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THE INCIDENCE OF CORONARY HEART DISEASE IN INDIVIDUALS WITH DIFFERENT GRADATIONS OF BLOOD PRESSURE AND BODY WEIGHT

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Abstract. *A group of six hundred and sixty-eight men was selected at random from the general population of men aged 20-69 years and examined to ascertain coronary heart disease (CHD) amongst those men on various levels of blood pressure and of body weight. Frequency of CHD rose with each successive body mass category and each successive blood pressure category; having arterial hypertension was associated with a 3.5-fold increase, compared with the same body mass category and normal bp ($p<0.01$); and obesity was associated with a 3.6-fold increase, compared to the underlying blood pressure category and normal body weight ($p<0.01$). Importantly, at even the high-normal blood pressure and overweight levels —levels traditionally considered to have little or no extra risk—the rate of CHD was already higher than at the same normal levels. The results suggest a differentiated risk stratification approach for cardiovascular risk which considers sub-threshold blood pressure elevations, body weight and not only binary risk thresholds.*

Keywords: *arterial hypertension, overweight, obesity, metabolic syndrome, coronary heart disease.*

Introduction.

Insulin resistance is now considered as the initiating factor of the metabolic syndrome (MS) and its sole common pathophysiological substrate, and the MS is at the center of cardiovascular research today. The four cardinal features of this syndrome are the presence of arterial hypertension (AH), overweight / obesity, dyslipidemia and impaired glucose tolerance (IGT), and are not randomly distributed among patients, but are co-occurring and share common underlying mechanisms. Due to the high, and even higher in some populations, prevalence of its individual components [2, 3, 8, 13] and as a result of this, MS and its sequelae have been identified as a key concern for prevention of cardiovascular and metabolic diseases at the international level, with recommendations for increased efforts in this area. Increasing prevalence of all the major components of MS over time has been observed in population-based studies [9] and the presence of various components and combinations of these components has been linked to higher cardiovascular and general risk [14], with risk rising disproportionately with the number of components present simultaneously. The clustering phenomenon is particularly clinically relevant because it suggests that the cardiovascular risk of each individual factor (elevated blood pressure) can't be understood without regard to the other factors in the broader metabolic picture that usually accompany these.

Patient age plays an important role in the composition of the syndrome as well as the downstream prognosis, in addition to the core components of MS. The number and type of MS components may vary significantly between different age groups: before age 40, factors such as unhealthy habits and hypertension often play a larger role as a result of the early effect of lifestyle and metabolic factors; after age 40, obesity and insulin resistance become more prominent, due to the

age-dependent loss of metabolic efficiency and the progressive accumulation of the visceral adipose tissue. This age-related change in the relative importance of each individual MS component has direct relevance to clinical practice because a risk-assessment approach tailored to a younger population may systematically underestimate the contribution of insulin resistance due to adiposity in an older population, and the other way around. Risk stratification for MS risk and associated diseases should thus be considered with the intention of using age-specific risk stratification, and not using a single risk algorithm throughout the adult life-span.

In this context, it is important to look at the severity in addition to the presence or absence of the main components of the MS, as threshold-based classification (e.g., simple presence or absence of hypertension or obesity) may conceal clinically relevant versions of the disease below the conventional disease cut-off. A more granular and gradation-centered risk assessment strategy may be able to identify a person who does not have formal diagnostic criteria, but is in between, such that they would benefit from a more intensive risk monitoring strategy. This is particularly relevant in large-scale population screening and it is important to have a tool that is non-invasive, widely available and not expensive, and among these, blood pressure and body weight measurement are of primary importance, due to being reliable, easily deployable, and usable even in primary-care or community-based settings that are lacking in biochemical or imaging-based diagnostic equipment.

Aim of the study. To examine the relationship between coronary heart disease and varying degrees of severity of elevated blood pressure and excess body weight.

Materials and Methods.

