

# Effect of physical activity on severity of primary angle closure glaucoma

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## Abstract

**Objective:** To determine the association between physical activity and severity of primary angle closure glaucoma in Malay patients.

**Methods:** A cross-sectional study was conducted involving 150 primary angle closure glaucoma patients between April 2014 and August 2016. Using the International Physical Activity Questionnaire, the physical activity status was assessed and divided into three categories: mild, moderate and heavy physical activity. The duration of physical activity and corresponding minimum energy requirements were calculated. Ocular examination was performed including Humphrey visual field 24-2 analysis assessment. Based on two consecutive reliable Humphrey visual fields, the severity of glaucoma was scored according to modified Advanced Glaucoma Intervention Study and classified as mild (0–5), moderate (6–11) and severe (12–20). Association between physical activity and Advanced Glaucoma Intervention Study score was determined with multiple linear regression analysis.

**Results:** A total of 150 Malay patients with primary angle closure glaucoma were included (50 patients with mild, 50 with moderate and 50 with severe glaucoma). Physical activity showed inverse association with the severity of primary angle closure glaucoma. After calculating adjustments for age, sex, duration of glaucoma, body mass index, systemic co-morbidities, family history of glaucoma, myopia and educational status [adjusted  $b$  –3.41, 95% confidence interval [–5.23, –1.59],  $p < 0.001$ ], there was also an inverse relationship with Advanced Glaucoma Intervention Study score. Every increase in physical activity level reduces the Advanced Glaucoma Intervention Study score by 3.4 point.

**Conclusion:** Physical activity is the potential modifiable risk factor in reducing the severity of glaucoma among primary angle closure glaucoma patients. However, there is possibility of the severity of glaucoma restricted the physical activity of primary angle closure glaucoma patients.

**Keywords:** Advanced Glaucoma Intervention Study score, Malay, physical activity, primary angle closure glaucoma, severity

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## Introduction

Physical activity provides health benefits that enhanced health and quality of life.<sup>1</sup> Disease outcomes such as cardiovascular disease, hypertension, thromboembolic stroke, diabetes mellitus, osteoporosis, obesity, colon or breast cancer,

anxiety and depression were inversely related to regular physical activity.<sup>2–4</sup> However, published reports on the association between physical activity and glaucoma are limited especially on primary angle closure glaucoma (PACG).<sup>5</sup> To the best of our knowledge, there is no study that look

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into association of physical activities and severity of PACG.

Physical activity is believed to lower the intraocular pressure (IOP) that indirectly decreases the progression of glaucoma.<sup>6-9</sup> However, there were evidences of transient rise of IOP during the initial stage of exercise.<sup>10,11</sup> This is due to contraction of abdominal and thoracic muscles, changes in body position and increased respiratory volumes, especially when Valsalva manoeuvre mechanisms are involved.<sup>12,13</sup> The changes in IOP during physical activity are dependent on types of exercise such as weightlifting, sit-up and bench press.

Deficiency in autoregulation of the optic nerve head (ONH) resulting in unstable ocular perfusion, ischaemia and reperfusion oxidative stress damage is believed to be part of the pathogenesis of glaucoma.<sup>12-15</sup> Lower diastolic perfusion pressure (DPP) and ocular perfusion pressure (OPP) have constantly been associated with increased risk for development and progression of glaucoma.<sup>16-19</sup> Physical activity is believed to improve blood perfusion, resulting in higher mean OPP and DPP.<sup>19-21</sup> Physical activity may provide relative protection against development and progression of glaucomatous damage.<sup>19,21</sup>

From the available studies, the evidences point towards a potential protective role of physical activity against progression of glaucoma.<sup>4,22-24</sup> Various reported studies have shown evidences of inverse relationship for the development of glaucoma especially in primary open angle glaucoma (POAG) but reports on PACG is scarce and no report was found on its association with the severity of PACG.<sup>4,21</sup> Detrimental effect of mechanical pressure induced by elevated IOP in PACG is believed to cause retinal nerve fibre layer damage especially with presence of acute presentation of angle closure (APAC). However, in Asians patients, more than 50% presented without APAC and behave like asymptomatic POAG.<sup>25</sup> This perhaps, make ways for potential effect of vascular factors and oxidative stress causing acceleration of optic neuropathy in PACG. Thus, identifying potential modifiable risk factors such as exercise and physical activity may halt progression of PACG. The objective of this study was to determine the association of physical activity and severity of PACG in Malay patients residing in Malaysia.

