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REVIEW

Scheimpflug-Derived Keratometric, Pachymetric and Pachymetric Progression Indices in the Diagnosis of Keratoconus: A Systematic Review and Meta-Analysis

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Abstract: Scheimpflug Pentacam Tomography is becoming crucial in the diagnosis and monitoring of keratoconus, as well as in pre- and post-corneal refractive care, but there are still some inconsistencies surrounding its evidence base diagnostic outcome. Therefore, this study aimed at employing meta-analysis to systematically evaluate the keratometric, pachymetric, and pachymetric progression indices used in the diagnosis of Keratoconus. The review protocol was registered with PROSPERO (Identifier: CRD4202310058) and followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. PubMed, MEDLINE, Web of Science, and EMBASE were used for data search, followed by a quality appraisal of the included studies using the revised tool for the quality assessment of diagnostic accuracy studies (QUADAS-2). Meta-analysis was conducted using the meta (6.5.0) and metafor (4.2.0) packages in R version 4.3.0, as well as Stata. A total of 32 studies were included in the analysis. All keratometry (K) readings (flattest meridian, K1; steepest meridian, K2, maximum, Kmax) were significantly steeper in keratoconic compared to normal eyes: [MD (95% CI)], K1 [2.67 (1.81; 3.52)], K1-back [−0.71 (−1.03; −0.39)], K1-front [4.06 (2.48; 5.63)], K2 [4.32 (2.89; 5.75)], K2-back [−1.25 (−1.68; −0.82)], K2-front [4.82 (1.88; 7.76)], Kmax [7.57 (4.80; 10.34)], and Kmean [2.80 (1.13; 4.47)]. Additionally, corneal thickness at the center, CCT [−61.19 (−73.79; −48.60)] and apex, pachy-apex [−41.86 (−72.64; −11.08)] were significantly thinner in keratoconic eyes compared to normal eyes. The pooled estimates for pachymetric progression index (PPI): PPImin [0.66 (0.43; 0.90)], PPImax [1.26 (0.87; 1.64)], PPIavg [0.90 (0.68; 1.12)], and Ambrosio relational thickness (ART): ARTmax [−242.77 (−288.86; −196.69)], and ARTavg [−251.08 (−308.76; −195.39)] revealed significantly more rapid pachymetric progression in keratoconic eyes than in normal eyes. The Pentacam Scheimpflug-derived keratometric, pachymetric, and pachymetric progression indices are good predictors in discriminating KC from normal eyes.

Keywords: corneal topography, keratometric readings, central corneal thickness, keratoconus, pachymetric progression

Introduction

Keratoconus (KC) remains an important ocular disorder with enormous implications for affected persons' quality of life.[1,2] It is known to be characterised with progressive corneal asymmetry, steepening and alteration, apical thinning and central corneal scarring.[3] There have been variations in the reported onset of the disease, including adolescence, early adulthood and childhood.[4]

As a disease of the cornea, the use of tomographic techniques for the diagnosis and progression of keratoconus is very crucial. In the advanced stages of the disease, it is easy to diagnose using the slit lamp assessment technique; however, in the early stages, its diagnosis can be tricky and easily missed.[5]

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Posterior corneal and pachymetric measures have proven useful in the early-stage diagnosis of this corneal ectasia.[6,7] The Scheimpflug system has incorporated a spectrum of indices for the objective diagnosis and staging of Keratoconus.[8,9] The system characterizes the anterior corneal curvature-based topometric measures together with the posterior corneal and thickness-oriented Belin/Ambrosio Enhanced Ectasia Display (BAD) and Ambrosio's related thickness maximum.[10,11]

The quest for refractive surgical interventions has brought to the fore the need for tests with high sensitivity and reliability, including non-tomographic techniques. The Scheimpflug imaging system, unlike others, allows for the visualization and measurement of corneal defects under standardized air puff indentation. The quality of published data on KC evaluation is often low due to various factors. Some studies had small sample sizes, which limited the generalizability of their findings. Other studies used different criteria in the classification of KC, leading to inconsistencies in the results. These limitations highlight the need for more rigorous research using standardized methods and larger sample sizes. The present study, therefore, investigated the use of the Scheimpflug -derived keratometric, pachymetric, and pachymetric progression indices in the diagnosis of Keratoconus.

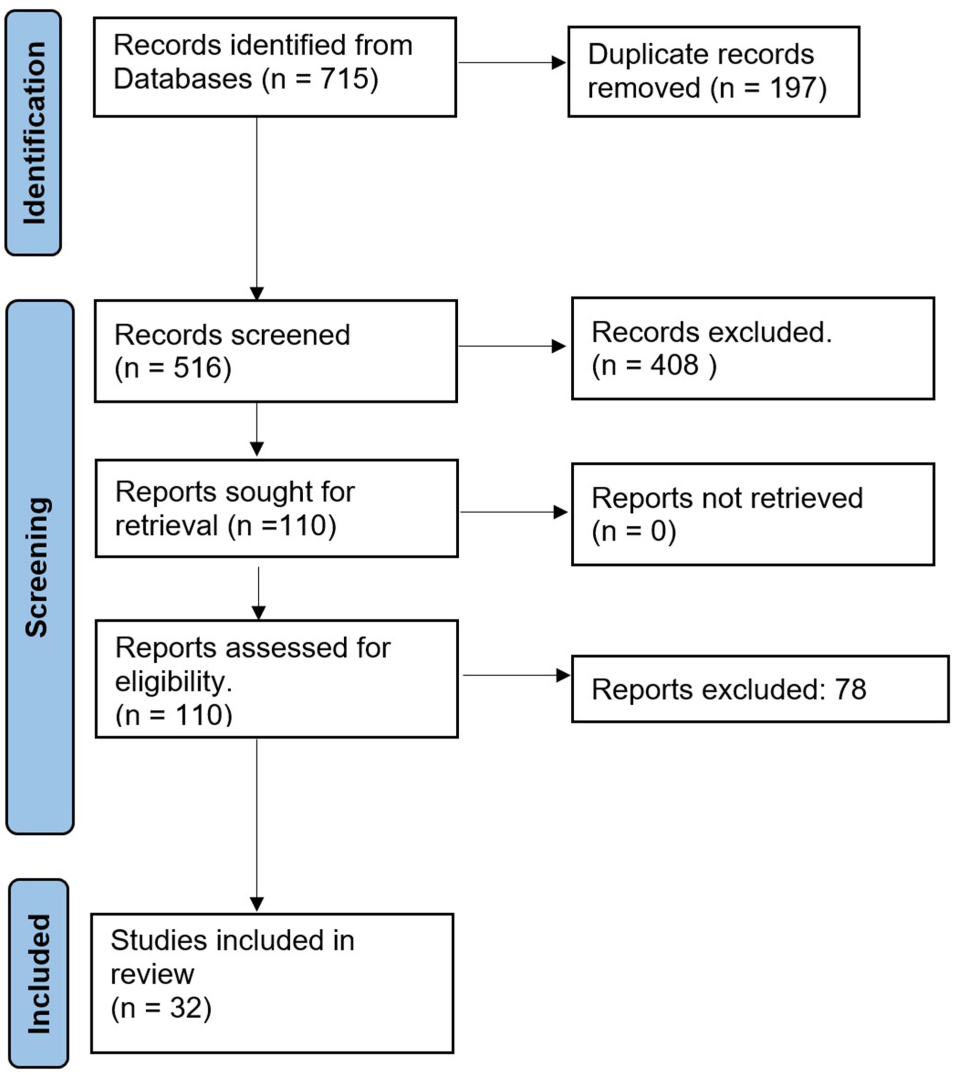

Figure 1 PRISMA flow chart of study selection.

Notes: PRISMA figure adapted from Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;29;n71. Creative Commons.[13]

Table 1 Summary of the Key Characteristics of the Studies That Were Analyzed

Study, Year (Reference)	Country	Setting	Subjects Analysed	Age (KC, NE)	Definition	Instrument, Method	Funding Source
Thulasidas And Teotia, 2020[14]	India	Out-patients	49	26.4, 25.22	The case study included patients with unilateral keratoconus (KC) while the control group were candidates for refractive surgery with normal corneas.	Pentacam	Nil
Galleti et al, 2014[15]	Turkey	Out-patients	190	32, 32	Healthy controls consisted of patients with unremarkable Scheimpflug tomography in both eyes, defined as showing normal values (less than 1.6) in the standardised indices (back elevation, corneal thickness progression, relational thickness, and overall indices) and for the Ambrosio's maximum relational thickness index (339 or greater). Patients with at least one abnormal value in any of the aforementioned indices (2.6 or greater for the standardised index or maximum relational thickness less than 339) were diagnosed as having keratoconus.	Pentacam HR, Placido disk	Not stated

(*Continued*)

Table 1 (Continued).

