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Title: Does vitamin E Highly-crosslinked polyethylene convey an advantage in primary total hip replacement? A systematic review and meta-analysis

Short title: Vitamin E HXLPE

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Abstract

Background:

Vitamin E highly-crosslinked polyethylene (HXLPE) was developed to reduce wear in total hip replacement (THR). This formal systematic review and meta-analysis aimed to provide independent synthesis of wear characteristics of Vitamin E treated HXLPE compared to HXPLE/UHMWPE. Secondary outcome measures were differences in revision rates and functional scores.

Methods:

We performed a formal systematic review as per PRISMA guidelines; literature searches were conducted on 14th November 2017 (MEDLINE, Embase on Ovid, and the Cochrane Library). We included randomized controlled trials, analyses of joint registries, and case-controlled studies of primary THR comparing cups with a Vitamin E HXLPE bearing with bearing surfaces made from other types of polyethylene. Initial screening was performed by two independent assessors; disagreement resolved in discussion with a third reviewer. Studies were evaluated using the Cochrane risk of bias tool. Data extraction permitted meta-analysis.

Results:

372 studies were identified on initial screening, 5 studies met the eligibility criteria. There was no significant heterogeneity between studies. There was variable risk of bias. At a mean of 35 months (range 20 to 60), Vitamin E HXLPE had significant advantages over highly crosslinked polyethylene with regards total femoral head penetration (p=0.004). Given the RSA measurement errors this may not be clinically significant.

There were neither significant differences in revision rates nor Harris Hip Scores (p=0.06).

Conclusion:

At a minimum of three years follow-up there was reduced total femoral head penetration for Vitamin E HXLPE over HXLPE. This bearing surface does not as yet have clinically significant advantages in terms of revision rates or patient function over HXLPE.

Keywords:

Vitamin E, Meta-analysis, Total hip replacement

Introduction:

Ultra-high molecular weight polyethylene (UHMWPE) has been in used for nearly 60 years yet historically many other bearing materials have been tried [1, 2]. According to National Joint Registry of England and Wales (NJR) UHMWPE is used in 88% of THR's [3]. Wear mediated aseptic loosening is a common cause of revision in THR [3]. UHMWPE wear by oxidative degradation decreases wear resistance and leads to increased osteolysis; a major cause of implant failure [1,3-6].

The sterilisation process is a major contributor to UHMWPE degradation [7,8]. High-energy radiation, used in sterilisation processes, induces oxidation. Bond scission occurs with the formation of free radicals [2]. This reduces molecular mass and alters the mechanical properties of the UHMWPE. The oxidation continues during storage and *in vivo* once implanted [9]. In 1998, highly-crosslinked and thermally treated polyethylenes (HXLPEs) were introduced to improve wear resistance. It was theorized they would reduce the incidence of revision. Crosslinking results in an increased molecular mass; improving wear resistance and mechanical properties compared to UHMWPE [10,11]. Following irradiation, the HXLPEs are thermally treated to remove residual free radicals. Two different processes, remelting and annealing, are used. Only remelting treatment effectively removes residual free radicals [12,13]. Other processing methods have been considered but have not been able to eradicate free radicals meaning oxidative degradation can occur [14].

Vitamin E (VE) is an antioxidant that can be added to the HXLPEs to combat oxidative degradation and improve fatigue properties by avoiding post-irradiation melting [15].

In vitro studies have demonstrated a protective effect of VE on oxidative degradation, with improved mechanical and wear properties [16-18]. Additionally, *in vitro* and animal studies have not demonstrated adverse reactions [19]. Despite this, there is currently limited clinical evidence to support the use of Vitamin E HXLPE.

There are two methods of adding Vitamin E: the first is by blending UHMWPE powder with vitamin E prior to consolidation and cross-linking (blended Vitamin E HXLPE); the second is by doping the consolidated and cross-linked material in a hot Vitamin E solution, allowing vitamin E to diffuse into the material (diffused Vitamin E HXLPE) [20]. The purpose of this study is to provide an independent synthesis of the wear characteristics of Vitamin E treated HXLPE compared to HXPLE or UHMWPE. Secondary outcome measures were differences in revision rates and functional scores.

Materials and Methods:

Before commencing the review, the study protocol was registered with PROSPERO (CRD42017074141) as recommended by the Quality of Reporting of Meta-analyses (QUOROM) statement [21]. We used a rigorous and systematic approach conforming to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) and a PRISMA checklist is included in Appendix 1.

Search strategy

We searched the electronic databases MEDLINE and Embase on the OVID platform, and The Cochrane Library using the search strategy shown in Figure 1. Searches were conducted from database inception to 15th November 2017. We did not limit the search to English language publications. We also evaluated the grey literature with hand searches of conference abstracts published in 6 major Orthopaedic journals in the 5 years before the search date. Bibliographies of relevant articles were checked and key citations tracked in Web of Science.

