# Association of *DVWA*, *MATN-3*, and *ADAMTS-14* Gene Polymorphisms with Knee Osteoarthritis Susceptibility: A Systematic Review and Meta-Analysis

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**KEYWORDS**

## ABSTRACT

**Background:**Knee osteoarthritis (KOA) is a common degenerative joint disorder characterized by the progressive deterioration of articular cartilage. Studies have suggested that *DVWA* (rs7639618) with KOA susceptibility. However, the results remain inconclusive.**Aim:**This meta-analysis aims to assess the association between the *DVWA* (rs7639618) gene and its potential role in susceptibility to KOA. **Methodology:**Meta-analysis was conducted in accordance with the PRISMA guidelines. Literature search was conducted up to January 2024 across several databases, including Science Direct, Pub Med, Web of Science, and Google Scholar, to identify appropriate case-control studies. Statistical analyses were performed using Metagenyo and Review Manager 5.4 software. Sub group analysis was performed based on ethnicity. Publication bias was analyzed using funnel plot and eggers test. **Results:**The meta-analysis included 13 studies with 14041 participants. The results revealed no statistical significant associations between any of the tested genetic models: allelic, recessive, dominant, or over dominant. Sub group analysis results revealed both Asian and Caucasian populations were not risk with KOA. Publication bias was analyzed by funnel plot and results revealed so significant bias.

**Conclusion:**Future large-scale well-controlled studies are necessary to validate present findings and to provide a clearer understanding of how *DVWA*, *MATN-3*, and *ADAMTS14* gene variants contribute to KOA. A better understanding of the genetic factors involved in KOA can lead to the development of targeted treatments and personalized management strategies for this debilitating condition.

## Introduction:

OA is a multifaceted joint disorder that impacts various joint tissues, including cartilage, subchondral bone, synovial membrane, meniscus, and the infrapatellar fat pad. Studies suggest that 30%–65% of the risk for OA is attributed to genetic factors (Aubourget al 2022; Ratneswaran et al 2021). KOA is the most common joint condition worldwide, with a systemic metabolic component (Allen et al 2022). Genetic factors, specifically polymorphisms such as double von willebrand factor A domains gene (*DVWA*), matrilin-3 (*MATN-3)*, and A Disintegrin and Metalloproteinase with Thrombospondin Motifs 14 (*ADAMTS-14*) genes, play a significant role in the onset and progression of knee OA.

The *DVWA* (rs11718863), also referred to as *COL6A4P1* (collagen type VI alpha 4 pseudogene 1), is primarily expressed in cartilage. It encodes a protein characterized by the presence of VWA domains, which plays a key role in cellular adhesion and protein-protein interactions. The *DVWA* domain has been demonstrated to interact with other protein domains, significantly influencing cartilage matrix formation and degradation. Genetic variations within the *DVWA* gene can profoundly impact the protein’s structure and function. Consequently, joint tissues and cartilage health may be affected. When *DVWA* gene polymorphisms occur, they have the potential to disrupt the normal organization of the extracellular matrix in the knee joint (Mostafa et al 2022). This disturbance compromises cartilage integrity and stability, rendering it more susceptible to degeneration and damage. Furthermore, these polymorphisms may also influence the function of chondrocytes, the cells responsible for cartilage production and maintenance. If chondrocyte function is impaired due to *DVWA* gene variations, it hinders the synthesize and repair the extracellular matrix. Ultimately, this contributes to cartilage breakdown and the development of OA. Additionally, *DVWA* gene polymorphisms can impact inflammatory and oxidative stress pathways within the joint, leading to increased inflammation and higher levels of oxidative damage in affected tissues, further exacerbating cartilage degradation and accelerating OA progression (Nakajima et al 2011; Bravata et al 2015). Previously, a meta-analysis has been conducted on *DVWA* gene polymorphisms and the risk of KOA. However, there remains a need for an updated study due to the emergence of new research and advancements in genetic analysis techniques. Recent studies may offer additional data and more refined methodologies, potentially leading to different conclusions or addressing inconsistencies in previous findings. Furthermore, changes in clinical practice, the growing relevance of genetic biomarkers for KOA, and the exploration of population-specific effects warrant a new meta-analysis to provide a clearer, more comprehensive understanding of the association between *DVWA* polymorphisms and KOA.

*MATN-3*(rs8176070) gene, situated on chromosome 2q37.3, predominantly expresses itself in cartilage tissue, with a specific focus on the extracellular matrix.*MATN-3*, a protein that is crucial for maintaining cartilage integrity (Sharma et al 2020). It achieves this by engaging in interactions with other extracellular matrix components and orchestrating cellular processes crucial for cartilage homeostasis (Gu et al 2012). Notably, genetic variations within the MATN3 gene can lead to skeletal dysplasia and osteoarthritis. These polymorphisms have been linked to the development and progression of KOA, impacting cartilage health, chondrogenesis, and interactions with other genes (Li et al., 2020). This is the first meta-analysis to examine the association between *MATN-3* gene polymorphisms and the risk of KOA. The need for this study arises from the potential role of *MATN-3* gene in cartilage integrity and degeneration, which has been suggested by individual studies but remains inconclusive. By pooling data from various studies, this meta-analysis aims to provide a more comprehensive and statistically powerful assessment of the relationship between *MATN-3* polymorphisms and KOA. Additionally, the growing interest in genetic markers for early diagnosis and personalized treatment of KOA underscores the importance of understanding the role of *MATN-3* in disease susceptibility and progression.

The *ADAMTS-14* gene (rs4747096) is a member of the ADAMTS family, which plays a critical role in the degradation of extracellular matrix (ECM) components (Li et al 2022). *ADAMTS-14* is specifically implicated in collagen processing and remodelling within connective tissues, including cartilage. It encodes a zinc-dependent protease that cleaves and regulates the assembly of collagen fibrils, contributing to the structural integrity and functionality of the ECM (Flannery et al 2006). Genetic polymorphisms in the *ADAMTS-14* gene can significantly alter its enzymatic activity and regulatory functions. These variations may affect the gene's expression levels, protein structure, or substrate affinity, thereby influencing ECM homeostasis. In KOA, *ADAMTS-14*gene polymorphisms have been associated with disrupted collagen turnover, leading to imbalances in cartilage synthesis and degradation. This disruption compromises the resilience and stability of articular cartilage, making it more vulnerable to wear and tear. Furthermore, polymorphisms in the *ADAMTS-14* gene have been linked to altered chondrocyte activity. Impaired chondrocyte function due to genetic variations can exacerbate cartilage degradation by reducing the synthesis of essential ECM components such as proteoglycans and collagen, while simultaneously increasing the activity of degradative enzymes like matrix metalloproteinases (MMPs). *ADAMTS-14* gene polymorphisms may also influence inflammatory and oxidative stress pathways within the joint (Kumavat et al 2021). This can result in elevated levels of pro-inflammatory cytokines and reactive oxygen species (ROS), creating an environment that promotes cartilage destruction and accelerates KOA progression. By impairing ECM integrity, chondrocyte function, and inflammatory regulation, *ADAMTS-14* polymorphisms contribute to the complex molecular mechanisms underlying KOA pathogenesis. The present study represents the first comprehensive investigation into the association between *ADAMTS-14* gene polymorphism and the susceptibility to KOA. The impetus for this study stems from the emerging evidence suggesting that *ADAMTS-14* gene involved in the regulation of cartilage extracellular matrix components, may influence the development and progression of KOA (Ma et al 2018). Although individual studies have explored this potential link, the results have been mixed and inconclusive. By synthesizing data from a range of studies, this meta-analysis seeks to clarify whether specific polymorphisms in *ADAMTS-14* are associated with an increased risk of KOA. Given the increasing focus on genetic markers as potential tools for early diagnosis of KOA and tailoring personalized therapeutic strategies, understanding the role of *ADAMTS-14*gene polymorphisms could offer valuable insights into the genetic underpinnings of the disease and pave the way for more effective diagnostic and therapeutic approaches.

