

Relationship of Choroidal Thickness With Age-Related Macular Degeneration in Asians: An Asian Eye Epidemiology Consortium Meta-Analysis

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PURPOSE. To compare the choroidal thickness (CT) of participants with various stages of age-related macular degeneration vs. normal controls through a meta-analysis of studies conducted within the Asian Eye Epidemiology Consortium.

METHODS. Eight population-based studies from China, Iran, Japan, and Singapore were included. Axial length and spherical equivalent measurements and imaging with color fundus photography and spectral-domain optical coherence tomography were performed. Random-effects meta-analysis was performed to examine the association between AMD and its stages (early AMD, intermediate AMD [iAMD], neovascular AMD [nAMD], and geographic atrophy [GA]) with CT, while adjusting for age, sex, current smoking status, and axial length/spherical equivalent.

RESULTS. Of 17,916 participants, 13,116 participants (mean age, 62.15 ± 9.66 years) were included into the study. The mean unadjusted CT was 245.01 ± 84.04 μm (mean CT, 255.4 μm [no AMD], 263.59 μm [early AMD], 270.64 μm [iAMD], 273.32 μm [nAMD], and 156.50 μm [GA]). The presence of AMD was associated with a thicker choroid

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($\beta = 11.51$; 95% confidence interval [CI], 4.10–18.92). AMD severity was also positively associated with CT. Early AMD ($\beta = 8.75$; 95% CI, 0.03–17.47), iAMD ($\beta = 19.68$; 95% CI, 13.20–26.16), and nAMD ($\beta = 34.15$; 95% CI, 6.84–61.46) were each positively associated with a thicker CT after adjusting for age, sex, smoking, and spherical equivalent. GA was not significantly associated with CT.

CONCLUSIONS. In a large Asian cohort, AMD is associated with a thicker choroid in early AMD, iAMD, and nAMD, but not in GA. Studying the CT will help to better characterize Asian AMD phenotypes, which may show differences compared with AMD phenotypes in Western populations.

Keywords: choroidal thickness, age-related macular degeneration, optical coherence tomography, age-related macular degeneration, asian

Age-related macular degeneration is a major cause of severe and irreversible visual impairment globally.¹ Asia constitutes 60% of the world's population and many populations are aging rapidly. Asia will contribute most to the global AMD prevalence by 2040 (projected to be 40% [113 of 288 million globally], compared with 35% [59 of 170 million globally] in 2014).² As such, AMD is an increasingly important public health problem in Asia.^{3–5}

The pathogenesis of AMD and the underlying mechanisms are not fully elucidated.^{6,7} Pathological changes in the outer retina, RPE–Bruch's membrane complex, and choroid have been implicated in AMD, with the accumulation of drusen and waste deposits and a resultant inflammatory response that can be modified by genetic and/or environmental factors.^{8–10}

There is increasing evidence of racial/ethnic differences between Western and Asian populations in AMD.^{11,12} For example, polypoidal choroidal vasculopathy (PCV), a subtype of neovascular AMD (nAMD), is more common in Asians (prevalence of approximately 20%–60%) compared with Western populations (approximately 8%–13%).¹¹ Geographic atrophy (GA) is also less common in Asians (prevalence of approximately 0.29%) compared with the Western populations (approximately 0.90%).¹² In early and intermediate AMD (iAMD), the prevalence and types of drusen appears also to differ between Asian and Western populations.^{13,14} This finding suggests possible underlying racial/ethnic variations in the pathogenesis of AMD.

The choroid provides systemic blood supply to the outer retinal layers,^{15,16} and studies have suggested that there is choroidal circulation dysfunction and loss of choriocapillaris in aging and AMD.^{8–10,17,18} These suggest plausible pathophysiological processes of AMD involving the choroid. It is now possible to measure subfoveal choroidal thickness (CT) measurements on optical coherence tomography (OCT) using either spectral-domain OCT or swept-source OCT.¹⁹

Previous studies that assessed the associations between subfoveal CT and AMD have reported conflicting results.^{20–41} See Supplementary Table S1 for a description of these studies. Many studies have suggested that CT is thinner in eyes with AMD.^{20,24,29–31,34,35,37,38} Although most of these studies represent Western populations,^{24,29,31,34,35,38} others include participants of Asian ethnicity.^{20,30,37} Velaga et al.²⁴ found in the Amish Eye Study that the CT was thinner specifically in non-nAMD eyes with RPD compared with normal eyes. In the largest study, which was an observational case series of a Western cohort, Sigler et al.³⁸ reported that eyes with early

AMD features without GA ($115 \pm 40 \mu\text{m}$), and/or soft drusen alone ($161 \pm 39 \mu\text{m}$) had a thinner choroid as compared with control eyes ($235 \pm 49 \mu\text{m}$) ($P < 0.001$).

Most of the studies that did not detect a clear difference in CT represent Western populations,^{25,27,32,33,40,41} whereas two remaining studies represent Asian populations.^{28,39} In a population-based study, Gattoussi et al.²⁵ reported in a French cohort that, after adjustment for age, sex, axial length (AL), and vascular and genetic risk factors, the subfoveal CT was thinner in eyes with central pigmentary abnormalities, but not with AMD and its stages.