Eligibility criteria

We included all randomized controlled trials (RCT's), analyses of joint registries and case-controlled studies including patients of all age groups receiving primary total hip replacement using Vitamin E HXLPE compared to any other type of polyethylene.

Screening

Title and abstracts were screened by two independent assessors with any disagreements resolved in discussion with a third reviewer. If any uncertainties relating to inclusion occurred we planned to contact authors for clarification.

Data extraction

Two of the authors worked independently to extract the data using standardized forms. We extracted data on: study country; recruitment dates; setting; participant characteristics; duration of follow-up; acetabular and femoral head bearing material and size; outcomes relating to primarily the degree and measurement of femoral head penetration; secondarily the revision rates, Harris Hip Score, patient reported outcome measures; and risk of bias. An electronic spreadsheet was constructed to summarise the findings of relevant studies.

Study quality

Potential sources of bias in RCTs were assessed using the Cochrane risk of bias tool [22]. This method assesses selection, performance, detection, attrition, and reporting biases. Summary assessments of risk-of-bias (high, low or unclear) for each outcome in each trial are reported. We planned to use alternative risk of bias assessment methods for assessment of non-randomised studies.

Statistical analysis

Data was combined in meta-analysis using Review Manager software (Review Manager (RevMan) 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration; 2014). Heterogeneity was assessed using the I^2 statistic representing the proportion of variability across studies not due to chance or random error. Pre-specified subgroup analysis was performed relating to different polyethylene comparators and femoral head materials.

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Results:

A total of 372 records were identified by literature searches. The titles and abstracts were screened to identify potentially useful articles for inclusion. After screening, 16 articles were assessed for eligibility. A flow diagram of the progression of studies through the systematic review is provided in Figure 2.

There were 5 articles that contributed to our estimates of femoral head penetration, revision and functional outcome. There were 4 prospective randomised controlled trials (RCT's), all from Europe with recruitment from 2008, of which 3 examined diffused Vitamin E HXLPE compared to HXLPE [23-25]. The remaining RCT compared Vitamin E blended HXLPE to conventional UHMWPE [26]. Study characteristics are summarized in Table 1. There was a low risk of bias amongst RCT's when we examined sequence generation, allocation/concealment, blinding, completedness of data and reporting (Table 2). One other study from Japan had a case-control design and compared blended Vitamin E HXLPE and HXLPE. Although the authors reported propensity matching we considered the study to be at high risk of bias because under a quarter of the 348 patients recruited were followed up [20].

Vitamin E HXLPE compared to HXLPE

All RCT's used radiostereometry (RSA) to examine femoral head penetration. In 2 studies with 187 patients followed up for 2 and 5 years [23,27], total reported femoral head penetration was presented. In the meta-analysis shown in Figure 3, total reported femoral head penetration was significantly less in the Vitamin E diffused HXLPE groups compared with conventional HXLPE, mean difference 0.08mm (95%CI 0.13, 0.02; p=0.004) and no heterogeneity was evident (Figure 3). However the RSA measurement errors in these two studies were 0.13mm and 0.14mm respectively therefore this numerically significant difference is unlikely to be clinically significant. Furthermore only one study was at low risk of bias [23] and in this study with 51 patients followed up, the difference between groups was not statistically significant (p=0.09). In one case-control study there was no difference between patients in femoral head penetration between Vitamin E blended HXLPE and HXLPE liners (p=0.161) but risk of bias was high due to the reporting of interim follow up of 24% of patients [20].

Meta-analyses of femoral head penetration by vector are shown in Figures 4-6. Transverse femoral head penetration was reported in 2 RCTs with data from 104 patients followed up for 2 [23] and 5 years [28]. In the meta-analysis shown in Figure 4, transverse femoral head penetration was lower in patients receiving a Vitamin E diffused HXLPE liner, mean difference 0.08mm (95%CI 0.03, 0.14; p=0.003) with no heterogeneity evident. In the one study at low risk of bias [23], the difference was statistically significant (p=0.004).

Three RCTs with 167 patients followed up for 2 [23] or 5 years [28] [27] reported vertical femoral head penetration. In the meta-analysis shown in Figure 5, vertical head penetration was lower in patients receiving a Vitamin E diffused HXLPE liner, mean difference 0.10mm (95%CI 0.07, 0.14; p<0.00001) and there was no heterogeneity between studies. In the one study with low risk of bias [23], the difference was statistically significant, p=0.035.