Study, Year (Reference)	Country	Setting	Subjects Analysed	Age (KC, NE)	Definition	Instrument, Method	Funding Source
Guo et al, 2021[16]	China		675	23.08, 22.56	The control group was made up of volunteers with normal eye (their right eyes were used), while the study group consisted of patients with keratoconus in both eyes.	Pentacam, Corvis ST	National Natural Science Foundation of China (31,600,758); the Beijing Nova Program (Z181100006218099); the Open Research Fund from Beijing Advanced Innovation Center for Big Data-Based Precision Medicine, Beijing Tongren Hospital, Beihang University & Capital Medical University (BHTR-KFJJ-202001); Beijing Nova Program [Z181100006218099];
Reddy et al, 2014[17]	USA	Out-patients	141	34, 31	The keratoconus group comprised patients with keratoconus diagnosed by a corneal specialist on the basis of clinical and topographic signs. The normal group comprised normal eyes of patients evaluated for refractive surgery.	Rotating Scheimpflug imaging system	Nil
Hashem et al, 2022[18]	Egypt	Out-patients	480	13.5, 15.3	The study group comprised normal paediatric right eyes while the study group comprised eyes of paediatric keratoconus	Rotating Scheimpflug Camera (Oculyzer II, Pentacam HR)	The Science and Innovation Funding in cooperation with The Egyptian Knowledge Bank
Bae et al, 2014[19]	South Korea	Out-patients	48	28, 25.08	Patients who had advanced KC in one eye and a normal fellow eye were considered unilateral KC. The normal control patients were candidates for refractive surgery with clinically normal corneas.	Pentacam rotating Scheimpflug camera (Oculus, Wetzlar, Germany).	Not stated
Chan et al, 2017[20]	Hong Kong	Out-patients	42	33.6, 34.9	Patients with clinically evident KC were recruited as the study group while an age-matched with normal corneas were recruited as control group.	Pentacam (Oculus Optikgeräte, Wetzlar, Germany) and Corvis (Oculus Optikgeräte)	Not stated

Dienes et al, 2014[21]	Hungary	Out-patients	194	39.95, 36.98	Persons with mild to moderate keratoconus (KC group) and eyes of refractive surgery candidates (control group) were evaluated in this study. Both eyes of each patient in both groups were used.		Hungarian Scientific Research Fund OTKA NN106649 research grant.
Henriquez et al, 2015 (KC)[22]	Peru	Out-patients	671		The study group were eyes with an increased area of corneal power surrounded by concentric areas of decreasing power while the control group were normal eyes with no family history of ectasia.	Scheimpflug Imaging Analyzer (Pentacam; Oculus GmBH, Wetzlar, Germany)	Nil
Henriquez et al, 2015 (VEKC)[22]	Peru	Out-patients	418		The study group consisted of eyes with very early keratoconus while the control group were normal eyes with no family history of ectasia.	Scheimpflug Imaging Analyzer (Pentacam; Oculus GmBH, Wetzlar, Germany)	Nil
Huseynli et al, 2018[23]	Azerbaijan	Out-patient	114	21.19, 21.75	The study group were patients with early stage of keratoconus after complete ophthalmologic evaluation also with minimal pachymetry ≤500µm while the control group were normal corneas.	Pentacam HR	Nil
Jafarinasab et al, 2013[24]	Iran		210	28.6, 30.7	The study group consisted of eyes with keratoconus on slit lamp biomicroscopy as well as asymmetric bowtie without SRAX while the control group were eyes without keratoconus.	Rotating Scheimpflug imaging system	Nil

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Table 1 (Continued).

Study, Year (Reference)	Country	Setting	Subjects Analysed	Age (KC, NE)	Definition	Instrument, Method	Funding Source
Kataria et al, 2018[25]	India	Out-patients	300		The keratoconus group comprised of one eye of patients with bilateral keratoconus; the eye chosen had a mean simulated keratometry (K) value of less than 48.0 diopters while patients who had remained visually and topographically stable for at least two years after a laser refractive procedure with no evidence of post-refractive surgery ectasia constituted the normal control group.	Scheimpflug tomography (Pentacam HR, Oculus Optikger€ate GmbH), Corvis ST	Not stated
Kosekahya et al, 2018[26]	Turkey	Out-patients	200	23.78, 26.06	The study group consisted of eyes with characteristic keratoconus signs in the anterior sagittal curvature maps while the normal group included eyes with a spherical equivalent less than 2.00 diopters (D) and a corrected distance visual acuity of 20/20 or better.	Pentacam HR	Not stated
Kovacs et al, 2010[27]	Hungary	Out-patients	111	39.69, 35.25	The study evaluated eyes with mild to moderate keratoconus and eyes (study group) of refractive surgery candidates with normal corneas (control group).	Pentacam HR rotating Scheimpflug camera (version 1.16 r:23, Oculus Optikgeräte GmbH)	Nil
Degirmenci et al, 2019[28]	Turkey	Out-patients	61	32.33, 30.07	The study group were eyes with keratoconus while the control were the fellow eyes that were clinically and topographically normal.	Pentacam (Oculus Optikgerate GmbH, Wetzlar, Germany)	Nil

Henriquez et al, 2012[29]	Peru	Out-patients	151	28.4, 29.29	The study group was defined as keratoconus in both eyes, with the presence of clinical signs and topographic evaluation while the control group were subjects who had normal corneas in both eyes.	Scheimpflug Imaging Analyzer (Pentacam; Oculus GmBH, Wetzlar, Germany)	Not stated
Huseynova et al, 2016[30]	Azerbaijan	Out-patients	85	23.77, 26.06	The study group were eyes with keratoconus while the control group were healthy corneas diagnosed according to Amsler–Krumeich criteria.[31]	Pentacam HR (Oculus Optikgeräte GmbH, Wetzlar, Germany	Not stated
Koc et al, 2020[32]	Turkey	Out-patients	402	26, 24.8	The diagnosis of clinical keratoconus was defined by characteristic keratoconus signs in the anterior sagittal curvature maps while the control group was randomly selected from a database of age-matched candidates' laser in situ keratomileusis (LASIK) for myopia (≤5.0 D) and myopic astigmatism (≤3.0 D) who had normal topographic, topometric and tomographic analysis and did not develop ectasia after at least 1-year follow-up.	Pentacam HR rotating Scheimpflug camera	Nil
Kovacs et al, 2016[12]	Hungary	Out-patients	120	39.95, 33.17	The study group were patients with unilateral or bilateral mild to moderate keratoconus while the control group were refractive surgery candidates with normal corneas.	Scheimpflug camera (Pentacam HR, Oculus Optikgeräte GmbH)	Nil

(*Continued*)

Table 1 (Continued).

Study, Year (Reference)	Country	Setting	Subjects Analysed	Age (KC, NE)	Definition	Instrument, Method	Funding Source
Lim et al, 2014[33]	Singapore	Out-patients	70	31, 29.4	Cases in the study group were patients with eyes that met the Amsler-Krumeich criteria[31] for keratoconus while the group were control group were selected from a database of candidates for refractive surgery with normal corneas and myopia or myopic astigmatism.	Scheimpflug corneal tomography (Pentacam; Oculus. Wetzlar, Germany)	The Health Research Endowment Fund of the Singapore Ministry of Health
Liu et al, 2021[34]	China		110	24.87, 22	The study group were eyes with keratoconus based on slit-lamp findings and the presence of abnormal topographic patterns on the sagittal front curvature map while the control group was healthy eyes with no ectasia.	Rotating Scheimpflug corneal tomography (Pentacam HR), Corvis ST II	The Key Clinical Innovation Program of Peking University Third Hospital, category A (No. Y65495-05).
Mihaltz et al, 2009[35]	Hungary	Out-patients	82	40.2, 38.7	The study group were patients with keratoconus diagnosed based on biomicroscopic and topographic findings in accordance with the criteria established by the Collaborative Longitudinal Evaluation of Keratoconus Study while the control group were refractive surgery candidates with healthy corneas.	Pentacam HR (version 1.16. r:23)	Not stated
Naderan et al, 2017[36]	Iran	Out-patients	738	25.3, 26.1	Patients with bilateral keratoconus (both eyes with KISA% >100) were assigned to the KC group and those with bilateral normal eyes (both eyes with KISA% <60) were assigned to the normal group.	Pentacam Scheimpflug analyser (OCULUS Optikgeräte, Wetzlar, Germany)	Not stated

Nicula et al, 2022[37]	Romania	Out-patients	252	30, 31	Patients diagnosed with KCN confirmed by slit-lamp examination keratometry and corneal topography, and tomography were included in the KCN group while the control group comprises subjects selected from the candidates for refractive corneal surgery with myopia (<-8.5D) and/or myopic astigmatism (<3.5D) and a normal corneal tomography and healthy eyes.	Pentacam R (HR Premium; Oculus Optikgeräte GmbH, Wetzlar, Germany)	Not stated
Ucakhan et al, 2011[38]	Turkey	Out-patients	111	29.1, 26.1	Patients with clinically evident keratoconus were recruited as the study group while the control group consisted of normal eyes with myopic astigmatism (sphere 7.00 diopters [D] and cylinder 4.00 D) and normal corneal and ocular findings.	Pentacam Comprehensive Eye Scanner (Oculus Optikgeräte GmbH)	Not stated
Orucoglu and Toker, 2015[39]	Turkey	Out-patient	1169	32.99, 31.18	The study group were eyes with keratoconus diagnosed mainly on the basis of clinical slit-lamp findings, keratometry, and associated characteristic topographic patterns while the control group were normal eyes with no ocular pathology, no previous ocular surgery, and no irregular corneal pattern.	Rotating Scheimpflug camera (Pentacam, Oculus Optikgeräte GmbH, Wetzlar, Germany)	Not stated

(*Continued*)

Table 1 (Continued).

Study, Year (Reference)	Country	Setting	Subjects Analysed	Age (KC, NE)	Definition	Instrument, Method	Funding Source
Shen et al, 2021[40]	China	Out-patient	335	25.1, 22.8	The study group were eyes with keratoconus, diagnosed according to the Global Consensus on Keratoconus Diagnosis from 2015[41] while the control were persons with healthy corneas.	Scheimpflug camera	National Natural Science Foundation of China (Grant No. 82101183) (Grant No. 81770955); Joint research project of new Frontier technology in municipal hospitals (SHDC12018103); Project of Shanghai Science and Technology (Grant No.20410710100), (Grant No. 21Y11909800); Clinical Research Plan of SHDC (SHDC2020CR1043B); Project of Shanghai Xuhui District Science and Technology (2020–015).
Shetty et al, 2017[42]	India	Out-patients	130	25.5, 24.25	The study group were eyes with keratoconus diagnosed mainly on the basis of clinical findings, while the control group were normal eyes with no ocular pathology.	Pentacam, Galilei and Sirius	Nil
Steinberg et al, 2015[43]	Germany and Austria	Out-patients	635	33, 34	The control group were normal eyes (both eyes KISA% <60); while the study group were clinical manifest keratoconus eyes (KISA% >100).	Rotating Scheimpflug imaging system (Pentacam, Oculus Inc	Not stated
Vazquez et al, 2014[44]	Argentina	Out-patients	281	32.3, 32.5	The study group were eyes with keratoconus diagnosed mainly on the basis of clinical slit-lamp findings, keratometry, and associated characteristic topographic patterns while the control group were normal eyes.	Placido disk topography and aberrometry (iTrace, Tracey Technologies, Houston, TX, USA) and Scheimpflug camera (Pentacam, Oculus Optikgeräte GmbH, Wetzlar, Germany)	Nil

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Table 2 Meta-Regression

Parameter	COVARIATE	B	95% CI	P
Average pachymetric progression index	Sample Size	0.00	−0.00, 0.00	0.36
	Publication Year	−0.01	−0.08, 0.06	0.73
Maximum Ambrosio relational thickness	Sample Size	−0.02	−0.16, 0.12	0.77
	Publication Year	0.92	−28.91, 30.75	0.95
Average Ambrosio relational thickness	Sample Size	−0.05	−0.40, 0.30	0.79
	Publication Year	1.82	−24.83, 28.46	0.89
Central corneal thickness	Sample Size	−0.07	−0.12, −0.01	0.02
	Publication Year	−2.89	−6.62, 0.84	0.13
Posterior corneal elevation	Sample Size	−0.09	−0.46, 0.28	0.63
	Publication Year	−27.79	−50.59, −5.00	0.02
K1	Sample Size	−0.00	−0.01, 0.01	0.49
	Publication Year	−0.10	−0.36, 0.17	0.48
K2	Sample Size	−0.00	−0.01, 0.01	0.43
	Publication Year	−0.07	−0.53, 0.38	0.75
Maximum keratometric power	Sample Size	0.00	−0.00, 0.01	0.4
	Publication Year	0.99	−0.36, 2.36	0.16
Maximum pachymetric progression index	Sample Size	0.00	−0.00, 0.00	0.99
	Publication Year	0.03	−0.12, 0.19	0.69

Methods

The review protocol was registered with PROSPERO (Identifier: CRD42023410058), and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement was followed.

