Αξιολόγηση Μελετών Γενετικής Συσχέτισης Ανάμεσα στους Γονιδιακούς Πολυμορφισμούς της Οικογένειας των Μεταλλοπρωτεϊνάσων και την Παθογένεση Ενδοκράνιων Ανευρυσμάτων Χρησιμοποιώντας τη Λίστα Ελέγχου STREGA: Ποιοτική Ανάλυση

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Ιατρός

Διπλωματική Εργασία

Πρόγραμμα Μεταπτυχιακών Σπουδών

«Μεθοδολογία Βιοϊατρικής Έρευνας, Βιοστατιστικής και Κλινικής Βιοπληροφορικής»

Ιατρική σχολή

Πανεπιστήμιο Θεσσαλίας

2016

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Assessment of Gene-Association Studies on Matrix Metalloproteinase Gene-Family Polymorphisms in Association to the Pathogenesis of Intracranial Aneurysms Using The STREGA checklist: A Quality Review

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2016

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Declaration

I declare that I composed all the work contained in this thesis entitled "Assessment Of Gene-Association StudiesOn Matrix Metalloproteinase Gene Family PolymorphismsIn Association To The Pathogenesis Of Intracranial Aneurysms Using The STREGA Statement: A Quality Review". This thesis is submitted for the Degree of Master of Science and has not been submitted for any previous degree application. All quotations have been distinguished by quotation marks and the source of information specifically acknowledged.

Signed_____

Date

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Acknowledgments

I would to thank all my Tutors for their priceless support and unlimited availability. Special appreciations to Dr. Doxani, Prof. Hatzigeorgiou, and Prof. Zintzaras for their supervision on my current effort. I would also like to thank every member of my Family for their encouragement to finish the MSc. Finally, lots of thanks to my colleagues at the Department of Neurosurgery for their vivid support and understanding.

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Assessment of Gene-Association Studies on Matrix Metalloproteinase Gene Family Polymorphisms in Association to the Pathogenesis of Intracranial Aneurysms Using The STREGA checklist: A Quality Review

Abstract

Background/Objectives: The role of matrix-metalloproteinase gene-family polymorphisms in the pathogenesis of the intracranial aneurysms hasnot been clearly established. Aim of the current study is to assess the transparency and reporting qualityof the medical literature focusing on role of matrix-metalloproteinase gene-family polymorphisms in the pathogenesis of the intracranial aneurysms.

Methods: We performed a qualityreview of gene association studiesfocusing the role of matrix-metalloproteinase gene-family polymorphismsas potential risk factors for intracranial aneurysms. The search was limited to English-written studies on adults. Two independent reviewers classified the gathered articles into "High", "Medium" and "Low"quality study reports, in terms of reporting transparency and completeness, using the STREGA checklist. The publication year, the journal's impact factor, the hosting country and the existence of fundingwere regarded as potential confounders**.** Comparison of the data between-groups was evaluated usingthe chi-square or Fisher' s test, as appropriate.

Results:A total of eight studies (2716 cases and 3569 controls) fulfilled our eligibility criteria and were included in this review. Nineteen polymorphisms involving five matrix-metalloproteinases (MMP-1, -2, -3, -9 and -12) were studied is association to intracranial aneurysms and/or subarachnoid hemorrhage. Sevenstudies were characterized as of "Medium" reporting quality, while the remaining one was classified as "Low". The publication year, the journal's impact factor, the hosting country and the existence of funding had no impact on the reporting quality.

Conclusions: The reporting quality in terms of completeness and transparency of gene-association studies focusing on the role of matrix-metalloproteinase gene-family polymorphism in the pathogenesis of intracranial aneurysms is moderate to low. Adherence to checklists, such as STREGA, is expected to lead the way towards high quality studies and

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transparent meta-analyses.

