events and mortality in several studies. Ix et al. [7] studied 990 participants in the Heart and Soul Study and demonstrated that compared to participants in the lowest cystatin C quartile, those in the highest quartile (those with CKD) were at increased risk of cardiovascular events (HR, 2.0; 95% CI, 1.0–3.8). Similarly, Deo et al. [29] studied 3,044 older adults ages from 70 to 79 over 6 years in the Health ABC cohort and found that those with CKD had significantly higher risk for cardiovascular death (HR, 2.24; 95% CI, 1.30–3.86) compared to those without CKD. This is similar to our findings where participants with CKD, as defined by $eGFR_{cysC} \leq 60$ mL/min/1.73 m^2 were at increased risk for CVD events (HR, 2.02, 95% CI, 1.43–2.79) in a multivariate analysis. However, when the CKD only group was compared to participants with no CKD and no MetS, the hazard for CVD events was statistically insignificant, which is a reflection of low statistical power (Table 2).

Similarly, MetS has been shown to predict CVD events and mortality [11]. A meta-analysis involving 43 cohorts consisting of 172,573 individuals showed that MetS had a relative risk of cardiovascular events and death of 1.78 (95% CI, 1.58–2.00). In our study, presence of MetS was an independent predictor of CVD events, and when the MetS only group was compared to the group with no CKD/no MetS, the hazard for CVD events remained statistically significant (Table 2).

Multiple studies [2–4] document the associations between CKD and MetS, and now mechanisms have been postulated that link the two conditions to each other. Recent findings, suggesting vitamin D being a modulator of both insulin resistance and the renin-angiotensin system [15] and the renin-angiotensin system in local pancreatic islet structure and function [16], suggest that perhaps renal dysfunction and MetS may share common pathological pathways. Clinically, it is seen that individuals with CKD have abnormalities in serum lipid concentrations and distribution (elevated triglycerides and lower high-density lipoprotein), diabetes mellitus, and hypertension [2, 12, 13] which are also part of the MetS construct. Additionally, it has been proposed that the presence of both conditions leads to increased inflammation and oxidative stress, increased total peripheral resistance, and impaired left ventricular relaxation which increases the risk for CVD events [30]. This interplay of risk factors and pathological mechanisms implies that perhaps the cooccurrence of CKD and MetS identifies a group of individuals at higher risk for cardiovascular events.

A few studies [30, 31] document the role of these two conditions together as it relates to CVD events. Martin et al. [31] studied 13,115 individuals aged ≥35 years from the NHANES III survey and found that the coclustering of CKD and MetS led to a significantly higher hazard for CVD mortality (HR, 3.23; 95% CI, 2.56–3.70) when compared with individuals with no CKD and no MetS. Similarly, Iwashima et al. [30] studied 1,160 essential hypertensive

individuals for a mean period of 4.8 years and found that the presence of both CKD and MetS conferred a higher risk for CVD events (HR, 3.58; 95% CI, 2.14–5.95) compared to the no CKD/no MetS group. Our findings are a validation and extension of these findings in a multiethnic cohort free of cardiovascular disease at baseline. In contrast to the study by Martins, we found no significant association in the CKD only group but found significant association in the MetS only group which is perhaps due to small numbers of CKD only individuals. Second, our study included a cohort with both with and without hypertension.

Our study has several limitations. First, MESA did not directly measure glomerular filtration rate (GFR); therefore, we cannot be certain that the association between elevated cystatin C level and CVD events are solely caused by its approximation of impaired GFR. This approach can lead to misclassification of individuals due to biased estimates. Second, although efforts were made to adjust for known confounders, there remains a possibility of failure to adjust for unknown confounders or inadequate adjustment of established risk factors (severity and duration of hypertension, diabetes) resulting in spurious results due to residual confounding. Third, some studies suggest that corticosteroids [32] and thyroid function [33] are associated with cystatin C, and since adjustment with these measures was not performed, results should be interpreted with caution in this subset of individuals. The distribution of metabolic syndrome components may vary from population to population, which may have an impact on the external validity of findings if the joint association/interaction is mostly due to one of the components. The results of the study are limited to individuals without cardiovascular disease and may not be generalizable to a population with known coronary artery disease due to selection bias. Also, due to the cross-sectional nature of the risk factors, the association between CKD, MetS, and CVD events could potentially be due to post assessment residual confounding.

5. Conclusion

This study shows that the co-occurrence of CKD and MetS results in an increased hazard for cardiovascular events in a multiethnic population. Although, no multiplicative interaction was demonstrated, there is significant presence of additive interaction. Both CKD and MetS are independent predictors of CVD but their combination furthers the risk independent of conventional risk factors. From the clinical viewpoint, physicians should become more cognizant that concomitant CKD and MetS lead to increased risk for CVD events. Additionally, assessment of renal function in individuals with MetS and vice versa may lead to improved risk stratification for cardiovascular disease in clinical practice. More studies are needed in the future to explore the temporal relationship between CKD, MetS and cardiovascular disease. Additionally, studies are needed to explore whether novel and aggressive pharmacological and behavioral modifications in individuals with both CKD and MetS, will lead to reduction in CVD risk.