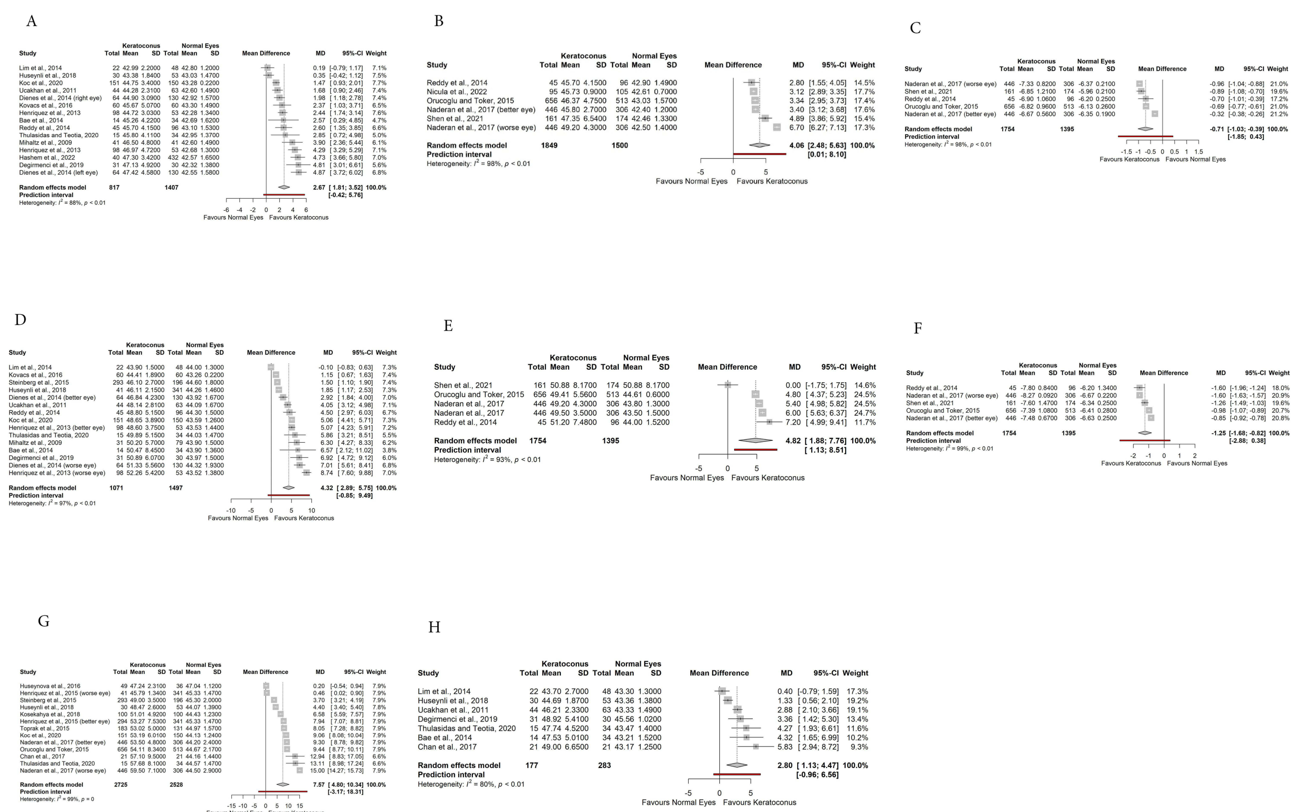

Figure 2 Forest Plots of keratometric readings in keratoconic and normal eyes **(A-H)** for K1, K1f, K1b, K2, K2f, K2b, Kmax and Kmean respectively.

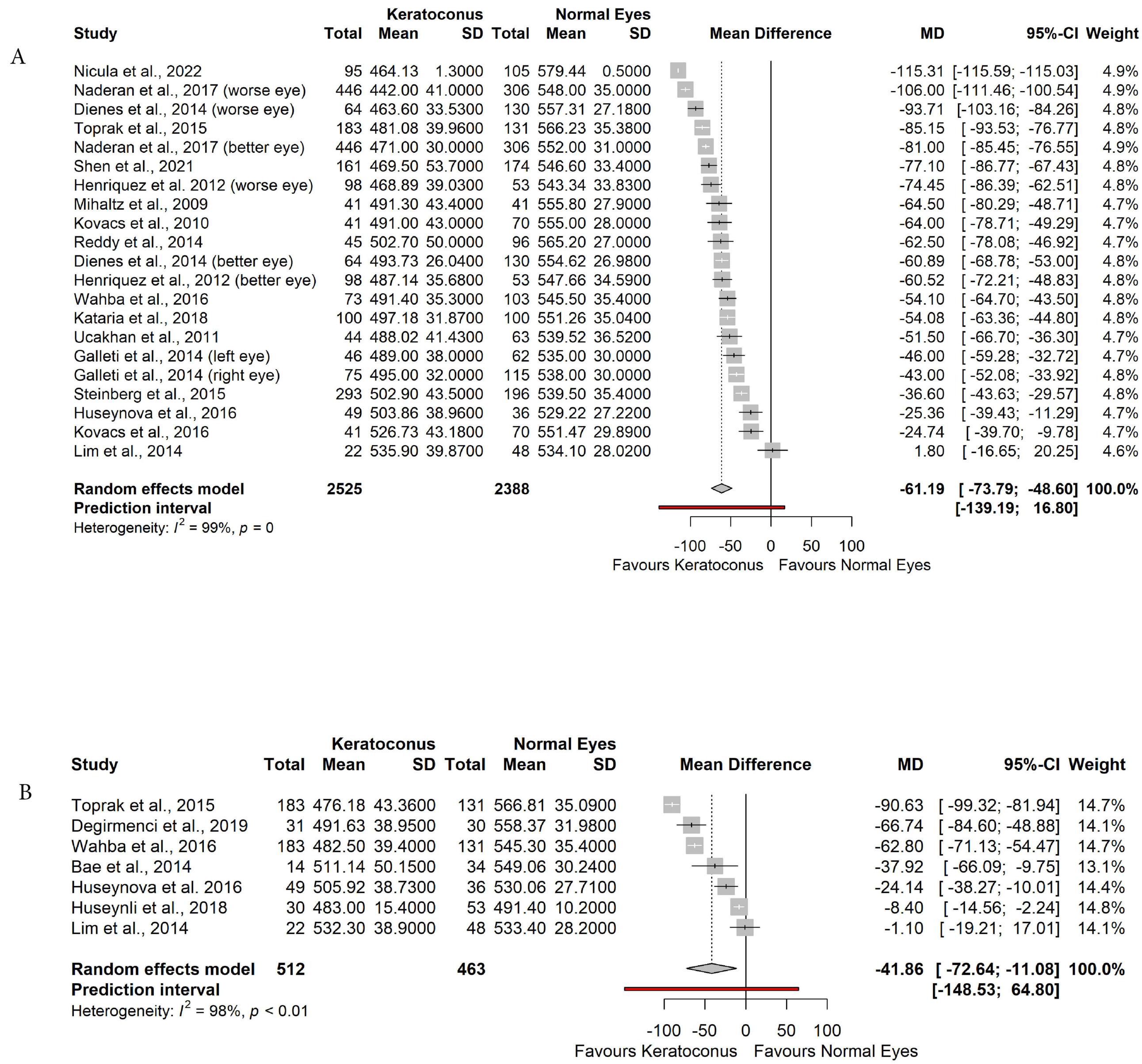

Figure 3 Forest Plots of CCT and Pachy-apex (**A** and **B** respectively) in keratoconic and normal eyes.