A few studies have suggested a positive association between CT and AMD.^{21–24,26} With the exception of one study on a Western population,²⁴ the remaining represented Asian populations.^{21–23,26} Sasaki et al.²² reported that the CT was associated positively with iAMD (odds ratio [OR], 1.43; 95% confidence interval [CI], 1.13–1.81 for each 1-SD mm increase) in a Japanese population study. In a population study performed in Northern China (the Beijing Eye Study), Zhao et al.²⁶ found that a thicker subfoveal CT was significantly associated with a higher prevalence of iAMD ($\beta = 0.07$; 95% CI, 11.2–27.9 and nAMD ($\beta = 0.04$; 95% CI, 4.22–46.4).

Nevertheless, current studies are mostly smaller hospital-based studies of relatively small AMD cohorts, and the majority have been performed on Western populations. There are few population-based studies that have studied AMD and CT in detail.^{22,24–26} Furthermore, the relationship of CT with different stages of AMD (early AMD, iAMD, nAMD, and GA) is not well-established. Thus, understanding the relationship of CT with AMD in population studies will provide valuable insights regarding AMD pathogenesis.

The Asian Eye Epidemiology Consortium represents a collaborative network of large, population-based studies performed across Asia. Large datasets are pooled with the aim of providing deeper insights into the trends and risk factors of major eye diseases in Asia.^{12,42–44} The existing agreements to collaborate provide a good opportunity to assess the association between CT and AMD using large population studies, and to elucidate the choroid's role in the pathogenesis of AMD.¹²

METHODS

In this study, we used a pooled meta-analysis approach to assess the association of CT with the presence and severity of AMD. Eight population-based studies from four

countries: China (two studies), Iran (one study), Japan (two studies), and Singapore (three studies) within the Asian Eye Epidemiology Consortium were included. Supplementary Figure S1 shows the geographic origin of the included studies. See Supplementary Table S2 for a summary of the individual studies. The respective methodologies of each study have been described elsewhere.^{45–49} These population studies represent nearly 18,000 participants and are the landmark studies in the respective regions. See Supplementary Table S3 for the quality control measures undertaken in the respective studies. This study was conducted in accordance with the Declaration of Helsinki. Each study obtained its own ethics approval,^{45,47–50} and the approval for the pooled analysis was obtained from the SingHealth Centralised Institutional Review Board. All participants provided written informed consent.

The inclusion criteria include the availability of systemic, ocular, and lifestyle-related demographic data such as age, sex, spherical equivalent (SE), AL, smoking status, body mass index, hypertension, cardiovascular disease history, diabetes mellitus, glycated hemoglobin, creatine, and lipid markers. Only participants aged 40 years and older were included, and the availability of color fundus photography (CFP) for AMD grading and subfoveal CT measurements on spectral-domain OCT or swept-source OCT. The exclusion criteria included poor OCT quality for subfoveal CT measurements, poor fundus photography quality for AMD grading, the presence of any anterior or posterior segment pathology that would influence subfoveal CT except AMD, and a history of ocular surgery (excluding cataract surgery), trauma, and/or ocular laser/anti-VEGF treatment.

This study was conducted in accordance with the Declaration of Helsinki. Each study obtained its own ethics approval,^{45,47–50} and the approval for the pooled analysis was obtained from the SingHealth Centralised Institutional Review Board. All participants provided written informed consent.

Study Population and Design

All studies had clearly defined methods of sampling and defining AMD and measuring CT. The studies either individual-level data ($n = 6$) or summary data ($n = 2$).

Classification of AMD

AMD classification was performed with CFP using the Beckman Initiative for Macular Research Classification system for AMD.⁵¹ Further details are presented in Supplementary Table S3. In the Beckman classification, fundus lesions within two-disc diameters of the fovea were assessed.⁵¹ The definitions were as follows: no apparent aging changes; no apparent aging-related changes, that is, no drusen and no AMD pigmentary abnormalities; normal aging changes: small drusen (drupelets) of 63 μm or smaller and no AMD pigmentary abnormalities; early AMD, medium drusen of greater than 63 μm and 125 μm or smaller, but without AMD pigmentary abnormalities; iAMD, large drusen greater than 125 μm and/or any AMD pigmentary abnormalities, or both; and late AMD, nAMD and/or GA.⁵¹

GA was defined using the modified Wisconsin Age-Related Maculopathy Grading System protocol, which closely follows the International AMD classification and grading system.⁵² Both grading systems define GA as an area of pallor of 175 μm in diameter (I-1 circle) with well-defined borders within which large choroidal vessel profiles

were visible. nAMD was defined as the presence of RPE detachment, neurosensory detachment, subretinal, or sub-RPE hemorrhage, or a disc-form subretinal scar within the macular area. The right eye of each participant was used for grading and classification. When nAMD and GA were present in the same individual (GA in one eye and nAMD in the fellow eye) or if both late-stage phenotypes were seen in the same eye, all studies classified these participants as having nAMD.

CT

The subfoveal CTs were measured with different commercially available spectral-domain OCT devices. The subfoveal CT was defined as the distance between the outermost edge of the RPE–Bruch's membrane complex and the choroid–scleral interface on the horizontal foveal cut of the OCT B-scan. Poor scan quality such as OCT segmentation error and poor signal strength were excluded from the analysis. Further details are presented in Supplementary Table S3.

