ORIGINAL ARTICLE

CARDIOVASCULAR DISEASE RISK ASSESSMENT WITH HIGH-SENSITIVITY CARDIAC TROPONIN I AND OTHER BIOMARKERS: AN OBSERVATIONAL COHORT STUDY IN JOHOR, MALAYSIA

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ABSTRACT

Although cardiovascular disease (CVD) is a major health challenge in Malaysia, many Malaysians are unaware of their CVD risk. The measurement of biomarkers in the general population may help to identify at-risk individuals before the onset of symptomatic CVD. The aim of this community health screening project was to determine the distribution of high-sensitivity troponin I (hsTnI) and other biomarkers of CVD risk in the general population of Johor, Malaysia. A sampling of self-declared healthy volunteers was conducted during the 2016 Kembara Mahkota community event in Johor. Levels of hsTnI, B-type natriuretic peptide (BNP) and homocysteine (HCY) were analyzed using the ARCHITECT immunoassay and clinical chemistry platforms utilizing fresh venous blood samples. Based on previous data, biomarker levels indicative of high risk were >10 and >12 ng/mL for hsTnI in women and men, respectively, BNP >50 pg/mL in the overall population, and HCY >13.6 µmol/L in women and >16.2 µmol/L in men. A total of 2744 volunteers participated in biomarker testing. Biomarker measurements showed that up to 10% of participants had moderate or high CVD risk based on hsTnI, approximately 2% were above the BNP threshold and >50% of subjects were above the HCY threshold. General population biomarker testing shows distribution of biomarker levels that may be indicative of CVD risk or the presence of disease and suggests that biomarker-guided risk strategies should be more widely implemented to determine the impact they would have on early detection and prevention of disease.

Key words: biomarkers, B-type natriuretic peptide, cardiovascular disease, homocysteine, troponin, Malaysia; risk classification, screening

INTRODUCTION

The increasing prevalence non-communicable diseases (NCDs) represents a key health challenge in Malaysia, with NCDs causing more deaths than all other causes combined.[1-3] Cardiovascular disease (CVD) is particularly problematic, developing at a relatively young age and accounting for 36% of all deaths in Malaysia in 2012.[1-4]

Most cases of CVD can be prevented, but many Malaysians have undiagnosed CVD risk factors and remain unaware of their increased CVD risk.[5,6] These patients often go on to present with late-stage coronary heart disease (CHD), heart failure (HF) or major adverse CV events, such as myocardial infarction (MI) and stroke.[1-4,6] It is therefore important to encourage participation in health checks for CVD prevention.[5,6] However, CVD screening in Malaysia is mainly performed opportunistically by healthcare providers or is initiated by the individual, and the uptake of health checks is low.[5] Furthermore, the subclinical cardiac dysfunction that precedes HF and other CVD is often undiagnosed because of a lack of screening and testing strategies.[7] The measurement of biomarkers in the general population may help to identify at-risk individuals for timely intervention and prevention before the

onset of clinically detectable risk factors or symptomatic CVD.[7,8]

To obtain clear local NCD risk data in the general population of Johor, Malaysia, we conducted a community-based project in which members of public were encouraged to undergo blood-based biomarker tests to screen for risk of various NCDs. Here, we report the results of the CVD arm of the project, in which high-sensitivity troponin I (hsTnI), B-type natriuretic peptide (BNP) and homocysteine (HCY) levels were measured to assess distribution of the population with previously reported risk thresholds.[9-20] Results of screening for other NCDs (type 2 diabetes, cancer and thyroid disease) will be reported separately.

MATERIALS AND METHODS

General population screening was conducted during the Kembara Mahkota event, which took place from the 14th to the 17th of May 2016. The Kembara Mahkota is a royal "meet the people" tour that covers the 10 districts of the state of Johor. A total of 2744 individuals over the age of 18 volunteered for biomarker testing at the event. They were briefed by district healthcare personnel, and asked basic questions regarding their medical, surgical and family disease history. All volunteers were free of known CVD based on self-declaration. Collected venous blood samples

were anonymized and then transported to KPJ Johor Specialist Hospital for analysis.

