Growth Rate of Geographic Atrophy Secondary to Age-Related Macular Degeneration: A Meta-Analysis of Natural History Studies and Implications for Designing Future Trials

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Keywords

Geographic atrophy · Growth rate · Natural history · Sample size · Clinical trial

Abstract

Introduction: There is no effective treatment for geographic atrophy (GA). To help design future GA treatment trials, we conducted a meta-analysis for GA growth rate and its variability in natural history studies. **Methods:** Literatures were searched up to April 30, 2020. Data were extracted independently by 2 authors and analyzed using random-effects models. **Results:** The pooled mean GA growth rate was 1.66 mm²/year (SD = 1.27 mm²/year, $I^2 = 97.0\%$, $p < 0.001$) from 23 studies (3,078 patients) reported with growth rate in mm²/year and 0.33 mm/year (SD = 0.17 mm/year, $I^2 = 83.0\%$, $p < 0.001$) from 12 studies (1,808 patients) reported with growth rate in mm/year. Larger mean baseline GA area in mm² was associated with larger mean growth rate in both mm²/year and mm/year ($p < 0.001$). The sample size at 85% power for detecting 15% reduction in growth rate in a 2-arm GA trial is 464 and 209 patients per arm, respectively, for using mm²/year and mm/year as the primary outcome. **Discussion/Conclusion:** GA natural history studies had a pooled mean (SD) GA growth rate of 1.66 (1.27) mm²/year or 0.33 (0.17) mm/year. Because GA growth rate using mm/year re-

quires smaller sample size than using mm²/year, GA growth rate in mm/year is recommended as the primary outcome measure for future GA trials.

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Introduction

Age-related macular degeneration (AMD) is the leading cause of blindness among the elderly in Western countries and is the third leading cause of blindness in the world affecting approximately 5 million globally [1, 2]. Neovascular AMD and geographic atrophy (GA) are 2 forms of advanced AMD with GA accounting for approximately 20% of legal blindness in the USA [3]. While anti-VEGF drugs provide effective treatment for neovascular AMD, there is no approved or effective treatment for GA, in spite that many GA clinical trials have been completed or are ongoing to find a viable treatment for preventing the onset of GA or for slowing down the growth of existing GA [4]. Our previous review of GA treatment trials registered in ClinicalTrials.gov found that 71% of phase 3 GA trials used GA growth rate as the primary outcome measure [4]. Well-designed GA trials require sufficient sample size to provide good power for detecting the treatment effect by comparing the GA growth rate between

the treated arm and the control (placebo or sham) arm. The GA growth rate and its variation from the observational studies or from the control arm of previous GA treatment trials provide important information on the natural GA growth rate and its variation (e.g., standard deviation, SD), which are needed for designing the future GA treatment trials. Thus, we performed a meta-analysis for the GA growth rate and its variation using data from natural history studies (i.e., observational GA growth studies and control arm of GA clinical trials for GA).

Methods

This meta-analysis was conducted following the Meta-analysis of Observational Studies in Epidemiology (MOOSE) statement [5].

Data Sources and Searches

The PubMed, EMBASE, Web of Science, and Cochrane Library databases were searched up to April 30, 2020, using combinations of the following search terms: “geographic atrophy,” “macular atrophy,” “atrophy,” “macular degeneration,” “progression,” “growth,” and “enlargement.” No language restrictions were imposed.

The titles and abstracts of the retrieved articles were reviewed to exclude any clearly irrelevant studies. The full texts of the remaining articles were reviewed to determine whether they contained any information on the growth rate of GA secondary to AMD. To find all relevant studies, the reference lists of systematic reviews on GA [6, 7], as well as the reference lists of each included study, were also comprehensively checked.

Study Selection and Data Extraction

The inclusion criteria for this meta-analysis were as follows: (1) the study patients had GA secondary to AMD, either already present at baseline (prevalent cases) or newly developed during follow-up (incident cases); (2) patients were not treated for GA, which included patients in the observational studies of GA growth or patients in the control arm of GA treatment trials who were treated only with placebo or sham; (3) the GA lesion size was measured at least in 2 time points for determining the GA growth rate using image modalities including color fundus photography (CFP), fundus autofluorescence (FAF), fluorescein angiography, or spectral domain optical coherence tomography (SD-OCT); and (4) the GA growth rate (either in mm^2/year or mm/year) and its variation (either SD or standard error) were reported. We excluded studies of GA in the patients with exudative AMD who were treated with anti-VEGF. We (J.Y.W. and G.S.Y.) independently assessed the eligibility of studies and extracted data from each eligible study, and discrepancies were discussed to reach an agreement.