## Methodology:

Meta-analysis was conducted in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines, a widely recognized framework that ensures transparency, rigor, and reproducibility in systematic reviews and meta-analyses.

## Search Strategy:

Literature search was conducted up to December 2024 across several databases, including Science Direct, PubMed, Web of Science, and Google Scholar, to identify appropriate case-control studies. Keywords and phrases such as "Osteoarthritis," "Knee Osteoarthritis," "*DVWA* gene polymorphisms," "*MATN-3* gene polymorphism", "*ADAMTS-14*" were employed, using Boolean operators like "AND" to narrow the search results. Only articles published in English were included, and the reference lists of the selected studies were examined for additional pertinent research.

**Inclusion and Exclusion Criteria:**

In the present meta-analysis, the studies were selected if they met the following inclusion criteria:

1. Studies with data of two groups such as cases and controls
2. Articles that published only in English
3. Distribution data on data genotype and allelic frequencies, along with sample size were provided.
4. Investigations assessing the association between *DVWA*, *MATN-3* and *ADAMTS-14* gene polymorphisms with the risk of Knee osteoarthritis.

Studies were excluded if they were

1. OA studies other than Knee
2. Not available in full-form
3. Lacking statistical data
4. Except English, remaining language articles were excluded.

**Extraction of Data:**

The extraction of data from several data bases (Science Direct, Pub Med, Web of Science, and Google Scholar) and tabulation in Microsoft excel were done by two independent authors (SK and VN). The extracted data consists of: name of author, ethnicity, publication year, sample size, distribution of genotype frequencies, demographic characteristics. In case of any disagreement, two authors reviewed the gathered data and resolved the issue through mutual discussion to reach an agreement. The extracted data are given in Tables 1-4.

**Quality of Study:**

The New Ottava Scale in case-control studies of gene polymorphism provides a structured framework for assessing methodological quality. It evaluates key domains such as selection of cases and controls, comparability of groups, and the robustness of exposure assessment. The total score ranges from 1-9. Study score greater than 7 was considered to be high quality (Table1).

**Statistical Analysis:**

Data included in the studies were expressed as odds ratio (OR) with confidence interval (CI) to check the association between gene polymorphisms and KOA risk. Heterogeneity was calculated based on chi-square based Q-test and $I^2$statistics. If the $I^2$>50%, and p<0.10, then it was considered to be of statistical significant and the pools effect was estimated by random effects model. Fixed effects model was used, if the $I^2$< 50%, and p >0.10. Subgroup analysis for ethnicity was performed based on heterogeneity. Publication bias was analysed by funnel plot. All the statistical analyses were carried out by metagenyo and review manger 5.4 software.

**Results:**

The literature search and mapping process was structured following the PRISMA guidelines, which are widely used for conducting systematic analyses. An initial search yielded a total of 477 articles, which 405 articles were retrieved, after removing 72 duplicates. Further, 363 articles were excluded according to exclusion criteria such as unrelated to KOA, reviews and overlapping studies, and 42 full text articles selected. In which, 26 articles again excluded due to lack of frequency and distribution and statistical data.

The full text articles were retrieved and further assessed. Finally, 16 case-control studies were included for quantitative analysis to assess the relationship between *DVWA*, *MATN-3*, and *ADAMTS-14* genes and susceptibility of KOA as stated in the flow chart (Figure 1). Out of these 16 studies, 10 were from Asian, and 6 from Caucasians population. Demographic data extracted from the studies and shown in Table 1. The characteristics data for the three genes shown in Table 2, Table 3 and Table 4.

| ***DVWA* (rs11718863)** | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **S.No** | **Study** | **Ethnicity** | **Controls** | | **KOA** | | **Total no of samples** | | **Age (Mean ± SD)** | | **Body mass index (kg/m2)** | |
| | | | **Male** | **Female** | **Male** | **Female** | **Controls** | **KOA** | **Controls** | **KOA** | **Controls** | **KOA** |
| 1 | Valdes et al 2009 | Caucasian | 0 | 512 | 0 | 264 | 512 | 264 | 63 ±5.8 | 66.3 ±6.2 | 26.2±4.3 | 28.1±5.3 |
| 2 | Valdes et al 2009 | Caucasian | 383 | 371 | 308 | 427 | 654 | 735 | 66.9 ±10.8 | 68.5 ±8.5 | 26.5±3.9 | 29.5±5.1 |
| 3 | Miyamoto et al 2008 | Asian | 323 | 308 | 117 | 529 | 631 | 646 | 54.1 ±15.5 | 72 ±7.7 | 25.3 ±3.3 | 24.8 ±3.5 |
| 4 | Miyamoto et al 2008 | Asian | 178 | 307 | 60 | 182 | 485 | 242 | 68.2 ±8.7 | 71.4 ±7.7 | 22.35± 2.8 | 24.4 ±3.3 |
| 5 | Zhang et al., 2023 | Asian | 23 | 105 | 17 | 86 | 128 | 103 | 60.70 ± 6.38 | 67.18 ± 9.53 | 25.54 ± 2.90 | 26.37 ± 3.70 |
| 6 | Mostafa et al., 2022 | Caucasian | 6 | 19 | 10 | 40 | 25 | 50 | 50.08 ± 7.04 | 52.92 ± 7.50 | 30.67 ± 4.24 | 31.59 ±4.89 |
| 7 | Hasan et al., 2022 | Asian | 25 | 35 | 25 | 35 | 60 | 60 | 61.47 ±1.54 | 69.52 ±1.17 | 27.46 ±0.74 | 31.49 ±1.0 |
| 8 | Hasan et al., 2022 | Asian | 25 | 35 | 25 | 35 | 60 | 60 | 61.47 ±1.54 | 60.98 ±1.42 | 27.46 ±0.74 | 30.67 ±0.87 |
| 9 | Bravata et al 2015 | Caucasian | NA | NA | NA | NA | 100 | 61 | NA | NA | NA | NA |
| 10 | Luo et al 2023 | Asian | NA | NA | NA | NA | 128 | 103 | 64 | 67 | 25.4 | 26.4 |
| ***ADAMTS-14* (rs4747096)** | | | | | | | | | | | | |
| 1 | Poonpet et al 2013 | Asian | 26 | 93 | 20 | 88 | 119 | 108 | 54.5 ±2.72 | 69.94 ±8.41 | 20.1 ±7.4 | 20.2 ±6.1 |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 2 | Sen et al 2018 | Asian | 248 | 232 | 170 | 176 | 480 | 246 | 56.6 ± 7.0 | 57.1 ±7.0 | 23.8 ± 3.1 | 23.6 ± 3.0 |
| 3 | Ghada et al 2024 | Caucasian | 63 | 45 | 98 | 38 | 108 | 136 | 51.6 ±9.3 | 55.2 ±7.1 | 25.65 ±4.25 | 26.29 ±4.45 |
| ***MATN-3* (8176070)** | | | | | | | | | | | | |
| 1 | Hashemzehi et al., 2021 | Asian | 59 | 61 | 51 | 54 | 120 | 105 | 56.9 ±6.4 | 55.6 ±7.4 | 20.1 ±7.4 | 20.2 ±6.1 |
| 2 | Diab et al., 2017 | Caucasian | 13 | 37 | 18 | 32 | 50 | 50 | 58.48 ±6.17 | 60.36 ±6.38 | 21.98 ±2.77 | 22 ±2.16 |
| 3 | Gu et al., 2012 | Asian | 156 | 156 | 204 | 216 | 312 | 420 | 58.7 ± 9.5 | 57.4 ±9.5 | 19.9 ± 8.3 | 20.1 ± 8.2 |

