SYSTEMATIC REVIEW

Factors Affecting Cartilage Damage: A Systematic Review and Meta-Analysis

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ABSTRACT

Introduction: Osteoarthritis (OA), a debilitating joint disorder, is characterized by progressive cartilage degradation in the knee. Identifying key factors influencing osteoarthritis (OA) development is crucial for early intervention and personalized treatment strategies. This systematic review and meta-analysis aimed to comprehensively assess the influence of age, body mass index (BMI), and cartilage thickness on osteoarthritis (OA) development. **Materials and Methods:** A comprehensive search using EndNote software and keywords like cartilage, knee, age, body mass index (BMI), and morphology yielded 22 relevant articles. Data on age groups, body mass index (BMI), and cartilage thickness were extracted and analyzed using Open MEE (Meta-analysis for ecology and evolutionary biology) software for meta-analysis. **Results:** Our analysis revealed a positive correlation between age, body mass index (BMI), and cartilage thickness (morphology) with osteoarthritis (OA) progression. Notably, body mass index (BMI) emerged as the most significant contributor to osteoarthritis (OA), followed by age and morphological features. **Conclusion:** This study confirms the positive association of age, body mass index (BMI), and cartilage thickness with osteoarthritis (OA). Our findings highlight the critical role of body mass index (BMI) in osteoarthritis (OA) risk, potentially aiding healthcare professionals in early identification and personalized treatment strategies for patients at greater risk.
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Keywords: Knee joint, cartilage, osteoarthritis (OA), body mass index (BMI), cartilage thicknes

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INTRODUCTION

Articular cartilage, the smooth, resilient tissue lining our knee joints, plays a vital role in enabling pain-free movement. Its crucial functions include absorbing shock, distributing load, and minimizing friction between bones (1). In addition, this tissue also functions to distribute load and minimize contact stress (2). As a result of these processes, the cartilage in the knee joint is very susceptible to interference or damage caused by various factors. Consequently, one of the most common disorders experienced by patients is osteoarthritis (OA).

Osteoarthritis (OA), particularly in the knee, is a major public health concern, affecting 15% of the global population and contributing to significant disability (3–6). This chronic, progressive disease manifests as gradual deterioration of cartilage thickness and mechanical properties, leading to decreased load-bearing capacity (7–10). Consequently, osteoarthritis (OA) patients suffer from pain, physical limitations, and diminished quality of life (11,12). The emergence and progression of knee osteoarthritis (OA) are influenced by a complex interplay of factors, including genetics, gender, trauma, age, body mass index, activity level, and mechanical behavior (4,13,14). These factors contribute to morphological changes in joint cartilage, reduced load-bearing capacity, and disruption of ligaments and surrounding muscles, ultimately compromising cartilage function (4). Interestingly, healthy knees exhibit a dynamic adaptation where specific areas of cartilage respond to load, while others remain relatively inactive. This dynamic equilibrium can be disrupted by various factors,

triggering the development of osteoarthritis (OA) (3). Ultimately, an imbalance between cartilage damage and repair processes disrupts joint homeostasis, leading to the progressive deterioration characteristic of osteo arthritis (OA) (15).

Current treatment strategies for osteoarthritis (OA) primarily focus on symptom management, leaving the underlying causes largely unaddressed (16). Therefore, a deeper understanding of the factors that orchestrate this debilitating condition is crucial. This study embarks on a quest to unravel the intricate web of contributors to osteoarthritis (OA), paving the way for future research and potentially revolutionizing patient care. Based on research by A. Prados-Torres et al. (41), the results of her meta-analysis show that there is a correlation between mental health, symptoms of the disease, and musculoskeletal symptom disorders that can initiate osteoarthritis (OA) (17). However, it does not follow up on the mechanistic factors that cause osteoarthritis (OA) to occur. Meanwhile, Liying Jiang et al. (39) research revealed that obesity has a positive contribution to osteoarthritis (OA), but this research focused on increasing body mass index (BMI) and had not reviewed and compared different factors. Therefore, this research addresses a relatively open space by comparing several factors through a review and meta-analysis to determine the greatest contributor to the emergence of osteoarthritis (OA).

The novelty of this research lies in its comprehensive approach. Unlike previous studies that focused on isolated factors, this systematic review will meticulously gather and analyze data from diverse research articles, employing the powerful lens of meta-analysis. This holistic perspective will not only shed light on the most influential factors in osteoarthritis (OA) development but also provide valuable insights for healthcare professionals, empowering them to tailor effective interventions and ultimately mitigate the burden of osteoarthritis (OA) on individuals and healthcare systems. By dissecting the intricate tapestry of factors that contribute to osteoarthritis (OA), this research aspires to illuminate a path toward a future where healthy joints and pain-free movement are not just a dream, but a tangible reality.

METHODS

Search Strategy
This systematic review followed the PRISMA guidelines to identify relevant articles. EndNote software was chosen for its user-friendly interface and efficient search capabilities. Articles were searched from June to December 2021, focusing on the PubMed database for publications between 2000 and 2021. Keywordstargeted factors related to cartilage damage in osteoarthritis (OA), including "cartilage" in all fields, "tibia and femur" in titles, and "morphology, contact stress, activity, age, and

stress distribution" in abstracts. English language was chosen for a broader search scope.

Study Selection
Two independent reviewers, the authors, screened titles and abstracts for relevance to the research topic. Articles meeting the pre-defined inclusion criteria were retained, while those failing to do so were excluded. Included articles must investigate cartilage/osteoarthritis (OA) in the knee joint, specifically within the femur and tibia, and report data on body mass index (BMI), age, gender, activity level, morphology, and mechanical behavior. Exclusion criteria included (1) lack of basic data reporting, (2) focus on healthy cartilage or absence of osteoarthritis (OA) reporting, and (3) investigation of joints other than the knee (Table I).