The study characteristics and results from eligible studies were extracted, including the name of the first author, the name of the study, the year of publication, the sample size (number of eyes and number of patients), the mean baseline GA area, the length of follow-up (in years), the imaging modalities used for measuring GA size, the mean GA growth rate (either in mm^2/year or square root transformed in mm/year) and SD, and the nature of the GA study (observational study or the control arm of the GA treatment trial).

Fig. 1. The flowchart for the selection of 26 GA natural history studies for the meta-analysis of GA growth rate from 3,666 eyes of 3,222 subjects. GA, geographic atrophy.

When a study published multiple papers on the GA growth rate during various lengths of follow-up, the results from the most recent paper with longest follow-up were used. For the GA treatment trials, only the data from the patients in the control group with placebo treatment or sham treatment were extracted. For studies that only reported the median (interquartiles) of GA size, we calculated mean (SD) using a calculator at the link: <http://www.comp.hkbu.edu.hk/~xwan/median2mean.html> [8]. The extracted data used for this meta-analysis are available from the corresponding author upon request. Ethical approval was not required because this is the meta-analysis of the published data.

Statistical Analysis

Open Meta-Analyst software [9] (version for Windows 8, downloaded from http://www.cebm.brown.edu/open_meta/download.html) was used for the statistical analysis. Random-effects models were used to estimate the pooled GA growth rate and its 95% confidence intervals (95% CI). Since some studies reported GA growth in mm^2/year and other studies reported growth rate in mm/year from square root transformation of GA area in mm^2/year , we performed 2 separate meta-analysis for GA growth rate in mm^2/year and in mm/year . We performed the meta-regression analysis to evaluate whether the mean baseline GA lesion size in mm^2 was associated with the mean GA growth rate calculated as mm^2/year and mm/year . The percentage of total variation in the estimate of GA growth rate across included studies due to heterogeneity was assessed using the I^2 statistic [10]. I^2 ranges from 0 to 100% (0% represents no heterogeneity) with higher value representing larger heterogeneity. A sensitivity analysis, removing 1 study one at a time, was performed to assess the robustness of pooled mean GA growth rate. For studies that reported GA growth rates from both FAF and CFP, we used the GA growth rate from FAF for the overall meta-analysis of GA growth rate (as their GA growth rate was very similar).

Table 1. The characteristics of eligible studies of GA growth [12, 15-17, 19, 20, 22, 24, 27, 30-45]

