

Hip

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Vitamin E highly cross-linked polyethylene reduces mid-term wear in primary total hip replacement: a meta-analysis and systematic review of randomized clinical trials using radiostereometric analysis

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- Vitamin E incorporation into highly cross-linked polyethylene (HXLPE) has been introduced to improve wear resistance, and vitamin E incorporated HXLPE (VEPE) has been used in total hip arthroplasty.
- The aim of this meta-analysis was to investigate the wear properties of VEPE in clinical practice by synthesizing the data provided in randomized clinical trials.
- The effects on implant stability, functional outcomes and revision rate of VEPE were also compared with those of HXPLE or ultra-high molecular weight polyethylene (UHMWPE).
- Literature searches were conducted on 1 January 2020 using MEDLINE, EMBASE, Cochrane and ClinicalTrials.gov databases. Randomized controlled trials (RCTs) comparing the aforementioned parameters between VEPE and standard HXPLE/UHMWPE liners were included.
- Methodological quality and the bias of the included studies were analysed. Meta-analyses were performed using the Review Manager software.
- Nine RCTs met the eligibility criteria and were included. At early and mid-term follow-up, the vertical penetration and the total penetration of the femoral head were both significantly reduced in the VEPE group. The steady state wear rate of the VEPE group was also remarkably lower.
- However, at two-year follow-up, significantly increased cup migration was observed in the VEPE group. Moreover, the mid-term clinical outcomes of the VEPE group were worse, while the total revision rates between the two groups were not significantly different.
- The limited number of included studies may compromise our conclusion regarding clinical outcomes of the VEPE bearing surface. More RCTs with longer follow-up periods

are needed to further investigate the effects of VEPE in total hip arthroplasty.

**Keywords:** total hip arthroplasty; ultra-high molecular weight polyethylene; vitamin E incorporated highly cross-linked polyethylene

Cite this article: *EFORT Open Rev* 2021;6:759-770. DOI: 10.1302/2058-5241.6.200072

# Introduction

Ultra-high molecular weight polyethylene (UHMWPE) is the most widely used material for liners in total hip arthroplasty (THA), and its long-term durability has been well demonstrated in several studies dating back to 1990s.<sup>1,2</sup> However, for THA involving a polyethylene (PE) liner, one of the major factors threatening long-term survival is the production of wear particles, resulting in periprosthetic osteolysis and aseptic loosening of the acetabular cup and/or the femoral component.<sup>3,4</sup> Fortunately, in the past two decades, the progress made in material manufacturing, especially the PE cross-linking technique, has dramatically increased the resistance to wear and reduced the PE debris. Using a higher irradiation dose than for normal sterilization, highly cross-linked UHMWPE (HXLPE) is produced and has been introduced into clinical use for more than 20 years.<sup>5</sup> In several follow-ups up to ten years, the clinical superiority of HXLPE has also been demonstrated as reduced PE wear rate, as well as excellent long-term survival.<sup>6,7</sup>

However, PE oxidation has been observed and considered as the major drawback of the HXLPE during its decades

of application. The free radicals produced during high-dose irradiation contributed largely to oxidative degradation. To minimize the effect of the free radicals, either a melting or an annealing procedure is needed. Melting can eliminate the free radicals; however, it compromises the mechanical properties, especially fatigue strength. For annealed HXLPE, the free radicals cannot be eradicated and this leads to oxidative degradation in non-weight-bearing regions.<sup>8</sup> Several potential solutions have been provided to minimize the free radicals, and incorporation of the antioxidant vitamin E ( $\alpha$ -Tocopherol) into HXLPE has been demonstrated to increase oxidative resistance without compromising mechanical strength.9 Until now, blending vitamin E with UHMWPE resin powder before irradiation, or diffusing vitamin E after UHMWPE cross-linking, have become the two methods available to manufacture the vitamin E incorporated HXLPE (VEPE).<sup>10,11</sup> Despite the improved wear properties and oxidative resistance of VEPE demonstrated in several in vitro studies, the VEPE liner has been introduced in THA and has displayed promising in vivo outcomes.<sup>9,12</sup>

Recently, a few prospective, blinded, randomized controlled trials (RCTs) comparing the outcomes of VEPE liner and conventional HXLPE or UHMWPE liner have also been published, most of which measured the PE wear using radiostereometric analysis (RSA).13-22 However, in these follow-ups up to seven years, the time points for RSA were not identical, making it difficult to elucidate the features of VEPE. Generally, within six months postoperatively, the femoral head penetration is mainly due to deformation of the PE cups, namely 'creep', rather than the volume loss of the PE liner, namely 'wear'. From six months to one year, the effects of creep and wear are equal to lead to the femoral head penetration. After one year, femoral head penetration is mainly caused by PE wear.<sup>23</sup> Thus, in this meta-analysis, we aim to synthesize the relevant data and provide comprehensive wear characteristics of VEPE compared to HXLPE or UHMWPE during different periods. We also provide a synthetical patient-reported outcome measure (PROM) in this meta-analysis.