Table I: Article selection process based on inclusion and exclusion

Criteria	Inclusion	Exclusion
Type	Indexed Journal	Non-idexed Journal, Conference
Tittle	Mention "Cartilage on knee, Osteoarthritis"	No Mentioned
Language	English	Non English
Topics	Cartilage	Non Cartilage
Study Control and Experiment (OA)	Report control and experimental data	No report control and experimental data
Participant	Human	Animals
Position	Knee	No Knee

Data Extraction and Analysis
Standard deviation and sample size were extracted from each included article. These were used to calculate standardized effect size (ES) and 95% confidence intervals (CI) using the interval method. ES assessed the impact of each factor on osteoarthritis (OA), considering the number of samples in each study. Positive ES values indicated a positive correlation between the factor and osteoarthritis (OA) occurrence. Statistically significant results were identified by non-overlapping 95% CI with the zero line. Subsequently, meta-analyses were performed using Open MEE software, chosen for its user-friendliness and ease of understanding. Forest plots were generated to visualize the meta-analysis results. Both subgroup and standard analyses were conducted. Subgroup analysis compared the metaanalysis results for each osteoarthritis (OA)influencing factor, thereby identifying the factors with the strongest contributions. Standard analysis provided detailed insights into the meta-analysis results for each analyzed factor.

RESULTS

Studies Included in the Meta-Analysis
Our initial search yielded a vast pool of 59,041 articles. After meticulously removing duplicates (44 articles), we screened the remaining 59,010 articles based on titles

and abstracts, narrowing the pool down to 574 studies. We then delved deeper, carefully reading and evaluating each study against our predefined criteria. This rigorous process identified 22 articles suitable for inclusion in the meta-analysis (Figure 1).
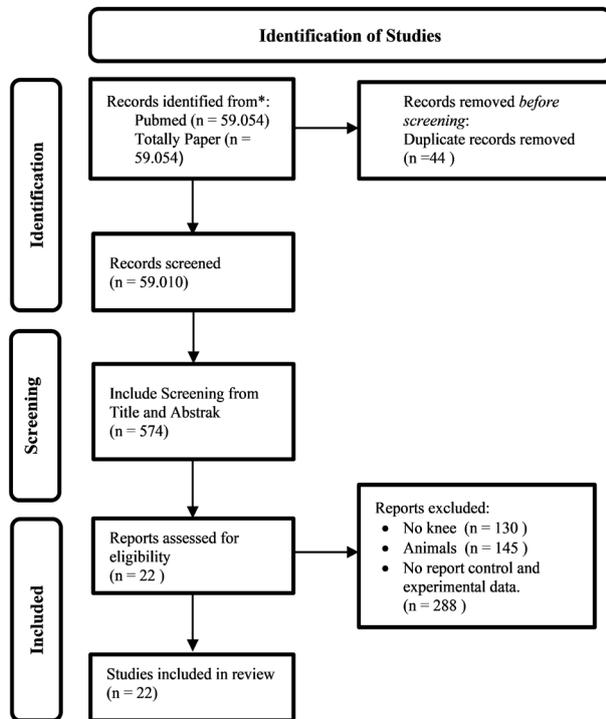

Fig. 1: Prism diagram in article filtering (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) for study inclusion.

Data Extraction and Analysis

Using EndNote software, we compiled the key information from each included article into a comprehensive review results table (Table II). This table serves as a central repository for all relevant data extracted from the studies, including author, publication year, country, study design, participant demographics, and, most importantly, data pertaining to the target parameters: Body Mass Index (BMI), age, and cartilage thickness.

Meta Analysis Age Group

The meta-analysis investigated the impact of age on the effectiveness of the intervention osteoarthritis (OA) by conducting a subgroup analysis based on age groups. The results, presented in Figure 2 and Table III, provide compelling evidence for a significant age effect.

Table III: Data summary effect on subgroup age.

Studies	Esti-mate	Lower bound	Upper bound	Std. error	p-Val
Subgroup Age	0.170	0.014	0.327	0.080	0.033

The forest plot (Figure 2) clearly demonstrates that the experimental group osteoarthritis (OA) consistently outperformed the control group across most studies. The majority of effect size estimates fall to the right of the zero line, indicating positive outcomes for the osteoarthritis (OA) group. Table III summarizes the quantitative results. The overall effect size is estimated at 0.170, with a 95% confidence interval ranging from 0.014 to 0.327. This statistically significant effect. (p-value < 0.05) confirms that the osteoarthritis (OA) intervention significantly enhances the outcome variable
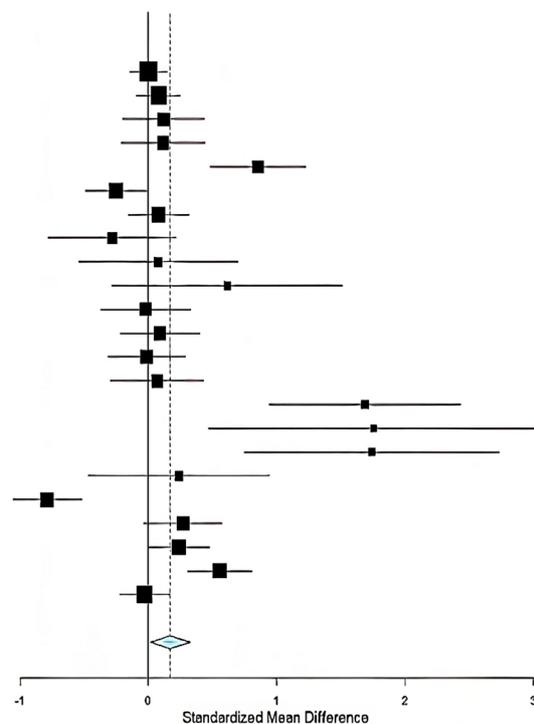

Fig. 2: Forest Study Plot Reporting the effect of Age on Osteoarthritis.

