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Original Article

Mediterranean diet as a modifiable risk factor for age-related macular degeneration: A systematic review and meta-analysis

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Abstract

Objectives: Age-related macular degeneration (AMD) is a chronic and degenerative disease of the retina that leads to irreversible blindness. There is no proven effective treatment for early AMD and advanced AMD. Mediterranean diet (MD) has been linked to reducing the risk or delaying the progression of AMD. Therefore, in this study, we aim to investigate the potential of MD as a modifiable risk factor for AMD. **Materials and Methods:** A systematic search was performed in three databases: PubMed, EBSCO host, and Proquest. We search for studies that determine the association of MD in AMD. Then, we pooled the data for meta-analysis. **Results:** Eight studies were included in our systematic review. Seven studies were included for meta-analysis. Subjects with medium–high (hazard ratio [HR] 0.82; 95% confidence interval [CI]: 0.75–0.90) adherence to the MD showed a reduced risk of developing AMD. Moreover, medium adherence AMD shows a significant and inverse relationship with the progression to advanced AMD (HR: 0.87; 95% CI: 0.81–0.93). Although it is still inconsistent, the reduction appears stronger for geographic atrophy than for neovascular AMD. **Conclusion:** Adhering to the MD, particularly at a medium to high level, appears to confer a protective effect against AMD. The sub-analysis demonstrates even that there is a protective effect associated with moderate adherence against advanced AMD. The presence of considerable heterogeneity within the results warrants cautious interpretation. Further research is needed to enhance our understanding.

Keywords: *Age-related macular degeneration, Dietary pattern, Mediterranean diet, Risk factor*

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Introduction

Age-related macular degeneration (AMD) is the primary cause of irreversible vision loss prevalent in developed countries, particularly among individuals aged 60 years and above [1]. Approximately 170 million people globally have been estimated to be affected by AMD. This number is expected to rise to 196 million in 2020, and 288 million in 2040 [2,3]. AMD is a chronic and degenerative disease of the central retina [4]. It is classified into early, intermediate, and late stages [5]. This late-onset degenerative disease drives patients to lose central vision gradually and significantly decreases their quality of life. The AMD event increases with age and, therefore, increases the burden on healthcare resources of industrialized countries [6].

The current pharmacological approach for treating AMD is anti-vascular endothelial factor growth agents, which are limited to slowing down the progression of neovascular AMD (NvAMD) [7,8]. There is no established effective treatment for early AMD and late AMD except for NvAMD [6].

For this reason, there has been increasing interest in identifying modifiable risk factors to prevent or slow down AMD progression [6]. Aging, genetics, and environmental factors, such as dietary factors, are other risk factors for AMD [5]. There are plenty of studies that have investigated the association between dietary intake components, food groups, antioxidants, and vitamin or mineral supplementation and the progression of AMD [5,8]. The age-related eye disease

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study (AREDS) followed by the AREDS 2 are two major studies [9-11].

Numerous studies have concentrated on investigating a dietary pattern rather than focusing on single nutrients or food. This may be more beneficial to interpret due to their minimal confounding by individual dietary factors and apprehend the synergistic effect of individual dietary behavior [12-14].

Adherence to the Mediterranean diet (MD) has been associated with decreased mortality and morbidity from chronic degenerative disease [15]. MD is inspired by the traditional eating habits of people in countries such as Greece, Spain, and Italy. It is characterized by a high consumption of fruits, vegetables, legumes, cereals, fish, and olive oil, a low-to-moderate consumption of dairy products, a low consumption of meat, very low consumption of red meat, and regular but moderate consumption of alcohol, namely wine [7,12]. This has been associated with decreasing incidence rates of cardiovascular disease [16], cognitive deterioration, dementia [17], and age-related ocular diseases including AMD [12].

Thus, in this study, we aim to investigate the potential correlations between adherence to MD as a modifiable risk factor of AMD.

Materials and methods

Data sources and search strategy

A systematic review and meta-analysis were conducted. Literature was retrieved from three search engines: PubMed, EBSCO host, and Proquest. We explored articles that reported the association of MD patterns with AMD. The following terms and their derivatives were used in the search strategy: ("Mediterranean diet" [Mesh] OR "leafy vegetable" OR "vegetarian diet" OR "dietary pattern") AND "Age-related macular degeneration" [Mesh] OR "macular degeneration"). Searches were not restricted by date but by the English language.

Eligibility criteria

Full-text articles were reviewed and were included on the foundation of predefined criteria based on the population, intervention/exposure, comparator, outcome approach as follows: (1) Population: Participants at risk of AMD or having AMD; (2) intervention: Adherence to the MD or MD intervention; (3) comparator: Participants with low adherence to MD; (4) outcome: AMD event or progression of AMD. Full text must be written in English. MD intervention must be examined as a whole dietary pattern instead of single nutrients or food components. The adherence of MD needed to be measured by standardized and validated tools. The AMD needed to be identified based on the medical records of clinical ophthalmic examinations. Exclusion criteria were: (1) Case report, literature reviews, and systematic review; (2) animal or *in vitro* studies; (3) Any irrelevant studies.

Study selection and data extraction

Mendeley™ was used to remove duplicates and manage the bibliography of the selected literature. Data extraction tables were created to gather the required data for the review.

Risk of bias

The quality of studies was assessed using the Newcastle–Ottawa Scale (NOS) for cohort and case-control studies. The modified NOS was used for assessing the cross-sectional study.

Statistical analysis

Among eight studies, we included three studies in statistical analysis. Hazard Ratios (HRs) with 95% confidence intervals (CIs) for all categories of exposure were extracted for the analysis. Random-effects models were used to calculate pooled HRs with 95% CIs for the highest compared with the lowest category of exposure (adherence to MD). Heterogeneity was assessed by I^2 statistics. The I^2 values ≤25%, ≤%, ≤75, and >75% refer to no, little, moderate, and significant heterogeneity, respectively. The CI (95% CI) and P value were presented. $P < 0.05$ was considered statistically significant. We also conducted a subgroup analysis to calculate pooled HR for the medium compared with the lowest category of MD score. All analyses were performed with Review Manager (RevMan) version 5.2 Publisher: Treasure Island (FL): StatPearls Publishing, United States.

Results

Study selection

A total of 610 abstracts were retrieved from the search engines. After eliminating 32 duplicate articles, there were 578 articles left for abstract screening. There were 530 articles excluded as they were not conducted in humans, were irrelevant studies, and were not reported in English. Therefore, 48 articles were included for full-text screening. Ten were excluded because full articles were not available and 30 studies were excluded due to the type of studies (case reports, literature reviews, and systematic reviews) and the adherence to MD not measured by standardized tools. Therefore, the remaining eight studies were included in the systematic review. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram is shown in Figure 1. Quality assessment was performed using NOS.

