# Conversion to Total Knee Arthroplasty After High Tibial Osteotomy

## **A Systematic Review and Meta-analysis**

Ryan Wai Keong Loke,<sup>\*</sup> Yang Kai Chan,<sup>†</sup> MBBS(Singapore), Yao Hui Lim,<sup>†</sup> MBBS(Singapore), Barry Wei Loong Tan,<sup>†‡</sup> MRCS(Edin), MMed(Ortho), and James Hoi Po Hui,<sup>†</sup> MD(Singapore) Investigation performed at the Department of Orthopaedic Surgery, National University Hospital, National University Health System, Singapore

**Background:** High tibial osteotomy (HTO) is a treatment option for younger, active patients with medial compartment knee osteoarthritis. Clinical results of HTO have been shown to deteriorate over time despite initial satisfactory results, requiring patients to eventually undergo conversion to total knee arthroplasty (TKA). Evidence monitoring survivorship of HTO remains scarce and potentially outdated.

**Purpose:** To investigate the impact of concomitant cartilage repair procedures, conversion to TKA, and associated complications for HTO.

Study Design: Systematic review; Level of evidence, 4.

**Methods:** We searched MEDLINE, Embase, Cochrane Library, and SCOPUS from inception to July 18, 2023, for studies reporting on survivorship and associated complications after medial opening-wedge HTO. Pooled analysis of conversion to TKO was categorized as occurring at <5 years, 5 to 10 years, or >10 years postoperatively. Further subgrouping was performed on studies reporting on HTO with concomitant cartilage repair procedures.

**Results:** Overall, 59 studies comprising 5162 patients were included. Rates of conversion to TKA were 4.5% at <5 years, 8.3% at 5 to 10 years, and 11.2% at >10 years. When comparing patients with isolated HTO versus HTO with concomitant cartilage procedures (including mesenchymal stem cell augmentation, osteochondral allograft transplantation, microfracture, abrasion arthroplasty, and autologous chondrocyte implantation), there was no significant difference in survival rates at <5 years (relative risk, 0.78 [95% CI, 0.45-1.33]; P = .36) or 5 to 10 years (relative risk = 0.76 [95% CI, 0.32-1.83]; P = .55). The overall complication rate was 12.1%; intraoperative lateral hinge and tibial plateau fractures had pooled complication rates of 1.6% and 2.0%, respectively. The rate of nonunion was 1.7%, and pooled rates of superficial and deep infections were 2.6% and 2.0% respectively.

**Conclusion:** Rates of conversion to TKA and complications were low and acceptable, although survival rates decreased with time. Concomitant cartilage repair procedures as a whole did not significantly improve survivorship; however, more high-quality studies are warranted to determine the impact of individual concomitant cartilage repair procedures.

Keywords: high tibial osteotomy; total knee replacement; osteoarthritis; meta-analysis

Surgical options for management of medial compartment osteoarthritis generally include total knee arthroplasty (TKA), unicompartmental knee arthroplasty (UKA), or high tibial osteotomy (HTO).<sup>62</sup> For relatively younger and active patients, treatment may be challenging, as patients seek to remain involved in sporting activities, and invasive procedures such as knee arthroplasty do not meet their expectations for continued highly active lifestyles; additionally, patients may be unwilling to deal with subsequent revision arthroplasty procedures.<sup>50</sup> These patients are often <60 years, with early- to midstage knee osteoarthritis (Kellgren-Lawrence grades 1-3).<sup>50</sup>

Knee realignment procedures may allow for arthroplasty to be avoided or delayed while preserving native

The Orthopaedic Journal of Sports Medicine, 13(2), 23259671241310963 DOI: 10.1177/23259671241310963 © The Author(s) 2025

This open-access article is published and distributed under the Creative Commons Attribution - NonCommercial - No Derivatives License (https://creativecommons.org/ licenses/by-nc-nd/4.0/), which permits the noncommercial use, distribution, and reproduction of the article in any medium, provided the original author and source are credited. You may not alter, transform, or build upon this article without the permission of the Author(s). For article reuse guidelines, please visit SAGE's website at http://www.sagepub.com/journals-permissions.

joint mechanics.<sup>49</sup> The most common procedure is an HTO to offload the affected medial compartment.<sup>49</sup> The procedure alters the mechanical axis of the lower limb to offload the arthritic medial compartment and relatively increase the load on the unaffected lateral compartment, thereby reducing pain and improving function.<sup>62</sup> Key indications for HTO are patients with significant varus malalignment with medial-side knee osteoarthritis (KOA) and younger, more active patients.<sup>58</sup>

The 2 most common techniques of HTO include a medial opening-wedge HTO (MOWHTO) and a lateral closing-wedge HTO.<sup>54</sup> MOWHTO offers several additional advantages—it is an easier surgical technique with less risk of neurovascular injury and offers the possibility of performing biplanar corrections, which is vital to restoring knee stability.<sup>80,89</sup> Thus, MOWHTO has now become an established and popular operative procedure for the correction of varus deformity of the knee. To reflect the current landscape in relation to performing HTOs, the present study focuses on MOWHTOs only.

Despite its popularity, clinical results of HTO have been shown to deteriorate over time despite initial satisfactory results, requiring patients to eventually undergo conversion to TKA.<sup>81</sup> Moreover, the survival rate reported across several studies is highly variable, with reported 5-year survival of HTO ranging from 71% to 95% and 10-year survival ranging from 51% to 98%.<sup>99</sup> This causes an inherent degree of confusion and uncertainty for patients in selecting their choice of procedure. Therefore, the need for pooled, surmised rates of TKA conversion is evident. The estimates provided in this study aim to aid the surgeon-patient conversation and decision making through the use of a time-based, comprehensive meta-analysis of conversion to TKA.

While a 2012 Finnish registry study reported survivorship to be 89% at 5 years and 73% at 10 years when taking conversion to TKA as an end point,<sup>69</sup> evidence monitoring outcomes and survivorship of HTO remains scarce and is potentially outdated.<sup>62</sup> Most current reviews report on clinical, functional, or biomechanical outcomes after HTO<sup>13</sup>; however, survivorship as a whole and at specific time periods during postoperative follow-up remains largely uninvestigated. Thus, the primary aim of this systematic review and meta-analysis was to determine survivorship of MOWHTO performed for medial compartment KOA at various postoperative time points and to report any associated complications. Secondarily, we investigated the effect of concomitant cartilage repair procedures on outcomes. It was hypothesized that survivorship of MOWHTO would be high but would decrease with time and that concomitant cartilage repair would improve survivorship.

#### METHODS

#### Data Sources and Search Strategy

This study was conducted in adherence with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines.<sup>67</sup> The study protocol was registered with the PROSPERO international prospective register of systematic reviews. We searched electronic databases MEDLINE, Embase, Cochrane Library, and SCOPUS from inception, on July 18, 2023, for relevant studies. Utilizing Medical Subject Headings (MeSH) and title abstract (tiab), our search terms were as follows: ((KOA [tiab] OR Knee Osteoarth\*[tiab] OR Knee Arth\* [tiab] OR Knee Degenerat\* [tiab]) AND (Knee [MeSH] OR Knee Joint [MeSH])) AND (High Tibial Osteotomy [tiab] OR HTO [tiab] OR Proximal Tibial Osteotomy [tiab] OR Tibial Plateau Osteotomy [tiab] OR Tibial Realignment [tiab] OR Medial Opening Wedge Osteotomy [tiab] OR Osteotomy [MeSH]). We limited our search to only articles written in English. Our full search strategy is found in the Supplementary Material (available separately).

#### Study Selection

Studies reporting on survival outcomes and associated complications in patients undergoing MOWHTO with or without concomitant cartilage repair procedures for medial compartment KOA were included. Study selection criteria were based of a priori relating to study population, intervention, outcomes measured, and study design (Table 1). Studies were included when they reported outcomes at specific time points postoperatively or at a mean follow-up rather than reporting a time-to-event survival analysis.

A patient's having undergone prior knee procedures before HTO was not a criterion for exclusion. HTOs that were performed with external fixation devices (eg, Taylor Spatial Frame, dynamic axial fixator, Ilizarov fixator) were excluded in our study, since external fixation is a separate technique from the traditional internal fixation method, with possible variations in postoperative management (eg, weightbearing protocols, physical therapy regimen, and monitoring) and documented increased rates of pin-site infections.<sup>94</sup> Hence, to maintain consistency and generalizability of our results, we focused on traditional plate-and-screw HTOs.

The inclusion of articles was evaluated by 3 independent blinded authors (R.W.K.L., Y.K.C., and Y.H.L.), with any disagreements being resolved by obtaining consensus of the senior authors (B.W.LT. and J.H.P.H.).

<sup>&</sup>lt;sup>‡</sup>Address correspondence to Barry Wei Loong Tan, MRCS(Edin), MMed(Ortho), Department of Orthopaedic Surgery, National University Hospital, National University Health System, NUHS Tower Block, Level 11, 1E Kent Ridge Road, Singapore 119288, Singapore (email: barry\_wl\_tan@nuhs.edu.sg). \*Yong Loo Lin School of Medicine, National University of Singapore, Singapore.

<sup>&</sup>lt;sup>†</sup>Department of Orthopaedic Surgery, National University Hospital, National University Health System, Singapore.

Final revision submitted July 29, 2024; accepted August 27, 2024.

The authors declared that there are no conflicts of interest in the authorship and publication of this contribution. AOSSM checks author disclosures against the Open Payments Database (OPD). AOSSM has not conducted an independent investigation on the OPD and disclaims any liability or responsibility relating thereto.

Inclusion Criteria	Exclusion Criteria
<ul> <li>Patients undergoing HTO for medial compartment osteoarthritis</li> <li>Isolated HTO and/or HTO with concomitant cartilage repair procedures</li> <li>Survival outcomes and/or complication outcomes</li> <li>Prospective/retrospective clinical studies</li> <li>Level of evidence 1 to 3</li> </ul>	<ul> <li>Patients undergoing HTO for indications other than medial compartment osteoarthritis</li> <li>Nonclinical, in vitro, or biomechanical studies</li> <li>Case reports, review articles, editorials, technical notes, commentaries, or animal or cadaveric studies</li> <li>HTO involving external fixation devices (PEEK implant, Taylor Spatial Frame, dynamic axial fixator, Ilizarov fixator)</li> <li>Lateral closing-wedge HTO</li> </ul>

 TABLE 1

 Inclusion and Exclusion Criteria for Studies<sup>a</sup>

<sup>a</sup>HTO, high tibial osteotomy; PEEK, polyether ether ketone.

#### Risk of Bias and Quality Assessment

Working independently, the same 3 blinded researchers assessed the risk of bias of the included studies. This was performed using the Cochrane risk-of-bias tool for randomized controlled trials and the ROBINS-I (Risk Of Bias In Non-randomized Studies–of Interventions) tool for nonrandomized observational studies.<sup>85</sup> For studies found to have moderate or serious risk of bias, sensitivity analyses were performed to ascertain the robustness of the extracted data. Studies with critical risk of bias were excluded.

#### Data Extraction and Outcomes

Data were extracted by the same 3 researchers independently, with discrepancies resolved by the 2 senior authors. For each included study, the following characteristics were recorded: first author, publication year, study design, level of evidence, sample size, mean patient age, sex, body mass index (BMI), follow-up duration, osteoarthritis grading, any concomitant cartilage procedure, and angle of correction. Primary outcomes considered were survival outcomes (conversion to TKA due to progression of KOA or persistence of symptoms at various mean time points postoperatively, and time to TKA). As secondary outcomes, overall complication rates, other specific complications, and time to return to work were noted when reported.

Means and standard deviations were extracted for the pooling of continuous outcome data. When means and standard deviations were unavailable and data were instead presented as medians with ranges, we derived the means and standard deviations in accordance with the method indicated by Wan and colleagues.<sup>95</sup> Binary outcome data were extracted in the form of number of events occurring per sample size.

#### Statistical Analysis

Statistical analyses were performed using RStudio (Version 2022.12.0 + 353). We performed a single-arm random-effects meta-analysis to synthesize observational data for continuous and binary outcomes using the

respective metamean and metaprop functions of the R meta package. Continuous baseline outcome data were pooled using the weighted mean approach with random effects, and the DerSimonian and Laird estimator was applied for between-study variance. Single-arm meta-analyses of proportions were conducted for primary and secondary outcomes using random-effects modeling. The lower and upper confidence limits of the 95% CIs were estimated using the Clopper-Pearson method, with the DerSimonian and Laird estimator applied for between-study variance. The P value was calculated directly based on the estimated proportions and their standard errors using the Z test.

We assessed statistical heterogeneity by visual inspection of forest plots,  $I^2$ , and  $\tau^2$ .  $I^2$  values of 25%, 50%, and 75% were thresholds for low, moderate, or high heterogeneity, respectively. Given the single-arm nature of our study, we expect greater heterogeneity observed. To assess heterogeneity more comprehensively, we performed prespecified subgroup analyses according to study design (prospective or retrospective) and risk of bias (low, moderate, or serious). Further sensitivity analysis was performed on studies with moderate or serious risk of bias.

Subgrouping was performed within studies reporting on HTO with concomitant cartilage procedures to assess the impact of additional cartilage repair on desired outcomes. Pooled analysis of conversion to TKA was categorized as occurring at 3 different time frames: <5 years, 5 to 10 years, or >10 years postoperatively. Additionally, TKA conversion was analyzed by age group (<40, 40-49, 50-59, or 60-69 years) to assess the effect of age as a factor influencing survival, given most HTO patients are highly active in sports.<sup>50</sup>

Publication bias was assessed by visual inspection of the funnel plot of primary outcomes.

#### RESULTS

Our search strategy yielded 2713 articles, of which 895 duplicate records were removed, leaving 1818 records for screening. We excluded 1608 studies based on study title and abstract, leaving 210 full-text articles for full-text review. Of these 210 articles, 151 were excluded for the



**Figure 1.** PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) diagram of the study selection process.

following reasons: biomechanical study (n = 3), review (n = 3), non-English article (n = 3), surgical technique article (n = 2), inappropriate outcomes per inclusion criteria (n = 49), inappropriate procedure/technique per inclusion criteria (n = 58), and full text unavailable (n = 33). Thus, 59 articles fit the inclusion criteria for this review (Figure 1). A summary of the characteristics of each included study is available in Appendix Table A1.

Of the included articles, 35 had a retrospective study design and 25 had a prospective study design, with 4 randomized controlled trials.<sup>19,26,27,32</sup> The majority of the studies were classified as having a low risk of bias. Only 2 studies<sup>44,77</sup> were deemed to have moderate risk of bias and hence underwent further sensitivity analysis before inclusion in the review, where it was deemed that the baseline characteristics and outcomes were comparable with those of other studies. A summary of the risk-of-bias and sensitivity assessments can be found in the Supplementary Material (Tables S1 and S2).

The funnel plot for publication bias is shown in Figure 2. Visual inspection of the symmetrical funnel plot indicated that no publication bias was present.

#### Patient Characteristics

Overall, 5162 patients (5478 knees) underwent either primary HTO or HTO with concomitant cartilage repair



Figure 2. Funnel plot for publication bias.

procedures; these procedures included mesenchymal stem cell (MSC) augmentation, osteochondral allograft transplantation (OCA), microfracture (MFX), abrasion arthroplasty, and autologous chondrocyte implantation (ACI). The weighted mean age of the patients was 50.4 years (95% CI, 49.9-51.0), and the weighted mean BMI was 27.3 kg/m<sup>2</sup> (95% CI, 26.8 kg/m<sup>2</sup>-27.8 kg/m<sup>2</sup>). Male patients constituted 54.8% of the cohort. The weighted mean follow-up duration was 68.0 months (95% CI, 60.2-75.8 months). Table 2 summarizes the characteristics of the patients in the included studies and the cartilage repair procedures.

There were 4647 patients who underwent isolated HTO (isolated HTO group), with a weighted mean age of 50.8 years (95% CI, 50.2-51.4 years) and a weighted BMI of 27.1 kg/m<sup>2</sup> (95% CI, 26.3 kg/m<sup>2</sup>-28.0 kg/m<sup>2</sup>). Male patients constituted 52.5% of this cohort. The weighted mean follow-up duration was 65.9 months (95% CI, 57.4-74.4 months). Patients who underwent HTO with concomitant cartilage repair procedures numbered 515 (concomitant repair group); their weighted mean age was 46.8 years (95% CI, 41.8-51.8 years) and weighted mean BMI was 27.1 kg/m<sup>2</sup> (95% CI, 26.3 kg/m<sup>2</sup>-28.0 kg/m<sup>2</sup>); 76.3% were male. The weighted mean follow-up was 79.1 months (47.7-110.5 months).

#### Survivorship Outcomes

Conversion to TKA. There were 32 studies<sup>§</sup> (2840 patients) that reported conversion to TKA with mean follow-up times. When categorized according to follow-up time frame, the rates of conversion to TKA were 4.52% at <5 years (95% CI, 2.29%-8.73% years), 8.32% at 5 to 10 years (95% CI, 5.67%-12.04% years) and 11.21% at >10 years (95% CI, 8.76%-14.23% years) (Figure 3).

<sup>&</sup>lt;sup>§</sup>References 2, 6, 8, 11, 12, 15, 17, 19, 23, 28, 34, 36, 38, 39, 44, 52, 56, 59, 60, 63, 65, 71, 73, 75, 76, 78, 79, 90, 92, 97, 101, 102.

	0,010				
Variable	Patients, n	Age, y	Follow-up, mo	Male, %	BMI, kg/m <sup>2</sup>
Overall	5162	50.4 (49.9-51.0)	68.0 (60.2-75.8)	54.8	27.3 (26.8-27.8)
Isolated HTO	4647	50.8 (50.2-51.4)	65.9 (57.4-74.4)	52.5	26.9 (26.2-27.7)
HTO + any concomitant procedure	515	46.8 (41.8-51.8)	79.1 (47.7-110.5)	76.3	27.1 (26.3-28.0)
HTO + ACI	65	43.4 (35.3-51.6)	84.6 (52.2-117.1)	63.1	26.8 (24.7-29.0)
HTO + MSC	117	55.3 (53.0-57.6)	32.1 (8.6-55.7)	62.5	25.8 (25.2-26.4)
HTO + OCA	45	32.4 (25.0-39.7)	79.6 (61.5-97.6)	82.2	27.0 (25.2-28.8)
HTO + abrasion/MFX	85	50.4 (48.7-52.1)	67.2 (61.3-73.1)	92.9	27.4 (26.7-28.1)
HTO + MFX	124	52.0 (50.1-54.0)	92.0 (90.3-93.7)	75.0	31.0 (28.7-33.3)
HTO + abrasion arthroplasty	79	$50.9 \ (49.2 \text{-} 52.6)$	$14.4\ (0.4-29.2)$	84.8	27.1 (26.4-27.8)

TABLE 2Overall Patient Characteristics<sup>a</sup>

<sup>a</sup>Data are presented as mean (95% CI) unless otherwise indicated. ACI, autologous chondrocyte implantation; BMI, body mass index; HTO, high tibial osteotomy; MFX, microfracture; MSC, mesenchymal stem cell; OCA, osteochondral allograft transplantation.