## Materials and methods

A cross-sectional study was conducted between April 2014 to August 2016 involving five ophthalmology clinics in Malaysia: Hospital Universiti Sains Malaysia (HUSM), Hospital Raja Perempuan Zainab II (HRPZ II), Hospital Kuala Lumpur (HKL), Hospital Sultanah Bahiyah (HSB) and Hospital Sultanah Nur Zahirah (HSNZ). This study received ethical approval from the Medical Research and Ethics Committee, Ministry of Health, Malaysia [d/m.KKM/NIHSEC/P14-234; (8)d/m.KKM/NIHSEC/P14-234 (annual renewal)] and Research and Ethical Committee, School of Medical Sciences, Universiti Sains Malaysia [USM/JEPeM/280.5.(2.2)]. This study was conducted in accordance to the Declaration of Helsinki for human research.

PACG patients were recruited during their follow-up in five ophthalmology clinics in Malaysia. Selection of PACG patients was based on International Society of Geographical and Epidemiological Ophthalmology (ISGEO).<sup>25</sup> Primary angle closure suspect (PACS), Primary angle closure (PAC) and PACG. PACS is defined as an eye in which 180° or more appositional contact between the peripheral iris and posterior trabecular meshwork is considered possible with normal IOP, no peripheral anterior synechiae (PAS) and no evidence of glaucomatous optic neuropathy (GON). PAC is defined as an eye with 180° or more occludable drainage angle and features indication that trabecular obstruction by the peripheral iris has occurred, such as raised IOP of more than 21 mmHg, PAS, iris whirling, 'glaucomflecken' lens opacities or excessive pigment deposition on the trabecular surface in the absence of GON. The term PACG is used to indicate PAC eyes with GON.<sup>26</sup>

Purposive sampling was conducted to select the PACG patients. PACG patients with three generations of Malay lineage without any interracial marriage were included. A pedigree chart was drawn to ascertain the Malay lineage. Those with an incomplete pedigree chart or unknown pedigree chart were excluded. Patients who had poor memory and history of cerebrovascular accident were also excluded. Principal investigator (N.T.) was responsible in selecting the patients in various centres.

A thorough ocular examination was conducted during recruitment process to rule out secondary

glaucoma such as neovascular glaucoma, pseudo-exfoliation glaucoma and angle recession glaucoma. Patients who could provide two consecutive reliable and reproducible visual fields within 3 months from the recruitment period were included in this study. Reliable visual field is defined as false positive and false negative error of <33% and fixation loss of <20%.<sup>27</sup> Patients with underlying retinal diseases, optic neuropathy other than glaucoma and brain pathology that may interfere with visual field assessment were also excluded. We have screened a total of 230 PACG patients (70 from HUSM, 50 from HRPZII, 40 from HKL, 36 from HSB and 34 from HSNZ). However, 20 patients were excluded due to presence of interracial marriage and incomplete pedigree chart, 50 were unable to produce two consecutive reliable visual field after maximum attempts and 10 unable to recall their physical activities.

Severity of PACG was scored using the modified Advanced Glaucoma Intervention Study (AGIS).<sup>28</sup> AGIS scoring was conducted on Humphrey visual field Swedish Interactive Threshold Algorithm Standard (SITA-Standard) strategy with 24-2 test pattern analysis. The scoring was carried out by two masked investigators who scored independently; the principal investigator (N.T.) and a glaucoma consultant (L.S.A.T.). The final score was based on the average score of two investigators. AGIS score of 1–5 was considered as mild glaucoma, 6–11 as moderate and 12–20 as severe glaucoma. If both eyes are eligible, the right eye is selected regardless of the severity.

Medical records of the recruited patients were retrieved. The duration and treatment of PACG, documented history of acute primary angle closure (APAC), systemic co-morbidities and refractive error were obtained from the medical record. Patients were also questioned on their education level, marital status and family history of glaucoma. Body mass index (BMI) was also calculated. Waist circumference was measured using a measuring tape.