Table II: Characteristic study of factors that contribute to osteoarthritis.

Study and Year (Ref)	Country	Study Design	Participant		BMI (Kg/m)		Age (Years)		Morphology (mm)		Site (Femur/ Tibia)	Adjustment
			Co	OA	Co	OA	Co	OA	Co	OA		
J. Chang et al., 2019(16)	China	Case Control Study	354	354	27.7 ± 4.4	28.9 ± 4.5	60.1 ± 8.4	60.1 ± 8.6	NA	NA	Tibia	BMI, number of knees bending activities, self-reported injury and self-reported knee surgery
J.E. Collins er al., 2017(17)	USA	Case Control Study	406	194	30.7 ± 4.8	30.7 ± 4.8	61.3 ± 8.9	62.0 ± 8.8	NA	NA	Tibia	KLG and BMI
M.D Crema et al., 2011(18)	USA	Case Control Study	99	62	24.9 ± 4.8	36.9 ± 5.3	56.1 ± 8.8	57.1±8.1	NA	NA	Tibia Femoral	Morphology
M.D Crema et al., 2010 (19)	USA	Case Control Study	94	58	24.8 ± 4.4	36.7 ± 5.4	56.3 ± 8.9	57.3 ± 8.2	NA	NA	Tibia Femoral	age and body mass index
D. Kumar et al., 2015(20)	USA	Case Control Study	110	41	24.0 ± 3.5	25.0 ± 3.4	50.1 ± 8.9	57.9 ± 9.6	NA	NA	Femur and Tibia	age and body mass index
D. Bobinac et al., 2002(21)	Croatia	Case Control Study	10	10	NA	NA	NA	NA	0.17 ± 0,01	0.33 ± 0,02	Tibia	Morphology
B. Dube et al., 2018(22)	Ukraine	Case Control Study	200	103	30.5 ± 4.8	31.1 ± 5.0	61.5 ± 9.1	59.2 ± 9.1	NA	NA	Femur and Tibia	BML size and change in bone shape.
F. Eckstein et al., 2017(23)	Austria	Case Control Study	406	194	30.7 ± 4.8	30.7 ± 4.8	61.3 ± 8.9	62.0 ± 8.8	NA	NA	Femur	BMI, baseline, WOMAC, min-JSW, cMFTC
OG Eryilmaz et al., 2012 (24)	Turkey	Case Control Study	30	33	23.2 ± 3.9	24.2 ± 4.6	24.8 ± 4.2	23.7 ± 3.5	0.16 ± 0.02 / 0.17 ± 0.03 / 0.17 ± 0.02 / 0.18 ± 0.03 / 0.16 ± 0.02 / 0.17 ± 0.02	0.20 ± 0.04 / 0.22 ± 0.05 / 0.21 ± 0.03 / 0.20 ± 0.03 / 0.22 ± 0.05 / 0.21 ± 0.04	Femur	Cartilage Thickness
Zihao He et al., 2020 (25)	China	Case Control Study	8	13	23.55 ± 2.53	24.13 ± 2.37	52.31 ± 13.39	65.25 ± 23.3	0.19 ± 0.03	0.19 ± 0.03	Femur	Structural, mechanical properties and cartilage degradation
F. Intema et al., 2011 (26)	Netherland	Case Control Study	20	20	NA	NA	NA	NA	2.10 ± 0.42 / 2.11 ± 0.41 / 2.12 ± 0.41 / 2.07 ± 0.25	1.00 ± 0.41 / 1.36 ± 0.34 / 1.33 ± 0.25 / 1.62 ± 0.24	Femur / Tibia / Femur / Tibia	MRI (Segmentation of cartilage morphology), Radiography, WOMAC
Jungmann et al., 2013(27)	USA	Case Control Study	50	85	28.2 ± 4.6	28.3 ± 4.1	64.2 ± 9.8	64.0 ± 9.2	NA	NA	Femur	Trochlear depth, Sulcus angle, facet ratio
Kamimura et al., 2018 (28)	Japan	Case Control Study	50	80	25.2 ± 2.8	25.5 ± 3.1	66.7 ± 7.6	67.4 ± 7.7	NA	NA	Tibia	Demographic variables, KL grade, type of meniscal tear, and postoperative follow-up period were evaluated.
Mosher et al., 2011(29)	Hershey	Case Control Study	16	15/15	NA	NA	NA	NA	1.78 ± 0.03 / 1.75 ± 0.02 / 2.32 ± 0.04	1.85 ± 0.04 / 1.86 ± 0.02 / 2.23 ± 0.04	Femur / Tibia / Patella	MRI, Kellgren-Lawrene Scores