				Events per			
	Study	Events	Total	100 observations	Events	95% CI	Weight
Α	treatmentarm = <5 years			:			
	Cavello et al 2018	0	24	B	0.00	[ 0.00: 14.25]	0.9%
	Chung et al 2021	0	93	B	0.00	[0.00: 3.89]	0.9%
	Giuseffi et al 2015	7	89		7.87	[ 3.22: 15.54]	3.9%
	Hoell et al 2005	1	40		2.50	[ 0.06: 13.16]	1.5%
	Maffulli et al 2013	0	52	m	0.00	[0.00: 6.85]	0.9%
	Miller et al 2009	3	46		6.52	[137:17.90]	2.9%
	Sawaguchi et al 2020	Ő	118		0.00	[0.00.3.08]	0.9%
	Laprade et al 2012	2	47		4 26	[0.52:14.54]	2.4%
	Schuster et al 2018	10	79		12.66	[ 6 24: 22 05]	4 2%
	Random effects model	10	588		4.52	[2 29 8 73]	18.5%
	Heterogeneity: $I^2 = 50\%$ , $\tau^2 =$	0.4728	500		4.52	[2.20, 0.75]	10.070
B	treatmentarm = 5-10 year	2					
-	Aganwalla et al 2021	10	37	·	27.03	[13 79:44 12]	4 0%
	Bhattachava et al 2023	18	96		18 75	[11 51 28 00]	4.6%
	DeMeo et al 2010	5	20		25.00	[11.51, 20.00]	3 3%
	Duivenvoorden et al 2014	3	36		8 33	[ 1 75: 22 47]	2.8%
	Forruzzi et al 2014	1	20		5.00	[0 13: 24 87]	1.5%
	Forruzzi of al 2014	2	18		11 11	[1.38.34.71]	2.3%
	Forruzzi et al 2014	2	10		16.67	[ 1.50, 54.7 ]	2.3 /0
	Herbet et al 2022	3	85		10.07	[ 3.56, 41.42]	2.7 /0
	Miettinen et al 2022	30	2/1		16.19	[4.90, 19.15]	4.1%
	Osti et al 2015	1	55		1 82	[11.77, 21.43]	1.5%
	Ruangsomboon et al 2017	2	50		1.02	[0.05, 3.72]	2.4%
	Schuster et al 2015	2	01		4.00	[0.49, 13.71]	2.4/0
	Van Eamond at al 2016	5	91		20.00	[0.03, 5.97]	2 20/
	Villete et el 2015	2	20		20.00	[0.03, 40.70]	3.3%
	Woodcore et al 2015	17	115		4.55	[0.91, 12.10]	2.9%
	lin at al 2020	12	220		14.70	[0.00, 22.01]	4.0%
	Jill et al 2020	13	339		7 1 4	[2.00, 0.47]	4.0 /0
	Liu et al 2020	2	100		7.14	[ 0.00; 23.00]	2.3%
	Fang et al 2023	5	100		3.1Z	[ 1.02; 7.14]	3.0%
	Riff et al 2016	2	122	-	0.02	[0.02, 4.40]	1.5%
	Zaki at al 2000	2	47		4.20	[0.52, 14.54]	2.4%
	Zaki et al 2009	1	4700		2.00	[ 0.05; 10.65]	1.5%
	Heterogeneity: $I^2 = 76\%$ , $\tau^2 =$	0.5734	1722		8.3Z	[ 5.67; 12.04]	02.0%
C	troatmontarm = >10 years						
U	Darage of al 2018	5	51		0.90	[ 2 26. 21 41]	3 50/
	Uantes et al 2018	5	20		9.00	[ 3.20, 21.41]	3.5%
	Hantes et al 2018	1	20		5.00	[0.13; 24.87]	1.5%
	Hernigou et al 2001	23	245	1.00	9.39	[ 6.04; 13.75]	4.9%
	Saragaglia et al 2011	15	124		12.10	[ 6.93; 19.17]	4.6%
	Bode et al 2022	14	90		15.56	[8.77; 24.72]	4.5%
	Random effects model		530	<b>\$</b>	11.21	[8.76; 14.23]	18.9%
	Heterogeneity: $I^- = 0\%$ , $\tau^- = 0$	)					
	Random effects model		2840	È	8.09	[ 6.18; 10.51]	100.0%
	Heterogeneity: $I^2 = 68\%$ , $\tau^2 =$	0.3996					
	Test for subgroup differences	$\chi_2^2 = 7.1$	4, df = 2	2(p = 0.03)0 10 20 30 4	0		

Figure 3. Forest plots of conversion to total knee arthroplasty at (A) <5 years, (B) 5-10 years, and (C) >10 years.

Α				Events per			
	Study	Events '	Γotal	100 observations	Events	95% CI	Weight
	treatmentarm = Concor	nitant Ca	rtilage	Procedure			•
	Cavello et al 2018	0	24		0.00	[0.00; 14.25]	5.1%
	Chung et al 2021	0	93	<b>B</b>	0.00	[0.00; 3.89]	5.2%
	Schuster et al 2018	10	79	<b>·</b> →	12.66	[6.24; 22.05]	21.9%
	Random effects model		196	<u> </u>	- 3.41	[0.40; 23.52]	32.2%
	Heterogeneity: $I^2 = 70\%$ , $\tau^2$	2 = 2.5224					
	treatmentarm = Isolated	HTO		_			
	Giuseffi et al 2015	7	89		7.87	[3.22; 15.54]	20.5%
	Hoell et al 2005	1	40		2.50	[0.06; 13.16]	8.6%
	Maffulli et al 2013	0	52	<b>B</b>	0.00	[0.00; 6.85]	5.2%
	Miller et al 2009	3	46		6.52	[1.37; 17.90]	15.5%
	Sawaguchi et al 2020	0	118	- <u>-</u>	0.00	[0.00; 3.08]	5.2%
	Laprade et al 2012	2	47	-	4.26	[0.52; 14.54]	12.9%
	Heterogeneity: $I^2 = 27\%$ , $\tau^2$	2 = 0.2073	392		4.47	[2.25; 8.70]	67.8%
	Pandom effects model		588		4 52	[2 20· 8 73]	100.0%
	Heterogeneity: $l^2 = 50\% r^2$	= 0.4728	300		4.52	[2.29, 0.73]	100.0 %
	Test for subgroup difference	= 0.4720 es: $\chi^2 = 0$	06 df =	(n = 0.81) 0 5 10 15 20			
_	rest for subgroup unicients	00. 1,1 0.	00, ui	1 (p 0.01) 0 0 10 10 20			
В				Events per			
	Study	Events	Total	100 observations	Events	95% CI	Weight
	treatmentarm = Isolated	HTO					
	Agarwalla et al 2021	10	37	_ <b>_ </b> →	27.03	[13.79; 44.12]	6.2%
	Bhattachaya et al 2023	18	96		18.75	[11.51; 28.00]	6.8%
	DeMeo et al 2010	5	20	<u>↓                                    </u>	25.00	[ 8.66; 49.10]	5.2%
	Duivenvoorden et al 2014	3	36		8.33	[ 1.75; 22.47]	4.7%
	Ferruzzi et al 2014	1	20		5.00	[0.13; 24.87]	2.7%
	Herbst et al 2022	9	85		10.59	[ 4.96; 19.15]	6.3%
	Octi et al 2015	39	241		10.10	[11.77; 21.45]	7.3%
	Ruangsomboon et al 2013	7 2	50		1.02	[0.05, 9.72]	2.0%
	Van Ermond et al 2016	5	25		20.00	[6.83:40.70]	5.3%
	Villate et al 2015	3	69		4.35	[0.91: 12.18]	4.8%
	Woodacre et al 2016	17	115		14.78	[ 8.85: 22.61]	6.8%
	Jin et al 2020	13	339		3.83	[2.06: 6.47]	6.7%
	Yang et al 2023	5	160	<u>-</u>	3.12	[1.02; 7.14]	5.6%
	Kim et al 2018	1	122	<b>H</b> -	0.82	[0.02; 4.48]	2.8%
	Zaki et al 2009	1	50		2.00	[ 0.05; 10.65]	2.8%
	Random effects model		1520	<b></b>	8.73	[ 5.69; 13.17]	80.9%
	Heterogeneity: $I^2 = 79\%$ , $\tau^2$	= 0.5889					
	treatmentarm = Concom	itant Car	tilage l	Procedure			
	Ferruzzi et al 2014	2	18		11.11	[ 1.38; 34.71]	3.9%
	Ferruzzi et al 2014	3	18	$\rightarrow$	16.67	[ 3.58; 41.42]	4.5%
	Schuster et al 2015	1	91	- <u>-</u> _	1.10	[0.03; 5.97]	2.8%
	Liu et al 2020	2	28		7.14	[ 0.88; 23.50]	4.0%
	Bode et al 2022	2	47		4.26	[ 0.52; 14.54]	4.0%
	Hotorogonaity: $I^2 = 420$ / $z^2$	= 0.4182	202	$\sim$	0.79	[ 2.96; 14.84]	19.1%
	neterogeneity: $T = 45\%$ , $\tau$	- 0.4103					
	Random effects model		1722	<b>\</b>	8.32	[ 5.67; 12.04]	100.0%
	Heterogeneity: $I^2 = 76\%$ , $\tau^2$	= 0.5734					
	Test for subgroup difference	s: χ <sub>1</sub> = 0.2	9, df = '	(p=0.59) 0 10 20 30 40			

**Figure 4.** Forest plots of conversion to total knee arthroplasty after high tibial osteotomy (HTO) and HTO with concomitant cartilage repair at (A) <5 years and (B) 5-10 years postoperatively.

All patients in the concomitant repair group underwent conversion to TKA at either <5 years or 5 to 10 years postoperatively. Comparison between the isolated HTO and concomitant repair groups indicated no significant difference in survival rates at either time frame (<5 years: relative risk [RR], 0.78 [95% CI, 0.45-1.33]; P = .36; 5-10 years: RR, 0.76 [95% CI, 0.32-1.83]; P = .55) (Figure 4).

50-59, or 60-69 years), the rates of conversion to TKA were 5.2% (95% CI, 2.8%-9.4%) for age group <40 years, followed by 14.2% (95% CI, 10.8%-18.4%) for 40 to 49 years, 6.7% (95% CI, 4.7%-9.6%) for 50 to 59 years, and 2.3% (95% CI, 1.0%-5.4%) for 60 to 69 years (Figure 5).

## When studies were further subgrouped based on the reported mean age of patients (age groups <40, 40-49,

#### Time to TKA

For patients who underwent conversion to TKA, the overall pooled mean time to TKA was 5.80 years (95% CI,