A face-to-face interview was conducted using validated International Physical Activity Questionnaire (IPAQ) in Bahasa Malaysia to assess the physical activity in this study.<sup>29</sup> The questionnaire assesses all physical activities including job-related physical activity, housework, transportation physical activity and

leisure-time physical activity. Each activity was categorized according to physical effort and breathing. Vigorous activities referred to activities that require hard physical effort and make patients to breathe harder than normal. Moderate activities referred to activities that require moderate physical effort and breathe somewhat harder than normal.<sup>30</sup> The time spent sitting at work, home and during leisure time was also assessed. Patients need to recall the number of days and duration they spent on their physical activities. Patients were asked to recall their physical activities within the last 7 days prior to the interview.

As part of IPAQ scoring protocol, continuous variable of IPAQ can be expressed as the measurement of the volume of activity. This can be computed by weighting each type of activity by its energy requirement defined as METs. METs are multiples of the resting metabolic rate. For example, walking, the METs = 3.3, moderate physical activity = 4.0 METs and vigorous physical activity = 8.0 METs. To calculate for MET-minute, the MET score is multiplied by the minutes of physical activity performed. MET-minute is another measurement of volume of physical activity. The scores are equivalent to kilocalories for a 60 kg person. MET-minutes per week (MET-min/week) is computed by multiplying the MET-minutes by the number of days of physical activity performed. For example, walking for 30 min for 3 days in a week means that the METs value =  $3.3 \times 30 \times 3 = 297$  MET-min/week scores. Total METs per week was calculated based on combined physical activities in a week. For example, physical activity MET-min/week is a sum of walking + moderate-intensity physical activity + vigorous-intensity physical activity. Finally, the scores by individual patient was used to determine the category of physical activity level. Based on IPAQ scoring protocol, patients were grouped into three levels of physical activity; category 1 – inactive, category 2 – minimally active and category 3 – health enhancing physical activity (HEPA). In the present study, we defined category 1 as mild, category 2 as moderate and category 3 as heavy physical activity.

Mild physical activity (inactive) is when patients have no activity reported or had some activity reported but not enough to meet moderate (category 2) or heavy (category 3) physical activity. Moderate physical activity (minimally active) is when patients have either 3 or more days of vigorous activity of at least 20 min per day, or 5 or

more days of moderate-intensity activity, or walking for at least 30 min per day, or 5 or more days of any combination of walking and moderate-intensity, or vigorous-intensity activities achieving a minimum of at least 600 MET-min/week. Heavy physical activity (HEPA active) refers to when patients had either vigorous-intensity activity on at least 3 days and accumulated at least 1500 MET-min/week, or 7 or more days of any combination of walking and moderate-intensity or vigorous-intensity activities achieving a minimum of at least 3000 MET-min/week.

The relevant data were entered and analysed using Statistical Package for Social Sciences (SPSS) for Window Version 22. All data were rechecked to avoid wrong data entry and missing data. Multiple linear regression analysis was used to determine the association of physical activity with the AGIS score. Predictors such as age, sex, mean BMI, myopia, family history, systemic diseases, treatment and physical activity categories were included. A *p* value of less than 0.05 was deemed as statistically significant.

## Results

A total of 150 Malay patients with PACG were included (50 patients with mild, 50 with moderate and 50 with severe glaucoma) (Table 1). There were significantly older patients with severe glaucoma (Table 1). Female to male ratio is approximately 2.5:1, but there was no statistical difference between sex and severity of glaucoma (Table 1). Only 18 (12%) patients presented with history of APAC. Higher number of patients with APAC was observed with mild glaucoma (Table 1). Those with higher education levels tend to have less severe PACG (Table 1).

A total of 43 (28.7%) of the recruited PACG patients were considered physically inactive. Majority of them have severe glaucoma (58.1%), while moderate and mild glaucoma are represented by 13 (30.2%) and 5 (11.6%) patients, respectively (Figure 1). In contrast, physically active patients showed an inverse association between physical activity and the severity of glaucoma with 19 (54.3%), 11 (31.4%) and 5 (14.3%) representing mild, moderate and severe glaucoma, respectively. The higher MET-minutes amassed the more number of days per week of physical activity and the greater numbers of minutes per day of physical activity culminate to mild PACG (Table 2).

There was a negative correlation between number of days per week of physical activity with AGIS score. Inverse correlations were also found between number of minutes per day of physical activity as well as MET-min/week with AGIS score. Hence, increase of the number of days of physical activity that is the longer the duration of physical activity per day and higher MET-min score accumulated during the week were associated with lower AGIS score (Figure 2a–c).

