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Treadmill Exercise Testing on Different Blood Genotypes among University Students

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Abstract

Background: The benefits of regular exercise are overwhelming, be it in children, teens or adult. The phrase “exercise is medicine” has continously been used to emphasize the physiological, pshychological and social benefits of exercise. This research aims at comparing the effect of blood genotype and exercise on some physiological parameters in fit and willing undergraduate students.

Methods: 75 undergraduate students in the faculty of Basic Medical Science volunteered to participate in the study. A predesigned, pre-tested, self-administered questionnaire was filled by the students. Physiological variables such as heart rate, blood pressure and respiratory variables was then measured before exercise and at time intervals after the exercise testing on a calibrated motorist treadmill.

Results: Blood genotype SS had the highest systolic blood pressure immediately after exercise (155.50 ± 6.91 mmHg) compared to blood genotype AS (155.40 ± 7.00 mmHg) and blood genotype AA (154.88 ± 8.70 mmHg) with significant difference ($P < 0.05$). Blood genotype AS had the highest systolic blood pressure 15 minutes after exercise (129.63 ± 9.79 mmHg) compared to blood genotype AA (129.13 ± 9.35 mmHg) and SS (122.13 ± 18.50 mmHg) with significant difference ($P < 0.05$). Blood genotype AS had the highest diastolic blood pressure immediately after exercise (95.29 ± 8.16 mmHg) compared to blood genotype AA (80.34 ± 11.46 mmHg) and SS (94.91 ± 11.81 mmHg) with significant difference ($P < 0.05$). Blood genotype AS had the highest diastolic blood pressure 15 minutes after exercise (85.60 ± 7.50 mmHg) compared to blood genotype AA (83.63 ± 9.18 mmHg) blood genotype SS (83.63 ± 9.18 mmHg) with significant difference ($P < 0.05$).

Conclusion: Given the benefits of exercise, students should be encouraged to engage in light and moderate exercise irrespective of their blood genotype.

Keywords

Blood genotype, Exercise testing, University students

Introduction

Physical Exercise is any bodily activity that enhances or maintains physical fitness and overall health and wellness [1]. During physical exercise muscle action and body movement is higher than it is when the body is at rest, this stimulates the sympathetic nervous system and causes an integrated response from organ systems of the body such as the circulatory, respiratory and endocrine system to maintain homeostasis [2].

The ancient physician Hippocrates stated that “all parts of the body, if used in moderation and exercised in labours to which each is accustomed, become thereby healthy and well developed and age slowly, but if they are unused and left idle, they become liable to disease, defective in growth and age quickly”. However, by the 21st century, the time and attention given to exercise has reduced considerably [3]. Lack of exercise was classified as an actual cause of chronic diseases and death [3,4]. Many studies have also reported that physical activity can be used as a non-invasive therapy for mental health improvements in cognition, depression, anxiety, neurodegenerative diseases and drug addiction [3,5-9]. Exercise is a powerful tool in the fight to prevent and treat numerous chronic diseases. Given its whole-body, health-promoting nature, the integrative responses to exercise should surely attract a detail of interest as the notion of “exercise is medicine” continues to its integration into clinical settings [3,10].

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There are three blood genotypes with the haemoglobin A and Haemoglobin S; blood genotype AA, AS and SS. Hb AA; this is the normal blood genotype in which no form or degree of sickling occurs as the abnormal haemoglobin S allele is absent [11].

Hb AS; also known as Sickle cell carriers. Sickle cell trait is a heterozygous genetic phenomenon with the alleles of haemoglobin A and haemoglobin S genotype [12].

HbS is a variant that is found in African Americans and Hispanic Americans/Latinos. It is also found in Africa, South or Central America (especially Panama), the Caribbean islands, Mediterranean countries (such as Turkey, Greece, and Italy), India, and Saudi Arabia.

Hb SS; is a genetic autosomal recessive disease where the genotype is homozygous as both alleles are of the S abnormal haemoglobin type [13]. This genetic anomaly is present predominantly in the African race of humans. It occurs the most in sub-Saharan Africa, making Sub-Saharan Africa to having the greater percentage of the population living with sickle cell disease and sickle cell trait [14].