Study       Events       93% CI       Weight         A reatmentarm = 40-49 years old metacharge et al 2013       0       37         Betacharge et al 2013       0       37         Duterencodine et al 2016       20       0.00       1.00: 14.25       0.716         Duterencodine et al 2016       7.83       8.43       1.46: 1661       3.26         Healt al 2021       39       241       10.84: 17.75; 22.471       2.78         Medite et al 2016       7.83       8.43       1.46: 1661       3.26         Van Egmond et al 2016       7.15       10.00: 13.16       1.36       1.87         Van Egmond et al 2016       17< 115       10.72       1.47.8       [1.82; 20.01]       3.87         Dodd acre et al 2012       2       47       4.26       [0.52; 14.54]       1.98         Caralle et al 2012       2       47       4.26       [0.52; 14.54]       1.98         Caralle et al 2012       9.85       1.41.8       [1.63; 12.2]       3.48         Breattentarm = 50-59 years old       1.111       1.11.11       1.38       0.7%         Carbel et al 2014       2       1.50       1.67       1.58       1.41.8       1.57       3.48         Herbos et a					Events per			
A real-mentarm = 40-49 years old Agarwalla et al 2021 10 37 Brattachaya et al 2023 18 93 Carvello et al 2010 5 20 Duiverwords et al 2014 7 83 Gravello et al 2016 7 25 Univerwords et al 2016 7 25 Woodscree et al 2016 7 25 Brattachaya et al 2021 39 241 Weitlinen et al 2021 39 241 Woodscree et al 2016 7 25 Brattachaya et al 2016 7 25 Brattachaya et al 2021 10 15 Brattachaya et al 2022 14 99 Brattachaya et al 2022 14 99 Brattachaya et al 2022 14 99 Brattachaya et al 2021 17 15 Heirogeneix, <i>I'</i> = 25%, <i>s</i> <sup>+</sup> = 0.1540 Brattachaya et al 2018 5 51 Heroseneix, <i>I'</i> = 25%, <i>s</i> <sup>+</sup> = 0.1540 Brattachaya et al 2011 15 Brattachaya et al 2018 15 Brattachaya et al 2018 15 Brattachaya et al 2018 122 Heroseneix, <i>I'</i> = 25%, <i>s</i> <sup>+</sup> = 0.1540 Brattachaya et al 2013 15 Brattachaya et al 2014 120 Brattachaya et al 2013 15 Brattachaya et al 2014 120 Brattachaya et al 2014 120 Brattachaya et al 2014 120 Brattachaya et al 2014 120 Brattachaya et al 2015 15 Brattachaya et al 2014 120 Brattachaya et al 2015 120 Brattachaya et al 2016 122 Brattachaya et al 2020 29 Brattachaya et al 2020 29 B		Study	Events	Total	100 observations	Events	95% CI	Weight
Agarwalla et al 2021       10       37         Agarwalla et al 2023       18       93         Carelio et al 2018       0       22         Dulverwoorden et al 2015       7       83         Gusseffi et al 2015       7       83         Medituren et al 2021       39       241         Van Egmond et al 2016       5       25         Van Egmond et al 2016       5       25         Orrego et al 2016       17       115         Orrego et al 2018       5       5         Bode et al 2012       2       47         Cavallo et al 2018       0       24         Ferruzzi et al 2018       0       24         Tocasallo et al 2018       0       24         Ferruzzi et al 2014       10       33         Ferruzzi et al 2014       10       33         Ferruzzi et al 2014       18       5         Darees et al 2018       5       5         Ferruzzi et al 2014       18       5         Perruzzi et al 2014       18       5         Corbeil et al 2013       5       50         Osti et al 2015       5       50         Schuster et al 2014       18       5	Δ	treatmentarm = 40-49 year	re old		:			-
Appendix value et al 2021       10       37         Bhattachaya et al 2021       10       37         DeWoe at 2010       220       18.35       18.32       3.36         Gavelio et al 2013       224       000       000.010.014.25       3.36         Duivernoorden et al 2014       3       36       8.33       1.76: 22.47       3.36         Giuseffie et al 2015       7       83       1.76: 22.47       2.500       1.66: 84.91.01       2.76         Meittine et al 2021       39.24       44.47       1.88: 22.81       1.38       1.39       1.38       1.38       1.	~	Aganwalla at al 2021	10	27		27.02	[12 70: 44 12]	2 20/
brattatchaya et al 2013 is 30 if 1.58 (a.5.2) is 30 if 1.58 (a.5.		Agaiwalia et al 2021	10	37		27.03	[13.79, 44.12]	3.3%
Cavelio et al 2018 0 24 Delveo et al 2018 0 24 Cavelio et al 2016 5 20 Duivervoorden et al 2014 3 36 Giuseffit et al 2015 1 40 Van Egmond et al 2015 1 40 Van Egmond et al 2016 5 25 Phote et al 2016 17 115 Carego et al 2020 1 55 Bhattacharya et al 2021 15 Bhattacharya et al 2022 14 90 Carvallo et al 2018 0 24 Franzenetarm = 50-59 years old Chung et al 2014 1 20 Chung et al 2014 2 31 Chung et al 2014 1 20 Chung et al 2014 2 31 Chung et al 2015 1 50 Chung et al 2015 1 50 Chung et al 2015 1 85 Chung et al 2016 1 123 Chung et al 2015 1 85 Chung et al 2015 1 85 Chung et al 2015 1 85 Chung et al 2014 1 20 Chung et al 2020 2 2 2 Chung et al 2020 2 2 4 Chung et al 2020 2 2 4 Chung et al 2020 2 2		Bhattachaya et al 2023	18	93		19.35	[11.89; 28.85]	3.8%
Dukeveroden et al 2010 5 20 Dukeveroden et al 2016 7 83 Giuseffi et al 2015 7 83 Giuseffi et al 2015 7 83 Hoell et al 2021 39 241 Wan Egmond et al 2016 5 2 5 Woodacre et al 2016 17 115 Orrego et al 2020 1 55 Brattacharya et al 2023 18 93 Bode et al 2022 2 47 Cavalo et al 2021 2 2 47 Cavalo et al 2021 1 76 Herogenety: $l^2 = 25x$ , $l^2 = 0.1540$ B reatmentarm = 50-59 years old Herose et al 2014 2 18 Ferruzzi et al 2014 2 18 Ferruzzi et al 2014 1 20 Ferruzzi et al 2014 1 5 51 Ferruzzi et al 2014 1 5 51 Ferruzzi et al 2015 1 56 Starte al 2021 1 5 10 Starte al 2021 1 3 339 Starte et al 2015 1 85 Starte et al 2016 1 2 106 Tratter starte al 2018 1 17 Miler et al 2020 1 2 3 Starte et al 2018 1 17 Miler et al 2020 2 2 8 Starte et al 2018 1 17 Miler et al 2020 2 2 8 Starte et al 2018 1 17 Miler et al 2020 2 2 8 Starte et al 2018 1 17 Miler et al 2020 2 2 8 Starte et al 2018 1 17 Miler et al 2020 2 2 8 Starte et al 2018 1 17 Miler et al 2020 2 2 8 Starte et al 2018 1 17 Miler et al 2020 2 2 8 Starte et al 2018 1 17 Miler et al 2020 2 2 8 Starte et al 2018 1 17 Miler et al 2020 2 2 8 Starte et al 2018 1 107 Miler et al 2020 2 2 8 Starte et al 2018		Cavello et al 2018	0	24	· · · ·	0.00	[ 0.00; 14.25]	0.7%
Duvervoorden et al 2014 3 36 Giuseffi et al 2015 7 83 Hoell et al 2015 7 4 32 Hoell et al 2016 1 40 Wondacre et al 2016 5 25 Woodacre et al 2016 17 115 Harts 2 1020 1 55 Bratacharya et al 2020 1 55 Bratacharya et al 2021 2 47 Laprade et al 2012 1 11 76 Darees et al 2018 5 51 Perruzzi et al 2014 2 18 Ferruzzi et al 2014 1 20 Ferruzzi et al 2014 2 18 Herrogeneity: $f^* = 52x$ , $f^* = 0.1500$ Start et al 2015 1 50 Coveli et al 2022 9 85 Harrows et al 2013 3 52 Laprade et al 2013 3 52 Laprade et al 2013 3 52 Laprade et al 2013 2 197 Harrows et al 2015 1 60 Carlowit et al 2015 1 60 Carlowit et al 2015 1 15 Table 7, 47x 2; 149 Herrigou et al 2020 1 23 197 Harrows et al 2015 1 85 Streett et al 2015 1 85 Table 7, 748 2; 149 Streett et al 2015 1 86 Wilkte et al 2015 1 86 Crime et al 2015 1 85 Table 7, 748 2; 149 Crime et al 2016 1 75 Table 7, 748 2; 149 Crime et al 2018 1 72 Ferruzzi et al 2018 1 79 Ferruzzi et al 2018 1 79 Ferruz et al 2018		DeMeo et al 2010	5	20	· · · · ·	25.00	[ 8.66; 49.10]	2.7%
Giuseffi et al 2015 7 8.3 Hoel et al 2015 7 8.3 Miettinen et al 2021 39 241 Van Egmond et al 2016 17 115 Orego et al 2016 17 115 Orego et al 2020 1 55 Bhatacharya et al 2023 18 93 Bhatacharya et al 2018 0 24 Faruzzi et al 2011 2 2 47 Cavallo et al 2018 0 24 Heterogeneity: $f^2 = 52\%$ , $s^2 = 0.1540$ B Change et al 2021 0 93 Croug et al 2021 1 76 B Treatmentarm = 50-59 years old Nillate et al 2011 2 197 Heterogeneity: $f^2 = 52\%$ , $s^2 = 0.1540$ B Treatmentarm = 50-59 years old Nillate et al 2015 1 50 Schuster et al 2018 1 79 Heterogeneity: $f^2 = 65\%$ , $s^2 = 0.3934$ C <b>C</b> Treatmentarm = 50e/9 years old Heterogeneity: $f^2 = 65\%$ , $s^2 = 0.3934$ C <b>C</b> <b>C</b> <b>D</b> <b>T</b> <b>T</b> <b>D</b> <b>T</b> <b>T</b> <b>D</b> <b>T</b> <b>T</b> <b>D</b> <b>T</b> <b>D</b> <b>T</b> <b>D</b> <b>T</b> <b>D</b> <b>T</b> <b>D</b> <b>T</b> <b>D</b> <b>T</b> <b>D</b> <b>T</b> <b>D</b> <b>T</b> <b>D</b> <b>T</b> <b>D</b> <b>T</b> <b>D</b> <b>T</b> <b>D</b> <b>T</b> <b>D</b> <b>T</b> <b>D</b> <b>T</b> <b>D</b> <b>T</b> <b>D</b> <b>T</b> <b>D</b> <b>T</b> <b>T</b> <b>D</b> <b>T</b> <b>T</b> <b>D</b> <b>T</b> <b>T</b> <b>T</b> <b>T</b> <b>T</b> <b>T</b> <b>T</b> <b>T</b>		Duivenvoorden et al 2014	3	36		8.33	[ 1.75; 22.47]	2.3%
Hoell et al 2005       1       40       ************************************		Giuseffi et al 2015	7	83		8.43	[ 3.46; 16.61]	3.2%
Mettinen et al 2021       39       241		Hoell et al 2005	1	40		2.50	[ 0.06; 13.16]	1.3%
Van Egmond et al 2016       5       25         Woodacre et al 2016       17       115         Modacre et al 2016       17       115         Bhattacharyn et al 2023       18       93         Bode et al 2012       2       47         Laprade et al 2012       2       47         Cavalio et al 2018       0       24         Cavalio et al 2018       0       24         Random effects model       1023         Heterogeneity. /* = 52%, r* = 0.1540       *         B       trastmentam = 50-59 years old         Chung et al 2021       11       76         Ferruzzi et al 2014       201       18         9       80       10.32       115         9       80       10.32       117         111       113       34.11       1.38         Ferruzzi et al 2014       20       9       85         10.59       14.85       1.35       1.3%         Ferruzzi et al 2011       50       10.05       1.687       1.3%         Schuster et al 2015       1       85       1.18       10.35       1.3%         Schuster et al 2015       1       85       1.38       1.38		Miettinen et al 2021	39	241		16.18	[11.77; 21.45]	4.1%
Woodscree et al 2016       17       115       47.8       [8.85:22 ef]       3.8%         Bodatcharya et al 2020       155       18.2       [0.05; 97.27]       1.3%         Bhatacharya et al 2021       193       1935       1125       1135       1125       1111       11354       1125       1125       1125       1111       11354       1125       1125       1125       1125       1111       1111       11354       1125       1125       1125       1125       1125       1125       1125       1125       1125       1125		Van Egmond et al 2016	5	25		20.00	[6.83:40.70]	2.7%
$ \begin{array}{c} \mbox{Orrego et al 2020} & 1 & 155 \\ \mbox{Bitatacharyya et al 2023} & 18 & 93 \\ \mbox{Bode et al 2012} & 2 & 14 & 90 \\ \mbox{Laprade et al 2012} & 2 & 47 \\ \mbox{Laprade et al 2012} & 2 & 47 \\ \mbox{Laprade et al 2012} & 2 & 47 \\ \mbox{Laprade et al 2012} & 2 & 47 \\ \mbox{Laprade et al 2012} & 2 & 47 \\ \mbox{Laprade et al 2012} & 0 & 24 \\ \mbox{Random effects model} & 1023 \\ \mbox{Heterogeneity: } l^2 = 52\%, \tau^2 = 0.1500 \\ \mbox{Bit restmemtarm} = 50-59 \ years old \\ \mbox{Corbel et al 2021} & 0 & 93 \\ \mbox{Corbel et al 2021} & 1 & 76 \\ \mbox{Corbel et al 2021} & 1 & 76 \\ \mbox{Corbel et al 2021} & 1 & 76 \\ \mbox{Corbel et al 2021} & 1 & 76 \\ \mbox{Corbel et al 2021} & 1 & 76 \\ \mbox{Corbel et al 2021} & 1 & 76 \\ \mbox{Corbel et al 2021} & 1 & 76 \\ \mbox{Ferruzzi et al 2014} & 2 & 18 \\ \mbox{Ferruzzi et al 2014} & 2 & 18 \\ \mbox{Ferruzzi et al 2014} & 2 & 18 \\ \mbox{Ferruzzi et al 2014} & 2 & 18 \\ \mbox{Ferruzzi et al 2014} & 1 & 20 \\ \mbox{Ferruzzi et al 2014} & 1 & 50 \\ \mbox{Coti et al 2020} & 23 & 197 \\ \mbox{Meffull et al 2013} & 1 & 50 \\ \mbox{Schuster et al 2015} & 1 & 50 \\ \mbox{Schuster et al 2015} & 1 & 85 \\ \mbox{Schuster et al 2015} & 1 & 85 \\ \mbox{Schuster et al 2015} & 1 & 85 \\ \mbox{Schuster et al 2016} & 1 & 120 \\ \mbox{Heterogeneity: } l^2 = 60.394 \\ \mbox{C} \mbox{Teratmarm} = 50-69 \ years old \\ \mbox{Heterogeneity: } l^2 = 60.394 \\ \mbox{C} \mbox{Teratmarm} = 8elow 40 \ years old \\ \mbox{Heterogeneity: } l^2 = 60\%, r^2 = 0.394 \\ \mbox{C} \mbox{Teratmarm} = 8elow 40 \ years old \\ \mbox{Heterogeneity: } l^2 = 60\%, r^2 = 0.394 \\ \mbox{C} \mbox{Teratmarm} = 60-69 \ years old \\ \mbox{Random effects model} \ 208 \\ \mbox{Random effects model} \ 258 \\ Random effect$		Woodacre et al 2016	17	115		14 78	[ 8 85 22 61]	3.8%
Bhattacharyya et al 2023 18 93 Bode et al 2012 2 14 90 Laprade et al 2012 2 47 (availo et al 2012 2 47 (cavallo et al 2012 2 47 (cavallo et al 2013 0 24 Farnatom effects model Chung et al 2021 11 76 Corbel et al 2014 1 20 Corbel et al 2014 1 20 Corbel et al 2014 1 76 Ferruzzi et al 2014 1 20 Ferruzzi et al 2014 1 100 Ferruzzi et al 2014 1 100 Ferruzzi et al 2014 3 18 Herbs et al 2015 1 85 Street et al 2016 1 122 Miller et al 2015 1 887 Crowel et al 2020 1 23 Street et al 2016 1 122 Street et al 2018 1 179 Schuster et al 2018 1 179 Random effects model 1887 Hertogeneity: $t^2 = 60\%$ , $t^2 = 0.3934$ C treatmentarm = Below 40 years old Hantes et al 2018 1 179 Random effects model 208 Random effects m		Orrego et al 2020	1	55		1.82	[0.05 9.72]	1.3%
bindetial 2022 14 90 Laprade et al 2012 2 47 Laprade et al 2012 2 47 Laprade et al 2013 0 24 Random effects model 1023 Heterogeneity: $l^2 = 52\%, \tau^2 = 0.150$ B treatmentarm = 50-59 years old Chung et al 2021 11 76 Darees et al 2018 5 51 Ferruzzi et al 2014 2 18 Ferruzzi et al 2014 2 18 Ferruzzi et al 2014 2 18 Herbst et al 2022 9 85 Herbst et al 2015 1 50 Strett et al 2015 1 50 Strett et al 2015 1 60 Strett et al 2018 1 122 Chung et al 2020 1 23 197 Heterogeneity: $l^2 = 65\%, \tau^2 = 0.393$ Colo (10.00; 6.85) 0.7% Strett et al 2015 1 60 Strett et al 2015 1 85 Strett et al 2015 1 60 Strett et al 2015 1 60 Strett et al 2018 1 122 Strett et al 2018 1 17 Strett et al 2018 1 172 Strett et al 2018 1 17 Strett et al 2018 1 172 Strett et al 2018 1 172 Strett et al 2018 1 172 Strett et al 2020 2 2 80 Strett et al 2018 1 172 Strett et al 2020 2 2 90 Strett et al 2020 2 90 Strett		Bhattachanwa at al 2023	18	03		10.35	[11 80: 28 85]	3.8%
booker at 2022 147 (7.4, 24.72) (7.4, 24.72		Bodo of al 2022	14	00		15.55	[11.05, 20.05]	3.0%
Laprade et al 2012 2 47 Cavallo et al 2018 0 24 Random effects model 1023 Heterogeneity: $l^2 = 52\%$ , $s^2 = 0.1540$ B treatmentarm = 50-59 years old Chung et al 2021 0 93 Corbell et al 2021 11 76 Darese et al 2018 5 51 Ferruzzi et al 2014 1 20 Ferruzzi et al 2014 1 20 Ferruzzi et al 2014 2 18 Herbst et al 2022 9 85 Herbst et al 2015 1 50 Schuster et al 2015 1 65 Viliate et al 2015 1 64 Viliate et al 2015 1 64 Viliate et al 2015 1 64 Viliate et al 2015 1 85 Schuster et al 2018 1 17 Kim et al 2020 2 2 8 Kim et al 2018 1 17 Kim et al 2020 2 2 8 Kim et al 2018 1 17 Kim et al 2020 2 2 8 Kim et al 2018 1 17 Kim et al 2020 2 2 8 Kim et al 2020 2 2 8 Kim et al 2021 2 2 4 47 Kim et al 2020 2 2 8 Kim et al 2020 2 2 8 Kim et al 2020 2 2 90 Sawaguchi et al 2020 2 90 Kandom effects model 258 Kim et al 2020 2 90 Kim et al 2020 2 90 Kim et al 2020 1 118 Kim et al 20		Bode et al 2022	14	90		15.50	[0.77, 24.72]	3.7 %
Cavalo et al 2018 0 24 Random effects model Heterogeneity: $l^2 = 52\%, x^2 = 0.1540$ B treatmentarm = 50-59 years old Chung et al 2021 11 76 Darees et al 2018 5 51 Perruzzi et al 2014 1 20 Ferruzzi et al 2014 1 20 Herbig et al 2022 9 85 Herbig et al 2014 1 10.59 [4.98; 19.15] 3.4% Herbig et al 2012 1 15 10 Schuster et al 2015 1 50 Saragaglia et al 2015 1 85 Herbig et al 2016 1 22 Herbig et al 2016 1 20 Herbig et al 2017 1 15 110 Schuster et al 2018 1 20 Herbig et al 2015 1 20 Herbig et al 2016 1 22 Herbig et al 2016 1 20 Herbig et al 2017 1 20 Herbig et al 2018 1 20 Herbig et al 2020 1 118 Herbig et al 2020 2 2 90 Herbig et al 2020 2 1 118 Herbig et al 2020 2 1 118 Herbig et al 2020 1 118 Herbig et al 2020 1 118 Herbig et al 2020 1 118 Herbig et al 2		Laprade et al 2012	2	47		4.26	[ 0.52; 14.54]	1.9%
Random effects model Heterogeneity: $l^2 = 52\%$ , $r^2 = 0.1540$ 1023       14.18 [10.83; 18.35]       39.3%         B       treatmentarm = 50-59 years old Chung et al 2021       0       93       0.00       [0.00; 3.89]       0.7%         Corbeil et al 2018       5       51       98.01       32.28; 21.411       2.9%         Ferruzzi et al 2014       1       20       500       [0.13; 24.87]       1.2%         Ferruzzi et al 2014       18       11.11       [1.38; 34.71]       1.9%         Ferruzzi et al 2014       18       11.11       [1.38; 34.71]       1.9%         Metrogeneity: $l^2$ = 0.210       23       97.0       11.18       [1.38; 34.71]       1.9%         Maffuill et al 2015       1       50       0.00       [0.00; 6.85]       0.7%         Street et al 2015       1       85       1.18       [1.32]       [5.99; 1.894]       36%         Vilate et al 2015       3       64       44.99       [0.98; 1.3.09]       2.4%         Jin et al 2020       13       339       3.83       [2.266; 6.47]       3.7%         Kim et al 2018       1       120       3.83       [2.266; 3.47]       3.7%         Hatterogeneity: $l^2$ = 66%, $r^2$ = 0.3934       120		Cavallo et al 2018	0	24		0.00	[ 0.00; 14.25]	0.7%
Heterogeneity: $l^2 = 52\%$ , $q^2 = 0.1540$ <b>B</b> treatmentarm = 50-59 years old Chung et al 2021 1 76 Darees et al 2018 5 51 Herbs et al 2014 1 20 Ferruzzi et al 2014 2 18 Ferruzzi et al 2014 2 18 Herbs et al 2022 9 85 Herbs et al 2015 1 50 Schuster et al 2015 1 50 Schuster et al 2015 1 85 Villate et al 2015 3 64 Hantes et al 2018 1 122 C treatmentarm = Below 40 years old Hantes et al 2018 1 122 Herbs et al 2018 1 122 C treatmentarm = Below 40 years old Hantes et al 2018 1 122 Haterogeneity: $l^2 = 66\%$ , $r^2 = 0.3934$ C treatmentarm = Below 40 years old Hantes et al 2018 1 172 Haterogeneity: $l^2 = 66\%$ , $r^2 = 0.3934$ C treatmentarm = Below 40 years old Ruangsombone et al 2017 2 50 Haterogeneity: $l^2 = 66\%$ , $r^2 = 0.3934$ C treatmentarm = Below 40 years old Ruangsombone et al 2017 2 50 Haterogeneity: $l^2 = 66\%$ , $r^2 = 0.3934$ C treatmentarm = Below 40 years old Ruangsombone et al 2017 2 50 Haterogeneity: $l^2 = 66\%$ , $r^2 = 0.3934$ C treatmentarm = Below 40 years old Ruangsombone et al 2017 2 50 Haterogeneity: $l^2 = 60\%$ , $r^2 = 0.3934$ C treatmentarm = Below 40 years old Ruangsombone et al 2018 1 172 Haterogeneity: $l^2 = 60\%$ , $r^2 = 0.3934$ C treatmentarm = Below 40 years old Ruangsombone et al 2018 1 172 Haterogeneity: $l^2 = 0\%$ , $r^2 = 0.3934$ C treatmentarm = Below 40 years old Ruangsombone et al 2017 2 50 Haterogeneity: $l^2 = 0\%$ , $r^2 = 0.3934$ C treatmentarm = Below 40 years old Ruangsombone et al 2017 2 50 Haterogeneity: $l^2 = 0\%$ , $r^2 = 0.3934$ C treatmentarm = Below 40 years old Ruangsombone et al 2017 2 50 Haterogeneity: $l^2 = 0\%$ , $r^2 = 0.3934$ C treatmentarm = Bology 2 2 80 Haterogeneity: $l^2 = 0\%$ , $r^2 = 0.3934$ C treatmentarm = Bology 2 2 80 Haterogeneity: $l^2 = 0\%$ , $r^2 = 0.3934$ C treatmentarm = 60-69 years old Ruangsombone et al 2020 2 90 Haterogeneity: $l^2 = 0\%$ , $r^2 = 0.3934$ Haterogeneity: $l^2 = 0\%$ , $r^2 = 0.4109$ Haterogeneity: $l^2 = 0\%$ ,		Random effects model		1023	<b></b>	14.18	[10.83; 18.35]	39.3%