Two RCTs with 104 patients followed up reported anteroposterior femoral head penetration at 2 and 5 years [23,28]. The meta-analysis in Figure 6 showed a high level of heterogeneity between the studies, I^2=56% and we only show the results for completeness. One study showed a trend favouring the group who received a Vitamin E diffused HXLPE liner [28] and the other a trend favouring the control group receiving HXLPE [23]. Neither trend was statistically significant and only the latter study was at low risk of bias.

Revision rates

Study sample sizes were small and revision rates low. Overall there were 3 revisions in the Vitamin E diffused group and 5 revisions in the control HXLPE group. Two revisions for dislocations occurred in patients receiving Vitamin E diffused HXLPE and 1 in control patients receiving HXLPE but all were in a study with unclear risk of bias due to uneven losses to follow up between groups at 5 years [28]. In the case control study with high risk of bias, there was 1 disclocation in patients receiving blended vitamin E HXLPE liners compared with 2 in those receiving an HXLPE liner.

Patient reported outcomes

Two RCTs with 104 patients and data suitable for meta-analysis reported the Harris Hip Score at 2 years [23] and 5 years [28] follow up. As shown in Figure 7, heterogeneity between studies was high. One study with low risk of bias showed no statistically significant difference between groups at 2 years (p=0.295). One RCT with data suitable for meta-analysis [28] and another only reporting medians and ranges [27] had unclear risk of bias due to uneven loss to follow up. In neither was there a statistically significant difference in Harris Hip Score between groups.

In two RCTs, patient reported health related quality of life was assessed using the EQ-5D [23,28]. There were no differences between outcomes in either study, including one at low risk of bias [23].

Vitamin E blended HXLPE compared to UHMWPE

In one RCT with 100 patients randomised and follwed up for 3 years, vitamin E blended HXLPE liners were compared with UHMWPE liners [26]. Total head penetration was lower in the vitamin E HXLPE group (p=0.04) but the study was at unclear risk of bias due to high losses to follow up. There was no difference in functional outcome measured using the Merle d'Aubigné score (p>0.99).

Discussion:

Total hip replacement is a clinically effective and cost-effective intervention [29]. Any improvement in the outcome of THR is likely to arise through reducing the incidence of adverse events or reducing the need for subsequent revision surgery. This formal systematic review and meta-analysis has shown that Vitamin E HXLPE has reduced femoral head penetration over highly-crosslinked and conventional polyethylenes. However the differences are small in comparison to the measurement error of the techniques used to measure it and there is no evidence from our rigorous systematic review to show a clinically significant benefit of Vitamin E HXLPE over HXLPE in terms of revision rate or function at this early stage. The lack of difference in functional scores is perhaps not surprising as Harris Hip Score is a score to assess the effect of THR as an intervention and not to tell the difference between patients undergoing THR with different types of bearing surface. Ceramic-on-HXLPE in primary total hip replacement has been shown to have the lowest all-cause revision rates in a large national joint registry study [30] and the reduced wear evident with the use of Vitamin E HXLPE may lead to further reduction in revision rates. A reduction in revision rates has not been shown in this study.

The findings of our study should be interpreted with caution. A recent high quality systematic review and network meta-analysis of 3177 THR's concluded that there was currently insufficient evidence to recommend any bearing combination over a traditional metal on UHMWPE THR [31]. However a prospective RCT of 122 patients at 10 years follow-up not included in this systematic review and network meta-analysis showed that HXLPE liners have a significantly reduced wear and greater survival rate compared to UHMWPE liners [32]. Furthermore although *in vitro* evidence has shown increased bacterial resistance with Vitamin E HXLPE [33], there was no evidence in our study to support a decreased rate of revision for periprosthetic infection with this bearing surface.

Systematic review and meta-analysis with assessment of risk of bias can help clinicians to interpret results of studies in diverse settings with different outcome measures. There are limitation to this study however. There are a limited number of randomized controlled trials all of limited follow-up from which to extract data and there were only 187 patients contributing to the meta-analysis of total femoral head penetration. Further RCT's examining Vitamin E HXLPE are underway however [34,35]. We did not perform a network meta-analysis to compare blended and diffused Vitamin E HXLPE especially given the high risk of bias determined in the only study that examined the latter. There were a variety of femoral head sizes used in the studies and both metal and ceramic femoral heads were included. However we extracted data using rigorous selection criteria and there was low heterogeneity for total femoral head penetration. Furthermore this study could not account for precise cup positioning, patient activity, Body Mass Index and whether the requisite hip biomechanics were restored in the cases used; such factors we acknowledge can affect wear rates.