Keywords:GAS, gene polymorphisms, MMP, intracranial aneurysm, subarachnoid hemorrhage, STREGA

Abbreviations:HWE: Hardy-Weinberg equilibrium, GAS: gene association studies, IA: intracranial aneurysms, MMP: metalloproteinases, SNP: single nucleotide polymorphisms, STREGA: Strengthening The REporting of Genetic Association studies

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1. Introduction

Intracranial aneurysms (IA) are the most common cause of spontaneous subarachnoid hemorrhage. They are associated with high morbidity and mortality rates.Their estimated prevalence has been reported to be as high as 2% of the general population[1]. Rupture of an intracranial aneurysm is a major neurosurgical emergency, which is characterized by a high re-bleeding rate, and might be complicated by a number of clinical entities that include and are not limited to permanent neurological deficit, vasospasm, seizures, hydrocephalus, electrolytic imbalances and electrocardiographic changes[2]. IA can occur either sporadically or might cluster in families[3].

The pathophysiology behind the development and rupture of the IA is not fully understood. It is assumed that there is a good interplay between a number of appreciated risk factors (hypertension, cigarette smoking, alcohol consumption and female sex) and genetic predisposition[4]. Familial occurrence of IA has been documented in association with hereditary disorders, such as polycystic kidney disease and Ehles-Danlos syndrome[3]. On the other hand, little is known about the genetic background of sporadic aneurysms[5]. Recent studies have focused on the degradation and remodeling process of the blood vessels, and their related genetic polymorphisms[6, 7]. Matrix-metalloproteinases (MMP), a group of 22 zinc-dependent proteins that carry a pivotal role in the degradation of collagen matrix proteins, have attracted a great deal of attention, especially in the pathophysiology of abdominal aneurysms[8, 9].

In the current communication we performed a literature review on gene association studies that deal with MMP gene-family polymorphisms in association to IA and/or subarachnoid hemorrhage in adults. Our goal is to study the quality of the reported articles in terms of transparency and completeness of reporting using an extension of the STROBE statement, known as STREGA[10]. This is the first step in a lengthy process of best-evidence synthesis, with an ultimate goal to prevent and treat this clinical entity.

2. Methods

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2.1 Publication search

We performed an electronic database search at the following medical databases: PubMed, Scopus, and HuGE Navigator. The search terms included: “gene associations” or “gene-linkage analysis” or “GAS” or “polymorphisms” AND “intracranial aneurysm*” or “subarachnoid hemorrhage” AND “MMP-*” or “metalloproteinases*”. The titles and abstracts of the gathered articles were retrieved and controlled for relevance and irrelevant articles were excluded. The full-text of the remaining articles were retrieved and further controlled for relevance. Additional articles were supplemented from the reference list of the full-text articles.

2.2 Eligibility criteria

The search was limited in observational studies (cohort, case-control, and cross-sectional studies), written in English, and focusing on adult human subjects. We excluded laboratory studies, studies with insufficient data or with family-based design. Similarly, we excludedduplicates, personal communications, systematics reviews, meta-analyses, and editorials.The flowchart of the literature search is depicted on Figure 1.

2.3 Quality Evaluation

Two independent reviewers (AGB and CD)assessed the reporting quality of the gathered articles in terms of transparency and completeness, using the STREGA checklist. The latter, in addition to the 22 questions of the STROBE statement, highlights specific aspects of gene association studies, such as population structure, genotyping errors, modeling haplotype variation, Hardy-Weinberg equilibrium (HWE), and replication. Each item wasscored a best-fitting value among “Yes”, “No”, or “NA” (Not Applicable)to evaluate for adherence to the STREGA checklist. A summative score represented the total endorsement of each item separately.

In addition, a summary score was given to each study, representing the study’s adherence to transparent and high-quality reporting. Studies with scores ranging from 15 to 22 were considered as “High” quality, 8-14 as “Medium” quality, and 0-7 as “Low” quality. It has to be clarified that the above-mentioned classification does not refer to the scientific value of

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the study.

2.4 Data Extraction

Thefollowing data were collected: 1) the name of the first author, the year of publication, the journal's impact factor, 2) the hosting country and the ethnicity of the participants, 3) the number of cases and controls, and 4) the SNPs under study. Journals with impact factor >10 were regarded as "High" impact-factor journals, while those with values between 10-3 and <3 were considered as "Medium" and "Low" impact-factor journals, respectively.