This study was part of a Johor State government community service project that was approved and conducted by the Johor State Health Department. All participants gave informed consent. Fresh blood sample analyses were performed daily at Johor Specialist Hospital. All hsTnI, BNP and HCY analyses were performed on the Abbott ARCHITECT immune assay and clinical chemistry system. Levels of hsTnI >10 ng/L in women and >12 ng/L in men were considered to be indicative of a high risk of CVD, 4-10 and 6-12 ng/L, respectively were considered moderate risk, whereas readings of <4 ng/L in women and <6 ng/L in men were considered low risk.[11,12,16,17,20] In the overall population, BNP >50 pg/mL was considered to be indicative of risk of HF, and BNP >100 pg/mL indicated high risk of HF.[10,14,15] Levels of HCY >13.6 µmol/L in women and >16.2 µmol/L in men were considered to be indicative of risk of CVD.[9,13,18,19]

RESULTS

Subject characteristics
Individuals who took part in biomarker screening (n=2744) were aged between 18 and >80 years old; subject to sample availability, each of the three cardiovascular biomarkers of interest was measured in a minimum of 2716 participants. Most participants (93%) were <60 years old, and 50.6% were female (Table I).

Table I. Demographic characteristics of the screened population

Characteristics	Total (N = 2716)
Gender, n/N (%)	
Female	1489 / 2716
Male	1227 / 2716
Age and gender, n/N (%)	
Females Aged < 60 years	1393 / 1489
Females Aged ≥ 60 years	96 / 1489 (6%)
Males Aged < 60 years	1097 / 1227
Males Aged ≥ 60 years	130 / 1227

The distribution of biomarker risk categories is shown in Figure 1. Based on hsTnI measurements, 1.1% of women and 3.4% of men were considered to be at high risk for CV events, 1.1% of women and 6.9% of men were at moderate risk, and 92.8% of women and 89.6% of men were considered low risk. The BNP level was >50 pg/mL, indicating a risk of future HF, in 3.2% of the population, and a BNP level >100 pg/mL, indicating high risk of HF, was present in 0.8%. HCY levels were indicative of CVD risk in 55.2% of women and 54.3% of men.

Median biomarker levels are shown in Table II. The interquartile range and 90th, 95th and 99th percentile values indicate that levels of BNP and hsTnI were not normally distributed but skewed towards the lower end of the range.

Table II. Median (interquartile range) cardiovascular biomarker levels, along with 90th, 95th and 99th percentiles

	BNP, pg/mL	hsTnI, ng/L	Homocysteine, µmol/L
Median (IQR)	11.0 (10.0–19.0)	1.4 (0.8–2.5)	16.6 (7.4-29.9)
90th percentile	30.0	4.6	41.4
95th percentile	42.0	7.0	46.9
99th percentile	83.0	19.0	50.0

