EVALUATION OF RETINAL VASCULAR CALIBERS IN OVERWEIGHT AND OBESE MALAY CHILDREN

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DISCLAIMER

I hereby certify that the work in this dissertation is my own except for quotations and summaries which have been duly acknowledged.

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ABSTRAK (BAHASA MALAYSIA)

Latar belakang:

Kajian berkenaan diameter salur darah retina di kalangan kanak-kanak yang mempunyai berat badan berlebihan dan obes adalah terhad, terutamanya bagi orang Melayu yang merupakan etnik utama di Asia Tenggara.

Tujuan:

Kajian ini bertujuan untuk menentukan ukuran purata dan perbezaan purata diameter arteriol and venul retina antara kumpulan obesiti dan kumpulan berat badan berlebihan di kalangan kanak-kanak Melayu.

Kaedah:

Ini adalah satu kajian keratan rentas yang melibatkan seramai 131 kanak-kanak Melayu berumur 6-12 tahun di Kota Bharu, Malaysia. Kumpulan berat badan berlebihan dan obesiti telah dikenalpasti berdasarkan carta pertumbuhan WHO (5 hingga 9 tahun) mengikut jantina dan umur. Pelbagai peringkat kaedah persampelan rawak digunakan dalam pengambilan peserta. Pemeriksaan mata, refraksi mata, fotografi retina dan pengukuranan tropometri termasuk ketinggian, berat badan dan tekanan darah telah diperolehi melalui protokol yang telah ditetapkan.

Diameter salur darah retina diukur menggunakan program perisian *Singapore I Vessel Algorithm* yang disahkan dan diterjemahkan sebagai *central retinal arteriolar equivalent* (CRAE) dan *central retinal venular equivalent* (CRVE) dengan menggunakan formula Kudtson-Parr-Hubbard. Ralat pada saiz salur darah retina disebabkan oleh magnifikasi okular telah diperbetul dengan menggunakan formula *Bengtsson*. Analisis *Covariance* telah dijalankan untuk menentukan data perbezaan purata di antara kanak-kanak Melayu yang berlebihan berat badan dan obesiti, setelah diselaraskan dengan faktor ketara yang lain.

Keputusan:

Data purata CRAE pada kanak-kanak Melayu yang berlebihan berat badan dan obes, masing-masing adalah 173.50 mikron dan 165.84 mikron, manakala data purata CRVE pada kanak-kanak Melayu yang berlebihan berat badan dan obes, masing-masing adalah 252.37 mikron dan 253.41 mikron. Keputusan ANCOVA menunjukkan bahawa terdapat perbezaan purata yang ketara pada diameter arteriolar retina antara anak-anak Melayu yang berlebihan berat badan dan obes, di mana saluran darah arteriol lebih sempit di kalangan subjek obes berbanding subjek berlebihan berat badan. Walau bagaimanapun, tiada perbezaan purata yang ketara pada diameter venul retina antara anak-anak Melayu yang berlebihan berat badan dan obes, setelah setelah penyelarasan pembolehubah yang lain.

Kesimpulan:

Diameter arteriol retina didapati lebih sempit di kalangan kanak-kanak Melayu obes berbanding subjek yang berlebihan berat badan. Walau bagaimanapun, purata diameter venul retina hampir sama dalam kedua-dua kumpulan. Ini menunjukkan bahawa obesiti kanak-kanak memberi kesan kepada salur darah halus seawal zaman kanak-kanak. Kajian ini mencetuskan kesedaran untuk mencegah seawal ketika berat badan berlebihan, dalam usaha untuk menghalang potensi penyakit sistemik yang tidak diingini di kemudian hari, akibat obesiti.

Kata kunci: berat badan berlebihan, obesiti, diameter arteriol retina, diameter venul retina, kanak-kanak, Melayu

ABSTRACT

Background:

There are limited studies on retinal vascular caliber in overweight and obese children especially for Malays who is the main ethnicity in South East Asia.

Purpose:

The present study aims to determine the mean and mean differences of retinal arteriolar caliber and retinal venular caliber between overweight and obese among Malay children.