Author (reference)	Type of study	Sample size (subjects/eyes)	Length of follow-up, yrs	Image modality	Mean baseline GA size (SD), mm ²	Mean growth rate (SD), mm ² /year	Mean growth rate (SD), mm/year
Schmitz-Valckenberg et al. [20]	Observational	321/321	1.5	FAF	7.0 (5.3)	1.85 (1.79)	na
Holz et al. [15]	Observational	129/195	1.8	FAF	6.7 (5.1)	1.56 (1.14)	na
Klein et al. [17]	Observational	32/53	5	CFP	4.6 (6.0)	1.27 (1.46)	na
Sunness et al. [33]	Observational	131/212	4.3	CFP	10.4	2.60 (1.85)	na
Mones and Biarnes [27]	Observational	128/128	3.1	FAF	7.31 (6.55)	1.86 (1.12)	0.33 (0.21)
Abdillahi et al. [34]	Observational	97/97	na	FAF	6.09 (5.10)	2.07 (1.01)	na
Yehoshua et al. [35]	Observational	64/86	1.24	SD-OCT	4.59 (4.17)	1.22 (0.88)	0.28 (0.17)
Jeong et al. [16]	Observational	86/86	1	FAF	11.1	1.14 (1.29)	na
Caire et al. [22]	Observational	73/73	2	FAF	na	1.49 (0.77)	na
Batioglu et al. [12]	Observational	35/54	1.5	FAF	3.68 (4.21)	0.65 (0.53)	na
Simader et al. [36]	Observational	24/48	1	FAF	8.88 (8.91)	2.34 (2.50)	na
Nunes et al. [37]	Observational	30/30	1	SD-OCT	5.62	na	0.37 (0.21)
Stetson et al. [38]	Observational	24/24	1	SD-OCT	na	na	0.40 (0.24)
Marsiglia et al. [19]	Observational	92/126	1.7	CFP	2.80 (2.90)	0.80 (0.60)	na
Holekamp et al. [30] (Proxima A)	Observational	295/295	2	FAF	8.1 (4.09)	2.07 (1.41)	0.35 (0.16)
Holekamp et al. [30] (Proxima B)	Observational	201/201	2	FAF	6.4 (3.62)	1.82 (0.96)	0.36 (0.15)
Keenan et al. [24]	Placebo arm	303/419	5	CFP	2.2 (3.2)	1.27 (1.07)	0.27 (0.17)
Jaffe et al. [39]	Placebo arm	260/260	2	FAF	7.6 (4.5)	1.71 (0.99)	na
Mata et al. [40]	Placebo arm	82/82	2	CFP	8.17 (4.50)	2.03 (1.24)	na
Yaspan et al. [41]	Sham arm	40/40	1.5	FAF	8.85 (4.18)	1.92 (1.34)	na
Zhang et al. [42]	Sham arm	12/12	1	CFP	9.84 (8.41)	2.42 (1.95)	na
Yehoshua et al. [43]	Placebo arm	10/10	0.5	SD-OCT	4.6 (3.6)	na	0.37 (0.22)
Holz et al. [31]	Sham arm	626/626	2	FAF	7.75 (3.96)	2.00 (1.10)	0.34 (0.17)
Kuppermann et al. [44]	Sham arm	20/20	2	CFP	9.76 (8.46)	1.92 (1.50)	0.33 (0.30)
Liao et al. [32]	Sham arm	80/80	1.5	FAF	8.2 (4.05)	na	0.35 (0.13)
Kim et al. [45]	Placebo arm	27/37	1.5	FAF	4.8 (3.30)	1.29 (1.20)	0.27 (0.21)

CFP, color fundus photography; FAF, fundus autofluorescence; SD-OCT, spectral domain optical coherence tomography; na, not available; SD, standard deviation; GA, geographic atrophy.

Fig. 2. Forest-tree plot for the GA growth rate in mm²/year that included 23 studies of 3,471 eyes from 3,078 patients. GA, geographic atrophy.

Because the sample size calculation for the future GA treatment trial requires the information on the SD of GA growth rate, we calculated the pooled SD of GA growth rate in both mm²/year and mm/year from all eligible GA studies using the following formula:

$$SD_{\text{pooled}} = \sqrt{\frac{(n_1 - 1)s_1^2 + (n_2 - 1)s_2^2 + (n_3 - 1)s_3^2 + L + (n_k - 1)s_k^2}{n_1 + n_2 + n_3 + L + n_k - k}}$$

where $n_1, n_2, \dots, n_k$ are the number of subjects from each of k studies and $s_1, s_2, \dots, s_k$ is the SD of GA growth rate from k studies.

Based on the estimated SD for the GA growth rate in both mm²/year and mm/year, we calculated the sample size for 2-arm GA treatment trials (1 treatment arm and 1 control arm) using GA growth rate of either mm²/year or mm/year as the primary outcome measure. The sample size calculation assumed the following: (1) 1 study eye per patient; (2) 2-sample t test for comparing GA growth rate between 2 arms; (3) type I error rate of 0.05; and (4) 85% power for detecting various magnitude reduction in mean GA growth rate (ranging from 10 to 30% reduction of pooled mean growth rate).

Results

The literature search identified 3,222 subjects (3,666 eyes) from 26 GA natural history studies that reported the mean GA growth rate (either in mm²/year or mm/year or both) and provided sufficient information for meta-analysis (Fig. 1). The characteristics of these 26 studies are summarized in Table 1.

GA Growth Rate in mm²/year

A total of 23 studies (3,471 eyes from 3,078 subjects) reported GA growth rate in mm²/year, including 1,975 eyes from observational studies and 1,496 eyes from the control arm of GA treatment trials. A total of 7 studies used CFP, 14 studies used FAF, 1 study used both CFP and FAF, and 1 study used SD-OCT (Table 1). Across these 23 studies, the mean baseline GA area ranges from 2.2 to 11.1 mm² and the mean GA growth rate ranges from 0.65 to 2.60 mm²/year during the length of follow-up ranging from 1 to 5 years.

