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ORIGINAL ARTICLE

Association of Age, Sex, Body Size and Ethnicity with Electrocardiographic Values in Community-based Older Asian Adults

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Background Existing electrocardiographic (ECG) reference values were derived in middle-aged Caucasian adults. We aimed to assess the association of age, sex, body size and ethnicity on ECG parameters in a multi-ethnic Asian population.

Methods Resting 12-lead ECG and anthropometric measurements were performed in a community-based cohort of 3777 older Asians (age 64.7 ± 9.1 years, 1467 men, 88.8% Chinese, 7.7% Malay, 3.5% Indian, body mass index [BMI] 24.0 ± 3.9 kg/m^2).

Results Men had longer PR interval, wider QRS, shorter QTc interval and taller SV3. In both sexes, older age was associated with longer PR interval, wider QRS, larger R aVL and more leftward QRS axis, while higher BMI was associated with longer PR interval, wider QRS, larger RaVL and more negative QRS axis. There were significant inter-ethnic differences in QRS duration among men, as well as in PR and QTc intervals among women (all adjusted $p < 0.05$). Findings were similar in a healthy subset of 1158 adults (age 61.2 ± 9.1 years, 365 men) without cardiovascular risk factors.

Conclusions These first community-based ECG data in multi-ethnic older Asians highlight the independent effects of age, sex, body size and ethnicity on ECG parameters.

Keywords Age • Sex • Ethnicity • Body size • Electrocardiogram • Asian

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Introduction

The 12-lead electrocardiogram (ECG) is commonly used in day-to-day clinical practice for screening of cardiovascular disease due to its availability, simplicity and low cost. Current ECG reference ranges were largely defined in middle-aged Caucasian populations [1]. However, it is well-recognised that these values are affected by age, sex, body size, and ethnicity [2–5].

Non-Caucasian ethnic groups in which normal ECG parameters have been studied include Black [3,6,7], Hispanic [3] and Chinese populations [2,8,9]. While these prior studies highlighted the need for ethnicity-specific considerations in the interpretation of ECG data, direct inter-ethnic comparisons have been limited by differences in age, sample selection (unselected population-based versus selected referral cohorts), methodology and geography. None included detailed characterisation among different Asian ethnicities. Little is known of ECG reference values in Malays, who constitute almost 28 million of the world's population with large populations in Malaysia and Indonesia. Furthermore, in the largest ECG study in Chinese to date [8], only 16% (857 out of 5360) of participants were $\geq$ 60 years old. Finally, while most prior studies accounted for age and sex differences, few simultaneously accounted for body size differences as well [4,5].

In this community-based study, we aimed to assess the association of age, sex, body size and ethnicity on ECG parameters in a multi-ethnic older Asian population inclusive of Chinese, Malay and Indian ethnicities. We hypothesised that demographic and anthropometric factors (age, sex, body size and ethnicity) would have independent effects on ECG characteristics.

Methods

Singapore is home to 5.5 million inhabitants with a mix of Chinese, Malays and Indians comprising, respectively, 74%, 13%, and 9% of the population. The current study population was derived from the Singapore Longitudinal Aging Study [10], aimed at identifying conditions associated with ageing. Participants were randomly sampled adults from the general community, identified by door-to-door census of all residents in contiguous precincts within five districts in the southeastern region of Singapore. Informed consent was obtained from each patient and the study conformed to the ethical guidelines of the 1975 Declaration of Helsinki. Ethics approval was obtained from the institutional review board.

Demographic and anthropometric data were obtained as part of the original studies and a resting baseline 12-lead ECG was done at the time of recruitment. Body mass index (BMI) was calculated as weight (Kg)/(height(m))^2 and body surface area (BSA) was calculated using the Mosteller formula ($\sqrt{}$(height(cm)x weight(kg)/3600). Waist:hip and waist:height ratios were also obtained. 12-lead ECGs were performed in a standardised fashion across all 10 centres in Singapore. These were done in the morning, between 1030H to 1200H, with participants resting quietly for 10-15 minutes lying on a couch after having their fasting blood samples taken. To further minimise inter-centre variability, the same ECG machine model (GE MAC 5500) was used in all 10 centres. Standard ECG parameters including PR interval, QRS duration, QTc interval and QRS axis were measured from lead II. Further ECG variables of interest including amplitude of R wave in aVL (RaVL) and S wave in V3 (SV3) were measured and recorded by a single, independent trained reader.