IQR, interquartile range

Mean and median levels of each individual biomarker tended to increase with age, peaking in patients aged 70 to 79 years (Table III and Figure 2), but did not vary significantly between men and women (Table III and Figure 3). The fact that most participants were under the age of 60 years may have influenced the distribution of hsTnI concentrations.
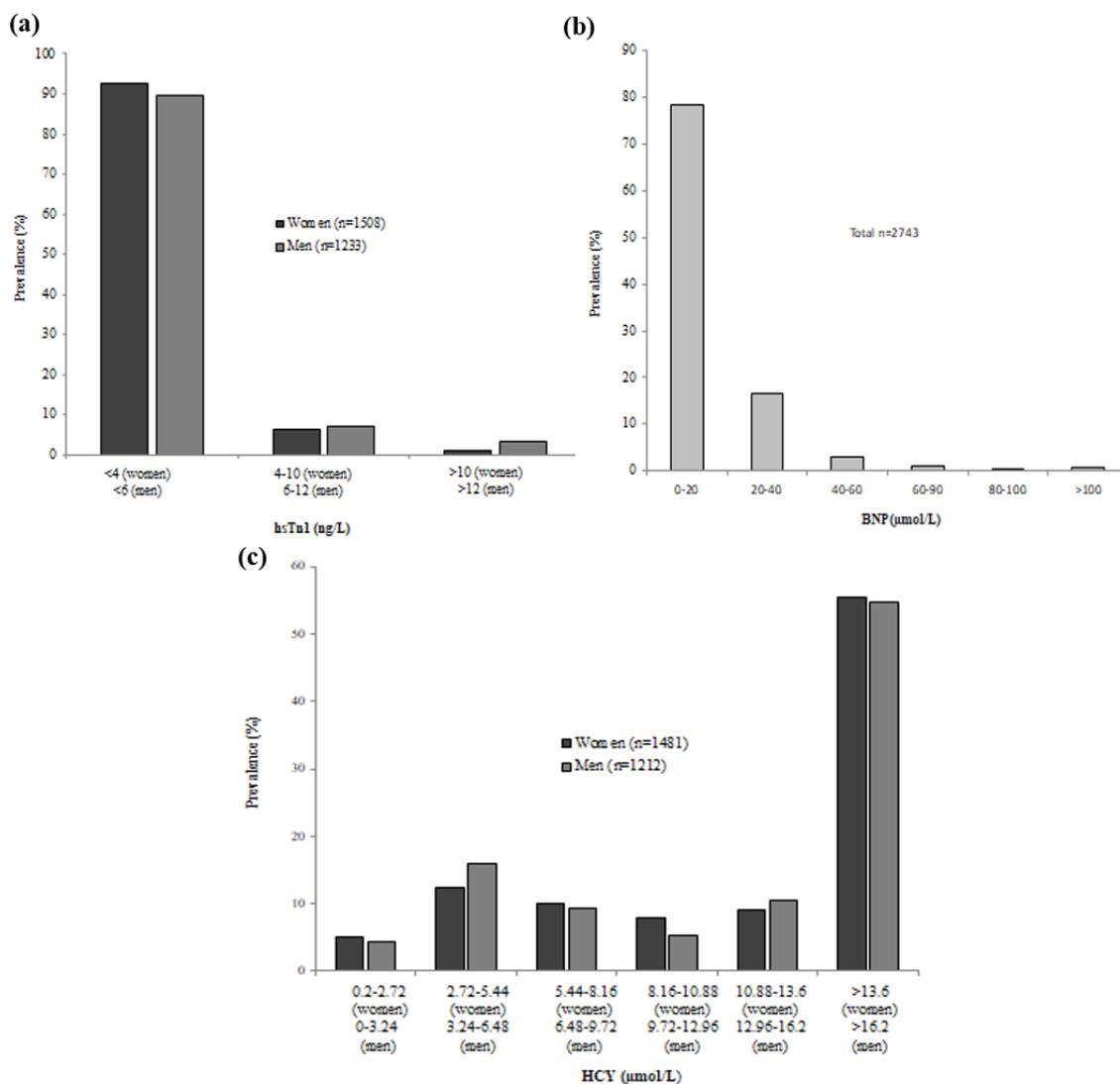
Figure 1. Distribution of CVD biomarker levels in the general population: (a) HsTNnI, high-sensitivity troponin-I; (b) BNP, B-type natriuretic peptide; and (c) HCY, homocysteine.

