Diabetology & Metabolic Syndrome

REVIEW

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Prevalence of metabolic syndrome in ankylosing spondylitis: a multi national meta-analysis study

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Abstract

Background Ankylosing spondylitis (AS) is a chronic inflammatory disease associated with an increased risk of metabolic syndrome (MetS), a cluster of cardiometabolic risk factors. However, the prevalence of MetS in AS remains uncertain. This meta-analysis estimates the global prevalence of MetS in AS patients and identifies factors contributing to its variability.

Methods A systematic search of PubMed, Scopus, Embase, and Web of Science was conducted for studies published up to January 18, 2024. A random-effects model was used to estimate pooled prevalence, while meta-regression and subgroup analyses explored sources of heterogeneity.

Results Seventeen studies meeting the eligibility criteria were included. The pooled prevalence of MetS in AS patients was 15.5% (95% confidence interval [CI]: 10.9–20.8%). The highest prevalence was reported in Africa (37.0%) and the lowest in Asia (8.0%). Variability in AS diagnostic criteria influenced prevalence estimates, with the highest MetS rates found in studies using the Assessment of SpondyloArthritis International Society (ASAS) criteria (37.0%). Meta-regression identified significant associations between MetS prevalence and older age ($\beta = 0.04$, $P < 0.01$), higher body mass index ($\beta = 0.09$, $P < 0.01$), triglyceride levels ($\beta = 0.01$, $P < 0.01$), waist circumference ($\beta = 0.03$, $P < 0.01$), diastolic blood pressure ($\beta = 0.04$, $P = 0.02$) and disease activity, measured by the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) ($\beta = 0.03$, $P = 0.02$). Erythrocyte sedimentation rate was significantly correlated with MetS prevalence ($\beta = 0.01$, $P = 0.04$), while C-reactive protein was not ($\beta = -0.01$, $P = 0.12$).

Conclusion MetS is a prevalent comorbidity in AS, significantly influenced by inflammation, obesity, and disease activity. Given its strong association with cardiovascular risk, routine metabolic screening should be incorporated into AS management. Clinicians should adopt an integrated approach that includes lifestyle modifications, targeted therapies, and careful cardiovascular risk assessment to mitigate long-term complications. Standardized diagnostic criteria for MetS in AS are needed to improve risk stratification and patient outcomes.

Keywords Ankylosing spondylitis, Metabolic syndrome, Prevalence, Cardiovascular risk, Inflammation, Obesity

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Introduction

Ankylosing spondylitis (AS) is a chronic inflammatory disorder primarily affecting the axial skeleton, characterized by pain, stiffness, and progressive spinal fusion [1–3]. AS is classified under the spondyloarthropathies, a group of diseases that also includes psoriatic arthritis, inflammatory bowel disease-related arthritis, and reactive arthritis [4–6]. While the primary clinical focus of AS remains its musculoskeletal manifestations, emerging evidence has suggested that patients with AS are at increased risk for comorbid conditions, including metabolic syndrome (MetS), which can significantly impact overall health and quality of life [7–10].

MetS, a cluster of interrelated risk factors such as abdominal obesity, dyslipidemia, hyperglycemia, and hypertension, is associated with an increased risk of cardiovascular disease, type 2 diabetes, and stroke [11–13]. The relationship between AS and MetS is complex and bidirectional, with inflammation, an essential feature of AS, potentially influencing the development of MetS components [14–17]. Furthermore, the sedentary lifestyle, prevalent in patients with AS due to pain and disability, may exacerbate the risk for metabolic disturbances [17, 18].

Recent studies have indicated a higher prevalence of MetS in individuals with AS compared to the general population [7, 8, 19]. However, the exact prevalence of MetS in this cohort remains unclear, with different studies reporting varying estimates due to differences in population characteristics, diagnostic criteria, and study methodologies [14, 20, 21]. This variability underscores the need for a comprehensive assessment of the prevalence of MetS in AS patients to better understand the burden of these comorbidities and guide clinical management.

The purpose of this meta-analysis is to synthesize the available data on the prevalence of MetS in patients with ankylosing spondylitis. By pooling results from multiple studies, this analysis aims to provide a more precise estimate of MetS prevalence in this population and explore potential factors that may contribute to its occurrence.

Methods

This meta-analysis was executed following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [22]. The study protocol was registered on the International Prospective Register of Systematic Reviews (Registration ID: CRD 42025640096). The main objective of this analysis was to calculate the global prevalence of MetS in individuals diagnosed with AS by synthesizing data from multiple studies published in peer-reviewed journals.

Search strategy

A comprehensive and systematic search was performed across databases including PubMed, Scopus, Embase, and Web of Science, covering studies published up to January 18, 2024. No restrictions were placed on the language of publication. Keywords used in the search included "Ankylosing Spondylitis," "Spondylitis Ankylosing," "Bechterew's disease," "Axial Spondyloarthritis," "Metabolic Syndrome," "Metabolic Syndrome X," and "Syndrome X." In addition, relevant articles were identified by reviewing the reference lists of key studies. The detailed search formula for each database is provided in Table S1.

Study selection and eligibility criteria

For this meta-analysis, studies that evaluated the prevalence of MetS in patients with AS, or studies that reported the raw number of patients with MetS and without MetS in AS patients within their respective settings, were considered eligible for inclusion. We excluded case reports, review articles, editorials, and studies that did not provide adequate data for comprehensive analysis.

Two independent reviewers screened the titles and abstracts of all identified studies. Full-text assessments were performed to verify the eligibility of the studies. Disagreements between the reviewers were resolved through discussion or consultation with a third reviewer.

Quality assessment

The studies included in the meta-analysis were independently assessed for quality by two reviewers using the Joanna Briggs Institute (JBI) Critical Appraisal Checklist [23–25]. Any differences in their assessments were resolved by involving a third reviewer to ensure a final consensus.

Data extraction

Data were independently extracted from each study using a standardized extraction form. The extracted data included study characteristics (author, year, country), demographic details (age, gender), diagnostic criteria for AS and MetS, sample size, and prevalence estimates for MetS and its individual components. If necessary, the corresponding authors were contacted to obtain any missing data or to clarify ambiguities in the reported results.

Statistical analyses

All statistical analyses were conducted using STATA software (version 18.0) to pool prevalence estimates. A random-effects model was used to account for the anticipated heterogeneity between studies. Prevalence rates with 95% confidence intervals (CIs) were reported as percentages.

The degree of heterogeneity was assessed using I^2 statistics, with values above 50% indicating substantial heterogeneity. Sensitivity analyses were performed to assess the impact of each study by sequentially removing individual studies.