Literature Search Strategy and Study Selection

We conducted a thorough literature search in PubMed, MEDLINE, Web of Science, and EMBASE to discover relevant articles, and the latest search was conducted on June 30, 2023. The search strategy was based on combinations of medical subject headings and free text words, and the search terms used included "Scheimpflug", "Pentacam", "keratoconus", "ectatic cornea", "diagnostic efficacy", "tomography", "topography", "outcome", "efficacy" "topographic", "tomographic", and "topometric" in varying combinations. The search was defined using the Boolean operators "AND" and "OR" and truncations. Figure 1 illustrates the PRISMA flowchart outlining the processes for obtaining the articles used in this review. The initial literature search turned up one hundred and ten (110) plausibly relevant articles, out of which thirty-seven[12] were included. Full-text articles that seemed relevant were retrieved after three reviewers (A.J.B.V., S.A., and S.O.) independently evaluated the titles and abstracts for possible eligibility. The three reviewers then independently evaluated these full-text articles to determine their suitability for inclusion. We reached a consensus on how to classify

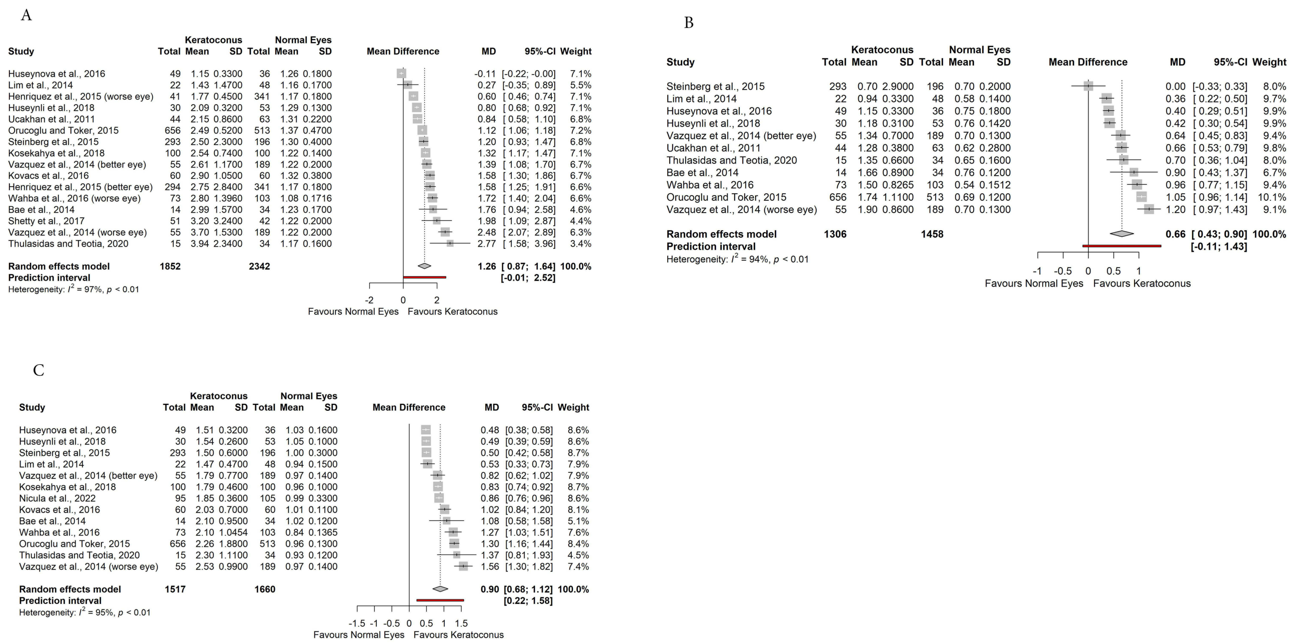

Figure 4 Forest Plots for the Pachymetric Progression indices in keratoconic and normal eyes (**A-C**) for PPImax, PPImin and PPIavg respectively.

the eligibility differences of the full-text articles through discussions, and where necessary, three other reviewers (S.K., M.A.K., and E.Z.) adjudicated the issue.

Published studies were considered eligible if they met the following criteria: Pentacam Scheimpflug Tomography was used in evaluating the cornea and compared any of the keratometry readings, pachymetric indices and/or pachymetric progression indices amongst participants with keratoconus and a control group (participants without keratoconus). Conference abstracts were included if they contained all relevant data. Review papers, studies without control groups, studies with no pertinent data, case reports, correspondence, and studies with missing or unidentifiable data were excluded from this review.

Study Appraisal and Data Extraction

Quality appraisal of the included studies was done using the revised tool for the quality assessment of diagnostic accuracy studies (QUADAS-2). The QUADAS-2 tool is commonly used in systematic reviews of diagnostic test accuracy studies to assess individual studies' risk of bias and applicability. It comprises seven categories of bias which are classified as "high", "low", or "unclear", but does not produce a single overall numerical score. For our study, two authors (S.O. and E.Z.) used the QUADAS-2 tool independently to evaluate the studies, and any disagreements were resolved by group discussion involving a third author (S.K.). This approach ensured a reliable and consistent assessment of the studies. Two authors (S.O. and A.J.B.V.) independently extracted data from each included study. Demographic characteristics of study subjects and means and standard deviations of the Scheimpflug Pentacam parameters were extracted using Microsoft Excel Spreadsheet, with accuracy confirmed by a third author (E.Z.). The parameters included in this review were keratometry readings (keratometric powers of the flat meridian [K1, K1-back, K1-front]; keratometric powers of the steep meridian [K2, K2-back, K2-front]; mean keratometric power, Kmean; keratometric power of the steepest point of the front surface, Kmax), pachymetric indices (central corneal thickness, CCT; corneal thickness at the apex, pachy-apex), and pachymetric progression indices (minimum pachymetric progression index, PPImin; maximum pachymetric progression index, PPImax, average pachymetric progression index, PPIavg; maximum Ambrosio relational thickness, ARTmax; average Ambrosio relational thickness, ARTavg).

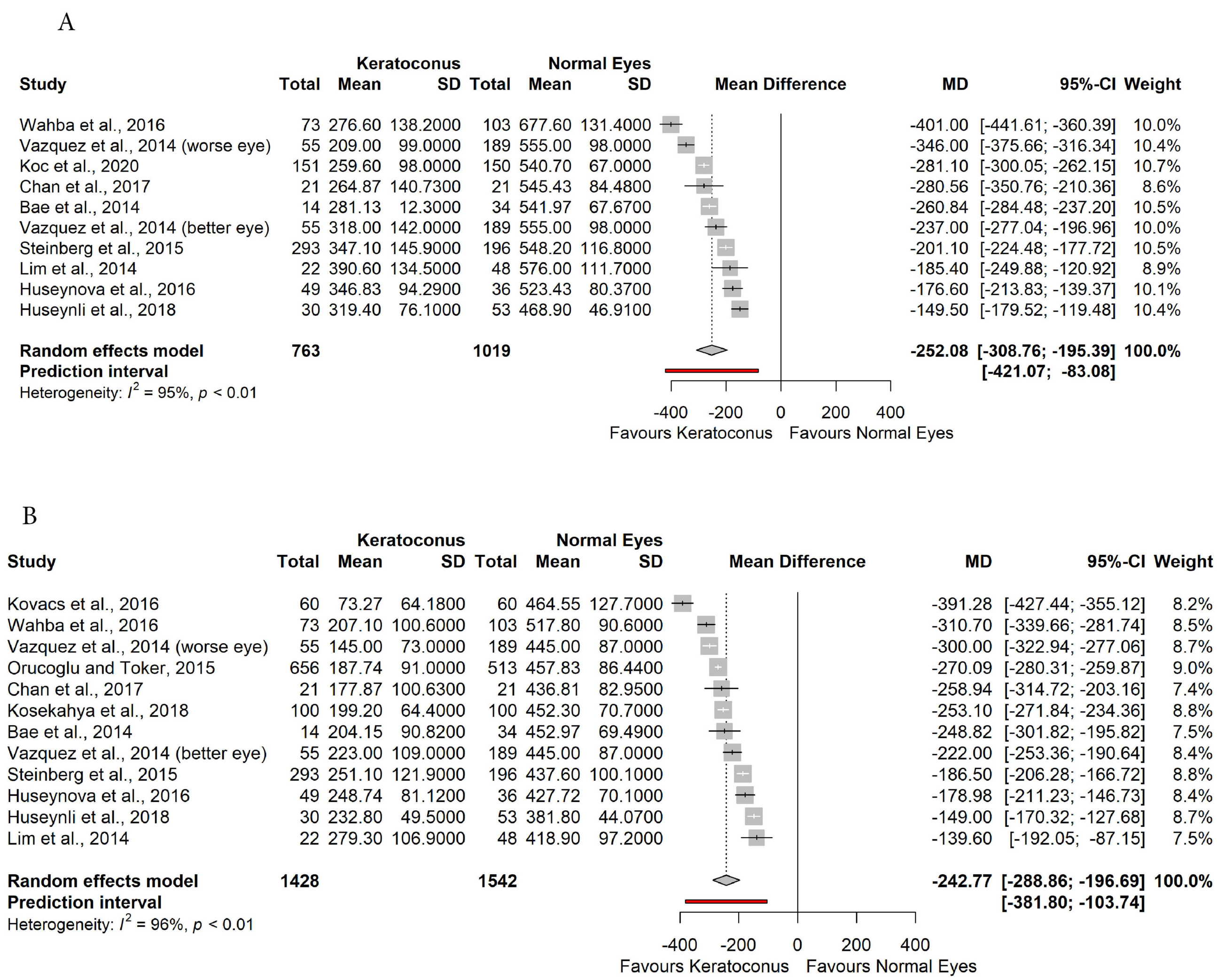

Figure 5 Forest Plots of the Ambrosio Relational Thickness (**A and B** respectively) for ARTavg and ARTmax in keratoconic and normal eyes.

Data Analysis

The meta-analysis (inverse variance random-effect model) was conducted using the meta (6.5.0) and metafor (4.2.0) packages in R version 4.3.0 (R Foundation) as well as Stata (StataCorp. 2021. Stata Statistical Software: Release 17. College Station, TX: StataCorp LLC.). We reported the estimates of effect size as mean differences (MD) with a 95% confidence interval (CI). A meta-regression was conducted for parameters with at least 10 studies to examine whether potential effect modifiers, such as sample size and publication year, could account for any variation in effect sizes. A sensitivity analysis was performed to ensure the robustness of the pooled estimates using a leave-one-out meta-analysis approach, wherein the impact of a particular study on the final combined estimate was assessed by systematically excluding each study in turn. Additionally, we evaluated publication bias for parameters with at least 10 studies by visually inspecting funnel plots and addressed any potential bias using the Trim and Fill method developed by Duval and Tweedie.

Results

Table 1 presents a summary of the key characteristics of the studies that were analyzed in the review. All the studies included in the meta-analysis were published within the period spanning from 2009 to 2022. Table 2 presents the meta-regression conducted for parameters with at least 10 studies.

