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Review

A scoping review of statistical methods to investigate colocalization between genetic associations and microRNA expression in osteoarthritis

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ABSTRACT

Background: Genetic colocalization analysis is a statistical method that evaluates whether two traits (e.g., osteoarthritis [OA] risk and microRNA [miRNA] expression levels) share the same or distinct genetic association signals in a locus typically identified in genome-wide association studies (GWAS). This method is useful for providing insights into the biological relevance of genetic association signals, particularly in intergenic regions, which can help to elucidate disease mechanisms in OA and other complex traits.
Objectives: To review the existing literature on genetic colocalization methods, assess their suitability for studying OA, and investigate their capacity to integrate miRNA data, while bearing in view their statistical assumptions.
Design: We followed scoping review methodology and used Covidence software for data management. Search terms for colocalization, GWAS, and genetic or statistical models were used in the databases MEDLINE and EMBASE, searched till March 4, 2024.
Results: Our search returned 546 peer-reviewed papers, of which 96 were included following title/abstract and full-text screening. Based on both cumulative and annual publication counts, the most cited method for colocalization analysis was coloc. Four papers examined OA-related phenotypes, and none examined miRNA. An approach to colocalization analysis using miRNA was postulated based on further hand-searching.
Conclusions: Colocalization analysis is a largely unexplored method in OA. Many of the approaches to colocalization analysis identified in this review, including the integration of GWAS and miRNA data, may help to elucidate genetic and epigenetic factors implicated in OA and other complex traits.

1. Introduction

Osteoarthritis (OA) is a multifactorial chronic joint disease representing a leading cause of disability and pain worldwide, with no currently approved disease-altering treatments [1,2]. A more thorough understanding of underlying biological mechanisms contributing to the development and progression of OA is expected to lead to novel treatment strategies. Insights into biological mechanisms are provided by genome-wide association studies (GWAS), which aim to identify single nucleotide polymorphisms (SNPs) that are associated with diseases/traits such as OA. Large-scale GWAS on OA have previously been conducted, the largest of which pinpointed previously unknown loci harbouring 52 genome-wide significant risk variants across 11 OA phenotypes in a multicohort of nearly 900,000 individuals [1]. Furthermore, through fine mapping of these GWAS signals and complementary computational approaches, this study identified 77 genes that have at least 3 lines of evidence in support of their role as effector genes. Of these genes, 48 strongly support previously reported OA-associated SNPs as likely effector genes, while 30 were associated with new signals.

Increasingly, GWAS are performed across multiple diseases (e.g., OA and type 2 diabetes [1]) and across multiple traits within a disease, which creates the need for investigating shared risk variants. This phenomenon,

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called genetic colocalization, occurs when genetic variants (e.g., SNPs) at a given locus are associated with two (or more) diseases/traits [3]. This association is important in the context of the disease(s) of interest because it suggests that the traits under examination share a common genetic underpinning, and thus, can identify the specific genes or regulatory regions involved in the pathology of the disease(s). Genetic colocalization is evaluated by various methods that decipher the statistical relationship between genetic variants and multiple diseases or traits, potentially revealing the most biologically-relevant mechanisms underlying complex diseases such as OA (Fig. 1).

In addition to exploring shared statistical genetic associations, colocalization can also be performed with other genetic factors such as quantitative trait loci (QTLs). QTLs are loci which explain variation in phenotypes of complex traits [4], and when integrated with genotypes, provide insight into the genetic basis of traits. Expression quantitative trait loci (eQTLs), genetic variants that correlate with variation in the expression levels of messenger RNAs (mRNAs), are the most common type of QTLs considered in colocalization analysis. Integrating eQTLs into colocalization analysis is especially useful in the context of loci with non-coding variants, which typically hinder straightforward interpretation of their functional impact. With eQTLs, the potential function of non-coding variants can be ascertained through expression levels [5].

With advances in epigenetics, opportunities to integrate GWAS and QTL studies for molecular factors such as microRNAs (miRNAs) present