In order to define ECG normal limits and associations in healthy Asians, we further defined a ''healthy population'' subgroup as participants without diabetes mellitus, hypertension, hyperlipidaemia, coronary artery disease, cerebrovascular accident (CVA), any smoking history, atrial fibrillation, bundle branch block, anaemia (Hb < 12 g/dL in men, < 11 g/dL in women) or renal impairment (Cr > 120umol/L).

Anthropometric and ECG data were expressed as mean $\pm$ standard deviation and ECG parameters with 5% and 95% confidence limits. One-way ANOVA and Student's T-test were used to compare ECG parameters among ethnic groups and between men and women respectively. Subsequently, sex-stratified analyses were performed: Univariable analyses were performed to assess the association of age and BMI with ECG parameters, and Pearson's correlation coefficients were obtained for each dependent variable in both the overall and healthy populations. In the overall population, multivariable analyses were performed where the dependent variable was the ECG variable of interest, and independent variables included age, BMI, ethnicity, diabetes mellitus, hypertension, hyperlipidaemia and CVA. In the subset of healthy population, multivariable analyses were similarly performed adjusting for age, BMI and ethnicity. Participants with morbid obesity (BMI > 30 kg/m^2) made up only 5% of the overall population, and were adjusted for in the analysis of the healthy population.

Results using different anthropometric measurements (body surface area, waist:hip and waist:height ratio) are included in the online Supplement. A p value of < 0.05 was considered statistically significant.

Results

Clinical Characteristics

A total of 3777 (age 64.7 $\pm$ 9.1 years, 1467 men) community-based adults were included, with 1158 (age 61.2 $\pm$ 9.1 years, 365 men) participants in the healthy subset. As shown in Table 1, the study population was predominantly Chinese (88.8%), and older with the expected age-related comorbidities such as diabetes, hypertension and hyperlipidaemia (consistent with Singapore population statistics). Also consistent with a community-based sample, participants generally had normal haemoglobin and renal function.

Table 1 Demographics of Study Population.