Characteristics of the studies

A total of eight studies were included in our systematic review: five cohort studies, one cross-sectional study, and two case–control study. It involves a total population of 26,343 subjects included in this study. The characteristics of the eight studies are presented in Table 1.

Dietary habits assessment is made using a semiquantitative food frequency questionnaire. The adherence to MD was evaluated using Mediterranean Score (Medi score) [18,22], and Alternate Mediterranean Diet score (aMedi score) [4].

The ascertainment of AMD was conducted based on ophthalmological examinations and color fundus photography in all studies. The grading systems to evaluate AMD were various and stated in Table 1.

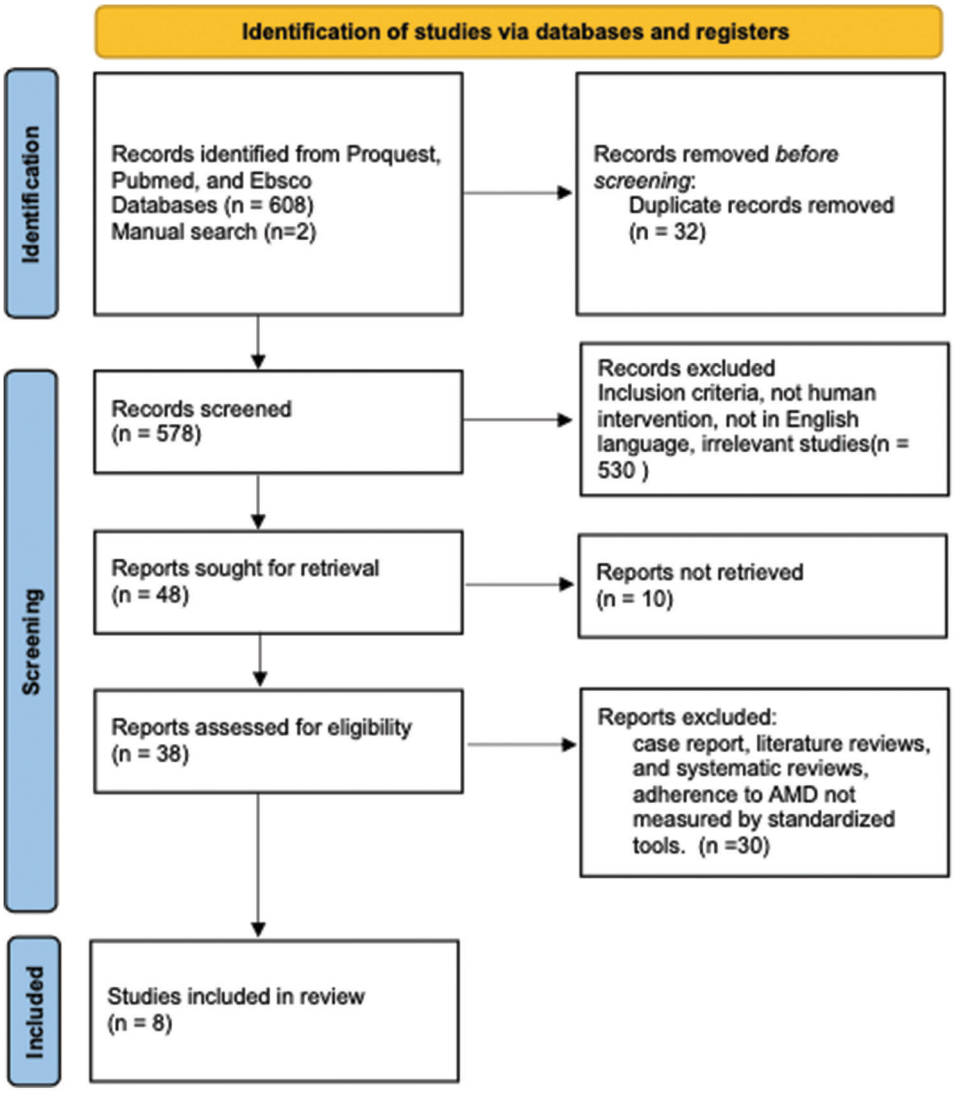

Figure 1: Flow diagram of screening studies based on Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020. AMD: Age-related macular degeneration

Risk of bias of included studies

The NOS assessment tool for cohort and cross-sectional studies employs a rating system ranging from 0 to 9 stars. Higher scores represent higher study quality. All studies that were included exhibited high quality, with minimal risk of bias. The quality of each study can be found in the Tables 1-3 and Figures 1, 2.

Risk factors of age-related macular degeneration

Genetics [4,5,19], older age [4,19], higher body mass index (BMI) [4], lower education [4], advanced AMD in the fellow eye [4], and history of smoking [4,19] are associated with the development of AMD.

On the other hand, physical activity [21], intake of vegetables [4,20], fruits [2,23], fish [4,5], caffeine [7], fibers [7], beta carotene [7], Vitamin C [7], Vitamin E [7], nuts [5,20], and higher monounsaturated fatty acid (MUFA)/ saturated fatty acid (SFA) seem protective against AMD [5].

The adherence to MD also appears to protect against the development of AMD. Raimundo *et al*. found that a higher Medi score seems to be associated with decreased prevalence of AMD in the Portuguese population (OR 0.63; 95% CI: 0.41–0.98, *P*: 0.043) [7]. Nunes *et al*. conducted a study within the same population, and their finding indicates that a higher adherence to Medi score significantly reduced the risk of AMD for 67.2% of participants without AMD and 32.8% of participants with AMD (OR 0.73; 95% CI: 0.58–0.93) [20]. However, the authors did not specify the stage of AMD that is associated with the consumption of MD.

Progression of advanced age-related macular degeneration

Higher adherence to MD was associated with a 26% [4], 41% [18], and 50.5% [7] lower risk of progression to advanced AMD and 50% [14] to nvAMD.

Three cohort studies demonstrated that higher adherence to MD (higher aMedi/Medi score) significantly reduced the risk of progression to advanced AMD [4,5,18].

Nevertheless, there were inconsistencies in the findings regarding the type of advanced AMD that was impacted.