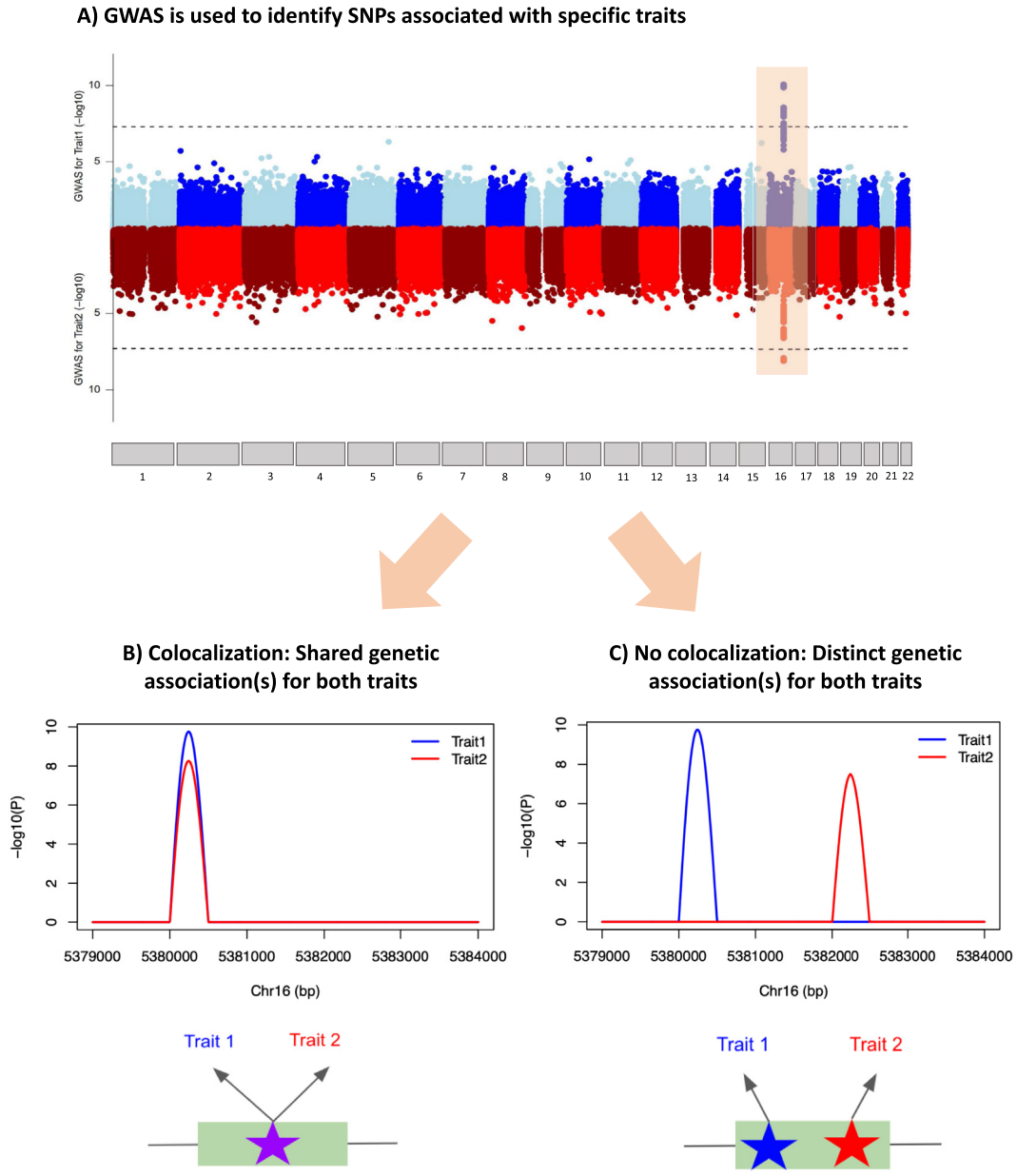

Fig. 1. Schematic illustrating the concept of genetic colocalization analysis between two traits of interest (referred as Trait1 and Trait2). Plot A) illustrates the results (-$\log_{10}$ *P*-value) on the Y axis along genomic positions for Trait1 (top panel) and Trait2 (bottom panel) in a standard GWAS approach for variant discovery. The region highlighted corresponds to a locus on chr16 with variant positions in base pairs (bp) which exhibits association signals for both traits at the genome-wide significance level. This locus can be investigated using colocalization analysis methods to decipher the possible underlying scenarios, as illustrated in plots B and C. Plot B illustrates a possible scenario of genetic colocalization between both traits, where both traits result from the same genetic variant (represented by a single purple star), while Plot C illustrates a possible scenario where the two traits result from distinct variants (as represented by different stars). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

new avenues for understanding genetic risk and identifying potential therapeutic avenues. MiRNAs are small, non-coding RNA molecules that are important post-transcriptional regulators of gene expression [6]. MiRNAs originate from precursor transcripts within a host gene, most often in intronic regions [7], then are processed in the cytoplasm into mature miRNA molecules (Fig. 2). A single miRNA precursor has the potential to produce two mature miRNAs, designated as "-5p" or "-3p" depending on if they originated from the 5′ or 3′ end of the precursor, respectively [8]. Mature miRNAs can act within the producing cells or in distal target cells following secretion into circulating biofluids (Fig. 2) [6]. Functionally, miRNAs regulate target genes through complementary binding to seed-sequence regions (encompassing the first 2–8 nucleotides at the 5' end), leading to subsequent mRNA degradation or translation repression (Fig. 2). A single miRNA can have many target genes, giving them powerful regulatory potential [6]. Additionally, miRNAs can be readily modulated using small molecules, making them ideal therapeutic candidates [7,8]. There is mounting evidence demonstrating the functional roles that miRNAs have in complex polygenic diseases such as OA [6]. For example, miRNAs have been shown to regulate a variety of cellular processes implicated in OA including inflammation, extracellular degradation, apoptosis, and chondrocyte differentiation, among others [6,9]. Genetic variants, such as SNPs, can affect both miRNA biogenesis and function. For example, loci within miRNA upstream regulators may be associated with altered mature miRNA expression levels (Fig. 2, scenarios 1,2), while loci within miRNA-mRNA binding complexes can interfere with miRNA regulation (Fig. 2, scenarios 3,4) [10]. The growing research behind miRNA in eQTL analysis has warranted databases to be created such as the GTEx portal for miRNA. Though not phenotype-specific, this provides early cataloguing of valuable miRNA expression data. This integration of multiomic data highlights the potential for colocalization analysis between miRNA and GWAS when leveraging gene expression data. Therefore, genetic colocalization analysis of OA with miRNA analysis has the potential to characterize epigenetic features and provide biological insights into OA risk, etiology, and progression, and consequently inform potential therapeutic strategies.

Here we perform a scoping review to summarize the current state of the OA literature on statistical colocalization methods integrating miRNA. After identifying colocalization studies that investigated OA and/or incorporated miRNA data, we characterize existing colocalization analysis methods and assess their applicability in integrating miRNAs for future studies on OA.

2. Methods

2.1. Search strategy

Two databases, MEDLINE (Ovid) and EMBASE, were chosen to perform the search due to their advanced search capabilities, including their ability to use controlled vocabulary. MEDLINE uses Medical Subject Headings (MeSH), whilst EMBASE uses Emtree, therefore the search strategy was adjusted slightly for each database. The search strategy involved two overall searches per database, (1) all terms and spellings for

