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# Height and Risk of Sudden Cardiac Death: The Atherosclerosis Risk in Communities and Cardiovascular Health Studies

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## Abstract

**Purpose—**Sudden cardiac death (SCD) is an important cause of mortality in the adult population. Height has been associated with cardiac hypertrophy and an increased risk of arrhythmias, but also with decreased risk of coronary heart disease, suggesting a complex association with SCD.

**Methods—**We examined the association of adult height with the risk of physician-adjudicated SCD in two large population-based cohorts: the Cardiovascular Health Study (CHS) and the Atherosclerosis Risk in Communities (ARIC) study.

**Results—**Over an average follow-up time of 11.7 years in CHS, there were 199 (3.6%) cases of SCD among 5,556 participants. In ARIC, over 12.6 years, there were 227 (1.5%) cases of SCD among 15,633 participants. In both cohorts, there was a trend towards decreased SCD with taller height. In fixed effects meta-analysis, the pooled hazard ratio per 10 cm of height was 0.84 (95%CI 0.73, 0.98, p=0.03). The association of increased height with lower risk of SCD was

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slightly attenuated after inclusion of risk factors associated with height, such as hypertension and left ventricular hypertrophy. The association appeared stronger among men than women in both cohorts.

**Conclusion—**In two population-based prospective cohorts of different ages, greater height was associated with lower risk of SCD.

### MeSH Key Words

Body height; risk factors; death; sudden; cardiac

Sudden cardiac death (SCD), with an estimated incidence of between 180,000 and 450,000 cases in the United States(1) and a global incidence of 4–5 million people per year(2), is a major public health issue. Although SCD can result from multiple pathological processes, the major cause for SCD is ventricular tachyarrhythmias, including ventricular tachycardia and fibrillation. Left ventricular (LV) mass, which has been associated with risk of both ventricular fibrillation, and SCD(3, 4), is also associated with increased height(5). Based on this association, many investigators have suggested the need to index LV mass to body stature, although the specific manner of this adjustment remains uncertain(6). Implicit in these adjustments is the concept that height itself is not associated with SCD, such that by adjusting for it, one is able to more clearly identify the 'pathological' increase in LV mass. However, if height itself is associated with SCD, then depending upon the nature of this association, such an adjustment might be counterproductive. Indeed, we recently demonstrated this phenomenon for the association of height with atrial fibrillation(7).

Analysis of the causes of SCD is complicated by the multiple pathological mechanisms that can lead to ventricular tachyarrhythmias (and other causes of SCD, such as asystole). Myocardial ischemia can cause ventricular fibrillation itself. This mechanism is well-described, with approximately 80% of cases of SCD(8) being associated with coronary artery disease. To complicate matters, height is inversely associated with risk of coronary heart disease (CHD)(9), emphasizing that the overall association of height and SCD, with potentially both adverse (via LV mass) and beneficial (via CHD) pathways, requires formal study.

To address these issues, we examined this association in two large prospective cohort studies that span a range of ages and include formal adjudication of cases of SCD.

## MATERIALS AND METHODS

In both cohorts, all study procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional or regional) and with the Helsinki Declaration of 1975, as revised in 2004.

### The Atherosclerotic Risk in Communities (ARIC) study

The ARIC Study(10) is a multicenter prospective cohort study investigating the etiology of atherosclerotic disease in a middle-aged biracial population. Participants at baseline (1987–1989) included 15,792 men and women aged 45–64, recruited from 4 communities in the US: Forsyth County, NC; Jackson, MS (African Americans only); the northwest suburbs of Minneapolis, MN; and Washington County, MD.

The ARIC Study protocol was approved by the institutional review board of each participating center. After obtaining written informed consent, participants underwent a baseline clinical examination and were re-examined in 1990–92, 1993–95, and 1996–98. Of

the original study population, 159 subjects were excluded due to missing data, leaving an analysis size of 15,633 participants.