Methods:

This was a cross-sectional study involved 131 Malay children aged 6-12 years in Kota Bharu, Malaysia. Overweight and obese groups were identified based on sex and age specific World Health Organization 5 to 19 years old growth chart. Multi-stage random sampling method was employed in participants' recruitment. Ocular examination, refraction, retinal photograph and anthropometric measurement including height, weight and blood pressure were obtained by standardized protocols.

Retinal vascular caliber was measured using a validated computer-based program Singapore I Vessel Algorithm software and were summarized as the retinal arteriolar equivalent (CRAE) and central retinal venular equivalent (CRVE) by using the Kudtson-Parr-Hubbard formula. Ocular magnification on retinal vascular vascular caliber measurement was corrected by using the Bengtsson formula. Analysis of Covariance was performed to determine mean difference

between overweight and obese Malay children after adjusted with significant confounding factors.

Results:

The mean corrected CRAE in overweight and obese Malay children were 173.50 μm and 165.84 μm respectively whereas the mean corrected CRVE in overweight and obese Malay children were 252.37 μm and 253.41 μm respectively. There was a significant mean difference of retinal arteriolar caliber between overweight and obese Malay children where narrower retinal arteriolar caliber was observed in obese than overweight. However, there was no significant mean difference of retinal venular caliber between overweight and obese Malay children after adjustment for confounding variable.

Conclusions:

Retinal arteriolar caliber was found narrower in obese than the overweight Malay children. However, The mean retinal venular caliber was almost similar in both groups. This may suggest that pediatric obesity has an effect on the microvasculature early in childhood. This study triggers the awareness of preventing children as early as overweight period in order to halt the potential undesired systemic diseases later on in obesity period.

Keywords: overweight, obesity, retinal arteriolar caliber, retinal venular caliber, children, Malay

Chapter 1

Introduction

1.1 INTRODUCTION

Obesity is the most prevalent nutritional disorder among children. In Malaysia, one out of five children aged 7-12 years old were overweight (Naidu *et al.*, 2013). The prevalence of obesity was highest amongst the Malays (13.6%) and Indians (13.5%) followed by the indigenous group of Sarawak Bumiputra (10.8%) and the Chinese (8.5%) (Rampal *et al.*, 2007). The national prevalence of overweight and obesity were 30.0% and 17.7% based on World Health Organization (WHO) 1998 classifications as reported in National Health and Morbidity Survey (NHMS) 2015 report (Institute for Public Health, 2015).

There are many factors, including genetics, environment, metabolism, lifestyle, and eating habits, are believed to play a role in the development of obesity. However, more than 90% of cases are idiopathic; less than 10% are associated with hormonal or genetic causes (Xu and Xue, 2016). The increasing public concern about obesity is related to its long term morbidity and mortality. Obesity related communicable diseases with early onset metabolic syndrome such as diabetes, hypertension, hyperlipidemia and future risk of coronary heart disease (Baker *et al.*, 2007). Obesity has also been postulated in the pathogenesis of carcinogenesis (Parekh *et al.*, 2013).

The human microvasculature are considered to be close relationship with retinal microvasculature. Previously retinal vessel caliber could be evaluated only by relatively invasive methods, is now gradually becoming non invasive computerized based of direct visualization of retinal vasculature via fundus photography (Patton *et al.*, 2005; Wong *et al.*, 2001). Recent studies

show that narrower retinal arteriolar caliber and larger retinal venular caliber have been associated with obesity (greater BMI, weight and larger waist circumference) and component of metabolic syndrome (Gopinath *et al.*, 2011). This suggesting that obesity may have an effect on the systemic microvasculature later on in adults (Wong et al., 2004). Alterations in retinal vessel structure may represent the earliest sign of microvascular damage from systemic cardiovascular disease. As narrower retinal arterioles have been associated in adults with a long-term risk of not only systemic conditions like stroke (Kawasaki *et al.*, 2012), diabetic retinopathy (Dirani *et al.*, 2010), coronary heart disease (Wong *et al.*, 2006), but also ocular conditions like glaucoma (Kawasaki *et al.*, 2013), it is of clinical interest to ascertain if the retinal vascular caliber in obese children truly differs significantly from that of normal children.