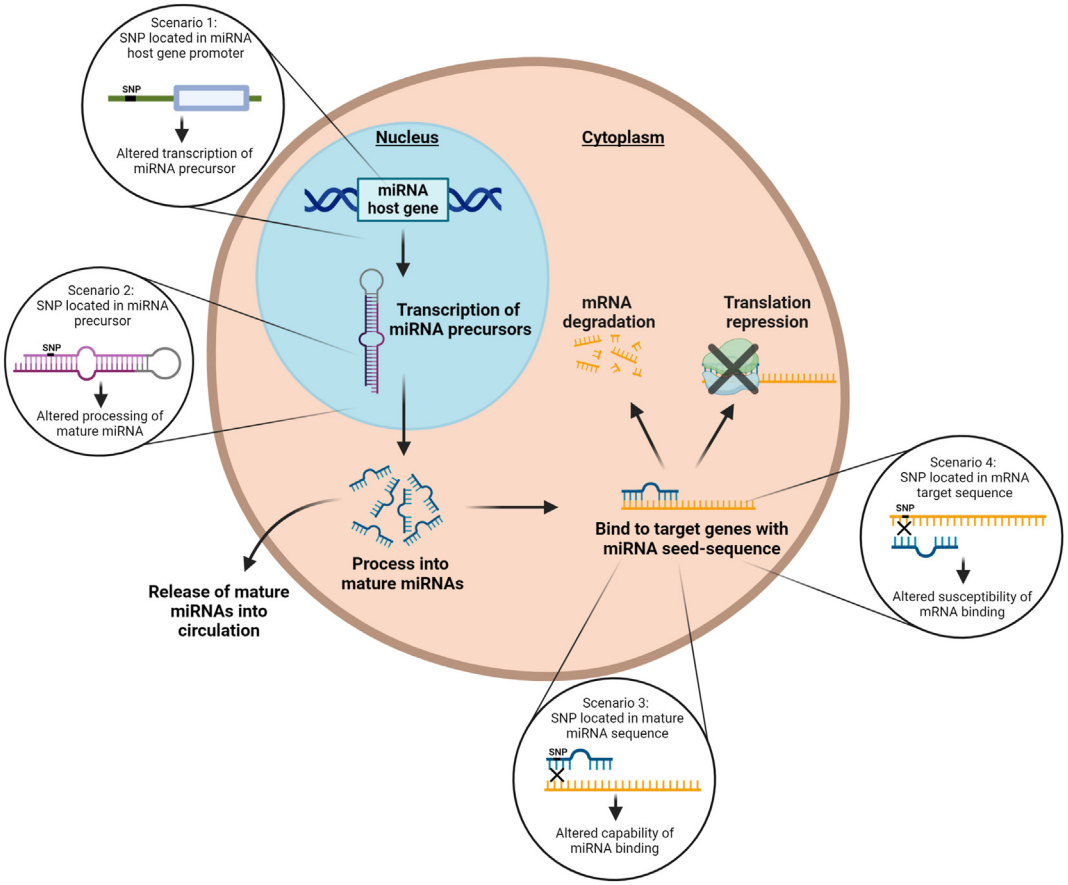

Fig. 2. Simplified overview of miRNA biogenesis and function in four scenarios showing how SNPs can impact miRNA expression and function. Typically, transcribed miRNA precursors are processed into mature miRNAs, which can lead to mRNA degradation or repression of translation through seed-sequence binding to complementary sequences. Common examples of possible miRNA-SNP interactions are illustrated in scenarios 1–4. SNPs can affect the processing of mature miRNAs or the transcription of miRNA precursors, thereby influencing their overall expression and function (scenarios 1–2). Alternatively, SNPs can alter the binding efficiency between miRNAs and mRNAs, effectively impairing these regulatory functions (scenarios 3–4). Colocalization analysis of OA-associated SNPs corresponding to each scenario, and other miRNA-SNP interactions, can help unravel the underlying miRNA biology that impacts OA pathology.

"colocalization" as text words and keyword fields (.tw,kf), in combination with MeSH/Emtree topics related to statistical methods, and (2) all terms and spellings for "colocalization" (.tw,kf) in combination with the MeSH/Emtree term for "GWAS". MEDLINE allowed for the MeSH term "GWAS" to be further filtered by its subheadings for "methods" and "statistics and numerical data". Since EMBASE does not use subheadings in the same way that MEDLINE does as a separate indexing element, "GWAS" could not be further filtered, and thus an additional item was added instead. The second search in EMBASE with "GWAS" was performed with the addition of Boolean operator "and" with Emtree topics "statistical" and "statistical analysis". A librarian was consulted during search strategy construction. Search terms for miRNA and OA were not included in the primary search strategy, as they yielded very limited results. However, colocalization methods using miRNA-data were hand-searched for in four databases: PubMed, Scopus, Web of Science, and EMBASE. The full search strategy, with the MeSH terms and Emtree topics, are available in Supplemental Tables S1–S3. All searches (excluding the hand-searched databases) were performed for articles published till March 4, 2024.

It is important to note that while identifying unique methods, not all the colocalization methods reported were directly retrieved from the search results. Some of these methods were referenced by the authors of included papers encountered during the literature search. These referenced papers were included if they appeared more than twice throughout multiple papers from the search.

2.2. Inclusion and exclusion criteria

Peer-reviewed publications in English were included if they: (1) described a new method for testing colocalization, (2) implemented a published method for genetic colocalization, (3) applied colocalization analysis to GWAS or QTL or miRNA data, or (4) involved statistical analyses or formal statistical tests of colocalization.

Publications were excluded if at least one of the following criteria was met: (1) no full-text was available, (2) colocalization referred to analyses unrelated to genetic signals (e.g., physical proximity of molecules), (3) colocalization did not use GWAS or QTL or miRNA data, (4) focused on genome mapping, or (5) GWAS or QTL studies were not performed on human traits.

2.3. Data administration and extraction

Search results were uploaded into Covidence systematic review software (Veritas Health Innovation, Melbourne, Australia) [11] to manage the screening process. The studies retained following title/abstract screening and full-text screening were subjected to data extraction using a pre-determined template. The template included the following characteristics: Author name, year of publication, phenotype (e.g., OA), type of genetic data, colocalization method, software/package used, rationale of method (when more than one method was used within one paper), and cited authors. The column for cited authors was used to account for the instances in which the author of the paper did not present a novel method, but applied an existing colocalization method. The PRISMA checklist adapted to scoping reviews was completed (PRISMA-ScR [12]) and is available in Supplemental Table S4.

3. Results

3.1. Overview of the findings

The searches yielded a total of 546 unique publications, of which 400 were found to be irrelevant after initial title and abstract screening. This exclusion led to 146 studies available for full-text screening, which subsequently led to 96 eligible studies (Fig. 3). These studies included both proposals for novel methods of colocalization and the implementation of existing methods, in addition to reviews of published methods. We chose to include these reviews since they illustrated (or compared) colocalization methods using simulation studies or real data and allowed for another gauge of method popularity within the literature. The characteristics of the 96 studies are summarized in Supplemental Table S5. [5,13–107] Colocalization studies were found utilizing a spectrum of QTL data. The use of different types of QTLs — including those associated with proteins (pQTL), metabolites (mQTL), splicing variations (sQTL), DNA methylation (meQTL), gene expression (xQTL), and molecular phenotypes (molQTL) — in each study are recorded in Supplemental Table S5 under the 'Type of genetic data' column.