**Table 1. Demographic Characteristics of participants**

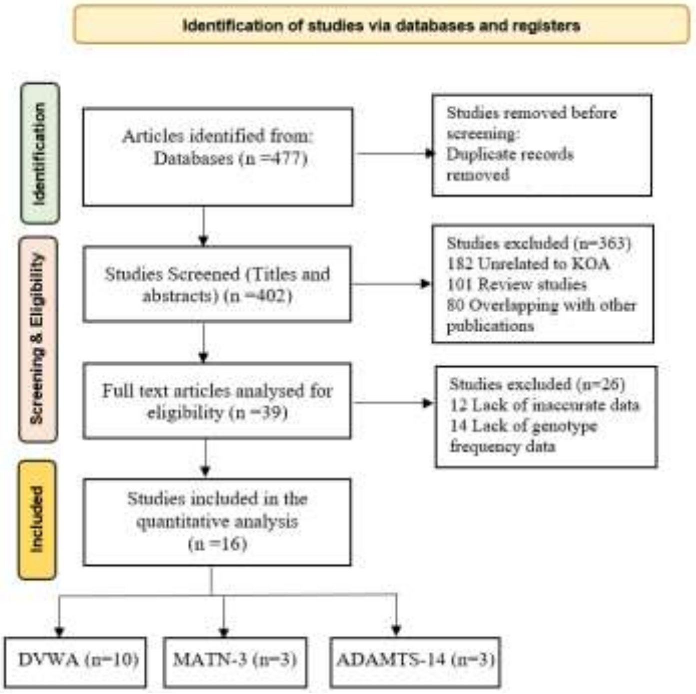


**Figure 1.** Flow chart for the literature search and Study selection

**Table 2.** Characteristics of included studies of *DVWA* (rs11718863) gene polymorphism with KOA risk

| Study | Ethnicity | TT | TA | AA | TT | TA | AA | Quality Scores | HWE P.value |
|---|---|---|---|---|---|---|---|---|---|
| | | **Cases** | | | **Controls** | | | | |
| Bravata et al 2015 | Caucasian | 41 | 18 | 2 | 72 | 25 | 3 | 8 | 0.8104 |
| Valdes et al 2009 | Caucasian | 505 | 201 | 27 | 474 | 169 | 11 | 7 | 0.8104 |
| Valdes et al 2009_1 | Caucasian | 188 | 68 | 8 | 357 | 143 | 12 | 8 | 0.8104 |
| Miyamoto et al 2008 | Asian | 255 | 294 | 95 | 162 | 327 | 137 | 7 | 0.8104 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Miyamoto et al 2008_1 | Asian | 98 | 106 | 36 | 168 | 220 | 94 | 8 | 0.7645 |
| Zhang et al 2023 | Asian | 18 | 56 | 29 | 9 | 71 | 48 | 6 | 0.117 |
| Luo et al 2023 | Asian | 29 | 43 | 31 | 52 | 57 | 19 | 7 | 0.8104 |
| Hasan et al 2022 | Asian | 55 | 5 | 0 | 57 | 3 | 0 | 6 | 0.8426 |
| Hasan et al 2022_1 | Asian | 31 | 29 | 0 | 57 | 3 | 0 | 6 | 0.8426 |
| Mostafa et al 2022 | Caucasian | 1 | 14 | 35 | 0 | 6 | 19 | 6 | 0.8104 |

**Table 3.** Characteristics of included studies of *MATN-3* (8176070) gene polymorphism with KOA risk

| **Study** | **Ethnicity** | **bb** | **bB** | **BB** | **bb** | **bB** | **BB** | **Quality Score** | **HWE P.value** |
|---|---|---|---|---|---|---|---|---|---|
| | | **Cases** | | | **Controls** | | | | |
| Hashemzehi et al 2021 | Asian | 22 | 40 | 43 | 13 | 48 | 59 | 7 | 0.5674 |
| Gu et al 2012 | Asian | 19 | 49 | 40 | 37 | 126 | 149 | 6 | 0.5674 |
| Diab et al 2017 | Caucasian | 12 | 30 | 8 | 6 | 20 | 24 | 7 | 0.5674 |

**Table 4.** Characteristics of included studies of *ADAMTS-14* (rs4747096) gene polymorphism with KOA risk

| **Study** | **Ethnicity** | **AA** | **AG** | **GG** | **AA** | **AG** | **GG** | **Quality Score** | **HWE P. value** |
|---|---|---|---|---|---|---|---|---|---|
| | | **Cases** | | | **Controls** | | | | |
| Poonpet et al 2013 | Asian | 50 | 46 | 12 | 48 | 46 | 25 | 6 | 0.0951 |
| Sen et al 2018 | Asian | 146 | 126 | 74 | 256 | 182 | 42 | 7 | 0.3612 |
| Ghada et al 2024 | Caucasian | 100 | 35 | 1 | 68 | 34 | 6 | 7 | 0.527 |

## Quantitative data analysis

A total of 3,171 cases and 3,964 controls from 16 studies were included to explore the association between the *DVWA*, *MATN-3*, and *ADAMTS-14* genes and susceptibility to KOA.

### Association between DVWA gene polymorphism with KOA risk

The analysis included 2,318 cases and 2,775 controls from 6 Asian and 4 Caucasian studies. The association tests for the *DVWA* gene did not show any statistically significant association with KOA risk across all four genetic models. For the allele contrast model, the overall OR was 0.931 (95% CI=0.6957–1.2454, p=0.630), with substantial heterogeneity ($I^2$=85%) (Figure 2A). For the recessive model, the overall OR was 0.929 (95% CI=0.6294–1.3703, p=0.709), with high heterogeneity ($I^2$=84%, $p<0.001$) (Figure 2B). For the dominant model, the overall OR was 0.974 (95% CI=0.6401–1.4810, p=0.901), with high heterogeneity ($I^2$=72%) (Figure 2C). For the over dominant model, the overall OR was 1.063 (95% CI=0.8273–1.3649, p=0.634), with moderate heterogeneity ($I^2$=67%) (Figure 2D).