Fig. 3. Scatter plot for mean GA growth rate (mm^2/year) with mean baseline GA area (in mm^2) with linear regression line from meta-regression. Mean GA growth rate is associated with mean baseline GA area ($p < 0.001$), with linear equation of (mean growth rate [mm^2/year] = $0.702 + 0.142 \times \text{mean baseline GA area } [\text{mm}^2]$). GA, geographic atrophy.

Fig. 4. Sensitivity analysis for mean GA growth rate in mm^2/year by removing 1 study at a time. It demonstrates the consistency of the pooled estimate of mean GA growth rate. GA, geographic atrophy.

The pooled overall mean GA growth rate is $1.66 \text{ mm}^2/\text{year}$ (pooled SD = $1.27 \text{ mm}^2/\text{year}$, 95% CI: $1.44\text{--}1.89 \text{ mm}^2/\text{year}$, Fig. 2). There was substantial heterogeneity of GA growth rate across studies ($I^2 = 97.0\%$, $p < 0.001$). In meta-regression analysis, larger baseline GA area (in

mm^2) was significantly associated with larger mean GA growth rate (slope = $0.142 \text{ mm}^2/\text{year}$, $p < 0.001$) (Fig. 3). For every mm^2 increase in mean baseline GA area, the mean GA growth rate increased by $0.14 \text{ mm}^2/\text{year}$ (95% CI: $0.08\text{--}0.21 \text{ mm}^2/\text{year}$).

Fig. 5. Forest-tree plot for the mean GA growth rate in mm/year that included 12 studies of 1,956 eyes from 1,808 subjects. GA, geographic atrophy.

Fig. 6. Scatter plot for mean GA growth rate (mm/year) with mean baseline GA area (mm²) with linear regression line from meta-regression. Mean GA growth rate (mm/year) is associated with mean baseline GA area ($p < 0.0001$), with linear equation of (mean growth rate [mm/year] = $0.247 + 0.013 \times \text{mean baseline GA area [mm}^2\text{]}$). GA, geographic atrophy.

To evaluate the robustness of our pooled estimate of a mean GA growth rate of 1.66 mm²/year, we performed a sensitivity analysis by removing 1 study at a time and recalculating the GA growth rate. In this sensitivity analyses, the pooled mean growth rate ranged from 1.62 to 1.71 mm²/year (Fig. 4), indicating the robustness of our estimate of the mean GA growth rate.

Estimate of GA Growth Rate in mm/year

A total of 12 studies (1,956 eyes, 1,808 subjects) reported GA growth rate in mm/year, including 904 eyes from observational studies and 1,052 eyes from the control arm of GA treatment trials. A total of 2 studies used CFP, 6 studies used FAF, and 4 studies used SD-OCT (Table 1). Across these 12 eligible studies, the mean baseline

GA area ranged from 2.2 to 9.8 mm², the mean GA growth rate ranged from 0.27 to 0.40 mm/year, and the mean follow-up length ranged from 0.5 to 5 years.

The pooled mean GA growth rate was 0.33 mm/year (pooled SD = 0.17 mm/year, 95% CI: 0.31–0.35 mm/year) with substantial heterogeneity across studies ($I^2 = 83.0\%$, $p < 0.001$) (Fig. 5). The mean baseline GA area in mm² was significantly associated with GA growth rate in mm/year (slope = 0.013 mm/year, $p < 0.001$) (Fig. 6). For every mm² increase in mean baseline GA area, the mean GA growth rate increased by 0.013 mm/year (95% CI: 0.008–0.017 mm²/year). In the sensitivity analysis, the pooled mean GA growth rate ranged from 0.326 to 0.338 mm/year (Fig. 7), indicating the very robustness of estimate of the GA growth rate in mm/year.

Fig. 7. Sensitivity analysis for GA growth rate in mm/year by removing 1 study at a time. It demonstrates the consistency of the pooled estimate of mean GA growth rate. GA, geographic atrophy.