3.2. Limited exploration of OA in colocalization analysis

Out of the 96 studies, four (Baird et al., 2018 [16]; Mullin et al., 2023 [59]; Qu et al., 2023 [71]; Tachmazidou et al., 2019 [81]) investigated OA-related phenotypes (Table 1). Baird et al. examined previously known hip OA susceptibility loci associated with hip shape in a cohort of peri-menopausal women and discovered colocalizing signals between OA risk and hip morphology profiles in *KLHDC5/PTHLH* and *COL11A1* loci. They concluded that hip shape is a risk marker for future OA development that could provide a means for early detection and prevention. Mullin et al. investigated the role of osteoclasts in the progression of OA. They performed colocalization analysis on existing OA-GWAS [1] and eQTL data extracted from osteoclast-like cells derived from peripheral blood mononuclear cells of 158 female patients. Ultimately, they found 38 genes potentially implicated in OA, including genes associated with single OA traits (e.g., *BCAM*, *PRKD2*, *BICRA* with hip OA) or multiple OA traits (e.g., *FAM53A, GCAT*, *HMGN1*). Qu et al. considered colocalization between osteoporosis and OA to investigate shared genes and potential mechanisms of their development. They found that four hip OA susceptibility genes (*LTBP3, MLXIP, SMAD3*, and *MAPT*) had variants colocalized on musculoskeletal tissues and concluded that osteoporosis may have a causal link to an increased risk in developing OA. Lastly, Tachmazidou et al. performed a meta-analysis for OA loci in nearly 500,000 individuals across four phenotypes (knee OA, hip OA, knee and/or hip OA, and other site OA) in 64 loci, the majority of which were novel. GWAS-eQTL colocalization was performed to identify putative effector genes of which ten (e.g., *TGFB1*, *FGF18*, *CTSK* and *IL11*) are currently being assessed for mechanisms consistent with potential use in OA treatments. Though limited in number, these studies cumulatively highlight how colocalization analyses can be leveraged to identify genetic risk variants associated with OA pathogenesis.

3.3. Insights into miRNA from hand-searched literature

We did not identify any studies that used miRNA expression data as input for colocalization analyses from the literature search. However, we hand-searched the literature with more specific search terms related to miRNA and identified six pertinent papers that leveraged miRNA data (Lafferty et al., 2023 [108]; Mustafa et al., 2023 [109]; Toste et al., 2023 [110]; Sonehara et al., 2022 [111]; Odhams et al., 2017 [112]; Huan et al., 2015 [113]). Though none explicitly examined OA phenotypes, their methodologies have been extrapolated for potential application in future OA research (see Discussion).

Briefly, these studies implemented eQTL-analysis on miRNA to identify miRNA-eQTLs before performing colocalization analysis. Most studies used blood samples and performed their own RNA-sequencing for miRNA-eQTL analysis. However, Mustafa et al. bypassed this step by using available information on miRNA-eQTLs conducted in past eQTL mapping studies, and directly analyzed this information against causal variants identified from GWAS in colocalization analysis. Notably, Mustafa et al. and Sonehara et al. explored various complex traits using GWAS information in their analysis. Toste et al. and Mustafa et al. conducted Mendelian Randomization (MR) analysis (further discussed in section 3.5.3 Additional Approaches). Specific results and methodologies are highlighted in Table 2.

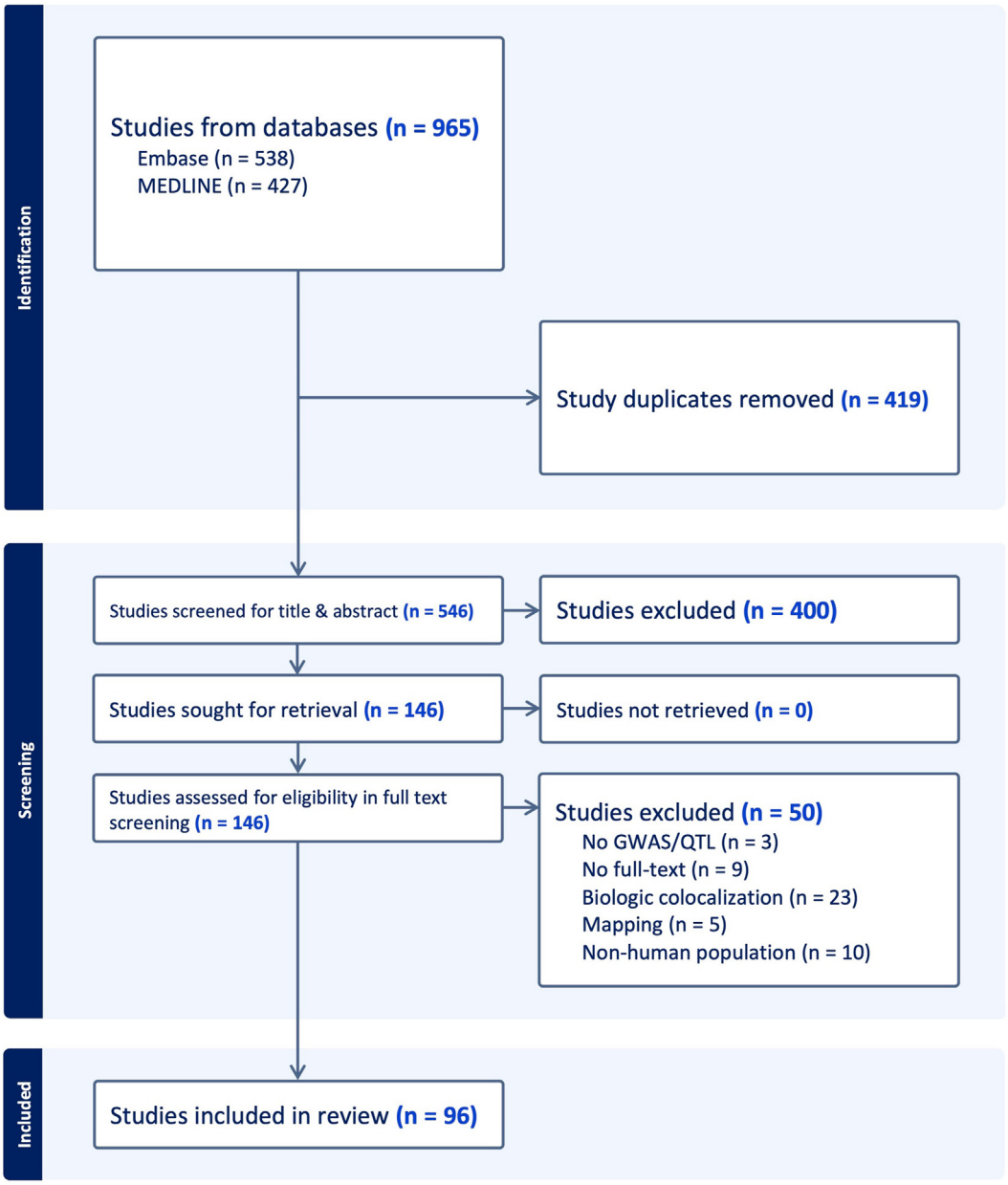

Fig. 3. PRISMA flow chart detailing the article search and screening process.