Long–term follow-up, high-quality independent RCT's involving large numbers of patients and using consistent outcome reporting or large generalisable observational cohorts with comprehensive coverage are required to determine if lower wear results in lower revision rates. Such studies should be undertaken however before guidance can be provided on clinical effectiveness of new technologies in THR.

Conclusions:

This systematic review and meta-analysis showed that there were numerically but not clinically significant wear advantages in terms of femoral head penetration for Vitamin E HXLPE over HXLPE. There was no improvement in revision rates or functional outcome at this stage. However there were few high quality studies and longer-term follow-up is required. This bearing surface has encouraging early results in terms of wear.

Tables:

Table 1. Study characteristics

Study **Country** **Baseline dates** **Setting**	**Inclusion** **Number randomised: intervention; control** **Mean age (SD)** **% female**	**Groups compared** **Common treatments**	**Key outcomes** **Longest follow up**	**Overall risk of bias** **Key results**
RCTs: Vit E diffused HXLPE vs HXLPE				
Salemyr et al. 2015 [23] Sweden 2009-2013 1 hospital	Primary OA 51: 25: 26 (24; 26 received allocated intervention) 62 (6); 62 (5) 58%; 56%	Vit E diffused HXLPE liner (E1, Biomet) vs standard HXLPE liner (Marathon, Depuy) Uncemented acetabular shell. Uncemented stem with 32mm cobalt chrome head	Radiography, RSA, HHS, EQ-5D, complications 24 months	Low risk of bias Included in meta-analysis Head penetration in transverse x (p=0.004) and vertical y (p=0.035) axes were lower in Vit E group. Similar in anteroposterior z axis (p=0.629). Total penetration similar between groups (p=0.09). Revisions: 1; 1 HHS (p=0.295) and EQ-5D (p=0.173) similar between groups. Overall number of complications similar between groups.
Nebergall et al 2017 [28] Denmark 2009-2011 1 hospital	Primary OA 82: 41; 41 (32; 35 received allocated intervention) Median (range) 67 (43, 76); 65 (40, 73) 50%; 54%	Vit E diffused HXLPE liner (E1, Biomet) vs medium cross- linked PE liner (ArcomXL, Biomet) Uncemented acetabular shell. Uncemented stem with 32mm ceramic head	Radiography, RSA, HHS, PROMs, osteolysis 5 years	Unclear risk of bias due to uneven loss to follow up at 5 years (4; 9) Included in meta-analysis Head penetration in mediolateral x, proximodistal y and anteroposterior z axes similar between groups.

				Revisions: 2; 3 No differences between groups in HHS, UCLA activity, SF-36 physical function, EQ-5D, VAS pain and satisfaction. No osteolysis observed
Shareghi et al. 2017 [27] Sweden 2008-2010 1 hospital	Osteoarthritis 61 (70 hips): 38; 32 hips Median (range) 58 (20, 73)	Vit E diffused HXLPE liner (E1, Biomet) vs heat-treated HXLPE (ArComXL, Biomet) Uncemented acetabular shell. Uncemented stem with 32mm CoCr head	Radiography, RSA, HHS (self-reported), pain score 5 years	Unclear risk of bias due to uneven loss to follow up (1; 6) and randomisation method Included in meta-analysis Total head penetration and head penetration in proximal y axis lower in Vit E group than heat treated group ($p=0.004$ and $p<0.001$ respectively). Revisions: 0; 1 No difference in HSS between groups ($p=0.90$) or pain score ($p=0.80$).
RCT: Vit E blended HXLPE vs UHMWPE				
Scemama et al. 2017 [26] France 2010-2011 1 hospital	Primary or secondary OA 100 (50; 50) Median (range) 67 (32, 74); 66 (49, 75) 48%; 56%	Vit E blended HXLPE (Vitamys, Mathys) vs UHMWPE (Mathys) Monoblock cementless acetabular component. Cemented stem with 28mm CoCr head	Radiography, Martell, Merle d'Aubigné grade, adverse events 3 years	Unclear risk of bias due to high losses to follow up (13; 11). No suitable data for meta-analysis Total head penetration lower in Vit E HXLPE group compared with UHMWPE ($p=0.04$). No differences between groups in Merle d'Aubigné grade ($p>0.99$). No adverse events related to Vit E HXLPE
Case control study: Vit E blended HXLPE vs HXLPE				
Tanino et al. 2017 [20] Japan	170; 178 (180; 193 hips). 44; 41 (45; 45 hips) followed up	Blended Vit E HXLPE liner vs conventional HXLPE liner 32mm CoCr head	Radiography, 2 years	High risk of bias. Propensity matched but only partial follow up

2013-2015 1 centre	61.1 (range 42, 89) Sex not reported			No differences between femoral head penetration (p=0.161). Dislocation 1; 2. Infection 1; 0.