To examine publication bias, funnel plots were visually inspected. Egger's and Begg's tests were used to assess publication bias, with a *p*-value of less than 0.1 considered indicative of significant bias.

Meta-regression analyses were conducted to explore potential factors contributing to the heterogeneity observed across studies, including variations in study year and sample size.

Results

Study selection

A total of 658 records were identified through database searches, including PubMed ($n = 52$), Scopus ($n = 189$), Embase ($n = 252$), and Web of Science ($n = 165$). After removing 299 duplicate records, 359 unique records remained for screening. During the screening process, 273 records were excluded. The remaining 86 reports were assessed for eligibility. Ultimately, 17 studies met the inclusion criteria and were included in the final review (Fig. 1).

Study characteristics

A total of 17 studies were included in this meta-analysis, covering a diverse range of geographic regions, study designs, and diagnostic criteria (Table 1). The sample sizes of the included studies varied from 24 to 5,905 participants, with total of 9,746 individuals diagnosed with AS. The studies were conducted across multiple countries, including Turkey [26–29], Romania [30], Italy [19, 31], Morocco [32], Egypt [33], Norway [34], Taiwan [35, 36], China [8, 37], Brazil [7], Greece [38], and Thailand [39].

In terms of diagnostic criteria, most studies employed the Modified New York Criteria (MNYC) for AS classification, while some utilized the International classification of diseases, 9th 9evision, clinical modification (ICD-9-CM) classification. The diagnosis of MetS was based on different criteria, including national cholesterol education program adult treatment panel III (NCEP-ATP III), international diabetes federation (IDF)/ joint consensus (JC), Chinese diabetes society (CDS), world health organization (WHO), European group for the study of insulin resistance (EGIR), and the harmonized definition, contributing to some variability in prevalence estimates. The detailed definition of each criterion is presented in table S2.

The methodological quality of included studies was assessed using the JBI Critical Appraisal Checklist, with all studies meeting the inclusion criteria for methodological rigor. The quality of included studies is presented in table S3.

Results of meta-analysis

Total prevalence of MetS in AS

The meta-analysis included 17 studies assessing the prevalence of MetS in patients with AS (Fig. 2). The pooled prevalence of MetS in AS patients was 15.5% (95% CI: 10.9–20.8%), with substantial heterogeneity across studies (I^2 = 96.39%). The prediction interval analysis determined that the prevalence of MetS in patients with AS ranges from 0.3 to 44.6% (Fig. 2.A). A sensitivity analysis was conducted by systematically omitting each study to evaluate the robustness of the findings. The results demonstrated that the pooled prevalence remained consistent, with no significant difference observed after the removal of any individual study (Fig. 2.B). The Galbraith analysis was also conducted in order to assess the influence of individual studies and identify any outliers that could disproportionately affect the meta-analysis results (Fig. 2.C).

Analyses based on sex revealed that the prevalence of MetS in men with AS was 26.5% (95% CI: 21.1–32.3%), with low heterogeneity (I^2 = 28.58%) (Fig. 2C), while in women, the prevalence was 23.3% (95% CI: 9.1–40.9%), with high heterogeneity (I^2 = 73.98%) (Fig. 2D).

Sex-based comparison of MetS in AS patients

The analysis indicated no significant difference between men and women in the prevalence of MetS among patients with AS (Fig. 3). The pooled odds ratio (OR) for the association between sex and MetS was 1.16 (95% CI: 0.30–4.44, $P = 0.78$). Substantial heterogeneity was observed across studies (I^2 = 65.72%). The prediction interval analysis revealed that the OR for sex differences in MetS in AS patients ranges from 0.05 to 26.72 (Fig. 3.A), highlighting the variability between studies.

A sensitivity analysis was conducted by systematically omitting each study to assess the robustness of the findings. The pooled OR remained stable, with no significant change after the removal of any individual study (Fig. 3.B). The Galbraith analysis was performed to assess the influence of individual studies and identify any outliers that might disproportionately affect the results. The study by Akaltun, 2021, was identified as an outlier (Fig. 3.C).

The contour-enhanced funnel plot did not suggest significant publication bias, which was further confirmed by the Egger's test ($p = 0.61$) and Begg's test ($P = 0.80$) (Fig. 3.D). The trim-and-fill analysis did not impute any studies (Fig. 3.E).