Furthermore, we evaluated the adherence tothe STREGA checklist items, and categorized the questions as highly endorsed questions (endorsement-rate ranging between 67-100%), moderately endorsed (34-66%), and inadequately-endorsed items (0-33%).

2.5 ConfoundersandBias Elimination

In order to eliminate the effect of confounding factors we stratified our results in terms ofyear of publication (before or after the publication of STREGA in 2009), the journals impact factor,the hosting country,and the funding.

Moreover, the reviewers were blinded to the author's name and journalto avoid information bias. Both reviewers received proper training in thechecklists, STROBE and STREGA. Each reviewer assessed the studies independently. In the case of disagreement between the two reviewers there was detailed discussion between them until both agreed to a common score.

2.6Statistical Analysis

Simple descriptive statistics were adopted for the realization of the current study using the statistical software "R".Between groups analysis was performed usingthe chi-square or Fisher' s test, as appropriate.

3.Results

3.1 Literature Review

The literature search identified 63 articles. An additional study was found from the

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reference list of the gathered articles. Thirty articles remained after duplicate removal. Thirteen articles were recognized as irrelevant after title and abstract review. Other 9 articles were of irrelevant context or methodology, and as such were eliminated from the qualitative analysis. One study without genotype distribution was considered not suitable for data synthesis. A total of eight studies[11-18] with 2716 cases and 3569 controls were included in this review (**Figure 1**).

3.2MMP-Family Gene Polymorphisms and IAs

Nineteen polymorphisms from five MMP-genes (MMP-1, -2, -3, -9 and -12) were studied is association to IA and/or subarachnoid hemorrhage. The most commonly studied MMP gene-family polymorphisms were related to MMP-9, followed by MMP-3. Similarly, articles related to IA outnumber those related to "subarachnoid hemorrhage", with 7 to 1. Three studies were performed in a mixed White European American/Black African American population, four in Caucasians, and one in Japanese (**Table 1**).

3.3Endorsement of STREGA and Reporting Quality

Items Q.1, Q.2, Q.4, Q.5, Q.20, and Q.22 were highly endorsed, while items Q.3, Q.7, Q.9, Q.10, Q.12, Q.13, Q.14, Q.16, Q.17, and Q.21belonged among the least commented arguments (low-endorsement). Items Q.6, Q.8, Q.11, Q.15, Q.19 were assessed as moderately endorsed topics(**Table 2**). All items in the "Title and abstract" and "Other" sections carry a low risk of reporting bias. On the contrary, more than 70% of the items in each of the sections under the headings of "Methods", "Results" and "Discussion" indicate potential sources of bias (**Figure 2**).

The median score of the gathered articles was 9.5 (range: 7-14). No study addressed all items of the STREGA checklist, or was categorized as a "High" qualitystudy. Seven studies were characterized asof "Medium" reporting quality according to STREGA checklist, while the remaining one was classified as "Low".

3.4Effect of Confounders

The gathered articles were published in the period between 1999 and 2011. There was no statistically important difference in the quality of reported studies before and after the

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release of STREGA (*p=0.531*).

No study was published in a "High" impact-factor journal (>10). "Medium" and "Low" impact-factor journals hosted five and three studies, respectively (**Table 1**). Among the seven studies of moderate quality, five have been published in medium impact factor journals, and the remaining two in low impact factor journals. Finally, one low quality study was published in a low impact factor journal. We could not identify a statistically significant role of the journal's impact-factor on the article's reporting quality (*p=0.168*).

Three studies took place in the USA, three in Europe and one in Asia. There was no statistically important effect of the hosting country (*p=0.135*) or the existence of funding on the reporting quality of the studies (*p=0.64*).

4.Discussion

4.1 Overview of the Study Findings

To the best of our knowledge this is the first quality review of studies reporting on MMP-family gene polymorphisms in association to IA or subarachnoid hemorrhage. Eight articles fulfilled our eligibility criteria[11-18]. The majority of the gathered articles were of medium reporting quality. It became clear that the adherence to the STREGA checklist is moderate. MMP-9 and MMP-3 gene polymorphisms were the most studied as potential risk factors ofIA pathogenesis or rupture. The small number of articles precluded the use of inferential statistics.