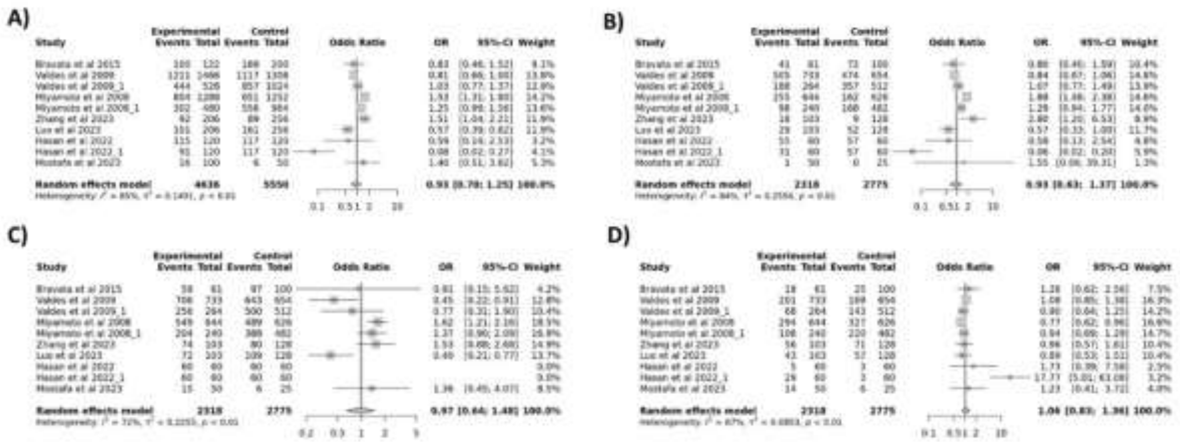


**Figure 2.**Forest plot for the association of *DVWA* (rs11718863) gene polymorphism with risk of KOA under A) Allelic B) Recessive C) Dominant D) Over dominant models

**Subgroup analysis evaluation in different ethnicities:**

Considering the heterogeneity and negative results, we have performed sub group analysis in different ethnicities divided into Asians and Caucasians population. The results revealed neither Asians nor Caucasians were at risk for KOA susceptibility (Table 5). Among the Asian population, the OR was 0.875 (95% CI=0.5608–1.3643, p=0.555), with high heterogeneity (I²=89%). In the Caucasian population, the OR was 0.887 (95% CI=0.7569–1.0388, p=0.137), and no heterogeneity was detected (I²=0%, p=0.460).Among Asians, the OR was 0.856 (95% CI=0.4451–1.6452, p=0.640), with high heterogeneity (I²=89%, p<0.001). In Caucasians, the OR was 0.906 (95% CI=0.7551–1.0871, p=0.288), with no heterogeneity (I²=0%, p=0.754). Among Asians, the OR was 1.140 (95% CI=0.6844–1.8977, p=0.615), with high heterogeneity (I²=80%). In Caucasians, the OR was 0.676 (95% CI=0.4183–1.0933, p=0.110), with no heterogeneity (I²=1%, p=0.388).Among Asians, the OR was 1.183 (95% CI=0.7592–1.8432, p=0.458), with high heterogeneity (I²=79%, p<0.001). In Caucasians, the OR was 1.037 (95% CI=0.8618–1.2481, p=0.700), with no heterogeneity (I²=0%).

**Table 5.** Summary estimates for ORs and 95% CI in different ethnicities for *DVWA* gene polymorphism

| **Model** | **Analysis Model** | **Pooling Model** | **Test of association** | | | **Test of heterogeneity** | | **Publication bias** |
|---|---|---|---|---|---|---|---|---|
| | | | **OR** | **95% CI** | **p-val** | **I^2** | **p-val** | **p-val (Egger's test)** |
| Overall | Allele contrast | Random | 0.931 | [0.6957; 1.2454] | 0.630 | 85% | 0.000 | 0.133 |
| | Recessive | Random | 0.929 | [0.6294; 1.3703] | 0.709 | 84% | 0.000 | 0.316 |
| | Dominant | Random | 0.974 | [0.6401; 1.4810] | 0.901 | 72% | 0.001 | 0.231 |
| | Overdominant | Random | 1.063 | [0.8273; 1.3649] | 0.634 | 67% | 0.002 | 0.058 |
| Asian | Allele contrast | Random | 0.875 | [0.5608; 1.3643] | 0.555 | 89% | 0.000 | 0.092 |
| | Recessive | Random | 0.856 | [0.4451; 1.6452] | 0.640 | 89% | 0.000 | 0.168 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Dominant | Random | 1.140 | [0.6844; 1.8977] | 0.615 | 80% | 0.002 | 0.479 |
| | Overdominant | Random | 1.183 | [0.7592; 1.8432] | 0.458 | 79% | 0.000 | 0.078 |
| Caucasian | Allele contrast | Fixed | 0.887 | [0.7569; 1.0388] | 0.137 | 0% | 0.460 | 0.446 |
| | Recessive | Fixed | 0.906 | [0.7551; 1.0871] | 0.288 | 0% | 0.643 | 0.754 |
| | Dominant | Fixed | 0.676 | [0.4183; 1.0933] | 0.110 | 1% | 0.388 | 0.331 |
| | Overdominant | Fixed | 1.037 | [0.8618; 1.2481] | 0.700 | 0% | 0.744 | 0.683 |

### Evaluation of the association between *MATN-3* polymorphism and KOA

For the *MATN-3* gene, the analysis included 263 cases and 482 controls from 2 Asians and 1 Caucasian studies. The association tests results showed statistically significant associations for dominant, recessive and allelic models (Table 6). For the allele contrast model, the overall OR was 1.583 (95% CI=1.2617–1.9864, p<0.001), with low heterogeneity ($I^2$=30%) (Figure 3A). For the recessive model, the overall OR was 1.874 (95% CI=1.2206–2.8784, p=0.004), with no heterogeneity ($I^2$=0%, p=0.740) (Figure 3B). For the dominant model, the overall OR was 1.922 (95% CI=1.0803–3.4190, p=0.026), with moderate heterogeneity ($I^2$=64%, p=0.064) (Figure 3C). For the over dominant model, the overall OR was 1.222 (95% CI=0.8928–1.6718, p=0.211), with low heterogeneity ($I^2$=39%, p=0.194) (Figure 3D). Subgroup analysis was not conducted due to the limited number of studies.

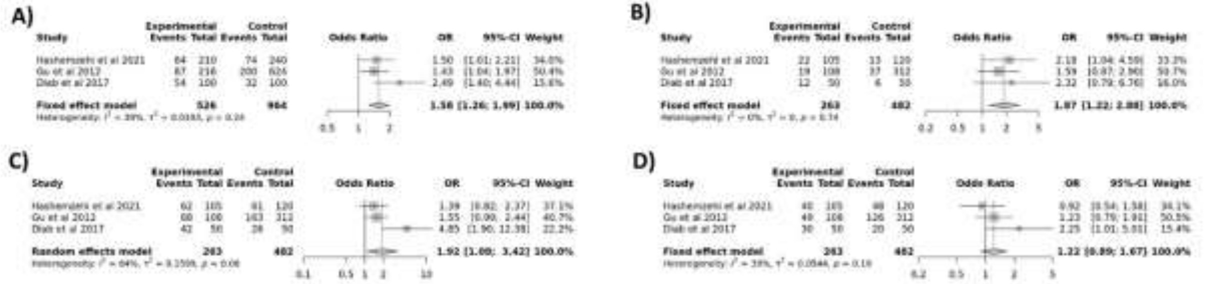


**Figure 3.**Forest plot for the association of *MATN-3* (8176070) gene polymorphism with risk of KOA under A) Allelic B) Recessive C) Dominant D) Over dominant models.