Table 1: Characteristics of included studies

Author (year); Country	Study design	Study population	Age at recruitment (years)	Sample size (subjects)	Follow-up (years)	MD assessment; range	Cofounder adjusted for	AMD definition	Outcome of interest	NOS
Hogg *et al*. (2017); Europe [14]	Cross-sectional	7 study centers across Europe	≥65	5040		Medi score; ≤4 (low), 5, 6, >6 (high)	Age, sex, country, education, smoking, drinking, self-reported history of cardiovascular disease, aspirin consumption, and diabetes	International classification system for ARM	Presence of early AMD and advanced AMD	8
Merle *et al*. (2015); US [4]	Prospective cohort	AREDS subjects	55–80	2525	8.7	aMedi score; 0–3 (low), 4–5 (medium), 6–9 (high)	Age, sex, AMD grade at baseline for both eyes, AREDS treatment, and TEI	CARMS system	Presence of advanced AMD	8
Raimundo *et al*. (2018); Portugal [7]	Case-control	Coimbra eye study participants	≥55	883		Medi score; 0–3 (low), 4–5 (medium), 6–9 (high)	Age, gender, and calories consumptions	International classification for ARM	Presence of AMD	7
Merle *et al*. (2019); Europe [18]	Prospective cohort	RS-I and ALIENOR study	RS-I ≥55; ALIENOR ≥73	4996	RS-I (9.9) ALIENOR (4.1)	Medi score; 0–3 (low), 4–5 (medium), 6–9 (high)	Gender, TEI, AMD grade at baseline, education, BMI, smoking, supplement use of multivitamins or minerals, diabetes, and hypercholesterolemia	Wisconsin age-related system and International classification system for ARM	Presence of advanced AMD	9
Merle *et al*. (2020); US [19]	Prospective cohort	AREDS subjects	55–80	1838	10.2	aMedi score; 0–3 (low), 4–9 (medium-high)	Age, sex, education, smoking, BMI, AREDS treatment, multivitamin supplement use, TEI, genetic variants, and maximum drusen size category at baseline in each eye	Drusen size	Progression of drusen (two grades)	9
Keenan *et al*. (2020); US [5]	Retrospective cohort	AREDS and AREDS 2 participants	50–85	7756	10.2	aMedi score; 0–3 (tertile 1), 4–6 (tertile 2), 7–9 (tertile 3)	Age, sex, smoking status, total calorie intake, BMI	Wisconsin age-related maculopathy grading system	Presence of advanced AMD	8
Nunes *et al*. (2018) [20]	Case-control	Coimbra eye study participants	≥55	1992		Medi score; 0–3 (low), 4–5 (medium), 6–9 (high)	Age, sex, BMI, abdominal perimeter, physical activity, smoking status, diabetes, and hypertension	Rotterdam classification	Presence of AMD	7
Mares *et al*. (2011) [21]	Prospective cohort	CAREDS participants	50–79	1313	6.3	aMedi score 0–1 (category 1), 2–3 (category 2), 4–5 (category 3), 6–9 (category 4)	Age, smoking, history of diabetes, family history of AMD, iris pigment color, history of cardiovascular disease, and hormonal therapy	Wisconsin Age-related system and International classification system for ARM	Presence of early AMD	9

ALIENOR: Antioxidants, Lipides Essentiels, Nutrition et Maladies Oculaires study, AMD: Age-related macular degeneration, Medi score: Mediterranean diet score, aMedi score: Alternated Medi score, AREDS/AREDS2: Age-related eye disease study, ARM/ARM1/ARM2: Age-related maculopathy, BMI: Body mass index, CAREDS: Carotenoids in age-related eye disease study, CARMS: Clinical age-related maculopathy staging, MD: Mediterranean diet, RS-I: Rotterdam study I, TEI: Total energy intake, NOS: Newcastle–Ottawa Scale

Two studies demonstrated that the association between higher adherence to MD is a greater to reduce the risk of GA than nvAMD [5,18] [Table 2]. On the other hand, a study from Hogg *et al*. exhibited a higher Medi score significantly reduced the odds of nvAMD compared with the lowest Medi score [14] [Table 2].

Early and intermediate stages of age-related macular degeneration

For the early stage of AMD (grade 1–3), there was no significant relationship with MD adherence (OR 0.94; 95% CI 0.85–1.03; *P*: 0.4) in Hogg *et al*.'s study [14]. However, Mares *et al*. discovered that category 4 of the aMedi score exhibited a

