BMC Rheumatology

REVIEW

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Towards stratification in osteoarthritis: a review of the scientific terminology used in published basic research

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On behalf of the European Cooperation in Science and Technology (COST) Action CA21110 - Building an open European Network on OsteoArthritis research (NetwOArk)

Abstract

Recent attempts to understand the pathophysiology and characteristics of osteoarthritis (OA) have led to the stratification of samples and data. An important part of this process is the use of specific terminology, although the lack of clear definitions for these terms can lead to misinterpretation across different disciplines. In this study, we aimed to assess the frequency of use and chronological appearance of key scientific terminology of four prevalent terms in the field of OA research: PHENOTYPE, SUBTYPE, SUBGROUP and ENDOTYPE. These terms were analysed in conjunction with tissues and fluids associated with OA research, specifically plasma/serum, synovial fluid, synovial membrane, cartilage, meniscus and bone. The method for screening the published literature focused on publications from January 2010 to September 2024, with priority given to studies that reported results from unmanipulated human tissues and applying unbiased analytical methods. Excluded from the analysis were reviews, clinical trials, animal studies, in vitro data, and analyses of pre-existing datasets. The data revealed that the most frequently used term was PHENOTYPE, followed by SUBGROUP and SUBTYPE, with ENDOTYPE being the most recently introduced term in 2019. These terms were rarely defined and often used interchangeably within a single paper, particularly in studies involving cartilage and serum. Notably, the use of these terms has tripled in total over the last 14 years, with an increase in the past decade, reflecting a growing interest in OA stratification, as well as the utility of advanced unbiased analytical methods including microarray and RNA sequencing. The term PHENOTYPE was broadly used and often when describing clinical features, whilst the term ENDOTYPE is used when describing molecular mechanisms related to OA pathogenesis. To improve communication of findings associated with OA stratification, we propose a harmonised application in the use of these stratification terms to prevent

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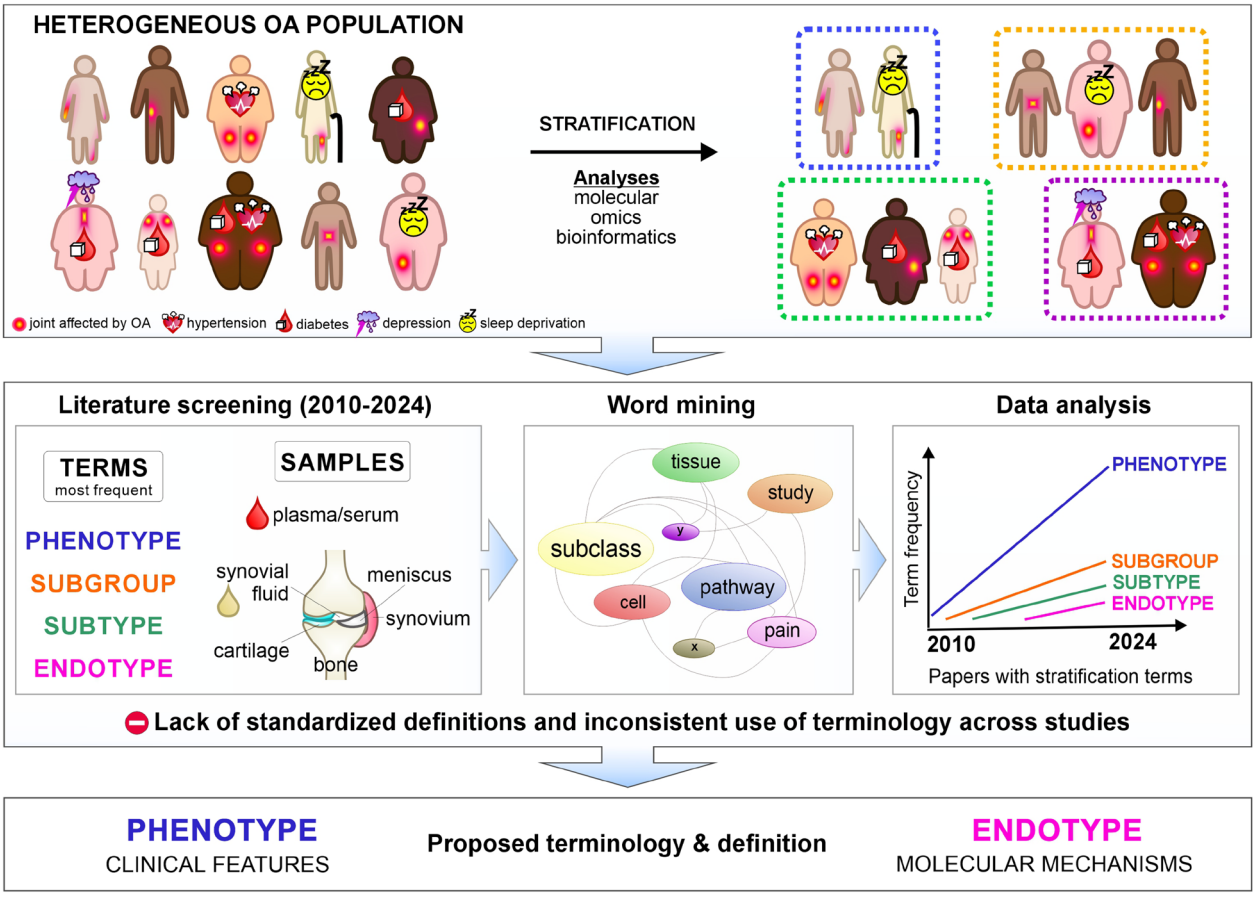
misinterpretation and support better communication of OA-related research findings. Building on published terminology, PHENOTYPE could be used to describe clinical features, while ENDOTYPE could be used to describe molecular mechanisms.

Clinical trail number

Not applicable.