Table 2. RCT risk of bias assessment

	Sequence generation	Allocation concealment	Blinding of participants, personnel and outcome assessors	Incomplete outcome data	Selective outcome reporting	Other sources of bias	Overall
Salemyr et al. 2015 [23]	Low. Block randomisation	Low. Opaque sealed envelopes	Low. Patients blinded	Low. 1 patient did not receive vit E HXLPE as allocated. 1;1 patients died	Low. None apparent	Low. HHS higher in Vit E HXLPE group but not significantly	Low
Nebergall et al 2017 [28]	Low. Pre-assigned	Low. Sealed envelopes	Low. “Blinded”	Unclear. Uneven loss to follow up at 5 years (4; 9)	Low. None apparent	Low. Vit E group older than comparison group	Unclear
Shareghi et al. 2017 [27]	Unclear. Unequal distribution of patients to groups due to method of allocating bilateral replacements	Low. Closed envelopes	Unclear. Blinding of patients and outcome assessment not described	Unclear. Uneven loss to follow up at 5 years (1; 6)	Low. None apparent	Low	Unclear
Scemama et al. 2017 [26]	Low. Computer generated	Low. Based on order of presentation	Low. Radiography by blinded observer. High. Clinical follow up by operating surgeon	High. Loss to follow up excluding 2 deaths high (13; 11)	Low. None apparent	Low. Similar baseline characteristics	Unclear

Tanino et al. 2017 [20]	Propensity matched case control study	Not applicable		High loss to follow up		High: partial follow up	High

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Figure 1

1. Hip Prosthesis/ or Arthroplasty, Replacement, Hip/ or hip replacement.mp.
2. vitamin e.mp.
3. Tocopherol.mp. or Tocopherols/
4. tocotrienol.mp. or Tocotrienols/
5. 2 or 3 or 4
6. 1 and 5