		Heterogeneity: $I^2 = 52\%$ , $\tau^2 =$	0.1540					
B treatmentarm = 50-59 years old Chung et al 2021 10 93 Darces et al 2018 5 51 Darces et al 2018 5 51 Perruzzi et al 2014 1 20 Herrogenetiz et al 2014 2 18 Ferruzzi et al 2014 3 18 Herrogenetiz et al 2014 3 18 Herrogenetiz et al 2014 3 18 Herrogenetiz et al 2014 3 197 Maffulli et al 2013 0 52 0.00 [0.05; 10.65] 1.3% Saragagila et al 2011 15 110 Schuster et al 2015 1 50 Villate et al 2015 3 64 Jin et al 2020 13 339 Villate et al 2015 3 64 Herrogenetiz : $f^2 = 66\%$ , $x^2 = 0.3934$ C treatmentarm = Below 40 years old Hantes et al 2018 1 122 Heterogenetiz: $f^2 = 66\%$ , $x^2 = 0.4109$ C treatmentarm = 60-69 years old Ruangsombon et al 2021 1 15 D treatmentarm = 60-69 years old Ruangsombon et al 2020 1 118 Random effects model 208 Heterogenetiz: $f^2 = 60\%$ , $x^2 = 0.4109$ Test for subgroup differences: $x_0^2 = 26.58$ , df = 3 ( $p < 0.01$ ) 0 10 20 30 40	_							
Chung et al 2021 0 93 0 7% Corbeil et al 2021 11 76 1 4.47 [7.45; 24.42] 3.5% Ferruzzi et al 2014 2 18 1 4.47 [7.45; 24.42] 3.5% Ferruzzi et al 2014 2 18 5 51 5 1 50 [0.13; 24.87] 1.2% Herrist et al 2022 9 85 1 5 1 50 2.00 [0.00; 0.65] 0.3% Maffulli et al 2013 0 52 0.00 [0.00; 0.65] 0.7% Osti et al 2015 1 50 2.00 [0.00; 0.65] 0.7% Osti et al 2015 1 50 2.00 [0.00; 0.65] 0.7% Schuster et al 2015 1 85 1.18 [0.03; 0.65] 0.7% Schuster et al 2015 1 85 1.18 [0.03; 0.65] 0.7% Gao et al 2022 0 39 3.88 [2.06; 6.47] 3.7% Kim et al 2021 10 12 106 1.13% Sterett et al 2010 12 3 339 3.88 [2.06; 6.47] 3.7% Gao et al 2022 0 39 0.00 [0.00; 2.95] 0.7% Gao et al 2022 0 39 0.00 [0.00; 2.95] 0.7% Gao et al 2022 0 39 0.00 [0.00; 2.95] 0.7% Kim et al 2018 1 122 0.13 3.87 Hartes et al 2018 1 122 0.13 3.187 Kim et al 2018 1 122 0.13 3.187 Hartes et al 2018 1 122 0.13 3.187 Kim et al 2018 1 122 0.22 0.394 D treatmentarm = Below 40 years old Hantes et al 2018 1 10 79 C treatmentarm = Below 40 years old Hantes et al 2018 1 10 79 C treatmentarm = Below 40 years old Hantes et al 2018 1 20 Miller et al 2020 2 288 F.14 [0.48; 23.50] 1.3% Random effects model 208 Random effects mode	в	treatmentarm = 50-59 yea	rs old					
Corbell et al 2021 11 76 Darees et al 2018 5 51 Perruzzi et al 2014 1 20 Ferruzzi et al 2014 1 20 Ferruzzi et al 2014 2 18 Herbst et al 2022 9 85 Herbst et al 2021 9 85 Herbst et al 2015 1 50 Schuster et al 2015 1 50 Villate et al 2015 1 85 Strett et al 2015 1 85 Herbst et al 2015 1 50 Schuster et al 2015 1 85 Herbst et al 2015 1 85 Strett et al 2015 1 85 Herbst et al 2015 1 85 Serett et al 2015 1 85 Herbst et al 2015 1 85 Herbst et al 2015 1 9 Schuster et al 2015 1 85 Herbst et al 2015 1 9 Schuster et al 2015 1 85 Herbst et al 2016 1 12 106 Hantes et al 2015 1 86 Herbst et al 2016 1 12 106 Hantes et al 2018 1 122 Hue et al 2018 1 122 Herbst et al 2018 1 10 Herbst et al 2020 2 2 88 Herbst et al 2020 2 2 88 Herbst et al 2020 2 2 88 Herbst et al 2020 2 2 90 Herbst et al 2020 2 90 Herbst et al 2020 1 118 Herbst e		Chung et al 2021	0	93	<b>I</b>	0.00	[0.00: 3.89]	0.7%
Darees et al 2018 5 51 Darees et al 2018 5 51 Ferruzzi et al 2014 2 18 Ferruzzi et al 2014 2 18 Herbst et al 2022 9 85 Herbst et al 2022 9 85 Herbst et al 2012 2 9 85 Herbst et al 2013 0 52 0.00 [0.00; 6.85] 0.7% Osti et al 2015 1 50 Saragaglia et al 2011 15 110 Street et al 2015 1 85 Villate et al 2015 1 85 Villate et al 2015 1 85 Herbst et al 2015 1 85 Street et al 2015 1 85 Herbst et al 2015 1 85 Cost et al 2015 1 85 Street et al 2015 1 85 Villate et al 2015 1 85 Cost et al 2012 1 0 123 Steret et al 2015 1 85 Villate et al 2015 1 85 Cost et al 2020 1 23 39 Steret et al 2015 1 85 Villate et al 2015 1 85 Cost et al 2020 1 23 39 Steret et al 2015 1 85 Cost et al 2020 1 23 487 Jin et al 2021 0 123 Cost et al 2022 0 39 Steret et al 2016 1 223 Cost et al 2022 0 39 Cost et al 2022 0 39 Cost et al 2023 5 160 Hantes et al 2018 1 122 Cost et al 2020 2 2 88 Ferrit et al 2018 1 122 Cost et al 2020 2 2 88 Ferrit et al 2018 1 127 Hante set al 2018 1 127 Cost et al 2020 2 2 88 Ferrit et al 2018 1 127 Cost et al 2020 2 2 88 Ferrit et al 2018 1 127 Ferrit et al 2018 1 127 Cost et al 2020 2 2 88 First et al 2018 1 127 Ferrit et al 2018 1 127 Ferrit et al 2018 1 120 Ferrit et al 2020 2 2 88 First et al 2020 2 2 90 Ferrit et al 2020 1 118 First for subgroup differences: $\chi_{i}^{2} = 0\%$ , $\chi_{i}^{2} = 0\%$ First for subgroup differences: $\chi_{i}^{2} = 0\%$ , $\chi_{i}^{2} = 0\%$ First for subgroup differences: $\chi_{i}^{2} = 0\%$ , $\chi_{i}^{2} = 0\%$ First for subgroup differences: $\chi_{i}^{2} = 0\%$ , $\chi_{i}^{2} = 0\%$ First for subgroup differences: $\chi_{i}^{2} = 0\%$ , $\chi_{i}^{2} = 0\%$ , $\chi_{i}^{2} = 0\%$ , $\chi_{i}^{2} = 0\%$ , $\chi_{i}^{2} = 0\%$		Corbeil et al 2021	11	76		14.47	[7.45: 24.42]	3.5%
Ferruzzi et al 2014 1 20 Ferruzzi et al 2014 2 18 Ferruzzi et al 2014 2 18 Ferruzzi et al 2014 3 18 Herbst et al 2022 9 85 Herbst et al 2022 9 85 Herbst et al 2021 23 197 Maffulli et al 2013 0 52 0.00 [0.00; 6.85] 1.3% Saragagila et al 2011 15 110 Schuster et al 2015 1 85 Herbst et al 2010 12 106 Herbst et al 2010 12 106 Herbst et al 2021 0 12 106 Herbst et al 2015 1 85 Herbst et al 2016 12 106 Herbst et al 2018 1 122 Herbst et al 2018 1 17 Herbst et al 2018 1 17 Herbst et al 2018 1 122 Herbst et al 2018 1 17 Herbst et al 2020 2 2 28 Herbst et al 2020 2 2 90 Herbst et al 2020 2 90 Herbst et al 2020 1 118 Herbst et al 2020		Darees et al 2018	5	51		9.80	3 26 21 41	2.9%
Ferruzzi et al 2014 2 18 Ferruzzi et al 2014 3 18 Herbst et al 2022 9 85 Herbst et al 2022 9 85 Herbst et al 2013 0 52 0.00 [0.00; 8.65] 0.7% Maffulli et al 2013 0 52 0.00 [0.00; 6.65] 0.7% Osti et al 2015 1 85 Saragagia et al 2011 15 110 Saragagia et al 2015 1 85 Strett et al 2015 1 85 Herbst et al 2010 12 106 Hartes et al 2015 3 64 Herbogoneity: $l^2 = 66\%$ , $r^2 = 0.3934$ C treatmentarm = Below 40 years old Hartes et al 2018 1 17 Herbogoneity: $l^2 = 66\%$ , $r^2 = 0.3934$ C treatmentarm = 60-69 years old Random effects model 208 Random effects model 258 Random		Ferruzzi et al 2014	1	20		5.00	[0.13:24.87]	1.2%
$ \begin{array}{c c c c c c c c c c c c c c c c c c c $		Forruzzi et al 2014	2	10		11 11	[ 1 20: 24 71]	1.2/0
$ \begin{array}{c c c c c c c c c c c c c c c c c c c $		Ferruzzi et al 2014	2	10		16.67	[ 1.30, 34.7 1]	1.9%
Herrisou et al 2022       9       85       10.59       [4.96; 19.15]       3.4%         Herrisou et al 2011       23       197       116.8       [7.55; 17.00]       3.9%         Maffulli et al 2013       0       52       0.00       [0.00; 6.85]       0.7%         Osti et al 2015       1       50       2.00       [0.05; 10.65]       1.3%         Schuster et al 2015       1       85       1.18       [0.03; 6.38]       1.3%         Sterett et al 2015       3       64       4.69       [0.98; 13.09]       2.4%         Villate et al 2015       3       64       4.69       [0.98; 13.09]       2.4%         Villate et al 2010       12       106       11.18       [0.00; 2.95]       0.7%         Gao et al 2022       0       39       0.00       [0.00; 2.95]       0.7%         Gao et al 2022       0       39       0.00       [0.00; 0.3]       0.7%         Yang et al 2018       1       79       12.66       [6.24; 22.05]       3.4%         Hetrogeneity: I <sup>2</sup> = 66%, x <sup>2</sup> = 0.3934       C       treatmentarm = Below 40 years old       4.64       4.65       9.55       4.5.5%         Heterogeneity: I <sup>2</sup> = 66%, x <sup>2</sup> = 0.3934       C		Ferruzzi et al 2014	3	18		10.07	[ 3.58; 41.42]	2.2%
$ \begin{array}{c ccccccccccccccccccccccccccccccccccc$		Herbst et al 2022	9	85		10.59	[ 4.96; 19.15]	3.4%
Matruli et al 2013 0 52 0 0.00 [0.00; 6.85] 0.7% Osti et al 2015 1 50 1 50 0 [0.05; 0.65] 1.3% Schuster et al 2015 1 85 1.18 [0.03; 6.38] 1.3% Sterett et al 2010 12 106 1.132 [5.99; 18.94] 3.6% Villate et al 2015 3 64 4.69 [0.98; 13.09] 2.4% Jin et al 2020 13 339 0 0.00 [0.00; 2.95] 0.7% Gao et al 2022 0 39 0 0.00 [0.00; 2.95] 0.7% Yang et al 2023 5 160 0 0.00 [0.00; 2.95] 0.7% Yang et al 2018 1 122 0 0.00 [0.00; 2.95] 0.7% Kim et al 2018 1 122 0 0.00 [0.00; 2.95] 0.7% Kim et al 2018 1 122 0 0.00 [0.00; 2.95] 0.7% Kim et al 2018 1 122 0.02 4.48] 1.3% Schuster et al 2018 1 0 79 12.66 [6.24; 22.05] 3.4% Random effects model 1887 6.70 [4.66; 9.55] 45.6% Heterogeneity: $l^2 = 66\%$ , $r^2 = 0.3934$ C treatmentarm = Below 40 years old Hantes et al 2020 2 2.88 7.14 [0.88; 23.50] 1.9% Bode et al 2022 2 47 4.26 [0.52; 14.54] 1.9% Bode et al 2020 2 2.88 7.14 [0.88; 23.50] 1.9% Bode et al 2020 2 2.88 7.14 [0.88; 23.50] 1.9% Bode et al 2020 2 2.88 7.14 [0.88; 23.50] 1.9% Bode et al 2020 2 2.88 7.14 [0.88; 23.50] 1.9% Bode et al 2020 2 2.88 7.14 [0.88; 23.50] 1.9% Bode et al 2020 2 2.90 7.14 [0.98; 13.71] 1.9% Random effects model 208 7.22 [0.27; 7.80] 2.0% Sawaguchi et al 2020 1 118 7.20 7.14 [0.48; 23.50] 1.9% Bode et al 2020 2 90 7.22 [0.27; 7.80] 2.0% Sawaguchi et al 2020 1 118 7.20 7.14 [0.48; 23.50] 1.9% Bode et al 2020 2 90 7.50 7.14 [0.49; 13.71] 1.9% Heterogeneity: $l^2 = 0\%$ , $r^2 = 0$ D treatmentarm = 60-69 years old Ruangsomboon et al 2017 2 50 7.22 [0.27; 7.80] 2.0% Sawaguchi et al 2020 1 118 7.22 [0.27; 7.80] 2.0% Sawaguchi et al 2020 1 118 7.22 [0.27; 7.80] 2.0% Sawaguchi et al 2020 1 118 7.22 [0.27; 7.80] 2.0% Sawaguchi et al 2020 1 118 7.22 [0.27; 7.80] 2.0% Sawaguchi et al 2020 7.29 [6.26; 10.16] 100.0% Heterogeneity: $l^2 = 0\%$ , $r^2 = 0.4109$ 7.99 [6.26; 10.16] 100.0% Heterogeneity: $l^2 = 0\%$ , $r^2 = 0.4109$ 7.99 [6.26; 10.16] 100.0%		Hernigou et al 2001	23	197		11.68	[7.55; 17.00]	3.9%
Osti et al 2015 1 50 2.00 [0.05; 10.65] 1.3% Saragaglia et al 2011 15 110 1.46 [7.84; 21.49] 3.7% Schuster et al 2015 1 85 1.13% Sterett et al 2010 12 106 1.3% Sterett et al 2010 12 106 1.3% Sterett et al 2010 12 106 1.3% Villate et al 2010 12 106 1.3% Wu et al 2020 13 339 3.20% Yang et al 2021 0 123 0.00 [0.00; 2.95] 0.7% Gao et al 2022 0 39 0.00 [0.00; 2.95] 0.7% Gao et al 2023 5 166 1.3% Schuster et al 2018 1 122 0.00 [0.00; 2.95] 0.7% Schuster et al 2018 1 122 0.00 [0.00; 2.95] 0.7% Heterogeneity: $l^2 = 66\%$ , $r^2 = 0.3934$ C treatmentarm = Below 40 years old Hantes et al 2018 1 20 1.387 Miller et al 2020 2 2.8 7.14 [0.88; 23.50] 1.9% Bode et al 2022 2 47 4.26 [0.52; 14.54] 1.2% Miller et al 2009 3 46 6.52 [1.37; 17.90] 2.4% Liu et al 2020 2 2.8 7.14 [0.88; 23.50] 1.9% Bode et al 2022 2 47 4.26 [0.52; 14.54] 1.9% Zaki et al 2018 1 20 5.00 [0.05; 10.65] 1.3% Random effects model 208 5.21 [2.82; 9.42] 9.9% Heterogeneity: $l^2 = 0.409$ 1.50 4.00 [0.49; 13.71] 1.9% Heterogeneity: $l^2 = 0\%$ , $r^2 = 0$ <b>D</b> treatmentarm = 60-69 years old Ruangsomboon et al 2017 2 50 4.00 [0.49; 13.71] 1.9% Heterogeneity: $l^2 = 0\%$ , $r^2 = 0$ <b>Random effects model</b> 258 6.21 [2.82; 9.42] 9.9% Heterogeneity: $l^2 = 0\%$ , $r^2 = 0$ <b>Random effects model</b> 258 6.23 [0.02; 4.63] 1.3% Random effects model 258 6.376 7.99 [6.26; 10.16] 100.0% Heterogeneity: $l^2 = 0\%$ , $r^2 = 0.4109$ 7.99 [6.26; 10.16] 100.0%		Maffulli et al 2013	0	52	<b>B</b>	0.00	[ 0.00; 6.85]	0.7%
Saragaglia et al 2011 15 110 13.64 [7.84; 21.49] 3.7% Schuster et al 2015 1 85 1.18 [0.03; 6.38] 1.3% Sterett et al 2010 12 106 11.32 [5.9; 18.94] 3.6% Villate et al 2015 3 64 4.69 [0.98; 13.09] 2.4% Jin et al 2020 13 339 $-$ 0.00 [0.00; 2.95] 0.7% Gao et al 2022 0 39 $-$ 0.00 [0.00; 2.95] 0.7% Gao et al 2023 5 160 $-$ 3.12 [1.02; 7.14] 2.9% Kim et al 2018 1 122 $-$ 0.82 [0.02; 4.48] 1.3% Schuster et al 2018 10 79 12.66 [6.24; 22.05] 3.4% Random effects model 1887 6.70 [4.66; 9.55] 45.6% Heterogeneity: $l^2 = 66\%$ , $r^2 = 0.3934$ C treatmentarm = Below 40 years old Hantes et al 2018 1 17 5.88 [0.15; 28.69] 1.2% Miller et al 2020 2 28 7.14 [0.88; 23.50] 1.9% Liu et al 2020 2 2.48 7.14 [0.88; 23.50] 1.9% Bode et al 2022 2 47 4.26 [0.52; 14.54] 1.9% Zaki et al 2009 1 50 7.14 4.26 [0.52; 14.54] 1.9% Random effects model 208 7.14 [0.88; 23.50] 1.9% Heterogeneity: $l^2 = 0\%$ , $r^2 = 0$ D treatmentarm = 60-69 years old Ruangsomboon et al 2017 2 50 4.00 [0.49; 13.71] 1.9% Heterogeneity: $l^2 = 0\%$ , $r^2 = 0$ D treatmentarm = 60-69 years old Ruangsomboon et al 2020 1 118 7.22 9.00 2.22 [0.27; 7.80] 2.0% Sawaguchi et al 2020 1 118 7.23 9.24 9.9% Heterogeneity: $l^2 = 0\%$ , $r^2 = 0$ Random effects model 258 2.31 [0.96; 5.44] 5.2% Heterogeneity: $l^2 = 0\%$ , $r^2 = 0$ Random effects model 258 2.31 [0.96; 5.44] 5.2% Heterogeneity: $l^2 = 0\%$ , $r^2 = 0$ Random effects model 258 2.31 [0.96; 5.44] 5.2% Heterogeneity: $l^2 = 0\%$ , $r^2 = 0$ Random effects model 258 2.31 [0.96; 5.44] 5.2% Heterogeneity: $l^2 = 0\%$ , $r^2 = 0$ Random effects model 3376 7.99 [6.26; 10.16] 100.0%		Osti et al 2015	1	50		2.00	[ 0.05; 10.65]	1.3%
Schuster et al 2015 1 85 Sterett et al 2010 12 106 Jin et al 2020 13 339 Wu et al 2021 0 123 Wu et al 2022 0 39 Wu et al 2022 0 39 Kim et al 2018 1 122 Schuster et al 2018 1 120 Schuster et al 2018 1 17 Schuster et al 2020 2 2 28 Triat (0.88; 23.50) 1.9% Bode et al 2022 2 47 Schuster et al 2019 1 50 Schuster et al 2017 2 50 Heterogeneity: $I^2 = 0\%$ , $r^2 = 0$ D treatmentarm = 60-69 years old Ruangsomboon et al 2017 2 50 Heterogeneity: $I^2 = 0\%$ , $r^2 = 0$ Sawaguchi et al 2020 1 118 Schuster et al 2020 1 10000 Schuster et a		Saragaglia et al 2011	15	110		13.64	[7.84; 21.49]	3.7%
Sterett et al 2010 12 106 13 339 13 339 10 00 $[0.00; 2.95]$ 0.7% 10 00 $[0.00; 2.95]$ 0.7% 12 $[0.02; 4.48]$ 1.3% 12 $[0.02; 4.48]$ 1.2% 12 $[0.02; 4.43]$ 1.3% 13 $[0.96; 5.44]$ 5.2% 14 $[0.02; 4.63]$ 1.3% 13 $[0.96; 5.44]$ 5.2% 14 $[0.96; 5.44]$ 5.2% 15 $[0.96; 5.44]$ 5.2% 16 $[0.95; 10.16]$ 100.0%		Schuster et al 2015	1	85	<b>m</b>	1.18	[0.03; 6.38]	1.3%
Villate et al 2015       3       64       4.69 $[0.98; 13.09]$ 2.4%         Jin et al 2020       13       339       3.83 $[2.06; 6.47]$ 3.7%         Wu et al 2021       0       123       0.00 $[0.00; 2.95]$ 0.7%         Gao et al 2022       0       39       0.00 $[0.00; 2.95]$ 0.7%         Yang et al 2023       5       160       3.12 $[1.02; 7.14]$ 2.9%         Kim et al 2018       1       122       0.82 $[0.02; 4.48]$ 1.3%         Schuster et al 2018       10       79       6.70 $[4.66; 9.55]$ 45.6%         Heterogeneity: $l^2 = 66\%$ , $r^2 = 0.3934$ 6.70 $[4.66; 9.55]$ 45.6%         C       treatmentarm = Below 40 years old       1.887       6.70 $[4.66; 9.55]$ 45.6%         Hiler et al 2018       1       17       5.88 $[0.15; 28.69]$ 1.2%         Miller et al 2020       2       28       7.14 $[0.88; 23.50]$ 1.9%         Zaki et al 2020       2       247       4.26 $[0.52; 14.54]$ 1.9%         Zaki et al 2020       2       90       5.21 $[2.82; 9.42]$ 9.9% </th <th></th> <th>Sterett et al 2010</th> <th>12</th> <th>106</th> <th></th> <th>11.32</th> <th>[ 5.99; 18.94]</th> <th>3.6%</th>		Sterett et al 2010	12	106		11.32	[ 5.99; 18.94]	3.6%
Jin et al 2020 Jin et al 2020 Jin et al 2020 Jin et al 2021 Gao et al 2022 O 39 Yang et al 2023 Schuster et al 2018 Heterogeneity: $l^2 = 66\%$ , $\tau^2 = 0.3934$ C treatmentarm = Below 40 years old Hantes et al 2018 Huntes et al 2018 Huntes et al 2018 Liu et al 2020 Zaki et al 2022 D treatmentarm = 60-69 years old Ruangsomboon et al 2017 Part of rushproup differences: $\chi_0^2 = 0.4109$ Heterogeneity: $l^2 = 66\%$ , $\tau^2 = 0.4109$ Test for subgroup differences: $\chi_0^2 = 26.58$ , df = 3 ( $p < 0.010$ ) Jin et al 2020 D treatmentarm = 60-69 years old Ruangsomboon et al 2017 Part of rushproup differences: $\chi_0^2 = 26.58$ , df = 3 ( $p < 0.010$ ) O to 20 30 40 Test for subgroup differences: $\chi_0^2 = 26.58$ , df = 3 ( $p < 0.010$ ) D to 20 30 40 Heterogeneity: $l^2 = 68\%$ , $\tau^2 = 0.4109$ Test for subgroup differences: $\chi_0^2 = 26.58$ , df = 3 ( $p < 0.010$ ) D to 20 30 40 Test for subgroup differences: $\chi_0^2 = 26.58$ , df = 3 ( $p < 0.010$ ) D to 20 30 40 Test for subgroup differences: $\chi_0^2 = 26.58$ , df = 3 ( $p < 0.010$ ) D to 20 30 40 Test for subgroup differences: $\chi_0^2 = 26.58$ , df = 3 ( $p < 0.010$ ) D to 20 30 40 Test for subgroup differences: $\chi_0^2 = 26.58$ , df = 3 ( $p < 0.010$ ) Test for subgroup differences: $\chi_0^2 = 26.58$ , df = 3 ( $p < 0.010$ ) Test for subgroup differences: $\chi_0^2 = 26.58$ , df = 3 ( $p < 0.010$ ) Test for subgroup differences: $\chi_0^2 = 26.58$ , df = 3 ( $p < 0.010$ ) Test for subgroup differences: $\chi_0^2 = 26.58$ , df = 3 ( $p < 0.010$ ) Test for subgroup differences: $\chi_0^2 = 26.58$ , df = 3 ( $p < 0.010$ ) Test for subgroup differences: $\chi_0^2 = 26.58$ , df = 3 ( $p < 0.010$ ) Test for subgroup differences: $\chi_0^2 = 26.58$ , df = 3 ( $p < 0.010$ ) Test for subgroup differences: $\chi_0^2 = 26.58$ , df = 3 ( $p < 0.010$ ) Test for subgroup differences: $\chi_0^2 = 26.58$ , df = 3 ( $p < 0.010$ ) Test for subgroup differences: $\chi_0^2 = 26.58$ , df = 3 ( $p < 0.010$ ) Test for subgroup differences: $\chi_0^2 = 26.58$ , df = 3 ( $p < 0.010$ ) Test for subgroup differences: $\chi_0^2 = 26.58$ , df = 3 ( $p $		Villate et al 2015	3	64		4.69	[0.98: 13.09]	2.4%
Wu et al 2021       0       123		lin et al 2020	13	339	-	3.83	[206 647]	3.7%