This report is based on the results of a cross-sectional analysis of 668 men, which were a random sample from the unorganized (general) population between the ages of 20 and 69 years. The sampling of age-heterogeneous individuals and random selection of subjects was designed to reflect the range of blood pressure and body weight gradations which are commonly seen in daily clinical and epidemiological work, and not just a selected sub-spectrum of blood pressure and body weight. The study utilized a multi-modal approach using a questionnaire-based approach, biochemical and instrumental methods, which was a strategy that would provide triangulation for diagnosis of coronary heart disease (CHD) rather than relying on one method alone.

The interview part was carried out with the standard questionnaire of the World Health Organization (WHO) for the detection of exertional angina pectoris, which is a validated instrument widely used in cardiovascular epidemiology in population-based studies and is internationally recognized [17]. Diagnosis of angina pectoris was made if retrosternal and/or left-sided chest and left arm pain occurred upon exertion, as indicated by the standardized diagnostic criteria outlined in the questionnaire. A parallel, standardized WHO questionnaire was also used to detect potential previous myocardial infarction, operationally defined as the presence of a history of severe chest pain for more than 30 minutes, in the absence of supporting changes in the electrocardiogram (ECG) - this criterion was added to minimize the rate of false positive cases based on symptom history alone.

Instrumental methods contained three main components, each addressing a different aspect of cardiovascular risk assessment.

a) Resting electrocardiography (ECG) was done in 12 standard leads under standard resting conditions, and the ECG tracings were classified qualitatively and quantitatively as per the Minnesota Code, a long-established and internationally accepted classification system used for qualitative and quantitative categorization of ECG abnormalities in epidemiological studies. This approach allowed the systematic identification of the characteristics of CHD: myocardial infarction, stable exertional angina, painless (silent) form of CHD (i.e. presence of ischemic ECG changes without pain syndrome) and a possible arrhythmic form of CHD. Standardization of the coding of all ECG tracings was planned to limit inter-observer variation in interpretation of the tracings and to ensure uniformity of CHD ascertainment throughout the entire study population.

b) Blood pressure (BP) was measured following the existing diagnostic criteria, and divided into three groups: normal BP, high-normal BP and arterial hypertension. The rationale for using this tri-partite classification was specifically to examine the intermediate blood-pressure (BP) sub-diagnostic range in accord with the wider justification provided in the Introduction for choosing a graded classification for risk rather than a dichotomized classification between normotensive and hypertensive.

c) Body weight was assessed based on the Quetelet index or more commonly body mass index (BMI), which is weight (kg) divided by height squared (m2). According to the internationally accepted anthropometric criteria, overweight was defined as BMI ≥ 25 and < 30 kg/m2, and obesity as BMI ≥ 30 kg/m2. Like the blood-pressure classification cited above, this three-classification of body weight was chosen to allow the overweight group to be considered as a separate intermediate level of adiposity rather than being aggregated with either the normal-weight or obese group.

Results.

Of the 668 men examined, 584 (87.4%) were without clinical and/or electrocardiographic evidence of CHD, and the other 84 (12.6%) were clinically and/or electrocardiographically classified as CHD with the WHO questionnaire. The overall sample was subsequently divided into the blood-pressure categories, and a distinct difference in the frequency of CHD was found between the three blood pressure groups (Figure 1). Specifically, CHD was seen to be more common in those with AH than in those with normal BP (28.35% vs 8.58%, $p<0.01$), indicating that the disease was not evenly distributed amongst those with a normal BP, but was concentrated in the hypertensive group. There was no statistical difference ($p>0.05$) in CHD frequency between the high-normal BP group and the normal BP group; in individuals with high-normal BP, CHD frequency was 10.67% — numerically higher, but not significantly different, from the normal BP group — and this difference was not statistically significant on the basis of the current sample size alone.