The overall prevalence of blood genotype SS remains high in Blacks at 1 per 396 births [15]. Physical activity helps to build stronger muscles, to give better support to joints, and to improve emotional wellbeing by improving self-esteem and providing social interaction [16]. To compare the exercise tolerance levels among different blood genotypes, we report the findings from 75 undergraduate students, including the blood genotype SS, as only few studies have compared cardiovascular and respiratory responses among undergraduate students, where SS blood genotypes are involved, using a treadmill. The treadmill is advantageous instrument to be accepted as a useful physical and clinical assessment for people in the laboratories or for patients in the hospitals.

Materials and Methods

Participants

The study was conducted on 75 students of the faculty of Basic medical sciences, Bingham University Karu, Nigeria. The participants were between the ages of 16-23, 32 are of the blood group AA, 35 are AS, while 8 are SS. The purpose and risks of this study was explained and all participants willingly volunteered to participate. The study protocol was reviewed and approved by Bingham University Research and Ethical Committee in accordance with the Helsinki recommendations. Participants provided informed consent before the study. Subjects are advised not to take any exercise enhancer such as caffeine, drugs or alcohol.

Questionnaire

The study was based on a questionnaire distributed to the students. Brief description of the test was made to each subject, followed by the consent form and questionnaire. The questionnaire consisted of two sections. A general section concerned with self-reported data of subject and those of their families such as age, ethnic affiliation, height, weight, BMI and level of education of parents, blood group, blood genotype and also routine exercise habit. The last section consisted of physiological data, specifically cardiopulmonary parameters which included heart rate, systolic blood pressure, diastolic blood pressure, pulse pressure, mean arterial pressure and respiratory variables.

Data collection protocol

Exercise testing procedures: The participants performed the submaximal treadmill jogging (TMJ) test in human physiology laboratory of the department of physiology, Bingham University Nigeria, using the method described by Vehrs, et al. [17] with some modifications. Participants were told to wear clothing they would be comfortable jogging in. Participants were briefed on the safety protocols of jogging on a treadmill. Participants stepped onto the treadmill with their hand on the support handles, they began by walking at a self-selected brisk walking speed, followed by jogging at a self-selected, submaximal jogging speed between 4.3 and 7.5 mph for 7 minutes. Once 7 minutes had elapsed, the treadmill speed was brought to 0 mph and participants stepped off. For the SS genotype however, their exercise was mild and they were allowed to take breaks as metabolic changes imposed by exercise may initiate pain, sickling and vaso-occlusive episodes as prescribed by Connes, et al. [18] and Liem [10].

Measurements

Anthropometric measurements

Height was measured using a tape rule, participants were asked to stand erect against the tape rule facing a wall with bare feet. height was measured in metres (m). Weight was measured using a weigh balance; participants were barefooted when their weight was taken. Weight was measured in kilograms (kg).

Blood pressure measurements:

Blood pressure was measured at 5 intervals.

- Before exercise
- Immediately after exercise
- 5 minutes after exercise
- 10 minutes after exercise
- 15 minutes after exercise

The participants were always seated with good posture when their blood pressure was measured. The sphygmomanometer was positioned on a table on the left side of the participant. The participant's left arm was put through the cuff loop, the cuff rested at the bottom edge of the arm just 2 cm above the cubital fossa and the arrow under the tube centred at the cubital fossa. The start button was pressed, the cuff inflated and blood pressure measurement had commenced, during this process participants were silent and with minimal body movement. After the measurement stopped, systolic, diastolic and heart rate were displayed and recorded. Pulse pressure was then calculated as the arimetic difference between systolic blood pressure and diastolic blood pressure. Mean Arterial Blood pressure was calculated as the sum of diastolic blood pressure and one third of pulse pressure.

Respiratory rate measurement:

Respiratory rate was taken at 5 intervals

- Before exercise
- Immediately after exercise
- 5 minutes after exercise
- 10 minutes after exercise
- 15 minutes after exercise

Participants were asked to count in their head how many breaths they take in one minute, a stopwatch was used to time the participants as they counted their breaths. They were alerted when to start counting and when to stop counting to avoid error.