Demographic, Ocular, and Systemic Measurements

Supplementary Table S4 summarizes the characteristics of each study's participants in this meta-analysis. The definitions of hypertension, hyperlipidemia, diabetes mellitus, and cardiovascular disease history are described in Supplementary Table S5. Other lifestyle factors such as current smoking status were self-reported. Body mass index was calculated as weight in kilograms divided by the square of body height in meters (kg/m^2). Refractive error was expressed as SE and was calculated from automated refractometry. AL was determined by ocular biometry.

Statistical Analysis

A random effects meta-analysis was performed. For each study, the right eye was chosen as the study eye if the required data were available. If the data for the right eye were incomplete, the left eye was used. Ocular and systemic factors were included in the final model based on their associations with CT as reported in previous studies. Potential outliers were identified in box plot graphs and verified by the corresponding authors. Generalized extreme studentized deviate test was used to exclude outliers if data checking were unfeasible.

Random effects meta-regression was performed separately to assess the associations between CT with (1) AMD vs. no AMD, and with (2) early AMD, iAMD, nAMD, and GA vs. no AMD. For each analysis, three models were created, each assessing the relationship between CT and AMD while adjusting for different factors. Model 1 adjusted for age and sex. Model 2 adjusted for age, sex, current smoking status, and SE. Model 3 adjusted for age, sex, current smoking status, and AL. SE and AL were evaluated in separate models owing to collinearity between these two variables.

The effect estimates derived from the multivariable linear regression model of each study were then combined using meta-analysis to produce a weighted pooled estimate. A random effects model was used to account for heterogeneity among the studies.⁵³ The I^2 statistic was used to determine the proportion of variation in the study owing to heterogeneity. The τ^2 statistic was used to assess the between-study variation of underlying effects among studies. All

statistical analyses were performed using R statistical software (version 3.5.3; R Foundation for Statistical Computing, Vienna, Austria). A *P* value of less than 0.05 was considered statistically significant.

RESULTS

Among 17,916 individuals who participated in the individual studies, 4800 individuals were excluded owing to missing or erroneous data on CT and/or AMD. The remaining 13116 participants (5581 [42.55%] male; 7535 [57.45%] female) with a mean age of 62.15 ± 9.66 years were included into the final analysis (Supplementary Fig. S2). See Table 1 for a summary of the participants' characteristics. Of these participants, 2500 (19.10%) had AMD, and 824 (10.21%) had early AMD, 1149 (14.24%) had iAMD, 43 (0.70%) had nAMD, and 8 (0.10%) had GA. The overall mean unadjusted CT was 245.01 ± 84.04 μm (mean CT, 255.40 μm [no AMD], 263.59 μm [early AMD], 270.64 μm [iAMD], 273.3 μm [nAMD], and 156.50 μm [GA]).

Overall, the presence of AMD was associated with a thicker choroid ($\beta = 11.51$, 95% CI, 4.10–18.92 after adjusting for age, sex, current smoking, and SE [model 2]; and $\beta = 7.83$; 95% CI, 1.54–14.12 after adjusting for age, sex, current smoking, and AL [model 3]). See Table 2 and Figure 1.

CT also showed a positive association with AMD severity with increasing CT in early AMD, iAMD, and nAMD. See Table 3 and Figures 2A–C.

Early AMD ($\beta = 8.75$; 95% CI, 0.03–17.47), iAMD ($\beta = 19.68$; 95% CI, 13.20–26.16), and nAMD ($\beta = 34.15$;

TABLE 1. Baseline Characteristics of Participants.

	Included (n = 13,116)
Systemic	
Age, years	62.15 ± 9.66
Female sex	7535 (57.45)
Current smoker	1442 (14.6)
BMI, kg/m ²	27.60 ± 5.24
Hypertension	5749 (58.2)
Cardiovascular disease	1337 (14.0)
Diabetes mellitus	2072 (21.0)
HbA1c, %	5.32 ± 1.47
Creatinine, mM/L	71.48 ± 32.08
Hypercholesterolemia	3053 (50.0)
Total cholesterol, mM/L	5.19 ± 1.10
HDL cholesterol, mM/L	1.23 ± 0.36
LDL cholesterol, mM/L	3.38 ± 0.92
Triglyceride, mM/L	1.87 ± 1.16
Ocular	
CT, μm	245.01 ± 84.04
SE, D	−0.25 ± 2.09
AL, mm	23.39 (1.16)
Any AMD*	2500 (19.1)
Early AMD	824 (10.2)
iAMD	1149 (14.2)
Late AMD	51 (0.6)
nAMD	43 (0.5)
GA	8 (0.1)

BMI, body mass index; HbA1c, glycated hemoglobin; HDL, high density lipoprotein; LDL, low density lipoprotein.

*The denominator used for the proportion of any age-related macular degeneration is the total of 13,116. The denominator used for early AMD, iAMD, late AMD (nAMD and GA) is 8079 instead as ShECS and TMUEH, which contributed data from 5037 eyes, did not provide AMD severity breakdown.

Values are mean ± standard deviation or number (%).