Disclosures

The authors had full access to the data and take responsibility for the integrity of the data. All authors have read and agree to the study as written.

Appendix

Using the output from Tables 4 and 5, the calculations of RERI and the test for the additive interaction are illustrated below.

(1) Relative Excess Risk due to Interaction (RERI) = $HR_{11} - HR_{10} - HR_{01} + 1$, where HR_{11} is hazard due to both CKD and MetS, HR_{10} is hazard due to CKD alone, and HR_{01} is hazard due to MetS alone.

$$\begin{aligned}
\text{RERI} &= e^{\beta 1+\beta 2+\beta 3} - e^{\beta 1} - e^{\beta 2} + 1 \\
&= 5.56 - 1.43 - 2.40 + 1 = 2.73, \\
\text{VAR(RERI)} &= a_2^1 \times \text{var}\beta_1 + a_2^2 \times \text{var}\beta_2 + a_3^2 \times \text{var}\beta_3 \\
&\quad + 2\,(a_1\, a_2 \times \text{Cov}(\beta_1\, \beta_2) + a_1 a_3 \\
&\quad \times \text{Cov}(\beta_1 \beta_3) + a_2 a_3 \times \text{Cov}(\beta_2 \beta_3)), \\
a_1 &= e^{\beta 1+\beta 2+\beta 3} - e^{\beta 1} \\
&= 5.56 - 1.43 = 4.13, \\
a_2 &= e^{\beta 1+\beta 2+\beta 3} - e^{\beta 2} \\
&= 5.56 - 2.40 = 3.16, \\
a_3 &= e^{\beta 1+\beta 2+\beta 3} = 5.56.
\end{aligned} \tag{A.1}$$

VAR (RERI) = 1.19, SE (RERI) = 1.09. Hence, t = RERI/VAR (RERI) = 2.73/1.19 = 2.28, $P = 0.02$, and a 95% confidence interval estimate for RERI, RERI $\pm$ 1.96 $\times$ SE (RERI) = (0.57 − 4.85):

(2) Attributable portion (AP) = $(e^{\beta 1+\beta 2+\beta 3} - e^{\beta 1} - e^{\beta 2} + 1)/(e^{\beta 1+\beta 2+\beta 3}) = 2.73/5.56 = 0.49$:

$$\begin{aligned}
a_1 &= \frac{e^{\beta 2-1}}{e^{\beta 1+\beta 2+\beta 3}}, \\
a_2 &= \frac{e^{\beta 1-1}}{e^{\beta 1+\beta 2+\beta 3}}, \\
a_3 &= \frac{e^{\beta 1+\beta 2-1}}{e^{\beta 1+\beta 2+\beta 3}}.
\end{aligned} \tag{A.2}$$

VAR(AP) = 0.016, SE(AP) = 0.126. Hence, 95% confidence interval estimate for AP, AP $\pm$ 1.96 $\times$ SE(AP) = (0.24 − 0.74).

(3) Synergy index (SI) = $e^{\beta 1+\beta 2+\beta 3} - 1/e^{\beta 1+\beta 2} - 2 = 4.56/1.83 = 2.49$.

$$\begin{aligned}
a_1 &= a_3 - \left(\frac{e^{\beta 1}}{e^{\beta 1+\beta 2}} - 2\right), \\
a_2 &= a_3 - \left(\frac{e^{\beta 2}}{e^{\beta 1+\beta 2}} - 2\right), \\
a_3 &= \left(\frac{e^{\beta 1+\beta 2+\beta 3}}{e^{\beta 1+\beta 2+\beta 3}} - 1\right).
\end{aligned} \tag{A.3}$$

Table 4: Output from proportional hazards models.

	Parameter	Estimated β	SE (β)	t-test	P value	HR	95% CI
Model*	CKD	0.36	0.33	1.14	0.29	1.43	0.74−2.75
	MetS	0.87	0.13	44.05	0.0001	2.40	1.85−3.10
	CKD × MetS	0.48	0.38	1.61	0.2	1.62	0.77−3.44

* Parameter estimates and test statistics for interaction between CKD (chronic kidney disease) and MetS (metabolic syndrome) adjusted for covariates.

Table 5: Covariance matrix of the set of β coefficients from the proportional hazards models.

	β_1 (CKD)	β_2 (MetS)	β_3 (CKD × MetS)
β_1(CKD)	0.1119220903	0.0087980044	−0.1097780898
β_2(MetS)	0.0087980044	0.0173595635	−0.0170957203
β_3(CKD × MetS)	−0.1097780898	−0.0170957203	0.1463599444

VAR(log S) = 0.125, SE(Log S) = 0.354. Hence, 95% confidence interval estimate for SI, SI ± 1.96 × SE(SI) = (1.24 − 4.98).

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