Risk factors examined in this analysis were ascertained at the baseline examination and were followed through December 31, 2001. Participants reported information on smoking status, education, history of cardiovascular disease, use of medications, and underwent examination that included standard height and weight measurements. Other prevalent risk factors examined included diabetes mellitus, resting blood pressure or use of anti-hypertensives, prevalent heart failure (HF)(11), coronary heart disease (CHD)(11), and stroke.

Participants underwent a standard supine digitally recorded 12-lead electrocardiogram with classification according to the Minnesota Code(12). Left ventricular hypertrophy (LVH) was defined electrocardiographically based on Cornell criteria(13).

**Determination of SCD in ARIC—**All participants were contacted annually by phone and all hospitalizations and deaths in the previous year were identified. For deaths, we obtained death certificates. If the death occurred out-of-hospital, we also sought next of kin interviews and physician, coroner, and autopsy information about the death. To classify SCD, all events classified as having fatal CHD (definite fatal myocardial infarction, definite fatal CHD, or possible fatal CHD, in- and out-of-hospital) were reviewed again and adjudicated by a committee of physicians, funded through the Johns Hopkins University Donald W. Reynolds Cardiovascular Research Center. SCD was defined as a sudden pulseless condition from a cardiac origin in a previously stable individual. After review of data available, cases were classified as ‘definite’ sudden arrhythmic death, ‘possible’ sudden arrhythmic death, ‘not’ sudden arrhythmic death, or unclassifiable.

## The Cardiovascular Health Study (CHS)

The design and objectives of the Cardiovascular Health Study have been previously described(14). In brief, CHS is a longitudinal study of men and women aged 65 years or older, randomly selected from Medicare lists in Pittsburgh, PA; Forsyth County, NC; Sacramento County, CA; and Washington County, MD. The original cohort of 5201 participants was enrolled in 1989–1990; a second cohort of 687 African Americans was recruited in 1992–1993. Except where specified otherwise, both cohorts were used in this analysis, providing a total of 5888 participants. The institutional review board at each center approved the study, and each participant gave informed consent.

The baseline examination included a standardized questionnaire assessing a variety of risk factors, including smoking, alcohol intake, history of stroke, coronary heart disease, and heart failure, self-reported health status, and medication use on enrollment. Methods of determining prevalent cardiovascular disease were previously validated.(15) The examination included measurements of standing height, weight, and seated blood pressure (measured with a random-zero sphygmomanometer)(15), as well as a resting 12-lead ECG.

Of the initial 5888 individuals in the study population, we excluded 332 participants missing data on height, leaving a total of 5556 individuals for the analysis (Table 1).

Participants were contacted every 6 months for follow-up, alternating between a telephone interview and a clinic visit for the first 10 years, and by telephone interview only thereafter. Participants were followed from baseline until June 30, 2006, or death from other causes. The maximum follow-up was 16 years (median 12.5 years).

**Determination of SCD in CHS—**Death certificates, inpatient records, nursing home or hospice records, physician questionnaires, interviews with next-of-kin, and autopsy reports,

where available, were reviewed to determine the cause of death. SCD was defined as a sudden pulseless condition, presumed to be due to a cardiac arrhythmia, in a previously stable individual that occurred out of the hospital or in the emergency room. For unwitnessed deaths, the participant must have been seen within 24 hours of the arrest in a stable condition and without evidence of a noncardiac cause of cardiac arrest. SCD cases could not be under hospice or nursing home care or have a life-threatening noncardiac comorbidity.