Table 2. Sample size required for the GA treatment trial based on pooled SD of GA growth rate (in mm²/year or mm/year) under various assumption reduction in GA growth rate*

GA growth rate, mm ² /year			GA growth rate, mm/year		
growth rate reduction in mm ² /year	% of reduction in mean GA growth rate from a pooled mean of 1.66 mm ² /year, %	sample size in each group*	growth rate reduction in mm/year	% of reduction in mean GA growth rate from a pooled mean of 0.33 mm/year, %	sample size in each group*
0.17	10	1,003	0.033	10	478
0.25	15	464	0.050	15	209
0.33	20	267	0.066	20	120
0.41	25	173	0.083	25	76
0.50	30	117	0.099	30	54

SD, standard deviation; GA, geographic atrophy. * Assuming type 1 error rate of 5%, statistical power of 85%, SD of 1.27 mm²/year and 0.17 mm/year for GA growth rate, and 2-sample *t* test for comparing GA growth rate between the treated arm and control arm, with 1 eye per patient included in the GA treatment trial.

Sample Size for Future GA Trial Based on Pooled SD of GA Growth Rate

Based on the pooled mean and SD of GA growth rate (1.66 [1.27] mm²/year or 0.33 [0.17] mm/year), we calculated the sample size (1 study eye per patient) for future 2-arm GA treatment trials (1 treatment arm and 1 control arm) using GA growth rate of either mm²/year or mm/year as the primary outcome measure. The sample size provided

in Table 2 assumed 85% power for detecting various magnitude reduction in mean GA growth rate (ranging from 10 to 30% reduction of pooled mean growth rate) in the GA treatment arm compared to the control arm. With the same % reduction in growth rate, the required sample size using GA growth rate in mm/year as the primary outcome measure was much smaller than that of using GA growth rate in mm²/year as the primary outcome measure. For exam-

ple, the required sample size for detecting 15% reduction in growth rate was 464 patients per group for using GA growth in mm²/year and only 209 patients per group for using GA growth in mm/year (Table 2).

Discussion

This study performed comprehensive meta-analysis for the GA growth rate and its variation from natural history studies of GA growth. Our meta-analysis found that the pooled mean GA growth rate (SD) was 1.66 (1.27) mm²/year or 0.33 (0.17) mm/year. We also found that mean GA growth rate calculated in either mm²/year or mm/year was significantly associated with mean baseline GA area in mm², with smaller baseline GA area having lower GA growth rate. This meta-analysis provides key information on the natural GA growth rate and its variation that are needed for designing the future GA treatment trials.

The change of total GA area over time is the most frequently used and accepted endpoint for assessing the efficacy of therapeutic intervention in GA clinical trials [4, 11]. Our previous systematic review of registered GA treatment trials in ClinicalTrials.gov found that GA growth rate was the most common outcome measure, used as a primary outcome in 71% of phase 3 trials and as a secondary outcome in 31% of phase 2 trials. In designing GA treatment trials, the natural GA growth rate and its variation from eyes without any intervention are needed for sample size determination. Our comprehensive meta-analysis provides this needed information for future GA treatment trials that use GA growth rate in either mm²/year or mm/year as the primary outcome measure.

Previous studies consistently showed that eyes with larger baseline GA lesion size had faster GA growth [12–21]. Consistent with these studies, this meta-analysis also found that studies with larger mean baseline GA area reported higher mean GA growth rate. For every mm² increase in the mean baseline GA area, the mean GA growth rate increased by 0.142 mm²/year or 0.013 mm/year. Thus, the baseline GA area should be considered in designing the GA treatment trials. Besides baseline GA size, previous studies also found that several other clinical and genetic factors were associated with faster GA growth, including the noncentrality, multifocality, bilateral GA, current smoking, ARMS2 risk genotype, C3 nonrisk genotype, and APOE nonrisk genotypes [15, 17, 22–26]. These risk factors for faster

GA growth should be considered in the design and analysis for GA treatment trials.

Besides the meta-analysis for the mean GA growth rate, we also calculated the pooled SD for GA growth rate in both mm²/year and mm/year to help design the future GA treatment trials because SD is a key parameter needed for sample size determination. Using the pooled SD and the natural mean GA growth rate, we calculated the sample size for detecting various treatment effect (10–30% reduction of the mean GA growth rate in either mm²/year or mm/year compared to the control arm). Interestingly, for detecting the same % of reduction in GA growth rate, we found that sample size using GA growth rate in mm/year was much smaller than using growth rate in mm²/year. For example, the required sample size for detecting 15% reduction in mean GA growth rate is 464 patients per group for using mm²/year as the primary outcome and is only 209 patients per group for using mm/year. This finding suggests that future GA treatment trials may consider using GA growth rate in mm/year rather than mm²/year as the primary outcome measure.