**Table 6.** Summary estimates for ORs and 95% CI in different ethnicities for*MATN-3* gene polymorphism

| **Model** | **Analysis Model** | **Pooling Model** | **Test of association** | | | **Test of heterogeneity** | |
|---|---|---|---|---|---|---|---|
| | | | **OR** | **95% CI** | **p-val** | **I^2** | **p-val** |
| Overall | Allele contrast | Fixed | 1.583 | [1.2617; 1.9864] | 0.000 | 30% | 0.238 |
| | Recessive | Fixed | 1.874 | [1.2206; 2.8784] | 0.004 | 0% | 0.740 |
| | Dominant | Random | 1.922 | [1.0803; 3.4190] | 0.026 | 64% | 0.064 |
| | Overdominant | Fixed | 1.222 | [0.8928; 1.6718] | 0.211 | 39% | 0.194 |

## Evaluation of the association between *ADAMTS-14*polymorphism and KOA

For the *ADAMTS-14* gene, the analysis included 590 cases and 707 controls from 2 Asians and 1 Caucasian study. The association tests results did not show statistically significant associations for all the four genetic models(Table 7). For the allele contrast model, the overall OR was 1.0996 (95% CI=0.5270–2.2944, p=0.800), with high heterogeneity ($I^2$=93) (Figure 4A). For the recessive model, the overall OR was 1.0621 (95% CI=0.5694–1.9814, p=0.849), with high heterogeneity ($I^2$=83%) (Figure 4B). For the dominant model, the overall OR was 1.4454 (95% CI=0.2782–7.5096, p=0.661), with high heterogeneity ($I^2$=91%) (Figure 4C). For the over dominant model, the overall OR was 0.9433 (95% CI=0.7497–1.1869, p=0.618), with no heterogeneity ($I^2$=0%) (Figure 4D).

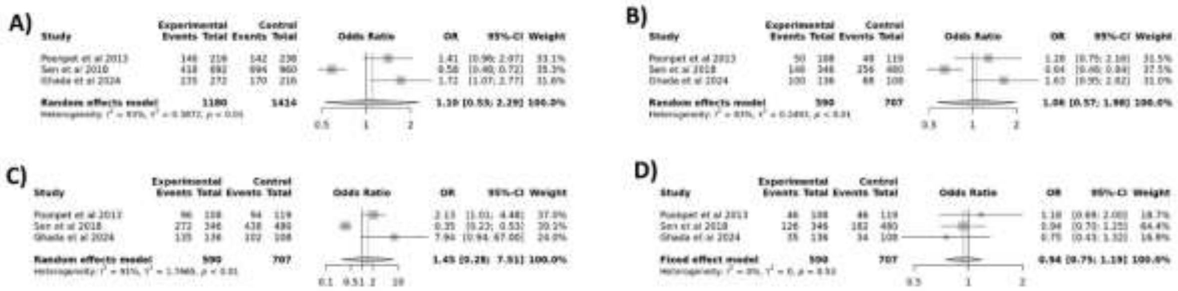


**Figure 4.** Forest plot for the association of *ADAMTS-14*(rs4747096) gene polymorphism with risk of KOA under A) Allelic B) Recessive C) Dominant D) Over dominant models

**Table 7.**Summary estimates for ORs and 95% CI in different ethnicities for *ADAMTS-14* gene polymorphism

| Model | Analysis Model | Pooling Model | Test of association | | | Test of heterogeneity | |
|---|---|---|---|---|---|---|---|
| | | | OR | 95% CI | p-val | I^2 | p-val |
| Overall | Allele contrast | Random | 1.0996 | [0.5270; 2.2944] | 0.800 | 93% | 0 |
| | Recessive | Random | 1.0621 | [0.5694; 1.9814] | 0.849 | 83% | 0.002 |
| | Dominant | Random | 1.4454 | [0.2782; 7.5096] | 0.661 | 91% | 0 |
| | Overdominant | Fixed | 0.9433 | [0.7497; 1.1869] | 0.618 | 0% | 0.525 |

## Sensitivity Analysis:

Sensitivity analysis is vital in gene polymorphism meta-analysis to assess the robustness and reliability of the pooled results. By testing how variations in study selection, statistical models, or methodological assumptions impact the outcomes, sensitivity analysis ensures that the observed associations are not driven by biases across studies. Sensitivity analysis for *DVWA* gene was carried out by forest plot by neglecting each study. The results showed except the study by Miyamoto et al 2008, other studies showed no significant impact on overall outcome (Figure 5). The sensitivity analysis was not carried out for *MATN-3* and *ADAMTS-14* genes due to small number of studies.

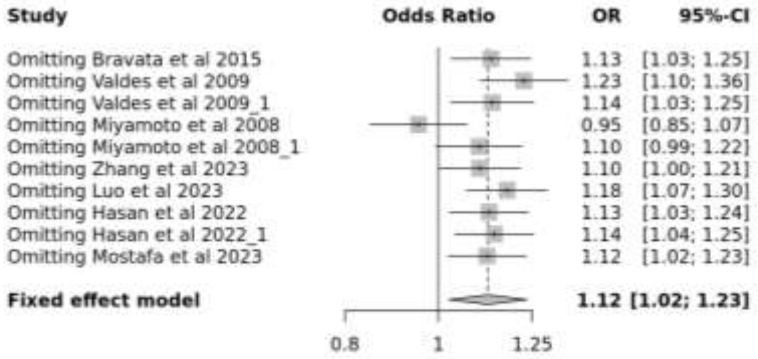


**Figure 5.** Sensitivity analysis for the association of *DVWA* (rs11718863) gene polymorphism

**Publication Bias:**

Publication bias analysis is crucial in gene polymorphism meta-analysis as it ensures the reliability and validity of the results. Eggers test was used to estimate the possible publication bias between the entire studies. In addition to Egger's test, we utilized a funnel plot to visually assess the presence of publication bias for the *DVWA* gene polymorphism (Figure 6). The funnel plot analysis did not reveal any significant asymmetry, supporting the conclusion that publication bias was not a concern in the present study.However, we have not performed the Eggers test and visualized funnel plot for the *MATN-3* and *ADAMTS-14* genes due to limited studies.

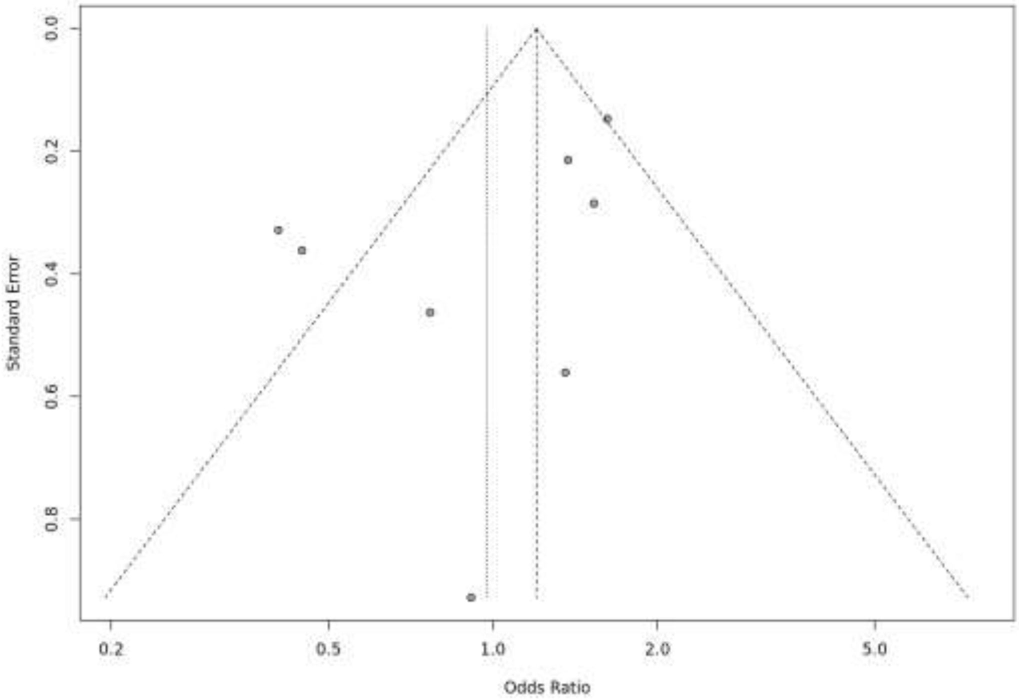


**Figure 6.** Funnel plot for the analysis of publication bias for the association of *DVWA* (rs11718863) gene polymorphism with risk of KOA