Study	Country	Study Type	Case	Control	Case	Control	Case	Control	Case	Control	Region	Parameter
M. Roth et al., 2018(30)	Austria	Case Control Study	87	81	24.4 ± 3.1	24.4 ± 3.2	55.0 ± 7.6	55.1 ± 7.6	3.39 ± 0.51	3.88 ± 0.53	Femur	Age and body mass index
									1.61 ± 0.24	2.05 ± 0.32	Tibia	
									1.78 ± 0.31	1.83 ± 0.27	Patella	
T. Baum et al., 2013(31)	USA	Case Control Study	41	101	23.4 ± 2.0	24.0 ± 1.8	50.6 ± 3.1	50.8 ± 2.9	1.29 ± 1.18	1.92 ± 1.66	Femur	Age, gender, BMI and baseline KL-score.
L.Wang et al., 2015(32)	China	Case Control Study	17	21	41 ± 16	65 ± 12	25.0 ± 2.7	25.0 ± 3.4	NA	NA	Femoral-Tibia	BMI, body mass index; KL2–3, Kellgren–Lawrence grade 2–3; OA, osteoarthritis; WORMS, Whole-Organ Magnetic Resonance Imaging Score
Favian Su et al., 2014 (33)	USA	Case Control Study	16	15	24.4 ± 2.8	23.3 ± 2.58	32.8 ± 10.9	35.1 ± 7.7	1.06 ± 0.21	1.13 ± 0.26	Femur	Cartilage Thickness
									1.15 ± 0.30	1.22 ± 0.30	Femur	
									0.82 ± 0.23	0.89 ± 0.18	Tibia	
									1.36 ± 0.49	1.44 ± 0.47	Tibia	
									2.04 ± 0.6	2.11 ± 0.43	Patella	
L.F. Ambra et al., 2019 (34)	USA	Case Control Study	100	135	28.7 ± 5.6	27.85 ± 4.7	41.19 ± 9.2	34.32 ± 8.29	NA	NA	Femur	Morphology (width, thickness, and angle)
G. Cai et al., 2020	Australia	Case Control Study	368	47	27.1 ± 4.0	26.8 ± 4.0	61.5 ± 7.1	63.4 ± 6.3	NA	NA	Tibia	Age, sex, body mass index, tibial cartilage volume at baseline
				83		28.9 ±4.7		63.2 ± 7.3				
				76		30.3 ± 5.5		65.6 ± 7.8				
N.Chanchek et al., 2018(35)	USA	Case Control Study	208	208	31.01 ± 4.4	31.18 ± 4.5	63.27 ± 9.13	63.00 ± 8.89	NA	NA	Femur and Tibia	Age, sex, baseline BMI, and KL score.

Co: Control
OA: Osteoarthritis
BMI: Body Mass Index
NA: No Available

compared to the control group.

Heterogeneity Analysis on Age Group

The heterogeneity analysis (Table IV) reveals a Tau^2 value of 0.103, suggesting moderate variability in effect sizes across studies. However, the Q statistic (123.272) with a highly significant p-value (< 0.001) indicates substantial heterogeneity among the study findings. Importantly, the I^2 value of 82.153% confirms that a considerable portion (82%) of the variance in effect sizes can be attributed to factors other than sampling error. This highlights the importance of exploring potential moderators that might explain this heterogeneity in future research.

Overall, the meta-analysis findings provide robust evidence for the effectiveness of the osteoarthritis (OA) intervention across age groups. While significant heterogeneity exists, the overall positive effect size and statistical significance support the beneficial impact of osteoarthritis (OA) on the outcome variable.

Table IV: Heterogenitas on age group.

Tau²	Q (df=22)	Het. p-Value	I²
0.103	123.272	< 0.001	82.153

Meta Analysis Body Mass Index (BMI) Group

This meta-analysis investigated the association between body mass index (BMI) and the development of osteoarthritis (OA). The analysis included data from 22 studies encompassing various osteoarthritis (OA) locations and diverse populations.

The risk associated with body mass index (BMI) and osteoarthritis (OA) is illustrated in Figure 3 (Forest plot), which visualizes effect sizes across studies. Most studies demonstrated a positive association between higher BMI and osteoarthritis (OA), indicated by effect size estimates positioned to the right of the zero line. Table V quantifies the overall association. Our analysis revealed a significant positive association between BMI and osteoarthritis (OA) risk. The pooled estimate of effect size was 0.325 (95% CI: 0.089–0.560; p < 0.007), indicating that for every 1 unit increase in BMI, the odds of developing osteoarthritis (OA) increase by 33%.

Table V: Data summary effect on subgroup BMI.

Studies	Estimate	Lower bound	Upper bound	Std. error	p-Val
Subgroup BMI	0.325	0.089	0.560	0.120	0.007

Heterogeneity Analysis on BMI Group

The heterogeneity analysis (Table VI) shows a Tau^2 value of 0.262 and a Q statistic of 269.351 (df=22) with a p-value < 0.001, indicating significant heterogeneity. The I^2 value of 92.575% suggests substantial heterogeneity among the included studies. These findings provide robust evidence for a positive association between BMI and osteoarthritis (OA) development. However, the high level of heterogeneity suggests potential influencing factors beyond BMI alone, warranting further research to explore these sources for a more nuanced understanding of the BMI–osteoarthritis (OA) relationship.

Table VI: Heterogenitas on BMI group.