### Analysis

Analyses were performed separately for each cohort, and then combined in a pre-specified meta-analysis. We examined *definite* SCD as the primary endpoint, with *total* SCD (includes both definite and possible) used as validation. For individual cohort analyses, a baseline model was employed using Cox proportional hazards regression with adjustment for age, sex, race, study location, smoking status and highest level of education achieved. If death during follow-up was due to other causes than SCD, the individual was censored at that time. We chose to include smoking status given the likelihood that achieved height and smoking status are markers of early life socioeconomic status(16). A second model was examined with inclusion of potential mediators (risk factors) of SCD potentially influenced by height, and included waist circumference, hypertension, resting heart rate, diabetes, prevalent heart failure, stroke, or coronary heart disease (CHD), and left ventricular hypertrophy as defined by ECG criteria(12, 17). These analyses were also repeated with stratification by sex and race. We tested multiplicative interactions between height and sex, prevalent CHD, and race. In a sub-analysis, we examined any incident non-fatal CHD as a time-varying covariate in the two models, with and without inclusion of prevalent CHD as a covariate (Note: In the model without prevalent CHD as a separate covariate, prevalent CHD is coded as a 1 for incident non-fatal CHD). We separately examined non-linear associations of height with risk in each cohort but found none and hence we report risks per 10-centimeter increments in height.

All CHS analysis was performed using the R statistical package(18) and statistical analysis of ARIC data was performed using SAS version 9.2 (SAS Institute Inc., Cary, NC). Fixed-effects meta-analysis was performed using the regression coefficients (natural log of the hazard ratio) and standard errors for each cohort, using Stata 11.2 (StataCorp, LP). We examined heterogeneity between the studies with the $I^2$ statistic. All authors had access to the final manuscript.

## RESULTS

Baseline characteristics of the two cohorts are shown in Table 1. The CHS cohort was older (mean age in CHS was 72.8 years vs. 54.2 years in ARIC) and generally had a greater prevalence of CHD, hypertension, and stroke, than the ARIC cohort.

### ARIC

In the ARIC cohort, we documented 276 cases of SCD, of which 227 cases were defined as *definite* SCD, 157 in men and 70 in women, during a mean follow-up time of 12.6 (Standard deviation 2.5 years). The crude incidence rate of definite SCD per 1000 person-years was 1.2 overall, and 0.6 for women and 1.8 for men. Height was inversely associated with the risk of SCD in ARIC (Figure 1A), an association that appeared to be related mainly to lower risk in men (Figure 1B). Adjustment for risk factors attenuated the observed risks only minimally. The result was similar for total SCD (Base model: $HR_{overall}$ 0.79, 95%CI 0.65, 0.95, p = 0.01; $HR_{women}$ 0.89, 95%CI 0.63, 1.26, p=0.51; $HR_{men}$ 0.72, 95%CI 0.57, 0.90,

p<0.01. Adjusted for Risk factors: $HR_{overall}$ 0.78, 95%CI 0.64, 0.95, p=0.01; $HR_{women}$ 0.85, 95%CI 0.60, 1.21, p=0.36; $HR_{men}$ 0.74, 95%CI 0.58, 0.94, p=0.01).

### CHS

In CHS, there were 319 cases of SCD, of which 199 were identified as *definite* SCD—123 in men and 76 in women—after a mean follow-up time of 11.7 (Standard deviation 4.9 years). The crude incidence rate of definite SCD per 1000 person-years was 2.9 overall; 1.9 in women and 4.9 in men. In CHS, we observed a trend toward an inverse association found between height and definite SCD (Figure 1A) that was again stronger in men (Figure 1B), although the association was not statistically significant. This result was also similar for total SCD (Base model: $HR_{overall}$ 0.86, 95%CI 0.71, 1.03, p = 0.11; $HR_{women}$ 0.92, 95%CI 0.68, 1.24, p=0.58; $HR_{men}$ 0.83, 95%CI 0.65, 1.05, p=0.11. Adjusted for Risk factors: $HR_{overall}$ 0.87, 95%CI 0.72, 1.04, p = 0.13; $HR_{women}$ 0.90, 95%CI 0.66, 1.22, p=0.49; $HR_{men}$ 0.87, 95%CI 0.68, 1.10, p=0.24).