Multivariate linear regression model applying backward method was used. There was an inverse linear relation with AGIS score (Table 3). Increased level of physical activity reduces AGIS score significantly by 3.4. Every increase of level of physical activity (e.g. mild to moderate) reduces the AGIS score (severity) by 3.4. Lower AGIS score indicates less severity of PACG. There was also significant association between educational level seen. Patients who are more educated have a lower AGIS score by 2.7.

## Discussion

This study is part of Malay Glaucoma Eye Study (MaGES), which aims to identify modifiable factors for development and progression of PACG and POAG in Malay patients. Most available data on PACG were from Chinese, Japanese and Indian population.<sup>31</sup> Malays account for 5% of the world's population.<sup>32</sup> As part of the global effort to prevent blindness due to glaucoma, understanding glaucoma in Malays is important.

In the present study, patients who are physically active tend to have less severe PACG. There was inverse correlation between AGIS score and physical activity: adjusted *b* –3.284 [95% confidence interval (CI) (–6.473, –0.095)]. Physical activity seems to play a protective role against progression of PACG. It is not entirely certain how physical activity affects glaucoma. It is postulated that physical activity may be responsible in reduction of IOP and indirectly cause retardation of glaucoma damage. There is a possibility that improvement in outflow facility of aqueous through increased systemic fibrinolytic activity during exercise,<sup>33,34</sup> increase in concentration of serum norepinephrine,<sup>35</sup> systemic autonomic stimulation<sup>36</sup> and increase in plasma osmolarity<sup>6</sup> may be responsible in reduction of IOP. In addition, changes in the colloidal osmotic pressure during dynamic exercise may also be responsible for reduction of IOP during physical activity.<sup>37</sup>

**Table 1.** Demographic data of PACG patients according to severity.

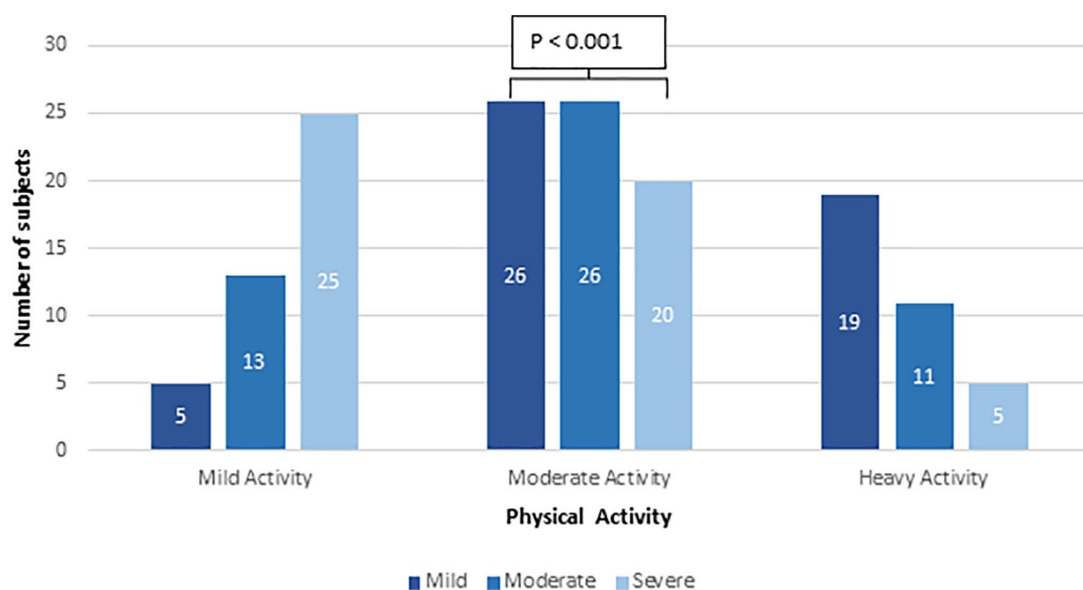
Variables	PACG (N = 150)			p value
	Mild (n = 50)	Moderate (n = 50)	Severe (n = 50)	
Mean age (years)	65.3	68.4	69.4	0.047 <sup>^</sup>
Sex (n, %)				
Male	11 (25.0%)	13 (29.5%)	20 (45.5%)	0.116 <sup>#</sup>
Female	39 (36.8%)	37 (34.9%)	30 (28.3%)	
Mean BMI (kg/m <sup>2</sup> )	24.3	24.9	25.3	0.416 <sup>^</sup>
Mean duration of PACG (years)	5.8	7.0	6.6	0.389 <sup>^</sup>
Educational level (n, %)				0.001 <sup>#</sup>
No formal education	6 (24.0%)	3 (12.0%)	16 (64.0%)	
Primary	18 (26.9%)	27 (40.3%)	22 (32.8%)	
Secondary	19 (38.8%)	18 (36.7%)	12 (24.5%)	
Tertiary	7 (77.8%)	2 (22.2%)	0 (0.0%)	
Systemic disease (n, %)				
Diabetes mellitus	14 (28.6%)	18 (36.7%)	17 (34.7%)	0.674 <sup>#</sup>
Hypertension	26 (31.0%)	32 (38.1%)	26 (31.0%)	0.378 <sup>#</sup>
Hyperlipidaemia	17 (31.5%)	17 (31.5%)	20 (37.0%)	0.771 <sup>#</sup>
Ischaemic heart disease	3 (23.1%)	4 (30.8%)	6 (46.2%)	0.555 <sup>#</sup>
Myopia (n, %)	6 (35.3%)	6 (35.3%)	5 (29.4%)	0.936 <sup>#</sup>
Family history of glaucoma (n, %)	5 (50.0%)	2 (20.0%)	3 (30.0%)	0.472 <sup>#</sup>
APAC	10 (55.6%)	6 (33.3%)	2 (11.1%)	0.048 <sup>#</sup>