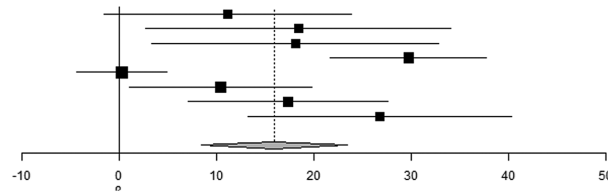
TABLE 2. Association Between Any Stage of AMD and CT Accounting for Age, Sex, Smoking Status, and SE/AL

	Model 1			Model 2			Model 3		
	β (95% CI)	P Value	R ²	β (95% CI)	P Value	R ²	β (95% CI)	P Value	R ²
Any AMD	15.93 (8.42 to 23.44)	<0.001	85.9%	11.51 (4.10 to 18.92)	0.002	81.6%	7.83 (1.54 to 14.12)	0.015	67.4%
Age per decade	−29.11 (−41.02 to −17.20)	<0.001	99.3%	−32.27 (−45.98 to −18.56)	<0.001	99.4%	−31.84 (−47.42 to −16.27)	<0.001	99.5%
Female sex	−10.03 (−14.21 to −5.86)	<0.001	46.6%	−8.33 (−13.63 to −3.04)	0.002	62.2%	−19.76 (−27.50 to −12.02)	<0.001	85.4%
Current smoker	—	—	—	2.85 (−4.53 to 10.24)	0.449	70.0%	2.18 (−4.32 to 8.68)	0.511	57.6%
SE (per negative diopter)	—	—	—	−10.48 (−14.56 to −6.40)	<0.001	99.0%	—	—	—
AL, mm	—	—	—	—	—	—	−20.76 (−31.12 to −10.39)	<0.001	99.4%

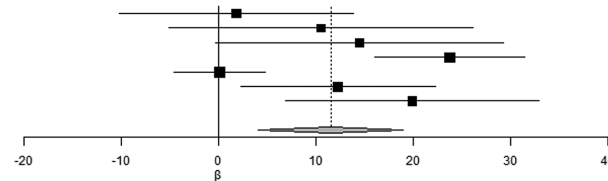
Model 1 is adjusted for age per decade and gender. Model 2 is adjusted for age per decade, gender, current smoking status, and SE. Model 3 is adjusted for age per decade, gender, current smoking status, and AL.

Model 1

Study	β	95% CI	Weight
SCES2	11.16	[-1.53; 23.85]	11.6%
SINDI2	18.39	[2.75; 34.03]	9.9%
SIMES2	18.09	[3.33; 32.85]	10.4%
BES	29.73	[21.71; 37.75]	14.4%
ShECS	0.26	[-4.41; 4.93]	16.2%
TMUEH	10.42	[1.05; 19.79]	13.6%
Hisayama	17.36	[7.11; 27.62]	13.0%
JPHCES	26.77	[13.18; 40.35]	11.0%
Total	15.93	[8.42; 23.44]	100.0%

Heterogeneity: $I^2 = 86\%$, $\tau^2 = 85.2158$, $p < 0.01$ **Model 2**

Study	β	95% CI	Weight
SCES2	1.84	[-10.21; 13.89]	13.5%
SINDI2	10.53	[-5.10; 26.16]	10.8%
SIMES2	14.44	[-0.36; 29.24]	11.4%
BES	23.75	[16.03; 31.47]	17.1%
ShECS	0.13	[-4.54; 4.81]	19.3%
Hisayama	12.29	[2.29; 22.28]	15.2%
JPHCES	19.91	[6.91; 32.91]	12.7%
Total	11.51	[4.10; 18.92]	100.0%

Heterogeneity: $I^2 = 82\%$, $\tau^2 = 68.2674$, $p < 0.01$ **Model 3**

Study	β	95% CI	Weight
SCES2	1.70	[-10.03; 13.44]	14.6%
SINDI2	7.35	[-7.51; 22.21]	11.2%
SIMES2	11.96	[-2.86; 26.79]	11.2%
BES	17.66	[9.99; 25.33]	20.6%
ShECS	0.77	[-3.88; 5.42]	25.5%
Hisayama	9.38	[-0.61; 19.37]	17.0%
Total	7.83	[1.54; 14.12]	100.0%

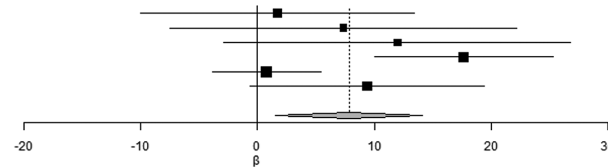
Heterogeneity: $I^2 = 67\%$, $\tau^2 = 34.7720$, $p < 0.01$ 

FIGURE 1. Forest plots of association of CT with presence of age-related macular degeneration. CT demonstrated a positive association with the presence of AMD. The reference group was the group without AMD. All three models yield similar observations. Model 1 was adjusted for age per decade and sex. Model 2 was adjusted for age per decade, sex, current smoking status, and SE. Model 3 was adjusted for age per decade, sex, current smoking status, and AL.

95% CI, 6.84–61.46) were associated positively with a thicker CT after adjusting for age, sex, smoking, and SE (Table 3; Model 2).

iAMD ($\beta = 15.00$; 95% CI, 9.13–20.87) and nAMD ($\beta = 35.30$; 95% CI, 6.88–63.72) remained positively associated with a thicker CT after adjusting for age, sex, smoking, and AL, whereas early AMD ($\beta = 4.79$; 95% CI, –3.88 to 13.46) was not (Table 3; Model 3).

CT was not significantly associated with GA, although CT tended to be decreased thinner in all models.