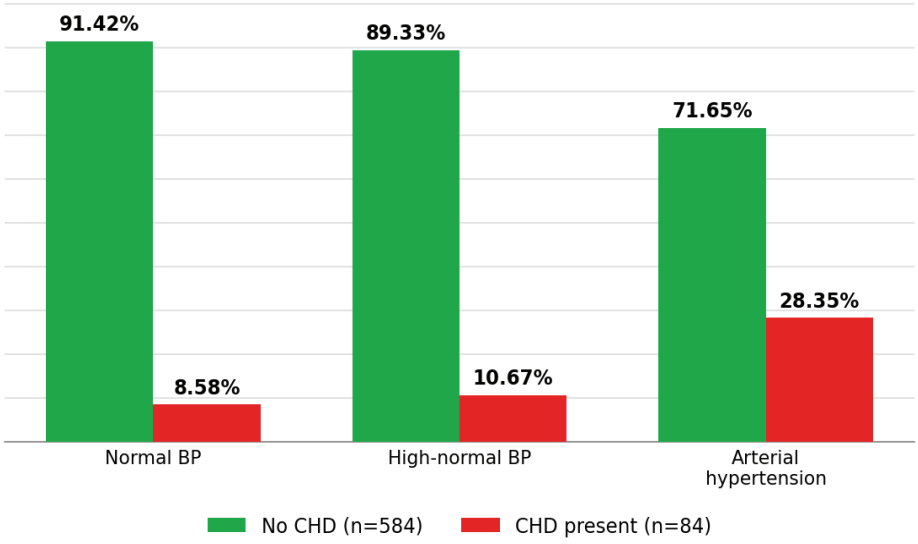


Fig. 1. Incidence of CHD in groups with normal BP, high-normal BP, and arterial hypertension

The same sample was then divided into the body-weight categories to look at the association between CHD frequency and body weight (Figure 2). The data indicates that there was a definite increase in frequency of CHD in the overweight and obese groups as well, similar to blood pressure, increasing from 7.51% of those of normal weight to 12.93% of those who were overweight and 26.73% of those who were obese. This translates to a 3.6-fold increase in CHD prevalence amongst those with obesity compared to those with normal body weight ($p<0.01$) and a 1.7-fold increase amongst the overweight compared with the normal body weight group. Both of these body-weight

comparisons were statistically significant, whereas in the case of blood pressure, the relationship of frequency of CHD with body weight was more clearly resolved within this sample.