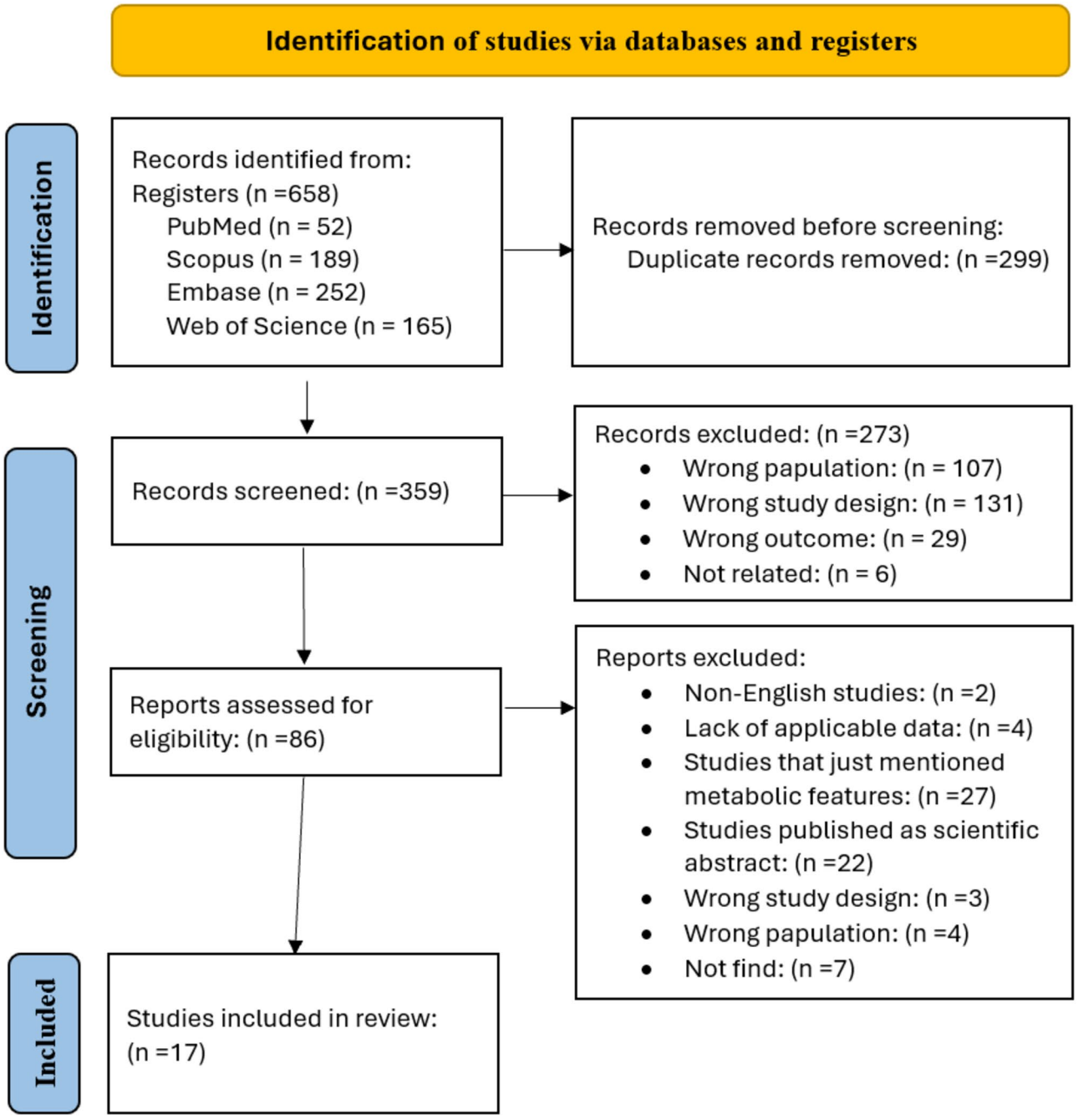

Fig. 1 Study selection process

Results of subgroup analysis

Subgroup analyses were conducted to explore sources of heterogeneity in the prevalence of MetS among patients with AS. Regarding geographical distribution, the highest prevalence of MetS was observed in Africa (37.0%; 95% CI: 23.0–53.0%), though this estimate was based on a single study. In contrast, Asia reported the lowest prevalence (8.0%; 95% CI: 5.0–13.0%), based on five studies. In Europe, the pooled prevalence was 16.0% (95% CI: 11.0%–21.0. A single study from South America estimated the prevalence at 27.0% (95% CI: 16.0–38.0%) (Table 2).

The prevalence of MetS also differed based on the AS definition criteria. Studies using the axial spondyloarthritis classification criteria (ASAS) criteria reported the highest prevalence (37.0%; 95% CI: 23.0–53.0%), whereas those employing the ICD-9-CM classification showed the lowest prevalence (3.0%; 95% CI: 2.0–3.0%). The Modified New York criteria, the most frequently

Table 1 Characteristics of included studies

No.	Authors	Year	Country	Study Papulation					MetS Prevalence		Disease Duration (Year)	As Criteria	MetS Criteria	AS Activity Scoring		Sample size Lab Data					Quality Assessment
				Sample size	Mean age	BMI	Male	Female	No. patients	Prevalence (%)				BASDAI	ASDAS-CRP	ESR (mm/h)	CRP (mg/L)	TG (mg/dl)	TC (mg/dl)	Glucose (mg/dl)	
1	Akaltun et al. [21]	2021	Turkey	67	36.79	28.15	55	12	23	34.3%	7.1	Modified New York criteria	NCEP-ATP III	4.33	NA	15.55	7.34	149.83	NA	96.64	8
2	Amaricai et al. [30]	2018	Romania	115	NA	NA	NA	NA	16	13.9%	NA	NA	NCEP-ATP III	NA	NA	NA	NA	NA	NA	NA	4
3	Batmaz et al. [27]t	2011	Turkey	50	34.14	NA	40	10	6	12.0%	NA	Modified New York criteria	NCEP-ATP III	NA	NA	16.08	2.1	147.17	175.89	93.32	9
4	Chimenti et al. [31]	2020	Italy	39	44.8	24.4	20	19	9	23.1%	12.5	Modified New York criteria	IRS	5.5	1.2	26.7	1.2	NA	NA	NA	10
5	El Hassani Sbai et al. [32]	2019	Morocco	110	35.8	24.17	75	35	9	8.2%	NA	Modified New York criteria	JC, IDF, NCEP, WHO, EGIR	4.41	NA	20.2	11.17	NA	NA	NA	8
6	Gado et al. [33]	2022	Egypt	40	42.78	24.65	40	0	15	37.5%	9.55	ASAS	IDF	NA	0.58	46.33	7.05	145.58	223	92.78	8
7	Halvorsen et al. [34]	2013	Norway	126	47.9	25.4	78	48	26	20.6%	NA	Modified New York criteria	IDF	NA	1	NA	3	106.3	NA	90	8
8	Kesikburun et al. [28]	2018	Turkey	57	42.33	28.13	25	32	14	24.6%	6.38	Modified New York criteria	IDF	2.4	NA	20	10.2	128.13	NA	87.61	8
9	Lai et al. [35]	2022	Taiwan	5,905	37.72	NA	3,255	2,650	194	3.3%	NA	ICD-9-CM	NA	NA	NA	NA	NA	NA	NA	NA	10
10	Lin et al. [36]	2022	Taiwan	2,650	37.72	NA	1,480	1,170	90	3.4%	NA	ICD-9-CM	NA	NA	NA	NA	NA	NA	NA	NA	10
11	Liu et al. [8]	2019	China	117	35	22.9	97	20	23	19.7%	NA	Modified New York criteria	CDS	NA	NA	NA	NA	106.3	162.4	90	8
12	Maia et al. [7]	2017	Brazil	63	41.6	27.6	53	10	17	27.0%	NA	Modified New York criteria	NCEP-ATP III	NA	NA	NA	NA	131.4	190.9	104.4	6
13	Malesci et al. [19]	2007	Italy	24	50.5	29.2	21	3	11	45.8%	NA	Modified New York criteria	NCEP-ATP III	21.3	NA	NA	NA	141	205	NA	9
14	Mok et al. [37]	2011	Hong Kong	122	39	23.3	94	28	13	10.7%	6	Modified New York criteria	IDF	NA	NA	NA	NA	88.6	196.1	89.6	8
15	Papadakis et al. [38]	2009	Greece	63	40	NA	63	0	22	34.9%	NA	Modified New York criteria	NCEP ATP III	NA	NA	NA	NA	114	197	91	9
16	Petcharat et al. [39]	2021	Thailand	153	41.7	23.4	94	59	29	19.0%	10	Modified New York criteria	Harmonized definition	NA	1.1	NA	NA	NA	NA	NA	8
17	Sari et al. [29]	2010	Turkey	45	37.4	25	35	10	0	0.0%	NA	Modified New York criteria	NA	NA	NA	11	NA	95.7	173.7	91	9