Sensitivity analyses of both models 2 and 3 demonstrated that the abovementioned associations remained similar regardless of the OCT device used (Supplementary Figs. S3 and S4).

DISCUSSION

In this study, we have examined the associations between CT with AMD and its severity across multiple large population-based studies of Asian ancestry. This has allowed us to build substantially upon the initial study by Sasaki et al.²² and other studies in Asia^{21,23,26} on choroidal thickening in AMD. We report that not only is the central choroid thicker in AMD, but also it increases step wise from early AMD, iAMD, to nAMD, except GA. These findings support the ideas of Sasaki et al.²² that a thicker choroid is associated with pathology in the early stages of AMD and its progression in Asians.

The exact significance of a thicker choroid in Asian patients with AMD remains unclear. nAMD in the presence of pachychoroid, which is often present in Asians, may demon-

strate features of choroidal hyperpermeability,^{54–56} which we hypothesize can lead to choroidal thickening. PCV is a subtype of nAMD that is more common among Asians and is often associated with pachychoroid and choroidal hyperpermeability⁵⁷; it may represent at least part of the reason for the thicker choroids in our study. More epidemiological studies that use advanced choroidal imaging techniques to assess choroidal structure and function in both Asian and Western populations are needed to further explain why thicker choroids are observed in Asian populations in earlier stages of AMD.

In this study, CT has a negative, albeit nonsignificant association with GA. A statistically significant relationship might have been missed owing to the small number of GA cases in this study. A reasonable postulate, assuming a real relationship, would be that the earlier processes contributing to choroidal thickening are not active or relevant in significantly atrophic tissue in GA.

Separately, studies have suggested that CT is also associated with specific features such as drusen subtypes and pigmentary abnormalities in AMD as well. Takahashi et al.¹³ assessed the characteristics of drusen subtypes in Asian populations and the associations with CT using population study data and reported that CT was the thickest in eyes with pachydrusen, followed by eyes with hard drusen, then those with soft drusen, and was the thinnest in eyes without drusen. Sasaki et al.²² had similarly assessed associations between CT and iAMD features in an Asian cohort and described that CT was associated positively with AMD and non-AMD pigmentary abnormalities. Cheung et al.⁵⁵ also

TABLE 3. Association Between AMD Severity and CT Accounting for Age, Sex, Smoking Status, and SE/AL

	Model 1			Model 2			Model 3		
	β (95% CI)	P Value	I ²	β (95% CI)	P Value	I ²	β (95% CI)	P Value	I ²
AMD severity									
No AMD	Reference			Reference			Reference		
Early AMD	14.26 (6.87 to 21.64)	<0.001	6.2%	8.75 (0.03 to 17.47)	0.049	41.7%	4.79 (−3.88 to 13.46)	0.279	28.2%
iAMD	26.93 (20.35 to 33.51)	<0.001	12.6%	19.68 (13.20 to 26.16)	<0.001	11.6%	15.00 (9.13 to 20.87)	<0.001	0.0%
nAMD	40.11 (11.75 to 68.47)	0.006	10.8%	34.15 (6.84 to 61.46)	0.014	1.4%	35.30 (6.88 to 63.72)	0.015	12.3%
GA	−25.71 (−97.91 to 46.48)	0.485	13.7%	−21.05 (−114.41 to 72.31)	0.659	55.3%	−69.45 (−140.32 to 1.41)	0.055	0.0%
Age per decade	−35.47 (−45.23 to −25.71)	<0.001	96.3%	−38.36 (−46.79 to −29.93)	<0.001	94.6%	−38.86 (−47.54 to −30.18)	<0.001	94.1%
Female gender	−8.35 (−14.60 to −2.11)	0.009	56.3%	−6.73 (−13.23 to −0.23)	0.043	54.0%	−22.17 (−30.53 to −13.80)	<0.001	73.2%
Current smoker	—	—	—	5.53 (−2.31 to 13.37)	0.167	38.0%	5.85 (−0.13 to 11.83)	0.055	0.0%
SE (per negative diopter)	—	—	—	−12.45 (−14.64 to −10.27)	<0.001	86.4%	—	—	—
AL, mm	—	—	—	—	—	—	−25.53 (−31.33 to −19.73)	<0.001	93.8%

Model 1 is adjusted for age per decade and gender. Model 2 is adjusted for age per decade, gender, current smoking status, and SE. Model 3 is adjusted for age per decade, gender, current smoking status, and AL.

reported that Asian patients with AMD were more likely to show pachydrusen than Western populations and that a thicker choroid was associated with pachydrusen. Thus, pachydrusen, which often accompany pachychoroid, are supportive findings of associated choroidal thickening. In this study, drusen subtype details were unavailable and this analysis was not performed.

Reasons for discrepancies between studies with respect to the relationship between CT and AMD prevalence and stage may include differences among the various AMD stages, that is, that the macular choroid may be thicker in early AMD and iAMD, while becoming thinner in GA, with a CT that is lower than the baseline value. Other reasons include the use of varying AMD definitions using different classifications^{51,52} and erroneously summarizing nAMD and GA into a single stage of late AMD.²⁵ The study methodology, size, ethnicity of the study populations, and the list of independent parameters included into a multivariable analysis also differ among studies.^{15,16} The effect of anti-VEGF injections on CT is also uncertain.⁵⁸ In all, we have attempted to account for many of these variables; however, we acknowledge as a limitation that not all these factors were available for analysis.

