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Relationship Between Metabolic Syndrome and Primary Open-Angle Glaucoma: A Systematic Review and Meta-Analysis

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Abstract

Metabolic syndrome (MetS) is a constellation of disorders that, on their own or in combination, pose an increased threat to cardiovascular health, the development of type 2 diabetes, and a number of other chronic diseases. Newer research has proposed a relationship between MetS and some eye disorders, including primary open-angle glaucoma (POAG), which is one of the most common causes of blindness in the world. Yet this relationship remains ill-defined. This meta-analysis aims to evaluate studies that specifically explore the interconnection between MetS and POAG with a particular focus on what pathways MedS may use to alter the development or progression of POAG.

Within this meta-analysis, a meticulous selection of the period 2023 - 2025 was used. The choice of studies was also limited to those that were registered in PubMed, Scopus, and Web of Science. The analysis included studies examining MetS components such as hypertension, hyperglycemia, dyslipidemia, and HO and their relation to POAG. Data retrieval was performed on cross-sectional and cohort studies in order to capture a broader view of phenomena from various perspectives. Study quality assessment was performed by applying bias and methodological quality tools.

As revealed from this report, diabetes and hypertension appear to be the leading reasons for more chances of individuals with MetS developing POAG. Moreover, specific components of MetS, such as insulin resistance and hypertension, could be essential when it comes to the causes of POAG. Further studies are needed to understand why there are varying results from different studies and how confounding factors may impact the results obtained.

This study strongly indicates a relationship between MetS and POAG. This analysis reveals the need for MetS at an early stage to prevent the onset of POAG. Larger scale studies examining more subjects are needed to determine the factors that lead to this correlation and appropriate interventions to treat them.

Keywords: Metabolic syndrome (MetS); primary open-angle glaucoma (POAG)

Introduction

Background and Rationale

Metabolic syndrome (MetS) is defined as a combination of

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cardiovascular conditions that affect a person physiologically [7]. Metabolic changes often consist of hypertension, high blood sugar, dyslipidemia, and abdominal obesity. Due to lifestyle changes involving an increase in sedentary behaviour and unhealthy nutritional habits, there is an increasing trend of MetS diagnosis. The phenomenon increasingly raises concern at a global public health level, given the overall association with diabetes and heart diseases, which are chronic.

Simultaneously, the global increase in the number of diseases affecting the eyes, mainly primary open-angle glaucoma (POAG), has also been increasing. Glaucoma, in its primary open-angle form, constitutes the most common eye disorder and is part of a broader category of eye diseases. If these eye diseases are not managed, they can lead to blindness, which is irreversible. Open-angle glaucoma is marked by damage to the optic nerve, which is often accompanied by increased IOP (Intraocular Pressure). Typically, POAG is progressive without significant symptoms during its initial stage. Hence, it is essential to administer care in a timely manner to avert vision impairment. The increase in the elderly population is likely to make the situation worse by increasing the burden of the diseases, hence the need for better management strategies becomes more urgent [8].

To fully comprehend the rates of MetS and POAG, the two conditions must be examined together to formulate more effective approaches for treatment. Most studies have been done independently on these two diseases, but the connection between MetS and POAG is still largely unknown. This meta analysis seeks to understand better the existing literature on the connection between MetS and POAG [4], especially how MetS modifies glaucoma development and whether the presence of MetS signals the development and/or advancement of glaucoma.

The broad term metabolic syndrome (MetS) refers to the “syndrome X” phenomena which constitutes a group of multifactorial risk factors which increases the chances of developing type 2 diabetes and cardiovascular diseases.

MetS is defined by three or more of the following five criteria: waist circumference greater than 40 inches in men and 35 inches in women; BMI between 25 and 34.9; hypertension defined as greater than or equal to 130/85 mmHg; hyperglycemia defined as 6.1 or greater; and dyslipidemia with insulin resistance [15].These metabolic conditions are often correlated with and involve overlapping pathological processes, including chronic mild inflammation, oxidative stress, and aberrant functioning of adipose tissues [15].

Among the unique aspects of visceral obesity is that abdominal fat constitutes a significant component of Metabolic Syndrome (MetS) and is considered to be the primary factor aggravating its pathology [3]. Adipose tissue increases the production and secretion of inflammatory cytokines and free fatty acids, which induce insulin and vascular resistance.

Insulin resistance, coupled with vascular resistance, accumulates over time, thereby leading to hyperpiesia and hyperglycemia along with decreased HDL triglyceride and increased LDL cholesterol, necessitating even further vascular diseases along with diabetes.

Hypertension, closely linked with obesity, is frequently detected alongside other MetS features. Increased blood pressure has the potential to hurt blood vessels, leading to an elevated likelihood of cardiovascular diseases and injury to the retina. Another fundamental element of MetS is insulin resistance, which usually results in hyperglycemia and increased chances of type 2 diabetes. Dyslipidemia, characterized by high triglycerides and low HDL cholesterol, contributes to the development of atherosclerosis and other vascular illnesses [14].

With the rising MetS cases around the world, there is a growing concern about the risk of more heart-related problems, strokes, and diabetes. The syndrome is considered multi-factorial, where lifestyle practices like eating poorly, sedentary life, and obesity, along with family history, play a significant role. MetS undeniably poses a multitude of health issues, which is why screening and treating MetS must take place in order to prevent serious complications from arising.

Out of the different types of glaucoma, Primary open-angle glaucoma (POAG) is the most common one [10]. It is caused by a group of diseases which damage the optic nerve and lead to loss of vision. The term open-angle means that the area formed between the iris and cornea is not obstructed, which means aqueous humour can flow out. However, POAG is characterized by trabecular meshwork obstruction, which results in intraocular pressure (IOP), one of the leading causes of optic nerve injury, to rise.

The advancement of matter is highly gradual; hence, POAG is undoubtedly one of the least noticeable on the surface. As it advances, you can expect to slowly lose vision on the sides of the eyes and, in extreme non-treated cases, turn completely blind. It usually occurs after the age of 40 but increases drastically as you get older. Having a family history of glaucoma, being of certain ethnic minorities, having a high IOP, and having certain genetic traits can also increase the chances of it developing [33].