Gao et al 2022       0       39       0.00       [0.00; 2.03]       0.7%         Yang et al 2023       5       160       3.12       [1.02; 7.14]       2.9%         Kim et al 2018       1       122       0.00       [0.00; 2.03]       0.7%         Random effects model       1887       0.00       [0.02; 4.48]       1.3%         Random effects model       1887       0.00       [0.13; 24.87]       1.2%         Hattes et al 2018       1       17       5.88       [0.15; 28.69]       1.2%         Miller et al 2020       2       28       7.14       [0.88; 23.50]       1.9%         Bode et al 2022       2       47       4.26       [0.52; 14.54]       1.9%         Zaki et al 2009       1       50       2.00       [0.05; 10.65]       1.3%         Random effects model       208       2.00       [0.05; 11.65]       1.3%         Random effects model       208       2.22       [0.27; 7.80]       2.0%         Sawaguchi et al 2020       2       90       2.22       [0.27; 7.80]       2.0%         Heterogeneity: $l^2 = 0\%, \tau^2 = 0$ 2.58       2.31       [0.96; 5.44]       5.2%         Heterogeneity: $l^2 = 68\%, \tau^2 = 0$ <		Wu et al 2021	0	123	-	0.00	[0.00: 2.95]	0.7%
Yang et al 2023 5 160 Yang et al 2023 5 160 Kim et al 2018 1 122 Schuster et al 2018 1 0 79 Random effects model 1887 Heterogeneity: $l^2 = 66\%$ , $\tau^2 = 0.3934$ C treatmentarm = Below 40 years old Hantes et al 2018 1 20 Hantes et al 2018 1 17 Hsu et al 2018 1 17 Hsu et al 2018 1 17 Miller et al 2020 2 28 Heterogeneity: $l^2 = 66\%$ , $\tau^2 = 0.3934$ C treatmentarm = Below 40 years old Hantes et al 2018 1 17 Hsu et al 2020 2 2 8 Heterogeneity: $l^2 = 0\%$ , $\tau^2 = 0$ D treatmentarm = 60-69 years old Ruangsomboon et al 2017 2 50 Heterogeneity: $l^2 = 0\%$ , $\tau^2 = 0$ D treatmentarm = 60-69 years old Ruangsomboon et al 2017 2 50 Random effects model 258 Random effects model 258 Heterogeneity: $l^2 = 0\%$ , $\tau^2 = 0$ Random effects model 258 Heterogeneity: $l^2 = 0\%$ , $\tau^2 = 0$ Random effects model 258 Heterogeneity: $l^2 = 0\%$ , $\tau^2 = 0$ Random effects model 3376 Heterogeneity: $l^2 = 0\%$ , $\tau^2 = 0$ Random effects model 3376 Heterogeneity: $l^2 = 68\%$ , $\tau^2 = 0.4109$ Test for subgroup differences: $\chi_3^2 = 26.58$ , df = 3 ( $p < 0.01$ ) 0 10 20 30 40		Gao et al 2022	0	30		0.00	[0.00, 2.00]	0.7%
Aing et al 2023       3 100       3.12       [1.02, 7.14]       2.3%         Kim et al 2018       1       122       -       0.82       [0.02; 4.48]       1.3%         Schuster et al 2018       10       79       -       12.66       [6.24; 22.05]       3.4%         Random effects model       1887       6.70       [4.66; 9.55]       45.6%         Heterogeneity: $l^2 = 66\%$ , $r^2 = 0.3934       5.00       [0.13; 24.87]       1.2%         Miller et al 2008       1       17       -       5.88       [0.15; 28.69]       1.2%         Miller et al 2020       2       28       -       7.14       [0.88; 23.50]       1.9%         Bode et al 2022       2       47       -       4.26       [0.52; 14.54]       1.9%         Zaki et al 2009       1       50       -       2.00       [0.05; 10.65]       1.3%         Random effects model       208       -       5.21       [2.82; 9.42]       9.9%         Heterogeneity: l^2 = 0\%, r^2 = 0       -       4.00       [0.49; 13.71]       1.9%         Random effects model       258       2.31       [0.96; 5.44]       5.2%         Heterogeneity: l^2 = 68\%, r^2 = 0       -       -       7.99$		Vang et al 2022	5	160	-	3 12	[102:714]	2 0%
Schuster et al 2016 1 122 $= 0.3234$ C treatmentarm = Below 40 years old Hantes et al 2018 1 20 Hantes et al 2018 1 20 Hantes et al 2018 1 17 Hautes et al 2018 1 17 Haute al 2020 2 28 Miller et al 2020 2 28 Bode et al 2022 2 47 Zaki et al 2009 1 50 Random effects model 208 Heterogeneity: $l^2 = 0\%, \tau^2 = 0$ D treatmentarm = 60-69 years old Ruangsomboon et al 2017 2 50 Heterogeneity: $l^2 = 0\%, \tau^2 = 0$ D treatmentarm = 60-69 years old Ruangsomboon et al 2017 2 50 Heterogeneity: $l^2 = 0\%, \tau^2 = 0$ C treatmentarm = 60-69 years old Ruangsomboon et al 2020 2 90 Heterogeneity: $l^2 = 0\%, \tau^2 = 0$ C treatmentarm = 60-69 years old Ruangsomboon et al 2020 2 90 Heterogeneity: $l^2 = 0\%, \tau^2 = 0$ C treatmentarm = 60-69 years old Ruangsomboon et al 2020 2 90 Heterogeneity: $l^2 = 0\%, \tau^2 = 0$ C treatmentarm = 60-69 years old Ruangsomboon et al 2017 2 50 Heterogeneity: $l^2 = 0\%, \tau^2 = 0$ C treatmentarm = 60-69 years old Ruangsomboon et al 2020 2 90 Heterogeneity: $l^2 = 0\%, \tau^2 = 0$ C treatmentarm = 60-69 years old Ruangsomboon et al 2017 2 50 Heterogeneity: $l^2 = 0\%, \tau^2 = 0$ C treatmentarm = 60-69 years old Ruangsomboon et al 2017 2 50 Heterogeneity: $l^2 = 0\%, \tau^2 = 0$ C treatmentarm = 60-69 years old Ruangsomboon et al 2020 2 90 Heterogeneity: $l^2 = 0\%, \tau^2 = 0$ C treatmentarm = 60-69 years old Ruangsomboon et al 2020 1 1118 Heterogeneity: $l^2 = 0\%, \tau^2 = 0$ C treatmentarm = 60-69 years old Ruangsomboon et al 2020 1 1118 Heterogeneity: $l^2 = 0\%, \tau^2 = 0$ C treatmentarm = 60-69 years old Ruangsomboon et al 2020 1 1118 Heterogeneity: $l^2 = 0\%, \tau^2 = 0$ C treatmentarm = 60-69 years old Heterogeneity: $l^2 = 0\%, \tau^2 = 0$ C treatmentarm = 60-69 years old Heterogeneity: $l^2 = 0\%, \tau^2 = 0$ C treatmentarm = 60-69 years old Ruandom effects model 3376 Heterogeneity: $l^2 = 0\%, \tau^2 = 0$ C treatmentarm = 60-69 years old Ruandom effects model 3376 Heterogeneity: $l^2 = 0\%, \tau^2 = 0$ C treatmentarm = 60-69 years old Ruandom effects model 3376 Heterogeneity: $l^2 $		Kim at al 2019	1	100		0.02	[1.02, 7.14]	4.9%
Schuster et al 2018 10 79 12.66 [6.24; 22.05] 3.4% Random effects model 1887 6.70 [4.66; 9.55] 45.6% Heterogeneity: $l^2 = 66\%$ , $\tau^2 = 0.3934$ C treatmentarm = Below 40 years old Hantes et al 2018 1 20 Hsu et al 2018 1 17 5.88 [0.15; 28.69] 1.2% Miller et al 2020 2 28 7.14 [0.88; 23.50] 1.9% Bode et al 2022 2 47 4.26 [0.52; 14.54] 1.9% Zaki et al 2009 1 50 2.00 [0.05; 10.65] 1.3% Random effects model 208 5.21 [2.82; 9.42] 9.9% Heterogeneity: $l^2 = 0\%$ , $\tau^2 = 0$ D treatmentarm = 60-69 years old Ruangsomboon et al 2017 2 50 4.00 [0.49; 13.71] 1.9% Heterogeneity: $l^2 = 0\%$ , $\tau^2 = 0$ Random effects model 258 2.31 [0.96; 5.44] 5.2% Heterogeneity: $l^2 = 68\%$ , $\tau^2 = 0.4109$ Test for subgroup differences: $\chi_3^2 = 26.58$ , df = 3 ( $p < 0.01$ ) 0 10 20 30 40		Kim et al 2018	10	122	-	0.02	[0.02; 4.46]	1.3%
Random effects model 1887 Heterogeneity: $l^2 = 66\%$ , $\tau^2 = 0.3934$ C treatmentarm = Below 40 years old Hantes et al 2018 1 20 Hantes et al 2018 1 17 Hantes et al 2018 1 17 Hantes et al 2018 1 17 Hantes et al 2020 2 28 Hantes et al 2020 2 2 8 Hantes et al 2020 2 2 9 Hantes et al 2020 1 50 Hantes et al 2020 1 150 Hantes et al 2020 2 90 Hanterogeneity: $l^2 = 0\%$ , $\tau^2 = 0$ Random effects model 258 Hanterogeneity: $l^2 = 68\%$ , $\tau^2 = 0.4109$ Test for subgroup differences: $\chi_3^2 = 26.58$ , df = 3 ( $p < 0.01$ ) 0 10 20 30 40 Hantes et al 2020 2 90 Hanterogeneity: $l^2 = 68\%$ , $\tau^2 = 0.4109$ Heterogeneity: $r^2 = 68\%$ , $\tau^2 = 0.4109$ Heterogeneity: $l^2 = 68\%$ , $\tau^2 = 0.4109$ Heterogeneity: $l^2 = 68\%$ , $\tau^2 = 0.010$ 10 20 30 40		Schuster et al 2018	10	/9		12.66	[ 6.24; 22.05]	3.4%
Heterogeneity: $l^2 = 66\%$ , $\tau^2 = 0.3934$ C treatmentarm = Below 40 years old Hantes et al 2018 1 20 Hsu et al 2018 1 17 Miller et al 2009 3 46 Liu et al 2020 2 28 Bode et al 2022 2 47 Zaki et al 2009 1 50 Random effects model 208 Heterogeneity: $l^2 = 0\%$ , $\tau^2 = 0$ D treatmentarm = 60-69 years old Ruangsomboon et al 2017 2 50 Heterogeneity: $l^2 = 0\%$ , $\tau^2 = 0$ Random effects model 258 Heterogeneity: $l^2 = 68\%$ , $\tau^2 = 0.4109$ Test for subgroup differences: $\chi_3^2 = 26.58$ , df = 3 ( $p < 0.01$ ) 0 10 20 30 40 Heterogeneity: $l^2 = 68\%$ , $\tau^2 = 0.4109$ Test for subgroup differences: $\chi_3^2 = 26.58$ , df = 3 ( $p < 0.01$ ) 0 10 20 30 40		Random effects model		1887	<b>\$</b>	6.70	[4.66; 9.55]	45.6%
$ \begin{array}{c c c c c c c c c c c c c c c c c c c $		Heterogeneity: $I^2 = 66\%$ , $\tau^2 =$	0.3934					
C treatmentarm = Below 40 years old Hantes et al 2018 1 20 Hsu et al 2018 1 17 Size and the start of the	~				-			
Hantes et al 2018 1 20 Hautes et al 2018 1 17 Hsu et al 2018 1 17 Miller et al 2009 3 46 Liu et al 2020 2 28 Bode et al 2022 2 47 Zaki et al 2009 1 50 Random effects model 208 Heterogeneity: $l^2 = 0\%$ , $\tau^2 = 0$ D treatmentarm = 60-69 years old Ruangsomboon et al 2017 2 50 Heterogeneity: $l^2 = 0\%$ , $\tau^2 = 0$ Random effects model 258 Heterogeneity: $l^2 = 0\%$ , $\tau^2 = 0$ Random effects model 258 Heterogeneity: $l^2 = 0\%$ , $\tau^2 = 0$ Random effects model 258 Heterogeneity: $l^2 = 0\%$ , $\tau^2 = 0$ Random effects model 258 Heterogeneity: $l^2 = 68\%$ , $\tau^2 = 0.4109$ Test for subgroup differences: $\chi_3^2 = 26.58$ , df = 3 (p < 0.01) 0 10 20 30 40 Test for subgroup differences: $\chi_3^2 = 26.58$ , df = 3 (p < 0.01) 0 10 20 30 40	C	treatmentarm = Below 40	years o	ld				
Hsu et al 2018 1 17 Miller et al 2009 3 46 Liu et al 2020 2 28 Bode et al 2022 2 47 Zaki et al 2009 1 50 Random effects model 208 Heterogeneity: $l^2 = 0\%$ , $\tau^2 = 0$ D treatmentarm = 60-69 years old Ruangsomboon et al 2017 2 50 Hernigou et al 2020 2 90 Sawaguchi et al 2020 1 118 Random effects model 258 Random effects model 258 Random effects model 258 Heterogeneity: $l^2 = 0\%$ , $\tau^2 = 0$ Random effects model 258 Heterogeneity: $l^2 = 0\%$ , $\tau^2 = 0$ Random effects model 258 Heterogeneity: $l^2 = 68\%$ , $\tau^2 = 0.4109$ Test for subgroup differences: $\chi_3^2 = 26.58$ , df = 3 (p < 0.01) 0 10 20 30 40		Hantes et al 2018	1	20		5.00	[ 0.13; 24.87]	1.2%
Miller et al 2009       3       46       6.52 $[1.37; 17.90]$ 2.4%         Liu et al 2020       2       28       7.14 $[0.88; 23.50]$ 1.9%         Bode et al 2022       2       47       4.26 $[0.52; 14.54]$ 1.9%         Zaki et al 2009       1       50       2.00 $[0.05; 10.65]$ 1.3%         Random effects model       208       5.21 $[2.82; 9.42]$ 9.9%         Heterogeneity: $l^2 = 0\%$ , $\tau^2 = 0$ 4.00 $[0.49; 13.71]$ 1.9%         Sawaguchi et al 2020       2       90       2.22 $[0.27; 7.80]$ 2.0%         Sawaguchi et al 2020       2       90       2.22 $[0.27; 7.80]$ 2.0%         Random effects model       258       2.31 $[0.96; 5.44]$ 5.2%         Heterogeneity: $l^2 = 0\%$ , $\tau^2 = 0$ 7.99 $[6.26; 10.16]$ 100.0%         Heterogeneity: $l^2 = 68\%$ , $\tau^2 = 0.4109$ 7.99 $[6.26; 10.16]$ 100.0%         Test for subgroup differences: $\chi_3^2 = 26.58$ , df = 3 ( $p < 0.01$ )       10       20       30       40		Hsu et al 2018	1	17		5.88	[ 0.15; 28.69]	1.2%
Liu et al 2020 2 28 Bode et al 2022 2 47 Zaki et al 2009 1 50 Random effects model 208 Heterogeneity: $l^2 = 0\%$ , $\tau^2 = 0$ D treatmentarm = 60-69 years old Ruangsomboon et al 2017 2 50 Hernigou et al 2020 2 90 Sawaguchi et al 2020 2 90 Random effects model 258 Heterogeneity: $l^2 = 0\%$ , $\tau^2 = 0$ Random effects model 258 Heterogeneity: $l^2 = 0\%$ , $\tau^2 = 0$ Random effects model 3376 Heterogeneity: $l^2 = 68\%$ , $\tau^2 = 0.4109$ Test for subgroup differences: $\chi_3^2 = 26.58$ , df = 3 ( $p < 0.01$ ) 0 10 20 30 40 Test for subgroup differences: $\chi_3^2 = 26.58$ , df = 3 ( $p < 0.01$ ) 0 10 20 30 40 Test for subgroup differences: $\chi_3^2 = 26.58$ , df = 3 ( $p < 0.01$ ) 0 10 20 30 40		Miller et al 2009	3	46		6.52	[ 1.37; 17.90]	2.4%
Bode et al 2022       2       47       4.26 $[0.52; 14.54]$ 1.9%         Zaki et al 2009       1       50       2.00 $[0.05; 10.65]$ 1.3%         Random effects model       208       5.21 $[2.82; 9.42]$ 9.9%         Heterogeneity: $l^2 = 0\%$ , $\tau^2 = 0$ 4.00 $[0.49; 13.71]$ 1.9%         D treatmentarm = 60-69 years old       4.00 $[0.49; 13.71]$ 1.9%         Hernigou et al 2020       2       90       2.22 $[0.27; 7.80]$ 2.0%         Sawaguchi et al 2020       1       118       -       0.85 $[0.02; 4.63]$ 1.3%         Random effects model       258       2.31 $[0.96; 5.44]$ 5.2%         Heterogeneity: $l^2 = 68\%$ , $\tau^2 = 0$ 7.99 $[6.26; 10.16]$ 100.0%         Heterogeneity: $l^2 = 68\%$ , $\tau^2 = 0.4109$ 7.99 $[6.26; 10.16]$ 100.0%         Test for subgroup differences: $\chi_3^2 = 26.58$ , df = 3 ( $p < 0.01$ ) 0       10       20       30       40		Liu et al 2020	2	28		7.14	[0.88; 23.50]	1.9%
Zaki et al 2009       1       50       2.00       [0.05; 10.65]       1.3%         Random effects model       208       5.21       [2.82; 9.42]       9.9%         Heterogeneity: $I^2 = 0\%, \tau^2 = 0$ 4.00       [0.49; 13.71]       1.9%         Learningou et al 2017       2       50       4.00       [0.49; 13.71]       1.9%         Sawaguchi et al 2020       2       90       2.22       [0.27; 7.80]       2.0%         Sawaguchi et al 2020       1       118       0.85       [0.02; 4.63]       1.3%         Random effects model       258       2.31       [0.96; 5.44]       5.2%         Heterogeneity: $I^2 = 0\%, \tau^2 = 0$ 7.99       [6.26; 10.16]       100.0%         Heterogeneity: $I^2 = 68\%, \tau^2 = 0.4109$ 7.99       [6.26; 10.16]       100.0%		Bode et al 2022	2	47		4.26	[ 0.52: 14.54]	1.9%
Random effects model Heterogeneity: $l^2 = 0\%$ , $\tau^2 = 0$ 208       5.21 [2.82; 9.42] 9.9%         D treatmentarm = 60-69 years old Ruangsomboon et al 2017 2 50       4.00 [0.49; 13.71] 1.9%         Hernigou et al 2020 2 90       2.22 [0.27; 7.80] 2.0%         Sawaguchi et al 2020 1 1118       0.85 [0.02; 4.63] 1.3%         Random effects model Heterogeneity: $l^2 = 0\%$ , $\tau^2 = 0$ 2.31 [0.96; 5.44] 5.2%         Random effects model Heterogeneity: $l^2 = 68\%$ , $\tau^2 = 0.4109$ 7.99 [6.26; 10.16] 100.0%		Zaki et al 2009	1	50		2.00	[0.05:10.65]	1.3%
Hardom effects model Heterogeneity: $l^2 = 0\%$ , $\tau^2 = 0$ <b>D</b> treatmentarm = 60-69 years old Ruangsomboon et al 2017 2 50 Hernigou et al 2020 2 90 Sawaguchi et al 2020 2 90 Random effects model 258 Heterogeneity: $l^2 = 0\%$ , $\tau^2 = 0$ <b>Random effects model</b> 3376 Heterogeneity: $l^2 = 68\%$ , $\tau^2 = 0.4109$ Test for subgroup differences: $\chi_3^2 = 26.58$ , df = 3 ( $p < 0.01$ ) 0 10 20 30 40		Random effects model		208	•	5.21	[2.82: 9.42]	9.9%
$ \begin{array}{c ccccccccccccccccccccccccccccccccccc$		Heterogeneity: $I^2 = 0\% r^2 = 0$	1	200	-	0.1.1	[ 2.02, 0.42]	0.070
$ \begin{array}{c c c c c c c c c c c c c c c c c c c $		neterogeneity. 7 = 0 %, t = t	,					
Ruangsomboon et al 2017       2       50       4.00 $[0.49; 13.71]$ $1.9\%$ Hernigou et al 2020       2       90       2.22 $[0.27; 7.80]$ $2.0\%$ Sawaguchi et al 2020       1       118       0.85 $[0.02; 4.63]$ $1.3\%$ Random effects model       258       2.31 $[0.96; 5.44]$ $5.2\%$ Heterogeneity: $l^2 = 0\%$ , $\tau^2 = 0$ 7.99 $[6.26; 10.16]$ $100.0\%$ Test for subgroup differences: $\chi_3^2 = 26.58$ , df = 3 ( $p < 0.01$ ) $10$ $20$ $30$ $40$	П	treatmentarm = 60.60 vea	re old					
Ruangsomboon et al 2017       2       50       4.00 $[0.49; 13.71]$ 1.9%         Hernigou et al 2020       2       90       2.22 $[0.27; 7.80]$ 2.0%         Sawaguchi et al 2020       1       118       -       0.85 $[0.02; 4.63]$ 1.3%         Random effects model       258       2.31 $[0.96; 5.44]$ 5.2%         Heterogeneity: $l^2 = 0\%$ , $\tau^2 = 0$ 7.99 $[6.26; 10.16]$ 100.0%         Heterogeneity: $l^2 = 68\%$ , $\tau^2 = 0.4109$ 7.99 $[6.26; 10.16]$ 100.0%         Test for subgroup differences: $\chi_3^2 = 26.58$ , df = 3 ( $p < 0.01$ )       10       20       30       40		Dueneembers at al COAT	is olu	50		4.00	10 40 40 741	4.00/
Terringou et al 2020       2       90       2.22 $[0.27; 7.80]$ 2.0%         Sawaguchi et al 2020       1       118 $0.85$ $[0.02; 4.63]$ 1.3%         Random effects model       258 $2.31$ $[0.96; 5.44]$ 5.2%         Heterogeneity: $I^2 = 0\%$ , $\tau^2 = 0$ 7.99 $[6.26; 10.16]$ 100.0%         Heterogeneity: $I^2 = 68\%$ , $\tau^2 = 0.4109$ 7.99 $[6.26; 10.16]$ 100.0%         Test for subgroup differences: $\chi_3^2 = 26.58$ , df = 3 ( $p < 0.01$ )       0       20       30       40		Ruangsomboon et al 2017	2	50		4.00	[0.49, 13.71]	1.9%
Sawaguchi et al 2020 1 118 Random effects model 258 Heterogeneity: $I^2 = 0\%$ , $\tau^2 = 0$ Random effects model 3376 Heterogeneity: $I^2 = 68\%$ , $\tau^2 = 0.4109$ Test for subgroup differences: $\chi_3^2 = 26.58$ , df = 3 (p < 0.01) 0 10 20 30 40 $T_{33} = 26.58$ , df = 3 (p < 0.01) 0 10 20 30 40		mernigou et al 2020	2	90		2.22	[0.27; 7.80]	2.0%
Random effects model       258       2.31       [0.96; 5.44]       5.2%         Heterogeneity: $I^2 = 0\%$ , $\tau^2 = 0$ <b>Random effects model 3376 7.99</b> [6.26; 10.16]       100.0%         Heterogeneity: $I^2 = 68\%$ , $\tau^2 = 0.4109$ <b>7.99</b> [6.26; 10.16]       100.0%         Test for subgroup differences: $\chi_3^2 = 26.58$ , df = 3 (p < 0.01) 0       10       20       30       40		Sawaguchi et al 2020	1	118	<b>H</b> -	0.85	[0.02; 4.63]	1.3%
Heterogeneity: $I^2 = 0\%$ , $\tau^2 = 0$ Random effects model 3376 Heterogeneity: $I^2 = 68\%$ , $\tau^2 = 0.4109$ Test for subgroup differences: $\chi_3^2 = 26.58$ , df = 3 ( $p < 0.01$ ) 0 10 20 30 40 7.99 [ 6.26; 10.16] 100.0%		Random effects model		258		2.31	[0.96; 5.44]	5.2%
Random effects model       3376       7.99       [ 6.26; 10.16]       100.0%         Heterogeneity: $I^2 = 68\%$ , $\tau^2 = 0.4109$ 7.99       [ 6.26; 10.16]       100.0%         Test for subgroup differences: $\chi_3^2 = 26.58$ , df = 3 ( $p < 0.01$ )       0       20       30       40		Heterogeneity: $I^2 = 0\%$ , $\tau^2 = 0$	)					
Random effects model         3376         7.99         [ 6.26; 10.16]         100.0%           Heterogeneity: $l^2 = 68\%$ , $\tau^2 = 0.4109$ 7.99         [ 6.26; 10.16]         100.0%           Test for subgroup differences: $\chi_3^2 = 26.58$ , df = 3 ( $p < 0.01$ )         0         20         30         40								
Heterogeneity: $l^2 = 68\%$ , $\tau^2 = 0.4109$ Test for subgroup differences: $\chi_3^2 = 26.58$ , df = 3 ( $p < 0.01$ ) 0 10 20 30 40		Random effects model		3376	\$	7.99	[ 6.26; 10.16]	100.0%
Test for subgroup differences: $\chi_3^2 = 26.58$ , df = 3 ( $\rho < 0.01$ ) 0 10 20 30 40		Heterogeneity: $I^2 = 68\%$ , $\tau^2 =$	0.4109					
		Test for subgroup differences	$\chi_3^2 = 26.$	58, df =	3 (p < 0.01) 0 10 20 30 40	)		