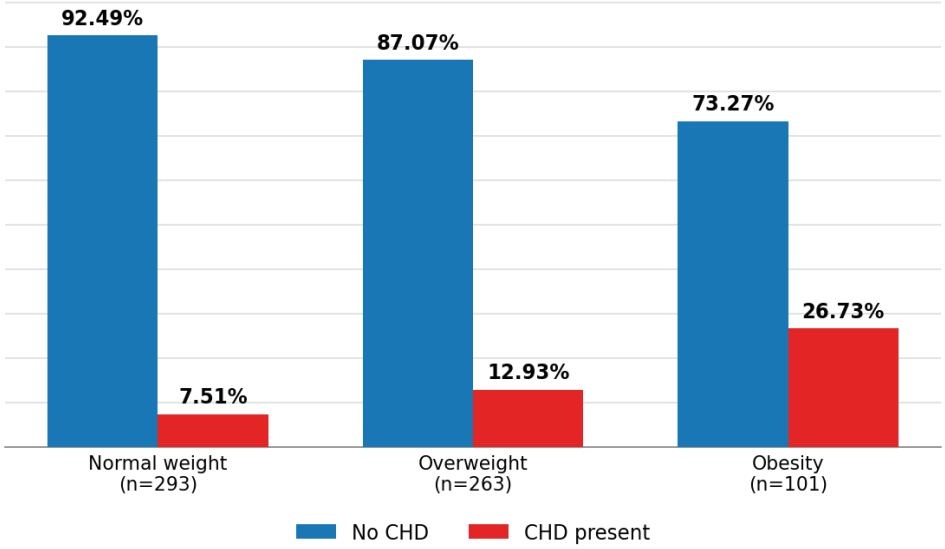


Fig. 2. Incidence of CHD in groups with different body weight categories

Collectively, these findings establish a graded, monotonic gradient in CHD prevalence across successive categories of both blood pressure (8.6% → 10.7% → 28.4% for normal, high-normal, and hypertensive BP, respectively) and body weight (7.5% → 12.9% → 26.7% for normal weight, overweight, and obesity, respectively), a pattern consonant with a dose-dependent relationship between the severity of these two metabolic syndrome components and the burden of coronary heart disease. Not only was this gradient true for direction, but it was also true for continuity: the prevalence of CHD rose gradually between each of the sub-diagnostic categories between normal-to-high normal and overweight and obesity categories, with the high normal and overweight diagnostic categories having prevalence positions intermediate between their respective normal and over-pathological counterparts. This is a continuous ordinal relationship, and is typical of cardiovascular risk factors in general, and provides quantitative support for the conceptualization of blood pressure and body weight as continua of risk, not as binary clinical states.

It is noteworthy however that CHD prevalence was by no means trivial in the healthy blood pressure and healthy weight referent groups (8.6% and 7.5% respectively). In absolute terms, this is a significant residual burden of disease in low-risk populations and argues against considering these two risk factors alone as an explanation of the overall coronary risk in these populations. It does not mean, however, that other unmeasured factors that influence disease susceptibility are not at work, which may include other features of the metabolic syndrome, such as dyslipidemia, hyperglycemia and insulin resistance, which were not directly evaluated in the analytic framework used in this study, but instead points to the multiple factors influencing the etiology of coronary heart disease, even among those who, based on BP and body weight alone, would be considered relatively low cardiovascular risk.

Discussion.

The observed increase in CHD prevalence in patients with AH is consistent with the well-established AH as a major CHD risk factor. Importantly, the relatively small (but not significant) BP increase found in those with high-normal BP also highlights that this level of BP may be a precursor for the development of CHD, as explored below in the context of the larger epidemiological literature on pre-hypertensive states.

The gradual increasing trend in CHD frequencies within each blood pressure and body weight range suggests that cardiovascular risk does not "just happen" after crossing over to the hypertension or obesity ranges, but builds up gradually in the intermediate ranges that lead up to those thresholds. Hence, people with high-normal blood pressure and overweight are already at an intermediate risk between the normal and the overtly pathological groups and deserve to be studied in the prediction of AH and as regards preventive measures for AH and overweight.

Additional risk factors not directly evaluated in the present study (such as other components of the metabolic syndrome like insulin resistance, dyslipidemia and hyperuricemia) may be partly responsible for the high proportion of CHD cases that occurred even in those with normal blood pressure and body weight.

The graded pattern seen in blood pressure and body weight is similar to that of the other components of metabolic syndrome, which are pathologically linked to atherosclerotic disease [15]. High blood pressure (even when it is not a diagnostic for hypertension) causes the blood vessel lining to become stressed by shear stress, early endothelial dysfunction, and vascular wall remodeling, which in turn leads to left ventricular hypertrophy (LVH) over time, increasing the oxygen demand of the heart and decreasing the ischemic threshold. In addition, excess adiposity (especially visceral fat) acts via a parallel pathway, by inducing insulin resistance, an atherogenic dyslipidemia profile defined by hypertriglyceridemia and hypoHDL-cholesterolaemia, and by promoting low-grade systemic inflammation and oxidative stress, both of which are known to contribute to endothelial dysfunction and atherogenesis on their own [16]. Patients with blood pressure and obesity in intermediate ranges are likely already on a common pathway (including both sympathetic and renin-angiotensin-aldosterone system activation and insulin resistance) and may well explain in a mechanistic way why their CHD prevalence is higher than that of people with strictly normal measurements.