**Association with demographic data:**

The results from the meta-analyses provide insights into the differences in demographic data such as BMI and age between experimental and control groups across multiple datasets (Figure 7-9). In the *DVWA* BMI analysis, the pooled mean difference was 1.97 (95% CI: -0.74 to 3.20, P = 0.002), indicating statistically significant difference, with substantial heterogeneity ($I^2$ = 98%). The *MATN-3* BMI analysis reported a minimal pooled mean difference of 0.08 (95% CI: -0.62 to 0.78, P = 0.82), with no observed heterogeneity ($I^2$ = 0%). Similarly, the *ADAMTS-14* BMI analysis also found no significant difference (mean difference: 1.53, 95%

CI: -0.99 to 4.05, P = 0.23), though heterogeneity was high (I² = 95%). In contrast, the *DVWA* age analysis showed a statistically significant mean difference of 5.37 (95% CI: 1.55 to 9.20, P = 0.006), despite high heterogeneity (I² = 99%). The *MATN-3* age analysis reported a mean difference of -0.45 (95% CI: -2.24 to 1.33, P = 0.62), with moderate heterogeneity (I² = 62%). Lastly, the *ADAMTS-14* age analysis found a non-significant mean difference of 6.49 (95% CI: -3.02 to 16.01, P = 0.18) and very high heterogeneity (I² = 99%). Overall, the *DVWA* gene showed statistical significant differences for both age and BMI, whereas the remaining both genes did not show any statistical significant differences for either age or BMI.

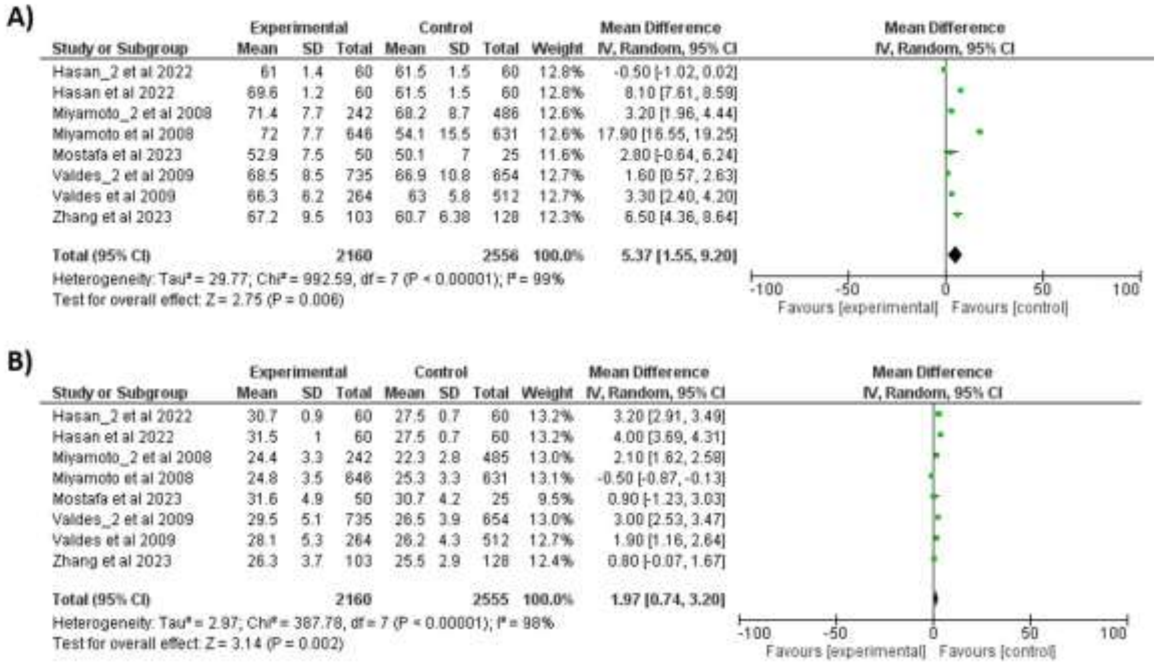


**Figure 7.** Forest plot for the demographic characteristics of *DVWA* gene A) Age B) BMI

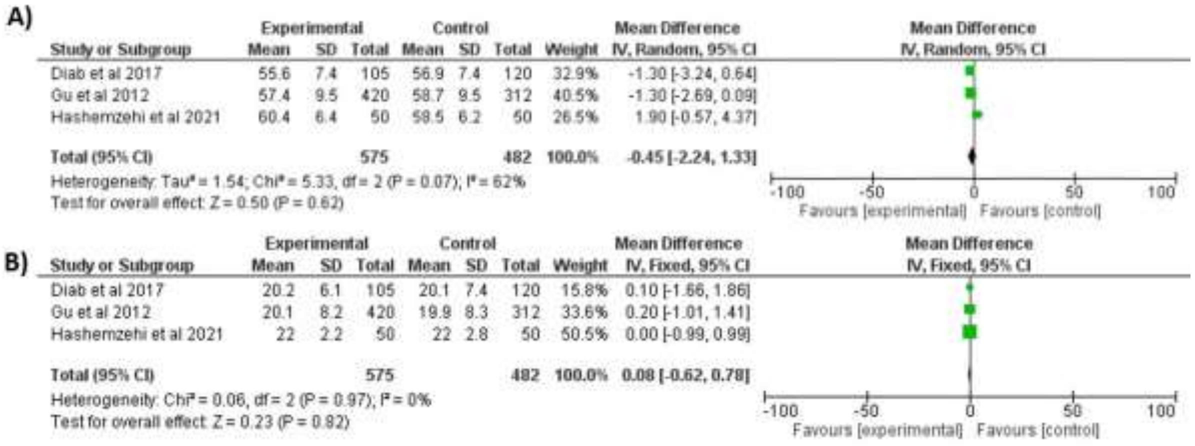
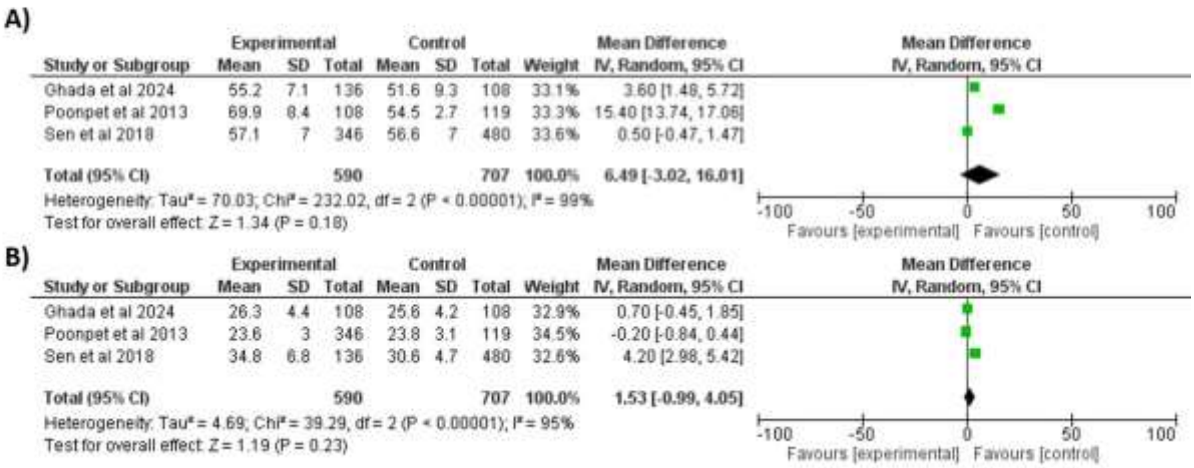


