Osteoarthritis and Cartilage (2008) **16,** 399–408

doi:10.1016/j.joca.2007.10.003

Osteoarthritis and Cartilage

International Cartilage Repair Society

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Review

Symptomatic efficacy of avocado–soybean unsaponifiables (ASU) in osteoarthritis (OA) patients: a meta-analysis of randomized controlled trials[1]

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Summary

Objective: To evaluate the efficacy of preparations with avocado–soybean unsaponifiables (ASUs) in osteoarthritis (OA) patients using meta-analysis on randomized controlled trials (RCTs).

Method: RCTs from systematic searches were included if they explicitly stated that hip and/or knee OA patients were randomized to either ASU or placebo. The co-primary outcome was reduction in pain and Lequesne index, leading to effect size (ES), calculated as the standardized mean difference. As secondary analysis, the number of responders to therapy was analyzed as odds ratios (ORs). Restricted maximum likelihood methods were applied for the meta-analyses, using mixed effects models.

Results: Four trials – all supported by the manufacturer – were included, with 664 OA patients with either hip (41.4%) or knee (58.6%) OA allocated to either 300 mg ASU (336) or placebo (328). Average trial duration was 6 months (range: 3–12 months). Though based on heterogeneous results, the combined pain reduction favored ASU ($I^2 = 83.5\%$, ES = 0.39 [95% confidence intervals: 0.01–0.76], $P = 0.04$). Applying the Lequesne index also favored ASU ($I^2 = 61.0\%$, ES = 0.45 [0.21–0.70], $P = 0.0003$). Secondarily, the number of responders following ASU compared to placebo (OR = 2.19, $P = 0.007$) corresponded to a number needed to treat of six (4–21) patients.

Conclusions: Based on the available evidence, patients may be recommended to give ASU a chance for e.g., 3 months. Meta-analysis data support better chances of success in patients with knee OA than in those with hip OA.

Key words: ASU, Meta-analysis, Osteoarthritis, Dietary supplements, Knee, Hip.

Introduction

Musculoskeletal diseases are prevalent and their impact is pervasive, affecting all age groups, and the associated physical disability is an enormous burden on individuals and society[1,2]. The socio-economic cost due to musculoskeletal conditions is huge, predominantly due to back pain, osteoarthritis (OA) and rheumatoid arthritis (RA)[2]. Pain is the major symptom in most arthritis patients[3], and is also the most important determinant of disability in patients with OA[4]. The prevalence of painful disabling knee OA in people over 54 years living in the United Kingdom is 10%, and 25% of these are severely disabled[5,6]. With an estimated prevalence of 3–11% in Western populations over 35 years, hip OA is the second-most frequent OA in large joints[7]. Current OA treatment aims at alleviating pain symptoms in different ways[8,9]. With rough categorization, the treatment is one of three types: non-pharmacological intervention, pharmacological treatment, or invasive/surgical intervention (including intra-articular injections, lavage, and arthroplasty)[6,7,9].

Complementary or alternative therapies (including nutraceuticals) for OA are commonly used, and it is therefore important that health care providers are aware of the evidence supporting the claims[10]. Available evidence would be easier to translate into clinical practice if the available (and published) data were analyzed and presented using an unbiased meta-analytic approach[11,12]. One proposed nutraceutical, which has shown promising results in OA patients, is avocado–soybean unsaponifiables (ASUs). Currently, the only ASU mixture investigated is made up of unsaponifiable fractions of one-third avocado oil and two-third soybean oil. Preclinical studies of ASU have shown some anti-OA properties. *In vitro*, ASU is seen to have an inhibitory effect on interleukin-1 (IL-1) and a stimulating effect on collagen synthesis in articular chondrocyte cultures[13]. Data support the notion of ASU preparations as potent inhibitors of the production of IL-8 and prostaglandin E_2 (PGE_2) by human articular chondrocytes[14]. *In vitro* data have shown ASU to stimulate aggrecan and matrix component synthesis, reduce catabolic and pro-inflammatory mediator production by human osteoarthritic chondrocytes, and partially

[1]This study was supported by grants from the Oak Foundation and Frederiksberg Hospital, Copenhagen Hospital Corporation.

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Received 21 June 2007; revision accepted 1 October 2007.

counteract the inhibitory effect of IL-1 (possibly *via* the production of transforming growth factor beta (TGF-β)) and growth factors associated with cartilage homeostasis[15,16]. Accordingly, ASU seems to prevent the osteoarthritic osteoblast-induced inhibition of matrix molecule production, suggesting that this compound may promote OA cartilage repair by acting on subchondral bone osteoblasts[17]. Ernst reviewed the available data on the efficacy of ASU in OA patients and concluded that the majority of rigorous trials suggest that ASU is effective in the symptomatic treatment of OA, although the only long-term trial was largely negative, and thus more research would be justified[18]. Ernst's conclusion corresponds to a review (in Danish) by Angermann, which concludes that the available studies indicate that ASU has an effect on the symptoms of knee and hip OA, but no effect on the structural changes occurring with OA[19].