Statistical analyses

Descriptive statistics for categorical variables were presented in frequencies and percentages, while those of continuous variables were presented in means and standard deviations. A repeated measurement analysis of variance (ANOVA) was first applied to determine whether timing the exercise tolerance of the various physiological parameters exhibited significant differences. In order to tests whether genotype has significant impact on exercise tolerance, it (genotype) was then included as between subject factor whereas, timing of exercise tolerance was used as within subject variable. Statistical analyses were performed using IBM SPSS version 26 (IBM SPSS Inc., Chicago, IL, USA). All statistics were two-tailed and a *P*-value < 0.05 was considered statistically significant.

Results

Results were obtained from all 75 participants of this study. The participants baseline characteristics are presented in Table 1. 44% of the participants are male and 56% are female. Blood genotype AA were 42.7%, AS

Table 1: Participants characteristics at baseline (n = 75).

Sex	Frequency	Percent
Male	33	44.0
Female	42	56.0
Ethnicity		
Hausa	4	5.3
Igbo	15	20.0
Yoruba	17	22.7
Others	39	52.0
Blood group		
A+	14	18.7
AB+	10	13.3
B+	28	37.3
O+	23	30.7
Genotype		
AA	32	42.7
AS	35	46.7
SS	8	10.6
Regular Exercise		
Yes	38	50.7
No	37 (49.3)	49.3
Anthropometrics	Mean ± SD	
Height (cm)	169.41 ± 9.44	
Weight (kg)	66.59 ± 10.44	
BMI (kgm^{-2})	23.25 ± 3.41	

Table 2: Results of repeated measures of ANOVA of physiological variables based on exercise tolerance levels.

	Time						
	T1	T2	T3	T4	T5		
Physiological parameters	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	F	*P*
Heart rate	74.81 ± 6.72	97.39 ± 8.01	88.75 ± 6.15	83.03 ± 6.22	77.59 ± 6.52	551.47	< 0.001
Systolic blood pressure (mm Hg)	124.97 ± 9.98	155.19 ± 7.67	144.03 ± 9.20	136.00 ± 9.03	128.61 ± 10.87	531.65	< 0.001
Diastolic blood pressure (mm Hg)	81.48 ± 10.24	94.84 ± 10.62	89.57 ± 12.16	86.07 ± 9.09	83.92 ± 8.99	95.23	< 0.001
PP	43.49 ± 8.88	60.35 ± 10.66	54.45 ± 12.35	-	44.69 ± 10.13	105.98	< 0.001
Mean arterial pressure	95.97 ± 9.26	114.96 ± 8.35	107.73 ± 9.63	-	98.82 ± 8.39	405.22	< 0.001
Respiratory rate	17.75 ± 2.10	31.13 ± 4.57	26.05 ± 3.00	22.40 ± 2.52	19.03 ± 2.19	700.87	< 0.001

T1 = Before exercise, T2 = Immediately after exercise, T3 = 5-Min later, T4 = 10-Min later, T5 = 15-Min later were 46.7%, while SS were 10.6. 18.7% were blood group A+, 13.3% were AB+, 37.3% were B+, while 30.7% were O+. 50.7% reported that they engage in regular exercise. The mean ± SD of height, weight and BMI of the participants are also presented on the same table. Table 2 presents exercise tolerance level of all 75 participants. HR, SBP, DBP, PP, MAP and HR are significantly ($p < 0.001$) higher after exercise. In Table 3 HR, SBP, DBP, PP, MAP and HR are significantly ($p < 0.001$) higher for all the three blood genotypes in the male subjects after exercise. Table 4 also shows that HR, SBP, DBP, PP, MAP and HR are significantly ($p < 0.001$) higher for all the three blood

Table 3: Results of repeated measures of ANOVA of physiological variables based on genotypes and times for male subjects.