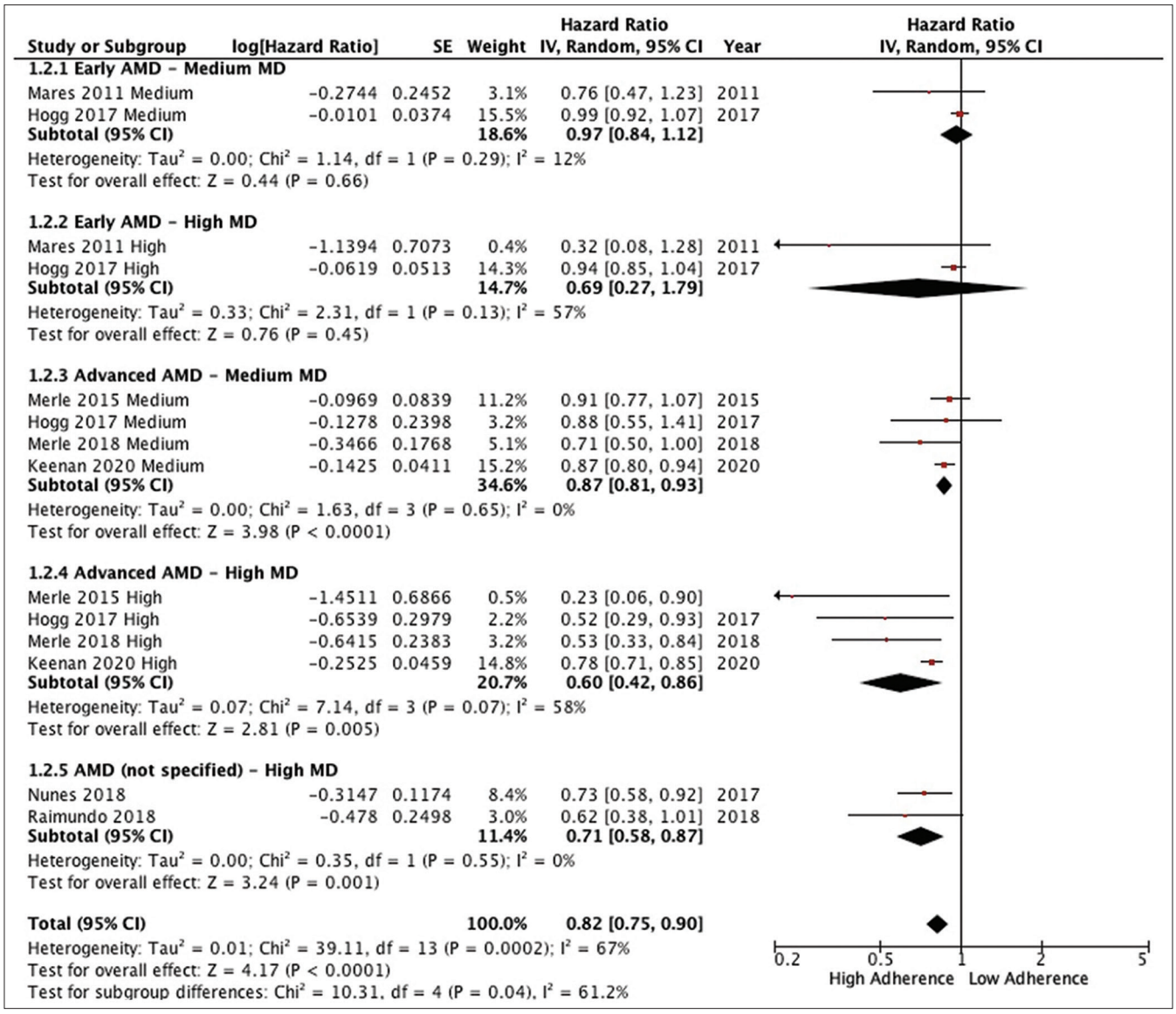

Figure 2: Forest plots of meta-analysis comparing medium adherence to Mediterranean diet (MD) (4-5) compared to the lowest (1-3) and highest adherence to MD (6-9) compared to the lowest for various stages of age-related macular degeneration. MD: Mediterranean diet, AMD: Age-related macular degeneration, CI: Confidence interval

protective effect against early AMD compared to category 1 within the CAREDS population (OR 0.34; 95% CI: 0.08–0.98) [21].

Merle *et al.* demonstrated a medium–high aMedi score compared to a low aMedi score tended to lower the risk for two-step drusen progression (HR: 0.83; 95% CI: 0.68–0.99, $P = 0.049$) [19].

This result was supported by two other studies: Hogg *et al*., which showed higher Medi score had significantly reduced the odds of large drusen by 20% (OR: 0.80; 95% CI: 0.65–0.98, *P*: 0.05) [14], and Keenan *et al*. (HR: 0.83; 95% CI: 0.75–1.01 and HR: 0.79; 95% CI: 0.68–0.93 for tertile 2 and 3, respectively) [5]. However, there was an insignificant result in Hogg *et al*. in the adjusted model.

Meta-analysis

Among eight distinct studies, we pooled the data from seven studies to comprehensively examine the association between adherence to the MD and AMD. Our analysis revealed an overall noteworthy and inverse correlation between adhering to the MD and the likelihood of developing AMD (HR: 0.82; 95% CI: 0.75–0.90). This observation, however, was accompanied by a moderate level of variability among the studies (I^2: 57%; *P*: 0.45).

The moderate adherence to the MD and the early AMD revealed no association (HR: 0.97; 95% CI: 0.84–1.12), with no heterogeneity (I^2: 12%; *P*: 0.66). Similarly, high adherence to MD also shows no association with early AMD (HR: 0.69; 95% CI: 0.27–1.79), with moderate heterogeneity (I^2: 57%; *P*: 0.45).

However, the medium adherence to MD, compared with the lowest adherence level, shows a significant and inverse relationship with the progression to advanced AMD (HR: 0.87; 95% CI: 0.81–0.93), and this outcome exhibited no heterogeneity across the studies (I^2: 0%; $P < 0.0001$). In addition, high adherence to the MD seemed to be protective

Table 2: The outcome for the association between medium and high adherence Mediterranean diet compared to low adherence to Mediterranean diet to the type of advanced age-related macular degeneration [5]

Author	NvAMD	GA
Merle *et al*. (2019) [18]	RS-1: Medium HR: 0.87 (0.51–1.51) and high HR: 1.03 (0.53–1.99); *P*: 0.91 ALIENOR: Medium HR: 0.80 (0.25–2.63) and high HR: 0.75 (0.20–2.91); *P*: 0.65 Combined: Medium HR: 0.78 (0.48–1.27) and high HR: 0.88 (0.49–1.57); *P*: 0.64	RS-1: Medium HR: 0.61 (0.34–1.10) and high HR: 0.41 (0.16–1.03); *P*: 0.046 ALIENOR: Medium HR: 1.08 (0.38–3.06) and high HR: 0.52 (0.13–2.12); *P*: 0.52 Combined: Medium HR: 0.70 (0.42–1.15) and high 0.42 (0.20–0.90); *P*: 0.04
Keenan *et al*. (2020) [5]	AREDS: Tertile 2 HR: 0.86 (0.72–1.02); *P*: 0.08 and tertile 3 HR: 0.81 (0.68–0.98); *P*: 0.03 AREDS 2: Tertile 2 HR: 0.97 (0.83–1.13); *P*: 0.68 and tertile 3 HR: 0.91 (0.77–1.06); *P*: 0.22 Combined: Tertile 2 HR: 0.90 (0.80–1.01); *P*: 0.08 and tertile 3 HR: 0.84 (0.75–0.95); *P*: 0.005	AREDS: Tertile 2 HR: 0.85 (0.73–1.00); *P*: 0.06 and tertile 3 HR: 0.73 (0.62–0.87); *P*: 0.001 AREDS 2: Tertile 2 HR: 0.78 (0.66–0.92); *P*: 0.004 and tertile 3 HR: 0.73 (0.62–0.87); *P*: 0.0003 Combined: Tertile 2 HR: 0.80 (0.71–0.90); *P*: 0.0002 and tertile 3 HR: 0.71 (0.63–0.80); *P*: 0.0001
Hogg *et al*. (2017) [14]	AOR 0.53 (0.27–1.04); *P*: 0.01	No data*

*The authors did not find any association between GA and advanced AMD; therefore, they neither perform further analysis nor mention the data in their study. All HR(s) have a 95% CI. ALIENOR: Antioxidants, Lipides Essentiels, Nutrition Et Maladies Oculaires Study, AREDS/AREDS2: Age-related eye disease study, GA: Geographic atrophy, HR: Hazard ratio, NvAMD: Neovascular age macular degeneration, RS-I: Rotterdam study, AOR: Adjusted odds ratio, CI: Confidence interval

Table 3: Risk of bias of the included studies using the Newcastle–Ottawa Scale

Studies	Selection	Comparability	Outcome	Total
Merle 15	****	**	**	8/9
Merle 18	****	**	***	9/9
Merle 20	****	**	***	9/9
Keenan 20	****	*	***	8/9
Hogg 17	****	*	***	8/9
Raimundo 18	****	*	**	7/9
Nunes 18	****	*	**	7/9
Mares 11	****	**	***	9/9

* 1 point, ** 2 points, *** 3 points, **** 4 points

with the progression of advanced AMD (HR: 0.60; 95% CI: 0.42–0.86) with a moderate degree of heterogeneity (I^2: 0%; *P*: 0.005), yet this finding did not attain statistical significance.