Figure 2

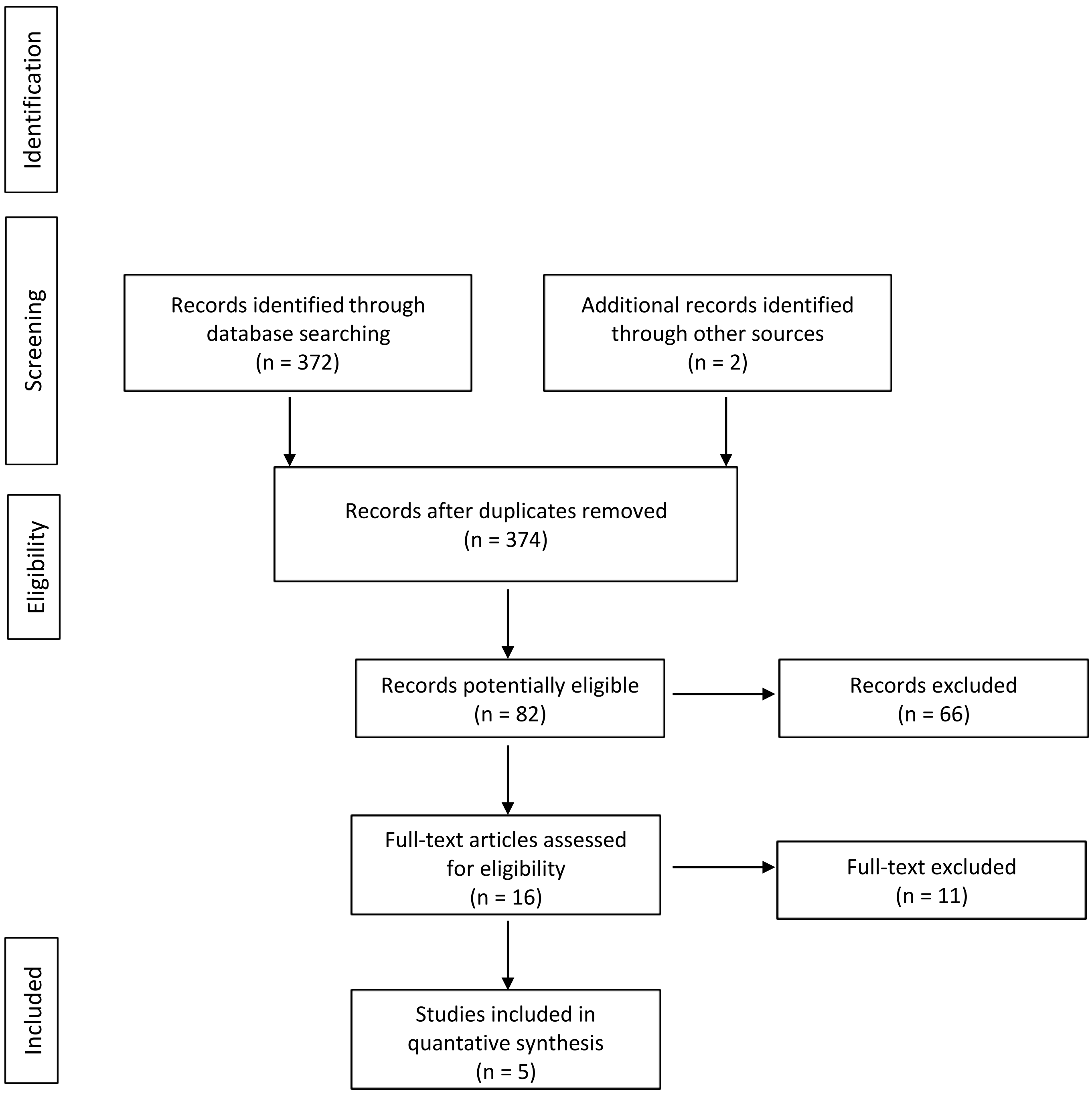
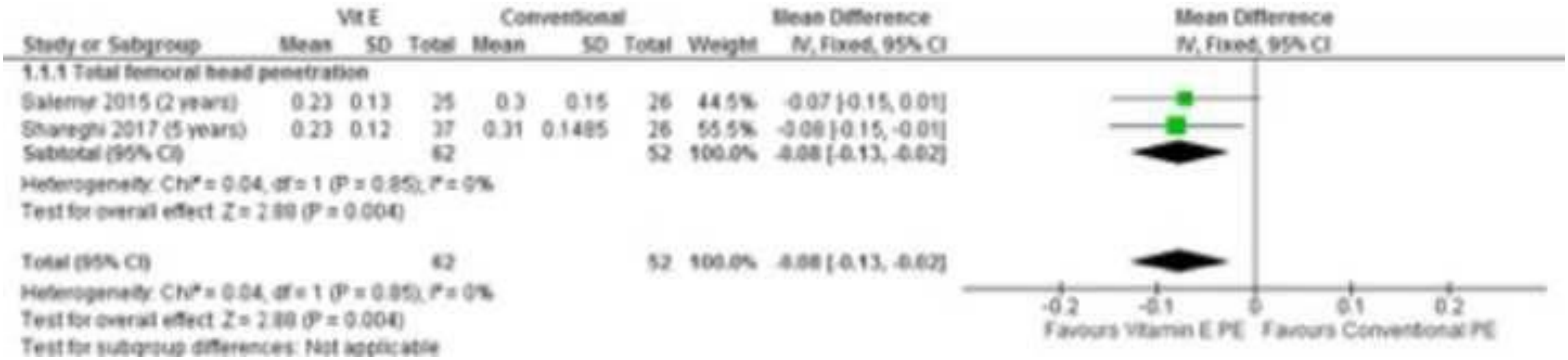


Figure 2. PRISMA flow diagram

Figure 3



Vit E
Conventional
Mean Difference
Mean Difference
Study or Subgroup Mean SD Total Mean SD Total Weight IV, Fixed, 95% CI
IV, Fixed, 95% CI
1.1.1 Total femoral head penetration
Salemyr 2015 (2 years) 0.23 0.13 25 0.3 0.15 26 44.5% -0.07 [-0.15, 0.01]
Shareghi 2017 (5 years) 0.23 0.12 37 0.31 0.1485 26 55.5% -0.08 [-0.15, -0.01]
Subtotal (95% CI) 62 52 100.0% -0.08 [-0.13, -0.02]
Heterogeneity: Chi² = 0.04, df = 1 (P = 0.85); I² = 0%
Test for overall effect: Z = 2.88 (P = 0.004)
Total (95% CI) 62 52 100.0% -0.08 [-0.13, -0.02]
Heterogeneity: Chi² = 0.04, df = 1 (P = 0.85); I² = 0%
Test for overall effect: Z = 2.88 (P = 0.004)
Test for subgroup differences: Not applicable
-0.2 -0.1 0 0.1 0.2
Favours Vitamin E PE
Favours Conventional PE