# Materials and methods

# Search strategy

We searched MEDLINE, EMBASE, Cochrane and Clinical-Trials.gov databases to retrieve relevant literature from the inception of each database to 1 January 2020. The following terms were used for searching: hip AND vitamin E/ tocopherols/ tocotrienols. The papers of interest were also screened for potential studies undiscovered in the primary search. Only articles published in English were included.

## Inclusion and exclusion criteria

- 1. Type of studies. Only prospective randomized clinical trials were included. Retrospective case-control studies, analysis of joint registries and in vitro simulations were excluded.
- 2. Subjects and intervention. The included studies recruited patients of all ages for primary total hip arthroplasty and compared the VEPE to other PEs.
- 3. Outcomes. Articles reporting at least one of the following parameters were included: RSA results of femoral head penetration, steady state wear, component migration, and patient-reported outcome measures (PROMs) were included.

## Data extraction and outcomes of interest

Data were extracted by two investigators independently, using a collection form we designed. Data presented only in graphs and figures were extracted whenever possible, but were included only if consensus was achieved. Data not published were acquired by contact with the original investigators and, if that failed, calculated with available data. Notably, if the data were presented as median with interquartile range or median with range, the mean and standard deviation were calculated using the methods offered by Luo et al and Wan et al.<sup>24,25</sup> The primary outcomes were proximal-distal penetration of the femoral head and overall penetration of the femoral head. And the secondary outcomes included steady state wear, component migration and PROMs.

## Quality assessment

The quality of included literature was assessed through seven evaluation factors including randomization, allocation concealment, blind intervention, blind outcome assessment, incomplete outcome data, selective reporting, and other bias.

## Statistical methods

Revman 5.3 software (Cochrane Collaboration, UK) was employed to perform the meta-analysis. For each included study, mean differences (MDs) were calculated for continuous outcomes, respectively. 95% confidence intervals (Cl) were also calculated for all outcomes. P < 0.05 was considered to be statistically significant for the outcomes. According to the Cochrane Handbook<sup>26</sup>,  $\chi^2$  and l<sup>2</sup> were calculated to evaluate the heterogeneity across studies. We selected a fixed effect model when l<sup>2</sup> < 50%, and a random effect model when l<sup>2</sup> > 50%.<sup>26</sup> Publication bias was also analysed by means of a funnel plot.

# Results

# Search results

A total of 236 records were acquired, of which 232 were acquired through database searching, and four additional records were identified through other sources. Two records were rejected because of duplication. After careful review of the title and abstract, 220 articles were excluded. We further reviewed the full texts of 18 papers and nine met the study inclusion criteria.<sup>13–21</sup> A flowchart of the literature search is shown in Fig. 1.

#### Characteristics of the included trials

Detailed information of the included trials is summarized in Table 1 and Table 2. A total of 412 hips were recruited in the VEPE group and 316 hips were included in the control group. All patients included in VEPE group received a THA with vitamin E blended highly cross-linked polyethylene liners or vitamin E diffused highly cross-linked polyethylenes. Ultra-high molecular weight polyethylene (UHMWPE) liners were selected for the patients in the control group in three included RCTs, while in another six RCTs, highly cross-linked polyethylene (HXLPE) liners were applied.

For the primary outcomes, all included RCTs reported RSA results relative to femoral head penetration, either using separated vertical (proximal-distal) measurement, coronal (medial-lateral) measurement, and sagittal (anteriorposterior) measurement or using a calculated overall (3D vector) measurement using the measurement mentioned above. Using the same reporting pattern, the results of the steady state wear were displayed in four RCTs. For the secondary outcomes, two RCTs provided the RSA results of cup migration and the clinical outcomes were reported in seven RCTs.

In terms of bias, the attrition bias was high in seven out of nine included RCTs due to uneven loss to follow-up in the two groups. In three studies, the selection bias was



#### Fig. 1 Literature search strategy.

Note. RCT, randomized controlled trial; RSA, radiostereometric analysis.

