

# Influence of pre-hypertension on all-cause and cardiovascular mortality: The Singapore Cardiovascular Cohort Study<sup>☆</sup>

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## Abstract

**Background:** The effect of “pre-hypertension” (pre-HTN) itself, and in combination with other cardiovascular disease (CVD) risk factors in relation to mortality has not been assessed in Asian populations.

**Methods:** From three cross-sectional studies conducted in Singapore (baseline 1982–1995), 5830 persons were grouped into normotensive (NT), pre-HTN or hypertensive (HTN). Follow-up (median 12.0 yrs, IQR 12–19 yrs) was done by linkage to the National Death Register. Outcomes included all-cause and CVD (ischaemic heart disease (ICD-9 410–414) and cerebrovascular accidents (ICD-9 430–438)). Cox’s proportional hazards model was used to obtain adjusted hazard ratios (HRs) for risk of mortality.

**Results:** After adjustment, pre-HTN was not associated with a statistically significant increased risk of all-cause or CVD mortality. However, an increased risk for all-cause and CVD mortality, in the presence of diabetes (adjusted HR 1.8; 95%CI 1.0–2.9 and 4.4; 95%CI 1.9–10.4), smoking (adjusted HR 2.2; 95%CI 1.3–3.5 and 4.9; 95%CI 1.8–13.3), and especially, pre-existing CVD (adjusted HR 3.1; 95%CI 1.5–6.4 and 9.3; 95%CI 3.3–25.9) was found.

**Conclusions:** Pre-HTN was not an independent risk factor for mortality. However an increased risk of mortality for pre-HTN in the presence of other CVD risk factors was observed. This finding supports current recommendations to screen for these risk factors in the pre-HTN Asian population.

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**Keywords:** Pre-hypertension; Cardiovascular risk factors; Cohort; Asian; Mortality

## 1. Introduction

Hypertension is one of the partially modifiable risk factors for cardiovascular disease (CVD) mortality and accounts for up to 30% of deaths worldwide [1]. Globally,

approximately two-thirds of stroke and one-half of coronary heart disease are attributable to non-optimal blood pressure [2]. The seventh report of the joint national committee on prevention, detection, evaluation, and treatment of high blood pressure (JNC 7) introduced a new blood pressure category termed “pre-hypertension” (pre-HTN) [3]. This comprises individuals who have either systolic blood pressure of 120–139 mm Hg or diastolic blood pressure of 80–89 mm Hg. The committee recommended the identification of these individuals as they are at increased risk for progression to hypertension (HTN) [4] and subsequently other CVD such as stroke and coronary heart disease [5]. Several other recent guidelines, including those of the European Society of Hypertension–European

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Society of Cardiology (ESH-ESC) [6] and the British Hypertension Society (BHS) [7], have also identified a similar category of individuals whereby individuals with systolic blood pressure 130–139 or diastolic blood pressure 85–89 are described as being high-normal. As a majority of pre-HTN and HTN patients have additional CVD risk factors [8] another recommendation is to identify other cardiovascular risk factors during the assessment of patients with documented pre-HTN and HTN in order to institute intervention to both blood pressure and the other risk factors.

So far, only a few prospective population-based studies have assessed the effect of pre-HTN on morbidity or mortality outcomes with both positive [9–12], and negative [13] findings. Although there is evidence that increasing blood pressure levels is associated with CVD in Asians [14,15], to the best of our knowledge, no studies have been published specifically assessing the effect of blood pressure by the new JNC 7 criteria alone, and in combination with other CVD risk factors on mortality outcomes in an Asian population. Singapore is an island nation comprising approximately 4 million inhabitants all residing in a completely urbanized environment with equitable healthcare coverage. The population is composed of three main ethnic groups; Chinese (76.9%), Malays (14.6%) and Asian Indians (6.4%). The aim of this study was to assess the effect of pre-HTN and HTN alone, as well as in combination with other CVD risk factors on all-cause and CVD mortality in an Asian population.

## 2. Methods

### 2.1. Participants

This population-based prospective study (Singapore Cardiovascular Cohort Study) was carried out using 3 previous cross-sectional surveys. These are the Thyroid Heart Study 1982–1985, the 1992 National Health Survey and the National University of Singapore Heart Study (1993–1995). The methodologies of these studies have been described in detail elsewhere [16]. These studies consist of a random sample of individuals living in Singapore. Informed consent was obtained from participants of all 3 studies.

### 2.2. Baseline measurements and variables

All subjects were examined in the morning following a 10-hour overnight fast. Plasma glucose and serum lipid concentrations (total cholesterol, triglyceride and high density lipoprotein cholesterol [HDL-C]) were measured. Low density lipoprotein cholesterol (LDL-C) was calculated using the Friedewald formula [17]. At least two readings of blood pressure were taken from participants who had rested at least 15 min before measurement, using a standard mercury sphygmomanometer. Participants were advised to

avoid cigarette smoking, alcohol, caffeinated beverages, and exercise for at least 30 min before their blood pressure examination. The reading to the nearest 2 mm Hg was obtained and the mean values of the two readings were calculated. In 2 of the studies (Thyroid Heart Study 1982–1985, the and the National University of Singapore Heart Study (1993–1995) blood pressure was measured by one individual (one of the authors, KH) whilst trained nurses took the measurements in the 1992 National Health Survey. Weight and height were also measured. Smoking history was categorized as current smoker or non- and ex-smoker. Alcohol intake was categorized as drinking less than once/month or greater than or equal to once/month as there were few drinkers in this Asian cohort study. Individuals were also asked if they have ever been diagnosed as having coronary artery disease, cerebrovascular accident, diabetes or hypertension; and whether medication was prescribed. Ethnicity was self reported at study entry and was classified into Chinese, Malay, Indian and Others.

Individuals were grouped according to their blood pressure measurements and classified as: Normotensive: SBP < 120 mm Hg and DBP < 80 mm Hg (NT), Pre-hypertensive: SBP 120–139 mm Hg or DBP 80–89 mm Hg (pre-HTN) or Hypertensive: SBP  $\geq$  140 mm Hg or DBP  $\geq$  90 mm Hg or currently being treated for hypertension (HTN).

The other CVD risk factors that corresponded approximately to the JNC 7 recommendations include: (i) obesity (BMI  $\geq$  27.5 kg/m<sup>2</sup> using the Asian Criteria (1), (ii) elevated total-cholesterol/HDL-cholesterol ratio of  $\geq$  5, (iii) presence of diabetes (previously diagnosed diabetes or current fasting plasma glucose  $\geq$  7.0 mmol/l), and (iv) personal history of coronary artery disease or cerebrovascular accident and (pre-existing CVD), (v) current cigarette smoking. Data on history of chronic kidney disease or retinopathy, microalbuminuria, and family history of premature CVD was not available for assessment in this study. Although age group ( $>$ 55 years for males and  $>$ 65 years for females) is a CVD risk factor in the JNC7 recommendations, it was not used as a CVD risk factor in this study as it was felt that adjustment for age in the statistical analysis would be more appropriate.

### 2.3. Outcomes

Events were obtained by linking individual records (using unique national registry identity card number) to the Singapore Registry of Births and Deaths. The registration of deaths is a compulsory requirement in Singapore. All outcomes were in coded form using the 9th revision of the *International Classification of Diseases* (ICD-9). All-cause mortality included all deaths that occurred in the cohort up till 31st December 2004. The primary cause of death was used. Cardiovascular (CVD) mortality included all deaths due to ischaemic heart disease (IHD) (ICD-9 410–414) and cerebrovascular accidents (CVA) (ICD-9 430–438).

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