A sub-analysis was performed on two studies that did not specify AMD classification with high MD, unveiled a significantly inverse association (HR: 0.71; 95% CI: 0.58–0.87), with no significant heterogeneity observed (I^2: 0%; *P*: 0.001).

In the Hartung-Knapp-Sidik-Jonkman model, our studies reveal an inverse and significant result between overall medium–high adherence and AMD events (HR: 0.02; 95% CI: 0.8–0.95). In addition, it appears that a medium adherence to the MD is associated with the progression of advanced AMD (HR: 0.05; 95% CI: 0.73–0.92) [24] [Supplementary Figures 1-6].

The quality of each study can be found in the Tables 1-3 and Figures 1, 2.

Discussion

The MD is a whole dietary rich in antioxidants, trace elements, minerals, and vitamins with anti-inflammatory properties [25]. It improves autophagy and T helper cell imbalance, downregulates the expression of cell adhesion and complement activity in circulating immune cells and regulates endothelial dysfunction [26].

Moreover, adherence to MD has been associated with impairments in dendritic cells, regulates cellular and humoral immunological pathways, and reduce resistin level, which increases with age and is induced by inflammation [27]. Plenty of studies have investigated MD's protective effects against chronic cardiovascular-inflammatory-metabolic-neurodegenerative-ocular diseases [23,25,28].

The MD is characterized by macro and micronutrient composition with high fat 35%–45% (50% MUFAs and 50% combination of polyunsaturated fatty acids- SFAs [PUFAs-SFAs]), 15%–20% protein, 35%–50% carbohydrates, and alcohol contributing up to 5% of total energy [29,30]. This high MUFA is mainly due to the daily consumption of extra virgin olive oil (EVOO) [29] or nuts [26]. EVOO contains polyphenols that drive anti-inflammatory and antioxidant benefits [29,31]. One of MD's components, fish, contains omega-3-PUFA which is consistently associated with decreased advanced AMD [32]. Fish were also found to be a protective factor for AMD in our study.

The complexity of AMD's pathogenesis includes endothelial dysfunction, inflammation, oxidative stress, and other processes that are common in other degenerative diseases [33]. As the MD is proposed to slow the progression of the oxidative damages, that play a role in AMD [29,34,35]. The MD was inversely associated with white blood cells [36], platelets count [36], and Nuclear factor kappa-light-chain-enhancer activation [31], which is the key factor in inflammation compared with another dietary pattern. Antioxidants are also related to the inhibition of VEGF release and to lower inflammation. Merle *et al*. showed protective effects of consuming an MD beyond simply the use of antioxidant and zinc supplementation [4].

This systematic review and meta-analysis demonstrated that adherence to MD seems protective to reduce the risk of AMD, drusen progression, and advanced AMD. Medium adherence to the MD yields a positive outcome in terms of the advancement of advanced AMD. Conversely, the highest level

of adherence to the MD does not demonstrate a statistically significant outcome in relation to the progression of advanced AMD.

However, there were inconsistent results between the progression to GA and nvAMD. The stronger association between MD adherence to the progression of GA compared to nvAMD is presumed because GA is hypothesized as an nvAMD precursor. Small GA can be detected even before the onset of nvAMD [37]. GA seems to be the initial step in the progression to late-stage AMD. Meanwhile, the development of nvAMD is linked to photoreceptor and retinal pigment epithelium loss [37].

We did not find any correlation between adherence to MD and early AMD. The assessment of AMD in all studies conducted by mydriatic color fundus might lead to misclassification of the early features of AMD and be ambiguous for determining important phenotypes, such as reticular pseudodrusen (RPD). Multi-imaging techniques such as fundus auto-fluorescence and optical coherence tomography might emphasize definitively identifying RPD [38,39].

We also found that genetics, older age, higher BMI, lower education, advanced AMD in the fellow eye, and history of smoking are associated with the development of AMD. Our result is consistent with Chakravarthy *et al*., who found that age, worse visual acuity, smoking, and cardiovascular disease was associated with increased risk of GA and nvAMD aside from diet [37]. Most of these risk factors have been adjusted to minimize the bias, but there is no study adjusted for the late-stage AMD in the fellow eye. Previous studies demonstrated that the highest risk of AMD progression was related to the presence of late stage in the fellow eye [37,40]. (HR 18.60; 95% CI: 2.5–141.1 and HR 22.54; 95% CI: 2.6–195.9 for GA and nvAMD respectively) [40].

To the best of our knowledge, our study represents the initial endeavor to conduct a meta-analysis investigating the correlation between AMD and MD. Furthermore, the studies incorporated into our analysis were characterized by large sample sizes, which serve as an additional factor reinforcing the strength of our study.

Several limitations should be considered in interpreting our findings. The limited quantity of eligible studies may influence the strength of our meta-analysis outcomes. Furthermore, noteworthy diversity exists among studies. There are variations in study design, measurement criteria, and study populations. Notably, the inclusion of cross-sectional and case–control studies could introduce selection bias. In addition, disparities in the methods of MD adherence's measurement across different study population may restrict the generalizability of our findings.

As dietary patterns in a population vary by culture, geography, economy, and availability of local food [14]. We suggest further research that investigates the relationship between a modified MD, aligned with regional dietary customs. We recommend applying the diet for prevention and slowing down the progression of AMD in the older population.

Conclusions

Overall, adhering to the MD, particularly at a medium to high level, appears to confer a protective effect against AMD. The sub-analysis demonstrates even that there is a protective effect associated with moderate adherence against advanced AMD. The presence of considerable heterogeneity within the results warrants cautious interpretation. Further research is needed to enhance our understanding.