This is consistent with a large amount of global evidence. Huang et al. [6] conducted a meta-analysis of eighteen prospective cohort studies of over 468,000 individuals that found that prehypertension (defined as what is most similar to the high-normal BP grade we used in the present study) was associated with a 50% increased risk for incident CHD (RR 1.50, 95% CI 1.30–1.74). This confirms the directionally consistent, albeit not statistically significant, increased CHD frequency seen in the high-normal BP subgroup in the present sample, which is most likely due to the relatively small number of CHD cases available for analysis within this group, compared to that of the larger normotensive subgroup (n=959 across the entire sample). Previous research has found a similar graded association between adiposity and cardiovascular risk; whereby excess body weight (even at lean body weights) is associated with clustering of coronary risk factors [5]; and more recent population-based analyses of NHANES data have found that metabolically unhealthy overweight and obese adults have a significantly higher prevalence of cardiovascular disease than do normal weight adults [18]. The present findings, which come from a Central Asian population, are consistent with previous regional studies, showing the relationships between the severity of each of the metabolic syndrome components and the prevalence and mortality due to CHD [11] and the prevalence of cardiovascular risk factors in this region is still relatively scarce.

Limitations. The findings of the study need to be considered with some limitations in mind. First, the cross-sectional design does not allow for conclusions on the temporal or causal relationship of blood pressure, body weight and CHD. Second, the study population consisted of men only, which may restrict the application of the results to women, where the prevalence and clinical characteristics of CHD, as well as the distribution of the components of metabolic syndrome, are also known to differ [12]. Third, classification of blood pressure was based on the criteria used at the time of examination, and the number of occasions on which blood pressure was measured, as well as the potential for single visit misclassification (e.g. associated with a white coat effect) were not reported separately. Lastly, other known components of the metabolic syndrome, such as fasting glucose, lipid

profile, waist circumference, and the more difficult-to-measure cardiovascular end points described in previous regional studies [10] have not been measured or adjusted in the current study, and may account for some of the observed gradient.

Clinical implications. The practical implications of the findings are especially relevant for cardiovascular prevention, particularly in resource-limited settings throughout Central Asia, where access to advanced biochemical or imaging-based risk assessment is not equally available [4, 19], as is also the case in non-communicable disease control. Given that blood pressure and body weight measurement is cheap, non-invasive, and accessible even at the primary-care level, it is an appealing method of opportunistic cardiovascular screening, consistent with the larger community's push for accessible and pharmacist- and primary-care-supported strategies for the screening and prevention of metabolic syndrome [1, 7]. The observed gradient argues against restricting clinical focus to those with diagnosed hypertension or obesity: those in the 'high-normal' blood pressure and overweight range already have a high frequency of CHD and may require earlier intervention with lifestyle counseling, more frequent monitoring and a lower threshold for additional screening of risk factors. These findings provide some basis for designing future intervention trials to determine if lifestyle interventions for these sub-threshold intermediate categories can have a significant impact on future CHD events.

Conclusions.

This study's results suggest that preventive efforts shouldn't be limited to those with a formal diagnosis of hypertension or obesity, but offered to individuals in a clinical evaluation who also need intervention. Instead, there is clear evidence that the sub-threshold gradations of high-normal blood pressure and excess body weight are associated with elevated rates of CHD and, as such, should be specifically considered when estimating risk. Accordingly proactive therapeutic and lifestyle measures geared towards the maintenance of normotension and suitable body weight need to be implemented in this intermediate risk group and not delayed if formal diagnostic thresholds are surpassed.

Conversely, the high prevalence of cardiac disease found even in people with perfect blood pressure and normal weight indicates that these measurements alone, rather than sufficient, may not predict cardiovascular risk. Hence, there is a need for additional screening for other known cardiovascular risk factors/aspect of MS in this seemingly less-risk group to identify any residual risks in such individuals which would otherwise remain undetected by BP/weight measurements alone.

The overall findings of this study seem to suggest that the connection between CHD and cardiovascular risk factors is a continuum instead of a series of distinct and separate diagnostic categories. The results of this large, population-based study provide empirical evidence for the application of gradation-based risk models in clinical and public-health practice to more effectively target available diagnostic resources, including simpler biochemical or imaging-based tools, in situations in which there is limited access to more advanced infrastructure tools. Future prospective studies should confirm these cross-sectional observations in a longitudinal fashion, include other components of metabolic syndrome (dyslipidemia, glycemic status) as part of a more inclusive risk-stratification system and explore whether targeted intervention in sub-threshold blood pressure and body weight levels can result in measurable reductions in the subsequent incidence of CHD.

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