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Table	

Generalities							Experimental	group							Control	group		
Author	Year Re	jion Q pr	Illow- Patien o (male, rriod female ars)	ts / (*)	ps Age )	BMI	Acetabular component	Liner	Femoral head	Femoral component	Patients H (male/ ( female)	lips Ag n)	9 8	₹ o	cetabular omponent	Liner	emoral head F	emoral omponent
Sköldenberg <sup>13</sup>	2019 Sw	eden 2	21 (10/11	21	67 (5)	27 (4)	Exceed ABT cemented cup; Zimmer Biomet	Vitamin E doped, highly cross-linked polyethylene VVEPE	32 mm chromium- cobalt	Bi-Metric HA; Zimmer Biomet	21 21 (11/10)	67	(4) 27	7 (4) E	xceed ABT emented cup; immer Biomet	ArCom	82 mm Bhromium- 2 Sobalt	i-Metric HA; Immer Biomet
Galea <sup>21</sup>	2019 US/	4	39 (22/17	39	66 (6)	27 (4)	Regenerex; Zimmer Biomet	VEPE (E1; Zimmer Biomet)	32 mm or 36 mm ceramic BIOI OX delta) 1	Bi-Metric; Zimmer Biomet	34 34 3 (20/14)	4 63	(8) 28	3 (4) R Z	egenerex; immer Biomet	ArComXL; Zimmer 3 Biomet	32 mm or 36 E mm ceramic E BIOLOXdelta)	il-Metric; Zimmer iomet
Nebergall <sup>20</sup>	2017 Del	nmark 5	32 (16/16	32	e7 (43 76)	to 27 (20 tc 35)	Zimmer Biomet	VEPE (E1; Zimmer Biomet)	32 mm ceramic	Bi-Metric; Zimmer Biomet	35 35 (16/19)	5 65 73	(40 to 2) ) tc	7 (22 R 145) Z	egenerex; immer Biomet	ArComXL; Zimmer 3 Biomet	82 mm E	il-Metric; Zimmer iomet
Rochcongar <sup>19</sup>	2018 Fra	nce 5	33 (17/16	33	60 (6)	27 ( 4)	RM Pressfit vitamys; Mathvs	VEPE	28 mm cobalt- chromium	Cemented femoral stem	29 2 (12/17)	9 61	(8) 27	7 (4) R N	M Pressfit; 1athy s	UHMWPE	28 mm cobalt- c thromium s	emented femoral tem
Galea <sup>15</sup>	2018 US,	۲ ک	136 (81/57	13	6 60 (10	) 28 (4)	Regenerex/ RingLoc, Zimmer Biomet	VEPE (E1; Zimmer Biomet)	32 mm/36 mm, chromium- cobalt/ceramic	Taperloc or Bimetric, Zimmer Biomet	57 5 (31/26)	7 61	(8) 28	3 (4) R B	egenerex/ ingLoc, Zimmer iomet	ArComXL; Zimmer 3 Biomet	82 mm/36 T nm, E thromium- E cobalt/	aperloc or imetric, Zimmer iomet
Salemyr' <sup>7</sup>	2015 Sw	eden 2	25 (11/14	() 25	62 (6)	28 (4)	Regenerex; Zimmer Biomet	VEPE (E1; Zimmer Biomet)	32 mm chromium-	Bi-Metric; Zimmer Biomet	26 26 2 (11/15)	6 62	(5) 27	7 (4) P	innacle, Depuy ohnson&Johnson	Marathon, Depuy	stanne 32 mm F 34romium- J	roxima, Depuy ohnson&Johnson
Scemama <sup>16</sup>	2017 Fra	nce 3	50 (22/28	50	) 67 (32 74)	to 25 (18 tc 37)	RM Pressfit vitamys; Mathvs	VEPE	28 mm cobalt- chromium	cemented Centris, Mathvs	50 5 (26/24)	0 66 75	(49 to 26 ) tc	5 (17 R 32) N	M Pressfit; 1athy s	UHMWPE	28 mm cobalt- c thromium N	emented Centris, Aathys
Shareghi <sup>14</sup>	2015 Sw	eden 2	38 (22/16	38	\$ 58 (32 75)	to 25 (19 tc 38)	RingLoc, Zimmer	VEPE (E1; Zimmer	32 mm chromium-	Bi-Metric; Zimmer	32 32 3 (15/17)	2 58 67	(36 to 27	7 (19 R 36) B	ingLoc, Zimmer iomet	ArComXL; Zimmer 3 Biomet	82 mm 24 chromium- 24 chromium- E	il-Metric; Zimmer ilomet
Shareghi <sup>18</sup>	2017 Sw	eden 5	38 (22/16	38	58 (32 75)	to 25 (19 tc 38)	biomet Zimmer Biomet	VEPE (E1; Zimmer Biomet)	33 mm chromium- cobalt	Bi-Metric; Zimmer Biomet	32 3 (15/17)	2 58 67	(36 to 27	7 (19 R 36) B	ingLoc, Zimmer iomet	ArComXL; Zimmer 3 Biomet	33 mm E S3 mm E chromium- E cobalt	ii-Metric; Zimmer iomet
Note. BMI, bod	y mass inc	lex; UHM	WPE, ultra-hi	gh mo	lecular w	eight polyeth	iylene.											