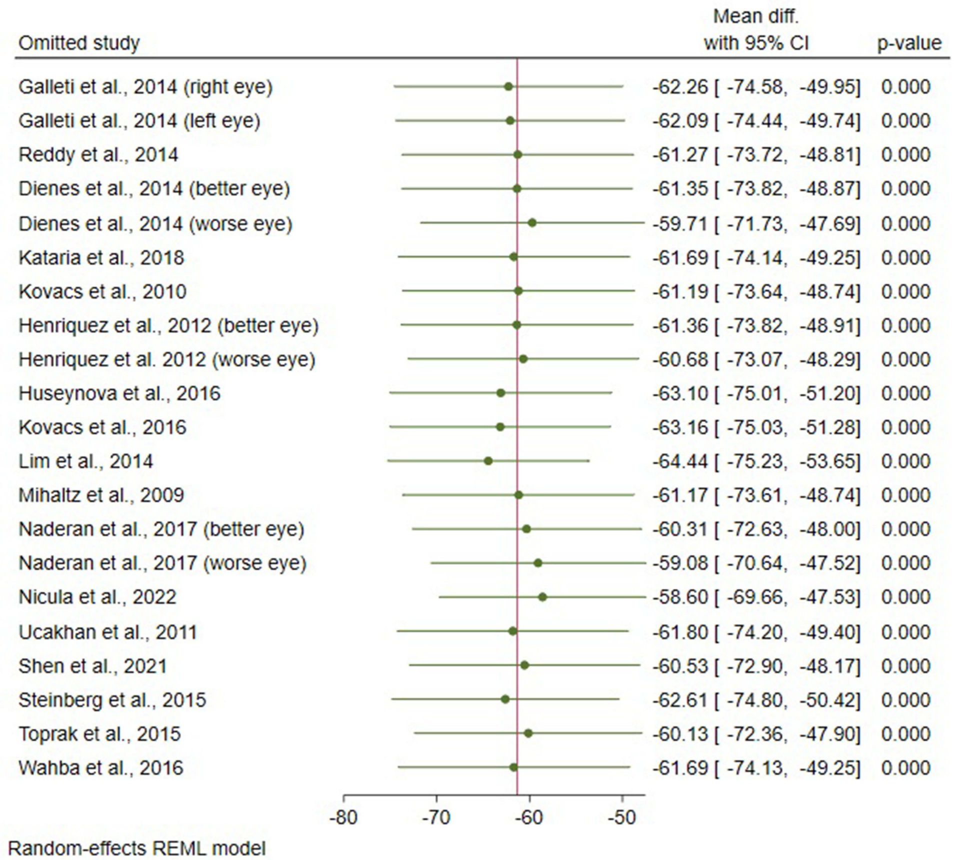

Figure 6 Leave-one-out meta-analysis for central corneal thickness (CCT).

As shown in Figure 2, all keratometry readings were significantly steeper in eyes with keratoconus than in normal eyes, [MD (95% CI)], K1 [2.67 (1.81; 3.52)], K1-back [−0.71 (−1.03; −0.39)], K1-front [4.06 (2.48; 5.63)], K2 [4.32 (2.89; 5.75)], K2-back [−1.25 (−1.68; −0.82)], K2-front [4.82 (1.88; 7.76)], Kmax [7.57 (4.80; 10.34)], and Kmean [2.80 (1.13; 4.47)]. Further, CCT [−61.19 (−73.79; −48.60)] and pachy-apex [−41.86 (−72.64; −11.08)] were significantly thinner in keratoconic eyes compared to normal eyes (Figure 3). The pooled estimates for PPImin [0.66 (0.43; 0.90)], PPImax [1.26 (0.87; 1.64)], PPIavg [0.90 (0.68; 1.12)], ARTmax [−242.77 (−288.86; −196.69)], and ARTavg [−251.08 (−308.76; −195.39)] showed significantly more rapid pachymetric progression in keratoconic eyes than in normal eyes (Figures 4 and 5). Notably, we observed significant heterogeneity in the meta-analysis for all the parameters (I^2>50%); however, the results of the leave-one-out sensitivity analysis indicated that the exclusion of any single study did not substantially alter the pooled effect size estimate for all parameters, suggesting that the overall findings were robust as the pooled effect size estimate remained relatively stable (Figures 6–9). The contour-enhanced funnel plots showed evidence of non-random publication bias for K2, CCT, PPImax, and PPIavg, with an excess of studies in the lower-right corners of the plots, implying that smaller studies with non-significant results may not have been published, and this might have over-estimated the treatment effects (Figures 10–13). Publication bias adjustments with Duval and Tweedie's trim and fill are shown in Figure 14. Publication-bias-corrected estimates of the true effect sizes were [2.53 (0.78; 4.27); outliers removed: 2.80 (1.10; 4.54)], [−104.82 (−128.69; −80.96); outliers removed: −106.19 (−128.68; −83.69)], [0.94 (0.52; 1.36); outliers removed: 1.08 (0.73; 1.42)], and [0.64 (0.38; 0.89); outliers removed: 0.64 (0.40; 0.87)] for K2, CCT, PPImax, and PPIavg, respectively. The adjusted effect sizes were relatively smaller for K2, PPImax, and PPIavg and relatively larger for CCT, than the unadjusted estimates, suggesting that there may have been publication bias favoring studies with larger effect sizes; however, the effect sizes remained statistically

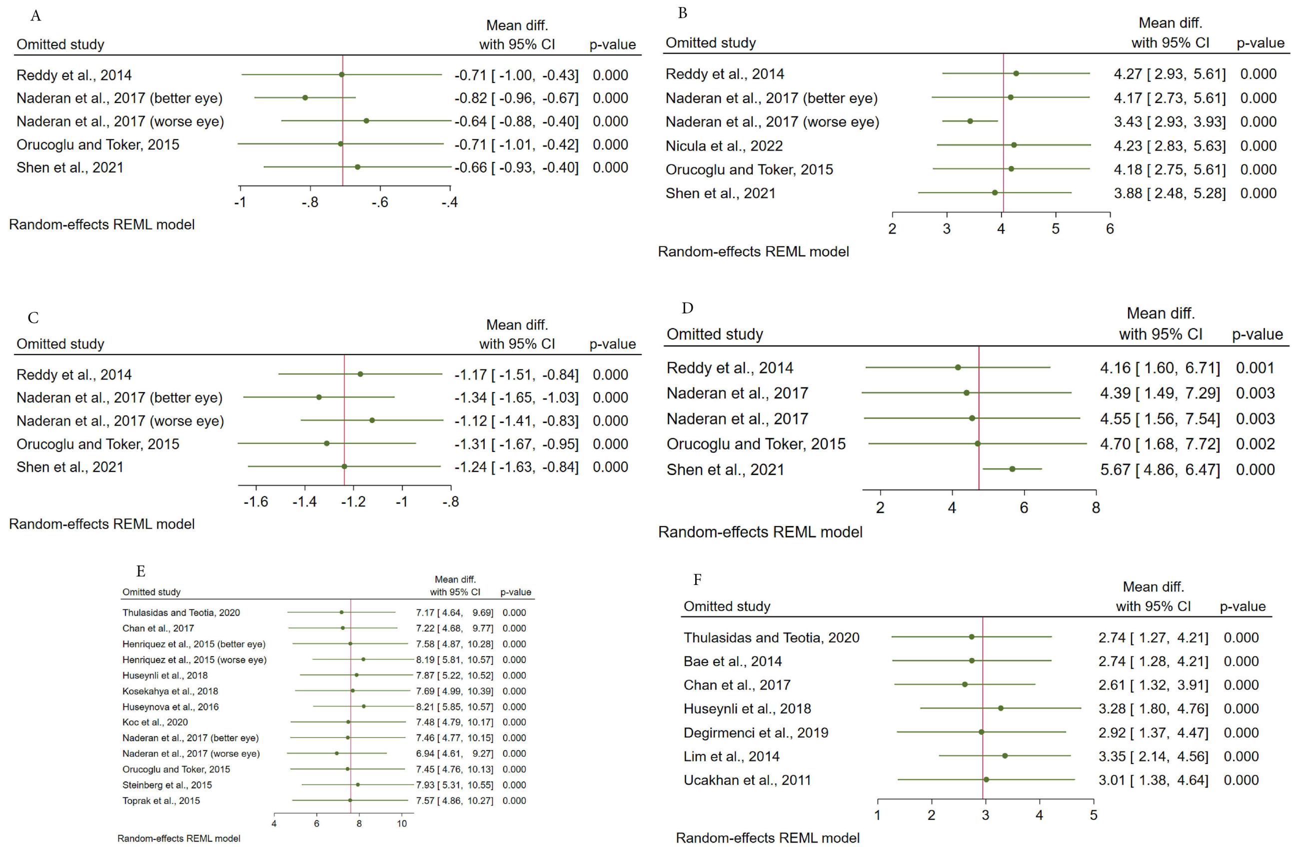

Figure 7 Leave-one-out meta-analyses for K1b, K1f, K2b, K2f, Kmax and Kmean (**A-F** respectively).

significant after adjustment. The results of the meta-regression analysis showed that sample size (β = −0.07, *P* = 0.02) was a significant predictor of the effect size estimate for CCT. Specifically, studies with larger sample sizes tended to report larger effect sizes. None of the covariates was a significant predictor of the remaining parameters (Table 2 and Figures 15–18). The study further established transparency of evidence synthesis results and findings by assessing the risk of bias and quality of the studies (Figure 19).

Discussion

Corneal topography is generally a non-invasive probing technique that examines qualitatively and quantitatively the anatomical structure of the cornea. It allows for geometric classification and affords a discriminating typical pattern of normal corneas from pathological ectatic ones.[10,45–48] Existing corneal topographers operates on either one or more of these principles; light reflection on the cornea, projection of a slit light onto the cornea, and asymmetric reflection of multicolor light-emitting diodes (LEDs).[49] Clinical characterization of the structure (shape) of the human cornea through topographic analysis is a common practice among eye care practitioners when the diagnosis of keratoconus is intended.