Tau²	Q (df=22)	Het. p-Value	I²
0.262	269.351	< 0.001	92.575

Meta Analysis Cartilage Thickness Group

Our meta-analysis focused on the subgroup examining the relationship between cartilage thickness and osteoarthritis (OA) development. The key findings are summarized in Table VII and Figure 4. The forest plot (Figure 4) shows a trend towards higher effect sizes for the experimental group compared to the control group,
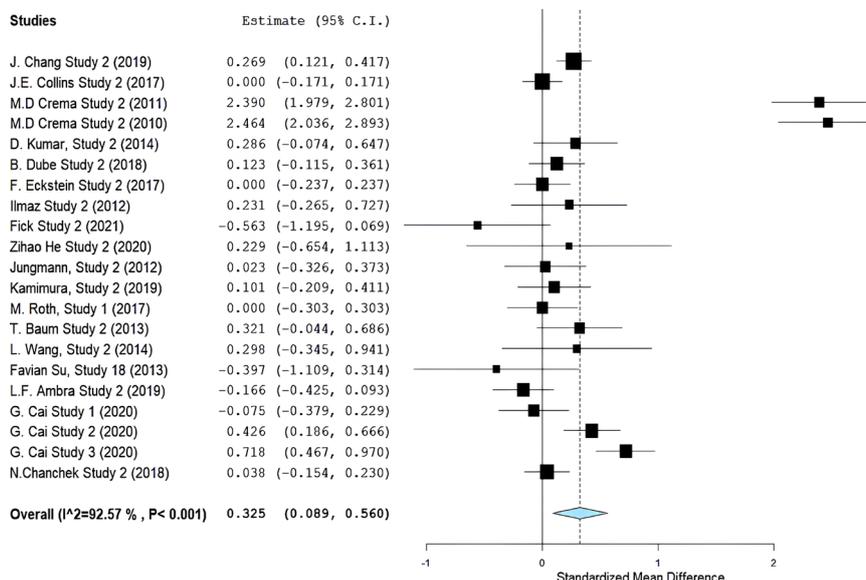

Studies	Estimate (95% C.I.)
J. Chang Study 2 (2019)	0.269 (0.121, 0.417)
J.E. Collins Study 2 (2017)	0.000 (−0.171, 0.171)
M.D Crema Study 2 (2011)	2.390 (1.979, 2.801)
M.D Crema Study 2 (2010)	2.464 (2.036, 2.893)
D. Kumar, Study 2 (2014)	0.286 (−0.074, 0.647)
B. Dube Study 2 (2018)	0.123 (−0.115, 0.361)
F. Eckstein Study 2 (2017)	0.000 (−0.237, 0.237)
Ilmaz Study 2 (2012)	0.231 (−0.265, 0.727)
Fick Study 2 (2021)	−0.563 (−1.195, 0.069)
Zihao He Study 2 (2020)	0.229 (−0.654, 1.113)
Jungmann, Study 2 (2012)	0.023 (−0.326, 0.373)
Kamimura, Study 2 (2019)	0.101 (−0.209, 0.411)
M. Roth, Study 1 (2017)	0.000 (−0.303, 0.303)
T. Baum Study 2 (2013)	0.321 (−0.044, 0.686)
L. Wang, Study 2 (2014)	0.298 (−0.345, 0.941)
Favian Su, Study 18 (2013)	−0.397 (−1.109, 0.314)
L.F. Ambra Study 2 (2019)	−0.166 (−0.425, 0.093)
G. Cai Study 1 (2020)	−0.075 (−0.379, 0.229)
G. Cai Study 2 (2020)	0.426 (0.186, 0.666)
G. Cai Study 3 (2020)	0.718 (0.467, 0.970)
N.Chanchek Study 2 (2018)	0.038 (−0.154, 0.230)
Overall (I^2=92.57 % , P< 0.001)	0.325 (0.089, 0.560)

Fig. 3: Forest Study Plot Reporting the Effect of BMI on Osteoarthritis.

with the majority of studies falling on the positive side of the axis. However, the summary effect size obtained was 0.159 (95% CI: -0.221 to 0.539), indicating a non-significant association between cartilage thickness and osteoarthritis (OA) development (p = 0.413, Table VII).

Table VII: Data summary effect on subgroup analysis.

Studies	Estimate	Lower bound	Upper bound	Std. error	p-Val
Subgroup Morphology/ Thickness	0.159	-0.221	0.539	0.194	0.413

Heterogeneity Analysis on Cartilage Thickness Group

The heterogeneity analysis (Table VIII) reveals a Tau^2 value of 0.262 and a Q-statistic of 269.351 (df=22, p < 0.001), indicating significant variation in effect sizes across studies. The I^2 value of 92.575% confirms high heterogeneity, suggesting diverse influences or underlying factors within the analyzed data.

Table VIII: Heterogenitas pada Group Morphology/Thickness.