NCEP/ATP III: National Cholesterol Education Program Adult Treatment Panel III, IRS: Internationally Recognized Standards, IDF: International Diabetes Federation, WHO: World Health Organization, EGIR: European Group for the study of Insulin Resistance, ASAS: Assessment of Spondyloarthritis International Society, NYCC: New York classification criteria, ICD-9-CM: International Classification of Diseases-Ninth Revision-Clinical Modification, CDS: Chinese Diabetes Society

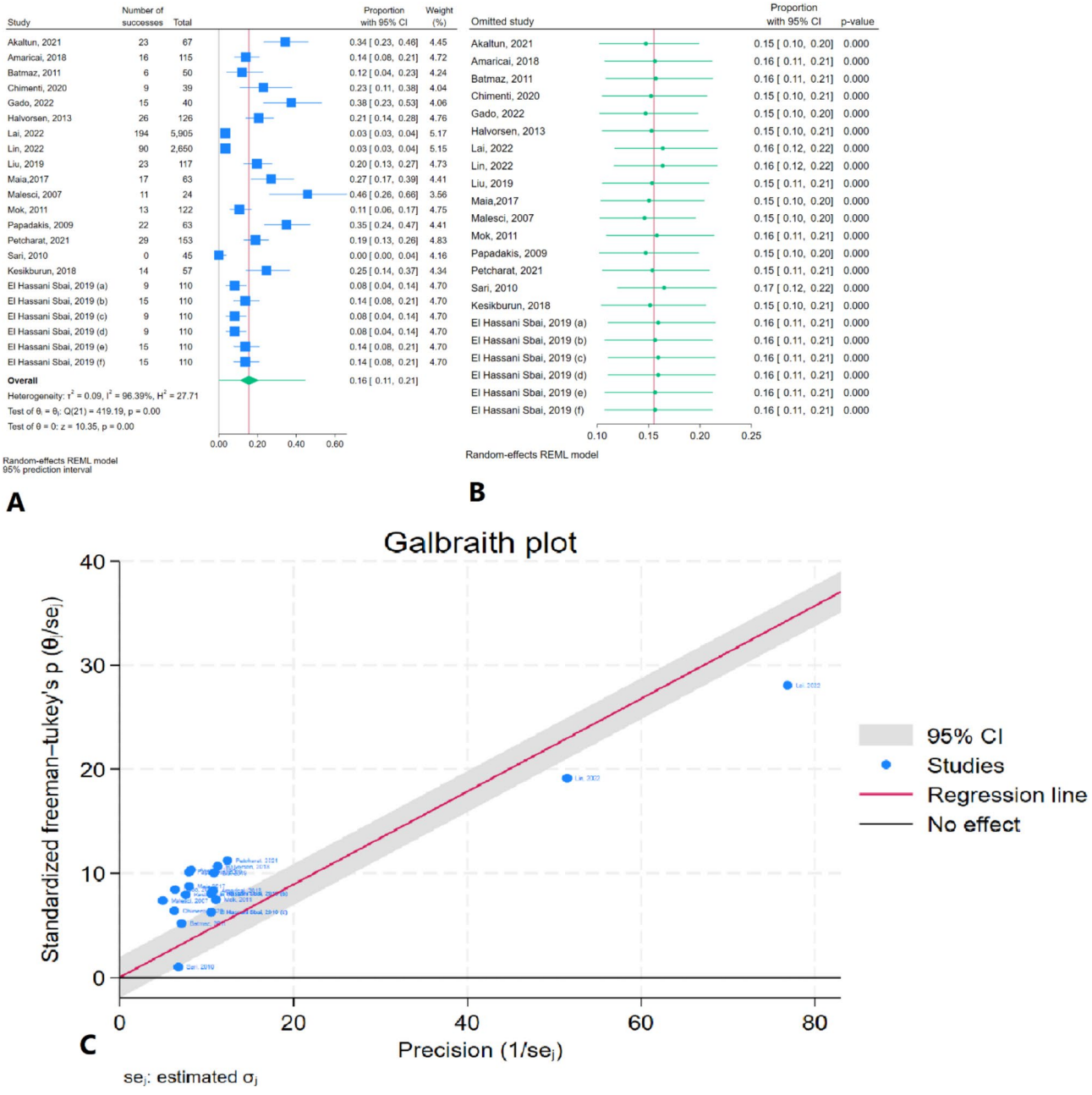

Fig. 2 **A**: Forest plot of the pooled prevalence of metabolic syndrome (MetS) in patients with ankylosing spondylitis. Overall prevalence of MetS in AS patients. **B**: Sensitivity analysis showing the impact of omitting each individual study on the pooled prevalence estimate. **C**: Galbraith plot showing outlier studies with disproportionate influence on the meta-analysis results

used classification, yielded a prevalence of 16.0% (95% CI: 12.0–22.0%) (Table 2).

In terms of MetS diagnostic criteria, studies employing the NCEP-ATP III definition reported a prevalence of 20.0% (95% CI: 12.0–31.0%), while those using the IDF criteria estimated a prevalence of 19.0% (95% CI: 12.0–28.0%). Harmonized definition and CDS criteria yielded an estimated prevalence of 13.0% (95% CI: 4.0–25.0%) and 19.0% (95% CI: 12.0–27.0%) respectively (Table 2).

In terms of sex-based differences, the pooled prevalence of MetS in men with AS was 26.5% (95% CI: 21.1–32.3%). In women, the prevalence of MetS was 23.3% (95% CI: 9.1–40.9%)(Table 2).

The prevalence of MetS in AS patients also varied across age groups. In the subgroup of patients aged 34–39.9 years, the prevalence was 9.0% (95% CI: 5.0–14.0%). In patients aged 40–44.9 years, the prevalence increased to 26.0% (95% CI: 20.0–32.0%), and for those