We carried out a systematic review with a meta-analysis of the available randomized controlled trials (RCTs)[20] of studies applying ASU in the symptomatic treatment of OA. Our primary aim was to obtain an up-to-date evidence based analysis which would provide a detailed view of the symptomatic activity of ASU used in the treatment of knee and hip OA[21,22]. Our secondary aim was to investigate possible causes behind the statistical heterogeneity, emphasizing clinical heterogeneity across the included studies[24]. We used meta-regression analyses[25] to implement clinical arguments, which could result in clinical inference[26].

Methods

RETRIEVAL OF PUBLISHED STUDIES

RCTs of ASU treatment vs placebo were identified by means of a systematic literature search in the following bibliographic databases: Medline *via* PubMed (mid 1950s to Feb. 19, 2007), EMBASE *via* WebSpirs (1980 to Feb. 19, 2007), CINAHL *via* WebSpirs (1982 to Feb. 19, 2007), BiosisPreviews *via* WebSpirs (1980 to Feb. 19, 2007), Web of Science (1945–54 to Feb. 19, 2007), Scifinder (1907 to Feb. 19, 2007), Scopus (1966 to Feb. 19, 2007), and the Cochrane Library (1966 to Jan. 31, 2007). This was followed by searches of reference lists of original reports and review articles, retrieved through the described searches. Finally, we searched conference abstracts over the past 2 years *via* the established international societies of rheumatology, i.e., the OsteoArthritis Research Society International (OARSI), EUropean League Against Rheumatism (EULAR) and the American College of Rheumatology (ACR).

The search strategy consisted of the relevant keywords/MESH words for OA combined with any combination of ASU, soy or avocado for wide coverage and to limit the search to controlled studies to take into account that randomization is not always clearly defined *via* keywords, and that some controlled studies may be of interest despite lack of proper randomization. With the awareness of a higher proportion of noise in the searches, titles and abstracts were reviewed for possible RCTs, and full text references were obtained for further scrutiny where relevant.

INCLUSION AND EXCLUSION CRITERIA

We included RCTs comparing a preparation of both avocado and soybean extracts with a (double masked) placebo intervention. Studies were selected if the included patients were described as having clinical or radiographic evidence of OA. Two reviewers (RC and HB) crosschecked and agreed on diagnostic criteria in each trial. We excluded studies in conditions such as non-OA joint pain, RA, pain due to surgery or injury, and studies with mixed patient groups such as those with both OA and RA, unless the subgroup data for OA were available. No language restrictions applied.

QUALITY ASSESSMENT

The quality of studies was assessed based on randomization, masking and withdrawal. The complete reports of the RCTs that were selected for inclusion in the meta-analysis were scored by two reviewers for quality (RC and EMB), using a validated instrument[27]. The score was given as follows: if the study was described as randomized (+1); if the study was described as double masked (+1); and if there was a (detailed) description of withdrawals and drop-outs (+1). In addition, if the random allocation and the double blinding were properly described and appropriately put into practice, each item received one point extra. Conversely, if the methods (randomization and masking) were not considered appropriate, one point was subtracted from each item.

DATA EXTRACTION

Two reviewers (RC and EMB) undertook data extraction independently. Disagreements were resolved by discussion. A customized form was used to record authors of the study, year of publication, trial design, study length,