Recent technological advances such as Pentacam Scheimpflug tomography allow for the assessment of both the anterior and posterior surfaces of cornea at different points.[41,49,50] Anteriorly, keratoconus is morphologically characterized by a cone-shaped protrusion of the cornea.[49,51,52] This protrusion is typically eccentric but inferior-temporally positioned, read off as an area higher than the curve of the best adjustment surface in the elevation maps, and as an area more curved in the curvature map. The outcomes of the meta-analysis reveal evidence of significant mean differences in both anterior and posterior cornea keratometry readings between keratoconus and normal eyes. Specifically, the results indicate that the keratometry readings were significantly steeper in the keratoconus eyes compared to the normal eyes. Studies have suggested that early changes in eyes with

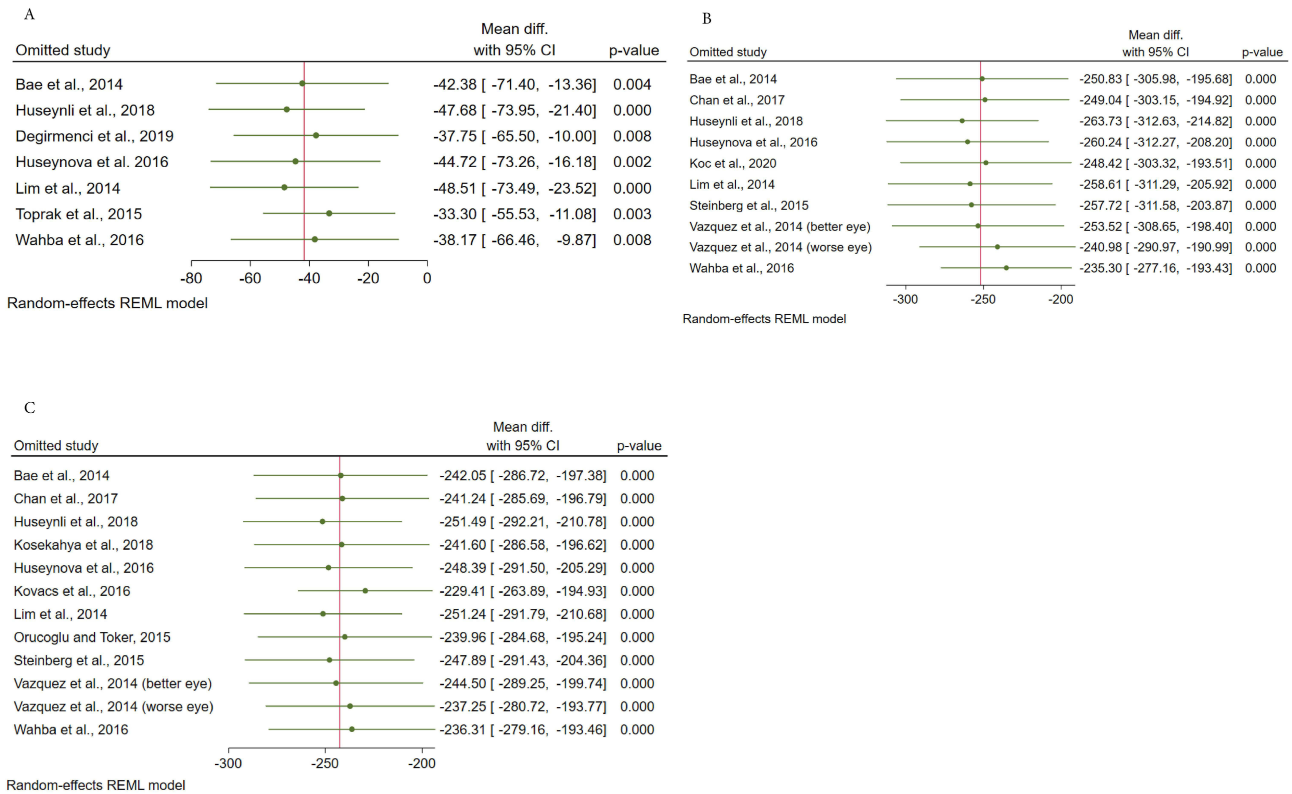

Figure 8 Leave-one-out meta-analyses for Pachy-apex, ARTavg and ARTmax (**A-C** respectively).

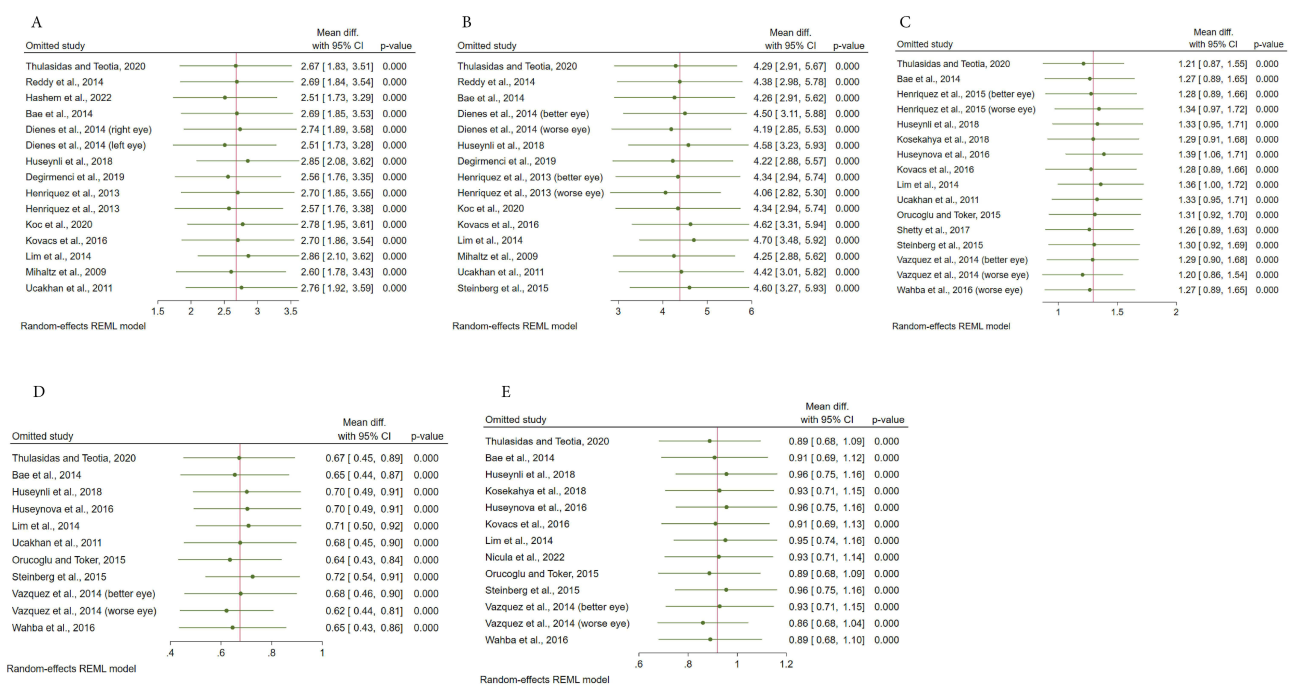

Figure 9 Leave-one-out meta-analyses for K1, K2, PPImax, PPImin and PPIavg (**A-E** respectively).

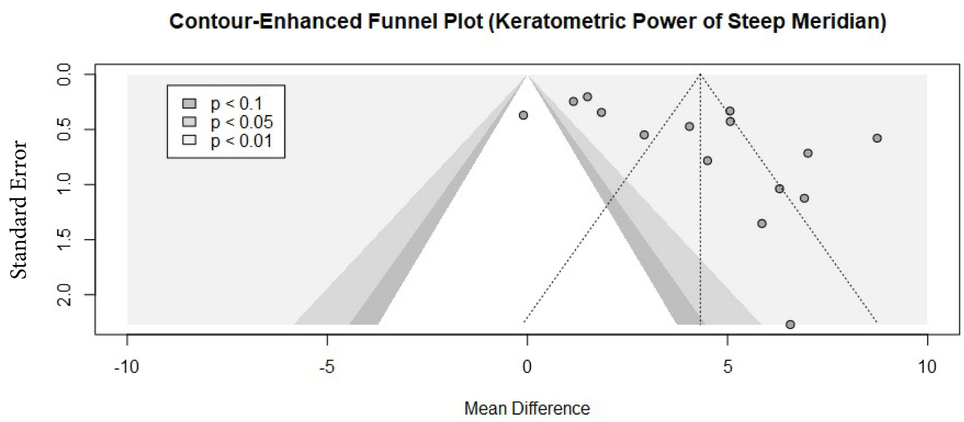

Figure 10 Contour-Enhanced Funnel Plot for the keratometric power at the steep Meridian (K2).

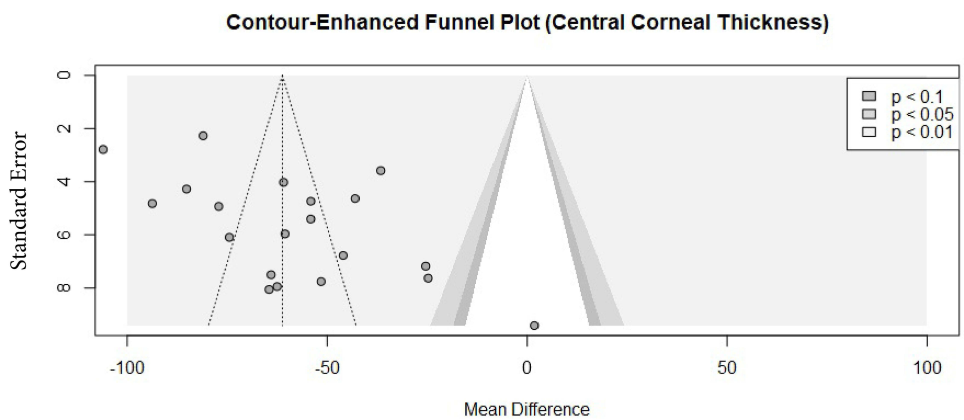

Figure 11 Contour-Enhanced Funnel Plot for the central corneal thickness (CCT).

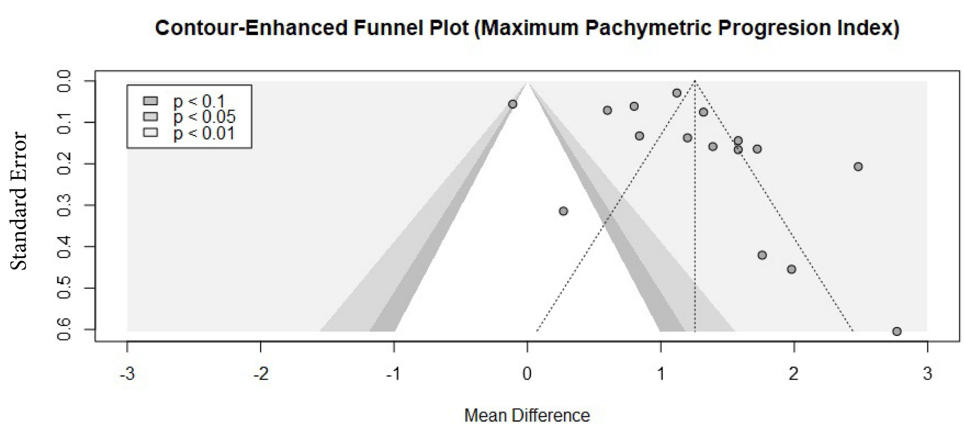

Figure 12 Contour-Enhanced Funnel Plot for the maximum pachymetric progression Indices (PPImax).