4.2 Correlation with Other Studies

The association of MMP-family gene polymorphisms and abdominal aneurysm, myocardial infraction and ischemic stroke has extensively been studied. A meta-analysis by Wen *et al*., showed that MMP-1 -1607 1G/2G andMMP-3 -1612 5A/6A were risk factors for ischemic stroke,while MMP-9 -1562C/T was not associated with ischemicstroke[19].Juan *et al*., reportedthatthe MMP9 -1562C/Tpolymorphismisariskfactorassociatedwith increased myocardial infarction susceptibilityinthetotalpopulationand in whitepopulations,althoughnosignificant associationwasobservedin Asian populations[20].

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Similarly, Morris *et al.*, revealed that a common SNP within the MMP3 promoter region, previously suggested to increase MMP3 expression, appears to be a moderate risk factor for abdominal aortic aneurysms[8]. However, the evidence in not clear enough when it comes toMMP gene-family polymorphisms and IA[11-18].

4.3 Reporting Gaps According toSTREGA

Our analysis revealed that reporting of GAS forMMP-family gene polymorphisms as potential risk factors in the pathogenesis and rupture ofIA moderately adhere to STREGA. We noticed a systematic failure to comply with particular items, especially in the "Methods" and the "Results" section. The gathered articles did not clearly state if the study was the first report of GAS, a replication or both (Q.3). The authors failed to address potential confounders and bias (Q.7, Q.9) or justify the size of their sample (Q.10). No article achieved to fully reportits statistical analysis, as mandated by STREGA (Q.12). There was no reporting on the number of individuals in whom genotyping was attempted and number of individuals in whom genotyping was achieved (Q.13). At the same time, there was total absence ofreference to missing data (Q.14),adjustment to confounders/multiple comparisons (Q.16), and other analyses performed (subgroup-, interaction-, and sensitivity analysis, Q.17).Equally important,there was lack of reference to study limitations (Q.19) and the generalizabilityof the results in the "Discussion" section (Q.21).

4.4 MediumandLow Quality Studies

Seven articles were classified as "Medium" quality [11, 13-15, 17, 21, 22] and one as "Low" quality. Low *et al.*, in an interesting article, studied the impact of LIMK-1, MMP-2 and TNF-α variations forIA in Japanese population (2050 IA patients and 1853 controls from the Biobank Japan). The authors failed to conform to all but two of the reporting recommendations in the "Methods" section and all the recommendations in the "Results" section[18]. There was no evidence for confounding effect in respect of the publication year;the journal's impact factor; the presence of funding, and the hosting country.

4.5Limitations

The current study has some important limitations. To start with, it is based on a small

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number of studies, especially in the post-STREGA era, that do not allow us to perform statistical analysis. In addition, the research study was limited in English-written articles and in adults so we might have important effects from selection bias.

In addition, the study might include information (allocation) bias. STREGA is a checklist that allows us to roughly evaluate the reporting quality of the gathered studies. However, it is a consortium product rather than a validated tool. As a result it lacks sensitivity and specificity evaluation. Moreover, not all items are of equal importance and special weight, therefore a summative score might not be representative of the reality. Thus, the current study is limited by these inherent characteristics of STREGA checklist.

Another measure of the quality of the gene association studies is the Hardy-Weinberg equilibrium (HWE). The use of HWE quality control is expected to further limit the gathered studies, as the study of Kaplan *et al*., does not provide the HWE values[16].The present review did not adopt the HWE as quality measure, as it did not intent to proceed further in quantitative analysis.

Furthermore, this review is exposed to publication bias, as we did not perform the relevant analysis (funnel plots and Egger's test) at the context of a quality control study.

4.6Future Recommendations

As mentioned above, the number of studies on the association of MMP family gene polymorphisms to IA is limited. More replicate studies are needed, both in the same and in different populations so as to allow for further quantitative analysis through a meta-analysis.

5. Conclusions

The reporting quality in terms of completeness and transparency of gene-association studies on the role of MMP gene-family polymorphisms on the pathogenesis of intracranial aneurysms is moderate to low. Adherence to checklists such as STREGA is expected to lead the way towards high-quality studies and transparent meta-analysis. The later forms the corner stone of personalized prevention and treatment of the lethal clinical entity related to IA rupture.