Although the studies in children are comparatively few, associations have been demonstrated between changes in retinal vasculature and blood pressure (Li *et al.*, 2011), body mass index (Gopinath *et al.*, 2013b), birth weight (Gopinath *et al.*, 2010) and gestational age (Hellstrom *et al.*, 2000; Kistner *et al.*, 2002). Other studies had found that ocular biometry such as axial length (Tai *et al.*, 2017), corneal curvature (Gopinath *et al.*, 2013a) and serum biomarkers (McFarlin *et al.*, 2013) has effect on retinal vessel alteration. Thus, all of the above could be potential confounding factors which might influence the accuracy of the true result of the retinal vascular caliber in this study.

Children are ideal subjects for the study between body mass and retinal vessel caliber as they are relatively free of systemic diseases. To our knowledge, no studies have been performed to evaluate the retinal arteriolar and venular caliber in overweight and obese Malay children. This

result will be useful to estimate the prevalence of undesired systemic disease in Malay children during later adulthood.

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Chapter 2

Objectives

2.1 GENERAL OBJECTIVE

To study the retinal vascular caliber in overweight and obese Malay children

2.2 SPECIFIC OBJECTIVES

i. To determine the mean retinal arteriolar caliber among overweight Malay children

ii. To determine the mean retinal venular caliber among overweight Malay children

iii. To determine the mean retinal arteriolar caliber among obese Malay children

iv. To determine the mean retinal venular caliber among obese Malay children

v. To compare the mean retinal arteriolar caliber in overweight and obese Malay children

vi. To compare the mean retinal venular caliber in overweight and obese Malay children

Chapter 3

Manuscript

3.1 TITLE PAGE

Evaluation of Retinal Vascular Calibers in Overweight and Obese Malay Children

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Author roles:

KSC carried out the study, data analyses, and wrote the manuscript. SI designed the study. ETLM is co-researcher to the study. YCK carried out the data analyses. TYW contributed retinal vessel analysis via the Singapore I Vessel Analysis (SIVA) 4.0 cloud system, as part of a collaborative research project between Universiti Sains Malaysia and Singapore Eye Research Institute.

3.2 ABSTRACT

Purpose:

There are limited studies on retinal vascular caliber in overweight and obese children especially for Malays who is the main ethnicity in South East Asia. The present study aims to determine the mean and mean differences of retinal arteriolar caliber and retinal venular caliber between overweight and obese Malay children.

Methods:

This was a cross-sectional study involved 131 Malay children aged 6-12 years in Kota Bharu, Malaysia. Overweight and obese groups were identified based on sex and age specific World Health Organization 5 to 19 years old growth chart. Multi-stage random sampling method was employed in participants' recruitment. Ocular examination, refraction, retinal photograph and anthropometric measurement including height, weight and blood pressure were obtained by standardized protocols.

Retinal vascular caliber was measured using a validated computer-based program Singapore I Vessel Algorithm software and were summarized as the retinal arteriolar equivalent (CRAE) and central retinal venular equivalent (CRVE) by using the Kudtson-Parr-Hubbard formula. Ocular magnification on retinal vascular vascular caliber measurement was corrected by using the Bengtsson formula. Analysis of Covariance was performed to determine mean difference between overweight and obese Malay children after adjusted with significant confounding factors.

Results:

The mean corrected CRAE in overweight and obese Malay children were 173.50 μm and 165.84 μm respectively whereas the mean corrected CRVE in overweight and obese Malay children were 252.37 μm and 253.41 μm respectively. There was a significant mean difference of retinal arteriolar caliber between overweight and obese Malay children where narrower retinal arteriolar caliber was observed in obese than overweight. However, there was no significant mean difference of retinal venular caliber between overweight and obese Malay children after adjustment for confounding variable.

Conclusions:

Retinal arteriolar caliber was found narrower in obese than the overweight Malay children. However, The mean retinal venular caliber was almost similar in both groups. This may suggest that pediatric obesity has an effect on the microvasculature early in childhood. This study triggers the awareness of preventing children as early as overweight period in order to halt the potential undesired systemic diseases later on in obesity period.