Keywords Osteoarthritis, Stratification, Phenotype, Subtype, Subgroup, Endotype, Terminology

Graphical Abstract



Background

Osteoarthritis (OA) is recognized as the most common musculoskeletal disease, affecting about 600million individuals worldwide, with its prevalence continuing to increase. This condition poses significant challenges to healthcare systems, driving up costs and increasing demands for personnel and technical resources [1]. Risk factors for developing OA include age, obesity, and joint trauma [2]. Individuals with OA represent a heterogeneous population characterized by common features such as joint pain, stiffness, and structural changes in cartilage, bone, meniscus and synovium. At the same time, the onset and progression of the disease varies significantly between individuals.

Despite the need of novel treatment options, promising therapies in preclinical development have often failed to translate into effective clinical treatments [3–5]. There is a growing recognition that the lack of advancement in clinical development is caused by the fact that OA encompasses distinct populations, each potentially driven by different underlying mechanisms [6–8]. The diversity in OA pathophysiology has likely resulted in inappropriate inclusion criteria and underpowered studies that lead to variable responses to treatment. To increase the chances of clinical trial success and advance development of targeted therapies, a revisit of patient enrolment and clinical trial design is required. To facilitate such patient stratification strategies, the OA field has experienced an increasing number of studies aimed

to better classify patients, paving the way for stratification methods that match treatments to individual clinical presentations.

Nonetheless, many reports attempting to characterize diversity of OA patients have used a variety of terms for sample or patient stratification where the most common ones are PHENOTYPE, SUBTYPE, SUBGROUP, and ENDOTYPE. The lack of clear definition or consensus and the inconsistent use of these terms may have caused confusion and misinterpretation of study results. This review aims to summarize the terminology used to stratify OA from a molecular perspective and describe research based on joint tissues (e.g. cartilage, meniscus, bone, synovial membrane), synovial fluid and plasma/serum samples. To this end, we reviewed the literature to describe the stratification terminology used in OA research from 2010 to 2024 and performed an unbiased analysis of words linked to the various terminologies. Furthermore, we examined the number of publications applying stratification in OA research and highlighted examples of terminology utilization in molecular stratification approaches reported in the literature.

Methodology

The search strategy was developed by three of the authors (SN, CA and MDG) and focused on four key terms: PHENOTYPE, SUBTYPE, SUBGROUP, and ENDOTYPE. The databases PubMed and Web of Science Core Collection were explored to collect publications. The search strategy included "OSTEOARTHRITIS OR (OA)" AND "term" (i.e. PHENOTYPE, SUBTYPE, SUBGROUP, and ENDOTYPE) AND "tissue" (PLASMA/SERUM, SYNOVIAL FLUID, SYNOVIAL MEMBRANE, CARTILAGE, MENISCUS or BONE). The search was restricted to studies published between January 2010 and September 2024.

Selection criteria

To be included in this review, full-text versions of relevant papers had to be published in English. The studies had to contain at least one of the four search terms in their title or abstract and include OA patients in the study design. Studies that presented findings derived from secondary analyses of data published in other articles or repositories, research involving animal models or derived tissue, interventional clinical trials and data derived from cells or tissues that were treated or genetically manipulated, were excluded. Literature reviews were not included in the data extraction but were kept for analysis and discussion purposes. The analysis was restricted to terminologies predefined by the authors, which may have introduced selection bias and limited the scope of included publications. As a result, relevant literature using alternative terminology may have been overlooked.

Screening and inclusion

Five groups of authors were assigned to screen publications divided by sample type: plasma/serum, synovial fluid, synovium, cartilage, meniscus and bone. The publications were independently screened for potential inclusion in two steps. In the first step by reading the title and abstract, whilst the second phase involved reading the entire manuscript. Any uncertainties or differences in opinions were resolved through discussion to reach a consensus decision within the group. The screening and selection procedure is presented in Fig. 1.

Data extraction

Data extraction included the following parameters: authors, journal, publication year, analysis methods, sample information, clinical OA assessment, number of terms used in each paper section, other terms used, and co-appearance of different terms in the same publication.

Data synthesis

A synthesis of included studies was conducted per sample type for each of the four terms to compile details on a number of publications included in the analysis. Additionally, authors considered the number of publications using multiple terms within the same publication, within a given year. Additional consideration was given to the position of a specific term or terms within the publications (i.e. term placed in introduction, main body or discussion). For the eligible papers, a narrative description was included to inform the use of the term(s) in view of the results displayed.

VOSviewer analysis

VOSviewer is a downloadable software tool (https://www.vosviewer.com) used for constructing and visualizing bibliometric networks, offering insights into relationships such as co-authorship, keyword co-occurrence, and citation patterns [9]. We used VOSviewer to identify relevant items (i.e. words or word combinations) and their associations using information from the title, abstract and keywords of the publications. Two VOSviewer analyses were performed for this review, the first was based on a Web of Science Core collection search for the stated review period and then a second analysis using the manually screened and included publications from PubMed Database. For the first analysis, items (words or word combinations) that appeared over 10 times in the text for the top 60% most relevant words (to narrow the number of items) based on relevance (strength of co-occurrence) were selected. In the second network analysis using