The study's principal strength is the large sample size owing to the inclusion of multiple large population-based studies of Asian ancestry. This factor conferred statistical power and allowed multivariable analyses and adjustment for factors that are known to influence CT and AMD. The use of population studies also provided good external validity. The use of a single classification system for AMD grading and standardization of inclusion criteria allowed direct comparison and assessment of the relationship between CT with AMD and its severities among various studies. The increase in CT across AMD stages remained significant in the multivariable analysis in various models, which suggests a true-positive relationship between CT and AMD.

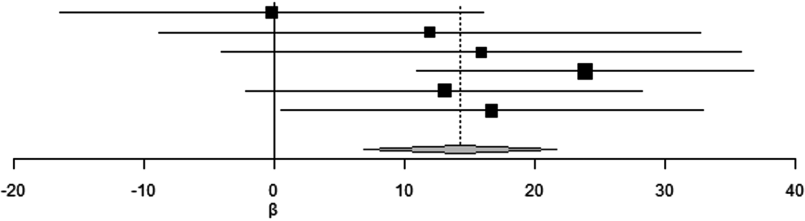
The limitations of this study include the heterogeneity among studies, such as differences in ethnicity. Additionally, the Beckman classification system for AMD only required CFP for grading and no other multimodal imaging was used. Cases with very early AMD, where changes were only seen on OCT but not on CFP, might have been missed, and GA and nAMD might have been misclassified as well. The potential presence of PCV and pachychoroid disease in the studies might have confounded the association between CT and AMD. The accurate prevalence of PCV in the general population would be difficult to detect owing to the challenges of diagnosing PCV solely from fundus photographs, and this issue is common in many epidemiological studies. There were also relatively few nAMD and GA cases relative to the entire cohort; thus, it was challenging to derive conclusions. Different studies measured CT using different OCT devices, although our sensitivity analysis showed that this is unlikely to be a significant issue. Last, the cross-sectional nature of this study also precluded the assessment of a temporal association, thereby preventing any conclusions on whether CT changes were a cause or consequence of AMD. It is possible that, rather than AMD causing changes in CT, individuals with thicker choroids may have a predilection for AMD. This issue could be resolved with an appropriate prospective longitudinal study.

In conclusion, CT was increased in early AMD, iAMD, and nAMD in a large Asian cohort. The association with GA was inconclusive. Studying CT and other choroidal features

Model 1

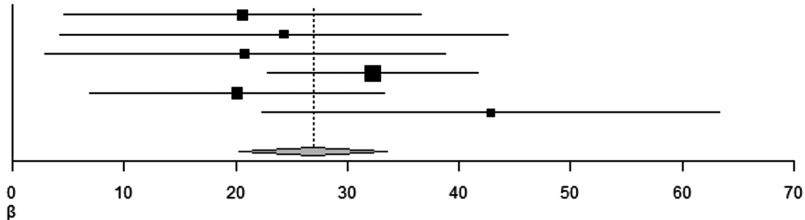
Early AMD

Study	β	95% CI	Weight
SCES2	-0.22	[-16.50; 16.07]	16.8%
SINDI2	11.93	[-8.81; 32.68]	11.2%
SIMES2	15.87	[-4.07; 35.80]	12.0%
BES	23.83	[10.93; 36.73]	24.3%
Hisayama	13.04	[-2.17; 28.25]	18.8%
JPHCES	16.69	[0.48; 32.90]	17.0%
Total	14.26	[6.87; 21.64]	100.0%
Heterogeneity: $I^2 = 6\%$, $\tau^2 = 15.2156$, $p = 0.38$			



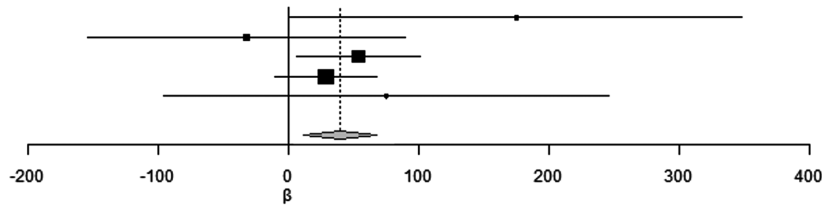
Intermediate AMD

Study	β	95% CI	Weight
SCES2	20.57	[4.62; 36.53]	14.7%
SINDI2	24.33	[4.29; 44.36]	9.8%
SIMES2	20.79	[2.86; 38.73]	12.0%
BES	32.26	[22.90; 41.63]	33.8%
Hisayama	20.11	[6.97; 33.25]	20.3%
JPHCES	42.84	[22.40; 63.28]	9.4%
Total	26.93	[20.35; 33.51]	100.0%
Heterogeneity: $I^2 = 13\%$, $\tau^2 = 10.4883$, $p = 0.33$			



Neovascular AMD

Study	β	95% CI	Weight
SCES2	175.29	[1.82; 348.76]	2.7%
SIMES2	-31.75	[-153.76; 90.26]	5.4%
BES	54.28	[7.06; 101.50]	36.1%
Hisayama	29.14	[-9.80; 68.07]	53.1%
JPHCES	75.59	[-94.88; 246.06]	2.8%
Total	40.11	[11.75; 68.47]	100.0%
Heterogeneity: $I^2 = 11\%$, $\tau^2 < 0.0001$, $p = 0.34$			