Keywords: overweight, obesity, retinal arteriolar caliber, retinal venular caliber, children, Malay

3.3 INTRODUCTION

Childhood overweight and obesity have been recognized as major international public health threat concern in developed and developing countries including Malaysia. Globally up to 10 % of children were labeled as overweight and obese (1, 2). In Malaysia, the prevalence of obesity among children in Malaysia is also on the rise. Malaysia is a middle-income country with multi-ethnic population. Prevalence of obesity was highest amongst the Malays (13.6%) and Indians (13.5%) followed by the indigenous group of Sarawak Bumiputra (10.8%) and the Chinese (8.5%) (3). Based on World Health Organization (WHO) 1998 classifications, the national prevalence of overweight and obesity were 30.0% and 17.7% as reported in National Health and Morbidity Survey (NHMS) 2015 report. The prevalence of overweight and obesity had increased by 0.6% and 2.6% respectively as compared with NHMS 2011. The prevalence of obesity in Malaysia is also higher than the world prevalence of 13% in 2014 (4).

The increasing public concern about obesity is related to its long term morbidity and mortality, as it is associated with early onset metabolic syndrome such as diabetes, hypertension, hyperlipidemia and future risk of coronary heart disease (5). Other non-communicable diseases such as cancers, gallbladder diseases, respiratory problems and musculoskeletal disorders are also associated with obesity (3). Previous studies in children and adult have shown that narrower retinal arteriolar caliber is associated with hypertension, diabetes, coronary artery disease (6-8). Meanwhile, wider retinal venular is related to systemic inflammation and obesity (9, 10). Adverse changes to the microvascular bed have been found to exist in early and late childhood, before the onset of cardiovascular and metabolic disease in adulthood (11).

The retinal vasculature is an easily accessible surrogate for the systemic microcirculation after the advent of fundus photo imaging device which provides a unique, non-invasive approach to the retinal vessel microcirculation (12). Children, who are relatively free of systemic diseases, are therefore ideal samples to study the direct association between body mass and retinal vessel caliber. Based on PubMed search, apart from Cheung et al (2007) described multi-ethnic variation of retinal vascular caliber in children and Evelyn et al (2017) studied on effect of axial length on retinal vascular caliber Malay girl, limited study has been performed to evaluate mean and comparison of retinal arteriolar and venular caliber in overweight and obese Malay children. The present study aims to determine the mean and mean differences of retinal arteriolar caliber and retinal venular caliber between overweight and obese among Malay children.

3.4 MATERIALS AND METHODS

Participants

This was a school and hospital based cross-sectional study of involving 131 Malay children aged 6-12 years commencing from January 2015 to December 2016. The Human Research Ethics Committee Universiti Sains Malaysia approved the study and the conduct of study followed the tenets of the Declaration of Helsinki. Parents of the selected children were provided with information to participant sheet prior to the study.

Multi-stage random sampling method was employed in participants' recruitment. Two primary schools were randomly selected from total 96 primary schools in Kota Bharu, Malaysia. Written approvals were obtained from the Kelantan State Education Department and Ministry of Education, Malaysia. The permission to conduct this study in the selected schools was obtained from the schools' principal. The eligible children who were overweight and obese were identified from each class of the selected schools. Then, the potential participants were randomly selected from this identified children list to be enrolled in the present study.

Definition of Term

The definition of overweight and obesity among children is a body mass index (BMI; the weight in kilograms divided by the square of the height in meters). Overweight and obese groups were identified based on sex and age specific based on WHO 5 to 19 years (percentiles) growth chart. Overweight is defined as body mass index (BMI) more than 85^{th} percentiles whereas obesity is more than 95^{th} percentiles (13).

Ethnic Definition: Malay (Melayu)

According to Article 160 of the Federal Constitution (i.e. the Constitution of Malaysia), "Malay" means a person who professes the religion of Islam, habitually speaks the Malay language, conforms to Malay custom and -

(a) was before Merdeka Day born in the Federation or in Singapore or born of parents one of whom was born in the Federation or in Singapore, or is on that day domiciled in the Federation or in Singapore; or

(b) is the issue of such a person.