**Figure 8.** Forest plot for the demographic characteristics of *MATN-3* gene A) Age B) BMI



A)

| | Experimental | | | Control | | | | Mean Difference |
|---|---|---|---|---|---|---|---|---|
| Study or Subgroup | Mean | SD | Total | Mean | SD | Total | Weight | IV, Random, 95% CI |
| Ghada et al 2024 | 55.2 | 7.1 | 136 | 51.6 | 9.3 | 108 | 33.1% | 3.60 [1.48, 5.72] |
| Poonpet et al 2013 | 69.9 | 8.4 | 108 | 54.5 | 2.7 | 119 | 33.3% | 15.40 [13.74, 17.06] |
| Sen et al 2018 | 57.1 | 7 | 346 | 56.6 | 7 | 480 | 33.6% | 0.50 [-0.47, 1.47] |
| **Total (95% CI)** | | | **590** | | | **707** | **100.0%** | **6.49 [-3.02, 16.01]** |

Heterogeneity: Tau² = 70.03; Chi² = 232.02, df = 2 (P < 0.00001); I² = 99%
Test for overall effect: Z = 1.34 (P = 0.18)

B)

| | Experimental | | | Control | | | | Mean Difference |
|---|---|---|---|---|---|---|---|---|
| Study or Subgroup | Mean | SD | Total | Mean | SD | Total | Weight | IV, Random, 95% CI |
| Ghada et al 2024 | 26.3 | 4.4 | 108 | 25.6 | 4.2 | 108 | 32.9% | 0.70 [-0.45, 1.85] |
| Poonpet et al 2013 | 23.6 | 3 | 346 | 23.8 | 3.1 | 119 | 34.5% | -0.20 [-0.84, 0.44] |
| Sen et al 2018 | 34.8 | 6.8 | 136 | 30.6 | 4.7 | 480 | 32.6% | 4.20 [2.98, 5.42] |
| **Total (95% CI)** | | | **590** | | | **707** | **100.0%** | **1.53 [-0.99, 4.05]** |

Heterogeneity: Tau² = 4.69; Chi² = 39.29, df = 2 (P < 0.00001); I² = 95%
Test for overall effect: Z = 1.19 (P = 0.23)

**Figure 9.** Forest plot for the demographic characteristics of *ADAMTS-14* gene A) Age B) BMI

## Discussion:

Meta-analysis is a statistical technique that combines data from multiple independent studies to derive a more comprehensive understanding of a research question (Borenstein et al 2021). It plays a crucial role in the study of gene polymorphisms by providing a comprehensive and statistically robust evaluation of data pooled from multiple studies. Gene polymorphism studies often yield conflicting or inconclusive results due to small sample sizes, population diversity, and methodological differences. By combining data from various sources, meta-analysis increases statistical power and enhances the reliability of findings, helping to identify true associations between specific genetic variations and diseases. This approach minimizes biases, resolves inconsistencies, and facilitates the identification of trends that may not be apparent in individual studies, thereby contributing to a deeper understanding of genetic predispositions and their clinical relevance.

KOA is a chronic, progressive condition characterized by cartilage degradation, subchondral bone remodeling, osteophyte formation, and synovial inflammation, leading to joint stiffness, pain, and reduced mobility (Du et al 2023). It is the most common form of arthritis, significantly impacting quality of life and posing a substantial socioeconomic burden. While mechanical stress, aging, obesity, and joint injury are recognized as key risk factors, genetic predisposition plays a critical role in determining an individual's susceptibility to knee OA. Recent studies have highlighted the importance of specific gene polymorphisms in pathways regulating cartilage metabolism, inflammation, and oxidative stress, such as variations in genes encoding matrix metalloproteinases (MMPs), collagen, and inflammatory cytokines (Mukherjee et al 2024, Young et al 2019).

The *DVWA* gene is located on chromosome 3p24.3, has been identified as a critical susceptibility gene for KOA (Bravatà et al 2015). The rs11718863 polymorphism within *DVWA* plays a significant role in cartilage integrity and the joint's ability to withstand mechanical stress. This gene is involved in the interaction between cartilage cells and the extracellular matrix, which is crucial for maintaining cartilage resilience under biomechanical loads. Variants such as rs11718863 can impair this interaction, making cartilage more vulnerable to wear and tear, thereby increasing the risk of KOA. Studies suggest that individuals carrying the risk allele for rs11718863 are more prone to cartilage degradation, particularly in populations subjected to high levels of physical activity or joint stress, underscoring its pathogenic role in KOA development (Chen et al 2024).

The *MATN-3* gene is situated on chromosome 2p24.1, encodes a key extracellular matrix protein involved in cartilage structure and assembly (Nakki et al 2012). The rs8176070 polymorphism in *MATN-3* has been linked to alterations in matrix composition, leading to a compromised cartilage framework. *MATN-3*is a crucial non-collagenous protein that contributes to the stability and organization of the cartilage extracellular matrix. Variants such as rs8176070 reduce the functional efficacy of MATN-3, resulting in a weaker matrix that is more susceptible to degeneration and inflammation (Shukla et al 2020). This genetic alteration is associated with both the early onset and progression of KOA, making it a significant contributor to disease susceptibility. The presence of this polymorphism can exacerbate cartilage degradation and accelerate the pathogenesis of osteoarthritis.

The *ADAMTS-14* gene is located on chromosome 10q22.1, plays an essential role in extracellular matrix remodeling and collagen fibril processing (Goertsches et al 2005). The rs4747096 polymorphism within this gene is implicated in abnormal collagen turnover, a hallmark of KOA pathology. *ADAMTS-14* contributes to the balance between matrix synthesis and degradation, which is vital for maintaining cartilage structure. Variants like rs4747096 disrupt this balance, leading to weakened cartilage and increased susceptibility to joint degeneration. Additionally, this polymorphism is associated with heightened inflammatory responses, further exacerbating cartilage damage and joint dysfunction (Li et al 2022). The pathogenicity of rs4747096 highlights its importance in understanding the genetic basis of KOA and its potential as a target for therapeutic interventions aimed at preserving cartilage integrity.