Table III. Mean and median (range) biomarker values in specific population subgroups

Participant subgroup	BNP, pg/mL		hsTnI, ng/L		Homocysteine, µmol/L	
	Mean	Median (Range)	Mean	Median (Range)	Mean	Median (Range)
Gender						
Females	19.02	13 (3-485)	1.74	0.6 (0-166.8)	19.01	15.4 (1.1-50)
Males	16.39	10 (9-536)	3.49	1.1 (0-153.2)	20.79	17.9 (1.1-50)
Age groups						
<20 years	13.19	10 (10-45)	1.26	0.9 (0-5.5)	11.93	9.65 (1.1-41.2)
20-29 years	14.67	10 (3-108)	1.59	0.9 (0-51.4)	15.80	12 (1.2-50)
30-39 years	14.50	10 (10-65)	1.73	1.1 (0-89.4)	17.33	14.6 (1.4-50)
40-49 years	16.53	11 (8-139)	2.07	1.45 (0-40.6)	20.44	18.5 (1.3-50)
50-59 years	21.29	13 (10-536)	3.64	1.2 (0-166.8)	22.57	20.2 (1.9-50)
60-69 years	28.04	18.5 (9-301)	5.38	2.5 (0.1-105.6)	27.69	26.8 (1.1-50)
70-79 years	50.14	16 (10-280)	6.01	3.8 (1-22.7)	34.48	39.8 (14.6-50)
>80 years	25.20	18 (10-51)	3.08	2.5 (1.1-6.8)	13.36	18.6 (3.5-20.7)

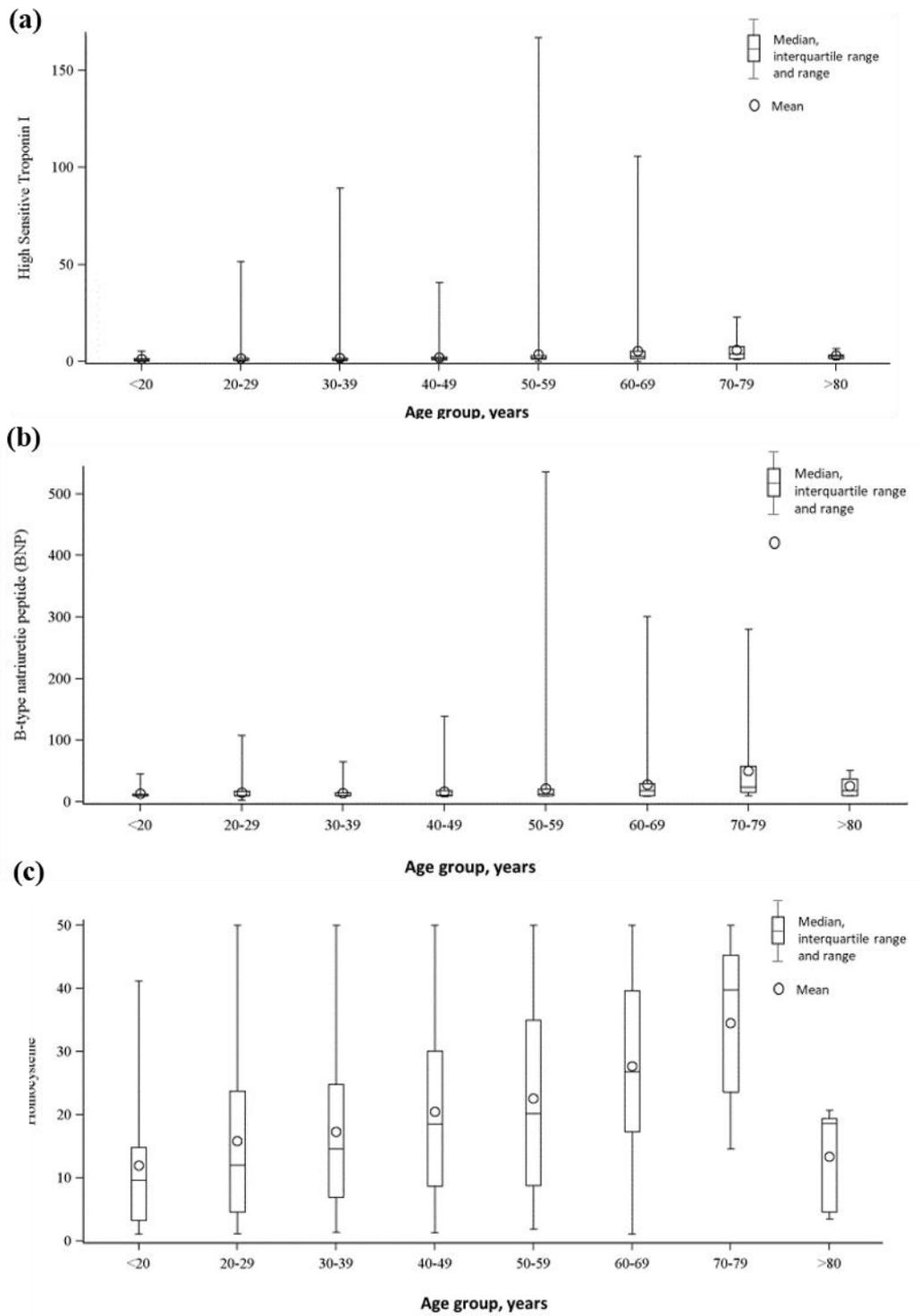*BNP, B-type natriuretic peptide; hsTnI, high-sensitivity troponin I.*