			Physiological parameters					
			HR	**SBP**	**DBP**	**PP**	**MAP**	**RR**
Times	**Genotypes**	**n**	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**
Before exercise	AA	15	71.40 ± 8.22	126.80 ± 11.57	80.67 ± 10.52	46.13 ± 10.25	96.04 ± 9.77	16.87 ± 1.85
	AS	13	72.31 ± 6.96	125.92 ± 6.95	83.85 ± 9.97	42.08 ± 10.59	97.86 ± 7.57	17.08 ± 1.32
	SS	5	79.00 ± 4.85	126.80 ± 7.05	87.20 ± 6.02	39.60 ± 5.32	100.40 ± 5.88	18.40 ± 2.07
Immediately after exercise	AA	15	93.40 ± 9.97	157.60 ± 9.67	94.40 ± 10.64	63.20 ± 11.55	115.46 ± 8.77	30.27 ± 5.62
	AS	13	95.69 ± 6.96	154.00 ± 8.57	95.46 ± 10.24	58.54 ± 11.35	114.98 ± 8.12	29.54 ± 2.88
	SS	5	99.20 ± 3.83	157.60 ± 5.59	102.00 ± 11.11	55.60 ± 7.83	120.54 ± 8.90	34.40 ± 2.41
5-Min later	AA	15	86.67 ± 6.97	146.33 ± 10.00	89.07 ± 9.14	57.27 ± 9.90	108.16 ± 8.19	24.80 ± 3.45
	AS	13	88.00 ± 7.51	143.85 ± 8.59	92.00 ± 11.13	51.85 ± 12.93	109.28 ± 8.35	25.23 ± 2.35
	SS	5	90.80 ± 3.96	145.60 ± 3.36	94.60 ± 5.32	51.00 ± 4.80	111.62 ± 4.19	28.60 ± 2.19
10-Min later	AA	15	80.13 ± 6.65	136.47 ± 9.26	84.47 ± 9.64	-	-	21.53 ± 2.59
	AS	13	82.23 ± 8.42	137.77 ± 7.90	88.00 ± 10.03	-	-	21.38 ± 1.85
	SS	5	87.40 ± 5.13	137.00 ± 5.83	91.80 ± 5.63	-	-	24.20 ± 3.42
15-Min later	AA	15	74.73 ± 7.89	131.20 ± 10.78	82.07 ± 9.79	49.13 ± 9.01	98.44 ± 9.19	18.07 ± 2.09
	AS	13	75.23 ± 7.45	129.46 ± 9.37	86.31 ± 8.98	43.15 ± 10.66	100.69 ± 7.60	18.23 ± 0.83
	SS	5	82.80 ± 4.87	130.40 ± 7.89	89.40 ± 5.86	41.00 ± 6.04	103.08 ± 5.94	19.80 ± 2.59
			$^1F = 144.37$	$^1F = 189.17$	$^1F = 55.37$	$^1F = 56.72$	$^1F = 170.79$	$^1F = 280.53$
			^1P < **0.001**	^1P < **0.001**	^1P < **0.001**	^1P < **0.001**	^1P < **0.001**	^1P < **0.001**
			$^2F = 0.63$	$^2F = 0.65$	$^2F = 0.55$	$^2F = 0.14$	$^2F = 0.63$	$^2F = 1.38$
			$^2P = 0.669$	$^2P = 0.651$	$^2P = 0.728$	$^2P = 0.965$	$^2P = 0.618$	$^2P = 0.252$

Boldface signifies statistically significant difference

^1F denotes ANOVA test statistics value for within subjects' variables (times), whereas, its corresponding *P*-value is denoted as ^1P

^2F denotes ANOVA test statistics value for between subjects' factors (genotypes), whereas, its corresponding *P*-value is denoted as ^2P

Table 4: Results of repeated measures of ANOVA of physiological variables based on genotypes and times for female subjects.