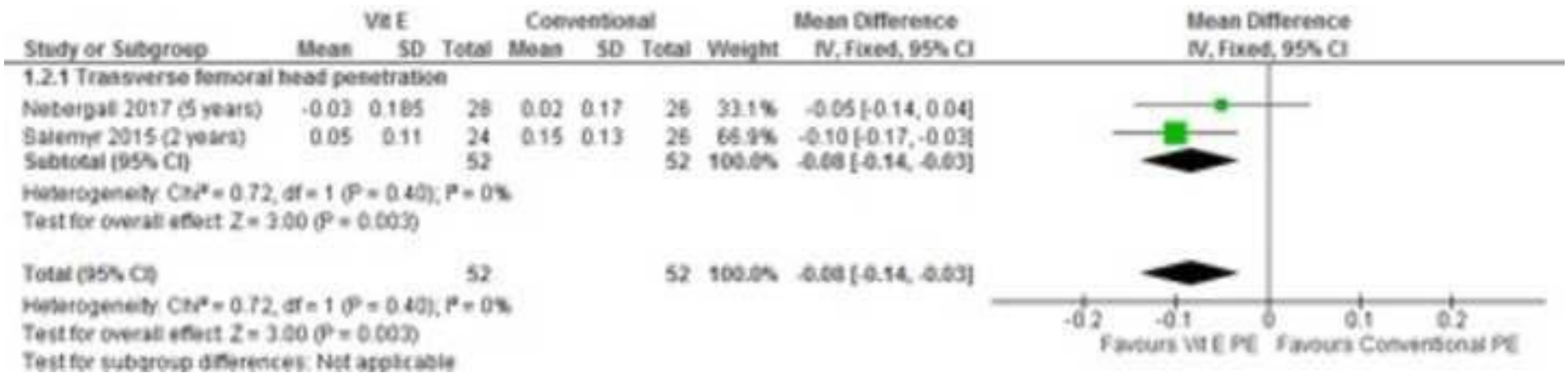

Vit E
Conventional
Mean Difference
Mean Difference
Study or Subgroup
Mean
SD
Total
Mean
SD
Total
Weight
IV, Fixed, 95% CI
IV, Fixed, 95% CI
1.2.1 Transverse femoral head penetration
Nebergall 2017 (5 years) -0.03 0.185 28 0.02 0.17 26 33.1% -0.05 [-0.14, 0.04]
Salemyr 2015 (2 years) 0.05 0.11 24 0.15 0.13 26 66.9% -0.10 [-0.17, -0.03]
Subtotal (95% CI) 52 52 100.0% -0.08 [-0.14, -0.03]
Heterogeneity: Chi² = 0.72, df = 1 (P = 0.40); I² = 0%
Test for overall effect: Z = 3.00 (P = 0.003)
Total (95% CI) 52 52 100.0% -0.08 [-0.14, -0.03]
Heterogeneity: Chi² = 0.72, df = 1 (P = 0.40); I² = 0%
Test for overall effect: Z = 3.00 (P = 0.003)
Test for subgroup differences: Not applicable
-0.2
-0.1
0
0.1
0.2
Favours Vit E PE
Favours Conventional PE

Figure 5 Click here to download 图5.jpg

Study or Subgroup	Vit E Mean	Vit E SD	Vit E Total	Conventional Mean	Conventional SD	Conventional Total	Weight	Mean Difference IV, Fixed, 95% CI
1.3.1 Vertical femoral head penetration								
Nebergall 2017 (5 years)	-0.04	0.096	28	0.07	0.14	26	31.9%	-0.11 [-0.17, -0.05]
Salemyr 2015 (2 years)	0.01	0.11	24	0.09	0.15	26	25.3%	-0.08 [-0.15, -0.01]
Shareghi 2017 (5 years)	0.11	0.09	37	0.22	0.1238	26	42.8%	-0.11 [-0.17, -0.05]
Subtotal (95% CI)			**89**			**78**	**100.0%**	**-0.10 [-0.14, -0.07]**
Heterogeneity: Chi² = 0.49, df = 2 (P = 0.78); I² = 0%								
Test for overall effect: Z = 5.51 (P < 0.00001)								
Total (95% CI)			**89**			**78**	**100.0%**	**-0.10 [-0.14, -0.07]**
Heterogeneity: Chi² = 0.49, df = 2 (P = 0.78); I² = 0%								
Test for overall effect: Z = 5.51 (P < 0.00001)								
Test for subgroup differences: Not applicable								