	Overall Population(n=3777)			Healthy Population(n=1158)		
	Male (n=1467)	Female (n=2310)	P value*	Male (n=365)	Female (n=793)	P value*
Ethnicity						
Chinese (%)	1306 (89)	2047 (88.6)		325 (89)	683 (86.1)	
Malay (%)	92 (6.3)	200 (8.7)		21 (5.8)	94 (11.9)	
Indian (%)	69 (4.7)	63 (2.7)		19 (5.2)	16 (2)	
Age (years)	65.1 ± 9.7	64.4 ± 8.6		61.9 ± 10.4	60.8 ± 8.4	
Height (m)	1.65 ± 0.06	1.54 ± 0.06		1.66 ± 0.07	1.54 ± 0.06	
Weight (kg)	65.5 ± 11.2	57.0 ± 10.0		63.8 ± 11.2	55.9 ± 9.9	
BMI (kg/m^2)	24.0 ± 3.6	24.1 ± 4.1		23.0 ± 3.5	23.5 ± 4.0	
BSA (m^2)	1.72 ± 0.21	1.54 ± 0.21		1.70 ± 0.23	1.53 ± 0.19	
Waist:hip ratio	0.91 ± 0.07	0.83 ± 0.08		0.90 ± 0.08	0.82 ± 0.08	
Waist:height ratio	0.40 ± 0.23	0.44 ± 0.20		0.34 ± 0.24	0.37 ± 0.23	
Haemoglobin (g/dL)	14.3 ± 1.4	13.0 ± 1.1		14.5 ± 1.1	13.0 ± 0.9	
Creatinine (umol/L)	94 ± 28	69 ± 18		87 ± 13	65 ± 12	
Diabetes mellitus (%)	261 (17.8)	376 (16.3)		-	-	
Hypertension (%)	706 (48.1)	997 (43.2)		-	-	
Hyperlipidaemia (%)	266 (18.1)	626 (27.1)		-	-	
Prior stroke (%)	75 (5.1)	53 (2.3)		-	-	
Smoking (%)	384 (26.2)	53 (2.3)		-	-	
PR (ms)	174 ± 24 (142,220)	168 ± 23 (136,206)	<0.001	169 ± 23 (140,209)	165 ± 21 (135,202)	<0.001
QRS (ms)	92 ± 15 (72,122)	85 ± 13 (70,106)	<0.001	89 ± 10 (74,106)	83 ± 10(70,100)	<0.001
QTc (ms)	412 ± 27 (375,454)	423 ± 24 (388,462)	<0.001	410 ± 23 (374,446)	422 ± 22 (387,460)	<0.001
QRS axis (°)	34 ± 47 (-40, 95)	34 ± 38 (-26,83)	0.744	37 ± 41(-32,88)	37 ± 36 (-26,81)	0.768
R in aVL (mm)	5.2 ± 3.2 (1.0,11.0)	4.9 ± 3.1 (1.0,10.0)	0.017	4.5 ± 2.9 (0.9,10.0)	4.2 ± 2.7(0.5,9.0)	0.078
S in V3 (mm)	9.5 ± 5.0 (3.0,18.0)	7.2 ± 4.0 (2.0,14.5)	<0.001	9.0 ± 4.3 (3.0,17.0)	6.5 ± 3.6 (1.5,13)	<0.001

*Adjusted for age, BMI and ethnicity.

ECG Characteristics

All participants were in normal sinus rhythm. The mean ± standard deviation (5th, 95th percentile) heart rate was 68 ± 10 (52, 86). The mean ± standard deviation (5th, 95th percentile) values of ECG values for both men and women in both populations are shown in Table 1.

Sex Associations

In the healthy population, adjusting for age, ethnicity and BMI, men had significantly longer PR interval, wider QRS, shorter QTc intervals and taller SV3 than women. There was no sex difference in QRS axis. This was similar to the findings in the overall population (Table 1).

Age Associations

In the overall population (Table 2a), older age was associated with longer PR interval, wider QRS, larger RaVL and more leftward QRS axis, in both men and women adjusting for BMI, ethnicity, diabetes mellitus, hypertension, hyperlipidaemia and stroke ($p < 0.05$). There was no association of age with QTc interval. Older age was also associated with larger SV3 in women. In the subset of healthy population (Table 2a), the associations between age and PR interval, QRS axis and amplitude of RaVL remained significant in both men and women, adjusting for BMI and ethnicity.

Anthropometric Associations

In the overall population (Table 2b), higher BMI was associated with longer PR interval, wider QRS, larger amplitude of RaVL and more negative QRS axis in both men and women adjusting for age, ethnicity, diabetes mellitus, hypertension, hyperlipidaemia and stroke. In women alone, higher BMI was related to longer QTc interval. In men alone, higher BMI was related to smaller SV3. In the subset of healthy population (Table 2b), the associations between BMI and QRS duration, QRS axis and amplitude of RaVL remained significant in both men and women adjusting for age and ethnicity. Higher BMI was also associated with longer PR interval in healthy women, as well as longer QTc interval and smaller SV3 in healthy men. Using BSA in both populations also showed largely similar results (Online Supplement: Table 1 and 2). Associations between waist:hip and waist:height ratio (Online Supplement: Table 1 and 2) were similar to BMI

Table 2a Relationship between ECG parameters and age in overall and healthy population.