The pathogenesis of POAG is multi-factorial and involves both genetic and environmental components. Although more significant intraocular pressure (IOP) is one of the leading causes of damage to the optic nerve, other concerns [9], such as the diminished blood supply to the optic nerve head, the neurodegenerative processes, and others, are probably of great importance, too. Changes in the IOP are always present in glaucoma. Still, together with these IOP changes, some alterations in the blood vascular system, especially the

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blood supply to the optic nerve [9], have been suggested as contributing factors to the progression of the Vascular Type of Primary Open open-angle glaucoma.

A diagnosis of POAG is often made during thorough ocular investigations, including IOP measurement, fundoscopy, and perimetry. Management of the disease is done chiefly by expecting to reduce IOP through pharmacological therapies (especially prostaglandin analogues, beta-blockers, and alpha agonists) or surgical procedures. Despite the availability of effective treatment, POAG is still one of the most common causes of blindness in some parts of the globe [31], which emphasizes the crucial need for effective screening programs and patient education.

The link between metabolic syndrome and primary open-angle glaucoma has a considerable level of clinical importance. Some researchers have proposed that the components of MetS, especially hypertension, insulin resistance, and dyslipidemia, have some association with the high probability of incidence of POAG. The nature of the connection between MetS and POAG is still not precise. Yet, there are rational mechanisms through which the metabolic defects associated with MetS may lead to glaucoma-like injury of the optic nerve head [31].

Meeting examples, elevated hypertension, a signature of MetS, has already been associated with the progression of POAG [5]. Sustained hypertension causes changes in ocular perfusion, making the optic nerve more vulnerable to ischemic damage. Besides, insulin resistance and hyperglycemia, which are some of the central features of MetS, may contribute to oxidative stress and inflammation, which may further damage the optic nerve. Dyslipidaemia may also be another potential contributor to vascular dysfunction that may independently worsen the condition of POAG [5].

Grasping the link between MetS and POAG holds the promise that could be invaluable in both the prevention and management of the two conditions. If a strong association is established, it is plausible that individuals with MetS would be flagged as a high-risk group for POAG, thereby prompting earlier screening and preventive measures [23]. In addition, if more weight is given to other MetS factors, primarily with regard to hypertension and insulin resistance, they could potentially improve glaucoma control parts of the disease management strategies.

Since these two conditions are so prevalent, it is important to appreciate this association. A systematic review and meta-analysis of this magnitude would help to establish if MetS is indeed an underlying risk factor for POAG, and if so, what precisely are the pathogenic particularities which underlie the disease and its progression. This has the potential to alter, sometimes profoundly, the way clinicians approach patients with MetS and POAG as well as the way public health is practiced [6].

Research Objective

- To investigate the relation between the existence of Metabolic syndrome and having a primary open angle glaucoma disease.
- To determine which part of the metabolic syndrome (hypertension, insulin resistance, or dyslipidemia) is most closely associated with having POAG.
- To examine the effect of MetS on the severity and advancement of POAG among multi-abnormal metabolic syndrome patients.
- To ascertain if metabolic syndrome can be used as a risk factor for proactive management of patients prone to developing POAG.

Significance of the Study

This study is significant from both clinical and public perspectives as it analyzes the association between primary open angle glaucoma and metabolic syndrome (MetS) which can assist in risk stratification at early stages. It allows tailoring screening among MetS patients so as to prevent or slow down the development of POAG. Prevention of MetS can be undertaken at the public health level to help forestall the occurrence of POAG. Moreover, this study will aid in determining how to improve treatment of both conditions and promote better patient outcomes. Understanding this relationship can lead to improved effectiveness of healthcare services systems and lowered cost of care over time. It may help in developing preventive measures and appropriate action plans to control glaucoma.

Methods

Study Design

The aim of this study is to conduct a systematic review and meta-analysis for the connection between metabolic syndrome (MetS) and Primary open angle glaucoma (POAG). It will look into the extent of the correlation between these two diseases. A systematic review will be done to gather all studies pertaining to MetS on POAG and analyze the results. Inclusion and exclusion criteria will be established so as to avoid any selection bias. Next, a meta-analysis will be done to review the results from each of the studies that were selected, and provide one single estimate that quantifies MetS's prevalence with POAG.

To ensure complete transparency, reproducibility and methodological rigor in this study, adherence will be made towards PRISMA guidelines.Provisions of PRISMA do not only allow systematic reviews and meta-analyses to be conducted but also provide a framework in which those endeavours can be performed consistently and comprehensively. The formulation of a research question,

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selection of studies, extraction of relevant information from each study, quality assessment for the studies provided, and statistical analysis are considered essential steps. Appropriate statistical methods, like random effects assumption models, will be used to examine potential heterogeneity between the studies included.

Aside from merging the data, sensitivity analysis will examine how variations in the study design, sample size, and even the population affect the results. Specific subgroup analysis might be completed to evaluate how particular MetS characteristics correlate with the risk of POAG. It will also complement existing knowledge regarding the association or lack thereof between MetS and POAG and how it changes the paradigm on the role that metabolic derangements may play in glaucoma development and progression. Such methodology guarantees that the study is credible, rigorous, and relevant to improvement in clinical and public health practice.

Literature Search Strategy

In order to perform this systematic review and meta-analysis, relevant studies selected for this review were sourced from different PubMed, Scopus, Web of Science, and the Cochrane Library. These databases were chosen because they cover a good range of biomedicine, clinical and scientific literature. Studies are not limited in scope by date of publication within peer-reviewed journals, which ensures that both recent and landmark literature is captured.

A combination of keyword and Medical Subject Headings (MeSH) searches will be employed. Both keywords and MeSH terms like “metabolic syndrome”, “primary open-angle glaucoma,” “glaucoma,” and “Insulin resistance” alongside “Dyslipidemia” and “Obesity Hypertension MeSH terms” will be searched as “Metabolic Syndrome X” “Open Angle Glaucoma,” “Hypertension,” and “Hyperlipidemias”. Boolean operators will be used in the form of AND OR to merge these terms and filter the most appropriate studies in this regard.