Figure 2. Levels of cardiovascular biomarkers in different age groups: (a) High-sensitivity troponin-I (ng/L); (b) B-type natriuretic peptide (µmol/L); (c) homocysteine (µmol/L).
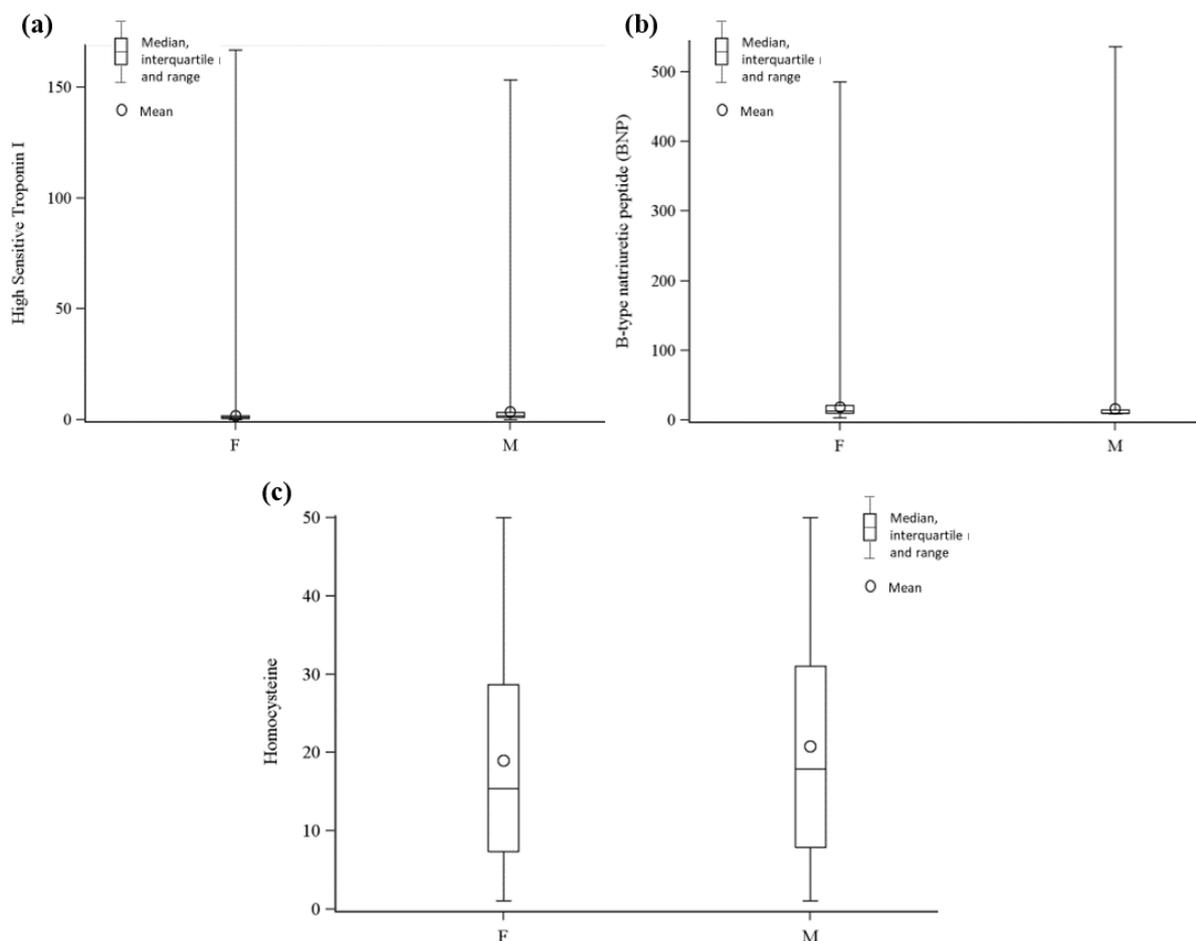
Figure 3. Cardiovascular biomarker levels in men and women: (a) High-sensitivity troponin-I (ng/L); (b) B-type natriuretic peptide (µmol/L); (c) homocysteine (µmol/L). F: female; M: male.