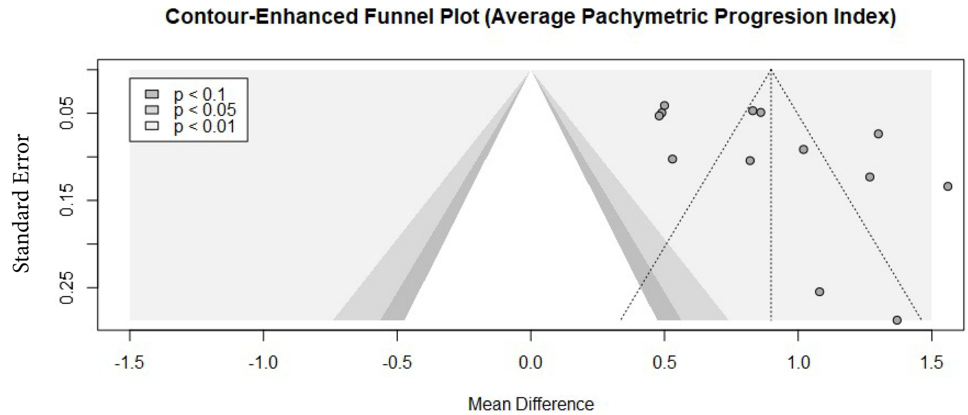

Figure 13 Contour-Enhanced Funnel Plot for the average pachymetric progression Indices (PPIavg).

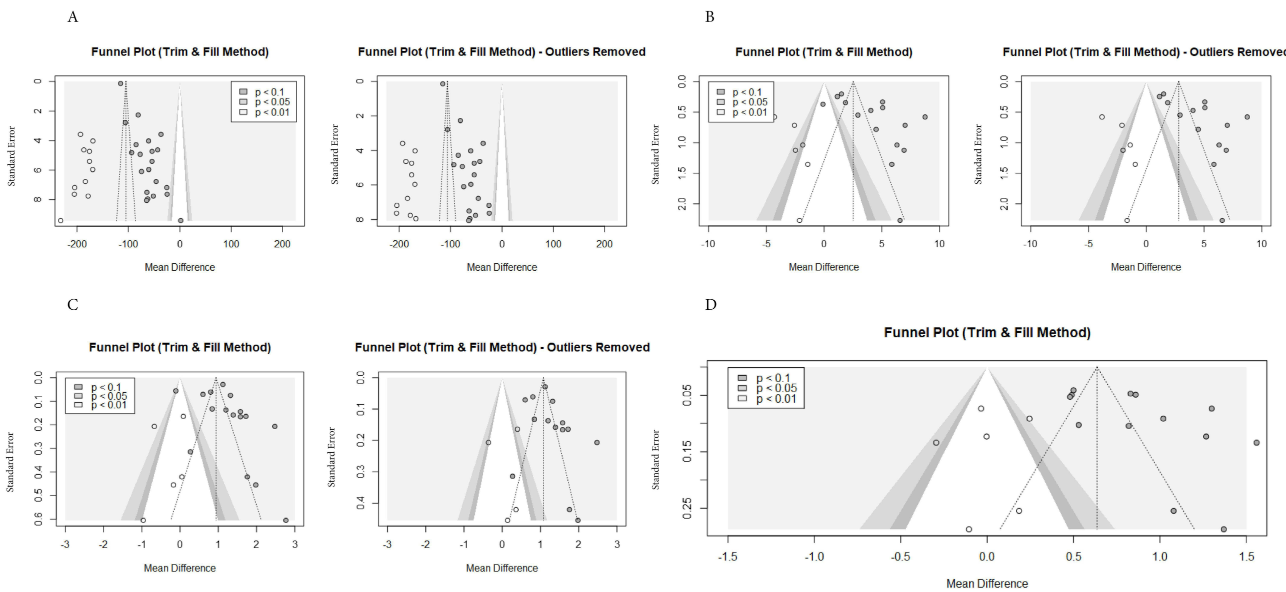

Figure 14 Tweedie's trim and fill for CCT, K2, PPImax and PPIavg (**A**–**D** respectively).

keratoconus are also present on the posterior corneal surface.[53] The geometric correlation between anterior and posterior cornea surfaces, have proven clinically useful in the discrimination of normal cornea from keratoconic corneas even at the subclinical stages.[54–56] The disparities observed in keratometry readings provide valuable insights into the structural changes occurring in keratoconus, highlighting the complex nature of the condition. Understanding these differences can have important clinical implications, as they can aid in the accurate diagnosis and monitoring of keratoconus, as well as the development of targeted treatment approaches.

Also, this review highlights the significance of considering pachymetric and pachymetric progression indices in differentiating keratoconic eyes from normal ones. This study found that CCT and pachy-apex were significantly thinner in keratoconic eyes than normal ones. The pooled estimates for pachymetric progression indices also showed significantly more rapid pachymetric progression in keratoconic eyes than in normal eyes. These findings indicate that these indices provide valuable insights into discriminating KC from normal eyes considering the severity, and the progression of KC, aiding in its early detection and management. Several studies have used only the pachymetry indices in evaluating and diagnosing KC.[57–59] Therefore, a comprehensive assessment of these factors is essential

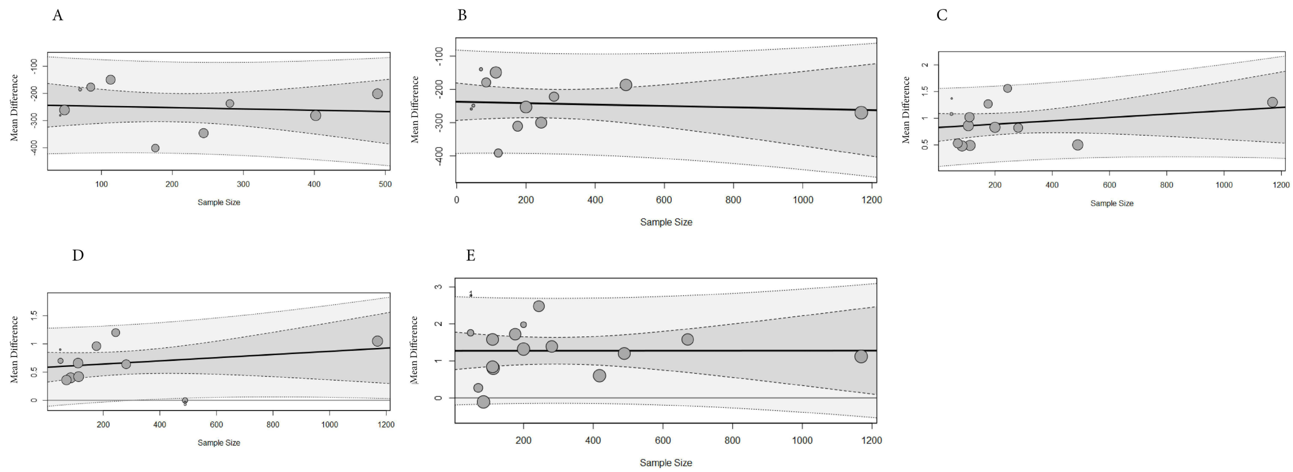

Figure 15 Bubble plots of meta-regression for the effect of sample sizes on ARTavg, ARTmax, PPIavg, PPImin and PPImax (**A-E** respectively).

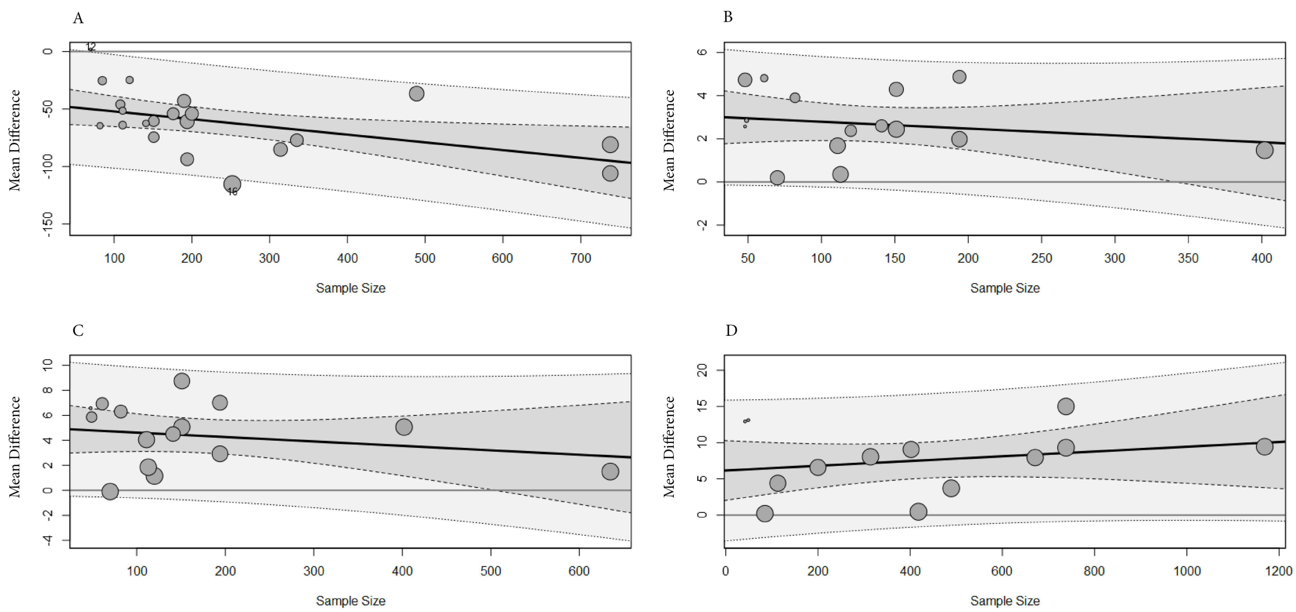

Figure 16 Bubble plots of meta-regression (**A-D**) for the effect of sample sizes on CCT, K1, K2 and Kmax respectively.

for an accurate diagnosis and personalised management of KC. In addition, using these indices can also help monitor the effectiveness of various treatment options for keratoconus. By regularly assessing these indices, healthcare professionals can make informed decisions with regards to the need for intervention or adjustment of treatment plans. This approach can potentially improve patient outcomes and minimise the risk of complications associated with advanced stages of keratoconus.