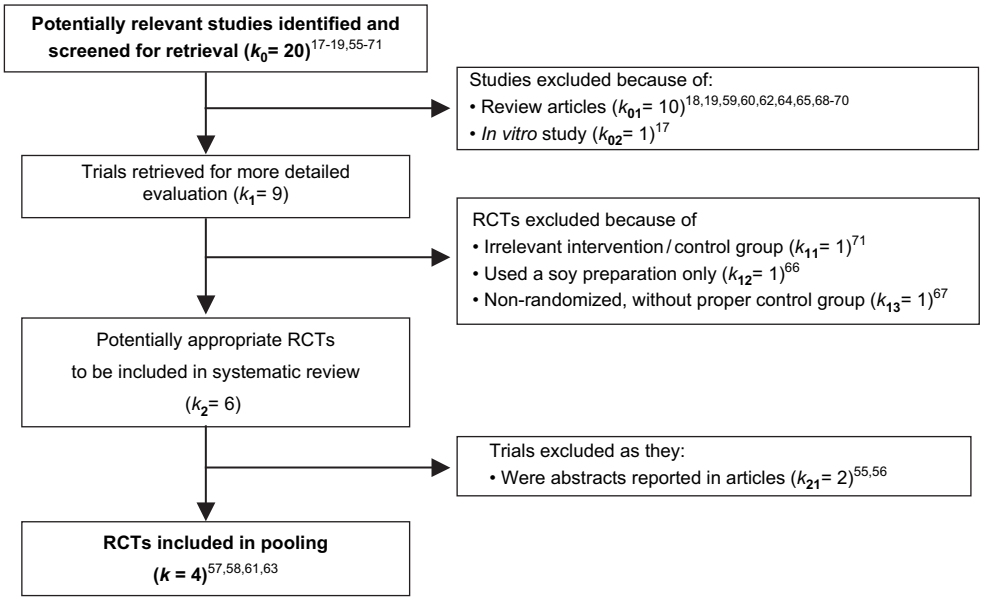


Fig. 1. Flow of RCTs included in the systematic review.

Table I
Characteristics of included RCTs: ASU for knee and hip OA

Trial	ITT population (number)	OA (%hip)	QS (score)	Duration (months)	Age (years)	Females (%)	Mean BMI (kg/m^2)	Mean KL (score)	Mean pain (0–100 mm VAS)	Mean Lequesne (index)	Definite sample size (ITT)	
											n_E	n_C
Blotman *et al.*[57]	163	38	5	3	64.1	108 (66%)	25.5	2.0	53.2	8.7	80	83
Maheu *et al.*[58]	164	31	5	6	64.1	118 (72%)	26.8	2.1	56.1	9.6	85	79
Appelboom *et al.*[61]	174	0	3	3	64.9	140 (81%)	28.8	2.0	53.9	9.4	86	88
Lequesne *et al.*[63]	163	100	5	12	63.2	61 (37%)	25.9	2.0	50.2	9.5	85	78
Combined	*664**	*41†*	*4.5†*	*6†*	*64.1†*	*107 (64%)†*	*26.8†*	*2.0†*	*53.4†*	*9.3†*	*336**	*328**

QS: quality score (Jadad) (ranging from 0 to 5); KL: radiographic score (estimated as the weighted-mean); n_E and n_C are the number of individuals in the exposed and control group (i.e., ASU and placebo), respectively.
*Calculated as the sum of the values above.
†Estimated as the pooled mean value, calculated as a weighted-average based on the number of patients included in each study.

number of patients randomized (N_{total}), number of patients in each group included in the intention-to-treat (ITT) individual study statistical tests (n_E and n_C), average patient age, sex, site of OA (knee, hip or both) handled as the fraction (%) of patients with OA in the hip. For each of the continuous outcomes extracted, the level at baseline was estimated for the following: weighted-mean Kellgren–Lawrence (KL) (radiographic) score, body mass index (BMI), pain, and the Lequesne index.

OUTCOME MEASURES

The primary outcome measure was the magnitude of pain reduction[28] with ASU compared to placebo. In addition, we looked at other outcome measures in rheumatology (OMER) ACT-III relevant outcomes[21], and the Lequesne index[29], applied in all the individual RCTs, were used to evaluate the patients' global assessment[22]. Finally, we extracted the reported number of responders per group after each intervention, ASU or placebo, respectively, for each included study.

STATISTICAL ANALYSIS

For each of the continuous outcomes (pain and the Lequesne index), we calculated the *z*-statistics based on the available data, using standard formulae[30,31]. Based on these *z*-statistics and the number of observations in each group, we estimated the standardized mean difference (SMD)[32], which was applied as effect size (ES): the ratio of the treatment effect to the pooled standard deviation of these differences[31,33]. The variance (associated with the SMD value) was estimated based on the individual study SMD and the number of patients included (n_E and n_C)[32,34]. Clinically, ES $\geq$ 0.2 is considered small, ES $\geq$ 0.5 is moderate (and would probably be recognized clinically[35]), and ES $\geq$ 0.8 is large[6,7]. The odds ratio (OR) was estimated for the dichotomous efficacy data[36], i.e., based on the number of responders in each group. Based on the combined OR, we estimated the number needed to treat [NNT, with 95% confidence intervals (CI)], as it enables direct translation into clinical practice[37,38]. To adjust for the individual study "baseline risk"[37], we applied the weighted, pooled control event-rate[39,40] applying visual Rx[41,42]. To combine the individual study results, we carried out meta-analyses, using SAS software[34] (version 9.1.3), applying restricted maximum likelihood (REML) within a mixed effects model setting[43]. Maximum likelihood approaches in meta-analysis[44,45] enable the meta-analyst to print the solutions: the EB estimates[46,47]. This methodology has previously been informally validated and described in detail[32,48]. We examined heterogeneity between trials with a standard *Q*-test statistic, which follows a χ^2 distribution[49], leading to the I^2 statistic, i.e., the proportion of variance unexplained[50,51]. The I^2 index quantifies the impact[50], rather than the extent (i.e., τ^2)[52] of heterogeneity in a meta-analysis. It is important to include *a priori* defined ways to investigate potential sources of clinical heterogeneity, even when applying a random effects model by default[23]. If this is not done, it might result in the exploratory investigations affecting the overall conclusions drawn[24], based on spurious chance findings. We assessed the extent to which study level variables were associated with the ES and ($\log_e$) OR by fitting multiple REML based meta-regression models[23,25]. *A priori*, we defined a relevant study level covariate[48,53] as one that would decrease all three I^2 statistics (one for each of the separate outcomes)[54] as the between study variance for each outcome decline as a consequence of inclusion in the (mixed effects) statistical model. Although tempting, covariates with errors around the estimate (e.g., average age) would not be characterized as a detailed trial feature, thus predictive inference based on these should generally be discouraged in study level meta-regression analysis[26].