Generalities										OU	tcomes							
				Femoral h	ead penet	ration		Cup migra	tion			Steady state	e wear			Clinical	outcome	s
Author	Year	Region	Follow-up period (years)	Proximal- distal	medial- lateral	anterior- posterior	overall	Proximal- distal	medial- lateral	anterior- posterior	overall	Proximal- distal	medial- lateral	anterior- posterior	overall	HHS EC	2- SF-3 0 phy: sum	6 sical imary
Sköldenberg <sup>13</sup>	2019	Sweden	2				×	λ	<u>ہ</u>	7	×							
Galea <sup>21</sup>	2019	NSA	7	×	×	7	×					×	٢	۲	×	۲ ۲	≻	
Nebergall <sup>20</sup>	2017	Denmark	5	×	×	~						×	٢	۲		۲ ۲	≻	
Rochcongar <sup>19</sup>	2018	France	5				×									≻		
Galea <sup>15</sup>	2018	USA	5				×									۲ ۲	≻	
Salemyr <sup>17</sup>	2015	Sweden	2	×	×	Y	Y									Υ		
Scemama <sup>16</sup>	2017	France	3				Y								Y			
Shareghi <sup>14</sup>	2015	Sweden	2	~	≻	Y	Y									Y		
Shareghi <sup>18</sup>	2017	Sweden	5	¥	≻	×	¥	٢	٢	¥	Y	¥			¥	≻		
Note. HHS, Han	ris Hip S	icore; EQ-51	D, EuroQol Fiv	ve Dimensio	ns Questio	nnaire; SF-3	6, the MC	OS item sho	rt from hea	lth survey.								

Table 2. Summary of the outcomes provided in the included randomized controlled trials

high due to unequal distribution of the patients to the two groups. The summary of the bias of the included studies is displayed in Fig. 2.

#### Primary outcomes

## Cumulative wear

Within six months, the vertical femoral head penetration of the VEPE group was 0.01 mm less than that of the control group (95% CI -0.04, 0.02), with no statistical significance (p = 0.47, Fig. S1A). However, the total creep was significantly less in the VEPE group, with a mean difference of -0.05 mm (95% CI -0.09, -0.02; p = 0.001, Fig. 3A). One year postoperatively, the difference of vertical femoral head penetration between the two groups was still insignificant, with a mean difference of -0.01 mm (95% CI -0.06, 0.04; p = 0.69, Fig. S1B), while the total penetration of the femoral head for the VEPE group was significantly less than that for the control group (mean difference -0.08 mm, 95% CI -0.12, -0.03; p = 0.001), indicating a significantly reduced creep and wear of the VEPE (Fig. 3B). The early wear of the liner was remarkably lessened in the VEPE group, indicated by both vertical penetration (mean difference -0.06 mm, 95% CI -0.09, -0.03; p < 0.0001, Fig. S1C) and total penetration (mean difference -0.08 mm, 95% CI -0.14, -0.02; p = 0.006) of the femoral head (Fig. 3C). At the mid-term follow-up, the reduced wear of the VEPE was further validated. The mean difference of vertical penetration and total penetration was significantly reduced by 0.09 mm (95% CI –0.13, –0.05; p < 0.0001, Fig. S3D) and 0.09 mm (95% CI –0.13, -0.05; p < 0.0001), respectively (Fig. 3D).

#### Steady state wear rate

The steady state wear rates in all included studies were calculated by comparing the measurement of a certain follow-up period to the measurement taken one year post-operatively. Although in several studies the follow-up was conducted at multiple time points, we only included the measurement of the final follow-up in this meta-analysis. The vertical steady state wear rate of the VEPE group was significantly lower than that of the control group, with a mean difference of -0.07 mm/y (95% CI -0.14, -0.00) and a p-value of 0.02. The total steady state wear rate of VEPE group was also significantly reduced by 0.05 mm/y (95% CI -0.14, -0.02; p < 0.0001, Fig. 4A and B).

# Secondary outcomes

# Cup migration

The RSA results of cup migration were provided in two RCTs. Both the vertical cup migration and the total cup migration of the VEPE group were higher, with mean differences of 0.16 mm (95% CI 0.04, 0.28; p = 0.009) and 0.11 mm (95% CI 0.00, 0.22; p = 0.04, Fig. 5A and B).





Fig. 2 Graph (A) and summary (B) of bias of the included RCTs.