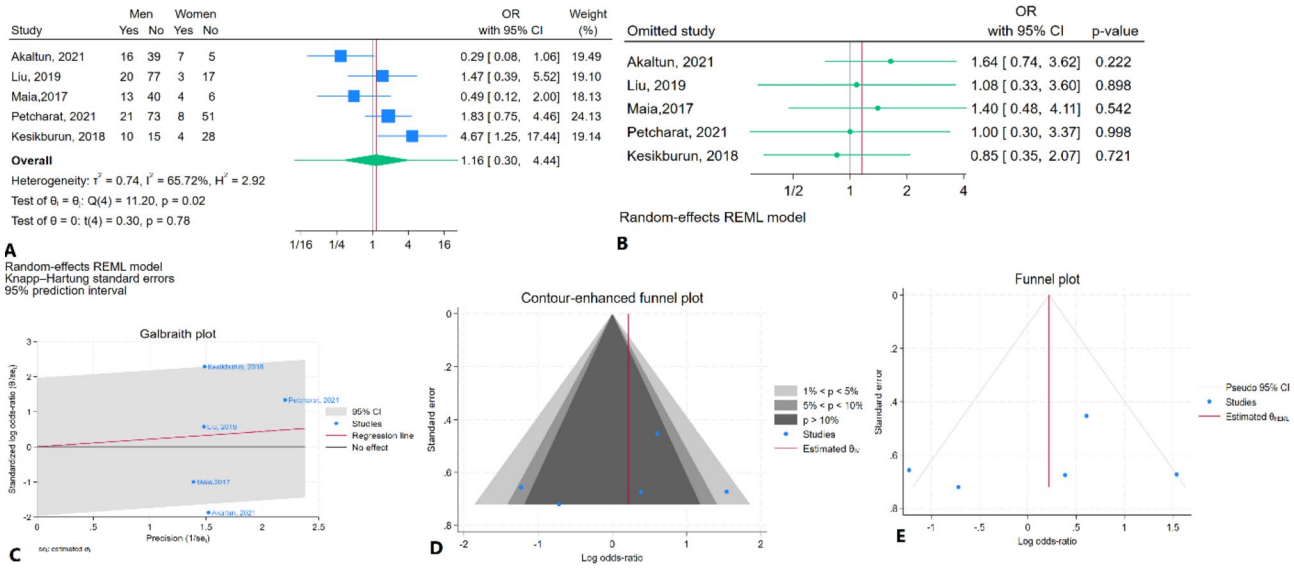

Fig. 3 Analysis of Sex-Based Differences in MetS Prevalence Among AS Patients. **A**: Forest plot of the pooled result. **B**: Sensitivity analysis plot. **C**: Galbraith plot. D: Contour-enhanced funnel plot. **E**: Trim-and-fill analysis

Table 2 Results of subgroup analysis

Variable		Number of effect sizes	Prevalence	95%CI	Tau2	I2	H2
Continent	Africa	1	0.37	0.23–0.53	0.00	---	---
	Asia	5	0.08	0.05–0.13	0.02	95.51	22.26
	Europe	15	0.16	0.11-21	0.05	82.95	5.87
	South America	1	0.27	0.16–0.38	0.00	---	---
AS definition	ASAS	1	0.37	0.23–0.53	0.00	---	---
	ICD-9-CM	2	0.03	0.02–0.03	0.00	0.00	1.00
	Modified New York criteria	18	0.16	0.12–0.22	0.06	85.75	7.02
Mets criteria	CDS	1	0.19	0.12–0.27	0.00	---	---
	EGIR	1	0.13	0.07–0.20	0.00	---	---
	Harmonized definition/JC	2	0.13	0.04–0.25	0.04	84.05	6.27
	IDF/JC	5	0.19	0.12–0.28	0.03	79.44	4.86
	Internationally Recognized Standards	1	0.23	0.11–0.37	0.00	---	---
	NCEP-ATP III	8	0.20	0.12–0.31	0.09	87.74	8.15
	WHO	1	0.13	0.07–0.20	0.00	---	---
Gender	Men	5	0.26	0.21–0.32	0.00	28.58	1.40
	Women	6	0.23	0.09–0.40	0.11	73.98	3.84
Quality score	10	3	0.07	0.003-0.20	0.11	99.53	213.26
	9	4	0.18	0.01–0.45	0.33	93.56	15.74
	8	13	0.16	0.12–0.21	0.03	79.93	4.98
	6	1	0.27	0.16–0.38	0.00	---	---
	4	1	0.13	0.08–0.20	0.00	---	---
Age	34-39.9	13	0.09	0.5 – 0.14	0.06	96.38	27.62
	40-44.9	6	0.26	0.20–0.32	0.01	46.52	1.87
	Over 45	1	0.30	0.09–0.57	0.12	83.41	6.03

ASAS: Assessment of SpondyloArthritis International Society, NCEP/ATP III: National Cholesterol Education Program Adult Treatment Panel III, IRS: Internationally Recognized Standards, JC: Joint Consensus, IDF: International Diabetes Federation, WHO: World Health Organization, EGIR: European Group for the study of Insulin Resistance, ICD-9-CM: International Classification of Diseases-Ninth Revision-Clinical Modification, CDS: Chinese Diabetes Society

over 45 years, the prevalence was 30.0% (95% CI: 9.0–57.0%) (Table 2).

Results of meta-regression analysis

Meta-regression analysis was performed to investigate potential sources of heterogeneity in the prevalence of MetS among patients with AS. Several variables were found to be significantly associated with MetS prevalence ($P < 0.05$) (Table 3).

Age was significantly associated with the prevalence of MetS ($\beta = 0.04$, $P < 0.01$), suggesting that older individuals with AS were more likely to have MetS (Fig. 4.A). Similarly, BMI showed a significant positive association with MetS prevalence ($\beta = 0.09$, $P < 0.01$), indicating that higher BMI values correlated with an increased likelihood of MetS (Fig. 4.B and Table 3).

WC was also a strong predictor of MetS prevalence ($\beta = 0.03$, $P < 0.01$) (Fig. 4.C). Additionally, inflammatory markers played a role, as erythrocyte sedimentation rate (ESR) demonstrated a significant association with MetS prevalence ($\beta = 0.01$, $P = 0.04$) (Fig. 4.D and Table 3).

Among metabolic parameters, triglyceride (TG) levels were significantly associated with MetS prevalence ($\beta = 0.01$, $P < 0.01$) (Fig. 4.F). Total cholesterol (TC) was also a significant factor ($\beta = 0.01$, $P = 0.05$) (Fig. 4.G and Table 3).

Regarding clinical measures, diastolic blood pressure (DBP) was significantly associated with MetS prevalence ($\beta = 0.04$, $P = 0.02$) (Fig. 4.K). Furthermore, disease activity, as measured by the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), was also a significant factor ($\beta = 0.03$, $P = 0.02$), indicating that higher disease activity scores correlated with an increased prevalence of MetS (Fig. 4.L and Table 3). TNF inhibitor consumption was another factor which had a significant positive effect on the prevalence of MetS in patients with AS ($\beta = 0.91$, $P < 0.01$) (Fig. 4.M and Table 3).

Discussion

Our meta-analysis provides a comprehensive assessment of the global prevalence of MetS in patients with AS, revealing an overall pooled prevalence of 15.5%. This finding highlights a substantial burden of MetS in AS patients. The presence of MetS in AS is particularly concerning, as it compounds cardiovascular risk and exacerbates disease morbidity [40].