Most individuals in the screened population had no or one elevated cardiovascular risk marker (Figure 4). The number of people with three elevated risk markers was 9 (0.4%) using a BNP risk threshold of >50 pg/mL and 5 (0.2%) using a BNP risk threshold of >100 pg/mL (Figure 4).
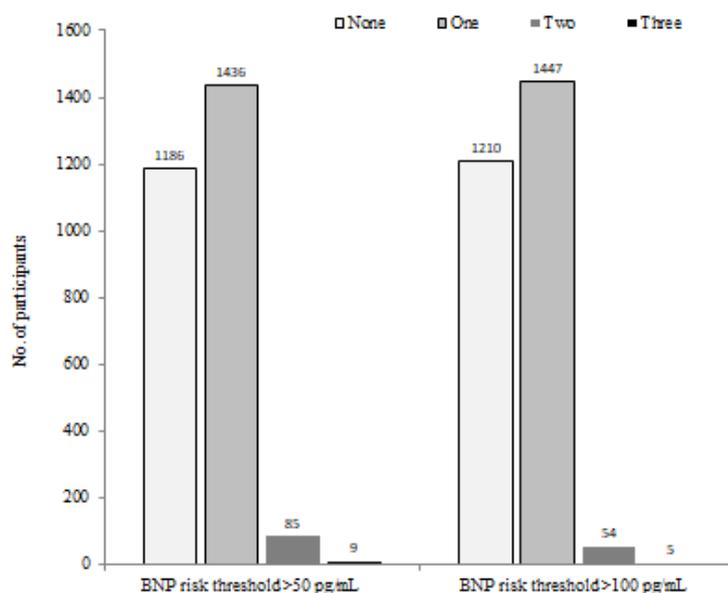

Figure 4. Distribution of participants by number of cardiovascular biomarkers showing an elevated risk stratified by B-type natriuretic peptide (BNP) threshold >50 pg/mL or >100 pg/mL.

DISCUSSION

The Kembara Mahkota event, which is traditionally well attended by a large cross-section of the community, provided an opportunity to identify individuals at high risk of CVD, and to improve awareness of CVD within the general Johor population. Information offered to people visiting our healthcare booth was aimed at improving awareness of disease and the importance of screening for early detection or prevention of disease. Consequently, 2744 individuals with no known CVD accepted our offer of blood-based biomarker testing to assess their disease risk.

It is important to identify individuals at risk of CVD, or early in the course of CVD, before they present with late-stage disease and disease-related complications. Although use of biomarkers to screen for CVD in the general population is not routinely performed, biomarkers have the potential to identify at-risk individuals for primary prevention earlier and more accurately than traditional screening strategies.[8,21-23] It is likely that no single biomarker will be sensitive or specific enough to be used on its own, so we used a panel of three blood-based biomarkers (hsTnI, BNP and HCY) to identify high-risk individuals that may not have been identified using traditional screening methods.