Inclusion and Exclusion Criteria

During school based screening, children who fulfilled the inclusion and exclusion criteria were invited to participate the study. Those children who were 6 to 12 years old Malay ethnicity, had best corrected visual acuity better than 6/12 with refractive error less than ±2.0, body mass index more than 85th percentiles based on WHO 5 to 19 years old (percentiles) growth chart, normal anterior and posterior segment and intraocular pressure included into the study. Children who were born premature, have syndromic, neurologic and optic disc or optic nerve abnormalities, history or presence of systemic microvascular disease, retinal disease, glaucoma, ocular trauma or surgery and squint or amblyopia excluded into the study.

Written informed consent was taken from at least one parent after the nature of the study was explained and verbal assent from the participants. These selected children were approached to participate in the present study. Letter was given to the subject parent and were invited with their children to pay a visit to Eye Clinic Hospital Universiti Sains Malaysia for systemic and ocular biometric parameters such as blood pressure, corneal curvature, spherical equivalent, axial length, anterior chamber depth and intraocular pressure and retinal photography.

BMI and Anthropometric Measurement

Initially, we examined 256 students from standard one to standard six of randomized two primary schools from 96 schools for the study. However, 125 children were excluded into the study due to not fulfill the inclusion and exclusion criteria and the remaining 131 students were qualified and recruited into the study. Height and weight measurements were performed by standing with barefoot and using standardized protocols. Height was documented to the nearest 1mm while weight was recorded to the nearest 0.1 kg. Calibrated standard portable weighting machine was used prior to weight measurement.

Systemic Examination

The children were examined in the Eye Clinic by the identified investigators, optometrists and research assistants. Blood pressure and heart rate was measured in the sitting position after five minutes of rest by using an appropriate paediatric cuff size and automatic Omron sphygmomanomer (Omron HEM 705 LP, Omron Healthcare Inc, USA). Three separate measurements were taken and average was calculated. Mean arterial blood pressure (MABP) was calculated as one third of the systolic blood pressure and two thirds of the diastolic blood pressure.

Ocular Examination

Distance visual acuity is measured monocularly with a standard Snellen chart at 6 meters (Reichert, Ny, USA). External eye examination was performed to assess eyelid abnormality and extraocular motility. Anterior segment examination was conducted using slit lamp biomicroscopy to assess conjunctiva, cornea, anterior chamber, iris, pupil and lens in both eyes by identified investigators.

Autorefraction was performed by using an autokeratorefractometer (model RK5; Canon, Inc). Spherical equivalent was calculated as the value of the sphere plus half of the value of the cylinder. Axial length was taken from an average of five consecutive readings by using a non-contact partial coherence interferometer (IOL Master, Carl Zeiss Meditec, Inc, Germany). All these parameters were performed by a trained research assistant.

Retinal Photography

After dilatation with topical phenylephrine 2.5% and tropicamide 1% 45 degree digital retinal photographs centered on optic disc and macula were taken from both eye using digital fundus camera (Model VX-10/KOWA/Japan). One grader masked to participant identity and characteristics performed for all retinal images and measurement.

By using the partially-automated computer software, Singapore I Vessel Algorithm (SIVA 4.0 cloud system) software (Fig 1), retinal images were analyzed with all retinal vessels greater than 25 μm n diameter located between one-half to two disc diameters from the optic disc margin are

outlined, their edges marked using a pixel density histogram, and the retinal arteriolar venular calibers calculated using the Kudtson-Parr-Hubbard formula (14-16).

This formula summarizes the diameters of the six largest arterioles and venules to generate a central retinal arteriolar equivalent (CRAE) and central retinal venular equivalent (CRVE) respectively. Right retinal vascular caliber was measured in case where these were ungradable, left eye measurement were used. Ocular magnification on retinal vascular caliber measurement was corrected by using the Bengtsson formula (17, 18).

Sample Size

Sample size determination was done using Power and Sample Size 3.0 for all the objectives in the present study. The largest sample size was presented in here. The parameters used in the sample size determination were: alpha = 0.05, power = 80%, mean difference of retinal venular caliber between overweight and obese groups = 9 (expert opinion), standard deviation = 16.1 based on Hanssen et al., 2012 study, m (ratio) = 0.5, sample size was estimated as 39 for overweight and 77 for obese.