### Combined analyses

In meta-analysis, taller height was significantly associated with lower risk of definite SCD overall (Figure 1A) with a 16% decrease in overall risk per 10 cm increase in height. This effect was significant only in men, where increased height was associated with a 20–25% decreased risk of definite SCD (Figure 1B). The overall association of height with definite SCD was minimally attenuated with inclusion of multiple other risk factors for SCD (Figure 1A, HR per 10 cm = 0.84 without risk factors vs. 0.86 with risk factors). There was no significant heterogeneity between studies in any of the analyses (see Figure 1A and 1B for statistics). When tested formally, the interaction term for height and sex was not statistically significant in either cohort at baseline or with inclusion of risk factors (pooled p interaction = 0.16). These results were also consistent with findings from *total* SCD (Supplemental Table 1).

The most common associated risk factor with SCD is CHD, which has been inversely associated with height in previous studies(19–21). We found no significant interaction of height with prevalent CHD in pooled analyses. We examined incident non-fatal CHD as a time-varying cofactor in models for effect attenuation, and found that inclusion of incident non-fatal CHD had minimal effect on the ability of height to predict risk of SCD ($HR_{With}$ 0.84 (95%CI 0.72, 0.98, p = 0.03; $HR_{Without}$ 0.85 (95%CI 0.73, 1.00, p = 0.05). This effect was consistent whether prevalent CHD was modeled as a separate variable or included as incident non-fatal CHD present at time 0 (Supplemental Table 2).

We observed no significant interaction between African American race and height in ARIC (p = 0.55) or CHS (p = 0.89), or in the combined analysis (p = 0.44).

## DISCUSSION

In this combined analysis of 21,189 participants with 426 cases of SCD, height was inversely associated with the risk of SCD, an association that was statistically significant in men. The association was not significantly attenuated with inclusion of other potential mediators, including left ventricular mass by ECG.

Sudden cardiac death is increasingly recognized as a public health concern, and remains a challenge from the research perspective. Aside from the heterogenous nature of the condition, which can occur through a variety of related and unrelated disease mechanisms, event confirmation is difficult, typically requiring formal adjudication by trained physicians, although previous studies using administrative coding have hinted at such a relationship.(22)

In our two cohorts of different age groups, the event rate was 0.1 – 0.3% per person-year (similar to previous results among individuals older than 35 years(23)), further emphasizing the challenge of studying this outcome. To our knowledge, this is the largest study of height and adjudicated SCD currently available.

Short stature is a well-described risk factor for CHD(19–21), and has been associated with an increased risk of congestive heart failure(24), stroke(25), and all-cause mortality(22). Vascular disease, and CHD in particular, is an important mechanistic link between height and risk of SCD. Coronary heart disease is a well-described risk factor for SCD, being responsible for an estimated 75% of all events(23, 26, 27), and lower CHD risk among taller individuals is one possible explanation for our findings. That we did not detect substantial attenuation of the association of height and SCD with inclusion of baseline CHD or incident non-fatal CHD as a covariate, nor a significant interaction of prevalent CHD with height, suggests that height may relate to lower SCD risk through other pathways as well.

Among our findings of subgroup analysis was the suggestion that men appeared to have a greater associations of height with lower SCD risk. Although we had no clear explanation for this finding, compared with women, men are at an increased risk of SCD. In a study of five primary prevention studies of implantable cardioverter-defibrillators (ICDs), women were found to have the same mortality as men, yet experienced fewer appropriate ICD interventions(28). This finding has been noted in other studies, in which women had less benefit of ICD implantation for primary or secondary prevention,(29) and less inducible ventricular tachycardia after myocardial infarction(30). These observations suggest that men may be particularly susceptible to ventricular arrhythmias (which benefit from ICD placement) as a cause of SCD and thus height may have particular importance for cases of SCD related to arrhythmias. However, no studies have directly examined the risk of ventricular arrhythmias *per se* and height to our knowledge.