			HR	**SBP**	**DBP**	**PP**	**MAP**	**RR**
	Genotype	**n**	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**
Before exercise	AA	17	73.82 ± 6.28	123.35 ± 8.18	80.06 ± 12.55	43.29 ± 9.46	94.48 ± 10.37	18.18 ± 2.79
	AS	22	78.18 ± 4.41	126.50 ± 9.33	82.41 ± 7.69	44.09 ± 7.20	97.11 ± 7.56	18.41 ± 1.89
	SS	3	76.67 ± 5.51	106.67 ± 17.79	67.00 ± 9.64	39.67 ± 8.14	80.20 ± 12.35	16.67 ± 1.53
Immediately after exercise	AA	17	97.12 ± 7.51	152.47 ± 7.19	95.35 ± 13.07	57.12 ± 12.13	114.39 ± 9.92	32.00 ± 4.80
	AS	22	99.55 ± 6.88	156.23 ± 5.94	95.18 ± 6.92	61.05 ± 7.76	115.54 ± 5.51	31.64 ± 4.62
	SS	3	107.33 ± 8.08	152.00 ± 8.66	77.00 ± 5.20	75.00 ± 3.46	101.97 ± 6.35	28.33 ± 3.51
5-Min later	AA	17	87.94 ± 6.71	140.76 ± 8.11	90.53 ± 10.71	50.24 ± 11.82	107.27 ± 8.20	26.41 ± 3.12
	AS	22	90.45 ± 4.58	145.73 ± 9.68	90.77 ± 5.84	54.95 ± 8.03	109.09 ± 6.29	26.77 ± 2.69
	SS	3	91.00 ± 4.36	136.67 ± 14.36	59.00 ± 35.79	77.67 ± 31.90	84.90 ± 26.38	24.33 ± 3.21
10-Min later	AA	17	82.00 ± 6.23	132.41 ± 8.60	85.47 ± 8.72	-	-	22.41 ± 2.76
	AS	22	85.05 ± 3.62	138.64 ± 7.44	87.00 ± 7.99	-	-	23.36 ± 2.15
	SS	3	84.67 ± 4.93	125.33 ± 20.55	72.67 ± 7.23	-	-	21.00 ± 1.00

15-Min later	AA	17	76.47 ± 6.05	127.29 ± 7.74	82.24 ± 10.98	45.06 ± 10.50	97.25 ± 8.71	19.53 ± 2.55
	AS	22	79.86 ± 3.73	129.73 ± 10.25	85.18 ± 6.68	44.55 ± 8.18	100.03 ± 7.06	19.77 ± 2.27
	SS	3	83.00 ± 6.24	108.33 ± 24.85	74.00 ± 2.00	34.33 ± 23.09	85.43 ± 9.46	17.67 ± 0.58
			^{1}F = 232.11	^{1}F = 221.30	^{1}F = 18.34	^{1}F = 67.93	^{1}F = 103.46	^{1}F = 168.42
			^1P < **0.001**	^1P < **0.001**	^1P < **0.001**	^1P < **0.001**	^1P < **0.001**	^1P < **0.001**
			^{2}F = 2.34	^{2}F = 4.77	^{2}F = 4.39	^{2}F = 9.19	^{2}F = 2.29	^{2}F = 0.52
			^2P = 0.056	^2P < **0.001**	^2P < **0.001**	^2P < **0.001**	^2P = 0.060	^2P = 0.699

Boldface signifies statistically significant difference

^{1}F denotes ANOVA test statistics value for within subjects' variables (times), whereas, its corresponding *P*-value is denoted as ^1P

^{2}F denotes ANOVA test statistics value for between subjects' factors (genotypes), whereas, its corresponding *P*-value is denoted as ^2P

Table 5: Results of repeated measures of ANOVA of physiological variables based on genotypes and times for the overall subjects.