Tau^2	Q (df=22)	Het. p-Value	I^2
0.262	269.351	< 0.001	92.575

DISCUSSION

Our meta-analysis, encompassing 22 articles investigating cartilage cases and 82 data points, focused on identifying factors influencing osteoarthritis (OA) development. We employed subgroup analysis for age, body mass index (BMI), and morphology/thickness. Our meta-analysis delved deeper into the interplay between specific factors and osteoarthritis (OA) development. Subgroup analysis revealed a statistically significant positive influence of age, body mass index (BMI), and cartilage thickness on osteoarthritis (OA), with P-values for each factor below 0.05. This confirms the independent contributions of these factors to cartilage degeneration. Notably, body mass index (BMI) emerged as the most influential factor, with an estimated value of 0.325, followed by age (0.170) and morphology/thickness (0.159). This finding aligns with our understanding of body mass index (BMI)'s direct impact on cartilage stress, particularly in individuals with unbalanced weight distribution. However, it is crucial to acknowledge the limitations of our subgroup analysis. While age, body mass index (BMI), and morphology are established risk factors, numerous others, such as smoking, activity levels, past injuries, and genetic predisposition, also
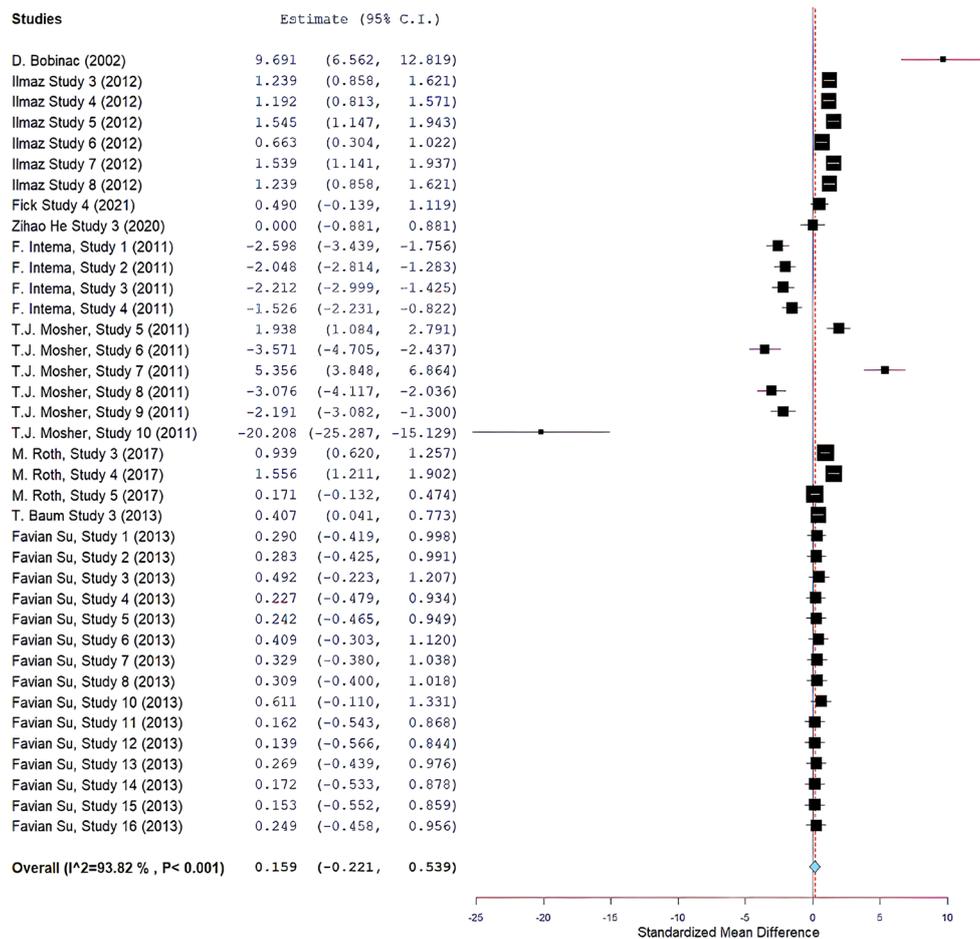

Studies	Estimate (95% C.I.)
D. Bobinac (2002)	9.691 (6.562, 12.819)
Ilmaz Study 3 (2012)	1.239 (0.858, 1.621)
Ilmaz Study 4 (2012)	1.192 (0.813, 1.571)
Ilmaz Study 5 (2012)	1.545 (1.147, 1.943)
Ilmaz Study 6 (2012)	0.663 (0.304, 1.022)
Ilmaz Study 7 (2012)	1.539 (1.141, 1.937)
Ilmaz Study 8 (2012)	1.239 (0.858, 1.621)
Fick Study 4 (2021)	0.490 (-0.139, 1.119)
Zihao He Study 3 (2020)	0.000 (-0.881, 0.881)
F. Intema, Study 1 (2011)	-2.598 (-3.439, -1.756)
F. Intema, Study 2 (2011)	-2.048 (-2.814, -1.283)
F. Intema, Study 3 (2011)	-2.212 (-2.999, -1.425)
F. Intema, Study 4 (2011)	-1.526 (-2.231, -0.822)
T.J. Mosher, Study 5 (2011)	1.938 (1.084, 2.791)
T.J. Mosher, Study 6 (2011)	-3.571 (-4.705, -2.437)
T.J. Mosher, Study 7 (2011)	5.356 (3.848, 6.864)
T.J. Mosher, Study 8 (2011)	-3.076 (-4.117, -2.036)
T.J. Mosher, Study 9 (2011)	-2.191 (-3.082, -1.300)
T.J. Mosher, Study 10 (2011)	-20.208 (-25.287, -15.129)
M. Roth, Study 3 (2017)	0.939 (0.620, 1.257)
M. Roth, Study 4 (2017)	1.556 (1.211, 1.902)
M. Roth, Study 5 (2017)	0.171 (-0.132, 0.474)
T. Baum Study 3 (2013)	0.407 (0.041, 0.773)
Favian Su, Study 1 (2013)	0.290 (-0.419, 0.998)
Favian Su, Study 2 (2013)	0.283 (-0.425, 0.991)
Favian Su, Study 3 (2013)	0.492 (-0.223, 1.207)
Favian Su, Study 4 (2013)	0.227 (-0.479, 0.934)
Favian Su, Study 5 (2013)	0.242 (-0.465, 0.949)
Favian Su, Study 6 (2013)	0.409 (-0.303, 1.120)
Favian Su, Study 7 (2013)	0.329 (-0.380, 1.038)
Favian Su, Study 8 (2013)	0.309 (-0.400, 1.018)
Favian Su, Study 10 (2013)	0.611 (-0.110, 1.331)
Favian Su, Study 11 (2013)	0.162 (-0.543, 0.868)
Favian Su, Study 12 (2013)	0.139 (-0.566, 0.844)
Favian Su, Study 13 (2013)	0.269 (-0.439, 0.976)
Favian Su, Study 14 (2013)	0.172 (-0.533, 0.878)
Favian Su, Study 15 (2013)	0.153 (-0.552, 0.859)
Favian Su, Study 16 (2013)	0.249 (-0.458, 0.956)
Overall (I^2=93.82 % , P< 0.001)	0.159 (-0.221, 0.539)

Fig. 4: Forest Study Plot Reporting the Effect of Thickness on Osteoarthritis.

contribute to osteoarthritis (OA). Therefore, our results, although statistically significant, cannot be considered exhaustive.