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Appendix

Table 1.Overview of GAS[a] on intracranial aneurysms and MMP gene family polymorphism.

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	Impact Factor (Class)	Country / Ethnicity	Clinical Entity	Study Design	Genotyping	Cases / Controls	Reporting Quality according to STREGA	MMP gene	Polymorphisms
Peters *et al.* (1999) [11]	5.787 (Medium)	USA / Mixed European White Americans	IA	PC	PCR	76/93	Medium	MMP-9	Microsatellite repeats (CA)n
Yoon *et al.* (1999) [12]	2.371 (Low)	Finland / Caucasian	fIA	PC	PCR	57/174	Medium	MMP-3	5A/5A
								MMP-9	Microsatellite repeats (CA)n
Zhang *et al.* (2001) [13]	5.787 (Medium)	UK / Caucasian	aSAH	PC	PCR	91/116	Medium	MMP-1	1G/2G
								MMP-3	5A/6A
								MMP-9	1562C>T
									Microsatellite Repeats (CA)n
								MMP-12	A-82G
Krex*et al.* (2004) [14]	3.780 (Medium)	Germany / Caucasian	IA	PC	PCR	40/44	Medium	MMP-9	59 C>T
									IVS4+3 G>T
									836 G>A
									IVS7+7 A>G
									1714 G>A
									1721 C>G
									1821 C>A
									2003 G>A
									2082 G>A
									*3 T>C
									*145 C>T
Pannu*et al.* (2006) [15]	3.443 (Medium)	USA / Black-African-American White-European American	sIA	PC	Pyrosequencing	125/234	Medium	MMP-2	-1306 C>T (rs243865)
									3307 G>A (hCV3225947)
									6447 G>C (rs17242319)
									10910 C>T (rs243847)
								MMP-9	-1562C>T (rs391242)
									Microsatellite repeats (CA)n
									1977 C>T(rs39182253)
									7476 CT (rs20544)
Kaplan *et al.* (2008) [16]	3.942 (Medium)	USA / Black-African-American White-	HS	PC	Illumina	66/2696	Medium	MMP-3	rs522616
									rs680753
									rs683878
									rs595840

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		European American						MMP-9	rs2664538
									rs2250889
									rs2274756
									rs3918262
Szczudlik *et al.* (2010) [17]	0.747 (Low)	Poland / Caucasian	HS	PC	PCR	211/212	Medium	MMP-9	-1562 C/T (rs391242)
Low *et al.* (2011) [18]	2.487 (Low)	Japan / Japanese	IA	PC	PCR	2050/ 1835	Low	MMP-2	rs243847
									rs243865

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Table 2. STREGA scoring. M:medium, L:low

	Question	*Peters (1999)*	*Yoon (1999)*	*Zhang (2001)*	*Krex (2004)*	*Pannu (2006)*	*Kaplan (2008)*	*Szczudlik (2010)*	*Low (2011)*	*Score (%)*
Title and abstract	1	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	**7 (77.7)**
Introduction										
	2	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	**8 (100)**
	3	No	No	Yes	No	No	Yes	No	Yes	**3 (33.3)**
Methods										
	4	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	**8 (88.8)**
	5	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	**8 (88.8)**
	6	Yes	Yes	Yes	No	No	Yes	Yes	No	**5(55.5)**
	7	No	No	No	No	No	Yes	Yes	Yes	**3 (33.3)**
	8a	Yes	Yes	Yes	No	Yes	No	No	No	**5 (55.5)**
	9	No	No	No	No	Yes	No	No	No	**1 (11.1)**
	10	No	No	No	Yes	No	No	Yes	No	**2 (22.2)**
	11	Yes	No	Yes	No	No	Yes	Yes	No	**4 (44.4)**
	12	No	No	No	No	No	No	No	No	**0 (0)**
Results										
	13a	No	No	No	No	No	No	No	No	**0 (0)**
	14a	No	No	No	Yes	No	No	No	No	**1 (11.1)**
	15a	No	Yes	Yes	No	No	Yes	Yes	No	**5(55.5)**
	16	No	No	No	No	No	No	Yes	No	**1 (11.1)**
	17	No	No	No	No	No	No	No	No	**0 (0)**
Discussion										
	18	Yes	No	No	Yes	Yes	Yes	Yes	Yes	**7 (77.7)**
	19	No	Yes	No	Yes	No	Yes	Yes	No	**4 (44.4)**
	20	Yes	No	Yes	No	Yes	Yes	Yes	Yes	**6 (66.6)**
	21	No	No	No	No	No	No	No	No	**0 (0)**
Other Information										
	22	Yes	Yes	Yes	Yes	Yes	No	Yes	No	**7 (77.7)**
Score (Quality)		10 (M)	8 (M)	11 (M)	9 (M)	9 (M)	12 (M)	14 (M)	7 (L)	