Although none of the studies identified through the hand search analyzed OA phenotypes, a similar approach could be adapted for investigating miRNA regulatory roles and potential causal pathways in OA. For example, upregulation of certain miRNAs, such as miR-146a-5p, can alleviate inflammation, cartilage degradation, and autophagy [114]. Accordingly, leveraging colocalization studies between miRNAs and OA traits, in conjunction with existing literature, could pinpoint similar promising epigenetic targets for OA intervention.

3.4. *Overview of existing colocalization analysis methods*

Among the 96 included studies, coloc [115] was the single most cited method for colocalization, with a total of 56 citations in reference to the original method from Giambartolomei et al., 2014 [115], followed by Wallace 2020 [88] (Table 3). This popularity was further demonstrated by all four OA studies returned from this search [15,59,71,81] opting to use coloc or a closely related extension. The remaining methods are listed in Table 3 with their respective authors and frequency of appearance in the literature. Decisions to opt for an alternative method to coloc often arose from concerns regarding the implicit assumption within its framework that only one causal variant exists. Furthermore, many papers used multiple colocalization methods, highlighted by the disagreement between the frequency of methods and the total count of papers in Table 3.

In addition to presenting the total citation counts in Table 3, Fig. 4 illustrates the annual citation counts to provide insight into the evolving popularity of each method. Methods that were cited once in Table 3 were removed from consideration in the bar chart. This analysis demonstrates that the most frequently cited methods were not solely attributed to their longstanding presence in the literature. No large discrepancies between annual (Fig. 4) and total citation counts (Table 3) were found, therefore initial assumptions of the popularity of particular colocalization methods remain consistent. Overall, Supplemental Table S6 illustrates the characteristics of each individual method, as well as their respective limitations and repositories. In Supplemental Table S6, an emphasis on the methods' ability to accommodate datasets with potentially overlapping samples and their capability to detect colocalization at loci with one or

Table 1
Summary of colocalization analysis in OA studies.

Study	Phenotype	Objective	Study sample/sample size for OA data	Types of data for colocalization analysis	Overall findings from the colocalization analysis
Baird et al., 2018 [16]	Hip shape and hip OA traits	To examine relationships between known OA susceptibility loci and hip shape to investigate whether hip shape contributes to OA development.	Perimenopausal women; avon longitudinal study of parents and children (ALSPAC), (n = 10,015)	GWAS	Colocalizing genetic signals for hip shape and hip OA for *KLHDC5/PTHLH* and *COL11A1* loci.
Mullin et al., 2023 [59]	Osteoclasts and OA	To consider the potential role of osteoclasts and subchondral bone remodeling in the pathogenesis of OA by integrating data from an osteoclast eQTL resource with published OA GWAS summary results.	Boer et al. GWAS dataset: (n = 826,690); 177,517 cases of OA	GWAS and eQTL	38 osteoclast-genes with a potential role in OA (e.g., *BICRA, EIF6*, *CHST3*, and *FBN2*). Several OA GWAS signals colocalized with eQTL signals (e.g., hip OA with *BCAM*, *PRKD2*, and *BICRA* eQTL).
Qu et al., 2023 [71]	Osteoporosis and OA	To investigate the causal relationship between low BMD and OA (hip, knee, at any site).	UK biobank; osteoarthritis genetics (arcOGEN); (total n = 384,838)	GWAS and eQTL	Four hip OA susceptibility genes (*LTBP3, MLXIP, SMAD3*, and *MAPT*) had variants colocalized on musculoskeletal tissues. No genes had variants colocalized with knee OA or OA at any sites.
Tachmazidou et al., 2019 [81]	Four OA phenotypes (knee, hip, knee/hip, any joint)	To perform a GWAS for OA and analyze four of its phenotypes to identify new therapeutic targets.	UK biobank, (n = 500,000); arthritis research UK arcOGEN, (n = 455,221); 77,052 cases: 378,169 controls	GWAS and eQTL	Putative effector genes identified by integrating eQTL colocalization (among other methods), and evidence of colocalization in at least one tissue for 49 out of 64 loci detected by GWAS.

more causal variants was undertaken given their potential utility in widespread applications. Notably, joint analysis of miRNA and OA measured in the same individuals can improve power to detect colocalization by borrowing information between these two traits [125], whilst assumptions of a single causal variant can be unrealistic and restricting for analysis.

3.5. Background of the methodology of coloc

The colocalization method, coloc, employed in the four OA studies [16,59,71,81] aligns with the prevailing approach found in the existing literature. Its general framework and its various extensions are described below. Further detail on the remaining methods from Table 3 and their general classifications according to (1) their statistical framework (Bayesian or frequentist), and (2) their resolution of colocalization (SNP vs. region-level) can be found in Supplemental Material **S7**.

3.5.1. Coloc's general framework

Coloc's framework is defined by 5 hypotheses: H0 (no genetic association with either trait), H1 (genetic association with trait 1, but not trait 2), H2 (genetic association with trait 2, but not trait 1), H3 (two independent genetic associations) and H4 (colocalization). In each locus of interest, each configuration of SNP association between the two traits can be assigned to one of these five hypotheses. The colocalization test assesses the support for each configuration against H4 under a Bayesian framework. Using Bayes factor and prior probabilities, a posterior probability supporting H4 can be estimated. Among coloc usage, certain papers used coloc as part of their analysis approach; for example, as the colocalization step in their proposed pipeline or framework, or as a web interface that integrates multiple GWAS datasets and coloc. Accordingly, we included these methods, such as colocQuiaL [23], FUSION [118], cscQTL [64], COLOCdb [66], and Open Targets Genetic Portal [57], in the coloc citation count in Table 3. A variety of methods occasionally appeared in the literature search that did not formally test for colocalization but were used in conjunction with colocalization methods. These methods included GCTA-COJO [126], PWCoCo (as cited in Howell et al., 2023 [39]), DAP [127], and SuSiE-coloc [116]. They perform various pre-processing steps to alleviate the single causal variant assumption of coloc, such as conditional analysis or finemapping, before applying the coloc framework. These methods were close extensions of coloc and were also added to coloc's overall study count.