## PROMs and revision rate

One year postoperatively, the Harris Hip Score (HHS) was higher in the VEPE group (mean difference 4.24, 95% CI 0.40, 8.09; p = 0.03, Fig. S2A), while the EuroQol Five Dimensions Questionnaire (EQ-5D) showed no difference between the two groups (p = 0.48, Fig. S2B). The early HHS and EQ-5D at two to three years postoperatively also failed to show significance (p = 0.21 and 0.14, respectively). However, statistical significance was observed in mid-term HHS (mean difference -2.54, 95% CI -4.08, 1.00; p = 0.001, Fig. 6A), EQ-5D (mean difference -0.05, 95% CI –0.10, 0.00; p = 0.05, Fig. 6B) as well as the MOS item short from health survey (SF-36) physical summary (mean difference -2.82, 95% CI -5.01, -0.64; p = 0.01, Fig. 6C), which were in favour of the control group. Six out of nine included RCTs reported the revision events of the two groups. According to our results, the revision rate was slightly lower in the VEPE groups (OR 0.49, 95% CI 0.18, 1.30; p = 0.15, Fig. 6D).

# Discussion

The primary expectation of introducing VEPE into THA is to reduce the free radicals produced during PE crosslinking, to diminish the oxidative degradation of the liner, improve the wear resistance, decrease the occurrence of the periprosthetic osteolysis caused by wear debris and finally achieve the secure fixation of the implant. A series of in vitro and in vivo studies have well demonstrated the improved oxidative stability of the VEPE, either using accelerated aging or real-time aging methods.<sup>28,29</sup> The superiority of mechanical properties, including wear resistance and fatigue strength after accelerated aging, were also observed in VEPE.<sup>9</sup> Besides, although controversial, there have also been in vitro studies reporting the anti-septic function of VEPE through preventing the adherence of several species of bacteria, including Staphylococcus epidermidis, Staphylococcus aureus and Escherichia coli.<sup>30-32</sup> Recently, several newly published RCTs have investigated the

(A)		VEPE		PE wi	ithout \	/E		Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Tota	l Mean	SD	Tota	l Weight	IV. Random. 95% CI	IV. Random. 95% CI
Galea 2019 6-week	0.25	0.22	39	0.24	0.27	34	6.4%	0.01 [-0.10, 0.12]	
Rochcongar 2018 6-week	0.128	0.034	33	0.151	0.046	29	23.6%	-0.02 [-0.04, -0.00]	-=-
Salemyr 2015 3-month	0.15	0.07	25	0.24	0.12	26	15.5%	-0.09 [-0.14, -0.04]	
Salemyr 2015 6-month	0.16	0.07	25	0.26	0.15	26	13.2%	-0.10 [-0.16, -0.04]	
Salemyr 2015 6-week	0.16	0.08	25	0.22	0.11	26	15.7%	-0.06 [-0.11, -0.01]	
Shareghi 2015 3-month	0.163	0.091	38	0.172	0.099	31	17.5%	-0.01 [-0.05, 0.04]	
Sköldenberg 2019 3-month	0.22	0.08	18	0.36	0.2	19	8.1%	-0.14 [-0.24, -0.04]	
Total (95% CI)			203			191	100.0%	-0.05 [-0.09, -0.02]	•
Heterogeneity: Tau <sup>2</sup> = 0.00;	$Chi^{2} = 1$	16.46, c	lf = 6	(P = 0.0)	1); I <sup>2</sup> =	64%			
Test for overall effect: $Z = 3$ .	20 (P =	0.001)							Favours [VEPE] Favours [PE without VE]

(в)		VEPE		PE wi	ithout \	/E		Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Tota	l Mean	SD	Total	Weight	IV. Random. 95% CI	IV. Random. 95% CI
Galea 2019 1-year	0.28	0.25	39	0.27	0.26	34	10.6%	0.01 [-0.11, 0.13]	
Rochcongar 2018 1-year	0.16	0.035	33	0.201	0.052	29	29.8%	-0.04 [-0.06, -0.02]	
Salemyr 2015 1-year	0.2	0.12	25	0.31	0.14	26	18.3%	-0.11 [-0.18, -0.04]	
Scemama 2017 1-year	0.074	0.239	38	0.136	0.413	36	7.1%	-0.06 [-0.22, -0.09]	
Shareghi 2015 1-year	0.156	0.055	38	0.237	0.192	31	18.7%	-0.08 [-0.15, -0.01]	
Sköldenberg 2019 1-year	0.21	0.08	18	0.38	0.17	19	15.6%	-0.17 [-0.25, -0.09]	
Total (95% CI)			191			175	100.0%	-0.08 [-0.12, -0.03]	◆
Heterogeneity: $Tau^2 = 0.00$ ;	$Chi^{2} = 1$	2.54, 0	lf = 5	(P = 0.0)	3); l <sup>2</sup> =	60%			
Test for overall effect: $Z = 3$ .	.24 (P =	0.001)							
									Favours (VEPE) Favours (PE without VE)