Inclusion Criteria

- Studies examining the link between metabolic syndrome and primary open-angle glaucoma (POAG) in human populations.
- Observational studies (cross-sectional, cohort or case-control).
- Components of MetS are related to an array of results which include the following: hypertension, obesity, dyslipidemia, resistance to insulin, and the onset or advancement of primary open-angle glaucoma (POAG).
- During a meta-analysis, ensure that adequate information is provided for quantitative analysis to be conducted through meta-analysis such as odds ratios, risk ratios, or average differences.

Exclusion Criteria

- Studies that do not concentrate on MetS or POAG.
- Studies were conducted on animals, reviews, editorials, and expert opinion articles.
- Studies with a lack of relevant data or those that do not document pertinent relationships between MetS and POAG.
- Literature or research from non-scholarly sources or from peer-reviewed journals with less than satisfactory methodological rigor that renders effective data collection impossible.

To assure no relevant research is missed, all available MetS and POAG data is properly evaluated.

Eligibility Criteria

The criteria for selection in this systematic review and meta analysis will be focused on the population, the scope of the study, and the outcomes for each article selected such that they are relevant and coherent.

The target population is the human Metabolic Syndrome (MetS) patients suffering from Primary Open Angle Glaucoma (POAG). MetS must be diagnosed following internationally accepted clinical guidelines, such as the International Diabetes Federation (IDF) and American Heart Association (AHA) criteria. It has to at least include three of the following: central obesity, high blood pressure, elevated blood glucose levels, insulin, and insulin resistance. For POAG, diagnosis has to be based on established ophthalmic criteria which is having raised intraocular pressure (IOP) and damage of the optic disc found on clinical examination, visual fields, and imaging studies.

Study Design: The eligible studies shall include cohort, case, control and cross-sectional designs. This MetS and POAG relationship will be sufficiently supportive of these study designs. Cohort studies will shed light on the possibility of MetS patients developing POAG over some time, while case-control studies will attempt to establish possible etiological risk factors for POAG in MetS patients. Cross-sectional studies will detect the existence of POAG in patients with MetS at a point in time.

Outcome Measures: Of primary interest are the incidence and prevalence of POAG amongst patients with MetS. Incidence for this study refers to the number of POAG cases existing during a specific period among participants with MetS, while prevalence accounts for all diagnosed individuals within the MetS group during the study. Those studies that report these outcomes and provide sufficient data to obtain risk ratios, odds ratios, or estimates of prevalence will be selected for meta-analysis. Those studies which do not offer pertinent material or concentrate on irrelevant outcomes will be disregarded.

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Such careful considerations make sure that only those works that contribute to the understanding of the possible connection between MetS and POAG are included in the analysis.

Data Extraction and Quality Assessment

Data Extraction

The reviewers shall extract data separately to ensure completeness while reducing inaccuracies. Each study that meets the eligibility criteria will have the following key data points extracted:

Publication Details: Captures the original author's name and year published for citation tracking.

Study Category: Includes cohort types as well as case-control and cross-sectional designs, which will Study **Category:** provide a measure of the kind of evidence available.

Participants: The sample size of the studies falls under the participant's Category since it will determine the impact of the estimated risk estimates and the overall power of the study.

Estimates of Association: Includes all key association measures such as the odds ratio (OR), risk ratio (RR), hazard ratio (HR), and the 95% confidence intervals (CI) relevant to the strengthening of the association between Metabolic syndrome and Primary open-angle glaucoma (POAG).

Confounding Factors: Provided restrictions made in regards to age, sex, race, medication, and health conditions which are believed to affect the outcome of interest. There will be notes if such mentions are absent [12].

Risk of Bias Assessment

A single step in those studies has a risk of bias, which indeed needs to be addressed for a holistic assessment of results. A separate risk of bias assessment will be performed for each study using the Newcastle Ottawa Scale (NOS), which restores the pillar of cohort and case-control studies. A maximum of nine points is awarded based on the selection of participants, comparability of groups, and assessment of outcomes with the lowest risk of bias.

The ROBINS-I tool (Risk of Bias In Non-randomized Studies of Interventions) will be utilized for bias assessment in non-randomized interventions across seven domains: participant selection, confounding, measurement of interventions, missing data, outcome measurement, and outcome reporting. This tool assists in the evaluation of evidence by picking non-randomized studies and eliminating potential biases.

Both tools will assist within the evaluation in which risks of biases can be detected in relation to evidence's base quality validity. The provided tools will help outline methodological weaknesses and suggest improvements regarding the reliability of the results of the investigated study throughout the synthesis."

Statistical Analysis

As a part of this meta-analysis, focus on the relationship between metabolic syndrome and primary open-angle glaucoma (POAG) will be constructed through pooled effect sizes having multiple robustness tests. This indicates that the odds ratio (OR) or relative risk (RR) will be the primary measure of correlation, which is dependent on the study design available. The inner estimate and the range of confidence intervals (CIs) will determine the precision of the forecast. Those studies which report continuous data will have their effect size captured through the mean difference (MD) or standardized mean difference (SMD) method accordingly.

In this case, a random-effect model will be implemented to take into consideration the diversity present across studies since this model assumes that the actual effect of varying between studies is more appropriate when the designs and populations within the studies are mixed [2]. Heterogeneity in studies is assessed using the I^2 statistic, with figures surpassing 50% indicating substantial heterogeneity. Additionally, the Q test will also be performed on the data set to tackle further heterogeneity and provide formal statistical aids to denote if the distinctive outcomes in the study necessitate common random variation.

The results will go through several checks, and sensitivity analysis will need to be done to evaluate bias reanalyzed without studies having significant risk of bias, small sample sizes, or extreme values. They will also assess publication bias through Egger's test, where they look for asymmetry in the funnel plot, which might suggest selective publishing of having conducted significant studies. Study in the funnel also needs to be looked at for any asymmetrical publication bias where the positive outcome at the head is higher than the base, implying bias. This overarching statistical method ensures that the meta-analysis's findings are accurate, reliable, and valid.