	Overall population				Healthy population			
	Male		Female		Male		Female	
	r	p*	r	p*	r	P**	r	P**
PR (ms)	0.221	**<0.001**	0.165	**<0.001**	0.173	**<0.001**	0.174	**<0.001**
QRS (ms)	0.08	**0.003**	0.121	**<0.001**	0.038	0.236	0.039	0.322
QTc (ms)	0.048	0.079	0.022	0.26	0.01	0.446	-0.09	0.193
QRS axis (°)	-0.018	**0.015**	-0.069	**0.009**	-0.05	**0.025**	-0.112	**<0.001**
RaVL (mm)	0.053	**<0.001**	0.151	**<0.001**	0.09	**<0.001**	0.151	**<0.001**
SV3 (mm)	0.09	0.151	0.109	**0.01**	0.011	0.654	0.075	0.095

*adjusted for BMI, ethnicity, hypertension, hyperlipidaemia, diabetes mellitus, prior stroke.
**adjusted for BMI, ethnicity.

Table 2b Relationship between ECG parameters and BMI in overall and healthy population.

	Overall population				Healthy population			
	Male		Female		Male		Female	
	r	p†	r	p†	r	P††	r	P††
PR (ms)	0.069	**<0.001**	0.083	**<0.001**	0.049	0.078	0.75	**<0.001**
QRS (ms)	0.076	**0.013**	0.111	**<0.001**	0.131	**0.007**	0.091	**0.006**
QTc (ms)	0.034	0.207	0.082	**0.023**	0.104	**0.041**	0.103	0.16
QRS axis (°)	-0.226	**<0.001**	-0.169	**<0.001**	-0.198	**<0.001**	-0.176	**<0.001**
RaVL (mm)	0.345	**<0.001**	0.275	**<0.001**	0.339	**<0.001**	0.27	**<0.001**
SV3 (mm)	-0.088	**0.001**	-0.015	0.098	-0.112	**0.039**	-0.012	0.708

†adjusted for age, ethnicity, hypertension, hyperlipidaemia, diabetes mellitus, prior stroke.
††adjusted for age, ethnicity.

and BSA but were not as strong. Waist:hip ratio had no association with PR and QTc interval, although women in the overall population and healthy males had longer QRS duration after adjusting for age and ethnicity. Waist:height ratio on the contrary, had significant associations with PR interval and QTc intervals in both men and women, and longer QRS duration in women alone, after correcting for age and ethnicity. The associations with QRS axis, R aVL and SV3 remained largely similar to that of BMI and BSA.

Ethnic Associations

In the overall population (Table 3), there were significant ethnic differences in QRS duration among men, and in PR and QTc intervals among women, after adjusting for age, sex, BMI, diabetes mellitus, hypertension, hyperlipidaemia and stroke. Among men, QRS duration was longest in Malays, followed by Indians and shortest in Chinese. Among women, Chinese women had the longest PR interval, followed by Malays and Indians. Malay women had the longest QTc interval compared to Indians and Chinese. Ethnic differences in ECG variables obtained from the subset of healthy population were not analysed due to the small numbers in the healthy ethnic subgroups.

Discussion

We provide the first community-based evidence of the independent effects of age, sex, body size and ethnicity on ECG parameters in an older multi-ethnic Asian population.

The sex differences seen in our cohort (men had a longer PR interval, wider QRS, shorter QTc interval and taller RaVL) are consistent with observations in prior studies in both Caucasian and Chinese cohorts [1,8,9]. We now extend these findings to an older and more ethnically diverse Asian population. Compared to the prior Chinese study [8], there were differences in absolute ECG values in our study; for example, PR interval was shorter (159ms and 152ms in men and women above the age of 60 years old respectively) in the prior Chinese study, compared to 169ms and 165ms in men and women in our study. Conversely, QRS duration was longer (93ms and 86ms in men and women above the age

Table 3 Relationship between ethnicity and ECG parameters in overall population.