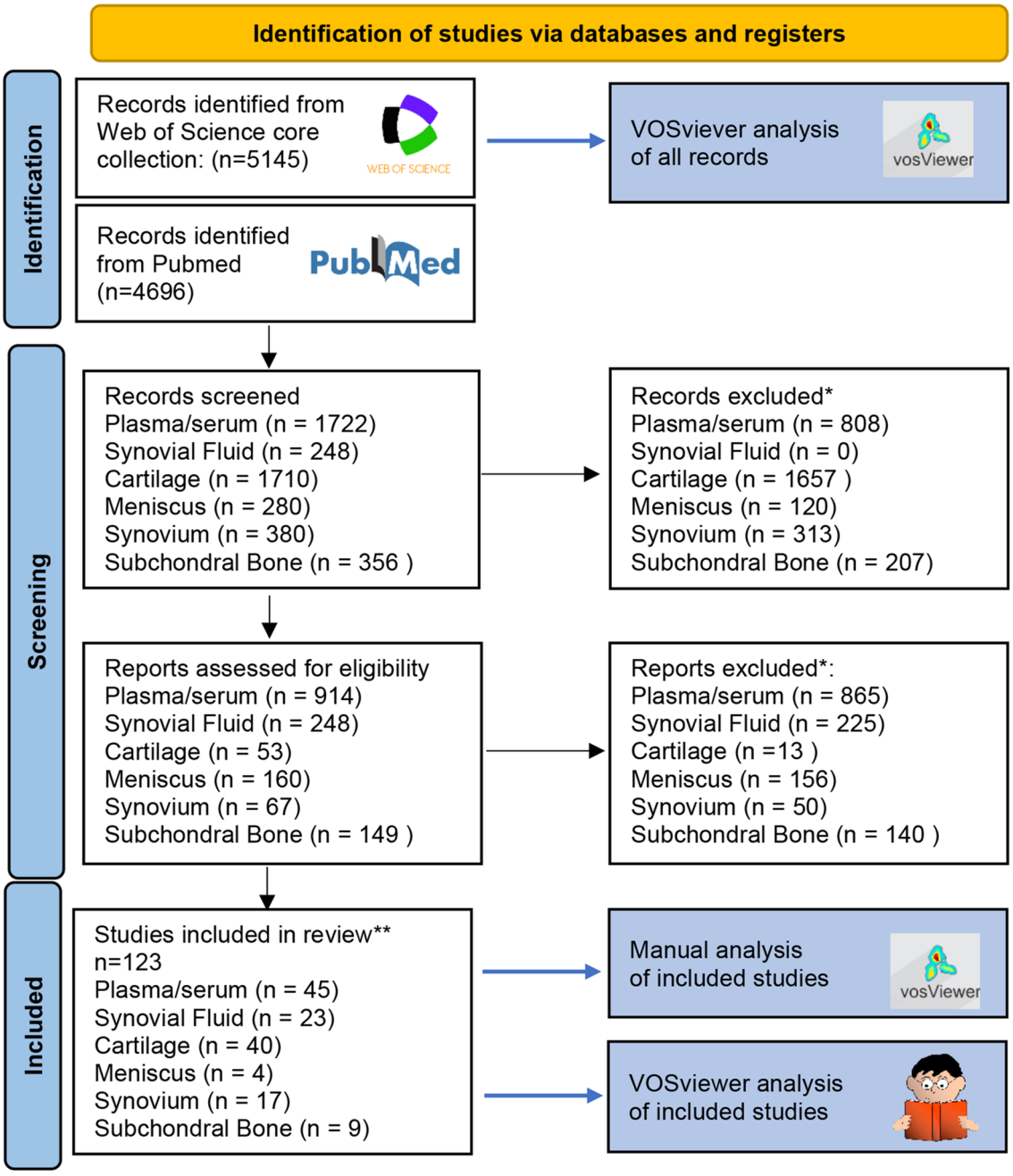


Fig. 1 PRISMA flow chart describing the manual screening and selection of publications included for the review under each tissue and fluid

the manually screened and included publications, we selected all items that occurred more than twice without excluding less relevant items. The items were then manually inspected and further categorized into either 1) Patient item, 2) Molecular/Biomarker item, or 3) Disease and Symptom items. Categorizing items identified by VOSviewer was completed using ChatGPT 4.0 with categorizing manually validated by NK. (For details on item categorization, see Supplemental Data 1).

Results

All publications retrieved from Web of Science Core collection using the search terms described were analysed with VOSviewer to understand the scope of the literature and to identify items and categories associated with the search terms.

All publications retrieved from Pubmed database using the search terms described were manually screened and publications selected based on the stated inclusion and exclusion criteria. VOSviewer was also used for manually

screened/selected publications to identify words and categories associated with the search terms. Furthermore, we investigated the trends of terminology utilisation and co-occurrence of words in the included publications. Additionally, we described the number of publications that stratify OA using their data and highlighted examples of molecular stratification approaches described in the literature.

VOSviewer network analysis for co-occurrence revealed distinct associations between terms used in clinical and molecular categories

All publications

We retrieved 5145 publications from the Web of Science Core Collection search. VOSviewer identified 1748 items (words or word combinations) in 3 clusters (Fig. 2a) from these publications, which defined co-occurrence of items regardless of context. As a next step, to delineate the context and relevance of items within the clusters, the items were inspected and divided into three contextual categories: Patient items, Molecular/Biomarker items and Disease/Symptoms items to clarify their use.

ENDOTYPE and SUBTYPE use

Neither items containing the words ENDOTYPE nor SUBTYPE were mentioned more than 10 times or were among the 60% most relevant items and hence did not qualify for clustering. This indicates that the ENDOTYPE and SUBTYPE terms are not widely used for stratification in OA literature.

PHENOTYPE use

Most items containing the word PHENOTYPE were found in cluster 2 (21 items out of 25, Table 1). As much as 71% of items in Cluster 2 was found to refer to the category "Biomarkers/Molecular" items (Table 1) suggesting