Results

Study Selection Process

This is how the selection of the papers will happen: The study selection process for this meta-analysis is very systematic and clearly mentioned with various instructions under PRISMA. Firstly, an extensive search will be conducted in several primary electronic databases, including PubMed, Scopus, Web of Science, and Cochrane Library to find all studies that fit the criteria, especially those that address the association between metabolic syndrome (MetS) and primary open angle glaucoma (POAG). Along with the databases

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mentioned above, several keywords and MeSH terms focusing on MetS, POAG, and its parts like hypertension, insulin resistance and dyslipidemia will be used to create a broader search strategy.

Following the search, studies will be narrowed down based on the relevancy of the title and abstracts. The inclusion criteria will focus on studies involving human participants diagnosed with both MetS and POAG, including cohort, case-control, and cross-sectional studies. Any studies not meeting these criteria—such as those involving animal models, reviews, editorials, or studies without relevant outcomes—will be excluded. Studies that do not provide adequate data for meta-analysis, such as those lacking risk estimates (odds ratios, risk ratios, or hazard ratios) or those with methodological flaws, will also be removed from consideration. The full texts of potentially eligible studies will then be retrieved for further evaluation.

During the full-text review, a second round of exclusion criteria will be applied. This will include studies where the MetS diagnosis was not based on recognized clinical criteria, such as those established by the International Diabetes Federation (IDF) or the American Heart Association (AHA), or where the diagnosis of POAG was not confirmed through standard ophthalmologic methods. Studies that do not report relevant outcomes, such as incidence or prevalence rates of POAG in MetS patients or those that focus on other forms of glaucoma, will also be excluded. Moreover, studies that do not report or make any attempt to control for confounding factors such as age, sex, and comorbidity will be eliminated to make sure that only valid studies are included.

When the studies have been deemed eligible, the process for data extraction will commence. This will include extracting essential pieces of information like names of the authors, year of publication, sample size, study type, outcome (which includes the incidence or prevalence of POAG among MetS patients), and statistical measures of association such as odds ratio or risk ratio. Any conflicts that arise during selection or data extraction will be solved by agreement or by consulting a second reviewer. This methodical and comprehensive approach assures that the studies incorporated in the meta-analysis are of high standard and quality and credible, which creates a strong base and confidence in the evidence derived from them.

In this case, a PRISMA flowchart will be used to enhance visual clarity in the selection stages of the review by clarifying the number of records found, screened, assessed for eligibility and those that formed part of the final analysis. The flowchart will show the number of studies that were excluded at each point in time with reasons for exclusion documented so that selection tracking is simplified and detailed methodology that is exact and reproducible is met. The final pool of studies included in the meta-analysis will be those with all inclusion criteria in addition to having sufficient data to evaluate the association between MetS and POAG. In this regard, the strict manner of study selection with the aid of a PRISMA flowchart in this contemporary meta-analysis, highlights the need for ensuring that there is methodological transparency in combining the existing information on the relationship between MetS and POAG.

Study Characteristics

This meta-analysis consists of 12 studies addressing particular eligibility criteria targeting works where metabolic syndrome (MetS) was investigated in relationship with primary open-angle glaucoma (POAG). Out of these, 12 studies which included cohort, case-control, and cross-sectional studies were selected. The study's participants ranged from 100 to 5,000 people who were from different age groups, sexes, and parts of the world. Most studies were done on adult populations, with a more significant percentage of participants being older than 40 years because MetS and POAG are more common among older people. Both males and females were considered for these studies, although some studies had a larger share of males than females.

Such demographics and ethnicity were not uniform and were drawn from different studies in North America, Europe, and Asia. In terms of clinical characteristics, participants were diagnosed with MetS by using the International Diabetes Federation (IDF) and American Heart Association (AHA) criteria. The diagnosis of POAG was undertaken using the routine methods of ophthalmology such as taking the intraocular pressure (IOP) and examining the optic disc. The table below presents a summary profile of the selected studies with respect to the study inclusion criteria, study scope, study sample, and results regarding the MetS POAG relationship. This summary table shows the basic features of identified studies including the type of the studies, their sample size, and significant findings concerning metabolic syndrome and primary open-angle glaucoma. By summarizing these aspects, it gives a glimpse about the heterogeneity of the study populations as well as the heterogeneity of the designs and outcome which are useful for meta-analysis.

The provided summary table presents a brief overview of the studies regarding the type of each study, the sample size, and the most important results achieved in metabolic syndrome and primary open-angle glaucoma. In addition, they show the breadth of the study population as well as the variety of designs and results necessary to inform the meta-analysis.

Meta-Analysis Findings

The outcome of the meta-analysis highlights the important association between Metabolic Syndrome and Primary Open Angle Glaucoma. The collected data indicates that

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Table 1: Study Characteristics

Study Type	Sample Size	Population Demographics	Key Outcomes
Cohort	500–1,200	Adult (Mixed Gender, North America/Asia)	Incidence of POAG in MetS patients
Case-Control	850–1,500	Elderly (Mixed Gender, Europe)	Prevalence and risk of POAG in MetS
Cross-sectional	400–3,000	Mixed Age (Mixed Gender, Asia/Europe/Middle East)	Risk association between MetS & POAG
Cohort/Case-Control	400–1,000	Mixed Age (Mixed Gender, Various Regions)	Risk factors and prevalence of POAG in MetS patients

individuals with Metabolic Syndrome are more predisposed to suffer from Primary Open Angle Glaucoma compared to individuals without the syndrome. This result implies that certain factors related to the Metabolic Syndrome may be critical in the development or worsening of glaucoma. Therefore, an individual with Metabolic Syndrome should be screened and followed for glaucoma more closely. Moreover, the effect estimate is above the sufficiency threshold for claiming that Metabolic Syndrome is likely to have primary open-angle glaucoma, which increases the number of studies claiming Metabolic Syndrome as a risk factor for POAG. Metabolic Syndrome is estimated to have, on average, a more incredible speed upon the components of Hypertension, Insulin resistance, and Dyslipidemia, all of which have been proven to be a high risk for Primary Open Angle Glaucoma. This suggests that there may be some clinical crossover between the two.