Data availability statements

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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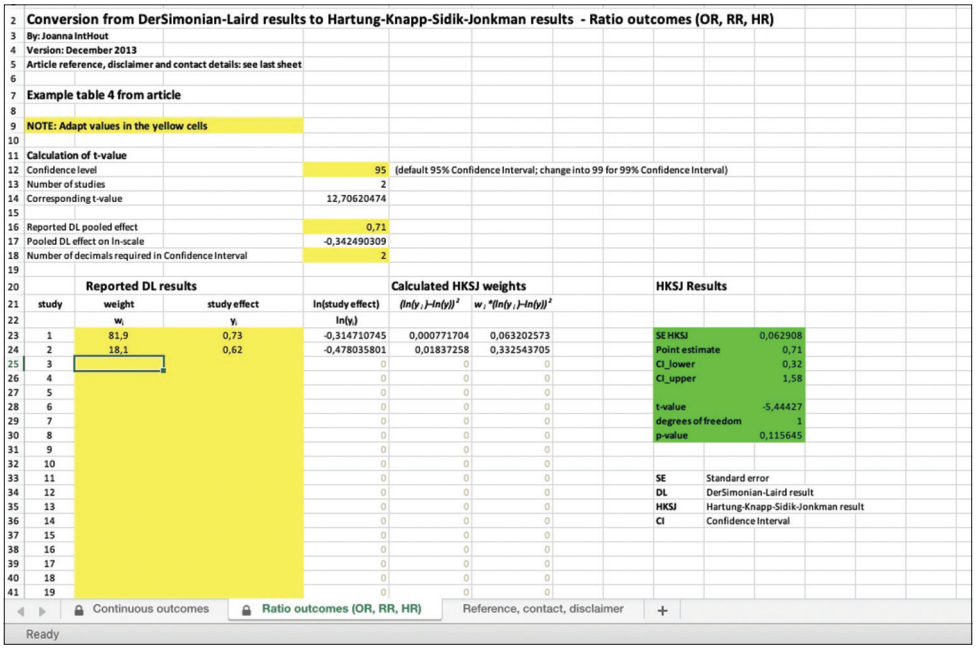
Supplementary Material



Conversion from DerSimonian-Laird results to Hartung-Knapp-Sidik-Jonkman results - Ratio outcomes (OR, RR, HR)

By: Joanna IntHout
Version: December 2013
Article reference, disclaimer and contact details: see last sheet

Example table 4 from article

NOTE: Adapt values in the yellow cells

Calculation of t-value

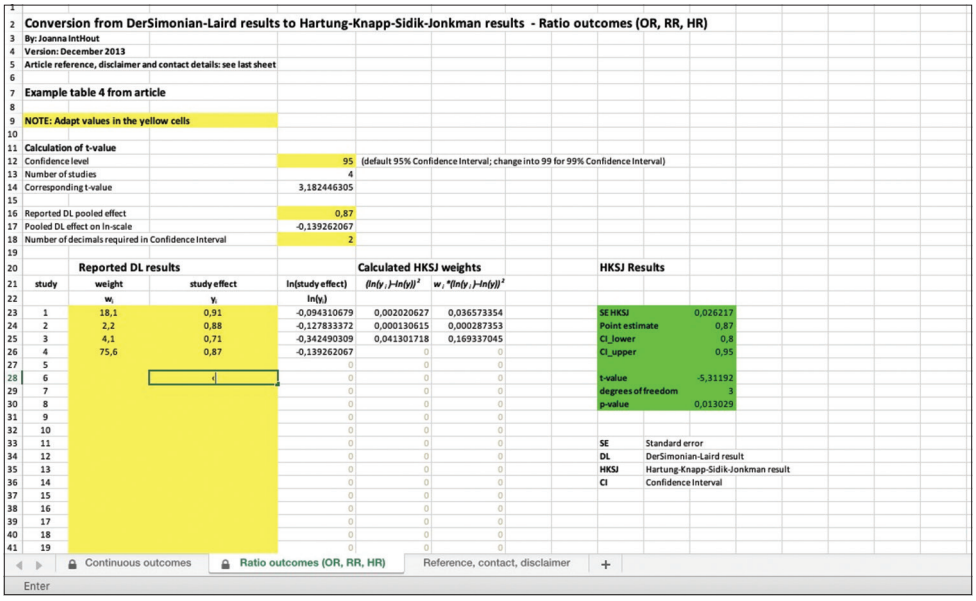
Confidence level	95	(default 95% Confidence Interval; change into 99 for 99% Confidence Interval)
Number of studies	2	
Corresponding t-value	12,70620474	
Reported DL pooled effect	0,71	
Pooled DL effect on ln-scale	-0,342490309	
Number of decimals required in Confidence Interval	2	

	Reported DL results			Calculated HKSJ weights		HKSJ Results	
study	weight	study effect	ln(study effect)	$(ln(y_i)-ln(y))^2$	$w_i*(ln(y_i)-ln(y))^2$		
	w_i	y_i	$ln(y_i)$				
1	81,9	0,73	-0,314710745	0,000771704	0,063202573	SE HKSJ	0,062908
2	18,1	0,62	-0,478035801	0,01837258	0,332543705	Point estimate	0,71
3			0	0	0	CI_lower	0,32
4			0	0	0	CI_upper	1,58
5			0	0	0		
6			0	0	0	t-value	-5,44427
7			0	0	0	degrees of freedom	1
8			0	0	0	p-value	0,115645
9			0	0	0		
10			0	0	0		
11			0	0	0	SE	Standard error
12			0	0	0	DL	DerSimonian-Laird result
13			0	0	0	HKSJ	Hartung-Knapp-Sidik-Jonkman result
14			0	0	0	CI	Confidence Interval
15			0	0	0		
16			0	0	0		
17			0	0	0		
18			0	0	0		
19			0	0	0		

Continuous outcomes | Ratio outcomes (OR, RR, HR) | Reference, contact, disclaimer | +

Ready

Supplementary Figure 1: Conversion to Hartung-Knapp-Sidik-Jonkman model on unspecified age-related macular degeneration with high adherence to Mediterranean diet. HKSJ: Hartung-Knapp-Sidik-Jonkman



Conversion from DerSimonian-Laird results to Hartung-Knapp-Sidik-Jonkman results - Ratio outcomes (OR, RR, HR)

By: Joanna IntHout
Version: December 2013
Article reference, disclaimer and contact details: see last sheet