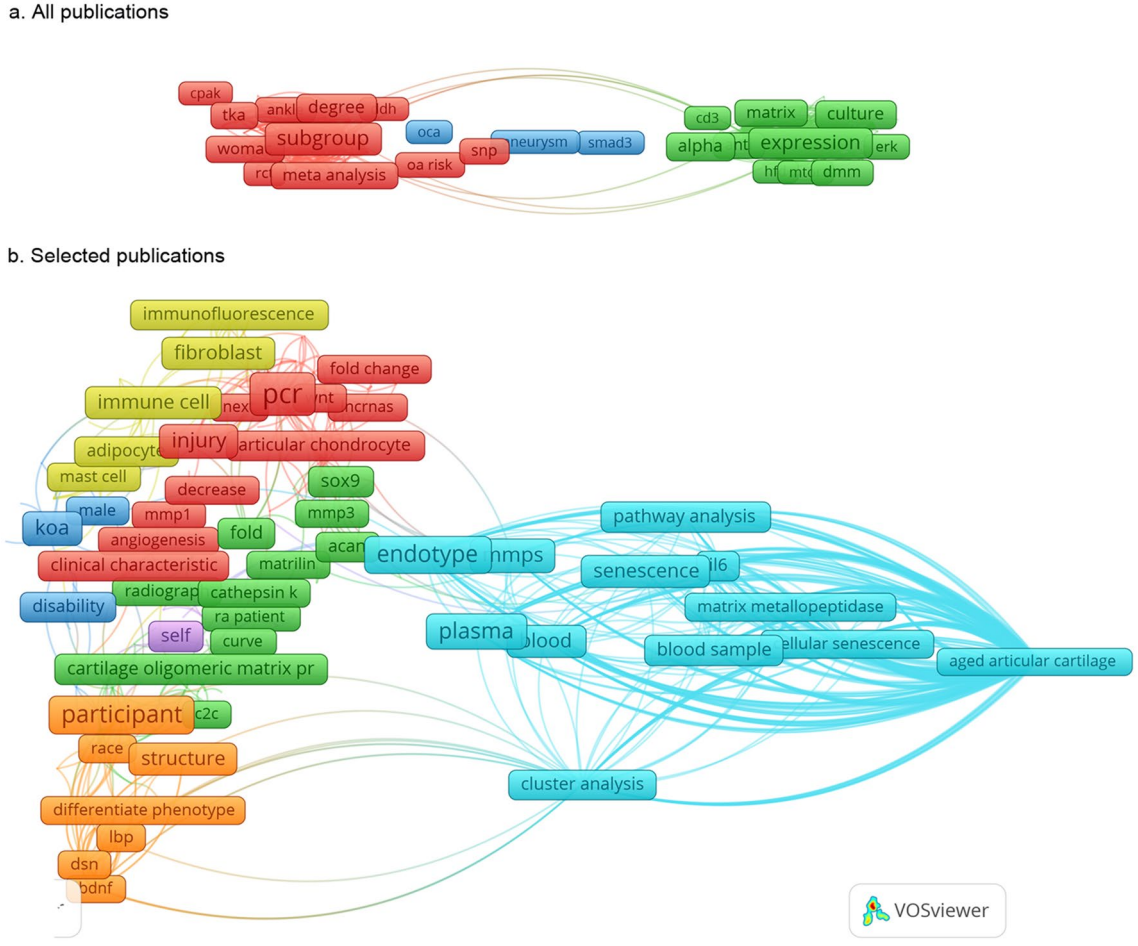


Fig. 2 VOSviewer item association of articles involving terms used for stratification of OA types. (**A**) Item association (1748 items) from 5145 articles retrieved before selection (see selection Fig. 1) in 3 clusters; Cluster 1 (red, 873 items), Cluster 2 (green, 842 items) and Cluster 3 (blue, 33 items). For overview of cluster content see Table 1, (**B**) Item association (476 items) from the 123 manually selected articles (see selection Fig. 1) in 8 clusters. Cluster 1 (red, 111 items), Cluster 2 (green, 86 items), Cluster 3 (blue, 70 items), Cluster 4 (yellow, 66 items), Cluster 5 (purple, 55 items), Cluster 6 (cyan, 55 items), Cluster 7 (orange, 36 items) and Cluster 8 (brown, 11 items). Cluster distance separation is depending on strength of association between cluster items. Only items with strongest association are shown for each cluster, for full list of items and association see Supplementary information

Table 1 Clustering of all identified publications in OA research using the stratification terminology between 2010 and 2024

Cluster	1	2	3
No of items	**873**	**842**	**33**
Search Terms			
PHENOTYPE	Coronal plane Alignment of the knee (CPAK) phenotype knee phenotype/ aggressive phenotype/	anti inflammatory phenotype/cartilage phenotype/ catabolic phenotype/ cell phenotype/cellular phenotype/chondrocyte phenotype/differentiated phenotype/hypertrophic phenotype/m1 phenotype/ m2 phenotype/macrophage phenotype osteoarthritic phenotype phenotypic phenotypic change secretory phenotype senescence phenotype senescent phenotype severe oa phenotype skeletal phenotype genotype phenotype correlation phenotypic spectrum	
ENDOTYPE	none	none	none
SUBGROUP	age subgroup aistinct subgroup homogeneous subgroup patient subgroup post hoc subgroup analysis specific subgroup subgroup subgroup analysis subgroup difference	none	none
SUBTYPE	none	none	none
Cluster Item Categories			
Patient data	29%	1%	18%
Biomarkers and Biological/Molecular items	25%	71%	82%
Disease related items	46%	28%	0%

that the term PHENOTYPE is more associated with publications containing molecular and biological features than clinical or imaging features.

SUBGROUP use

Items containing the word SUBGROUP were exclusively found in Cluster 1 (8 items, Table 1). The items in Cluster 1 were predominately from the "Disease/Symptoms" Category (46%), such as "participant," "pain score," and "implant." In addition, in Cluster 1, items were also found relating to the "*Patient*" and "Molecular/Biomarkers categories, but to a less extent with approximately 20% for each. Hence, the use of SUBGROUP is a preferred word for the "Disease/Symptoms" category but at the same time, represents a term for general stratification, according to the even distribution of item categories within Cluster 1.

Manually selected publications

In the manually screened and selected data set containing 123 unique publications [10–132], the VOSviewer analysis identified 476 items in 8 clusters (Fig. 2b, Table 2). Overall, these clusters were not very well defined and segregated from each other based on the distribution of items amongst the three categories Patient items, Molecular/Biomarker items and Disease/Symptoms items.