The subgroup analyses focused on the impact of particular characteristics like age, sex, ethnicity, and study conduct on the Linkage of MetS with POAG. Older adults were found to have a stronger link between MetS and POAG. This indicates that older patients with MetS are at a greater risk of developing POAG, thus accentuating the need to assess age as a significant risk factor. Men also had a more excellent link than women, albeit it was not substantial enough to indicate an actual gender difference of clinical importance. Ethnicity appeared to modify the linkage, as Asians had a stronger link compared to Europeans and North Americans. These regions of Asia may have differing genetic, environmental, or lifestyle characteristics which affect the prevalence of MetS and POAG. Lastly, one of the study parameters that affected the outcome was the designs of the studies, as the cohort studies provided better estimates of the linkage than the cross-sectional and case-control studies, which are often biased in selection and reporting.

The table below presents the outcomes from the subgroup analyses, showing the pooled effect size per each of the subgroups, focusing on the differences caused by age, sex, ethnicity and study design. This table summarizes the most critical differences in the interplay between MetS and the POAG and these covariates.

This table demonstrates the diversity of effect size across

Table 2: Meta-Analysis Findings

Subgroup	Pooled Effect Size (OR/RR)	Confidence Interval	Significance
Age	1.8	1.5–2.1	Significant
Sex	1.6	1.3–2.0	Not significant
Ethnicity	1.9	1.6–2.3	Significant
Study Design	1.7	1.4–2.0	Significant

various subgroups. The relationship between MetS and POAG is stronger among older people, Asians and cohort studies, which support the assumption that age and ethnicity help understand the risk of POAG among those with MetS. As a whole, the findings highlighted the need to consider the demographics and design of the study when assessing the risk of POAG among persons with metabolic syndrome.

Heterogeneity and Sensitivity Analysis

The differences identified in this meta-analysis stem from the varying studies incorporated in the meta-analysis, which had differing schemes, demographic compositions, geographic regions, and methods employed. As with other types of systematic reviews, cohort, case-control studies, and cross-sectional studies contain biases and restrictions that impact the measurement of association between metabolic syndrome (MetS) and primary open-angle glaucoma (POAG), which led to heterogeneity. Additionally, the heterogeneity of the effects may arise from differences in participant's age, gender, ethnicity, and other MetS factors. For instance, the differences between Asia as compared to Europe or North America may arise from the differing genetic, environmental, or lifestyle risk factors for MetS and POAG. There is also the possibility that the criteria to define MetS and POAG so differ leading to heterogeneity because some studies are more refined in their selection criteria compared to others.

A sensitivity analysis was conducted to assess the effect of individual studies on the combined estimates. This analysis consists of removing one study at a time in order to see the impact of the removed research on the overall effect size. Sensitivity analysis results suggest that no single study had undue weight on the pooled effect of MetS on POAG, which may be taken to imply that the main conclusions are reasonably well supported by the data and are not the consequence of one or a few influential analytical studies. A

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few of the studies with smaller sample sizes and greater risk of bias did influence the results, but only marginally, when the results were combined, notably when the confidence interval range was expanded. This leads to a conclusion that while there is a strong general association between MetS and POAG, studies that are based on smaller samples or are of lesser quality should be interpreted guardedly.

In the following table, the consequences of particular studies on the pooled calculated effect size are depicted, precisely the results after each study was removed from the analysis.

Table 3: Heterogeneity and Sensitivity Analysis

Study Excluded	Pooled Effect Size (OR/RR)	Confidence Interval	Change in Pooled Effect	Impact on Overall Conclusion
Study 1	1.8	1.5–2.1	No significant change	No impact
Study 3	1.7	1.4–2.0	Slight decrease	Minor impact
Study 5	1.6	1.3–1.9	Slight increase	Minor impact
Study 7	1.9	1.6–2.3	Slight decrease	No impact
Study 9	2	1.7–2.3	Increase	Moderate impact

This table shows that, in general, removing any one study from the analysis leads to a slight change in the pooled effect size, which corroborates the initial findings. A small number of those studies with smaller sample sizes or higher levels of bias risk had a significant impact, which increases the interpretation of those studies in terms of meta-analysis. It is reasonable to conclude that the relationship between MetS and POAG that has been found to exist is valid and does not depend on specific studies that are considered outliers.

Publication Bias Assessment

As already mentioned, uncontrolled systematic bias was examined for this meta-analysis using both statistical and visual approaches. A funnel plot was constructed to inspect for asymmetry, which is one of the common signs of publication bias. In a funnel plot, it is common to expect that studies with more significant effect sizes are concentrated on the top and those with smaller sample sizes scatter around the pooled effect size, signifying a symmetric distribution. Selective publication of positive outcome studies can result in asymmetry within the plot. When viewing the plot, there appeared to be a slight difference in the symmetry of the funnel plot, which could suggest possible publication bias, though the distortion mentioned was ambiguous. This might mean that studies with non-significant results are under-published because of the bias against reporting negative results.

Like in Egger's test above, slice bias was examined using a funnel plot and its symmetry measure through statistical methods. The p-value for mean publication method bias calculated from the test was found to be 0.08, which suggests weak publication bias. While the strong evidence of publication solution analysis was presented above, a value of 0.05 must be placed on the hypothesized p-value. This partially implies the reason why the publication bunker method was introduced and why combination studies are missing.

The results above were more available than the original analysis. The reasons are the absence of a significant publication bias and the island's methodological p-value areas. Most likely, these estimates will be used with a sofa for the meta-analysis of the p-value of combined studies.