Example table 4 from article

NOTE: Adapt values in the yellow cells

Calculation of t-value

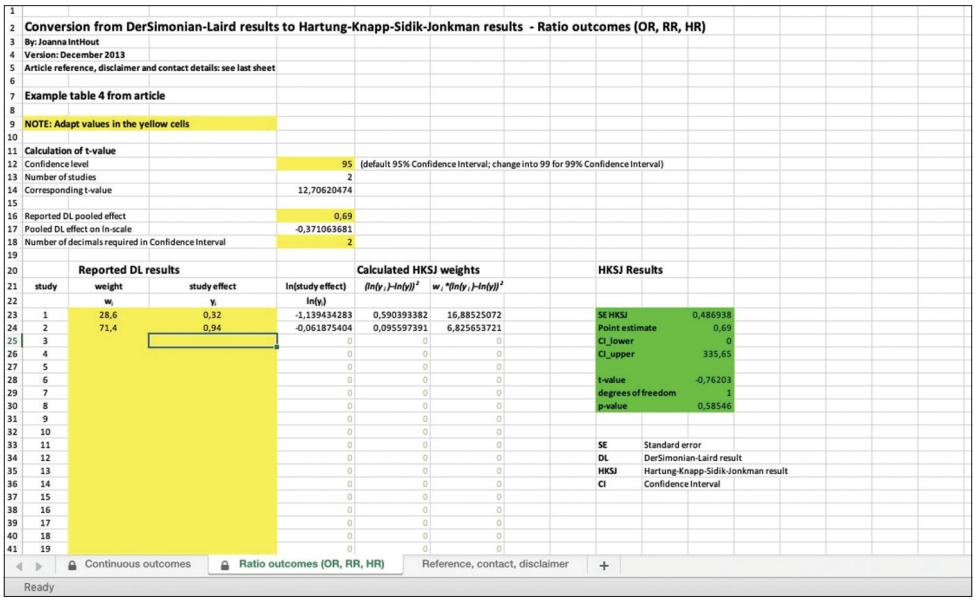
Confidence level	95	(default 95% Confidence Interval; change into 99 for 99% Confidence Interval)
Number of studies	4	
Corresponding t-value	3,182446305	
Reported DL pooled effect	0,87	
Pooled DL effect on ln-scale	-0,139262067	
Number of decimals required in Confidence Interval	2	

	Reported DL results			Calculated HKSJ weights		HKSJ Results	
study	weight	study effect	ln(study effect)	$(ln(y_i)-ln(y))^2$	$w_i*(ln(y_i)-ln(y))^2$		
	w_i	y_i	$ln(y_i)$				
1	18,1	0,91	-0,094310679	0,002020627	0,036573354	SE HKSJ	0,026217
2	2,2	0,88	-0,127833372	0,000130615	0,000287353	Point estimate	0,87
3	4,1	0,71	-0,342490309	0,041301718	0,169337045	CI_lower	0,8
4	75,6	0,87	-0,139262067	0	0	CI_upper	0,95
5			0	0	0		
6			0	0	0	t-value	-5,31192
7			0	0	0	degrees of freedom	3
8			0	0	0	p-value	0,013029
9			0	0	0		
10			0	0	0		
11			0	0	0	SE	Standard error
12			0	0	0	DL	DerSimonian-Laird result
13			0	0	0	HKSJ	Hartung-Knapp-Sidik-Jonkman result
14			0	0	0	CI	Confidence Interval
15			0	0	0		
16			0	0	0		
17			0	0	0		
18			0	0	0		
19			0	0	0		

Continuous outcomes | Ratio outcomes (OR, RR, HR) | Reference, contact, disclaimer | +

Enter

Supplementary Figure 2: Conversion to Hartung-Knapp-Sidik-Jonkman model on advanced age-related macular degeneration with medium adherence to Mediterranean diet. HKSJ: Hartung-Knapp-Sidik-Jonkman



Conversion from DerSimonian-Laird results to Hartung-Knapp-Sidik-Jonkman results - Ratio outcomes (OR, RR, HR)

By: Joanna IntHout
Version: December 2013
Article reference, disclaimer and contact details: see last sheet

Example table 4 from article

NOTE: Adapt values in the yellow cells

Calculation of t-value

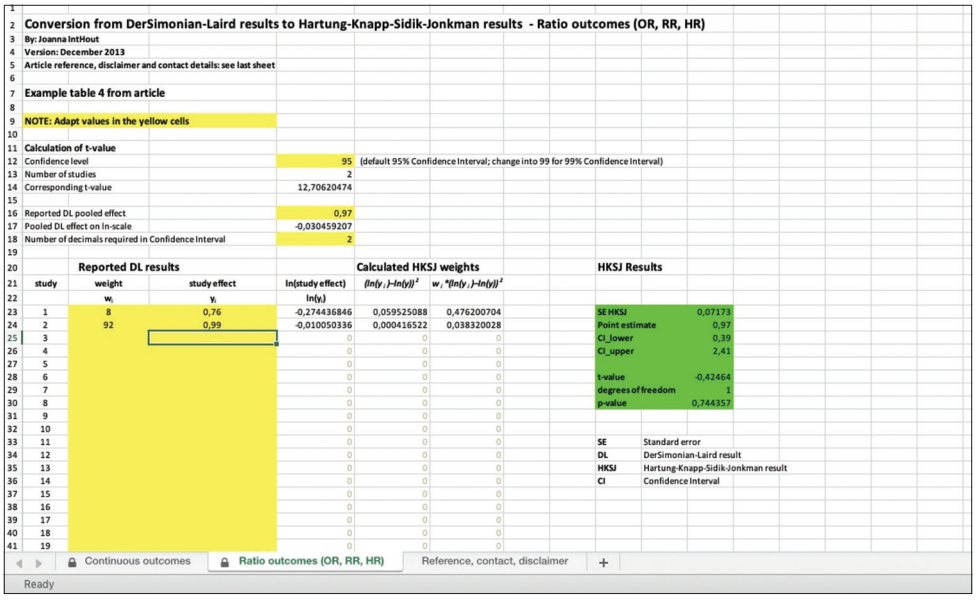
Confidence level	95	(default 95% Confidence Interval; change into 99 for 99% Confidence Interval)
Number of studies	2	
Corresponding t-value	12,70620474	
Reported DL pooled effect	0,69	
Pooled DL effect on ln-scale	-0,371063681	
Number of decimals required in Confidence Interval	2	

	Reported DL results			Calculated HKSJ weights		HKSJ Results	
study	weight	study effect	ln(study effect)	$(ln(y_i)-ln(y))^2$	$w_i*(ln(y_i)-ln(y))^2$		
	w_i	y_i	$ln(y_i)$				
1	28,6	0,32	-1,139434283	0,590393382	16,88525072	SE HKSJ	0,486938
2	71,4	0,94	-0,061875404	0,095597391	6,825653721	Point estimate	0,69
3			0	0	0	CI_lower	0
4			0	0	0	CI_upper	335,65
5			0	0	0		
6			0	0	0	t-value	-0,76203
7			0	0	0	degrees of freedom	1
8			0	0	0	p-value	0,58546
9			0	0	0		
10			0	0	0		
11			0	0	0	SE	Standard error
12			0	0	0	DL	DerSimonian-Laird result
13			0	0	0	HKSJ	Hartung-Knapp-Sidik-Jonkman result
14			0	0	0	CI	Confidence Interval
15			0	0	0		
16			0	0	0		
17			0	0	0		
18			0	0	0		
19			0	0	0		

Continuous outcomes | Ratio outcomes (OR, RR, HR) | Reference, contact, disclaimer