			HR	**SBP**	**DBP**	**PP**	**MAP**	**RR**
	Genotype	**n**	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**
Before exercise	AA	32	72.69 ± 7.24	124.97 ± 9.90	80.34 ± 11.46	44.63 ± 9.78	95.21 ± 9.96	17.56 ± 2.45
	AS	35	76.00 ± 6.12	126.29 ± 8.42	82.94 ± 8.49	43.34 ± 8.52	97.39 ± 7.46	17.91 ± 1.80
	SS	8	78.13 ± 4.85	119.25 ± 15.08	79.63 ± 12.51	39.63 ± 5.93	92.83 ± 13.14	17.75 ± 1.98
Immediately after exercise	AA	32	95.38 ± 8.81	154.88 ± 8.70	94.91 ± 11.81	59.97 ± 12.07	114.89 ± 9.27	31.19 ± 5.19
	AS	35	98.11 ± 7.07	155.40 ± 7.00	95.29 ± 8.16	60.11 ± 9.17	115.33 ± 6.48	30.86 ± 4.15
	SS	8	102.25 ± 6.69	155.50 ± 6.91	92.63 ± 15.67	62.88 ± 11.80	113.58 ± 12.21	32.13 ± 4.09
5-Min later	AA	32	87.34 ± 6.75	143.38 ± 9.33	89.84 ± 9.87	53.53 ± 11.36	107.69 ± 8.08	25.66 ± 3.33
	AS	35	89.54 ± 5.86	145.03 ± 9.21	91.23 ± 8.07	53.80 ± 10.06	109.16 ± 7.01	26.20 ± 2.64
	SS	8	90.88 ± 3.80	142.25 ± 9.32	81.25 ± 26.86	61.00 ± 22.23	101.60 ± 20.00	27.00 ± 3.25
10-Min later	AA	32	81.13 ± 6.40	134.31 ± 9.00	85.00 ± 9.03	-	-	22.00 ± 2.68
	AS	35	84.00 ± 5.92	138.31 ± 7.51	87.37 ± 8.67	-	-	22.63 ± 2.24
	SS	8	86.38 ± 4.90	132.63 ± 13.29	84.63 ± 11.45	-	-	23.00 ± 3.12
15-Min later	AA	32	75.66 ± 6.91	129.13 ± 9.35	82.16 ± 10.27	46.97 ± 9.89	97.81 ± 8.81	18.84 ± 2.42
	AS	35	78.14 ± 5.78	129.63 ± 9.79	85.60 ± 7.50	44.03 ± 9.05	100.28 ± 7.16	19.20 ± 2.00
	SS	8	82.88 ± 4.97	122.13 ± 18.50	83.63 ± 9.18	38.50 ± 13.61	96.46 ± 11.37	19.00 ± 2.27
			^{1}F = 357.61	^{1}F = 402.48	^{1}F = 59.46	^{1}F = 98.65	^{1}F = 273.86	^{1}F = 471.62
			^1P < **0.001**	^1P < **0.001**	^1P < **0.001**	^1P < **0.001**	^1P < **0.001**	^1P < **0.001**
			^{2}F = 0.79	^{2}F = 2.61	^{2}F = 2.75	^{2}F = 4.03	^{2}F = 1.89	^{2}F = 0.71
			^2P = 0.567	^2P = **0.023**	^2P = **0.017**	^2P = **0.003**	^2P = 0.103	^2P = 0.581

Boldface signifies statistically significant difference

^{1}F denotes ANOVA test statistics value for within subjects' variables (times), whereas, its corresponding *P*-value is denoted as ^1P

^{2}F denotes ANOVA test statistics value for between subjects' factors (genotypes), whereas, its corresponding *P*-value is denoted as ^2P

genotypes in the female subjects after exercise. The HR, SBP, DBP, PP, MAP and HR of all the subjects, blood genotype AA, AS, SS significantly increases (p < 0.001) after exercise (Table 5).

Discussion

Exercise in all forms triggers epigenetic changes in several pathways that underlie the physiological benefits of exercise [10]. Exercise prescription in the general healthy population has been found to reduce future cardiovascular risk, chronic diseases and deaths [3,4,10]. Research have shown that physical inactivity is associated with the development of 40 chronic diseases [3,19]. In the present study using a treadmill, BP, MAP, PP, HR and RR increased steadily with exercise. Wielemborek-Musial, et al. [20] also reported, a statistical significance in blood pressure from rest to after exercise in healthy adults. There was no significant difference in the systolic and diastolic blood pressure, mean arterial pressure, pulse pressure and respiratory rate between participants of different blood genotype.

All physiological variables, heart rate, systolic blood pressure, diastolic blood pressure, pulse pressure, mean arterial blood pressure and respiratory rate, showed no significant differences between male and female participants of different blood genotype. Our results showed no significant difference in exercise tolerance levels between the AA, AS and SS groups. This result is in line with previous research done by Badawy, et al. [21] who reported that, higher body mass was associated with exercise capacity and overall fitness in adults, but blood genotype was not associated with exercise capacity.

Conclusion

From our result, we can conclude that blood genotype does not have an effect on exercise tolerance among the students. Physical activity among students provides a platform for social interaction, help improve emotional wellbeing and self-esteem, in addition to improving their health and fitness status. Blood genotype SS students can be advised to also participate in exercise. Especially that they are still young and need to build up their muscles and joints. Moreover, exercising with gradual increase in intensity appears to be safe for them, and it may not result into adverse events.

Conflicts of Interest

The authors declare no conflicts of interest.

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