After adding non-response rate of 20%, total sample were 49 for overweight and 97 for obese. Based on sample size determination from objective 1 to objective 6, the largest sample size for the present study was N = 146. Among the eligible participants of 49 overweight and 97 obese, only 46 overweight and 85 obese children data were included for subsequent data analysis. Children who did not co-operative during the retinal photograph imaging were excluded from the data pool.

Statistical Analyses

Statistical analyses were performed using SPSS version 24.0. Normal distributions of numerical variables were checked using histograms and normality tests (see Appendix 1, 2, 3). Descriptive statistics were used to describe the study variables. Mean and standard deviation (SD) were used to describe the numerical variables. Frequency and percentage were used to describe the categorical variables.

Pearson Chi-square was used to determine the difference between categorical variables. Independent t-test was used to determine the mean differences between overweight and obese groups. Analysis of Covariance (ANCOVA) was performed to determine the mean differences of retinal arteriolar caliber and retinal venular caliber among overweight and obese children. The possible confounding variables such as axial length and spherical equivalent were included in the analysis as covariates.

3.5 RESULTS

A total of 131 Malay children were recruited into this study. The overall mean age children participated in the present study was 9.76 (1.67). The mean age of overweight and obese children was 10.20 (1.68) and 9.53 (1.62) respectively. There were more female (51.1%) than male (49.9%) participated in this present study. The mean BMI of overweight was 20.83 (1.49) whereas obese was 25.16 (3.88). There were total 46 participants who were overweight (35.1%) and 85 participants who were obese (64.9%). Table 1 shows the descriptive statistics of participants' demographic characteristics based on overweight and obese groups. The majority of the participants were obese than overweight. Among the obese children, two were morbid obesity based on cut of point BMI > 35.

The mean corrected CRAE in overweight and obese Malay children became 173.50 μm from uncorrected 172.39 μm and 165.84 μm from uncorrected 164.42 μm respectively whereas the mean corrected CRVE in overweight and obese Malay children became 252.37 μm from uncorrected 250.76 μm and 253.41 μm from uncorrected 251.21 μm respectively as shown in Table 2.

ANCOVA result shows that there was a significant mean difference of retinal arteriolar caliber between overweight and obese Malay children after adjustment for confounder variable of axial length (refer to Table 3). Based on the adjusted mean value, overweight Malay children had higher mean of retinal arteriolar caliber than obese Malay children. In addition, axial length was confounder variables significantly associated with retinal arteriolar caliber. There was no significant mean difference of retinal venular caliber between overweight and obese Malay

children after adjustment for confounder variable of axial length and spherical equivalent (refer to Table 3). However, axial length and spherical equivalent were significantly associated with retinal venular caliber.

3.6 DISCUSSION

Among a total of 31.7 million Malaysian citizens, ethnic Malay and Bumiputera comprise the majority (68.6%), followed by Chinese (23.4%), Indians (7.0%), based on Current Population Estimates, Malaysia from 2014 to 2016 (19). In Malaysia, Naidu et al. in 2013 reported one out of five children aged 7-12 years old were overweight (20). A previous study by Manan et al. in 2012, who reported on overweight and obesity prevalence among Malay primary school children in Kota Bharu, Kelantan showed that 13.1% of a total 175 Malay children were categorized as overweight and obese (21). Table 4 summaries published literature regarding mean CRAE and CRVE in overweight and obese children from 2007 to 2014. Our study provides new insight on the mean differences of arteriolar caliber and retinal venular caliber between obese and overweight Malay children.

We documented that the mean CRAE was narrower in obese (165.84μm) than overweight children (173.50μm). These results were consistent with a study conducted by Gopinath et al. in 2011 who examined 2179 multi-ethnic children in Australia with mean aged 12.7 and reported that obese children (149.20μm) had narrower mean CRAE than overweight children (150.90μm) (11). The children in that study had smaller mean CRAE in both overweight and obese children than our

study. One potential reason is ethnic differences in retinal vessel caliber. However, the mean age between their study and ours also differed, in which our study participants (9.76 years old) were slightly younger than Gopinath's study participants (12.70 years old).