Once identified with the appropriate biomarker assays, high-risk individuals can be targeted for early intervention and prevention of symptomatic CVD. For example, compared with care guided by standard clinical assessment, significant reductions in HF and major adverse CV events have been reported in clinical trials using BNP assays to identify patients with CV risk factors at the highest risk of CVD who then received specialist primary preventative intervention.[14,24] In our project, we utilized biomarkers indicative of ischemic damage, myocardial stretch and general CVD risk to stratify the subjects and this may be a strategy to consider when utilizing biomarkers for risk stratification.

Cardiac troponin and natriuretic peptide biomarkers are associated with long-term risk of major adverse CV events and HF in the general population.[8,20-21,23,25] hsTnI and BNP were chosen for our panel of CVD risk biomarkers because they are well established independent and complementary assays that facilitate the detection of subclinical cardiac disease and increased CV risk before the onset of clinically detectable risk factors.[8,20,26,27] HCY is a novel biomarker that is considered an independent predictor of CV events in low- and high-risk populations, and elevated levels of HCY are associated with increased risk of CHD in the general population.[18,28,29]

It has been demonstrated that factors such as age and gender are associated with circulating BNP[33], HCY[34], and hsTnI[35]. However, the aim of this observational study was to determine the CV risk profile of the general healthy population of Johor, Malaysia, using these biomarkers, to aid the development of screening strategies specific to the local population. It is noteworthy that there is a continuous association between CV risk and levels of BNP, hsTNI and HCY, and while there are no precisely-defined cut-offs for these biomarkers[14,25-26,29,31], the cut-off levels interpreted as being indicative of the highest risk of CV events (hsTnI >10 ng/L in women and >12 ng/L in men), HF (BNP>50 pg/ml) and CHD (HCY >13.6 µmol/L in women and >16.2 µmol/L in men) in this study were based on Abbott biomarker assay sensitivities and evidence-based values that are now utilised in clinical guidelines.[14-16,26,30,31,36] Indeed, Maisel et al. demonstrated that BNP at threshold of 50 pg/ml has a negative predictive value of 96% for heart failure, while the diagnostic accuracy of BNP at cut-off of 100 pg/ml was 83.4%.[15] Additionally, Sigurdardottir et al.[37] recently showed that the addition of hsTnI to established CV risk prediction models led to a net reclassification improvement that was superior to that of C-reactive protein. These studies support the threshold values of the specified CV biomarkers that were utilised in this study.

In our study, approximately 1–3% of the population were identified as being at the highest risk of having a CV event or developing HF based on hsTnI and BNP assay results. In comparison, previously published studies in general American and German populations have reported troponin levels >10 ng/L in 1.5% to 7.3% of individuals.[22,32] The age and ethnic mix of general populations may translate into differences in circulating cardiac troponin levels, with lower levels in younger and/or predominantly Chinese populations.[22,32]

Compared with our hsTnI and BNP results, high proportions (>50%) of men and women were classified as high-risk for CHD on the basis of their HCY level. Whereas hsTnI and BNP are very specific biomarkers for cardiac problems,[7,25,26] plasma HCY levels are increased by a wide range of factors, including certain lifestyle factors, vitamin deficiencies and drugs,[13,25] which may have contributed to this result.

CONCLUSION

We believe that to effectively reduce the incidence and improve the prognosis of CVD in Malaysia, projects such as ours are required to raise disease awareness and encourage seemingly healthy individuals to participate in biomarker disease screening programmes so that high-risk individuals can be identified and offered timely intervention and prevention. Overall, using a multi-biomarker approach, more than 50% of our self-declared healthy population were identified

as being potentially at risk of CVD. Further studies with follow-up are required to assess whether interventions to reduce CV risk have an impact on outcomes in these individuals.

ACKNOWLEDGMENTS

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