Besides the advantage of reduced sample size, using GA growth rate in mm/year as the primary outcome may minimize the impact of baseline GA size on the GA growth rate because previous studies found that square root transformation decreased test-retest variability and the dependence of GA growth rate on baseline lesion size [12–21] although a recent study suggested that square root transformation did not completely eliminate the dependence of GA growth rate on the baseline size [27]. Use of the square root transformation assumed that the leading edge of a single GA lesion expands at a relatively constant rate; that is, its radius increases over time in a relatively linear fashion. Because of the relationship between radius and area (πr^2), the GA area in mm² would be associated with an exponential increase over time. Hence, comparison using change in area over time would artefactually suggest that larger GA lesions grow much faster than smaller lesions. However, this artifact can be minimized (may not be completely eliminated) by using change over time in the square root of area, so that GA growth rate can be considered at the level of increase in radius rather than area. In this way, fair comparison might be made between treatment groups for the growth rate of various baseline GA size. However, using the GA growth rate in mm/year as the primary outcome measure has limitation in that the interpretation of GA growth rate in mm/year is less straightforward than in mm²/year because the GA size was measured in mm², and the square root transformation assumes the GA lesion is circular and unifocal, which may not be the case for most

GA lesions. Thus, the dependence of GA growth rate on baseline GA size may still be existent even after square root transformation as shown in our meta-analysis.

If validated in future studies, our finding of the dependence of GA growth rate (in mm²/year or mm/year) on the baseline GA size (in mm²) has several important implications on the design and analysis of the future GA treatment trials. First, the trial enrollment criterion should consider baseline GA size. Because larger baseline GA size is associated with larger GA growth rate, enrolling eyes with larger GA size may increase the opportunity of observing treatment effect over a shorter follow-up time period. Second, baseline GA size should be made comparable between treatment groups, such as through stratified randomization by baseline GA size. Third, the statistical modeling of GA growth needs to incorporate the baseline GA size. For the GA treatment trials with long-term follow-up (e.g., >2 years of follow-up), the GA size increases substantially over years which implies the GA growth rate also increases over time. Thus, the assumption of constant GA growth rate may not be held. The nonlinear GA growth model may be needed to allow for the increasing GA growth rate over time.

Different from the previous systematic review and meta-analysis of GA growth [7, 28, 29], this study is unique in that our meta-analysis is restricted to natural history eyes (from observational studies or control arm of GA trials) and is the most comprehensive meta-analysis to date that evaluated the overall GA growth rate and its variation calculated in both mm²/year and mm/year. Our meta-analysis included several recently published large GA studies including the Proxima natural history study of 496 eyes [30], 2 phase 3 trials (Chroma and Spectri) involving a total of 626 eyes in the control arm [31], the AREDS2 study involving 419 eyes in the placebo group [24], and the APL-2 trial with 80 eyes in the control arm [32]. Our comprehensive meta-analysis was based on 26 eligible studies (involving 3,666 eyes of 3,222 patients) with the mean baseline GA area ranging from 2.2 to 11.1

mm², representing wide range of eyes with GA. Thus, our study provides the most robust estimate of GA growth rate and its variation, which will be useful for designing the future GA treatment trials.

In conclusion, our comprehensive meta-analysis provided a pooled mean (SD) GA growth rate of 1.66 (1.27) mm²/year and 0.33 (0.17) mm/year. The mean growth rate calculated in either mm²/year or mm/year was dependent on their mean baseline GA area. Using GA growth rate in mm/year may have the advantage of smaller sample size than using growth rate in mm²/year. Our meta-analysis provides key information on the natural growth of GA for designing the future GA treatment trials.

Statement of Ethics

This research complies with the guidelines for human studies in accordance with the World Medical Association Declaration of Helsinki. Ethical approval was not required because this is the meta-analysis of the published data.

Conflict of Interest Statement

None of the authors has any financial or nonfinancial interest.

Funding Sources

The authors did not receive any funding.

Author Contributions

Dr. Jianyong Wang wrote the main manuscript text and Dr. Gui-shuang Ying performed the statistical analysis, prepared all the tables and figures for the paper, and reviewed and approved the manuscript.

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