The relationship between AS and MetS is likely bidirectional, with chronic inflammation playing a crucial role in metabolic dysregulation [1]. Systemic inflammation, a hallmark of AS, has been implicated in insulin resistance, lipid abnormalities, and endothelial dysfunction, all of which contribute to MetS development [19, 41, 42]. Furthermore, sedentary behavior due to pain and disability in AS patients may aggravate metabolic disturbances [43, 44].

Previous studies have reported a higher MetS prevalence in AS patients [7, 8, 19, 45]. The genetic interplay between MetS and AS is substantial, primarily driven by shared immune-mediated pathways. For instance, Shi et al. identified a significant genetic overlap between these conditions, highlighting common genes involved in metabolic regulation, inflammation, and autophagy [46]. Their findings reinforce a causal link between MetS and AS, independent of potential confounders.

Our meta-regression analysis revealed a significant association between BMI and TG levels with MetS prevalence, underscoring the role of obesity and dyslipidemia in this comorbidity. Consistent with our findings, Liu et al. [8] identified BMI as an independent risk factor for MetS in AS patients (OR = 5.165; 95% CI = 1.935–13.787;

Table 3 Results of meta-regression analysis

Variable	Coefficient (β)	*P* value	Residual Tau2	Residual I2	Residual H2	R2
Age	0.04	< 0.01	0.05	94.18	17.17	18.75
BMI	0.09	< 0.01	0.03	76.39	4.24	30.09
WC	0.03	< 0.01	0.00	0.00	1	100
ESR	0.018	0.04	0.05	81.57	5.42	12.10
CRP	-0.01	0.12	0.03	73.71	3.80	10.91
TG	0.01	< 0.01	0.05	78.44	4.64	37.02
TC	0.01	0.05	0.11	87.67	8.11	2.93
HDL	-0.01	0.12	0.08	84.87	6.61	0.00
LDL	0.01	0.09	0.10	87.22	7.82	0.00
SBP	< 0.01	0.72	0.04	78.18	4.58	0.00
DBP	0.04	0.02	0.02	67.63	3.09	35.25
BASDAI	0.03	0.02	0.03	77.48	4.44	21.90
TNF inhibitors consumption rate	0.44	0.45	0.01	61.33	2.59	66.43
Duration of the Disease	-0.05	0.18	0.08	86.81	7.58	0.00

BMI: Body Mass Index; WC: Waist Circumference; ESR: Erythrocyte Sedimentation Rate; CRP: C-Reactive Protein; TG: Triglycerides; TC: Total Cholesterol; HDL: High-Density Lipoprotein; LDL: Low-Density Lipoprotein; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; TNF inhibitors: Tumor Necrosis Factor inhibitors

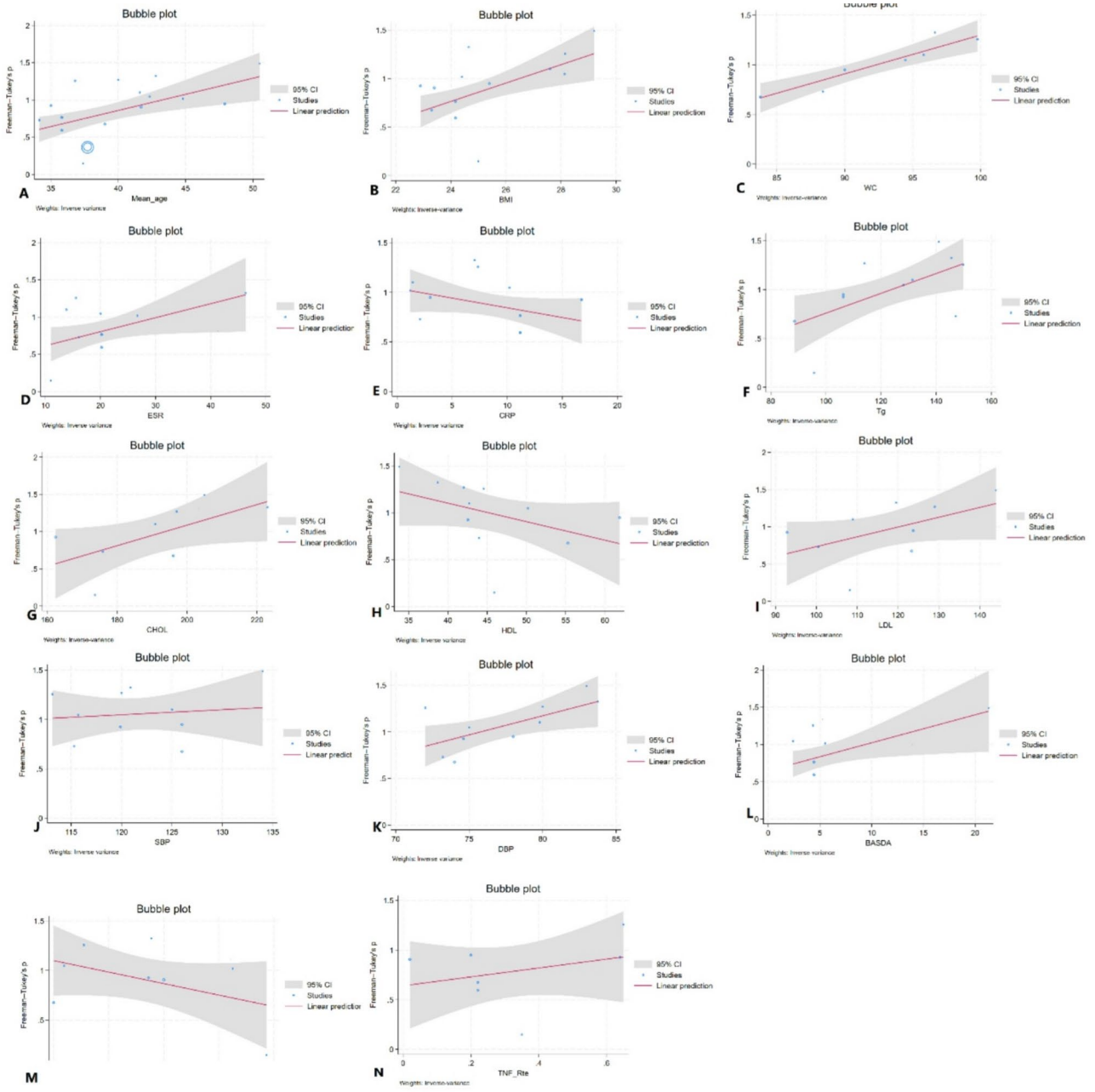

Fig. 4 Bubble plots of the meta-regression analysis of different variables in the prevalence of metabolic syndrome (MetS) in patients with ankylosing spondylitis. Age (**A**), Body Mass Index (BMI) (**B**), Waist Circumference (WC) (**C**), Erythrocyte Sedimentation Rate (ESR) (**D**), C-Reactive Protein (CRP) (**E**), Triglycerides (TG) (**F**), Total Cholesterol (TC) (**G**), High-Density Lipoprotein (HDL) (**H**), Low-Density Lipoprotein (LDL) (**I**), Systolic Blood Pressure (SBP) (**J**), Diastolic Blood Pressure (DBP) (**K**), Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) (**L**), Duration of the Disease (**M**), Tumor necrosis factor alpha (TNF-a) inhibitor consumption (**N**)

$P = 0.001$). They also reported a higher prevalence of overweight/obesity in AS patients with MetS (78.3% vs. 31.9%; $P < 0.001$), aligning with previous studies [37, 47]. These findings highlight the critical role of BMI management in reducing MetS risk in AS patients.