There was study reported that older people have narrower CRAE than younger people (11). In a population based Beaver Dam eye study by Wong et al 2003, retinal arteriolar diameter decreased by 2.1μm (95% confident interval CI 1.5-2.7) for every decade increase in age (22). We observed that the overall mean CRAE in all participants in our study was 168.45μm, which was slightly smaller than in a recent study by Evelyn et al, in which the mean CRAE was 171.40 μm (23). In their study, the participants were normal weight Malay children, which may explain the disparity with the present study, which focuses on overweight and obese Malay children.

We observed the mean CRVE was wider in obese (253.41μm) than overweight children (252.37μm) which is in line with the results of Gopinath et al., which reported that obese children (222.60μm) had a wider mean CRVE than overweight children (219.00μm) (11). As compared to mean CRVE baseline study by Evelyn et al. which was 248.02 μm, our mean CRVE result was larger retinal venular caliber which was 253.5μm (23). Evelyn et al. conducted a cross sectional study on 86 normal weight Malay girl aged 6 to 12 years old to evaluate retinal vascular caliber in Malay children.

Several population-based studies have reported an association between obesity and retinal vascular caliber but the results are inconsistent (24, 25). Similar to our study, there were few studies showed an inverse relationship between BMI and retinal arteriolar caliber and a direct relationship with

retinal venular caliber (11, 25-27). Some studies reported that greater BMI is related to narrower retinal arteriolar caliber (24, 28, 29) whereas other studies demonstrated that higher BMI is associated with retinal venular widening (1, 11, 24, 30, 31). The actual reason of such a disparity is not clear as it could be due to the age of the participants or small sample saiz (24). Lacking of standardized protocols and differences in ocular magnification during retinal imaging sampling could be the cause of the disparity (23).

Our results also demonstrated that there was a significant mean difference of retinal arteriolar caliber between overweight and obese Malay children after adjustment of variable of axial length. Based on the adjusted mean value, obese Malay children had narrower retinal arteriolar caliber than overweight Malay children. Our study supports the findings from previous reported studies that narrowing of the retinal arterioles is related with increasing BMI (11, 24, 26, 28, 32, 33). Furthermore, narrower retinal arterioles have been associated with an increased risk of chronic diseases such as hypertension and diabetes, in adult-based sample studies (34, 35). The present study thus suggests the potential of identifying microvascular abnormalities in early childhood as part of primary prevention of chronic disease, specifically in obese and overweight Malay children.

Our study also documented that there was no significant mean difference of retinal venular caliber between overweight and obese Malay children after adjustment of variable of axial length and spherical equivalent. Our findings are consistent with Gishti et al. in 2015, who reported that there was no significant association with CRVE. Gishti et al. evaluated 4145 school-age children median aged 6 years old in Netherland and reported that higher total body mass were associated with retinal arteriolar caliber but not venular caliber.

In contrast, other studies showed that retinal venular caliber is wider with increasing BMI (11, 24, 30). Gopinath et al. and Kurniawan et al. conducted on a relatively larger sample saiz which were 2179 and 421 respectively as compared to our sample saiz 131 which was slightly smaller. Whereas Li et al. and Kurniawan et al. have shared the similiarity of both studies were conducted in Singapore where Chinese ehthic is the majority of the population. We postulate that different ethnicity and population sample saiz could be the factor of the disparity of our result.

Retinal microvasculature changes are observed in adult and children with increasing BMI, suggesting that these changes are not only age-dependent but under biological mechanism influences. There are several possible biological mechanisms explaining the association of obesity with retinal arteriolar constriction and retinal venular dilatation (1, 35). Decrease in nitric oxide (NO) endothelium-derived vasodilator (36) and increase in vasoconstrictor molecules (endothelin-1, angiotensin-II and other metabolites of arachidonic acid) have been observed in obese children with retinal arteriolar narrowing (37, 38). Obese subjects have excess release of biological markers such as tumour necrotizing factor α (TNFα) and angiotensin II, leading to vasoconstriction (39). The venous system is a major reservoir for blood volume, which may be increased in obese children. Increased total blood volume causes retinal venular dilatation in obese children (40). Obesity has also been linked to altered microvascular autoregulation by adipocytokines. A hormone called leptin has been found to be elevated in obese subjects, and modulates endovascular nitric oxide synthesis, causing further vasodilatation (41-44).