Women				
	Chinese	**Malay**	**Indian**	**P value***
N	2047	200	63	
PR (ms)	169 (138, 207)	164 (128, 200)	161 (124, 221)	<0.001
QRS (ms)	85 (70, 106)	84 (70, 102)	85 (68, 112)	0.137
QTc (ms)	422 (387, 460)	432 (399, 472)	424 (386, 470)	0.001
QRS axis (°)	35 (-26, 84)	32 (-26, 80)	19 (-26, 71)	0.301
RaVL (mm)	4.9 (1, 10)	4.8 (1, 9.2)	6.3 (2, 12)	0.791
SV3 (mm)	7.2 (2, 15)	7.2 (2, 14.1)	6.1 (1, 13.5)	0.404
Men				
	Chinese	**Malay**	**Indian**	**P value***
N	1306	92	69	
PR (ms)	174 (142, 220)	173 (139, 221)	171 (134, 240)	0.987
QRS (ms)	91 (74, 119)	96 (76, 139)	93 (75, 132)	0.004
QTc (ms)	412 (375, 454)	419 (375, 459)	414 (375, 458)	0.064
QRS axis (°)	34 (-40, 95)	32 (-48, 96)	30 (-37, 96)	0.876
RaVL (mm)	5.1 (1, 11)	5.6 (0.5, 11.3)	5.4 (1.5, 10)	0.955
SV3 (mm)	9.5 (3, 18)	10 (3, 19.2)	8.3 (2, 17.6)	0.872

*Adjusted for age, BMI, diabetes mellitus, hypertension, hyperlipidaemia, prior stroke.
Values are mean (5%, 95% confidence limits).

of 60 years old respectively) in the prior Chinese study, compared to 89ms and 83ms in men and women in our study. The opposing differences suggest that this is not due to a systematic measurement difference between the studies. Nonetheless, the relative sex differences were preserved and the remarkable consistency across multiple cohorts suggests that these are due to intrinsic differences between men and women, independent of geography, ethnicity or comorbidities.

We found that older age was independently associated with longer PR interval, wider QRS, larger RaVL and more leftward QRS axis in both men and women. Although the correlations between age and various ECG parameters were not strong (r<0.3), previous studies also showed similar age trends [2,3,8,11], including a large study of more than 5,000 healthy Chinese participants, where age-related increases in PR interval and RaVL, and change in QRS axis, were reported in both men and women [8]. The weaker correlations observed could also be explained by the limited age range in this study. The age-related prolongation of PR and QRS durations even in our healthy subset suggests the presence of general age-related conduction pathway degeneration leading to conduction delays. Given the association between increased PR intervals and risk of development of atrial fibrillation [12,13], prolonged PR intervals may potentially be a marker for atrial fibrillation and stroke development in the older population. Interestingly, while we found an age-related widening in QRS duration, the prior large Chinese study [8] showed no change in QRS duration with age, whereas the Framingham Heart Study reported an age-associated narrowing of QRS duration among Caucasian men [1]. Differences in age range among cohorts (ours was the oldest cohort) may have contributed to these different trends, although methodological and population differences cannot be ruled out. The leftward shift of QRS axis with age was consistently seen across populations of Chinese, Caucasians, Blacks and Hispanics [3,8,11]. In the latter three ethnic groups, the QRS frontal plane angle was estimated to decrease by 8° per decade in both men and women [3]. The age-related increase in RaVL, found in this and other studies [3,8], could potentially affect ECG detection of left ventricular hypertrophy (LVH) in the older population, suggesting that age-specific cutoffs may be required in the detection of LVH [14].

Body size had important independent effects on ECG variables in our study. Higher BMI was associated with longer PR interval, wider QRS, larger RaVL and more negative QRS axis in both men and women. Similarly, while the correlations of BMI and various ECG parameters were not strong (r<0.4), these findings are consistent with prior studies: The association of body size with ECG abnormalities was described in MESA [15], where central obesity (waist:hip ratio) was significantly associated with major and minor ECG abnormalities. The effect of weight loss on the reversal of ECG abnormalities [12] further supports the effect obesity has on individual ECG parameters. The ARIC study showed a significant association between higher BMI groups and larger P wave indices including PR interval, P wave maximum duration and P wave terminal force [16]. A positive correlation between increasing body weight and QRS duration has been demonstrated in some [4,17], but not all prior studies [18]. Dhingra et al. showed that increasing QRS duration was positively related to LV mass, and a stronger association was seen in obese men [19]. Thus the wider QRS in association with a larger body size may be related to increased conduction time across a larger left ventricular mass. Excessive chest wall fat in obesity has been postulated to attenuate electrical signals from the left ventricle leading to lower QRS voltages in precordial leads [20,21]. However, weight loss was also associated with a reduction in ECG voltages that were not reliant on precordial voltages, in particular RaVL [3,20]. This is congruent with our findings of larger RaVL amplitudes with increased BMI in both men and women, and increased SV3 in men. Rautaharju et al. found that being overweight was associated with a more leftward axis by 14 degrees [3]. The more leftward axis was postulated to be due to the more horizontal orientation of the heart in response to the upward displacement of the diaphragm.