PHENOTYPE use

The word PHENOTYPE was found in various item combination and was present in all clusters except cluster 3 and 8. Hence, for the selected 123 publications, where we actively excluded clinical publications, the word PHENOTYPE appeared to be the preferred generic terminology, whilst before selection, SUBGROUP was the most generic term in the 5145 screened articles. This is proven in our manually selected publications (n = 123), whereby we actively excluded articles involving animal models, *in vitro*, clinical trials, and genetic association data (see selection in Fig. 1) and demonstrates the generic use of term that PHENOTYPE is preferentially used as a generic terms within the 123) [10–132], molecular and biological characterisation publications in human OA research.

SUBGROUP use

The only cluster where the word SUBGROUP was found was in item combinations within Cluster 1, which was also the cluster that contained most items related to the Disease/Symptoms category (49%). This is consistent with the use of a word preferentially used for clustering in human OA research.

SUBTYPE use

The word SUBTYPE was found only as part of an item combination in cluster 3, in specific reference to "distinct osteoarthritis subtype" and is consistent with the fact that this term is mostly used in association with patient stratification.

ENDOTYPE use

In contrast to VOSviewer analysis of all publications, the analysis of the selected ones categorized items containing ENDOTYPE. The items containing ENDOTYPE were associated with cluster 6 that had items, which contained

Table 2 Clustering of selected publications in OA research using the stratification terminology between 2010 and 2024

Cluster	1	2	3	4	5	6	7	8
No of items	111	86	70	66	55	41	36	11
Search Terms								
PHENOTYPE	abnormal **phenotype/** chondrocyte **phenotype**	biomarker **phenotype**	none	activated **phenotype**/ distinct metabolic **phenotype/** metabolic, **phenotype/** osteoarthritis **phenotype**	oa **phenotypic** outcome	secretory **phenotype**	differentiate **phenotype/** radiographic **phenotype**	none
ENDOTYPE	none	none	none	none	oa e**ndotype**	**endotype/** Identified senescence **endotype/ r**obust cellular senescent **endotype**	none	none
SUBGRUOP	patient **subgroup**	none	none	none	none	none	none	none
SUBTYPE	none	none	distinct osteoarthritis **subtype**	none	none	none	none	none
Cluster Item Categories								
Patient data	6%	9%	10%	13%	17%	4%	25%	56%
Biomarkers and Biological/Molecular Terms	44%	83%	87%	84%	80%	96%	64%	44%
Disease related information	49%	8%	3%	3%	3%	0%	11%	0

most Molecular/Biomarker items (97%). The word ENDOTYPE was found in item combinations mostly relating to senescence (Table 2).

Increased use of all investigated terms in OA research over time with the recent introduction of the term 'endotype'

The total frequency of publications in which the searched terms (PHENOTYPE, SUBTYPE, SUBGROUP and ENDOTYPE) were used increased over time and displayed an increasing occurrence of the terms both in all retrieved publications (Fig. 3a) and after manual screening and selection (Fig. 3b). In the manually selected publications PHENOTYPE was the most prevalent term, followed by SUBGROUP, SUBTYPE, and ENDOTYPE. The relative increase of each term normalized to the number of publications in 2010 showed that SUBTYPE had the highest relative increase (9 times since 2010) compared to PHENOTYPE and SUBGROUP (4 times). The term ENDOTYPE was first introduced in OA in 2019 in 5 papers and tripled within the next five years to 15 publications in 2023. The proportion of publications using any of the terminologies to the total number of publications in OA research is stable over time, indicating a steady interest in stratification within OA research (Fig. 3c).

Patient stratification studies in OA are primarily performed in plasma/serum samples and cartilage tissue publications

Next, we described stratification research in OA based on sample type, in which terminology prevalence in selected publications was monitored and analysed separately for a given tissue sample (i.e. cartilage, meniscus, synovium and bone), synovial fluid and blood (plasma/serum) samples were analysed separately. Assessing terminology used across tissues confirmed that PHENOTYPE is the most frequently used term and is most prevalent in cartilage and plasma/serum reports (Fig. 4a and f). An increasing number of publications per year was observed for different terms over time. Cartilage and plasma/serum displayed a total number of 40 and 46 publications respectively over the last 14 years, being the most assessed sample types. In contrast, meniscus and bone only displayed 4 and 9 publications respectively (Fig. 4b and c), whilst synovium displayed 17 publications (Fig. 4d) with a greater interest in this particular tissue after 2020. Notably, the term ENDOTYPE did not appear before 2019 and has been primarily used in synovial fluid and plasma/serum publications since the term was introduced. These patterns were also reflected in respect to overall use, wherby PHENOTYPE was the most prevalent term used in all sample types whilst ENDOTYPE had the lowest percentage. ENDOTYPE was more frequently used in synovial fluid and plasma/serum samples compared to tissues (Fig. 4g).