The present meta-analysis aimed to evaluate the association between gene polymorphisms of *DVWA*, *MATN-3*, and *ADAMTS-14* and the susceptibility to KOA. The search and selection process followed the PRISMA guidelines to ensure comprehensive and unbiased inclusion of studies. After screening 477 initial articles, 16 case-control studies were selected, consisting of a total of 3,171 cases and 3,964 controls. The studies were grouped based on ethnicity (Asian and Caucasian populations) to identify potential differences in genetic susceptibility to KOA.

The results for the *DVWA* gene polymorphism (rs11718863) did not show any significant association with KOA susceptibility across all four genetic models tested (allelic, recessive, dominant, and over-dominant). However, these results were not persistent with previously reported study by Wang et al 2015. Wang et al.'s subgroup analysis demonstrated that this genetic variant was linked to an increased risk of KOA in Asians, but not in Caucasians. However, in our study, this association appears to be absent in both Asian and Caucasian populations. This difference could be due to various factors, such as the size and diversity of the study populations, differences in study designs, or the methods used to assess KOA (Lu et al 2025, Rosenberg et al 2010). It’s also possible that the effect of rs11718863 on KOA might depend on other genetic or environmental factors not considered in either study (Georgiev et al 2019). This highlights the need for further research to better understand the genetic factors involved in KOA. The forest plot (Figure 2) revealed high heterogeneity among the studies, indicating substantial variability in the results. The sensitivity analysis conducted to confirm the robustness of the results, as excluding most studies had little impact on the overall outcome. However, the study by Miyamoto et al. (2008) was identified as a potential outlier that influenced the findings, suggesting that the study may have had methodological or population-specific factors that caused divergence from the rest of the studies. While this does not invalidate the overall conclusion, it underscores the importance of careful study selection and quality control when conducting meta-analyses. Regarding publication bias, the funnel plot analysis did not show significant asymmetry, suggesting that publication bias is not a major concern.

In contrast to the *DVWA* gene, the *MATN-3* gene polymorphism demonstrated significant associations with KOA risk in several genetic models (allelic, recessive, and dominant) with pooled OR and CI indicating a notable contribution of the *MATN-3* gene to the disease. These findings are in line with previous studies suggesting that *MATN-3* plays an important role in the structural integrity of the cartilage and might contribute to cartilage degradation in KOA (Shukla et al 2020). However, the limited number of studies available for *MATN-3* prevented subgroup analysis, which may have provided more granular insights into ethnic differences or environmental factors influencing this gene's role in KOA. The forest plots (Figure 3) demonstrated relatively lower heterogeneity, supporting the robustness of the findings for *MATN-3*.

For the *ADAMTS-14* gene polymorphism (rs4747096), no significant association with KOA susceptibility was found across any genetic models (recessive, allelic, dominant, and over-dominant). As with the *DVWA* gene, high heterogeneity in the studies (Figure 4) complicated the interpretation of the results. Moreover, the limited number of studies included for *ADAMTS-14* restricted the potential for subgroup analyses or further investigation of ethnic-specific associations. Despite the lack of significant findings, further research with larger sample sizes and more diverse populations would be necessary to establish whether *ADAMTS-14* may play a more subtle or context-dependent role in KOA susceptibility.

The demographic results from the meta-analyses highlight significant variability in BMI and age across the datasets. Both age-related and BMI-related outcomes showed statistical significance in *DVWA* analyses, suggesting that these variables may be responsive to the interventions or factors studied within this specific context. However, the broader meta-analyses exhibited high heterogeneity ($I^2$ up to 99%), which complicates the interpretation of the findings. This variability likely stems from differences in study populations, methodologies, and intervention strategies across the datasets. Such diversity underscores the need for more standardized approaches in future research to better isolate the effects of the interventions on both BMI and age-related outcomes. Notably, the lack of heterogeneity in the *MATN-3* BMI analysis ($I^2 = 0\%$) and the moderate heterogeneity in the *MATN-3* age analysis ($I^2 = 62\%$) underscore the importance of methodological consistency in achieving reliable results. The non-significant findings in the *ADAMTS-14* BMI analysis, despite high heterogeneity, may suggest that genetic influences like *ADAMTS-14* do not have a direct or observable effect on BMI across the studied populations. However, the gene could still play a role in specific conditions, such as osteoarthritis, where its action might impact physical mobility and, consequently, BMI. Future research should focus on addressing the high heterogeneity by employing standardized study protocols, larger and more diverse sample sizes, and more robust study designs. Additionally, more targeted studies on BMI could explore the influence of different types of interventions and examine whether longer durations or specific population characteristics might yield more significant findings. By improving methodological rigor and considering these factors, future studies can better address the inconsistencies observed and strengthen the validity of the findings.

## Strengths

This meta-analysis demonstrates several notable strengths, starting with its comprehensive approach, analysing data from 16 case-control studies comprising 7,135 subjects. This large sample size enhances the robustness of its conclusions about the association between specific gene polymorphisms and susceptibility to KOA. By adhering to the PRISMA guidelines, the study ensures transparency, methodological rigor, and reproducibility, making the findings more credible. It offers valuable gene-specific insights by focusing on *DVWA*, *MATN-3*, and *ADAMTS-14*polymorphisms, addressing previously inconclusive results in this domain. The inclusion of ethnicity-based subgroup analyses enables a comparative evaluation of genetic susceptibility among Asian and Caucasian populations, providing a more nuanced understanding of the genetic factors in KOA. Methodological rigor is further emphasized through sensitivity analysis and publication bias assessment, which validate the reliability of the results. Moreover, the use of multiple genetic models—allelic, recessive, dominant, and over-dominant—ensures that the associations are thoroughly evaluated across different genetic perspectives, adding depth to the analysis.

## Limitations

The study has notable limitations that need to be considered. A significant limitation is the small number of studies available for the *MATN-3* and *ADAMTS-14* genes, which restricts the depth of analysis and precludes subgroup analyses that could provide a more granular understanding of these genes' roles. High heterogeneity among the included studies, especially for *DVWA* and *ADAMTS-14*, poses challenges to the consistency and interpretation of the findings. Additionally, sensitivity analysis revealed outliers, such as the study by Miyamoto et al. (2008), suggesting potential methodological or population-specific biases that could influence the overall results. The reliance on case-control designs limits the ability to capture longitudinal developments in KOA, which could provide further insight into the progression of the disease. Furthermore, the exclusion of non-English publications introduces selection bias, potentially omitting relevant research and limiting the study’s comprehensiveness. Finally, the study does not explore gene-environment interactions, which are crucial in understanding the multifaceted nature of KOA and how genetic predispositions interplay with environmental factors.

## Conclusion:

This meta-analysis provides valuable insights into the association between *DVWA*, *MATN-3*, and *ADAMTS-14* gene polymorphisms and susceptibility to KOA. While significant associations were observed for *MATN-3*gene polymorphisms, no such relationships were found for *DVWA* and *ADAMTS-14* across the tested genetic models. The study underscores the critical role of genetic factors, particularly *MATN-3*, in influencing KOA susceptibility, while highlighting the need for further research to confirm these findings for *DVWA* and *ADAMTS-14*. Despite the strengths of a large sample size, rigorous methodology, and ethnicity-based subgroup analyses, limitations such as high heterogeneity, small number of studies for specific genes, and a lack of longitudinal or gene-environment interaction data underscore the need for future studies. Larger, more diverse cohorts and advanced analytical approaches could further refine our understanding of the genetic underpinnings of KOA, potentially leading to targeted interventions and personalized treatment strategies for this debilitating condition.

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