The results of the meta-regression analysis revealed sample size as a significant moderator of the effect size estimate for CCT, indicating that it plays a crucial role in explaining the heterogeneity observed among the studies. This finding suggests that the impact of sample size on CCT should be carefully considered when interpreting the results. However, other factors not accounted for in this analysis may also contribute to the between-study variation.

There is the need to acknowledge the limitations of this review study. Firstly, the included studies may have had variations in their methodologies and sample sizes, which introduced high heterogeneity in the pooled estimates. However, the leave-one-out sensitivity analysis results indicated that the pooled effect size estimate for all

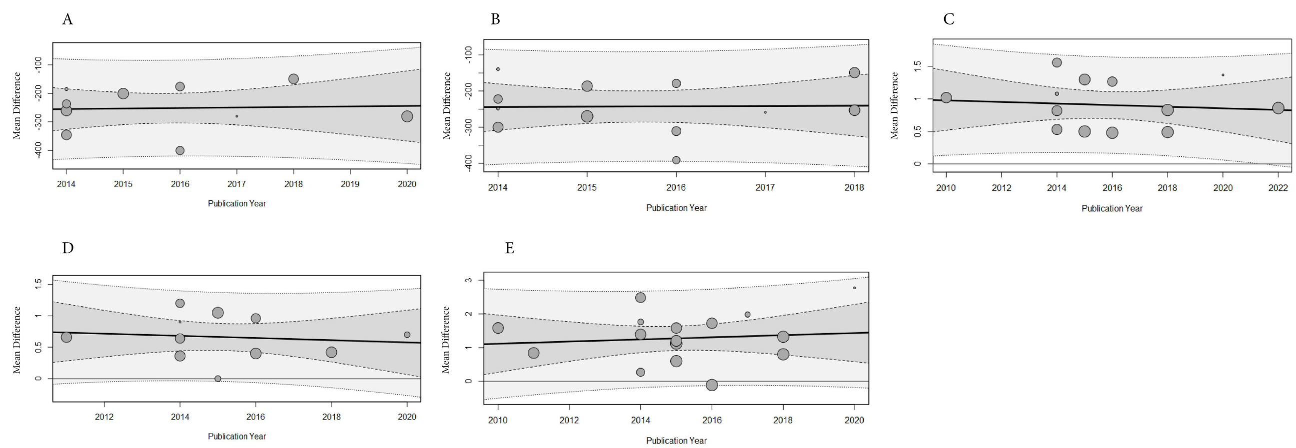

Figure 17 Bubble plots of meta-regression for the effect of publication year on ARTavg, ARTmax, PPIavg, PPImin and PPImax (**A-E** respectively).

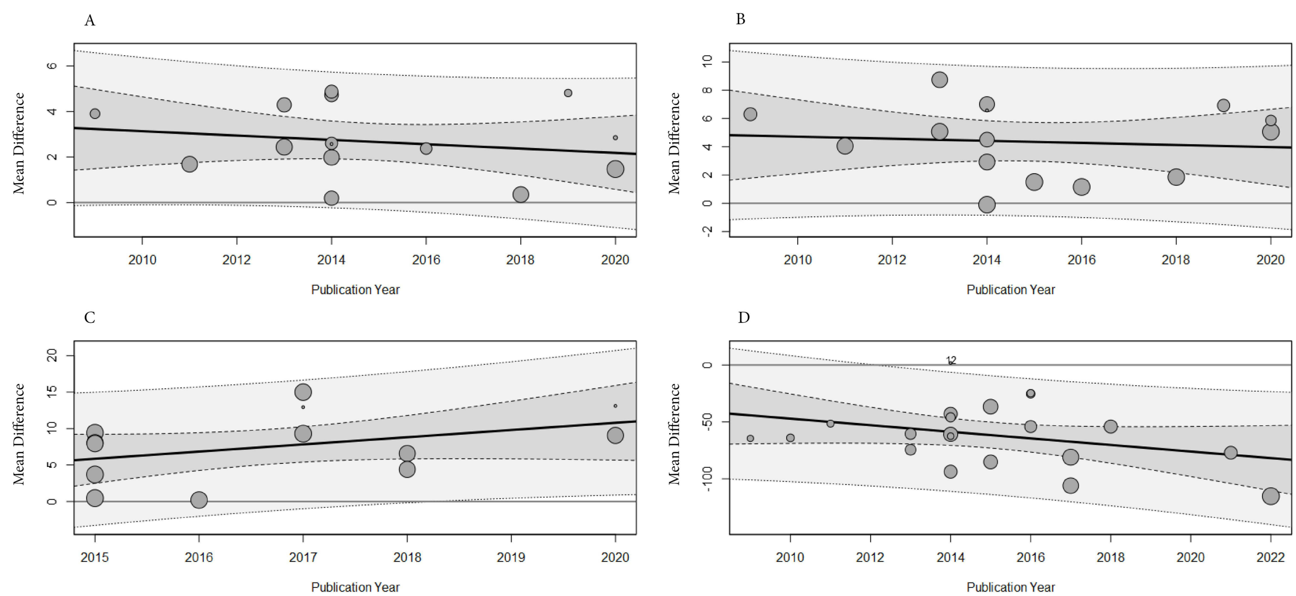

Figure 18 Bubble plots of meta-regression for the effect of publication year on K1, K2, Kmax and CCT (**A-D** respectively.

parameters was stable suggesting that the results were not heavily influenced by any single study or group of studies. Secondly, the review study focused primarily on keratometric, pachymetric and pachymetric progression indices, and other factors related to keratoconus were not explored. Future review studies should consider other elements used in diagnosing KC.

Conclusion

The Pentacam Scheimpflug-derived keratometric, pachymetric, and pachymetric progression indices are good predictors in discriminating KC from normal eyes. The findings of this review study have important implications for the diagnosis and management of keratoconus. By incorporating these indices into the diagnostic process, healthcare professionals can improve the accuracy of their assessments and provide personalised treatment plans.

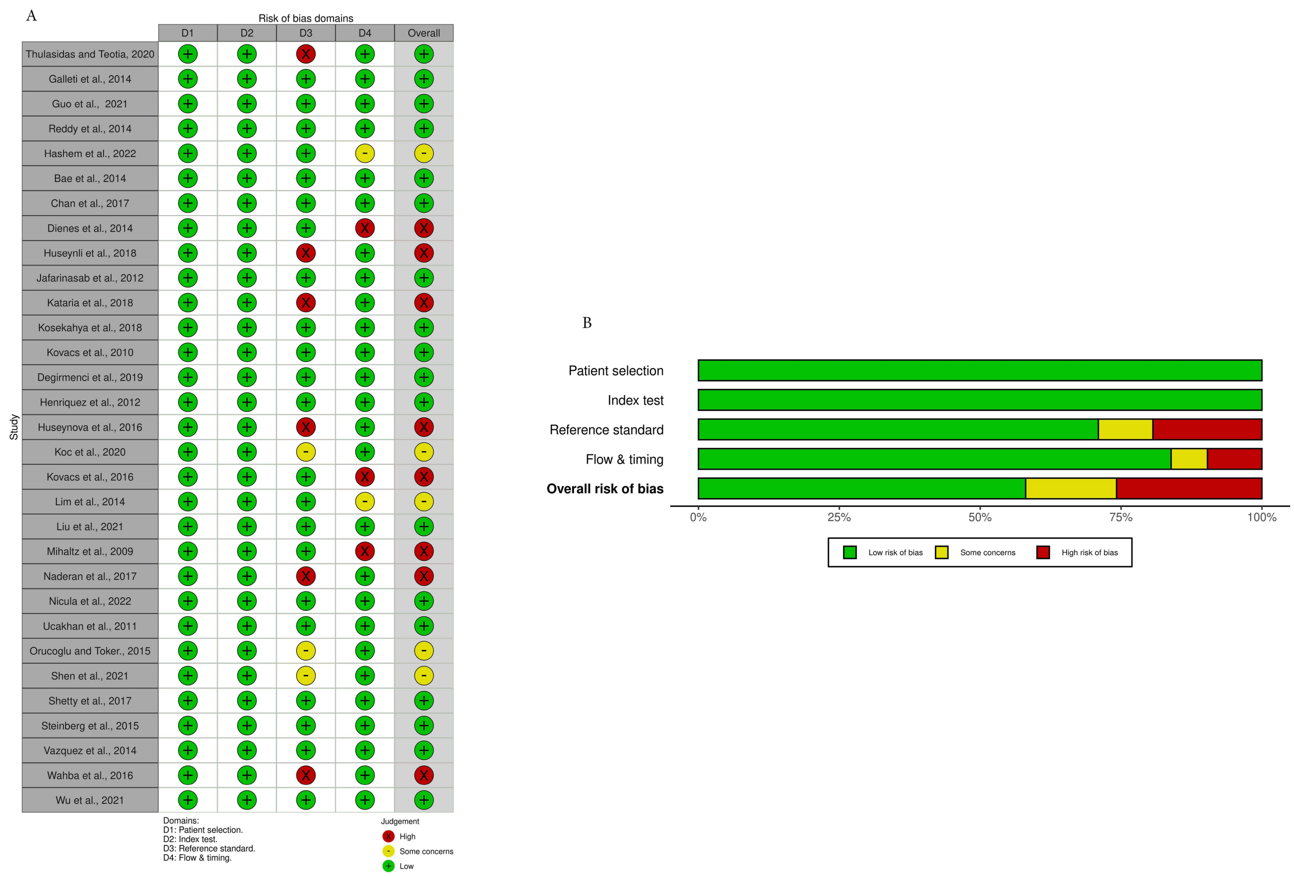

Figure 19 Traffic Light and Weighted Bar Plot for Risk of Bias Assessment using QUADAS-2 (**A** and **B** respectively).

Disclosure

The authors report no conflicts of interest in this work.

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