Geographic Atrophy

Study	β	95% CI	Weight
SIMES2	-46.68	[-218.23; 124.87]	15.5%
BES	-57.64	[-166.15; 50.88]	32.4%
Hisayama	-79.03	[-209.54; 51.49]	24.4%
JPHCES	70.58	[-50.08; 191.24]	27.7%
Total	-25.71	[-97.91; 46.48]	100.0%
Heterogeneity: $I^2 = 14\%$, $\tau^2 = 1116.4998$, $p = 0.32$			

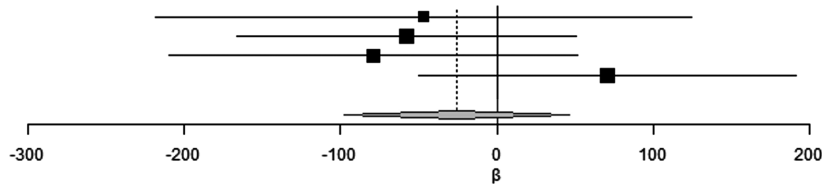
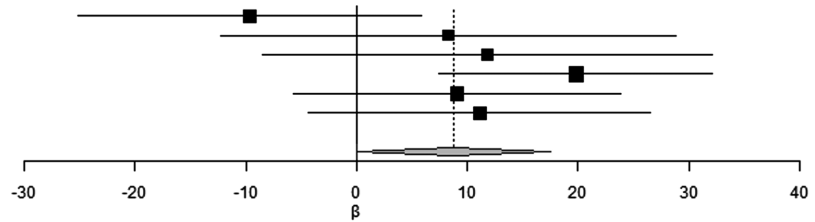


FIGURE 2. Forest plots of association of CT with severity of AMD. CT demonstrated positive associations independently with early AMD, iAMD, and nAMD. The effect size of CT increased with increasing severity of AMD from early AMD to nAMD. There was a negative, albeit non-significant association between CT and GA. Late AMD was categorized into nAMD and GA. The reference group was the group without AMD. All three models yield similar observations. (A) Model 1 was adjusted for age per decade and sex. (B) Model 2 was adjusted for age per decade, sex, current smoking status, and SE. (C) Model 3 was adjusted for age per decade, sex, current smoking status, and AL.

Model 2

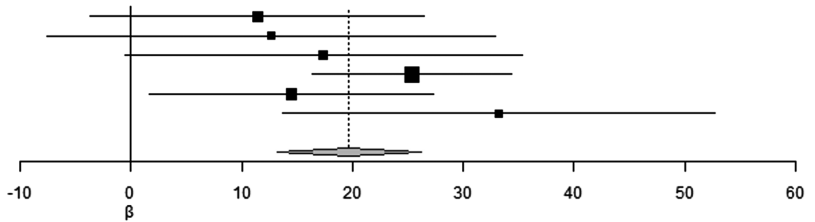
Early AMD

Study	β	95% CI	Weight
SCES2	-9.61	[-25.12; 5.91]	17.4%
SINDI2	8.29	[-12.23; 28.82]	12.3%
SIMES2	11.78	[-8.47; 32.04]	12.5%
BES	19.78	[7.41; 32.16]	21.8%
Hisayama	9.07	[-5.72; 23.85]	18.4%
JPHCES	11.10	[-4.34; 26.54]	17.5%
Total	8.75	[0.03; 17.47]	100.0%
Heterogeneity: $I^2 = 42\%$, $\tau^2 = 50.8222$, $p = 0.13$			



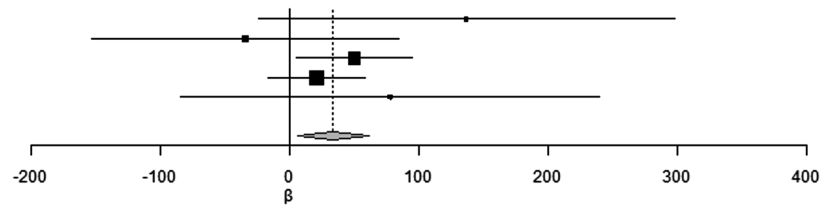
Intermediate AMD

Study	β	95% CI	Weight
SCES2	11.41	[-3.69; 26.50]	15.5%
SINDI2	12.68	[-7.53; 32.89]	9.3%
SIMES2	17.40	[-0.49; 35.28]	11.6%
BES	25.35	[16.34; 34.37]	33.6%
Hisayama	14.49	[1.69; 27.29]	20.2%
JPHCES	33.22	[13.69; 52.76]	9.9%
Total	19.68	[13.20; 26.16]	100.0%
Heterogeneity: $I^2 = 12\%$, $\tau^2 = 11.4287$, $p = 0.34$			



Neovascular AMD

Study	β	95% CI	Weight
SCES2	137.28	[-23.47; 298.04]	2.9%
SIMES2	-33.75	[-152.40; 84.91]	5.3%
BES	50.36	[5.45; 95.27]	37.0%
Hisayama	21.43	[-16.43; 59.29]	52.0%
JPHCES	78.18	[-84.22; 240.58]	2.8%
Total	34.15	[6.84; 61.46]	100.0%
Heterogeneity: $I^2 = 1\%$, $\tau^2 < 0.0001$, $p = 0.40$			