In many ways, height is an intriguing risk factor. It is more easily objectively measured than other risk factors, including blood pressure, and the measures do not fluctuate over time, as with ECG intervals. It also reflects two factors in chronic disease that are difficult to quantify: environment and genetics. A number of genome-wide association studies have identified genes associated with height(31–38). The largest of these to date, the GIANT study, was performed in 183,727 people of European ancestry and identified 180 loci associated with height(38), which explain 0.3%(32) to 20%(38) of the heritable variation in height. Although no study has directly cross-referenced an association between these SNPs and the risk of SCD, in a genome-wide association study of the Oregon Sudden Unexpected Death Study (Oregon-SUDS), a minor allele of GPC5 (Glypican 5) was associated with a lower risk of SCD(39) and interestingly, this same gene was found to be associated with height in the GIANT study(38). While this finding may be spurious, it suggests that there could be genetic mechanisms for the protective effect of height on SCD.

In addition to the typical limitations discussed above relevant to study of SCD—event adjudication and limited numbers for power—our study was also limited in the combination of two somewhat different populations in terms of age and race. ARIC is a cohort of middle-aged individuals, with a larger percentage of African Americans than CHS, which is predominantly older. Middle-age height likely has different implications in terms of health overall than height in older age, which might imply the absence of conditions such as osteoporosis. Although we observed no significant heterogeneity, and there is not a well-described association between osteoporosis and sudden cardiac death, this difference could potentially limit meta-analysis of these two populations. We also had small numbers of individuals in particular sex-race categories, limiting our ability to study the observed interactions with precision.

In conclusion, in this combined meta-analysis of two large prospective cohorts, taller height was associated with lower risk of SCD. Subgroup analyses suggested that this association was most prominent in men, a group associated with an increased risk of SCD. More research is necessary to understand the mechanisms by which height relates to SCD and whether these can be harnessed for clinical benefit.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## Acknowledgments

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## List of Abbreviations (in order of appearance)

| | |
|---|---|
| **SCD** | Sudden cardiac death |
| **CHS** | Cardiovascular Health Study cohort |
| **ARIC** | Atherosclerosis Risk in Communities study cohort |
| **LV** | Left ventricular |
| **CHD** | Coronary heart disease |
| **HF** | Heart failure |
| **LVH** | Left ventricular hypertrophy |
| **ECG** | Electrocardiogram |
| **HR** | Hazard ratio |
| **CI** | Confidence interval |
| **ICD** | Implantable cardioverter-defibrillator |
| **GPC5** | Glypican 5 |