APAC, acute presentation of angle closure; BMI, body mass index; PACG, primary angle closure glaucoma.  
<sup>#</sup>Pearson chi-square test ( $p < 0.05$  is significant).  
<sup>^</sup>One-way analysis of variance test ( $p < 0.05$  is significant).

Physical activity is also known to improve the systemic and ocular blood circulation.<sup>21,38,39</sup> A study by Hambrecht and colleagues<sup>40</sup> observed that regular physical activity may improve endothelium-mediated vasodilatation of peripheral vasculature and increase the basal nitric oxide formation, and subsequently cause reduction of blood vessels resistance. There was an improvement in OPP and retina blood flow immediately after exercise.<sup>41</sup> In addition, based on a large population-based study, 75% of physically active individuals have a higher mean OPP.<sup>21</sup> Moreover, regular exercise causes a sustained effect in improving the blood flow to chorioid and retina.<sup>41-43</sup> The potential benefit of

physical activity in improving the dysregulation of blood perfusion to the ONH may decelerate the progression of glaucoma.

Physical activity especially regular exercise is known to have positive effects on anti-oxidative processes.<sup>44,45</sup> Promptly after running a half-marathon, there was a transient rise in plasma concentration of ascorbic acid.<sup>46,47</sup> Ascorbic acid is an important protector against free radicals.<sup>48</sup> The elevation of plasma ascorbic acid concentration decreases 35 min after a treadmill exercise<sup>49</sup> and decline further below pre-exercise levels in the days after prolonged physical activity.<sup>47</sup> This suggests that regular exercise is important to