While ethnic differences in ECG parameters have been well-described [2,3,22], direct inter-ethnic comparisons across cohorts have been limited by differences in age, sample selection (unselected population-based versus selected referral cohorts), methodology and geography. We therefore ensured uniform sampling and standardised measurements in multiple ethnic groups from the same population in our study, thus ensuring internal validity of our comparisons. We further adjusted for age, BMI and comorbidities in our inter-ethnic comparisons. We found inter-ethnic differences in PR and QTc intervals in women, as well as in QRS duration in men, in our community-based Asian cohort. Prior studies in other ethnic groups did not show significant ethnic differences in PR interval [2,22]. However we were able to demonstrate that Chinese women had significantly longer PR interval compared to Malay and Indian ethnicities. Whether this predisposes older Chinese women in particular to future atrial fibrillation deserves further study. Macfarlane et al. noted ethnic differences in QTc intervals between Caucasians and Chinese [2], with longer QTc intervals in Chinese. We now further show that QTc intervals are even longer in Malay compared to Chinese women. The prognostic significance of this is unclear but worrying in light of the known association between prolonged QTc intervals and mortality [23]. Whereas Mansi et al. found no significant ethnic differences in QRS duration in men [22], we showed a significantly longer QRS duration in Malay men compared to Chinese and Indian men. Conversely, Mansi et al. showed ethnic differences among women, where Jordanian women had longer QRS duration than Filipino women [22], whereas we did not find ethnic differences among women. Similarly, Rautaharju et al. found larger ECG amplitudes in Hispanics than Caucasians [3], but we did not see any ethnic differences in ECG amplitudes in our study. These varying results are likely a result of the different types of ethnic groups sampled in the different studies. Although observed inter-ethnic differences in ECG variable amplitudes are small, these are consistent with previous studies [2,3,22] (<10ms). Yet, individual associations of abnormal ECG indices and cardiovascular outcomes have been previously well-studied, including the risk of atrial fibrillation with longer PR intervals [12,13], congestive heart failure with prolonged QRS duration [24] and long-term mortality risk with prolonged QTc [23]. Nonetheless in view of the lack of clinical outcome data, the clinical relevance of these differences remains unclear and further study is required. The small numbers of minor ethnic groups (Indians and Malays in our cohort), and lack of clinical outcome data, are acknowledged limitations of this and prior studies.

When compared with historical data from the 1987 Framingham Heart Study [1], where a subset of healthy participants were studied to derive normative reference ranges, Asian men and women from the healthy population, were observed to have longer PR interval, narrower QRS and more leftward QRS axis (Online Supplement: Table 3). These comparisons were however, limited by the average age of participants in the Framingham Heart Study, who were almost 20 years younger, which may have contributed to the differences in ECG parameters between the two study populations. Differences noted were purely observational as no statistical analysis was performed in the comparison with the Caucasian population, further adding to the inadequacy of comparisons between Asians and Caucasians. The differences observed do however suggest the existence of baseline differences in ECG parameters between Asians and Caucasians, and calls for further study to delineate if Western references ranges are applicable to Asians.

Conclusions

These first community-based ECG data from a large multiethnic Asian population of older adults highlight the independent effects of age, sex, body size and ethnicity on ECG parameters. The implications of these findings for future risk of cardiovascular events deserve further study.

Disclosures

None

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.hlc.2016.01.015.

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