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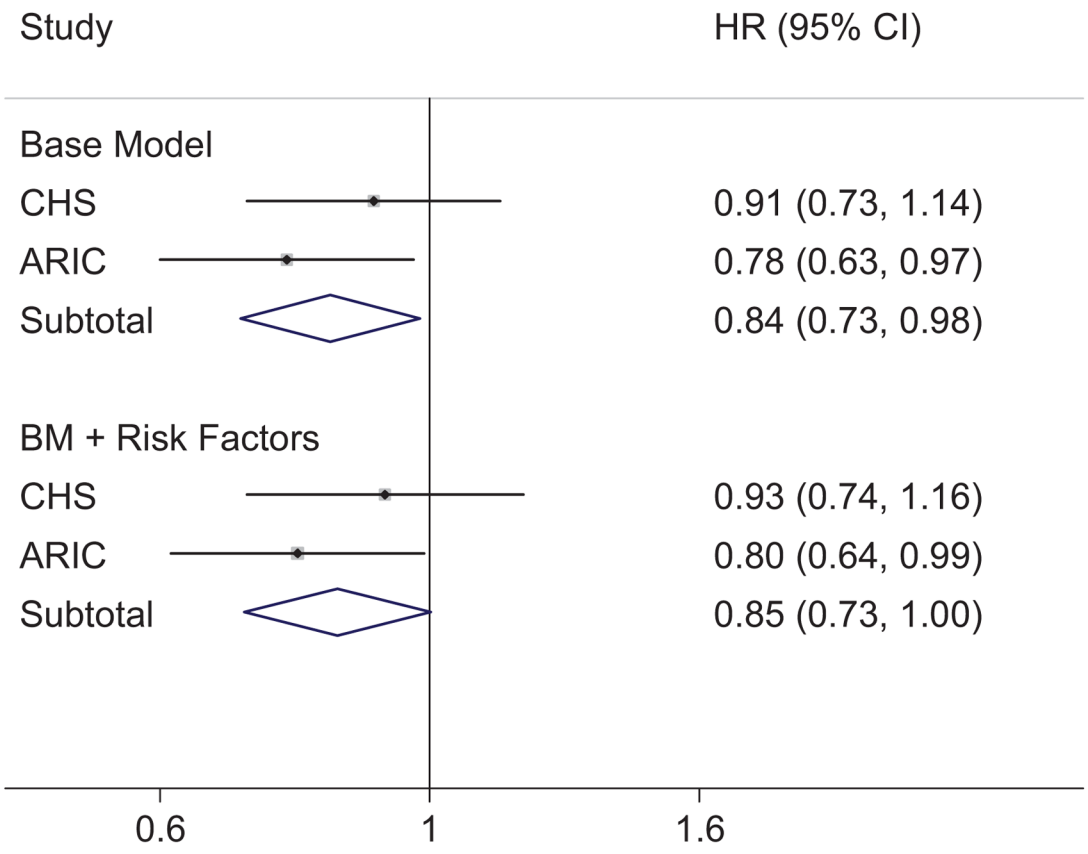


**Figure 1A.**

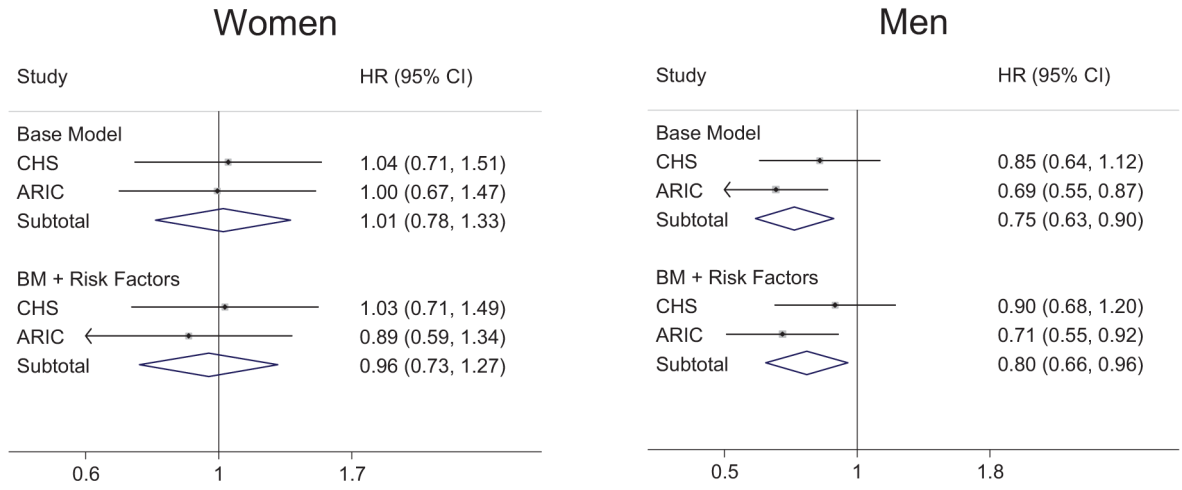


**Figure 1B.**

**Figure 1.**

**Figure 1A. Combined Meta-analysis.** Combined Meta-Analysis. Base Model (BM): Adjusted for age, sex, race, study location, Smoking status (current, former, and never), and

education. Risk Factors: Waist Circumference, HTN, resting heart rate (bpm), diabetes, prevalent heart failure, stroke, or coronary heart disease, and ECG-defined LVH. (Baseline Meta-analysis $I^2 = 0.0\%$, $p = 0.34$; BL + Risk Factors Meta-analysis I2 = 0.0%, p = 0.36). Note: Hazard ratio (HR) defined per 10cm of height.