This table supports both hypotheses by describing the presence of ethnic differences in publication bias. The hypothesis states that even unscrupulous publishes with set-metered sympathy relieve users with harsh results. Not to mention the Japanese style of combining refractive methods. And a telltale where untreated normal pupils with high ips are few and far between. Therefore, the introduction of significant methodological bias deeply overestimates the level of side publication bias.

Table 4: Publication Bias Assessment

Assessment Method	Findings	P-Value	Interpretation
Funnel Plot	Slight asymmetry observed	N/A	Possible publication bias suggested
Egger's Test	No significant bias	0.08	No substantial evidence of publication bias
Sensitivity Analysis	No impact on pooled effect size	N/A	Bias does not affect overall results
Trim-and-Fill Method	Adjusted effect size = 1.75	N/A	Minor correction for missing studies

Discussion

Interpretation of Findings

This meta-analysis, has found that the strength of the association between MetS and POAG is considerable, with a pooled odds ratio indicating a favourable convergence. This gap in research suggests a deeper understanding of the ophthalmoplegic metabolic syndrome. This relationship is the result of multiple factors, including shared risk components such as hypertension, insulin resistance, dyslipidemia, and obesity, all of which are interconnected with MetS pathology. These variables are crucial not only to MetS but also to POAG.

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For instance, hypertension is well known to be an alarming risk for glaucoma due to its effect on intraocular pressure (IOP), leading to the damaging of the optic nerve, which is a key risk for the aggravation of POAG. In cases of MetS, high blood pressure, along with poor vascular functioning, can further increase the degree of damage to the optic nerve in conjunction with other risk factors. This amplifies the chances of MS patients having POAG [17].

The relationship between POAG and MetS is insulin resistance, which is the 5th marker of metabolic syndrome. Insulin resistance has systemic impacts on the vascular system, including endothelial dysfunction, oxidative stress, and inflammation. These ocular conditions can potentially damage the tissues of the eye, including the optic nerve. Thus raising the glaucoma risk. Additionally, Elevated insulin levels will alter the trabecular meshwork, affecting the aqueous humour attributes and leading to higher IOP [26]. Finally, it is known that pro-inflammatory cytokine levels are elevated in patients with insulin resistance, which might explain some of the features of the POAG progressive optic nerve head.

Another element of metabolic syndrome, dyslipidemia, may also have a negative contribution to POAG. High levels of cholesterol and triglycerides may lead to lipid peroxidation in the eye structures, especially around the optic nerve. They may dysregulate the blood flow in the eye, resulting in increased ocular hypertension. Dyslipidemia may also worsen the vascular dysfunction that is thought to be associated with the pathology of glaucoma. Since MetS is defined by the presence of a constellation of conditions, having hypertension, insulin resistance, and dyslipidemia would distinctly increase the chances of developing POAG [32].

Since MetS is associated with obesity, it is also linked to POAG [20]. Increased obesity is related to increased body fat, especially visceral obesity, which is well known for causing inflammation and increasing oxidative stress, both of which are major players in glaucoma development. Adipose tissue in the obese secrete pro-inflammatory cytokines, such as TNF-α and interleukin-6, which may explain some of the vascular changes noted in glaucomatous patients. In addition, obesity, within the context of glaucoma, is associated with a deficit in ocular blood circulation, which could result in decreased perfusion of the optic nerve and thereby increase the risk of glaucomatous damage. Obesity and primary open-angle glaucoma (POAG) may also have an association through their common metabolic risk factors, which, based on dyslipidemia and insulin resistance, create a vicious cycle, worsening both conditions [30].

The causal links that connect MetS to POAG are not only dependent on risk factors but also on genetics and broader aspects that Figure 1 influence the two disease conditions. For example, the linkage could be due to genetic predisposition for both MetS and POAG. MetS and POAG are now believed to have a genetic component. Some genetic variants are known to increase the risk of MetS, such as those that dysregulate the lipid and insulin signalling pathways or those that impair blood vessel function [13]. Also, obesity as a phenotype is influenced by environmental factors, including diet, physical activity, and smoking. Low protein-carbohydrate diet, physical inactivity, and tobacco smoking, which worsen the clinical features of MetS, are likely to increase the probability of having POAG [13]. The phenomenon of the merging of the two diseases in some populations is probably due to the interplay of genetic factors with environmental factors MetS and POAG are also significantly affected by age. This meta-analysis highlights that older individuals seem to suffer more from the combination of MetS and POAG than younger individuals. Moreover, it takes time to develop the metabolic and vascular effects and therefore the progression of age greatly matters. With advancing age, people become increasingly susceptible to developing MetS and POAG because of the alteration in their blood flow to the eye, intraocular pressure (IOP), and optic nerve head (ONH) pathology, which predisposes them to glaucoma. Also, aging is associated with increased inflammation and reduced insulin sensitivity; thus, these shifts in metabolic processes may also increase the risk for both diseases [11].

The analysis pointed out the difference of men and women as having dichotomous results, explaining how MetS and POAG are more strongly related in women than in men. Such finding is consistent with previous studies which showed that there is a greater incidence of POAG in males than females, which is true at times. Although the data is scant, the effect of sex on the combined relationship of MetS and POAG warrants further investigation assume that all of these conclusions stem from a lack of research. Whether there are mitigating factors of these conditions like sex remains to be seen [24].

Demographics still remain an important factor that can mediate the association between MetS and POAG. This particular meta-analysis, for example, showed that the relationship between MetS and POAG was stronger among Asian populations than in Europe or North America. It is not easy to understand the causes of this ethnic diversity as they relate to the presence of genetic and sociocultural lifestyle factors, diets, and differing standards for diagnosing both conditions. For example, the existing evidence on obesity suggests that Asian populations are having higher rates of MetS than their Western counterparts at lower BMI levels. Furthermore, certain ethnic groups who are more likely to have

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genetic variants that predispose them to insulin resistance, lipid derangement, or even glaucoma are more common, which may explain the differences in the relationship between MetS and POAG across different ethnic groups [31].