**Figure 1.** Distribution of physical activity according to severity of PACG.

**Table 2.** Association of physical activity component based on IPAQ and severity of PACG.

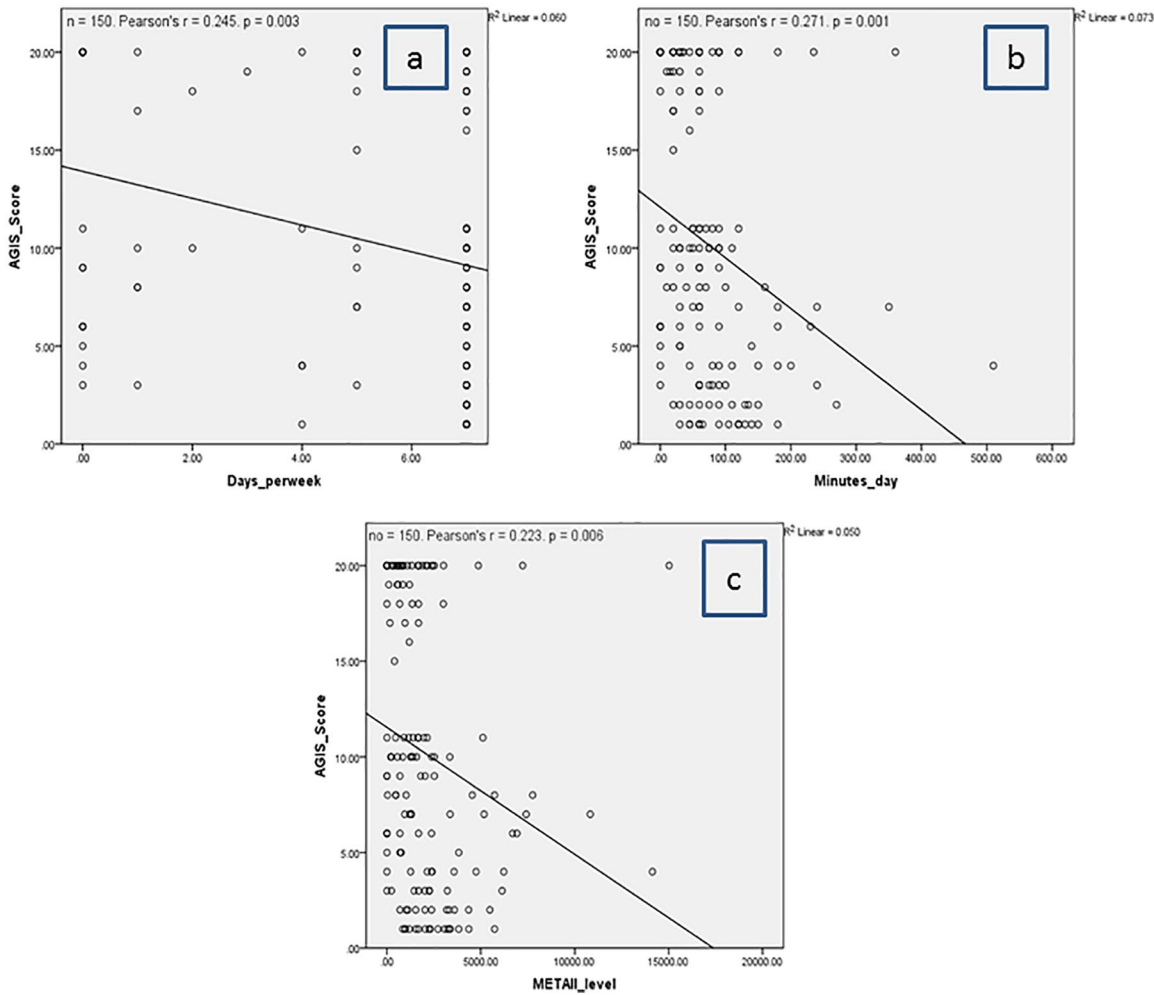
Physical activity	PACG (N=150)			p value
	Mild (n=50)	Moderate (n=50)	Severe (n=50)	
Mean MET-minute/week	2668	2181	1421	0.031 <sup>^</sup>
Mean days per week (days)	6	5	4	0.014 <sup>^</sup>
Mean minutes per day (mins)	100	73	50	0.003 <sup>^</sup>

IPAQ, International Physical Activity Questionnaire; MET, measurement of energy requirement; PACG, primary angle closure glaucoma.  
<sup>^</sup>One-way analysis of variance test ( $p < 0.05$  is significant).

sustain the potential beneficial effect of reduction of oxidative stress.

There was strong inverse correlation between the duration of physical activities (minutes/day and days/week) and AGIS score (Figure 2a and b). Erythrocyte activities of the antioxidant enzymes, glutathione peroxidase and catalase were significantly enhanced and positively correlated with the duration of physical activity.<sup>45,50</sup> There was also a significant increased pulsatile ocular blood flow seen with regular exercise.<sup>24,51</sup> Regular duration of exercise has the potential to sustain the beneficial properties on glaucoma progression. However, major limitation in this study was the definition of physical activity was considered as all type of activities and movements daily without looking into specific exercise.

In the present study, we found a significant difference in MET-minute according to severity. Patients with more constricted peripheral visual field have lower mean MET-min. Glaucoma patients were found to walk 10% slower compared with age-matched controls.<sup>52</sup> The speed of walking correlated with the severity of visual field of the worst eye.<sup>52</sup> The IPAQ considered walking as low intensity activity without considering the speed of walking.<sup>29</sup> The intensity of physical activities was only an assumption in this study. For example, we were unable to identify the walking activity as an exercise or part of leisure activities. This may affect the calculation of MET-minute. Ramulu and colleagues<sup>53</sup> quantify the physical activities and walking using accelerometer in glaucoma patients. Glaucoma patients with bilateral visual field loss were found to walk



**Figure 2.** Correlation between physical activity (PA) parameters and AGIS score: (a) duration of PA in days per week, (b) duration of PA in minutes per day and (c) MET-min/week score.