(C)		VEPE		PE wi	ithout <b>\</b>	/E		Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Tota	l Mean	SD	Total	Weight	IV. Random. 95% CI	IV. Random. 95% CI
Galea 2019 3-year	0.34	0.22	39	0.32	0.35	34	10.5%	0.02 [-0.12, 0.16]	
Rochcongar 2018 3-year	0.18	0.037	33	0.26	0.061	29	25.4%	-0.08 [-0.11, -0.05]	-
Salemyr 2015 2-year	0.23	0.13	25	0.3	0.15	26	17.9%	-0.07 [-0.15, 0.01]	
Scemama 2017 3-year	0.056	0.364	38	0.296	0.319	36	8.9%	-0.24 [-0.40, -0.08]	
Shareghi 2015 2-year	0.205	0.108	38	0.205	0.104	29	22.0%	0.00 [-0.05, 0.05]	
Sköldenberg 2019 2-year	0.23	0.12	18	0.41	0.17	19	15.4%	-0.18 [-0.27, -0.09]	_ <b>-</b> -
Total (95% CI)			191			173	100.0%	-0.08 [-0.14, -0.02]	•
Heterogeneity: $Tau^2 = 0.00$ ; Test for overall effect: $7 = 2$	$Chi^2 = 1$ 75 (P =	9.24, c	df = 5	(P = 0.0	002); I <sup>2</sup> :	= 74%		-0.5	-0.25 0 0.25 0.5
	., э (і =	0.000)							Favours [VEPE] Favours [PE without VE]
(D)									

		VEPE		PE w	ithout ۱	/E		Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Tota	l Mean	SD	Total	Weight	IV. Random. 95% C	CI IV. Random. 95% CI
Galea 2018 5-year CoP	-0.006	0.069	37	0.063	0.124	31	20.5%	-0.07 [-0.12, -0.02]	
Galea 2018 5-year MoP	0.076	0.038	99	0.208	0.086	26	26.0%	-0.13 [-0.17, -0.10]	
Galea 2019 5-year	0.32	0.24	39	0.33	0.29	34	6.5%	–0.01 [–0.13, 0.11]	
Galea 2019 7-year	0.39	0.29	39	0.39	0.29	34	5.7%	0.00 [-0.13, 0.13]	
Rochcongar 2018 5-year	0.2	0.032	33	0.317	0.074	29	27.9%	-0.12 [-0.15, -0.09]	
Shareghi 2017 5-year	0.258	0.169	37	0.31	0.134	26	13.3%	-0.05 [-0.13, 0.02]	
Total (95% CI)			284			180	100.0%	-0.09 [-0.12, -0.05]	
Heterogeneity: Tau <sup>2</sup> = 0.00	; Chi <sup>2</sup> =	11.75, d	df = 5	(P = 0.0)	94); I <sup>2</sup> =	57%			
Test for overall effect: $Z = 4$	1.98 (P <	0.0000	1)						Favours [VEPE] Favours [PE without VE]

**Fig. 3** Meta-analysis of total penetration of the femoral head. (A) Within six months postoperatively (Creep). (B) One year postoperatively (Creep and wear). (C) Two to three years postoperatively (Early wear). (D) More than five years postoperatively (Midterm wear).

Note. VEPE, vitamin E incorporated highly cross-linked polyethylene; PE, polyethylene.

performance of VEPE in clinical practice using RSA, concluding that VEPE was at least non-inferior to conventional PE.<sup>19,21,22</sup> In this study, we tried to synthesize the data from the RCTs and comprehensively reveal the properties of VEPE in clinical use.

(D)

In this meta-analysis, when using vertical penetration of the femoral head as a surrogate, no significant difference of PE creep was observed between VEPE and standard PE, while at early follow-up (two to three years postoperatively) and mid-term follow-up (more than five years), the cumulative wear of VEPE was significantly reduced. When using the total femoral head penetration to denote the cumulative wear of PE, the cumulative wear of VEPE was significantly reduced compared to both HXLPE and

( )		VEPE		PE wi	thout	/E		Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV. Random. 95% CI	IV. Random. 95% CI
Galea 2019 Nebergall 2017 Shareghi 2017	-0.07 -0.101 0.01	0.16 0.109 0.021	39 28 37	0 0.039 0.04	0.22 0.173 0.015	34 26 26	26.1% 29.1% 44.8%	-0.07 [-0.16, 0.02] -0.14 [-0.22, -0.06] -0.03 [-0.04, -0.02]	
<b>Total (95% CI)</b> Heterogeneity: Tau <sup>2</sup> Test for overall effect	= 0.00; C t: Z = 2.0	Chi <sup>2</sup> = 8 2 (P = 0	<b>104</b> .29, df ).04)	= 2 (P =	= 0.02);	<b>86</b> I <sup>2</sup> = 76	<b>100.0%</b> 5%	-0.07 [-0.14, -0.00]	-0.2 -0.1 0 0.1 0.2 Favours [VEPE] Favours [PE without VE]
(B)									