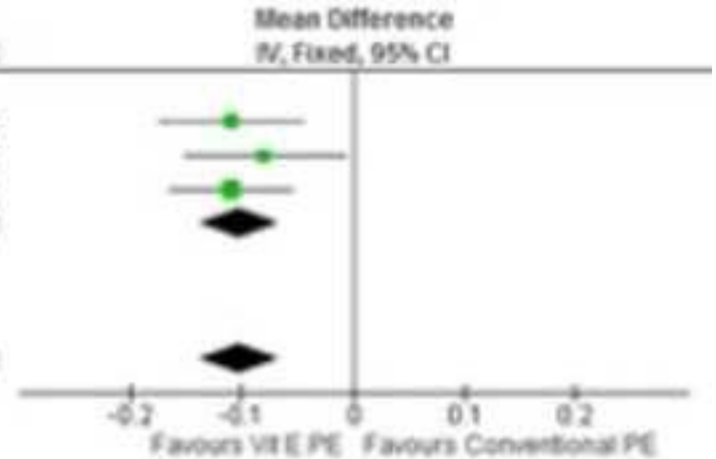


Figure 6

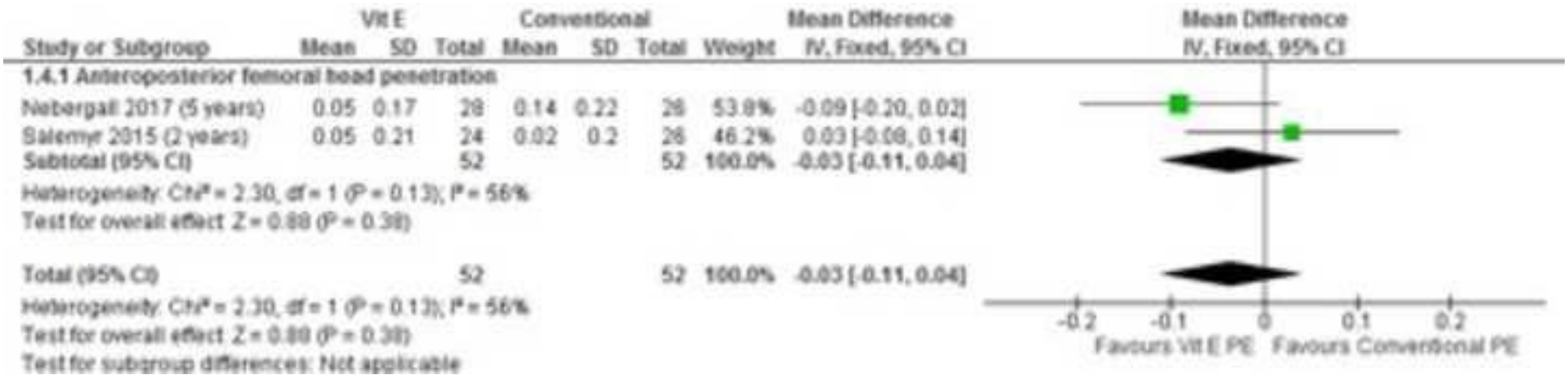

Vit E
Conventional
Mean Difference
Mean Difference
Study or Subgroup
Mean
SD
Total
Mean
SD
Total
Weight
IV, Fixed, 95% CI
IV, Fixed, 95% CI
1.4.1 Anteroposterior femoral head penetration
Nebergall 2017 (5 years) 0.05 0.17 28 0.14 0.22 28 53.8% -0.09 [-0.20, 0.02]
Salemyr 2015 (2 years) 0.05 0.21 24 0.02 0.2 26 46.2% 0.03 [-0.08, 0.14]
Subtotal (95% CI) 52 52 100.0% -0.03 [-0.11, 0.04]
Heterogeneity: Chi² = 2.30, df = 1 (P = 0.13); I² = 56%
Test for overall effect: Z = 0.88 (P = 0.38)
Total (95% CI) 52 52 100.0% -0.03 [-0.11, 0.04]
Heterogeneity: Chi² = 2.30, df = 1 (P = 0.13); I² = 56%
Test for overall effect: Z = 0.88 (P = 0.38)
Test for subgroup differences: Not applicable
-0.2
-0.1
0
0.1
0.2
Favours Vit E PE
Favours Conventional PE

Figure 7

Study or Subgroup	Vit E Mean	Vit E SD	Vit E Total	Conventional Mean	Conventional SD	Conventional Total	Weight	Mean Difference IV, Fixed, 95% CI
1.5.1 Harris Hip Score								
Nebergall 2017 (5 years)	-93	7.41	29	-97	5.19	26	85.1%	4.00 [0.61, 7.39]
Salemyr 2015 (2 years)	-90	12	24	-87	17	26	14.9%	-3.00 [-11.11, 5.11]
Subtotal (95% CI)			52			52	100.0%	2.96 [-0.17, 6.09]
Heterogeneity: Chi² = 2.44, df = 1 (P = 0.12); I² = 59%								
Test for overall effect: Z = 1.85 (P = 0.06)								
Total (95% CI)			52			52	100.0%	2.96 [-0.17, 6.09]
Heterogeneity: Chi² = 2.44, df = 1 (P = 0.12); I² = 59%								
Test for overall effect: Z = 1.85 (P = 0.06)								
Test for subgroup differences: Not applicable