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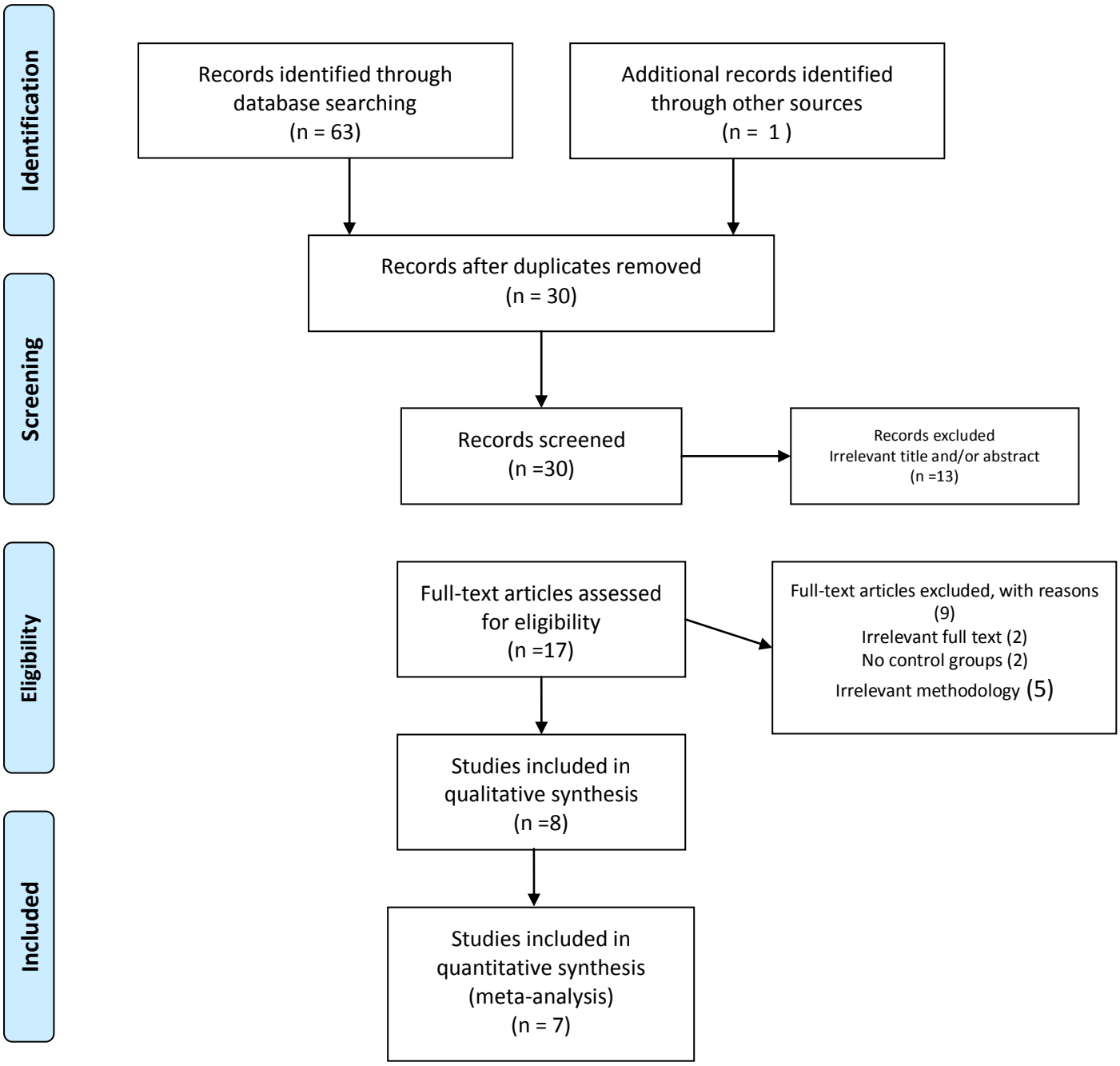
Figure 1. Flowchart