In application, conditional analysis can help pinpoint secondary association signals within a locus and evaluate whether the primary signal remains statistically independent of these nearby correlated variants. This is a common procedure when interpreting GWAS, as linkage disequilibrium (LD) - the non-random inheritance of alleles - can potentially introduce confounding influences. For instance, three of the six studies we identified that implemented miRNA data used approaches of conditional analysis within their colocalization analyses [108,112,113] and adapted existing colocalization methods to accommodate miRNA data. One study (Lafferty et al., 2023) [108] first identified candidate causal variants by finding overlapping variants with LD $r^2 \geq 0.8$, then performed conditional analysis incorporating the genotypes of the miRNA-eQTLs to assess colocalization. Another study (Odhams et al., 2017) [112] was not focused on miRNAs specifically, but rather mapping RNA-sequencing and microarray data to eQTLs. However, from this analysis, the authors were able to map one miRNA, miR-146a, to an eQTL/eGene, and used conditional analysis (COJO-GCTA) and coloc to examine colocalization for all their candidate causal eQTLs and SLE-associated SNPs from a GWAS.

3.5.2. Other coloc extensions

While the original coloc does not account for more than two traits, HyPrColoc [29] and moloc [34] were developed to address this limitation. Both approaches apply coloc to any pair of traits, though moloc becomes computationally impractical beyond 4 traits, while HyPrColoc was developed to increase efficiency and improve on moloc. Among other coloc extensions, CAFEH [123] incorporates LD structure and integrates genetic association data across multiple traits to identify causal variants, with the additional capability of performing fine mapping, while gwas-pw [122] extends coloc with a hierarchical model; coloc2 [121] incorporates changes from gwas-pw – specifically the implementation of likelihood estimation of mixture proportions for the five hypotheses – and includes a pre-processing step to align eQTL and GWAS summary statistics for each eQTL *cis*-region. Moreover, Fortune et al. proposed an extension to coloc and the proportional approach (further discussed in Supplemental Material **S7**) to account for overlapping individuals between two GWAS under investigation. Other coloc extensions were further distinguished if they appeared over twice in the literature, or if they were more divergent from the original methodology (such as CAFEH). Divergence from coloc entailed additions to the capabilities of the original framework, excluding pre-processing steps.

Table 2
Available sources and main features of miRNA-eQTL data from colocalization analyses.

Source	Tissue type	Coverage	Population and sample size	Experimental method	Main findings	Summary statistics repositories
Lafferty et al., 2023 [108]	Human prenatal cortical tissues	Local miRNA-eQTL mapping (total of 866 miRNAs with an expression of at least 10 counts across at least 10 samples); 907 genomic loci.	212 genetically distinct donors (96 females:127 males, 14–21 gestation weeks) following voluntary termination of pregnancy.	miRNeasy-mini kits (QIAGEN 217004); TruSeq small RNA library prep kits (illumina RS-200); illumina HiSeq2500 sequencer	Measured 907 expressed miRNAs, discovering 111 of which were novel, and identified 85 local-miRNA-eQTLs; colocalization of miRNA-eQTLs with GWAS summary statistics yielded colocalization of miR-4707–3p expression with educational attainment and brain size phenotypes, where the miRNA expression increasing allele was associated with decreased brain size.	Colocalization of local-miRNA-eQTLs with brain-relevant trait GWAS summary statistics available in supplementary file 4.
Mustafa et al., 2023 [109]	Blood samples from donors with a wide range of clinical diagnoses	Genotyping was performed on all participants, covering ~805,000 markers; colocalization for each miRNA-disease pair used genomic region extending 200 kb on either side of mature miRNA position according to miRBase.	Individual-level data from the UK Biobank aged 40–69 years old living in the UK between 2006 and 2010.	Genotyping was conducted at Affymetrix research services laboratory; quality control of data was carried out at the Wellcome Trust Centre for Human Genetics	Identified 122 associations for 6 variants in the seed region of miRNAs, 9 variants in the mature region of miRNAs, and 27 variants in the precursor miRNAs; strongest association being reported between rs4285314 in the precursor of miR-3135b and celiac disease risk; colocalization and MR analysis highlighted potential causal role of miR-6891-3p in dyslipidemia.	GWAS summary statistics available from DIAGRAM, Forgetta et al., 2020, Global Lipid Genetics Consortium; miRNA-eQTL summary statistics available at Mustafa et al., 2022 and Nikpay et al., 2019; supplemental information for more statistics related to analyses.
Toste et al., 2023 [110]	Human fetal brain tissue	SNPs from 11 neurodevelopmental, neurological or psychiatric conditions; most significant eQTL for the 30 variably *cis*-regulated miRNA were identified.	Elective terminations of pregnancy (12–20 post-conception weeks); 112 independent samples (51 female:61 male) were available for both genotype and small RNA sequencing measures.	TruSeq small RNA library preparation kits (illumina); illumina HiSeq 4000 system	Increased prenatal expression of miR-1908-5p suggested as a risk mechanism for bipolar disorder; common genetic variation associated with increased miR-1908-5p expression additionally associated with depressive symptoms, irritability, increased right cerebellum exterior volume and increased sleep duration in the general population.	Summary statistics for miRNA expression, covariates and all eQTL are provided through a publicly accessible figshare repository: https://doi.org/10.6084/m9.figshare.22674109.v1.
Sonehara et al., 2022 [111]	Peripheral blood samples	Mapped miRNA-eQTL for 343 miRNAs, integrating this information with GWAS for colocalization analysis.	141 participants of Japanese ancestry.	HiSeqX (Illumina, San Diego, CA, USA); miRNeasy Micro Kit (Qiagen, Duesseldorf, Germany); SMARTer smRNA-Seq Kit (Takara, Tokyo, Japan)	Identified 1275 *cis*-miRNA-eQTL variants for 40 miRNAs; identified miR-1908-5p as a potential mediator for adult height, colorectal cancer and type 2 diabetes using resulting miRNA-eQTL data and existing Japanese GWAS of 25 complex traits.	Summary statistics/eQTL analysis deposited in the National Bioscience Database Center (NBDC) human database (https://humandbs.biosciencedbc.jp/en/) with the accession number of hum0197. The data is also available at website pheweb.jp (https://pheweb.jp/).
Odhams et al., 2017 [112]	Whole blood samples	Gene-level: 520 genes were tested against in *cis*; exon-level: 4786 exons corresponding to 716 genes were taken forward for analysis.	GWAS on 7219 cases of systemic lupus erythematosus, 15,991 controls; expression profiling on TwinsUK registry & MuTHER cohort.	Illumina human HT-12 V3 BeadChips; illumina HiSeq2000	Identified novel SLE susceptibility genes, specifically for our interest, eQTL rs2431697/eGene MIR146A, coding for microRNA 146a, expressed in lateral collateral ligament (LCL) tissues.	Supplementary material.
Huan et al., 2015 [113]	Whole blood samples	Based on the coordinates of 280 mature miRNAs and 9.8×10^6 SNPs, estimation of 13,935,272 potential SNP-miRNA pairs, where the SNP was located within 1 Mb on either side of the corresponding mature miRNA (1.4×10^7 potential *cis* SNP–miRNA pairs, and 2.7×10^9 potential trans SNP–miRNA pairs).	Framingham heart study; 2272 offspring cohort attendees at examination cycle 8 (2005–2008) and 3057 third generation cohort attendees at examination cycle 2 (2008–2010).	qRT–PCR (BioMark real-time PCR system)	Mapping study; identified 5269 *cis*-miR-eQTLs for 76 mature microRNAs; identified 270 *trans*-miR-eQTLs for 15 miRNAs.	Supplementary data.