		VEPE		PE wi	thout \	VE 🛛		Mean Difference		Mea	an Diff	ference		
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV. Fixed. 95% CI		IV. I	ixed.	95% CI		
Galea 2019	0.18	0.29	39	0.29	0.17	34	7.6%	-0.11 [-0.22, -0.00]						
Scemama 2017	-0.031	0.356	38	0.106	0.399	36	3.0%	-0.14 [-0.31, 0.04]			_	-		
Shareghi 2017	0.04	0.044	37	0.08	0.073	26	89.4%	-0.04 [-0.07, -0.01]						
Total (95% CI)			114			96	100.0%	-0.05 [-0.08, -0.02]						
Heterogeneity: Chi <sup>2</sup> =	= 2.55, d	lf = 2 (P	9 = 0.28	3); I <sup>2</sup> = 2	2%				_0.5	_0 25	0	0	25	0.5
Test for overall effect	: Z = 3.1	8 (P = 0	0.001)						-0.5	Favours [V	EPE] I	Favours [PE	withou	t VE]

Fig. 4 Meta-analysis of steady state wear rate. (A) Vertical steady state wear rate. (B) Total steady state wear rate.

Note. VEPE, vitamin E incorporated highly cross-linked polyethylene; PE, polyethylene.

(A)									
		VEPE		PE wi	thout \	/E		Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV. Fixed. 95% CI	IV. Fixed. 95% CI
Shareghi 2017 2-year Sköldenberg 2019 2-yea	-0.567 ar 0.28	1.099 0.17	36 18	-0.533 0.11	0.959 0.21	28 19	5.6% 94.4%	-0.03 [-0.54, 0.47] 0.17 [0.05, 0.29]	
Total (95% CI)			54			47	100.0%	0.16 [0.04, 0.28]	
Heterogeneity: Chi <sup>2</sup> = 0 Test for overall effect: Z	.59, df = = 2.60 (	1 (P = P = 0.0	0.44); 09)	I <sup>2</sup> = 0%					-0.5 -0.25 0 0.25 0.5 Favours [VEPE] Favours [PE without VE]
(B)									
· /									
		VEPE		PE wi	thout \	/E		Mean Difference	Mean Difference
Study or Subgroup	Mean	VEPE SD	Total	PE wi Mean	thout \ SD	/E Total	Weight	Mean Difference IV. Fixed. 95% Cl	Mean Difference IV. Fixed. 95% Cl
Study or Subgroup Shareghi 2017 2-year Sköldenberg 2019 2-yea	<b>Mean</b> -0.636 ar 0.41	VEPE SD 1.363 0.18	<b>Total</b> 36 18	PE wi Mean -0.479 0.29	thout V SD 1.044 0.16	/E Total 28 19	Weight 3.4% 96.6%	Mean Difference IV. Fixed. 95% CI -0.16 [-0.75, 0.43] 0.12 [0.01, 0.23]	Mean Difference IV. Fixed. 95% CI

# Fig. 5 Meta-analysis of cup migration at 2-year follow-up. (A) Vertical migration of the acetabular cup. (B) Total migration of the acetabular cup.

Note. VEPE, vitamin E incorporated highly cross-linked polyethylene; PE, polyethylene.

UHMWPE at any time point. Our study is not the first metaanalysis comparing the femoral head penetration of VEPE liner to the standard PE liner. In an early published metaanalysis, Wyatt et al<sup>33</sup> also reported reduced wear of VEPE, along with similar clinical outcomes between THA with VEPE liners and conventional liners. Although the heterogeneity in most of their meta-analysis was low ( $I^2 = 0$ ), the small number of included RCTs was the major drawback of their study. Due to limited studies included in their study, the results of early-stage follow-up and mid-term follow-up were not distinguished. In our study, we separately investigated the PE creep, early-stage wear and midterm wear between VEPE and conventional PE. In several RCTs, the wear of the liner was reflected by total penetration of the femoral head, while in others, the proximaldistal penetration of the femoral head was regarded as the surrogate. Herein, both approaches were analysed in our study to reflect the wear resistance. Although discrepancy between the two approaches was found in measuring the creep of the liners, the superiority of VEPE in wear resistance was demonstrated in both approaches.