**Figure 5.** Forest plots of conversion to total knee arthroplasty after high tibial osteotomy according to age group: (A) 40-49 years, (B) 50-59 years, (C) <40 years, and (D) 60-69 years.

4.49-7.11 years). The pooled mean time to TKA was 5.50 years (95% CI, 4.10-6.90 years) in the isolated HTO group and 7.94 years (95% CI, 5.59-10.29 years) in the

concomitant repair group, with no significant group differences in time to TKA (RR, 0.69 [95% CI, 0.10-5.02]; P = .73). Heterogeneity was high in both groups ( $I^2 = 100\%$ )



Figure 6. Forest plots of time to total knee arthroplasty for (A) isolated high tibial osteotomy (HTO) and (B) HTO with concomitant cartilage repair. MRAW, raw means.

for isolated HTO and 85% for concomitant repair) (Figure 6).

#### Complications

Overall Complications. The overall pooled complication rate was 12.4% (95% CI, 9.8%-15.6%), with high heterogeneity ( $I^2 = 87\%$ ). In the isolated HTO group, the rate was 12.83% (95% CI, 10.03%-16.27%), with high heterogeneity ( $I^2 = 88\%$ ). In the concomitant repair group, the rate was 8.23% (95% CI, 3.40%-18.61%), with moderate heterogeneity ( $I^2 = 61\%$ ) (Figure 7).

Fractures, Nonunion, and Infections. There was a pooled rate of intraoperative lateral hinge fractures of 1.6% (95% CI, 1.0%-2.5%), with moderate heterogeneity ( $I^2 = 71\%$ ). Intraoperative tibial plateau fractures had a pooled rate of 2.0% (95% CI, 1.4%-2.8%), with low heterogeneity ( $I^2 =$ 43%). Postoperative fractures had a pooled rate of 0.9% (95% CI, 0.7%-1.3%). No heterogeneity was found in this group. The pooled rate of nonunion was 1.7% (95% CI, 1.3%-2.2%), with no heterogeneity. The pooled rate of superficial infection was 2.6% (95% CI, 1.9%-3.5%), with moderate heterogeneity ( $I^2 = 53\%$ ), and the pooled rate of deep infection was 2.0% (95% CI, 1.5%-2.6%), with no heterogeneity. The related forest plots are available in the Supplemental Material (Figures S3-S8).

#### Return To Work

Four studies<sup>2,39,77,86</sup> reported on patients' time to return to work, all of which were from the isolated HTO

# (95% CI, 2.8-3.6 months). Heterogeneity was high ( $I^2 = 97\%$ ) (Figure 8).

group. The pooled time to return to work was 3.2 months

#### DISCUSSION

The most important finding of this systematic review and meta-analysis was a reinforcement of the present consensus that HTO is an effective procedure that does provide low rates of conversion to TKA and complications; hence, it is a viable option along with UKA for medial compartment KOA. We found that 4.52% of patients underwent conversion to TKA within the first 5 years after HTO; this increased to 8.32% within 5 to 10 years and 11.21% after 10 years. Subgroup analyses for patients who underwent HTO with concomitant cartilage repair procedures was performed, and results reflected similar, nonsignificant rates of conversion to TKA within the <5 year and 5- to 10-year follow-up time frames, with no studies reporting patients who converted to TKA at >10 years. This main finding of survival rates decreasing with time is to be expected. The majority of patients opting for HTO are younger and more active, resulting in increased wear on an already osteoarthritic knee joint, accelerating osteoarthritis progression. Given that the medial compartment experiences 60% to 80% of the weightbearing load,<sup>93</sup> loss of correction and return of varus malalignment and thus osteoarthritis symptoms are inevitable. Having only approximately 1 in 10 HTOs convert to HTO after >10years postoperatively lends support to the procedure's effectiveness at delaying or postponing the need for

				Events per			
	Study	Events	Total	100 observations	Events	95% CI	Weight
Α	treatmentarm = Isolated I	ITO					
	Agarwalla et al 2021	15	37	+ →	40.54	[24.75: 57.90]	2.1%
	Asik et al 2006	5	65		7.69	[ 2.54; 17.05]	1.9%
	Bhattachaya et al 2023	6	96		6.25	[2.33; 13.11]	2.0%
	Birmingham et al 2009	10	128		7.81	[ 3.81; 13.90]	2.1%
	Brosset et al 2011	4	51		7.84	[2.18; 18.88]	1.8%
	Corbeil et al 2021	35	84	$\longrightarrow$	41.67	[31.00; 52.94]	2.3%
	Darees et al 2018	4	51		7.84	[ 2.18; 18.88]	1.8%
	DeMeo et al 2010	5	20		25.00	[ 8.66; 49.10]	1.8%
	Duivenvoorden et al 2014	5	36		13.89	[ 4.67; 29.50]	1.9%
	Duivenvoorden et al 2017	16	112		14.29	[ 8.39; 22.16]	2.2%
	Han et al 2019	48	209		22.97	[17.45; 29.27]	2.4%
	El Assal et al 2010	4	58		6.90	[ 1.91; 16.73]	1.8%
	Essenkaya et al 2007	25	58	<b>→</b>	43.10	[30.16; 56.77]	2.2%
	Ferruzzi et al 2014	1	20		5.00	[ 0.13; 24.87]	1.0%
	Floerkemeier et al 2013	32	533		6.00	[4.14; 8.37]	2.4%
	Gaasbeek et al 2010	1	25		4.00	[ 0.10; 20.35]	1.0%
	Giuseffi et al 2015	40	89	<b>_</b>	44.94	[34.38; 55.86]	2.3%
	Goshima et al 2015	12	60	÷ • •	20.00	[10.78; 32.33]	2.2%
	Hantes et al 2018	0	20	<b>B</b>	0.00	[ 0.00; 16.84]	0.7%
	Herbst et al 2022	5	85		5.88	[ 1.94; 13.20]	1.9%
	Hernigou et al 2001	14	245		5.71	[ 3.16; 9.40]	2.2%
	Hernigou et al 2013	23	170		13.53	[ 8.77; 19.61]	2.3%
	Hoell et al 2005	5	40		12.50	[ 4.19; 26.80]	1.9%
	Maffulli et al 2013	5	52		9.62	[ 3.20; 21.03]	1.9%
	Miettinen et al 2021	19	241		7.88	[ 4.81; 12.04]	2.3%
	Miller et al 2009	14	46		30.43	[17.74; 45.75]	2.2%
	Nelissen et al 2010	22	49	+	44.90	[30.67; 59.77]	2.2%
	Osti et al 2015	12	55		21.82	[11.81; 35.01]	2.2%
	Ruangsomboon et al 2017	2	50		4.00	[ 0.49; 13.71]	1.5%
	Saragaglia et al 2011	25	124		20.16	[13.49; 28.31]	2.3%
	Song et al 2010	14	90		15.56	[8.77; 24.72]	2.2%
	Villate et al 2015	5	69		7.25	[2.39; 16.11]	1.9%
	Woodacre et al 2016	28	115		24.35	[16.83; 33.23]	2.3%
	Schroter et al 2013	(	32		21.88	[9.28; 39.97]	2.0%
	Hagnpanan et al 2021	2	46		4.35	[0.53; 14.84]	1.4%
	Arrage et al 2020	10	180		0.00	[2.70; 9.98]	2.2%
	Urrego et al 2020	6	55		10.91	[4.11; 22.25]	2.0%
	lurkmen et al 2014	22	220		0.00	[0.00; 8.00]	0.7%
	Sawagushi at al 2020	33 27	339		9.73	[0.00, 13.40]	2.4%
	Sawaguchi et al 2020	31	110		51.50	[23.13, 40.34]	2.3%
		0	120		0.00 5 1 2	[2.00, 12.41]	2.170
	Kim of al 2022	2	122		1.64	[0.03, 17.32]	1.4/0
	Tabrizi at al 2013	2	16		18 75	[4.05:45.65]	1.5%
	Lanrade et al 2012	5	47		10.75	[ 3 55: 23 10]	1.0%
	Snahn et al 2006	29	85		34 12	[24 18: 45 20]	2.3%
	lacono et al 2020	20	75		2 67	[0.32.9.30]	1.5%
	Zaki et al 2009	3	50		6.00	[ 1.25: 16.55]	1.7%
	Random effects model	Ŭ	4551		12.83	[10.03: 16.27]	92.0%
	Heterogeneity: $I^2 = 88\%$ , $\tau^2 =$	0.7516				[]	, -
P	(	4 4 4					
D	cevelle et el 2019	tant cart	nage p	rocedure	25.00	[0 77: 46 74]	1.00/
	Cavello et al 2018	0	24	-	25.00	[9.77,40.71]	1.9%
	Forruzzi et al 2021	2	10		11 11	[0.00, 3.09]	1 /0/
	Ferruzzi et al 2014	2	10		11.11	[1.30, 34.7]	1.4%
	Schuster et al 2014	2	Q1		6.50	[2.46.13.90]	2.0%
	Liu et al 2020	0	28		0.09	[0.00.12.34]	0.7%
	Random effects model	0	272		8.23	[ 3.40: 18.61]	8.0%
	Heterogeneity: $I^2 = 61\%$ , $\tau^2 =$	0.7389	-14		0.20	[ 0.40, 10.01]	0.070
	Dandom offects mod-l		4000		40.00	[ 0 70, 4E EO]	100.00/
	Heterogeneity: $I^2 = 87\%$ . $\tau^2 =$	0.7520	4823		12.39	[ 9.78; 15.58]	100.0%
	Test for subgroup differences	$\chi_1^2 = 0.9$	9, df = 1	(p = 0.32)0 10 20 30 40 50	)		

Figure 7. Forest plots of overall complication rates for (A) isolated high tibial osteotomy (HTO) and (B) HTO with concomitant cartilage repair.



Figure 8. Forest plot for return to work after high tibial osteotomy (HTO) after isolated HTO. MRAW, raw or untransformed mean.

arthroplasty. A previous meta-analysis by Kim et  $al^{51}$  reported a 95.1% survival rate (95% CI, 93.1%-97.1%) at 5 years postoperatively, which is comparable with that of the current study.

Other options available to patients with medial compartment KOA are a TKA or UKA. Consensus has yet to be determined whether an HTO or a UKA is preferable for this group of patients. A registry study by Di Martino et al<sup>18</sup> found a 92.6% survival rate for UKA, slightly lower but still comparable with the HTO survival rate in the present study at 5 years postoperatively. On the other hand, a propensity score-matched study by Jin et al<sup>45</sup> found that UKA had superior survival rates at 10-year follow up. A meta-analysis by Huang et al<sup>41</sup> found no significant differences between HTO and UKA with respect to conversion to TKA. The current literature does not definitively favor one over the other, and so the choice should take into consideration patient preferences and lifestyle factors. Huang et al and Santoso and Wu74 suggested that UKA was more appropriate for older patients, while HTO provided a better performance of physical activity for younger patients, due to a shorter rehabilitation period and quicker functional recovery. Finally, a TKA is known to have the highest survival of all options; however, not only are patients aged <55 years more likely to outlive their prosthesis and require revision surgery, but their higher activity level predisposes the implant to early failure.<sup>10</sup> Hence, a TKA may not be such a suitable alternative in this patient group.

Given that HTOs are commonly performed in a relatively younger population, it was important to assess the survival of HTOs across different age groups. This is a vital clinical point that will aid further personalizing of the surgeon-patient conversation. Interestingly, we found with the exception of patients who underwent HTO before the age of 40 years, the HTO survival was proportional to age: the highest rate of conversion to TKA was in the 40 to 49 year group, with rates of 14%, approximately double that of the 50 to 59 year group. The 60 to 69 year group saw lower rates of conversion at 2.3%. Indeed, this is likely due to progression of medial compartment osteoarthritis in the more physically active, younger demographic (older patients are documented to have reduced physical activity<sup>64</sup>), which places more strain on the arthritic knee. Presently, the literature is inconclusive on the effect of age on

HTO survival; the registry study by Niinimäki et al<sup>69</sup> suggested that older age indicated worse HTO survivorship, and other studies have deemed younger age as a predictor of HTO survival.<sup>42,48</sup> However, it is worth noting that the latter studies defined failure as also including revision HTO or looked at early conversion to TKA—these are more indicative of patients' ability to achieve quick and full postoperative recovery, or complications of HTO, rather than the potential of limiting the progression of osteoarthritic changes that our study sought to highlight. Taken together, we believe our data yield an important adjunctive point in clinical discussion with patients, to aid reiteration that a joint-preserving surgery such as MOWHTO is not a substitute for joint replacement, but rather delays its necessity.

For patients with poor outcomes or progression of osteoarthritis, the time to TKA reported in the present study was comparable with those in previous studies, such as 8.1 years by Abdelaal et al<sup>1</sup> and 7.3 years by Haddad and Bentley.<sup>31</sup>

With regard to complications of HTO, the prominent ones related to the HTO procedure are intraoperative fractures (particularly of the lateral cortex), nonunion, and postoperative infections. Our study found that the rates of occurrence of these complications were all extremely low, consistent with previous findings; Miltenberg et al<sup>66</sup> in their 2024 systematic review found a 1 in 11 chance of lateral cortex fracture intraoperatively, along with 1.9% risk of nonunion and 2.9% risk of infection. Even the overall complication rates found by our study—between 10% and 15%—is within what is known and currently accepted in the orthopaedic community in relation to HTOs.<sup>66</sup>

Evidence has emerged that concomitant cartilage repair procedures may be effective in symptomatic pain relief.<sup>16,25,47,53,61,100</sup> Yet, other studies have also shown that degenerated cartilage could be completely regenerated in just 2 years after isolated HTO.<sup>46</sup> Hence, in practice there is no established consensus on the benefits of these procedures on long-term outcomes. Our study included studies that combined HTO with ACI, MSC, OCA, MFX, or abrasion arthroplasty and found that on the whole, concomitant cartilage procedures did not significantly improve survival outcomes. A previous systematic review of 839 knees found that concomitant procedures delayed conversion to UKA or TKA and reduced odds of failure; however, that review only included HTOs combined with either ACI or OCA.<sup>15</sup> Another review by Lee et al<sup>57</sup> suggested that concomitant procedures (included were ACI, MFX, abrasion arthroplasty, and MSC) had little benefit on clinical outcomes. This discrepancy among studies suggests that different concomitant procedures have varying degrees of benefit. HTO with ACI has consistently shown benefit in outcomes across several studies,<sup>5,57,72</sup> and MSC augmentation for HTO was suggested in a meta-analysis by Tan et al<sup>87</sup> to modestly improve functional outcomes, although the impact on survival outcomes was not quantified. There are few studies comparing HTO with OCA to isolated HTO, so no conclusions can be drawn at present. MFX and abrasion arthroplasty, on the other hand, have been shown to have no significant improvement on HTO survival or clinical outcomes.<sup>3,58,96,100</sup> Although studies on survival outcomes relating to HTO with concomitant cartilage repair procedures are limited, the establishment of nonsignificant clinical improvement would likely correspond to nonsuperior survival outcomes, as poor clinical outcomes has been suggested to be a predictive factor for the need for conversion to TKA.83

In our meta-analysis, 10 of the 79 patients who underwent HTO with abrasion arthroplasty converted to TKA before the >10-year follow-up time frame, and that number was 15 of 124 in patients who underwent HTO with MFX. Comparatively, only 4 of 65 patients who underwent HTO with ACI, 0 of 117 of patients with combined HTO and MSC, and 3 of 45 of patients with combined HTO and OCA converted to TKA. The single-arm nature of this meta-analysis means there was significant disparity in sample size between the isolated HTO and the individual concomitant repair groups, compromising generalizability of results should comparisons be made between the groups. Nonetheless, the raw proportions and pooled rates of conversion suggest the varying effectiveness of each individual cartilage procedure in affecting survival outcomes, and that likely is the reason for the nonsignificant general finding for rates of conversion to TKA in the overall concomitant repair group. Nonetheless, our study underscores the need for larger, well-balanced cohorts to further investigate and validate any observed trends in survival outcomes associated with different procedural variations in HTO.

#### Strengths and Limitations

There are several hypothesized prognostic factors in the literature that affect the survival rate after HTO, including BMI, osteoarthritis severity, age, degree of correction, and postoperative weightbearing protocol.<sup>30,55,98,100</sup> In the present study, the methodological quality meant that we were unable to ascertain the significance of all of these prognostic factors. However, care was taken to ensure that all of the included studies had groups that were comparable at baseline in relation to these prognostic factors, the study design, and even the bias of each study. Heterogeneity in study design and bias in studies are other factors that affected the robustness of the present study, and so further subgrouping by study design and sensitivity analyses for studies that had moderate risk of bias were performed. Results indicated that the studies were comparable, and hence the studies were included in our review. Publication bias was also assessed to be low given the symmetry of funnel plots.

The current review also has several limitations. First, we were unable to reach conclusions on the effect of specific cartilage procedures on overall outcomes, and the associations between the isolated HTO and HTO with concomitant cartilage repair procedure group should be interpreted with caution given the relatively smaller sample size in the latter group compared with the former. Second, there was potential heterogeneity across studies. High or moderate  $I^2$  values were observed across all outcomes due to inherent properties of  $I^2$  values in single-arm meta-analysis, making it difficult to quantify betweenstudy heterogeneity. Last, we were unable to confirm the significance of hypothesized prognostic factors on survival outcomes. This was due to the similarity in patient demographics within the studies. Although this prevented us from ascertaining prognostic factors, it helped us ascertain that those are not sources of confounding and thus assess heterogeneity more comprehensively.

#### CONCLUSION

Rates of conversion to TKA and complications were found to be low and acceptable, although survival rates decreased with time. Concomitant cartilage procedures as a whole did not significantly improve survivorship; however, more high-quality studies are warranted to determine the impact of individual concomitant cartilage repair procedures, given that the sample sizes of individual, specific cartilage repair types were too small for meaningful comparison. The provision of survivorship of HTOs at various postoperative time points gives both clinicians and patients important discussion points in selection of surgical options for KOA in younger populations, while answering the question on effectiveness of concomitant cartilage repair procedures, which is becoming increasingly popular, albeit with limited literature.

Supplemental Material for this article is available at https://journals.sagepub.com/doi/full/10.1177/23259671241310963#supplementary-materials.

#### REFERENCES

- Abdelaal AM, Khalifa AA. Total knee arthroplasty post-high tibial osteotomy, results of an early experience from a North African arthroplasty unit, and a comprehensive review of the literature. *J Orthop Surg Res*. 2023;18:705. doi:10.1186/s13018-023-04199-1
- Agarwalla A, Christian DR, Liu JN, et al. Return to work following isolated opening wedge high tibial osteotomy. *Cartilage*. 2021;12(4): 468-474. doi:10.1177/1947603519852417
- Akizuki S, Yasukawa Y, Takizawa T. Does arthroscopic abrasion arthroplasty promote cartilage regeneration in osteoarthritic knees with eburnation? A prospective study of high tibial osteotomy with

abrasion arthroplasty versus high tibial osteotomy alone. Arthroscopy. 1997;13(1):9-17. doi:10.1016/s0749-8063(97)90204-8

- Asik M, Sen C, Kilic B, Goksan SB, Ciftci F, Taser OF. High tibial osteotomy with Puddu plate for the treatment of varus gonarthrosis. *Knee Surg Sports Traumatol Arthrosc.* 2006;14:948-954. doi:10. 1007/s00167-006-0074-1
- Bentley G, Bhamra JS, Gikas PD, et al. Repair of osteochondral defects in joints—how to achieve success. *Injury*. 2013;44(suppl 1):S3-S10. doi:10.1016/S0020-1383(13)70003-2
- Bhattacharyya R, Alloush A, Wilson C, et al. Survivorship of high tibial osteotomy in the treatment of osteoarthritis of the knee: a retrospective cohort study with fourteen years' follow-up. *Int Orthop*. 2023;47(7):1765-1770. doi:10.1007/s00264-023-05802-0
- Birmingham TB, Giffin JR, Chesworth BM, et al. Medial opening wedge high tibial osteotomy: a prospective cohort study of gait, radiographic, and patient-reported outcomes. *Arthritis Rheum*. 2009;61(5):648-657. doi:10.1002/art.24466
- Bode L, Eberbach H, Brenner AS, et al. 10-year survival rates after high tibial osteotomy using angular stable internal plate fixation: case series with subgroup analysis of outcomes after combined autologous chondrocyte implantation and high tibial osteotomy. *Orthop J Sports Med*. 2022;10(2):23259671221078003.
- Brosset T, Pasquier G, Migaud H, Gougeon F. Opening wedge high tibial osteotomy performed without filling the defect but with locking plate fixation (TomoFix and early weight-bearing: prospective evaluation of bone union, precision and maintenance of correction in 51 cases. Orthop Traumatol Surg Res. 2011;97(7):705-711. doi:10. 1016/j.otsr.2011.06.011
- Camus T, Long WJ. Total knee arthroplasty in young patients: factors predictive of aseptic failure in the 2nd-4th decade. *J Orthop*. 2017;15(1):28-31. doi:10.1016/j.jor.2017.11.004
- Cavallo M, Sayyed-Hosseinian SH, Parma A, Buda R, Mosca M, Giannini S. Combination of high tibial osteotomy and autologous bone marrow derived cell implantation in early osteoarthritis of knee: a preliminary study. *Arch Bone Jt Surg.* 2018;6(2):112-118.
- Chung Y-W, Yang H-Y, Kang S-J, Song E-K, Seon J-K. Allogeneic umbilical cord blood-derived mesenchymal stem cells combined with high tibial osteotomy: a retrospective study on safety and early results. *Int Orthop*. 2021;45(2):481-488. doi:10.1007/s00264-020-04852-y
- Coakley A, McNicholas M, Biant L, Tawy G. A systematic review of outcomes of high tibial osteotomy for the valgus knee. *Knee*. 2023;40:97-110. doi:10.1016/j.knee.2022.11.007
- Corbeil V, Synnott PA, Al-Shakfa F, Lavoie F. Medial opening wedge proximal tibial osteotomy: lessons learned from a series of 175 consecutive cases. *Cartilage*. 2021;13(1)(suppl):1265S-1279S. doi:10. 1177/19476035211011503
- Darees M, Putman S, Brosset T, Roumazeille T, Pasquier G, Migaud H. Opening-wedge high tibial osteotomy performed with locking plate fixation (TomoFix) and early weight-bearing but without filling the defect. A concise follow-up note of 48 cases at 10 years' follow-up. *Orthop Traumatol Surg Res.* 2018;104(4):477-480. doi:10. 1016/j.otsr.2017.12.021
- de Windt TS, Vonk LA, Brittberg M, Saris DB. Treatment and prevention of (early) osteoarthritis using articular cartilage repair-fact or fiction? A systematic review. *Cartilage*. 2013;4(3)(suppl):5S-12S. doi:10. 1177/1947603513486560
- DeMeo PJ, Johnson EM, Chiang PP, Flamm AM, Miller MC. Midterm follow-up of opening-wedge high tibial osteotomy. *Am J Sports Med.* 2010;38(10):2077-2084. doi:10.1177/0363546510371371
- Di Martino A, Bordini B, Barile F, Ancarani C, Digennaro V, Faldini C. Unicompartmental knee arthroplasty has higher revisions than total knee arthroplasty at long term follow-up: a registry study on 6453 prostheses. *Knee Surg Sports Traumatol Arthrosc.* 2021;29:3323-3329. doi:10.1007/s00167-020-06184-1
- Duivenvoorden T, Brouwer RW, Baan A, et al. Comparison of closing-wedge and opening-wedge high tibial osteotomy for medial compartment osteoarthritis of the knee: a randomized controlled trial

with a six-year follow-up. *J Bone Joint Surg Am*. 2014;96(17):1425-1432. doi:10.2106/JBJS.M.00786