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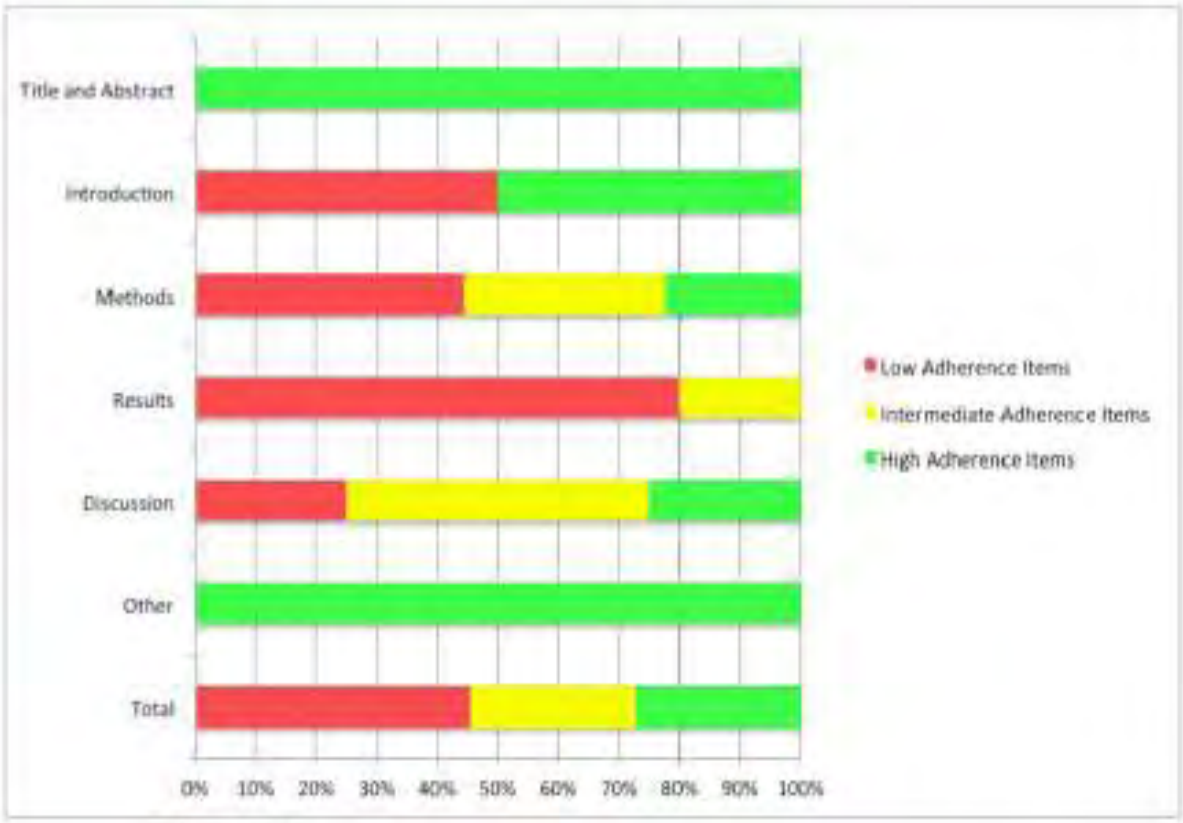

Figure 2

Adherence to STREGA and Reporting Bias in each Section. All items in the "Title and abstract" and "Other" sections carry a low risk of reporting bias. On the contrary, more than 70% of the items in each of the sections under the headings of "Methods", "Results" and "Discussion" indicate potential sources of bias

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