**Table 3.** Multiple linear regression analysis on factors affecting AGIS score.

Variables	Single linear regression		Multiple linear regression	
	<i>b</i> <sup>^</sup> (95% CI)	<i>p</i> value	<i>b</i> <sup>#</sup> (95% CI)	<i>p</i> value
Physical activity	-4.584 (-7.836, -1.331)	0.006	-3.284 (-6.473, -0.095)	0.044
Age	0.180 (0.049, 0.311)	0.007	0.017 (-0.130, 0.164)	0.823
Education level	-3.119 (-4.457, -1.781)	<0.001	-2.764 (-4.319, -1.210)	0.001

Backward multiple linear regression method applied. Model assumption is fulfilled. There was no interaction among independent variables. No multicollinearity detected. CI, confidence interval.

<sup>^</sup>Crude regression coefficient.

<sup>#</sup>Adjusted regression coefficient.

13% less and 22% less involvement in moderate to vigorous physical activities compared with those with unilateral visual field loss.<sup>53</sup> In

addition, as majority of them also have systemic co-morbidities, that too can further limit their physical activity.<sup>54,55</sup>

The limitation of this study include the design of the study (cross-sectional) that may not be able to provide causal relationship between physical activities and severity of glaucoma. Reduction of physical activities may not associate with severity of glaucoma. There is possibility that severity of glaucoma that reduces the physical activities of glaucoma patients. Constriction of visual field was also found to reduce the travel pattern in daily routine of glaucoma patients using cellular tracking devices.<sup>56</sup> In the future, prospective cohort study may provide a better understanding of the effect of physical activity and severity of PACG.

Another limitation in this study, only the severity of unilateral eye (if both eyes are eligible) was used for analysis. There are also patients in our study who have PACG in one eye, the other eye is diagnosed as PAC and PACS. Perhaps, in this type of patients, visual disability is not so prominent. Thus, this may not reflect the actual visual disability related to daily activities in this study. There was significant reduction of walking steps and moderate to vigorous physical activities between glaucoma patients with bilateral and unilateral field loss.<sup>54</sup>

PACG is highly prevalent among women.<sup>57,58</sup> In the current study, there was also preponderance to female with a ratio of approximately 2.5:1. Generally, men are known to be more physically active than women.<sup>59,60</sup> Thus, it is expected, men to have less severe glaucoma. However, there was no significant association between sex and severity of glaucoma. This could be due to the majority of the recruited patients were already in their retirement age. The retirement age in Malaysia is 60 years old. Most probably, they were less physically active during the recruitment period compared with when they were younger.<sup>55,61</sup>

On the contrary, due to lower education level (61.3% were without formal education or just up to primary school level), perhaps they were still actively working in the farm or menial labour. On contrary, there is evidence suggested that lower education level was associated with less physical activities in the United States.<sup>62</sup> However, low level of education was associated with poor awareness of health, leading to late detection of disease, and poor compliance to treatment.<sup>63</sup> This perhaps explained the significant association between educational level and the severity of glaucoma.

Assessment of physical activity using IPAQ is not ideal which is another source of limitation in this study. IPAQ questionnaire assessed the physical activity for the past 7 days that may not reflect the accurate long-term habits or routine of physical activity of an individual. In addition, there was possibility of recall bias as most of patients were elderly; mean age of 65 years and above. A prospective study will be the ideal methods in the future. Physical activity in our study includes all types of activities; daily activity, working activity, leisure-time activity and exercise. Thus, we are unable to specifically recommend the type, duration or level of intensity of physical activity for PACG patients that may halt or slow down progression of this sight-threatening disease. However, this study provides a baseline data for our future planning to develop a safe and effective exercise regime for glaucoma patients with constricted visual field.

In conclusion, physical activity may help in preventing further GON in Malay patients with PACG. PACG patients are encouraged to cultivate a healthier and active lifestyle as an adjunct to the existing treatment.

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### Conflict of interest statement

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### Ethical approval

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