Another primary outcome was that the steady state wear rate and its synthesized result was reported for the first time. Generally, within the first year after THA, there is a bedding-in period in which the deformation of the liner, namely 'creep', overwhelms the wear of the liner but has



Fig. 6 Meta-analysis of mid-term clinical outcomes and revision rate. (A) Mid-term HHS. (B) Mid-term EQ-5D. (C) Mid-term SF-36 physical summary. (D) Revision rate.

Note. VEPE, vitamin E incorporated highly cross-linked polyethylene; PE, polyethylene; HHS, Harris Hip Score; EQ-5D, EuroQol Five Dimensions Questionnaire; SF-36, the MOS item short from health survey.

little influence on the more detrimental long-term volumetric wear.<sup>34,35</sup> Thus, steady state wear, which excluded creep, is more accurate in evaluating the wear resistance of the liner, and should be independently addressed. In the included studies referring to the steady state wear rate, it is calculated using the RSA result at one year follow-up as baseline data and either using the vertical penetration or total penetration as a surrogate.<sup>16,18–20</sup> In our metaanalysis, both the vertical steady state wear rate and the total steady state wear rate significantly favour the VEPE group, further confirming a better wear resistance of VEPE compared with conventional PE, regardless of creep. According to the only two RCTs reporting the result of cup migration, controversial conclusions were reached. Sköldenberg et al found a continuous proximal migration along with increasing abduction angle of the cup in the VEPE group, and this migration pattern exceeded the safety threshold and might become a warning of early aseptic loosening.<sup>13</sup> However, in the RCT conducted by Shareghi et al, no significant difference was found between the two groups referring to the cup migration.<sup>18</sup> In our meta-analysis, the cup migration at two-year follow-up was larger in the VEPE group when synthesizing their results. However, we recommend a cautious interpretation of

our results. Firstly, the revision rate in our meta-analysis was lower in the VEPE group, although without statistical significance. This equivalent revision rate partly indicates that the VEPE liner might not jeopardize the stability of the implants. Secondly, despite the low bias calculated in our meta-analysis, the two included RCTs used thoroughly different fixation patterns when implanting the cups. The incorporation of vitamin E into PE increases the number of cross-linking and gives the VEPE better mechanical strength.<sup>9,36</sup> In THAs with cemented cups, the stiffer VEPE might increase the stress at the cement-bone interface, a phenomenon previously described in metal-backed cemented components.<sup>37</sup> However, whether the hypothesis is applicable to the uncemented cups is still beyond understanding. More research with longer follow-up periods is still needed to demonstrate whether VEPE affects the implant stability of cemented cups as well as uncemented cups.

When evaluating the PROMs, HHS, EQ-5D, and SF-36 physical summary were applied in several of the included RCTs. Conflicting results were observed. The HHS at one year postoperatively favoured the VEPE group, while other parameters of early clinical outcomes were not different. However, the HHS at a minimum five years follow-up significantly favoured the control group, as well as the EQ-5D and SF-36 physical summary, which was very different from the equivalent PROMs reported by Wyatt et al in their meta-analysis.<sup>33</sup> However, it is arbitrary to conclude that the use of VEPE liner resulted in worse PROMs with such a limited number of studies included. We are inclined to attribute these surprising results to the THA procedure itself rather than to the materials used in the bearing surface.

The main limitation of this meta-analysis is that we failed to distinguish blended VEPE from diffused VEPE in the VEPE group when performing the meta-analysis; neither did we distinguish HXLPE from UHMWPE in the control group. Furthermore, the different sizes and materials of the femoral head were also not taken into consideration when performing the meta-analysis in this study. A network meta-analysis is needed to cover all comparisons lacked in this study when more research is available. Another limitation is due to inadequate original data provided with mean and standard deviation patterns and we can only calculate the mean and standard deviation using analytic methods previously described. This might more or less produce inaccuracy during our meta-analysis.

# Conclusion

In this study, superior wear resistance of VEPE was identified. The total penetration of the femoral head within six months (creep), one year postoperatively (creep and wear), at two to three years postoperatively (early wear) and mid-term wear of the VEPE group was significant lower. In terms of clinical outcomes, although the PROMs of the VEPE group at mid-term follow-up seem worse, this conclusion may be compromised by the limited number of the included studies. More high quality RCTs with longer follow-up periods are still needed to clarify the effect of VEPE bearing surface on cup migration, as well as on clinical outcomes.

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#### **ICMJE CONFLICT OF INTEREST STATEMENT**

The authors declare no conflict of interest relevant to this work.

## **FUNDING STATEMENT**

No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

#### **OPEN ACCESS**

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## SUPPLEMENTAL MATERIAL

**Supplemental material** is available for this paper at https://online.boneandjoint. org.uk/doi/suppl/10.1302/2058-5241.6.200072

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