- Duivenvoorden T, van Diggele P, Reijman M, et al. Adverse events and survival after closing- and opening-wedge high tibial osteotomy: a comparative study of 412 patients. *Knee Surg Sports Traumatol Arthrosc.* 2017;25(3):895-901. doi:10.1007/s00167-015-3644-2
- El-Assal MA, Khalifa YE, Abdel-Hamid MM, Said HG, Bakr HM. Opening-wedge high tibial osteotomy without bone graft. *Knee Surg Sports Traumatol Arthrosc.* 2010;18(7):961-966. doi:10.1007/ s00167-010-1104-6
- Esenkaya I, Misirlioglu M, Kelestemur MH, Elmali N, Fadillioglu E. Biomechanical evaluation of different fixation plates in medial opening upper tibial osteotomy. *Knee*. 2007;14(1):46-50. doi:10.1016/j. knee.2006.10.003
- Ferruzzi A, Buda R, Cavallo M, Timoncini A, Natali S, Giannini S. Cartilage repair procedures associated with high tibial osteotomy in varus knees: clinical results at 11 years' follow-up. *Knee*. 2014;21(2):445-450. doi:10.1016/j.knee.2013.11.013
- Floerkemeier S, Stäubli AE, Schroeter S, Goldhahn S, Lobenhoffer P. Outcome after high tibial open-wedge osteotomy: a retrospective evaluation of 533 patients. *Knee Surg Sports Traumatol Arthrosc*. 2013;21(1):170-180. doi:10.1007/s00167-012-2087-2
- Franceschi F, Longo UG, Ruzzini L, Marinozzi A, Maffulli N, Denaro V. Simultaneous arthroscopic implantation of autologous chondrocytes and high tibial osteotomy for tibial chondral defects in the varus knee. *Knee*. 2008;15:309-313.
- Gaasbeek RD, Nicolaas L, Rijnberg WJ, van Loon CJ, van Kampen A. Correction accuracy and collateral laxity in open versus closed wedge high tibial osteotomy. A one-year randomised controlled study. *Int Orthop.* 2010;34(2):201-207. doi:10.1007/s00264-009-0861-7
- 27. Gao F, Yang X, Wang C, et al. Comparison of clinical and radiological outcomes between calibratable patient-specific instrumentation and conventional operation for medial open-wedge high tibial osteotomy: a randomized controlled trial. *Biomed Res Int.* 2022;2022:1378042. doi:10.1155/2022/1378042
- Giuseffi SA, Replogle WH, Shelton WR. Opening-wedge high tibial osteotomy: review of 100 consecutive cases. *Arthroscopy*. 2015;31(11):2128-2137. doi:10.1016/j.arthro.2015.04.097
- Goshima K, Sawaguchi T, Sakagoshi D, Shigemoto K, Hatsuchi Y, Akahane M. Age does not affect the clinical and radiological outcomes after open-wedge high tibial osteotomy. *Knee Surg Sports Traumatol Arthrosc.* 2015;25(3):918-923.
- Guarino A, Farinelli L, Iacono V, et al. Long-term survival and predictors of failure of opening wedge high tibial osteotomy. *Orthop Surg.* 2023;15:1002-1007. doi:10.1111/os.13674
- Haddad FS, Bentley G. Total knee arthroplasty after high tibial osteotomy: a medium-term review. J Arthroplasty. 2000;15(5):597-603. doi:10.1054/arth.2000.6621
- 32. Haghpanah B, Kaseb MH, Espandar R, Mortazavi SMJ. No difference in union and recurrence rate between iliac crest autograft versus allograft following medial opening wedge high tibial osteotomy: a randomized controlled trial. *Knee Surg Sports Traumatol Arthrosc*. 2021;29(10):3375-3381. doi:10.1007/s00167-020-06240-w
- Han SB, In Y, Oh KJ, Song KY, Yun ST, Jang KM. Complications associated with medial opening-wedge high tibial osteotomy using a locking plate: a multicenter study. *J Arthroplasty*. 2019;34(3):439-445. doi:10.1016/j.arth.2018.11.009
- 34. Hantes ME, Natsaridis P, Koutalos AA, Ono Y, Doxariotis N, Malizos KN. Satisfactory functional and radiological outcomes can be expected in young patients under 45 years old after open wedge high tibial osteotomy in a long-term follow-up. *Knee Surg Sports Traumatol Arthrosc.* 2018;26(11):3199-3205. doi:10.1007/s00167-017-4816-z
- 35. Herbst M, Ahrend MD, Grünwald L, Fischer C, Schröter S, Ihle C. Overweight patients benefit from high tibial osteotomy to the same extent as patients with normal weights but show inferior mid-term results. *Knee Surg Sports Traumatol Arthrosc.* 2022;30(3):907-917.

- Hernigou P, Ma W. Open wedge tibial osteotomy with acrylic bone cement as bone substitute. *Knee*. 2001;8(2):103-110. doi:10.1016/ s0968-0160(00)00061-2
- Hernigou P, Queinnec S, Picard L, et al. Safety of a novel high tibial osteotomy locked plate fixation for immediate full weight-bearing: a case-control study. *Int Orthop.* 2013;37(12):2377-2384. doi:10. 1007/s00264-013-2066-3
- Hernigou P, Giber D, Dubory A, Auregan JC. Safety of simultaneous versus staged bilateral opening-wedge high tibial osteotomy with locked plate and immediate weight bearing. *Int Orthop.* 2020;44(1):109-117. doi:10.1007/s00264-019-04385-z
- Hoell S, Suttmoeller J, Stoll V, Fuchs S, Gosheger G. The high tibial osteotomy, open versus closed wedge, a comparison of methods in 108 patients. Arch Orthop Trauma Surg. 2005;125(9):638-643. doi:10.1007/s00402-005-0004-6
- Hsu AC, Tirico LEP, Lin AG, Pulido PA, Bugbee WD. Osteochondral allograft transplantation and opening wedge tibial osteotomy: clinical results of a combined single procedure. *Cartilage*. 2018;9(3):248-254. doi:10.1177/1947603517710307
- Huang L, Xu Y, Wei L, et al. Unicompartmental knee arthroplasty is superior to high tibial osteotomy for the treatment of medial unicompartmental osteoarthritis: a systematic review and meta-analysis. *Medicine (Baltimore)*. 2022;101(30):e29576. doi:10.1097/MD. 000000000029576
- Hui C, Salmon LJ, Kok A, Williams HA, et al. Long-term survival of high tibial osteotomy for medial compartment osteoarthritis of the knee. *Am J Sports Med.* 2011;39(1):64-70. doi:10.1177/ 0363546510377445
- Iacono V, De Franco C, Auletta N, et al. New plates with polyaxial locking system and PSI technique in medial open wedge high tibial osteotomy: preliminary results. J Biol Regul Homeost Agents. 2020;34(3)(suppl 2):111-113.
- Jin C, Song EK, Santoso A, Ingale PS, Choi IS, Seon JK. Survival and risk factor analysis of medial open wedge high tibial osteotomy for unicompartment knee osteoarthritis. *Arthroscopy*. 2020;36(2):535-543. doi:10.1016/j.arthro.2019.08.040
- Jin QH, Lee W-G, Song E-K, Jin C, Seon J-K. Comparison of longterm survival analysis between open-wedge high tibial osteotomy and unicompartmental knee arthroplasty. *J Arthroplasty*. 2021;36(5):1562-1567.e1. doi:10.1016/j.arth.2020.11.008
- Jung WH, Takeuchi R, Chun CW, et al. Second-look arthroscopic assessment of cartilage regeneration after medial opening-wedge high tibial osteotomy. *Arthroscopy*. 2014;30(1):72-79. doi:10.1016/j. arthro.2013.10.008
- Kahlenberg CA, Nwachukwu BU, Hamid KS, Steinhaus ME, Williams RJ. Analysis of outcomes for high tibial osteotomies performed with cartilage restoration techniques. *Arthroscopy*. 2017;33(2):486-492. doi:10.1016/j.arthro.2016.08.010
- Keenan OJF, Clement ND, Nutton R, Keating JF. Older age and female gender are independent predictors of early conversion to total knee arthroplasty after high tibial osteotomy. *Knee*. 2019;26(1):207-212. doi:10.1016/j.knee.2018.11.008
- 49. Khakha RS, Bin Abd Razak HR, Kley K, van Heerwaarden R, Wilson AJ. Role of high tibial osteotomy in medial compartment osteoarthritis of the knee: indications, surgical technique and outcomes. *J Clin Orthop Trauma*. 2021;23:101618. doi:10.1016/j.jcot.2021.101618
- Khan M, Adili A, Winemaker M, Bhandari M. Management of osteoarthritis of the knee in younger patients. *CMAJ*. 2018;190(3):e72-e79. doi:10.1503/cmaj.170696
- Kim JH, Kim HJ, Lee DH. Survival of opening versus closing wedge high tibial osteotomy: a meta-analysis. *Sci Rep.* 2017;7(1):7296. doi:10.1038/s41598-017-07856-8
- 52. Kim KI, Kim GB, Kim HJ, Lee SH, Yoon WK. Extra-articular lateral hHinge fracture does not affect the outcomes in medial open-wedge high tibial osteotomy using a locked plate system. *Arthroscopy*. 2018;34(12):3246-3255. doi:10.1016/j.arthro.2018.07.022
- 53. Koh YG, Kwon OR, Kim YS, Choi YJ. Comparative outcomes of open-wedge high tibial osteotomy with platelet-rich plasma alone

or in combination with mesenchymal stem cell treatment: a prospective study. *Arthroscopy*. 2014;30:1453-1460.

- Kuwashima U. High tibial osteotomy: the past, present, and future. J Joint Surg Res. 2023;1(1):103-107. doi:10.1016/j.jjoisr.2023.03.001
- 55. Lansdaal JR, Mouton T, Wascher DC, et al. Early weight bearing versus delayed weight bearing in medial opening wedge high tibial osteotomy: a randomized controlled trial. *Knee Surg Sports Traumatol Arthrosc.* 2017;25(12):3670-3678. doi:10.1007/s00167-016-4225-8
- LaPrade RF, Spiridonov SI, Nystrom LM, Jansson KS. Prospective outcomes of young and middle-aged adults with medial compartment osteoarthritis treated with a proximal tibial opening wedge osteotomy. *Arthroscopy*. 2012;28(3):354-364. doi:10.1016/j.arthro. 2011.08.310
- Lee OS, Ahn S, Ahn JH, Teo SH, Lee YS. Effectiveness of concurrent procedures during high tibial osteotomy for medial compartment osteoarthritis: a systematic review and meta-analysis. *Arch Orthop Trauma Surg.* 2018;138(2):227-236. doi:10.1007/s00402-017-2826-4
- Lee O-S, Lee SH, Mok SJ, Lee YS. Comparison of the regeneration of cartilage and the clinical outcomes after the open wedge high tibial osteotomy with or without microfracture: a retrospective case control study. *BMC Musculoskelet Disord*. 2019;20:267. doi:10.1186/s12891-019-2607-z
- Liu JN, Agarwalla A, Christian DR, et al. Return to sport following high tibial osteotomy with concomitant osteochondral allograft transplantation. *Am J Sports Med*. 2020;48(8):1945-1952. doi:10.1177/03635 46520920626
- Maffulli N, Loppini M, Longo UG, Denaro V, Oliva F. Bovine xenograft locking Puddu plate versus tricalcium phosphate spacer non-locking Puddu plate in opening-wedge high tibial osteotomy: a prospective double-cohort study. *Int Orthop.* 2013;37(5):819-826. doi:10.1007/ s00264-013-1817-5
- Matsunaga D, Akizuki S, Takizawa T, Yamazaki I, Kuraishi J. Repair of articular cartilage and clinical outcome after osteotomy with microfracture or abrasion arthroplasty for medial gonarthrosis. *Knee*. 2007;14(6):465-471. doi:10.1016/j.knee.2007.06.008
- Mccormack DJ, Puttock D, Godsiff SP. Medial compartment osteoarthritis of the knee: a review of surgical options. *EFORT Open Rev.* 2021;6:113-117. doi:10.1302/2058-5241.6.200102
- Miettinen S, Nyländen H, Jalkanen J, Miettinen H, Kröger H, Joukainen A. Midterm follow-up results of two different types of implants in opening wedge high tibia osteotomy. *Knee*. 2021;31:11-21. doi:10. 1016/j.knee.2021.05.006
- Milanović Z, Pantelić S, Trajković N, Sporiš G, Kostić R, James N. Age-related decrease in physical activity and functional fitness among elderly men and women. *Clin Interv Aging*. 2013;8:549-556. doi:10.2147/CIA.S44112
- Miller BS, Downie B, McDonough EB, Wojtys EM. Complications after medial opening wedge high tibial osteotomy. *Arthroscopy*. 2009;25(6):639-646. doi:10.1016/j.arthro.2008.12.020
- Miltenberg B, Puzzitiello RN, Ruelos VCB, et al. Incidence of complications and revision surgery after high tibial osteotomy: a systematic review. *Am J Sports Med.* 2024;52(1):258-268. doi:10.1177/036354 65221142868
- Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: the PRISMA statement. *PLoS Med.* 2009;6(7):e1000097. doi:10.1371/ journal.pmed.1000097
- Nelissen EM, van Langelaan EJ, Nelissen RG. Stability of medial opening wedge high tibial osteotomy: a failure analysis. *Int Orthop.* 2010;34(2):217-223. doi:10.1007/s00264-009-0723-3
- Niinimäki TT, Eskelinen A, Mann BS, Junnila M, Ohtonen P, Leppilahti J. Survivorship of high tibial osteotomy in the treatment of osteoarthritis of the knee. *J Bone Joint Surg Br.* 2012;94(11):1517-1521. doi:10.1302/0301-620X.94B11.29601
- Orrego M, Besa P, Orrego F, et al. Medial opening wedge high tibial osteotomy: more than ten years of experience with Puddu plate technique supports its indication. *Int Orthop*. 2020;44(10):2021-2026. doi:10.1007/s00264-020-04614-w

- Osti M, Gohm A, Schlick B, Benedetto KP. Complication rate following high tibial open-wedge osteotomy with spacer plates for incipient osteoarthritis of the knee with varus malalignment. *Knee Surg Sports Traumatol Arthrosc.* 2015;23(7):1943-1948. doi:10.1007/s00167-013-2757-8
- Perera JR, Gikas PD, Bentley G. The present state of treatments for articular cartilage defects in the knee. Ann R Coll Surg Engl. 2012;94(6):381-387. doi:10.1308/003588412X13171221592573
- Ruangsomboon P, Chareancholvanich K, Harnroongroj T, Pornrattanamaneewong C. Survivorship of medial opening wedge high tibial osteotomy in the elderly: two to ten years of follow up. *Int Orthop.* 2017;41(10):2045-2052. doi:10.1007/s00264-017-3517-z
- Santoso MB, Wu L. Unicompartmental knee arthroplasty, is it superior to high tibial osteotomy in treating unicompartmental osteoarthritis? A meta-analysis and systemic review. J Orthop Surg Res. 2017;12(1):50. doi:10.1186/s13018-017-0552-9
- Saragaglia D, Blaysat M, Inman D, Mercier N. Outcome of opening wedge high tibial osteotomy augmented with a Biosorb wedge and fixed with a plate and screws in 124 patients with a mean of ten years follow-up. *Int Orthop.* 2011;35(8):1151-1156. doi:10.1007/s00264-010-1102-9
- 76. Sawaguchi T, Takeuchi R, Nakamura R, et al. Outcome after treatment of osteoarthritis with open-wedge high-tibial osteotomy with a plate: 2-year results of a Japanese cohort study. J Orthop Surg (Hong Kong). 2020;28(1):2309499019887997.
- Schröter S, Mueller J, van Heerwaarden R, Lobenhoffer P, Stöckle U, Albrecht D. Return to work and clinical outcome after open wedge HTO. *Knee Surg Sports Traumatol Arthrosc.* 2013;21(1):213-219. doi:10.1007/s00167-012-2129-9
- Schuster P, Geßlein M, Schlumberger M, et al. Ten-year results of medial open-wedge high tibial osteotomy and chondral resurfacing in severe medial osteoarthritis and varus malalignment. *Am J Sports Med.* 2018;46(6):1362-1370. doi:10.1177/0363546518758016
- Schuster P, Schulz M, Mayer P, Schlumberger M, Immendoerfer M, Richter J. Open-wedge high tibial osteotomy and combined abrasion/microfracture in severe medial osteoarthritis and varus malalignment: 5-year results and arthroscopic findings after 2 years. *Arthroscopy*. 2015;31(7):1279-1288. doi:10.1016/j.arthro.2015.02. 010
- Song EK, Seon JK, Park SJ, Jeong MS. The complications of high tibial osteotomy: closing- versus opening-wedge methods. *J Bone Joint Surg Br.* 2010;92(9):1245-1252. doi:10.1302/0301-620X.92B9. 23660
- Song SJ, Bae DK, Kim KI, Lee CH. Conversion total knee arthroplasty after failed high tibial osteotomy. *Knee Surg Relat Res.* 2016;28(2): 89-98. doi:10.5792/ksrr.2016.28.2.89
- Spahn G. Complications in high tibial (medial opening wedge) osteotomy. Arch Orthop Trauma Surg. 2004;124(10):649-653. doi:10.1007/ s00402-003-0588-7
- Spahn G, Kirschbaum S, Kahl E. Factors that influence high tibial osteotomy results in patients with medial gonarthritis: a score to predict the results. Osteoarthritis Cartilage. 2006;14(2):190-195. doi:10. 1016/j.joca.2005.08.013
- Sterett WI, Steadman JR, Huang MJ, Matheny LM, Briggs KK. Chondral resurfacing and high tibial osteotomy in the varus knee: survivorship analysis. *Am J Sports Med.* 2010;38(7):1420-1424. doi:10.1177/ 0363546509360403
- Sterne JAC, Higgins JPT, Elbers RG, Reeves BC; Development Group for ROBINS-I. Risk Of Bias In Non-randomized Studies of Interventions (ROBINS-I): detailed guidance. Updated October 12, 2016. Accessed September 1, 2023. https://www.riskofbias.info/welcome/home/original-2016-version-of-robins-i/robins-i-detailed-guidance-2016
- Tabrizi A, Soleimanpour J, Sadighi A, Zare AJ. A short term follow up comparison of genu varum corrective surgery using open and closed wedge high tibial osteotomy. *Malays Orthop J*. 2013;7(1):7-12. doi:10.5704/MOJ.1303.009