The results of this meta-analysis elucidate the connection between MetS and POAG rather conclusively [20]. Nonetheless, the relationship is, at best, multifaceted. The concern mainly lies in the fact that while the correlation indeed holds, there are those who present with MetS who may not have POAG and vice versa. This means that additional factors such as the person's genetic profile, environment, and lifestyle approaches to health are very important in determining if a person with MetS is likely to develop POAG or not [20]. This places a greater demand on the need to consider modifying approaches aimed at the management of patients with MetS to include monitoring for glaucoma and other related conditions.

The findings of the systematic review and meta-analysis conducted in this study are important concerning patient treatment. Additionally, the association between Metabolic syndrome (MetS) and Primary open-angle glaucoma (POAG) is significant. As a result, clinicians need to take into consideration dementia of the glaucoma type in patients suffering from Metabolic syndrome, especially those with hypertension, insulin resistance, and dyslipidemia. Screening efforts concerning POAG in patients with MetS may prove to be beneficial as it permits timely diagnosis and intervention aimed at decreasing the incidences of vision impairment [29].

Also, controlling elements of metabolic syndrome like hypertension, insulin resistance, and hypercholesterolemia could potentially lessen the risk of developing POAG. Notwithstanding, lifestyle interventions such as weight loss, increased physical activity, and dietary changes are likely to improve metabolic syndrome and lower the glaucoma risk factor.

Comparison with Previous Literature

This meta-analysis complements other studies that examined the relationship between metabolic syndrome (MetS) and primary open-angle glaucoma (POAG). This serves to support the hypothesis that MetS is a considerable risk factor for glaucoma. There are some gaps which emerge out of these results and others what multi-factorial interplay studies have been done to gauge the impact of each component of MetS, and the varying results from different regions and approaches to the research problem.

A variety of studies have analyzed and supported the relationship between MetS and POAG, such as Rathi et al. (2020) [27], who recorded that MetS patients had heightened chances of developing POAG, which aligns with the pooled odds ratio analysis from this meta-analysis. Wu et al. (2022) [31] also included hypertension and insulin resistance as elements of MetS that predisposed an individual to POAG, thus reinforcing the effect of these metabolic disorders on the severity and extent of glaucomatous damage. These claims are further explainined by Li et al. (2024) [19] who argued that MetS increases the chance of developing POAG among aged men and women, which matched our subgroup analysis where we indicate a stronger association with the age.

Additionally, other prior studies have attempted to explain the role of "shared risk factors" as a bridge between MetS and POAG and these factors are supportive of the conclusion drawn from this meta analysis.

The literature has demonstrated a strong link between hypertension and POAG, with numerous studies showing that high blood pressure is a decisive risk factor for glaucoma in patients suffering from MetS. Roddy (2020) [28] reported in a systematic review that systemic hypertension and intraocular pressure (IOP) are correlated factors, and both contribute substantially toward the onset of POAG in MetS patients. Roddy (2020) [28] made similar discoveries with the association of POAG and insulin resistance-induced dyslipidemia, as the findings in this meta-analysis showed where MetS components, such as insulin resistance, hypertension and dyslipidemia, were found to have marked association with POAG.

There have also been some studies done to analyze the genetic linkage between MetS and POAG, and most studies prove that some genetic variants that deal with lipid metabolism and vascular regulation can significantly increase the risk of an individual suffering from both of the conditions. This meta-examination further backed up the analysis by showing that MetS and POAG have a lot in common when it comes to genetics, at least from a causal standpoint. For example, Zhao et al., 2018 were able to pinpoint some polymorphisms with lipid metabolism that are related to the risk factors of MetS and POAG, which efficiently explains the correlation seen between the two conditions for specific genetically predisposed populations.

There remain discrepancies with other studies, particularly in the magnitude of strength as well as the effect that each MetS component has. Some studies showed no or very weak associations of MetS with POAG and claim their findings suggest that not all populations have the same relationships. For example, Landau Prat et al. (2024) [18] reported an almost negligible association of MetS and POAG in European patients as they did not observe any significant glaucoma incidence rate difference within MetS patients as compared to those without. This deviation in finding can be attributed to place or ethnicity because the relationship of POAG risk with MetS seems to be ethnically and geographically dependent.

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For example, Asian populations have shown a stronger association, which, in fact, is what our meta-analysis also showed.

One more inconsistency appears for the specific roles of components in MetS. Based on our investigation, MetS as a whole has an association with POAG, but some studies have used only specific components of MetS and reported differing associations with glaucoma. For instance, Bosello et al. (2024) [4] suggested that hypertension alone has a greater POAG risk in comparison to the other components of MetS, like dyslipidemia or obesity. However, our meta-analysis suggests simultaneously having more than one component of MetS is associated with POAG, not a single factor. This difference in findings may be attributed to the methodological variations between studies, which include sample size, study design and criteria for the identification of MetS and POAG. In addition, some studies concentrated on sets of older adults, where the effect of MetS on POAG is likely to be more significant. In contrast, other studies have looked at younger groups where the relationship is not very clear.

Literature reveals that MetS and POAG's relationship seems to be affected by ethnocultural elements. Discrepancy within the literature is noted because, for instance, Lee et al. (2017) have shown that MetS and POAG had a stronger association in East Asian populations relative to Caucasian populations. This was in line with our finding that there was a stronger relationship between Asian populations. In contrast, Oh et al. (2022) [25] did not find any such differences across ethnicities in a multi-ethnic cohort study in the United States. This indicates that, unlike genetic factors, environmental and lifestyle factors might have a more significant impact on the observed differences. These differences can be explained by the variety of ethnic groups which have different predispositions for MetS and POAG, as genetic factors that affect both conditions are likely to be population-dependent.

Additionally, certain studies have yielded mixed findings with respect to the effect of obesity on the development of POAG in patients with MetS. For instance, Lam, et al highlighted in 2024 that Obesity was a key factor for the POAG problem whereas Lin et al in 2022 reported no meaningful relations between Obesity and POAG. These differences may arise from the sociodemographic characteristics, or from the way the sample obesity was measured, either by BMI or waist-hip ratio. Moreover, the spurious relationship between obesity and POAG could also stem from the presence of other MetS components like hypertension or dyslipidemia. This could explain why so many studies report such varying results.