Table 3
Methods of colocalization analysis and their popularity in the literature ordered by citation count.

Method	Citations count	Authors (i.e., original proposals)
coloc (+close extensions)	56	Giambartolomei et al., 2014 [115]; Wallace 2020 [88], 2021 [115]; Fortune et al., 2015 [30]; Zheng et al., 2020 [117]; Gusev 2022 [118]; Robinson et al., 2021 [72]; Nguyen 2023 [64]; Pan et al., 2024 [66]
eCAVIAR	17	Hormozdiari et al., 2016 [5]; Zeng et al., 2019 [101]
SMR + HEIDI	10	Zhu et al., 2016 [119]
HyPrColoc	7	Foley et al., 2021 [29]
ENLOC/fastENLOC	6	Wen et al., 2017 [91]; Hukku et al., 2022 [42]; Okamoto et al., 2023 [65]
moloc	5	Giambartolomei et al., 2018 [34]
Proportional approach	4	Plagnol et al., 2009 [68]; Wallace et al. 2012 [86]; Wallace 2013 [87]; Fortune et al., 2015 [30]
Simple Sum (SS) & Simple Sum 2 (SS2)	4	Gong et al., 2019 [35]; Panjwani et al., 2020 [67]; Wang et al., 2022 [89]
JLIM	3	Chun et al., 2017 [120]
coloc2	3	Dobbyn et al., 2018 [121]; Panjwani et al. 2020 [67]
gwas-pw	2	Pickrell et al., 2016 [122]
jointsum	1	Deng & Pan 2020 [27]
UNITY	1	Johnson et al., 2018 [43]
CAFEH	1	Arvanitis et al., 2022 [123]
MRLocus	1	Zhu et al., 2021 [105]
RTC	1	Nica et al., 2010 [124]
causal-TWAS	1	Zhao et al., 2024 [103]
Other (coloc-stats, ezQTL, Perturbnet)	3	Simovski et al., 2018 [79]; Zhang et al., 2022 [102]; McCarter et al., 2020 [55]

3.5.3. *Additional approachess*

Outside of coloc, some colocalization studies used MR analyses. MR is the investigation into the causal nature of exposures (or risk factors) on observed outcomes or traits. In MR analysis, SNPs associated with risk factors represent instrumental variables to capture the exposure while controlling for potential confounding factors, and thus observational studies are leveraged with GWAS to elucidate causal pathways [128]. Although summary-data-based Mendelian randomization (SMR) [119] and heterogeneity in dependent instruments (HEIDI) [119] are not technically colocalization methods, they achieve very similar goals in the context of identifying whether a transcript and phenotype are associated by a shared causal variant, with the use of GWAS and eQTL studies. SMR and HEIDI adapted the principles of MR analysis to use summary-level statistics, since MR analysis typically demands exceptionally large sample sizes that are seldom available in a setting requiring phenotype, genotype and gene expression datasets [119]. There are two steps in this process, first the SMR step which tests for pleiotropy, followed by the HEIDI step which distinguishes the previous step from linkage. SMR is analogous to testing H3 from coloc's framework, while HEIDI is analogous to testing H4, suggesting that it can be a useful tool for examining colocalization, nonetheless. For instance, after the pre-processing steps taken by Lafferty et al., 2023 [108] in their investigation which mapped miRNA and eQTLs as previously discussed, further analysis using SMR and HEIDI was subsequently performed on the miRNA-eQTLs and GWAS summary statistics to confirm colocalization.

4. Discussion

This scoping review maps existing literature on the applicability of colocalization methodology in OA research, and the suitability of miRNA integration into these methodologies. Crucially, this review identifies a lack of colocalization studies in OA research, in addition to an overall lack of miRNA expression integrated in colocalization analyses. Despite this, we believe that integration of miRNA data is highly useful and feasible within the scope of current methods for colocalization analysis, and therefore can be leveraged for future GWAS to provide novel mechanistic insights in OA.

The limited information currently available points to the potential for colocalization to enhance our understanding of OA. This can include identification of OA risk genetic variants linked with confounding factors (e.g., bone morphology [16]) or comorbidities (e.g., osteoporosis [71]) that could drive or accelerate OA pathogenesis. Furthermore, assessment of the associations between OA traits and gene eQTLs can determine whether the changes in expression seen in a target gene are linked to a specific OA phenotype(s) [59,81]. Given the varying mechanisms by which OA can destroy the joint (e.g., breakdown of articular cartilage, synovial inflammation, thickening of the subchondral bone, osteophyte formation) [129], future colocalization studies could also be expanded to assess shared tissue-specific eGenes for more precise characterization of OA disease mechanisms.