Our meta-analysis revealed significant heterogeneity, likely due to variations in data across included studies regarding body mass index (BMI), age, and morphological factors. This was confirmed by the highly significant p-values (<0.001) of all heterogeneity analyses. While this might raise concerns, it's important to acknowledge that heterogeneity is not inherently problematic, especially in real-world data. However, recognizing potential bias in observational studies is crucial. Therefore, we restricted our analysis to case-control and observational-analytical osteoarthritis (OA) designs, aiming for a more robust understanding of factors influencing osteoarthritis (OA) development.

Further mitigating bias concerns, the funnel plot in Figure 5 paints a reassuring picture. The symmetrical arrangement of lines forming triangles indicates small standard errors for most studies, evident in the cluster at the top of the plot. Only two studies deviate with slightly higher errors at the bottom. This pattern suggests minimal publication bias within our analyzed articles. Overall, these results provide confidence in the robustness andreliability of our findings, suggesting no major concerns regarding either heterogeneity or bias.
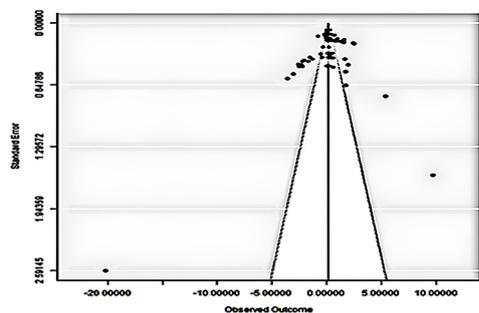
Fig. 5: Funnel plots interpreting potential publication bias in meta-analysis studies.

The present meta-analysis highlights the strong influence of body mass index (BMI) on the development of osteoarthritis (OA). High heterogeneity (92%) within body mass index (BMI) groups indicates consistency in findings across studies, demonstrating a strong association. In particular, significant P-values (<0.05) for all factors examined within body mass index (BMI) groups highlight their collective contribution. However, the results suggest that imbalanced body mass index (BMI) plays a dominant role, potentially increasing with age, making it a stronger risk factor for osteoarthritis (OA) compared to the other two factors. Participant age is a crucial factor contributing to heterogeneity in meta analyses on osteoarthritis (OA). Sub-group analysis further strengthens this notion, revealing the highest estimated value for body mass index (BMI) compared to other factors. This reinforces the concept that unbalanced body mass index (BMI) acts as a potential initiator of

osteoarthritis (OA), likely through increased mechanical load on cartilage, as corroborated by previous studies (36–38). This finding suggests a link between body mass index (BMI) and cartilage thickness in early osteoarthritis (OA) development, possibly arising from the bone's response to pressure associated with unbalanced BMI, particularly obesity (22). While our findings align with previous research by Liying Jiang et al. (39) in acknowledging body mass index (BMI)'s contribution to osteoarthritis (OA), there are some key differences. Our study focused solely on body mass index (BMI), age, and osteoarthritis (OA) type, while Liying Jiang et al. included additional factors like gender and different osteoarthritis (OA) definitions. Conversely, our analysis included factors not investigated by Liying Jiang et al. Similarly, the study by A. Batushansky et al. (40) also confirms a positive association between osteoarthritis (OA) and body mass index (BMI) but emphasizes the interplay with age and cartilage thickness. These findings highlight the complex interplay of multiple factors in osteoarthritis (OA) development, necessitating further research to elucidate the precise sequence and relative contributions of each factor.

Body mass index (BMI) measurement method is one source of heterogeneity in meta-analyses assessing the association between body mass index (BMI) and osteoarthritis (OA). It is widely used to assess overweight or obesity, although measurement methods vary across studies. This variation includes factors such as the type of device used, how often the measurement is taken, and how it is calculated. For example, some studies use modern, more accurate digital measurement methods, while others use manual weighing methods that are less accurate. In addition, body mass index (BMI) measurements can be affected by factors such as the time of measurement, as well as different methods for measuring body mass and height. Differences in the time interval between body mass index (BMI) measurement and osteoarthritis (OA) data collection may also affect the results. Studies that use more recent body mass index (BMI) data or that take into account changes in BMI over time may provide a more accurate picture of the association between body mass index (BMI) and osteoarthritis (OA). Conversely, studies with nonstandardized or outdated body mass index (BMI) data may show more variable results. In addition, some studies may have classified body mass index (BMI) categories differently, such as using different cutoffs for mild, moderate, and severe obesity, which may affect conclusions about the association between body mass index (BMI) and osteoarthritis (OA) risk Therefore, differences in body mass index (BMI) measurement methods may lead to variations in study results and underscore the importance of using consistent and standardized methods in osteoarthritis (OA) research. Future studies should prioritize multi-factorial analyses encompassing a broader range of potential osteoarthritis (OA) risk factors. This comprehensive approach will yield more accurate

and nuanced insights into the complex mechanisms underlying osteoarthritis (OA) development, paving the way for more targeted preventive and therapeutic strategies.

The substantial variation (82%) in the inclusion of age data across studies highlights the heterogeneity of the analyzed articles. This diversity in data types strengthens our meta-analysis by mitigating potential bias and enhancing the generalizability of our findings. Importantly, the absence of significant heterogeneity problems further underscores the quality of the included articles. Eighteen studies examined the influence of age on ostearthtritis (OA) development. Interestingly, 14 focused on older adults (>50 years), while only 4 addressed younger individuals (<50 years). While age undoubtedly plays a role in ostearthtritis (OA) onset and severity, exacerbated by factors like unbalanced body mass index (BMI), inactivity, and smoking, our findings suggest it may not be the primary driver. Rather, the evidence points towards a complex interplay of factors where age acts as a contributing element. This observation is further supported by the meta-analysis, where age ranked second in importance among analyzed factors.