Geographic Atrophy

Study	β	95% CI	Weight
SIMES2	-46.69	[-213.56; 120.17]	18.6%
BES	-74.58	[-177.78; 28.63]	29.4%
Hisayama	-78.52	[-205.36; 48.33]	24.9%
JPHCES	107.48	[-7.47; 222.43]	27.1%
Total	-21.05	[-114.41; 72.31]	100.0%
Heterogeneity: $I^2 = 55\%$, $\tau^2 = 4937.3882$, $p = 0.08$			

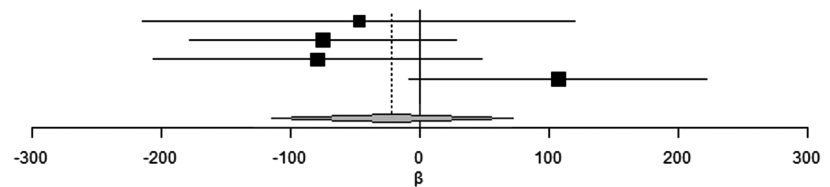
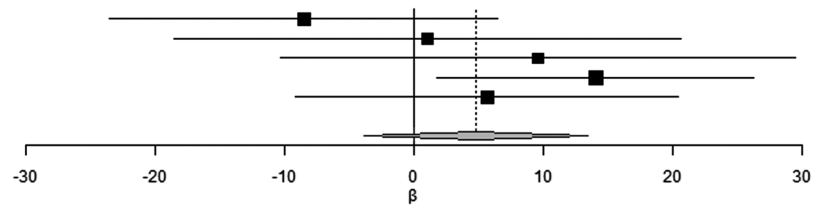


FIGURE 2. Continued.

Model 3

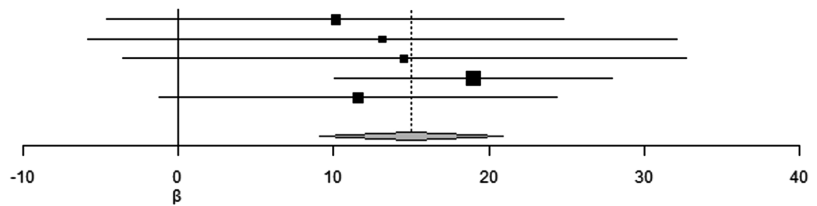
Early AMD

Study	β	95% CI	Weight
SCES2	-8.51	[-23.53; 6.50]	21.5%
SINDI2	1.04	[-18.57; 20.64]	14.8%
SIMES2	9.57	[-10.35; 29.48]	14.4%
BES	14.05	[1.81; 26.29]	27.4%
Hisayama	5.63	[-9.12; 20.39]	22.0%
Total	4.79	[-3.88; 13.46]	100.0%
Heterogeneity: $I^2 = 28\%$, $\tau^2 = 32.3680$, $p = 0.23$			



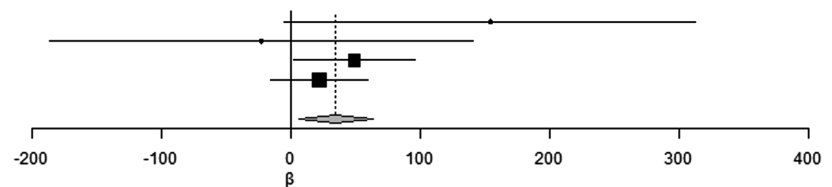
Intermediate AMD

Study	β	95% CI	Weight
SCES2	10.13	[-4.58; 24.84]	15.9%
SINDI2	13.16	[-5.80; 32.11]	9.6%
SIMES2	14.55	[-3.62; 32.71]	10.4%
BES	19.00	[10.06; 27.95]	43.0%
Hisayama	11.58	[-1.20; 24.35]	21.1%
Total	15.00	[9.13; 20.87]	100.0%
Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.83$			



Neovascular AMD

Study	β	95% CI	Weight
SCES2	154.60	[-4.30; 313.49]	3.2%
SIMES2	-22.74	[-186.45; 140.97]	3.0%
BES	49.18	[2.41; 95.95]	36.9%
Hisayama	22.65	[-15.03; 60.33]	56.9%
Total	35.30	[6.88; 63.72]	100.0%
Heterogeneity: $I^2 = 12\%$, $\tau^2 < 0.0001$, $p = 0.33$			



Geographic Atrophy

Study	β	95% CI	Weight
SIMES2	-49.06	[-212.20; 114.09]	18.9%
BES	-66.81	[-167.39; 33.78]	49.6%
Hisayama	-85.85	[-212.14; 40.43]	31.5%
Total	-69.45	[-140.32; 1.41]	100.0%
Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.94$			

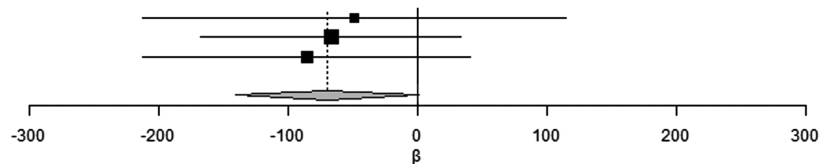


FIGURE 2. Continued.

will help to better characterize AMD phenotypes in Asians, providing insight into different AMD phenotypes and pathogenesis, which may be different when compared with Western populations.

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