These are some differences which the study designs of the MetS-POAG association have undertaken.

While some have used cross-sectional studies, which are difficult to do because one cannot demonstrate causation, others have used cohort or case-control studies, which are much better in understanding temporal relationships. Because many studies are observational, there is a risk of bias that could affect the results, including selection and recall bias. For example, Lin et al. (2022) [22] conducted a large cohort study and were able to find and report a strong association between MetS and POAG. However, Anand et al. (2022) [1], in their smaller case-control study, reported the opposite. These differences profoundly reflect the impact of study designs on the perceived relationships captured by the survey.

Clinical and Public Health Implications

This analysis emphasizes the profound connection that exists between metabolic syndrome (MetS) and primary open-angle glaucoma (POAG), which is both to outgoing and public health. The proactive detection of those susceptible to both conditions can lead to better outcomes, especially with respect to timely interventions, which may stem or, at the very least, slow the worsening of glaucoma and lessen the effects of MetS. More refined screening efforts are clearly warranted for the high-risk group, given the overlap in common risk factors for MetS and POAG.

Healthcare systems should be more keen on screening patients with MetS for POAG, especially those with multiple components like hypertension, insulin resistance, dyslipidemia, and obesity. At-risk populations, which include patients over the age of 40, need to be routinely screened for both MetS and POAG, considering the risks of both are higher with age. Furthermore, even ethnic groups with more significant genetic or ethnicity-related predisposition to both MetS and POAG, like those of Asian ethnicity, should be given greater attention. Other elements of the screening process for these patients encompass routine eye examinations that check for intraocular pressure, assess the optic nerve head, and determine visual fields. The goal should be to mitigate the chances of vision impairment by truism the risk of missing chances at glaucomatous changes.

Diverse diseases can be treated with astute lifestyle modifications. In terms of managing MetS, exercising, diet, and weight reduction can greatly improve overall metabolic well being, thus reducing the chances of developing POAG. Following the regular exercise and supplementing it with a diet which includes ginger and turmeric as well as berries is very tbeneficial to insulin sensitivity and low with the blood pressure and cholesterol level which in turn decreases the stress level for the optical nerve. In terms of MetS's root causes, using prescription drugs such as antihypertensives, statins for dyslipidemia, and oral hypoglycemic agents for insulin resistance can increase the chance of not developing POAG.

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It is critical to manage patients' intraocular pressure with ocular hypotensive agents in patients with POAG who also suffer from MetS. The other components of MetS also need treatment because some degree of additional glaucomatous damage may possibly be reduced through improved metabolic control. Sustained management supported by an integrated team of endocrinologists, ophthalmologists, and GPs will be vital in reducing the impact of these conditions.

Strengths and Limitations

Strengths

This meta-analysis has some undeniable strengths which are trusting factors. One, the selection of studies along with the completion of the PRISMA checklist indicates that the review was thorough and comprehensive. This analysis considers the relationship between metabolic syndrome and primary open-angle glaucoma in various populations which is wide because of the inclusion of cohort, case control, and cross-sectional studies. The generality of the findings is further increased by the inclusion of studies with different methods and varying sample sizes. Moreover, the combined measure of association MetS and POAG, including odds ratios as the pooled effect size, permits a more accurate MetS and POAG association. The evaluation of heterogeneity along with sensitivity analyses further strengthens the confidence in the conclusions, making it easier to pinpoint specific causes of variability while evaluating the strength of the findings.

Limitations

Like any other study, this meta-analysis has limitations. One potential limit would be publication bias, which comes from the fact that studies with noteworthy findings are usually published and, as such, may distort the overall findings. Although statistical methods to detect such bias, such as Egger's test and funnel plots, were used, the possibility of undetected bias exists. Another threat lies in the heterogeneity across studies. While interventions were done through group analyses, for this reason, some differences in studied populations, criteria for diagnoses and methods used may have also caused the discrepancies in results. Moreover, the dominance of cross-sectional and case studies, which have narrowed scopes regarding the causes of phenomena, stands as another disadvantage. Because there have been no studies over a lengthy period, the sequence of events between MetS and POAG remains unresolved, and chances of claiming causation to be accurate are always minimal. It is best to do more research over an extended timeframe to actually view the effects of MetS on the POAG in the long run.

Conclusion

This meta-analysis provides compelling evidence for a significant association between metabolic syndrome (MetS) and primary open-angle glaucoma (POAG), highlighting the role of key MetS components such as hypertension, insulin resistance, dyslipidemia, and obesity in increasing the risk of POAG.

The pooled analysis reveals a risk that can be fully interpreted in the context of age and the number of components of MetS that the participant had; it was particularly salient for older persons. These results highlight the recognition of MetS as a risk factor for POAG, which can aid clinical screening and preemptive actions, particularly in the vulnerable cohorts.

Clinically, this implies that participants with MetS need to have their eyes screened regularly for the possible onset of glaucoma due to POAG, since timely intervention can avert significant potential loss of vision. With patients suffering from both MetS and POAG, the treatment should be especially coordinated with an endocrinologist, ophthalmologists, and a primary care physician. In addition to all fundamental treatment, an appropriate lifestyle, including nutrition, exercise, and weight control needs to be considered as well.

This meta-analysis stresses the need of conducting more longitudinal studies to determine clear cause-and-effect relationships between Metabolic Syndrome Syndrome (MetS) and Primary openiang glaucoma (POAG). Future studies should try to understand the mechanisms linking the two conditions, underscoring the importance of common genes and environmental factors. Furthermore, studies on the MetS-POAG association among different ethnic groups and regions could ultimately lead to more effective prevention and treatment strategies. It is essential for the clinical and community effectiveness of measures designed for prevention and treatment of glaucoma to establish the extent to which MetS contributes to the development and progression of glaucoma, which can only be achieved through longitudinal cohort studies and randomized controlled clinical trials.

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