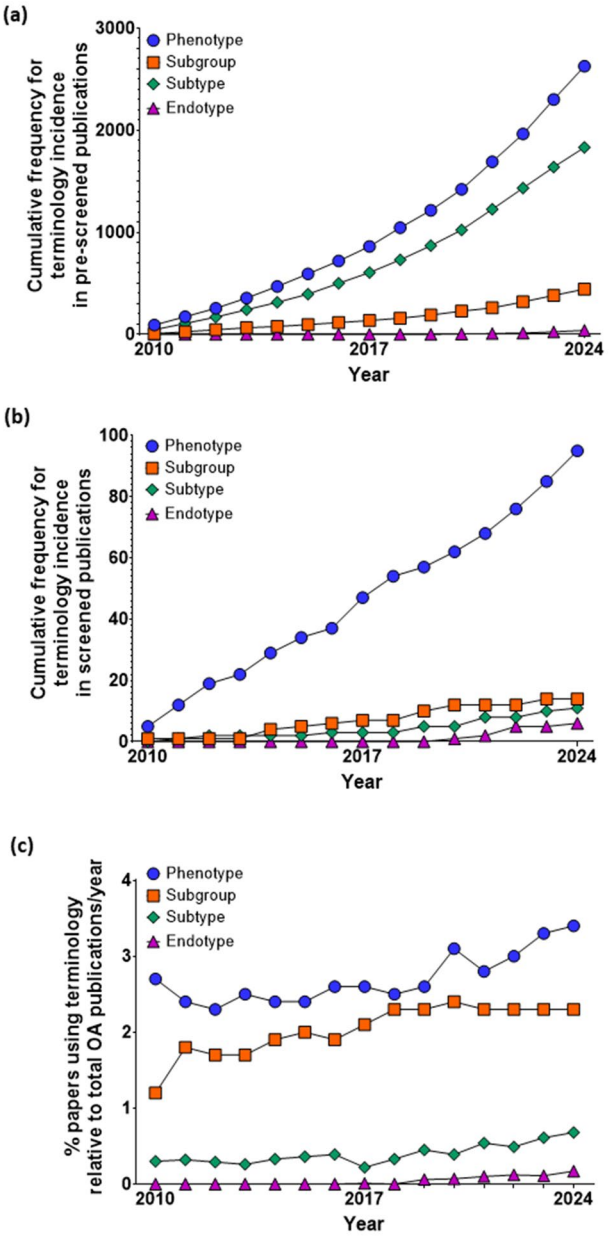


Fig. 3 Increased use of all investigated terms in OA research. Cumulative frequency curves for the incidence of the terms, PHENOTYPE, SUBTYPE, SUBGROUP, and ENDOTYPE in (**a**) all OA research publications and (**b**) manually screened publications. (**c**) The percentage use of terms relative to all OA publications per year

Current utilisation of stratification terminology lacks a coherent definition

To assess the current understanding and utilisation of the terms in OA research, the publications were systematically investigated for the use of the terms in the main text (materials and methods and results section) and the cross-use of different terminology within the same publication. (Fig. 5) We assumed that the appearance of the terms in the main text were more likely to be studies aimed at sample stratification based on their experimental work. The total number of publications that included any of the four terms in the main text was 102 of 191 (53%). In depth analysis of the conclusion from these publications showed that 38/102 (37%) of these studies actually stratified OA into groups based on their data. When exploring the separate terms, a similar frequency was observed across terminology, with PHENOTYPE being the most used (57 out of 113 publications (50%)) followed thereafter by SUBGROUP (25/40 publications (63%)) and then SUBTYPE as well as ENDOTYPE (10/19 publications (53%)) each. Detailed examination revealed that SUBTYPE and PHENOTYPE were used most inconsistently and varied. Stratification as an outcome was only found in 20 % and 30 % of the publications in which these terms were used in the main body. For the term, SUBGROUP 63% of the publications stratified based on data, whilst 100% of the publications using the ENDOTYPE terminology did so.

Cross-use and variation in definition of stratification terms

To assess the cross-use of terminology, we analysed whether more than one term appeared together within the same publication. PHENOTYPE frequently co-occurred with SUBGROUP (45% of studies using PHENOTYPE also included SUBGROUP), and to a lesser extent with SUBTYPE (15%). Notably, PMID: 32885253 utilized all three terms—PHENOTYPE, SUBGROUP, and SUBTYPE. In this study, the term PHENOTYPE was applied in a clinical context, whilst SUBTYPE and SUBGROUP were not sufficiently defined based on the study results. The term PHENOTYPE was often used vaguely and referred to clinical features of OA cohorts or radiographic phenotypes [22, 36, 41, 69, 74, 95], or, in some cases, to molecular, cellular, histological, or biochemical phenotypes [38, 51, 64, 70]. The term SUBGROUP was explicitly defined in one study [19], where OA stratification was performed based on biomarker levels and their correlation with cartilage volume loss over two years. The terms SUBGROUP and SUBTYPE were often used without clear distinctions and not determined by unique study data.

In our detailed examination, we observed that even in the stratified publications (the lowest tier in Fig. 5, i.e. the ones using stratification approaches based on molecular findings) terminology was used interchangeably, and the use and definition of stratification terminology was inconsistent between publications.

Many studies applying stratification approaches using omics, machine learning, and/or clustering techniques referred to the term ENDOTYPE [10, 121, 122]. However, within the same publications, the terms SUBTYPE [121], PHENOTYPE, and SUBGROUP [10] were also used. Some studies primarily use PHENOTYPE while