The underlying mechanisms have been well-documented, with adipose tissue secreting proinflammatory cytokines (e.g., TNF-α) and adipokines (e.g., leptin, adiponectin), which disrupt metabolic homeostasis [21, 48–50]. Furthermore, AS patients often experience reduced physical activity due to chronic pain and disability, making them more susceptible to weight gain and increased BMI, further exacerbating metabolic disturbances [43, 51].

Also, TG levels have been implicated in the metabolic disturbances associated with AS. Maia et al. reported

that AS patients undergoing anti-TNF-α therapy exhibited significantly higher TG levels than controls, with a markedly elevated TG-to-HDL ratio ($p = 0.002$), underscoring its predictive value for MetS and cardiovascular risk [7]. Similarly, Azarpazhooh et al. identified the TG/HDL-C ratio as a key marker of MetS, insulin resistance, and atherosclerosis severity. Their findings suggest that an increased TG/HDL-C ratio substantially raises the risk of MetS, highlighting its clinical relevance in AS and other chronic inflammatory conditions [52].

Furthermore, in our study age was found to be a significant predictor, with older AS patients demonstrating a higher prevalence of MetS. According to Dominguez and Barbagallo, aging is a major contributor to the increasing prevalence of MetS, with older individuals showing higher rates due to factors such as central obesity, insulin resistance, sarcopenic obesity, and systemic inflammation. Their review highlights that MetS prevalence rises from 18.3% in individuals aged 20–39 years to 46.7% in those over 60 years, emphasizing the impact of aging on metabolic health [53].

Similarly, Goodpaster et al. conducted a study on 3,035 individuals aged 70 to 79, demonstrating that aging is directly associated with lower HDL cholesterol levels, elevated blood glucose, and increased blood pressure—key metabolic abnormalities contributing to MetS [54]. These findings underscore the role of aging as a critical risk factor for MetS, particularly in individuals with ankylosing spondylitis, where its predictive value warrants further investigation in clinical assessments. Also, Papadakis et al., reported a significantly higher prevalence of MetS in AS patients (34.9% vs. 19.0%, $p < 0.05$) [38]. The study highlighted a strong age-dependent effect, with MetS prevalence reaching 50.0% in AS patients over 41 years, compared to 23.8% in controls ($p = 0.017$), whereas no significant difference was observed in younger patients ($p = 0.401$). These findings suggest that AS patients face an elevated risk of MetS and cardiovascular complications, particularly with increasing age, emphasizing the interplay between systemic inflammation and metabolic disturbances in AS.

Additionally, inflammatory markers revealed distinct associations with MetS prevalence. While ESR, a marker of chronic inflammation, was positively correlated with MetS, CRP, an acute-phase reactant, did not show a significant association. This indicates that persistent systemic inflammation, rather than acute inflammatory episodes, may play a more substantial role in metabolic disturbances among AS patients [55, 56].

A Study by de Vries MK et al. found that ESR performed better than CRP in assessing disease activity and predicting treatment response in AS patients receiving anti-TNF therapy. Among 155 patients, ESR showed the strongest correlation with BASDAI ($\beta = 0.49$) compared to CRP ($\beta = 0.43$). Elevated baseline CRP levels had a high predictive value (81%) for treatment response. These findings suggest that ESR may be a more reliable marker for monitoring disease activity, while CRP could help predict response to therapy [57].

Furthermore, our findings suggest that the BASDAI, which is commonly used to assess disease activity in AS, is significantly associated with MetS prevalence. Higher BASDAI scores indicate increased disease activity and inflammation, which could contribute to metabolic disturbances [58–60]. This suggests that patients with more severe AS may have a heightened risk of MetS, emphasizing the need for integrated management strategies that address both inflammatory and metabolic components of the disease. Recent studies indicate a significant correlation between BASDAI scores and various health parameters, including disability indices and inflammatory markers, highlighting its relevance in clinical practice [61, 62]. Consistent with our findings, the study by Papadakis et al. [38] also reported that AS patients with MetS were older ($p = 0.005$) and exhibited greater disease activity (BASDAI: 5.1 vs. 3.7, $p = 0.043$).

Moreover, DBP was significantly associated with MetS prevalence, whereas SBP did not exhibit a notable effect. Elevated blood pressure, including both systolic and diastolic, is a recognized component of MetS [63, 64]. A study involving 5,809 Koreans without baseline MetS found that elevated DBP levels were significantly associated with an increased hazard ratio (HR) for MetS. Specifically, DBP levels of 71–74 mm Hg and 75–79 mm Hg were associated with HRs of 1.31 and 1.51, respectively, compared to the reference group with DBP < 70 mm Hg [65]. This highlights the potential importance of DBP as a more sensitive cardiovascular risk indicator in AS patients with MetS, warranting further investigation into its pathophysiological relevance. This relationship persists even after adjusting for various covariates, indicating a robust association between DBP and MetS prevalence.

Our subgroup analyses revealed substantial regional differences in MetS prevalence among AS patients, with the highest prevalence observed in Africa (37.0%) and the lowest in Asia (8.0%). However, this high prevalence in the African region must be interpreted with caution, as it is based on a single study conducted in Egypt, which may not be representative of the broader African population [33]. The limited data raises the potential for selection bias. Supporting this, obesity rates in Africa differ widely across the region. In countries like South Africa, prevalence can reach as high as 54% among specific groups, whereas in nations such as Ethiopia and Madagascar, rates are considerably lower [66–68]. This discrepancy suggests that the elevated MetS rate reported in the Egyptian study may reflect unique sample characteristics rather than a regional trend. Additionally, variability in

healthcare infrastructure and accessibility—particularly in the availability of routine metabolic screening—may contribute to differences in detection and diagnosis of MetS across regions [69, 70]. Genetic diversity may also play a role; for instance, the distribution of HLA-B27 subtypes varies significantly across ethnic groups and may influence the interplay between inflammatory and metabolic pathways in AS [71–73]. Future multi-center studies in African populations are essential to provide a more accurate regional estimate and explore potential environmental and genetic factors unique to this population.