- Tan SHS, Kwan YT, Neo WJ, et al. Outcomes of high tibial osteotomy with versus without mesenchymal stem cell augmentation: a systematic review and meta-analysis. *Orthop J Sports Med.* 2021;9(6): 23259671211014840.
- Türkmen F, Sever C, Kacıra BK, Demirayak M, Acar MA, Toker S. Medial opening-wedge high tibial osteotomy fixation with short plate without any graft, synthetic material or spacer. *Eur J Orthop Surg Traumatol*. 2014;24(8):1549-1555. doi:10.1007/s00590-014-1417-0
- Vaishya R, Bijukchhe AR, Agarwal AK, Vijay V. A critical appraisal of medial open wedge high tibial osteotomy for knee osteoarthritis. *J Clin Orthop Trauma*. 2018;9(4):300-306. doi:10.1016/j.jcot.2018. 02.004
- 90. van Egmond N, van Grinsven S, van Loon CJ, Gaasbeek RD, van Kampen A. Better clinical results after closed- compared to openwedge high tibial osteotomy in patients with medial knee osteoarthritis and varus leg alignment. *Knee Surg Sports Traumatol Arthrosc.* 2016;24(1):34-41. doi:10.1007/s00167-014-3303-z
- van Wulfften Palthe AFY, Clement ND, Temmerman OPP, Burger BJ. Survival and functional outcome of high tibial osteotomy for medial knee osteoarthritis: a 10-20-year cohort study. *Eur J Orthop Surg Traumatol*. 2018;28(7):1381-1389. doi:10.1007/s00590-018-2199-6
- 92. Villatte G, Erivan R, Fournier PL, et al. Opening-wedge high tibial osteotomy with a secure bone allograft (Osteopure) and locked plate fixation: retrospective clinical and radiological evaluation of 69 knees after 7.5years follow-up. Orthop Traumatol Surg Res. 2015; 101(8):953-957. doi:10.1016/j.otsr.2015.09.023
- Vincent KR, Conrad BP, Fregly BJ, Vincent HK. The pathophysiology of osteoarthritis: a mechanical perspective on the knee joint. *PM R*. 2012;4(9)(suppl):S3-S9. doi:10.1016/j.pmrj.2012.01.020
- Viskontas DG, MacLeod MD, Sanders DW. High tibial osteotomy with use of the Taylor Spatial Frame external fixator for osteoarthritis of the knee. *Can J Surg*. 2006;49(4):245-250.
- 95. Wan X, Wang W, Liu J, Tong T. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. *BMC Med Res Methodol*. 2014;14:135. doi:10. 1186/1471-2288-14-135
- 96. Wong KL, Lee KB, Tai BC, Law P, Lee EH, Hui JH. Injectable cultured bone marrow-derived mesenchymal stem cells in varus knees with cartilage defects undergoing high tibial osteotomy: a prospective, randomized controlled clinical trial with 2 years' follow-up. *Arthroscopy*. 2013;29(12):2020-2028. doi:10.1016/j.arthro.2013.09.074
- Woodacre T, Ricketts M, Evans JT, et al. Complications associated with opening wedge high tibial osteotomy—a review of the literature and of 15 years of experience. *Knee*. 2016;23(2):276-282. doi:10. 1016/j.knee.2015.09.018
- Wu CY, Huang JW, Lin CH, Chih WH. Preoperative overweight and obesity do not cause inferior outcomes following open-wedge high tibial osteotomy: a retrospective cohort study of 123 patients. *PLoS One*. 2023;18(1):e0280687. doi:10.1371/journal.pone.0280687
- Wu K, Zeng J, Han L, Feng W, Lin X, Zeng Y. Effect of the amount of correction on posterior tibial slope and patellar height in open-wedge high tibial osteotomy. *J Orthop Surg.* 2021;29(3):23094990211 049571.
- 100. Yamada Y, Nakamura N, Hiramatsu K, Mitsuoka T. Abrasion arthroplasty promotes improvement of degenerated femoral trochlear cartilage after medial open wedge high tibial osteotomy. *J ISAKOS*. 2021;6(3):147-152. doi:10.1136/jisakos-2020-0
- 101. Yang HY, Cheon JH, Lee CH, Song EK, Seon JK. Effect of prior knee arthroscopy on midterm outcomes after medial openingwedge high tibial osteotomy: a propensity score-matched analysis. *Orthop J Sports Med.* 2023;11(6):23259671231175457. doi:10. 1177/23259671231175457
- 102. Zaki SH, Rae PJ. High tibial valgus osteotomy using the Tomofix plate-medium-term results in young patients. Acta Orthop Belg. 2009;75(3):360-367.

#### APPENDIX

## $\begin{array}{c} {\rm TABLE~A1}\\ {\rm Characteristics~of~the~Included~Studies}^{a} \end{array}$

Lead Author and Year	Study Design	Isolated HTO or HTO With Cartilage Repair	No. of Patients (Knees)	Male, n	Age, y <sup>b</sup>	BMI, kg/m <sup>2b</sup>	K-L Grade	Degrees of Correction <sup><math>b</math></sup>	Follow-up, mo <sup>b</sup>
Agarwalla <sup>2</sup> 2021	Retrosp	Isolated HTO	37 (37)	31	$43.4\pm7.8$	$27.3\pm3.7$	3 Gr 1 or 2; 34 Gr 3 or 4	$9.9\pm3.3$	$108\pm39.6$
Asik <sup>4</sup> 2006	Retrosp	Isolated HTO	60 (65)	13	$54\pm9.25$	NR	NR	NR	$34\pm10.5$
Bhattacharyya <sup>6</sup> 2023	Retrosp	Isolated HTO	93 (96)	71	$47.5 \pm 5$	NR	NR	NR	$107.4 \pm 42$
Birmingham <sup>7</sup> 2009	Prosp	Isolated HTO	128 (128)	102	$47.48\pm9.53$	$29.5\pm4.82$	4 Gr 1; 32 Gr 2; 41 Gr 3; 51 Gr 4	NR	$24\pm 0$
Bode <sup>8</sup> 2022	Prosp	(1) Isolated HTO	$(1) \hspace{0.1 cm} 90 \hspace{0.1 cm} (90)$	(1) 59	$(1) \ 46.64 \ \pm \ 9.87$	$(1) \ 27.75 \ \pm \ 4.64$	(1) 1.99 $\pm$ 0.62 <sup>c</sup>	$(1) \hspace{0.1 cm} 9.07 \hspace{0.1 cm} \pm \hspace{0.1 cm} 4.49$	(1) 120.8 $\pm$ 28.02
		(2) HTO $+$ ACI	(2) 47 (47)	(2) 29	(2) $39.53 \pm 8.76$	(2) $25.77 \pm 3.62$	(2) NR	(2) $7.42 \pm 4.04$	(2) $113.29 \pm 23.73$
Brosset <sup>9</sup> 2011	Prosp	Isolated HTO	51 (51)	36	$53 \pm 7.5$	_	NR	$9\pm4.36$	$24\pm0.75$
Cavallo <sup>11</sup> 2018	Prosp	HTO + MSC	24 (24)	15	$47.9 \pm 12.3$	NR	NR	NR	$44.4 \pm 17.7$
Chung <sup>12</sup> 2021	Retrosp	HTO + MSC	93 (93)	NR	$56.6 \pm 5.5$	$25.8 \pm 3.08$	All Gr 3	NR	$20.4 \pm 7.5$
Corbeil <sup>14</sup> 2021	Retrosp	Isolated HTO	76 (84)	54	$50 \pm 10.5$	$30.2 \pm 5.6$	NR	NR	NR
Darees <sup>15</sup> 2018	Retrosp	Isolated HTO	51 (51)	33	$53 \pm 7.5$	$28.9 \pm 3.5$	NR	$9 \pm 4.36$	$122.4 \pm 5$
DeMeo <sup>17</sup> 2010	Prosp	Isolated HTO	20 (20)	14	$49.4 \pm 7.75$	NR	NR	$11.1 \pm 2.75$	$99.6 \pm 11.25$
Duivenvoorden <sup>19</sup> 2014	Prosp RCT	Isolated HTO	36 (36)	24	$49.9 \pm 7.9$	$27.3 \pm 5.4$	_	$11.6 \pm 3.4$	$87.6 \pm 13.2$
Duivenvoorden <sup>20</sup> 2017	Retrosp	Isolated HTO	112 (112)	73	$48.7 \pm 10.1$	$28.5 \pm 4.5$	NR		$88.8 \pm 38.4$
El-Assal <sup>21</sup> 2010	Prosp	Isolated HTO	58 (58)	21	$47.5 \pm 10.25$	$28.5\pm0.1$	NR	$10.7 \pm 3.7$	$38 \pm 0.1$
Esenkaya <sup>22</sup> 2007	Retrosp	Isolated HTO	56 (58)	9	$52 \pm 7.5$	NR	NR	NR	$21 \pm 9.5$
Ferruzzi <sup>23</sup> 2014	Retrosp	(1) Isolated HTO	(1) 20 (20)	(1) 10	(1) 54	(1) $26 \pm 4$	(1) 12 Gr 3; 8 Gr 4	NR	(1) $106 \pm 7.75$
		(2) HTO $+$ ACI	(2) 18 (18)	(2) 12	(2) 51	(2) $28 \pm 3$	(2) 12 Gr 3; 6 Gr 4		(2) $96 \pm 5.5$
		(3)  HTO  +  MFX	(3) 18 (18)	(3) 13	(3) 53	(3) $31 \pm 5$	(3) 10 Gr 3; 6 Gr 4		(3) $92 \pm 3.75$
Floerkemeier <sup>24</sup> 2013	Retrosp	Isolated HTO	533 (533)	367	$49.3 \pm 16.5$	$27.2 \pm 4$	NR	NR	$43.2~{\pm}~6.9$
Gaasbeek <sup>26</sup> 2010	Prosp RCT	Isolated HTO	25 (25)	14	$47 \pm 8.5$	$29.7\pm4.2$	NR	$8.1\pm4.4$	$12 \pm 0$
Gao <sup>27</sup> 2022	Prosp RCT	Isolated HTO	39 (39)	16	$57.84 \pm 7.83$	$24.58 \pm 3.08$	1 Gr 1; 4 Gr 2; 11 Gr 3	$9.02 \pm 1.64$	NR
Giuseffi <sup>28</sup> 2015	Retrosp	Isolated HTO	83 (89)	62	$48.1 \pm 0.1$	NR	All Gr $\leq 3$	9.6	$48 \pm 27$
Goshima <sup>29</sup> 2015	Retrosp	Isolated HTO	60 (60)	23	$61.6\pm8.6$	$24.7 \pm 2.5$	4 Gr 1; 23 Gr 2; 22 Gr 3; 5 Gr 4	—	$51.1 \pm 21.9$
Haghpanah <sup>32</sup> 2021	Prosp RCT	Isolated HTO	46 (46)	24	$25.55 \pm 7.44$	$24.2\pm1.99$	NR	NR	$96 \pm 0$
Han <sup>33</sup> 2019	Retrosp	Isolated HTO	209 (209)	29	$56.4~\pm~5.9$	$26.5\pm3.2$	NR	NR	$NR \pm NR$
Hantes <sup>34</sup> 2018	Retrosp	Isolated HTO	20 (20)	18	$35.4\pm4$	NR	NR	$8.3\pm4.3$	$147.6~\pm~15$
$\text{Herbst}^{35}$ 2022	Prosp	Isolated HTO	85 (85)	60	$54.6~\pm~6.4$	$28.6\pm4.6$	NR	$6.9\pm3.2$	$72 \pm 0$
Hernigou <sup>36</sup> 2001	Retrosp	Isolated HTO	197(245)	78	$59\pm9.5$	$0 \pm 0$	NR	_	$120\pm2.25$
Hernigou <sup>37</sup> 2013	Retrosp	Isolated HTO	170 (170)	76	$62.9~\pm~7.5$	$23.9\pm3.8$	NR	$13.6 \pm 4.37$	$12 \pm 0$
Hernigou <sup>38</sup> 2020	Retrosp	Isolated HTO	90 (180)	NR	$61.7 \pm 4.67$	$28\pm3.33$	NR	NR	NR
Hoell <sup>39</sup> 2005	Retrosp	Isolated HTO	40 (40)	40	$46.4~\pm~8$	$30\pm5.2$	NR	NR	$22.5 \pm 6.125$
$Hsu^{40} 2018$	Retrosp	HTO + OCA	17(17)	15	$36.5 \pm 11.3$	$26.1\pm3$	NR	NR	NR
Iacono <sup>43</sup> 2020	Prosp	Isolated HTO	75 (75)	46	$45.7\pm0.01$	NR	NR	NR	$8\pm0$
Jin <sup>44</sup> 2020	Retrosp	Isolated HTO	339 (339)	91	$56~\pm~7.25$	$25.3\pm5.88$	67 Gr 1; 151 Gr 2; 109 Gr 3; 12 Gr 4	NR	$115.2~\pm~96$
Kim <sup>52</sup> 2018	Retrosp	Isolated HTO	122(122)	14	$55.96 \pm 4.99$	$25.89\pm2.6$	60 Gr 2; 49 Gr 3; 13 Gr 4	NR	$90\pm23.4$
LaPrade <sup>56</sup> 2012	Prosp	Isolated HTO	47 (47)	32	$40.5\pm8$	$28.3\pm7.05$	All Gr 1-2	NR	$43.2 \pm 20.7$
Liu <sup>59</sup> 2020	Retrosp	HTO + OCA	28 (28)	22	$28.97 \pm 7.52$	$27.92 \pm 3.87$	25 Gr 1 or 2; 3 Gr 3 or 4	$8.48\pm2.24$	$79.56 \pm 48.72$
Maffulli <sup>60</sup> 2013	Prosp	Isolated HTO	52 (52)	36	$58.75 \pm 6.6$	$29.9\pm1.8$	NR	$12.05 \pm 3.5$	$41~\pm~6.6$
Miettinen <sup>63</sup> 2021	Retrosp	Isolated HTO	241 (241)	208	$48.84 \pm 8.18$	$29.9\pm5.2$	51 Gr 1; 149 Gr 2; 41 Gr 3	$8.30\pm3.68$	$72\pm3$
Miller <sup>65</sup> 2009	Retrosp	Isolated HTO	46 (46)	34	$38.2 \pm 11.75$	NR	NR	NR	$12\pm 0$
Nelissen <sup>68</sup> 2010	Retrosp	Isolated HTO	45 (49)	29	$48\pm19.9$	NR	NR	NR	$NR \pm NR$
Orrego <sup>70</sup> 2020	Retrosp	Isolated HTO	55 (55)	37	$43.25 \pm 4.75$	NR	NR	NR	NR
Osti <sup>71</sup> 2015	Retrosp	Isolated HTO	50 (55)	33	$54.7 \pm 12.6$	$26.8\pm3.6$	NR	$3.8\pm3.3$	$60\pm16.8$
Ruangsomboon <sup>73</sup> 2017	Retrosp	Isolated HTO	50 (50)	17	$66 \pm 5$	$25.9\pm2.8$	15 Gr 2; 35 Gr 3	$10.6\pm3.6$	$72\pm36$
Saragaglia <sup>75</sup> 2011	Prosp	Isolated HTO	110 (124)	74	$53.23 \pm 10.68$	$27.1 \pm 4.37$	NR	NR	$124.68 \pm 23.76$
Sawaguchi <sup>76</sup> 2020	Prosp	Isolated HTO	118 (118)	19	$64.7\pm8.4$	$24.6\pm2.8$	29 Gr 1; 47 Gr 2; 34 Gr 3; 7 Gr 4	NR	$24\pm0$
Schröter <sup>77</sup> 2013	Prosp	Isolated HTO	32 (32)	22	$47\pm9$	$28.6 \pm 4.7$	NR	$5.7\pm3.6$	$77~\pm~19$
Schuster <sup>79</sup> 2015	Prosp	HTO +	85 (91)	79	$50.4\pm8$	$27.4 \pm 3.1$	All Gr 3 or 4	$10.2\pm5.3$	$67.2 \pm 27.6$
		abrasion/MFX							
Schuster <sup>78</sup> 2018	Prosp	HTO + AA	79 (79)	67	$50.9\pm7.6$	$27.1 \pm 3$	NR	NR	$120 \pm 14.4$
Song <sup>81</sup> 2010	Retrosp	Isolated HTO	90 (90)	21	$51\pm6.5$	$25.5 \pm 2.18$	All Gr 1-3		$26.7\pm9$
Spahn <sup>82</sup> 2004	Prosp	Isolated HTO	85 (85)	49	$44.2 \pm 11.6$	NR	NR	$9.66 \pm 2.12$	NR
Sterett <sup>84</sup> 2010	Retrosp	HTO + MFX	106 (106)	80	$52\pm10.25$	NR	NR	NR	NR
Tabrizi <sup>86</sup> 2013	Prosp	Isolated HTO	16 (16)	13	$36.5 \pm 8.1$	NR	NR	NR	NR
Türkmen <sup>88</sup> 2014	Prosp	Isolated HTO	38 (41)	3	NR	NR	NR	NR	$6\pm 0$

(continued)

TABLE A1 (continued)									
Lead Author and Year	Study Design	Isolated HTO or HTO With Cartilage Repair	No. of Patients (Knees)	Male, n	Age, y <sup>b</sup>	BMI, kg/m <sup>2b</sup>	K-L Grade	Degrees of Correction $^b$	Follow-up, mo <sup>b</sup>
van Egmond <sup>90</sup> 2016	Prosp	Isolated HTO	25 (25)	15	$47.1\pm8.5$	$29.7 \pm 4.2$	NR	$7.8\pm2.6$	$94.8\pm6$
van Wulfften Palthe <sup>91</sup> 2018	Retrosp	Isolated HTO	14 (14)	_	_	_	_	_	_
Villate <sup>92</sup> 2015	Retrosp	Isolated HTO	64 (69)	43	$51.8 \pm 10.75$	$27.2\pm6.4$	NR	NR	$90\pm12.6$
Woodacre <sup>97</sup> 2016	Retrosp	Isolated HTO	115 (115)	NR	$47~\pm~7.5$	$29.1\pm4.98$	NR	NR	$100.8 \pm 42$
Wu <sup>99</sup> 2021	Retrosp	Isolated HTO	123 (123)	39	$59.64 \pm 6.64$	$27.9\pm3.76$	88 Gr 3; 35 Gr 4	NR	NR
Yang <sup>101</sup> 2023	Retrosp	Isolated HTO	160 (160)	44	$55.75 \pm 5.45$	$26.15\pm3.41$	61 Gr 2; 97	NR	$96\pm0.1$
							Gr 3; 2 Gr 4		
Zaki <sup>102</sup> 2009	Prosp	Isolated HTO	50 (50)	50	$39.5 \pm 4.75$	NR	NR	NR	$60 \pm 9$

<sup>a</sup>Dashes indicate areas unable to be calculated. AA, abrasion arthroplasty; ACI, autologous chondrocyte implantation; BMI, body mass index; Gr, grade; HTO, high tibial osteotomy; K-L, Kellgren-Lawrence; MFX, microfracture; MSC, mesenchymal stem cell; NR, not reported; OCA, osteochondral allograft transplantation; Prosp, prospective; RCT, randomized controlled trial; Retrosp, retrospective.  $^{b}$ Data are presented as mean or mean  $\pm$  SD.

<sup>*c*</sup>Mean  $\pm$  SD.

#### PubMed/Medline:

Domains	Search	Terms					
	#1	KOA OR Knee Osteoarth* OR Knee Arth* OR Knee					
Populations		Degenerat* [tiab]					
(P)	#2	nee [MeSH] OR Knee Joint (MeSH)					
	#3	Arthritis (MeSH) OR Osteoarthritis, Knee (MeSH)					
	#4	#2 AND (#1 OR #3)					
	#5	High Tibial Osteotomy OR HTO OR Proximal Tibial					
Interventions		Osteotomy OR Tibial Plateau Osteotomy [tiab]					
(I)	#6	Osteotomy[MeSH]					
and	#7	Tibial Realignment [tiab]					
Comparators	#8	Medial Opening Wedge Osteotomy OR Lateral					
(C)		Closing Wedge Osteotomy [tiab]					
	#9	#5 OR #6 OR #7 OR #8					
Filters		Blank to capture RCTs and Observational Studies					
(Study design)		alike					
P and I and	#10	#4 AND #9					
C, Filters							

Embase:

- 1. Knee/exp OR Knee Joint/exp
- 2. KOA OR Knee Osteoarth\* OR Knee Arth\* OR Knee Degenerat\*: ti,ab
- 3. Arthritis/exp OR Osteoarthritis, Knee/exp
- 4. 1 AND OR/2-3
- 5. High Tibial Osteotomy OR HTO OR Proximal Tibial Osteotomy OR Tibial Plateau Osteotomy: ti,ab
- 6. Tibial Realignment: ti,ab
- 7. Medial Opening Wedge Osteotomy OR Lateral Closing Wedge Osteotomy: ti,ab
- 8. Osteotomy/exp
- 9. OR/5-8
- 10. 4 AND 9

### Cochrane:

- 1. Knee [MeSH] OR Knee Joint (MeSH)
- 2. KOA OR Knee Osteoarth\* OR Knee Arth\* OR Knee Degenerat\*
- 3. Arthritis (MeSH) OR Osteoarthritis, Knee (MeSH)
- 4. #1 AND (#2 OR #3)
- 5. High Tibial Osteotomy OR HTO OR Proximal Tibial Osteotomy OR Tibial Plateau Osteotomy
- 6. Tibial Realignment
- 7. Medial Opening Wedge Osteotomy OR Lateral Closing Wedge Osteotomy
- 8. Osteotomy[MeSH]
- 9. #5 OR #6 OR #7 OR #8
- 10. #4 AND #9

## Scopus:

- 1. Knee OR Knee Joint
- 2. KOA OR Knee Osteoarth\* OR Knee Arth\* OR Knee Degenerat\*
- 3. Arthritis OR Osteoarthritis, Knee
- 4. #1 AND (#2 OR #3)
- 5. High Tibial Osteotomy OR HTO OR Proximal Tibial Osteotomy OR Tibial Plateau Osteotomy
- 6. Tibial Realignment
- 7. Medial Opening Wedge Osteotomy OR Lateral Closing Wedge Osteotomy
- 8. Osteotomy
- 9. #5 OR #6 OR #7 OR #8
- 10. #4 AND #9