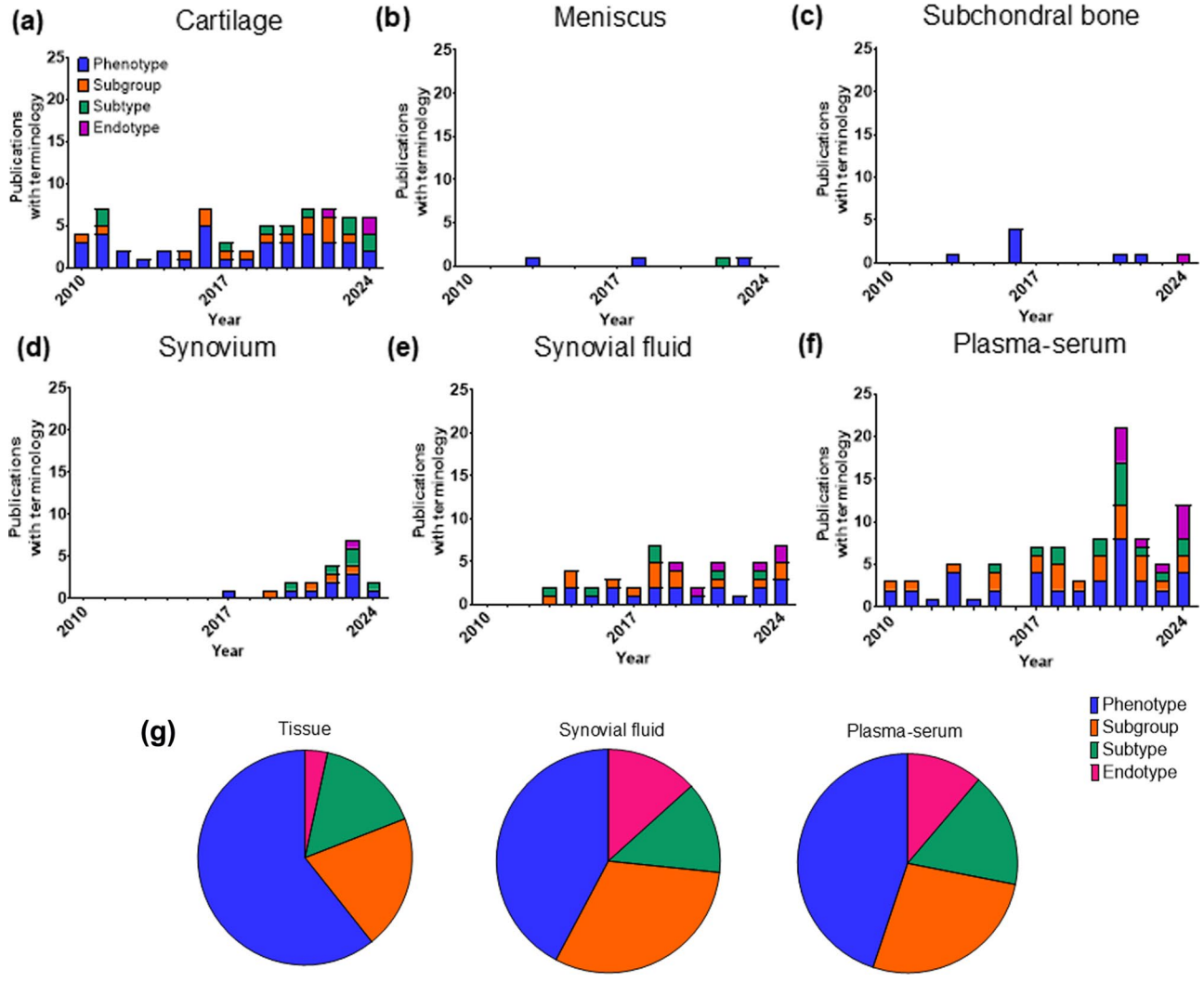


Fig. 4 Patient stratification studies in OA are primarily performed in plasma/serum samples and cartilage tissue. Number of publications using the specific terminology (PHENOTYPE SUBGROUP, SUBTYPE, ENDOTYPE within manually screened publications for (**a**) cartilage, (**b**) meniscus, (**c**) bone, (**d**) synovium, (**e**) synovial fluid and (**f**) plasma/serum (**g**) Pie charts representing the percentage use of the terms within the screened publications for tissues (cartilage, meniscus, subchondral bone and synovium), synovial fluid and plasma/serum

also referencing ENDOTYPE, SUBTYPE, and SUBGROUP to a lesser extent [28]. Additionally, studies focusing on tissue transcriptomics often defined SUBTYPE [130]. Among these terms, ENDOTYPE exhibited more consistent usage compared to others, though a universally accepted definition is lacking. Overall, our analysis underscores the inconsistent and variable application of terminology in OA stratification research.

Discussion

In this review we performed a bibliometric network analyses and manual text mining of publications containing stratification terminologies (PHENOTYPE, SUBTYPE, SUBGROUP and ENDOTYPE) to map the use of terminology related to the stratification of OA and identify current state of the art in this research area. Publications that contained the stratification terms were included and analysed based on sample types (tissue samples, synovial fluid and blood samples). Prevalence, definition and co-occurrence of terminology was assessed, as well as words associated with the different terminologies. The incidence of stratification terminology in OA research has steadily increased over time, reflecting growing efforts to stratify OA patients.

Our analysis displayed PHENOTYPE as the most prevalent term, linked to molecular and biological features, particularly in cartilage and plasma/serum studies. SUBGROUP appeared predominantly in clinical and patient related contexts, whilst SUBTYPE was associated with studies investigating disease and symptoms. The term ENDOTYPE emerged in OA literature in 2019, and was primarily related to biomarker studies in synovial fluid

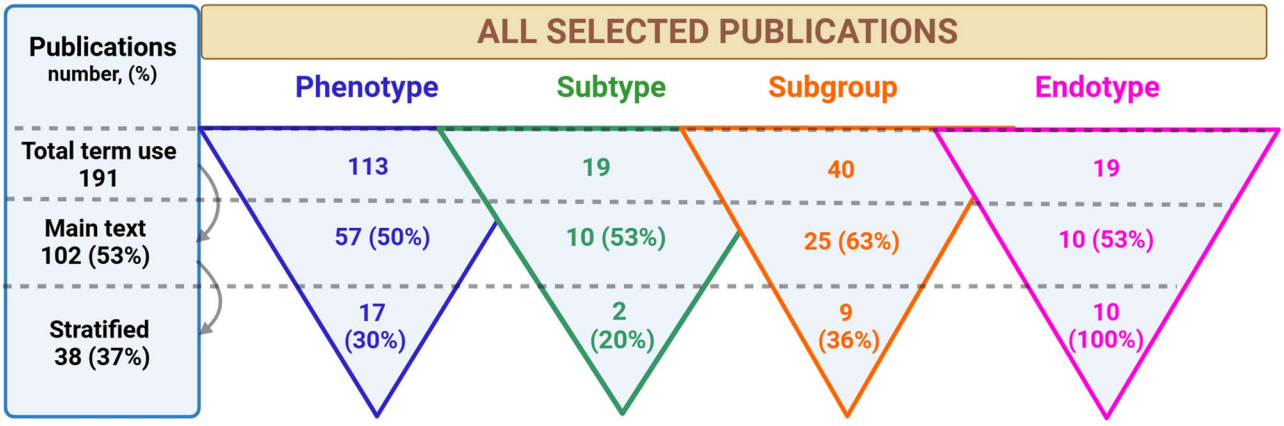


Fig. 5 Discrepancy in terminology usage and definitions. The Funnel scheme displays all reports using the terminology extracted from the text mining results (top tier), while the middle tier displays the reports wherein the term (i.e. PHENOTYPE, SUBTYPE, SUBGROUP and ENDOTYPE) appeared in the main text of each report, including the percentage of these papers from the total count. The lowest tier displays the number of papers that presented data justifying patient stratification based on identified molecular signatures, whilst percentages displayed, are the number of papers that showed a distinct molecular stratification of all papers mentioning the term in the main text (i.e. middle tier). In total, 38 of the 102 (37%) using the term in the main text actually stratified OA, which is 20% (38/191) of all papers applying the terminology