**Figure 1B. Sex-stratified Meta-analysis.** Base Model (BM): Adjusted for age, race, study location, Smoking status (current, former, and never), and education. Risk Factors: Waist circumference, HTN, resting heart rate (bpm), diabetes, prevalent heart failure, stroke, or coronary heart disease, and ECG-defined LVH. (*Women*: Baseline Meta-analysis $I^2 = 0.0\%$, $p = 0.86$; BL + Risk Factors Meta-analysis $I^2 = 0.0\%$, $p = 0.61$; *Men*: Baseline Meta-analysis $I^2 = 15.0\%$, $p = 0.28$; BL + Risk Factors Meta-analysis $I^2 = 36.6\%$, $p = 0.21$). ). Note: Hazard ratio (HR) defined per 10cm of height.

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**Table 1**

Baseline Characteristics

| | CHS | | | ARIC | | |
|---|---|---|---|---|---|---|
| | **Total (N=5541)** | **Women (N=3183)** | **Men (N=2358)** | **Total (N=15,633)** | **Women (N= 8630)** | **Men (N=7003)** |
| Age (yrs) | 72.8±5.6 | 72.5±5.5 | 73.2±5.7 | 54.2±5.8 | 53.8±5.7 | 54.6±5.8 |
| African American | 837 (15%) | 521 (16%) | 316 (13%) | 4181 (27%) | 2594 (30%) | (23%) |
| BMI (kg/m2) | 26.7±4.7 | 26.9±5.3 | 26.5±3.8 | 27.7±5.4 | 27.9±6.1 | 27.5±4.2 |
| Standing Height (cm) | 165.0±9.5 | 158.9±6.3 | 173.1±6.6 | 168.5±9.3 | 162.3±6.0 | 176.1±6.6 |
| Waist Circumference (cm) | 94.6±13.2 | 92.2±14.4 | 97.7±10.4 | 97.0±13.9 | 95.4±15.7 | 99.1±11.1 |
| Treated HTN | 2608(47%) | 1556(49%) | 1052(45%) | 5446(35%) | 3043(35%) | 2403(34%) |
| Diabetes | 901 (16%) | 456 (14%) | 445 (19%) | 1856 | 1016 | 840 (12%) |
| Prevalent CHF | 243 (4%) | 130 (4%) | 113 (5%) | 743 (5%) | 516 (6%) | 227 (3%) |
| Prevalent CHD | 1068(19%) | 494 (16%) | 574 (24%) | 762 (5%) | 189 (2%) | 573 (8%) |
| Prior CVA | 229 (4%) | 102 (3%) | 127 (5%) | 283 (2%) | 161 (2%) | 122 (2%) |
| Current Cigarette smoking | 647 (12%) | 395 (12%) | 252 (11%) | 4088(26%) | 2145(25%) | 1943(28%) |
| Former Cigarette | 2315(42%) | 965(30%) | 1350(57%) | 5038(32%) | 1932(22%) | 3106(44%) |
| LVH on ECG | 274 (5%) | 158 (5%) | 116 (5%) | 346 (2%) | 195 (2%) | 151 (2%) |
| Resting heart rate (bpm) | 68.0±11.2 | 69.1±10.8 | 66.4±11.5 | 66.7±10.4 | 68.0±10.1 | 65.1±10.4 |

For measurements, values displayed are mean±standard deviation.