Ready

Supplementary Figure 3: Conversion to Hartung-Knapp-Sidik-Jonkman model on early age-related macular degeneration with high adherence to the Mediterranean diet. HKSJ: Hartung-Knapp-Sidik-Jonkman



Conversion from DerSimonian-Laird results to Hartung-Knapp-Sidik-Jonkman results - Ratio outcomes (OR, RR, HR)

By: Joanna IntHout
Version: December 2013
Article reference, disclaimer and contact details: see last sheet

Example table 4 from article

NOTE: Adapt values in the yellow cells

Calculation of t-value

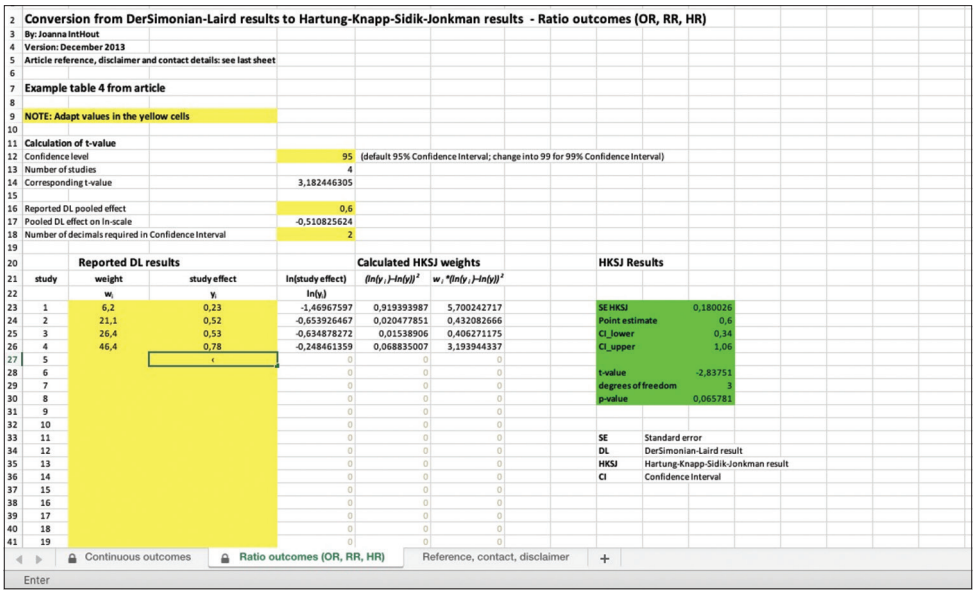
Confidence level	95	(default 95% Confidence Interval; change into 99 for 99% Confidence Interval)
Number of studies	2	
Corresponding t-value	12,70620474	
Reported DL pooled effect	0,97	
Pooled DL effect on ln-scale	-0,030459207	
Number of decimals required in Confidence Interval	2	

	Reported DL results			Calculated HKSJ weights		HKSJ Results	
study	weight	study effect	ln(study effect)	$(ln(y_i)-ln(y))^2$	$w_i*(ln(y_i)-ln(y))^2$		
	w_i	y_i	$ln(y_i)$				
1	8	0,76	-0,274436846	0,059525088	0,476200704	SE HKSJ	0,07173
2	92	0,99	-0,010050336	0,000416522	0,038320028	Point estimate	0,97
3			0	0	0	CI_lower	0,39
4			0	0	0	CI_upper	2,41
5			0	0	0		
6			0	0	0	t-value	-0,42464
7			0	0	0	degrees of freedom	1
8			0	0	0	p-value	0,744357
9			0	0	0		
10			0	0	0		
11			0	0	0	SE	Standard error
12			0	0	0	DL	DerSimonian-Laird result
13			0	0	0	HKSJ	Hartung-Knapp-Sidik-Jonkman result
14			0	0	0	CI	Confidence Interval
15			0	0	0		
16			0	0	0		
17			0	0	0		
18			0	0	0		
19			0	0	0		

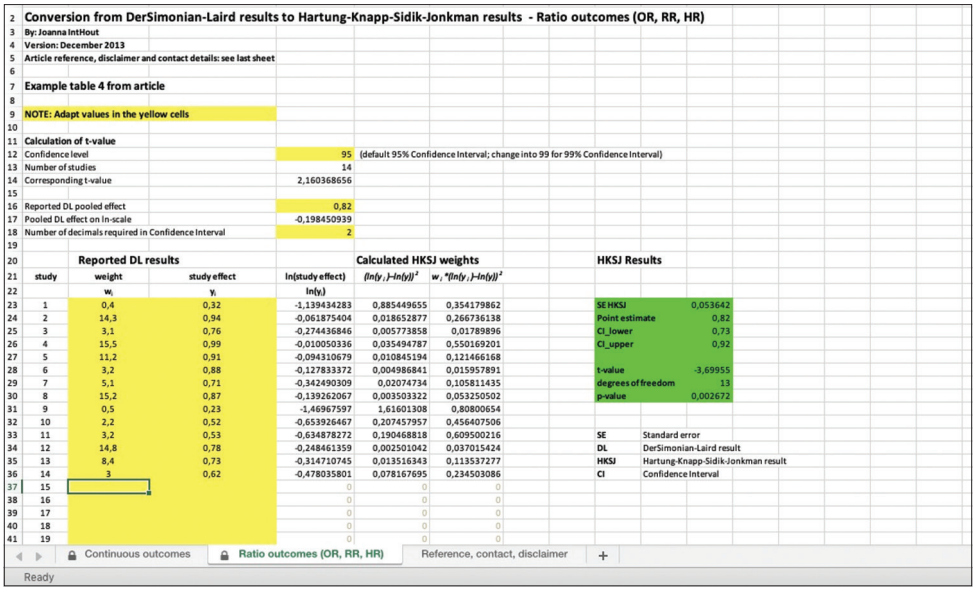
Continuous outcomes | Ratio outcomes (OR, RR, HR) | Reference, contact, disclaimer

Ready

Supplementary Figure 4: Conversion to Hartung-Knapp-Sidik-Jonkman model on early age-related macular degeneration with medium adherence to Mediterranean diet. HKSJ: Hartung-Knapp-Sidik-Jonkman



Supplementary Figure 5: Conversion to Hartung-Knapp-Sidik-Jonkman model on advanced age-related macular degeneration with high adherence to the Mediterranean diet. HKSJ: Hartung-Knapp-Sidik-Jonkman



Supplementary Figure 6: Conversion to Hartung-Knapp-Sidik-Jonkman model on overall age-related macular degeneration with medium–high adherence to Mediterranean diet. HKSJ: Hartung-Knapp-Sidik-Jonkman