and plasma/serum. Despite the term PHENOTYPE was the most frequently used stratification term in the molecular context, it needs to be addressed that the common understanding likely refers to PHENOTYPE to the observable expression of an individual's genotype [133].

A substantial body of OA research explores biomarkers alongside clinical parameters to understand patient characteristics and underlying biological mechanisms. However, consensus on terminology is lacking. Many studies used imprecise or inconsistent terms, often mixing multiple definitions within a single publication. This inconsistency complicates systematic reviews and hinders knowledge synthesis. Term usage also varied by publication section: introductions typically provide background on OA types, whilst discussions often referenced clinical data without true sample stratification. In contrast, studies using either of the terms frequently in the main body were more likely to stratify patients experimentally, though only 48% actually did so, ranging from 20% for SUBTYPE to 100% for ENDOTYPE (Fig. 5). Hence, ENDOTYPE most consistently reflected molecular stratification, further supported by its significance in the VOSviewer cluster analysis of selected publications.

The term ENDOTYPE appeared in the published literature in the late 2000s, although its conceptual roots trace back earlier. This terminology was introduced in 2008 to distinguish between subtypes of asthma based on underlying biological mechanisms, as opposed to observable clinical features (phenotypes) [134]. This and subsequent publications in the field of asthma played a pivotal role in establishing ENDOTYPE as a term to describe mechanistic subtypes of diseases defined by distinct functional or pathobiological mechanisms. At this point asthma researchers began looking at the syndrome by dividing it into distinct disease entities with specific mechanisms, which they described as "asthma endotypes" [135]. The increased use of the term ENDOTYPE in the asthma and respiratory disease field and its gradual inclusion in other disciplines of medicine including OA, reflects a gradual shift from symptom-based observation to mechanism-driven understanding of disease, which is crucial for the development of targeted therapies.

The limitations of the "one-drug-fits-all" approach in drug development, evidenced by numerous clinical trial failures in OA, have prompted a paradigm shift toward enhanced patient stratification. Stratification approaches seek to tailor treatments to subpopulations most likely to benefit. National and international initiatives have been launched to align, improve, and consolidate data related to OA stratification and this review identified several publications involving large cohorts and omics data. However, molecular markers alone are insufficient to fully characterize the disease, which involves a complex interplay of molecular data, biological triggers, conditions, and pathways.

The literature provides compelling evidence that OA is a multifaceted syndrome, comprising several subsets with distinct pathophysiological pathways, but without defining them further. This complexity may explain some of the inconsistencies observed in earlier research on stratification in OA and the challenges in translating findings into clinical practice. Whilst some studies define the terminology used, others do not, and the definitions often vary between publications. This variability underscores the urgent need for standardization and clear definitions of stratification terminology. Biological signatures or biomarkers must be integrated with clinical characteristics and molecular mechanisms to define proper patient

stratifications. Standardized terminology is crucial for enabling meaningful meta-analyses, systematic reviews, and aggregated assessments, ultimately advancing the field of OA research.

Conclusion

This review displays an overview of the terminology used for stratification of OA patients in studies published between January 2010 and September 2024. The increasing use of specific stratification terms in OA research, highlights growing efforts to stratify patients and identify targeted treatments. However, the lack of standardized definitions and inconsistent use of terminology across studies hinders progress in the field. The term PHENTOYPE was commonly used to describe clinical features, whereas ENDOTYPE referred to molecular mechanisms underlying OA pathogenesis. To build on published terminology, the term PHENTOYPE could be applied when describing clinical features, whilst the term ENDOTYPE could be applied when describing molecular mechanisms. Applying standard definitions of terminology in OA research will enable better data interpretation, communication of research findings and meaningful systematic reviews, meta-analyses, and collective evaluations that would ultimately advance patient stratification and the development of tailored therapies

Proposed research goals

- To consensually establish a standardized terminology definition to align the language and information in relation to OA stratification
- To match molecular stratification with clinical classifications to identify markers for the diagnosis and prognosis of OA disease.
- To identify molecular markers or groups of markers to classify OA patients, as to administer the treatment to which they respond best.
- To describe cellular and molecular mechanisms under different OA stratifications
- To define a core set of clinical parameters describing the status of the patient
- To define criteria of sample description and handling for biochemical analysis

Acknowledgements
We would like to acknowledge WG3 in the COST Action CA21100: Building an open European Network on OsteoArthritis research (NetwOArk). This publication is based upon work from supported by COST (European Cooperation in Science and Technology).

Author contributions
All authors contributed to study concept and design. GP, BSF, MDG, EB, FZ, GR, IU, JLR, MK, MAB, SN, VG, ZL, ZJL and CA performed the screening and selection. All authors approved the final inclusion of publications. NK performed the VOSviewer analysis. CA, NK, GP, MDG and ZJL prepared the figures. All authors participated in analysis and data interpretation. SN, MDG and CA drafted the first version of the manuscript. All authors revised the manuscript and approved the final version.

Funding
This project is a joint publication developed under and supported by the European Cooperation in Science and Technology (COST) Action CA21110 - Building an open European Network on OsteoArthritis research (NetwOArk).

Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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Received: 12 January 2025 / Accepted: 12 August 2025
Published online: 30 September 2025

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