Aging is a biological process that significantly affects joint health, and its effects vary widely between individuals. With age, the quality of cartilage tends to decline; it becomes thinner and less elastic, which reduces its ability to absorb and distribute loads effectively. This process can lead to increased cartilage damage and joint degeneration. In addition, aging also affects the subchondral bone beneath the cartilage, with changes such as increased bone density and the formation of osteophytes (bone spurs) that can worsen ostearthtritis (OA). Chronic low-grade inflammation, which of ten accompanies aging, may also worsen joint damage by accelerating the degenerative process. Variation in study results often depends on the age range of participants. Studies involving older age groups tend to show a stronger association between age and ostearthtritis (OA), given the greater accumulation of joint damage and the more pronounced effects of aging. Conversely, studies involving younger participants may show a weaker association, because the cartilage changes associated with ostearthtritis (OA) may not have fully developed at that age. Younger individuals may also have better regenerative capacity, which may delay the onset of ostearthtritis (OA) symptoms. Therefore, differences in participant age may explain variation in study results, and it is important to consider this factor when designing and interpreting studies of ostearthtritis (OA).

Eight articles, comprising 38 data points, provided data on cartilage thickness for our meta-analysis. The 92% homogeneity value confirms the diversity within these articles. Analysis reveals that cartilage thickness ranks third in importance, as evidenced by comparing estimated values across the three factors. Cartilage thick-ness significantly impacts its ability to handle physiological loads. Notably, studies like Bobinac et al. (21) demonstrate a significant difference between cartilage thickness in healthy and ostearthtritis (OA) groups, high- lighting the role of factors like unbalanced BMI and advanced age in influencing thickness. Increased thickness can be a response to the abnormal mechanical loads caused by uncontrolled BMI.

The method of cartilage thickness measurement is a major source of heterogeneity in meta-analyses. Cartilage thickness plays an important role in understanding the development of ostearthtritis (OA). Therefore, the measurement method can vary significantly between studies, which can affect the results of the analysis. Studies use various scanning techniques, such as radiography, MRI (Magnetic Resonance Imaging), and others, each of which has advantages and disadvantages. Radiography, although often used, provides less detailed images and a coarser form of viewing changes in cartilage thickness compared to MRI. MRI, on the other hand, can provide a more detailed picture of thickness and structural changes at the micro level, but is often more expensive and takes longer to process. In addition to differences in scanning techniques, analysis methods also vary, including the method of measurement, segmentation techniques, and software used. This variability can affect the results and interpretation of the data. In addition, some studies may use different criteria to define and classify the process of change, which can add to the variability of the results. Therefore, the heterogeneity in cartilage thickness assessment methods emphasizes the importance of standardization in imaging and analysis techniques to ensure consistency and reliability of research results on ostearthtritis (OA).

Our study acknowledges several limitations. First, the complex interrelationships between the various factors contributing to osteoarthritis (OA) remain underexplored. Future research should explore these correlations in more depth using cohort methods to examine the extent to which these factors are correlated with osteoarthritis (OA). Second, our inclusion criteria limited us to case control studies, excluding valuable insights from studies exploring osteoarthritis (OA) through other methodologies. For example, we found studies investigating the effects of smoking, activity, gender, and trauma/injury, but the use of different methodologies did not allow these studies to be included in our analysis. We also recommend reviewing demographic and geographic factors in more depth to diversify the results and illustrate how interventions or phenomena apply across different population groups, increasing the validity and relevance of the results. Despite these limitations, our meta-analysis provides strong evidence that age, body mass index (BMI), and cartilage thickness are major factors influencing knee osteoarthritis (OA). This conclusion is supported by the diverse nature of the articles we included, as evidenced by the high

heterogeneity values (>80%) across the factors analyzed. Therefore, future studies that combine more factors and methodologies may provide more comprehensive conclusions and have significant implications for the advancement of healthcare.

Based on the results of the meta-analysis, our findingsunderscore the importance of body mass index (BMI) management for preventing the initiation of osteoarthritis (OA). There are several important efforts in the body mass index (BMI) management process, namely by doctors, patient behavior, and policy makers. Physicians play an important role in efforts to prevent and manage body mass index (BMI) by regularly monitoring patients, particularly those who are elderly. Therefore, it is important to provide education from policy makers and doctors to the public regarding the importance of maintainning a healthy body mass index (BMI) by following a healthy lifestyle. Furthermore, accessible healthcare services are essential to encourage regular health monitoring, especially related to body mass index (BMI). Meanwhile, for patients, it is important to be aware of and identify significant changes in body mass index (BMI) and consult with the relevant doctor. Forming a healthy lifestyle community can also help patients maintain and transition to a healthier lifestyle.

CONCLUSION

This meta-analysis investigated the factors influencing osteoarthritis (OA) development by analyzing data from existing research. Our results identified three key contributors: age, body mass index (BMI), and cartilage thickness. While all three factors played a role, body mass index (BMI) emerged as the most significantly associated with osteoarthritis (OA) onset. This suggests that body mass index (BMI) management may be crucial in preventing osteoarthritis (OA) development. Our findings contribute to the understanding of osteoarthritis (OA) pathogenesis by highlighting the importance of body mass index (BMI) in initiating the disease process. This knowledge can guide future research efforts towards more targeted prevention and intervention strategies focused on weight management. Furthermore, healthcare professionals can utilize these insights to identify patients at higher risk and tailor treatment approaches accordingly. In conclusion, this study provides valuable insights into the factors influencing osteoarthritis (OA) development, with body mass index (BMI) playing a pivotal role. By emphasizing the importance of weight management, this research offers a foundation for improved osteoarthritis (OA) prevention and management strategies, ultimately benefiting both the research community and healthcare practice.

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