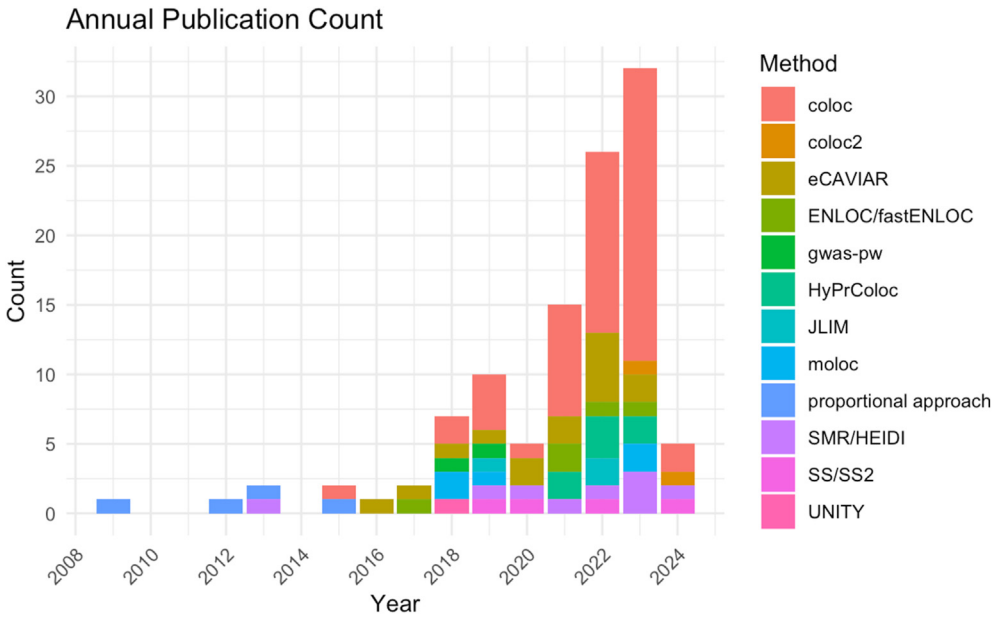

Fig. 4. Annual count for each colocalization method by year of publication. Methods that appeared once in the literature search were excluded. Simple Sum (SS) and SS 2 (SS2) were combined. Empirical COnfiguration of Associations with VAriants in R (eCAVIAR); Enrichment Estimation Aided Colocalization Analysis (ENLOC); Pairwise analysis of GWAS (gwas-pw); Hypothesis Prioritisation in multi-trait Colocalization (HyPrColoc); Joint Likelihood Mapping (JLIM); multiple-trait-coloc (moloc); Summary data-based MR/Heterogeneity in Dependent Instruments (SMR/HEIDI).

The identification of gene expression variations correlated to OA traits invites investigation into the epigenetic factors that may be driving these transcriptional changes, such as miRNAs. With the established roles that miRNAs are already known to have in OA pathophysiology [6], it is logical to expect that correlations between OA GWAS loci and miRNA genetic associations are present. As the majority of reported GWAS SNPs are intronic [130], there is the strong potential for overlap with miRNA sequences, which can also be located in intronic regions [7]. Furthermore, variants located within seed-sequence binding sites of miRNA target genes can impact overall effectiveness of their regulatory ability [131]. Once discovered, OA-specific colocalized miRNAs and/or their target gene binding sites will allow for greater insight into how genetic variation within disease phenotypes impact both miRNA biogenesis during OA and subsequently, their downstream regulation that drives OA pathological processes [6]. This discovery may lead to the development of improved targeted therapies against OA and its most burdensome complications.

Potential challenges in assessing miRNA expression in colocalization analyses can arise in library preparation methods, as they commonly and effectively remove small RNAs in eQTL studies [108]. However, library preparation methods have been recently developed that have the ability to quantify the expression of small RNAs to measure miRNA expression in large sample sizes [132]. From the hand-search, the six studies followed one similar approach to conducting colocalization analysis between GWAS and miRNA [108–113]. This intuitive approach utilizes miRNA-eQTL mapping association analysis before colocalization analysis. This is preferred since most colocalization methods can already accommodate both GWAS and eQTL datasets. This approach also demonstrates the process of transcriptome-wide association studies, which compare factors of gene expression and genetic variants to determine their relationship. One method identified in the scoping review called causal-TWAS [103] attempts to incorporate this methodology with eQTLs and GWAS data within a formal software. Transcriptome-wide association studies examining GWAS and miRNA-eQTL to functionally characterize genetic variants and improve biological annotation are gaining prominence, which can be a natural extension to the traditional approach of colocalization analysis between two GWAS or eQTL studies [133].

There are a few limitations of this review to note. First, we only queried two databases and excluded grey literature, limiting full coverage of the literature. The two databases were chosen for their unique indexing capabilities, which allowed for the retrieval of studies pertaining to methodologies and statistical models, but came with the drawback of restricting the breadth of literature coverage. Second, the specificity of focus on OA and miRNA with particular statistical assumptions (i.e., correlated datasets and more than one causal variant) may limit the scope of generalizability of the findings. In this vein, most of the published colocalization methods are developed for summary statistics from GWAS in the context of a two-sample study design. However, as multiomic data integration becomes increasingly prevalent, methods that perform combined analysis of both traits in a single statistical model are warranted. Therefore, we foresee a need for developing colocalization methods for individual-level data.

5. Conclusion

In sum, this scoping review summarizes the most common genetic colocalization methods in use and concludes that a limited number of studies have integrated miRNA, and none have focused on OA with the use of miRNA. Thus, OA remains a largely unexplored area in this niche, representing a window of opportunity to leverage GWAS, eQTL and miRNA analyses to better understand OA-related outcomes and disentangle the genetic and epigenetic factors of OA etiology and progression.

Authors contributions

K.Z. and O.E. contributed to the conception of the review. K.Z. developed and implemented the search strategy, extracted and interpreted the data, and drafted the review. M.B., T.W., O.E., and S.A.A. critically reviewed the work, and gave the final approval for publication. K.Z., M.B., T.W., O.E., and S.A.A. are accountable for all aspects of the review in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Declaration of competing interest

The authors have no relevant competing interests to declare.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ocarto.2024.100540.

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