Additionally, the discrepancies in AS criteria contributed to observed heterogeneity. Among the diagnostic criteria used across studies for AS diagnosis, those employing the ASAS classification reported the highest MetS prevalence, whereas studies relying on ICD-9-CM criteria documented the lowest prevalence. Similarly, variations in MetS prevalence were evident across different diagnostic definitions. Each set of criteria varies in terms of the number and type of metabolic components required, as well as the threshold values applied. For example, the NCEP-ATP III criteria define MetS as the presence of any three out of five metabolic abnormalities, which may result in broader classification and a higher reported prevalence. In contrast, the JC criteria apply stricter standards, and produced a substantially lower prevalence in our analysis [74–76]. For instance, a key distinction between ATP-III and JC is the emphasis on central obesity. While JC mandates waist circumference with ethnicity-specific cutoffs, ATP-III adopts a flexible, risk-based approach, diagnosing MetS if any three of five risk factors are present. This makes ATP-III more inclusive, particularly for individuals with metabolic dysfunction but lower waist circumference. Moreover, ATP-III exhibits greater sensitivity in detecting cardiovascular risk and insulin resistance, as it does not strictly depend on central obesity. Studies indicate that ATP-III identifies more high-risk individuals than JC, especially in non-obese populations with dyslipidemia and hypertension [75, 77, 78]. These inconsistencies underscore the critical need for standardized diagnostic criteria to improve the accuracy and comparability of MetS prevalence estimates in AS patients. Selecting a uniform diagnostic approach will support better risk stratification, improve patient monitoring, and facilitate more comparable research outcomes across diverse populations of AS patients. Based on these observations, we recommend that future studies consider adjusting diagnostic criteria according to population-specific characteristics such as ethnicity, regional obesity patterns, and metabolic profiles. Such tailored thresholds could improve diagnostic accuracy, enhance inter-study comparability, and provide more meaningful estimates of MetS prevalence in diverse AS populations [75, 79].

Given the substantial prevalence of MetS in AS patients, early screening and management of metabolic risk factors should be integrated into AS treatment strategies. Lifestyle interventions, including regular physical activity and dietary modifications, should be prioritized to mitigate cardiovascular risk. Moreover, the long-term metabolic impact of biologic therapies, particularly TNF inhibitors warrants further investigation [7, 8, 14].

Limitations and future directions

Despite the robust methodology employed, our meta-analysis has several limitations. First, significant heterogeneity was observed among studies, likely due to differences in study populations, diagnostic criteria, and geographic distribution. Although we addressed this through extensive subgroup and meta-regression analyses, residual confounding factors may remain.

Second, the cross-sectional nature of the included studies precludes any conclusions regarding causality between ankylosing spondylitis and metabolic syndrome. Longitudinal studies are needed to elucidate these temporal relationships.

Third, while we attempted to evaluate the impact of biological therapies—particularly TNF inhibitors—on the prevalence of MetS through meta-regression, only a limited number of studies reported relevant data. As such, these results should be interpreted cautiously. Future research should prioritize collecting and reporting data on biologic treatment regimens, especially TNF inhibitors, to better understand their potential role in modifying metabolic risk among AS patients.

Fourth, we conducted publication bias assessment for the sex-based subgroup analysis, incorporating Egger's test, Begg's test, funnel plots, and trim-and-fill methods. Although we did not find significant publication bias, it cannot be entirely ruled out due to the relatively small number of included studies. More well-designed and transparently reported studies are needed to enhance the validity of future meta-analyses and allow for a more robust assessment of potential publication bias.

Fifth, while we explored sex-based differences in MetS prevalence and found a higher rate in males compared to females, the difference was not statistically significant. However, the limited number of gender-stratified studies remains a notable gap, and we recommend that future research further investigate sex-based differences in MetS risk among AS patients, including potential roles of sex hormones and age-matched subgroup effects.

Additionally, the relatively small number of included studies and the lack of representation from certain regions may limit the generalizability of our findings. We recommend that future studies include more diverse populations and standardized diagnostic criteria to improve global comparability and risk stratification.

Conclusion

This meta-analysis highlights a significant prevalence of MetS in patients with AS. The findings suggest that metabolic abnormalities in AS are influenced by chronic inflammation, obesity, disease activity, and demographic factors. Notably, older age, higher BMI, elevated triglycerides, and increased disease activity (BASDAI) were significantly associated with MetS prevalence, emphasizing the need for proactive metabolic monitoring in AS management.

From a clinical perspective, routine metabolic screening can be incorporated into AS care to identify high-risk patients early. Given the interplay between systemic inflammation and MetS, integrating lifestyle interventions with pharmacologic management may provide dual benefits in controlling both AS symptoms and metabolic complications. Rheumatologists should work closely with cardiologists and endocrinologists to optimize cardiovascular risk reduction strategies for AS patients.

To enhance consistency in diagnosis and improve comparability across studies, we recommend adopting standardized or population-adjusted diagnostic criteria for MetS in AS patients. While criteria such as the JC framework offer clinically practical approaches that account for ethnic variation in metabolic thresholds, it is essential that future studies further refine these definitions based on regional, anthropometric, and metabolic characteristics. Tailoring thresholds in this way can improve diagnostic accuracy and better reflect true metabolic risk in diverse AS populations. Additionally, ongoing research should continue to explore the long-term effects of biologic therapies and the impact of personalized lifestyle interventions in reducing MetS prevalence and improving outcomes for AS patients.

Abbreviations

AS	Ankylosing spondylitis
MetS	Metabolic syndrome
BASDAI	Bath Ankylosing Spondylitis Disease Activity Index
BMI	Body mass index
CI	Confidence interval
ESR	Erythrocyte sedimentation rate
IDF	International Diabetes Federation
JC	Joint Consensus
NCEP-ATP III	National Cholesterol Education Program Adult Treatment Panel III
TG	Triglycerides
TNF	Tumor necrosis factor

Supplementary Information

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Supplementary Material 1

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Author contributions

The conceptualization of the research idea was conducted by E.AS, P.B, SS.N, and M.J. The study design, which involved planning the methods to achieve the results, was managed by M.J, M.A.L, and E.AS. Oversight, coordination, and manuscript preparation were supervised by E.AS, N.R.K, and N.S. Data collection and processing, which included conducting experiments and managing patients, along with data analysis and interpretation, were carried out by N.R.K, M.J, M.A.L, M.H, and P.B. All authors made significant contributions to drafting the manuscript.

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