Results

CHARACTERISTICS OF TRIALS

The quality of reporting of meta-analyses (QUOROM) recommended flowchart[20] in Fig. 1 displays the eligibility details of the studies identified by the combined search strategy. After removing abstracts from studies with obviously irrelevant objectives/designs, a restricted set of potentially relevant articles and possibly relevant reviews were scrutinized and reviewed ($k_0 = 20$) according to the inclusion/exclusion criteria[17–19,55–71]. Among these potential papers for inclusion, the majority was excluded for the following reasons: one paper was a review article assessing the placebo effect across several anti-arthritic preparations (among which ASU)[59], nine of the papers were reviews focusing on herbs (and ASU) in general[18,19,60,62,64,65,68–70],

and one article was based on an *in vitro* study[17]. Accordingly, these papers were excluded after thorough reading and examined for further studies that might be revealed in their references. Of the nine remaining, potentially possible RCTs: one study was excluded due to not applying a relevant intervention/control group[71], another paper used a soy-only preparation[66], and one (although large scale) study was omitted due to use of an open-label (non-randomized) design, without a proper control group[67]. After a second reading, we decided to exclude yet two abstracts[55,56], as they presented preliminary data from RCTs later published in full[58,63].

As a result we obtained four trials[57,58,61,63] that fulfilled the inclusion criteria and were included in the meta-analysis. All studies were supported by the Laboratoires Expanscience, Courbevoie, France: applying PIASCLEDINE®300 (avocado:soybean ratio 1:2). These four studies represent 664 OA patients with hip (41.4%) and knee (58.6%) joint affected, randomly allocated to either one capsule a day containing 300 mg ASU ($n_E = 336$) or an identical masked placebo ($n_C = 328$). The (N_{total}) weighted-mean trial duration corresponded to a 6-month trial on average, generally assessed in high quality studies (weighted-average Jadad: 4.5). Patient characteristics are presented in Table I.

EFFICACY

Figure 2(A) shows the ES in pain reduction with ASU vs placebo. Pooling the data from the four individual trials reporting pain as an explicit outcome produced a REML based (i.e., random effects model) combined ES of 0.39 (95% CI: 0.01−0.76, $P = 0.04$), supporting efficacy of ASU as opposed to placebo. The result is based on studies showing a severe impact of heterogeneity ($I^2 = 83.5\%$) with a between study variance of more than zero ($\tau^2 \approx 0.1202$). Therefore possible sources of heterogeneity need to be investigated. Figure 2(B) shows the ES in the algo-functional Lequesne index reduction with ASU vs placebo. Pooling the data from the four individual trials reporting Lequesne as an explicit outcome produced a highly significant REML based (i.e., random effects model) combined ES of 0.45 (95% CI: 0.21−0.70, $P = 0.0003$). This strongly supports efficacy of ASU treatment as opposed to placebo. The result is based on studies showing a large impact of heterogeneity ($I^2 = 61.0\%$) with a between study variance of more than zero ($\tau^2 \approx 0.0380$). Accordingly, possible sources of heterogeneity should therefore be investigated. Figure 2(C) shows the OR corresponding to the number of patients responding to treatment, that is, the number (r_E and r_C) each individual RCT explicitly reports on responders to treatment. Pooling the data from the four individual trials produced a significant REML based (i.e., random effects model) combined OR of 2.19 (95% CI: 1.24−3.86, $P = 0.007$), in favor of ASU opposed to placebo, as more patients responded to therapy. By adjusting this OR with the weighted, pooled control event-rate of 33.4%, data correspond to a NNT of six (95% CI: 4−21) patients. The result is based on studies showing a large impact of heterogeneity ($I^2 = 68.9\%$) with a between study variance of more than zero ($\tau^2 \approx 0.2324$). Accordingly, possible sources of heterogeneity should be investigated.

EXPLORING CLINICAL HETEROGENEITY

As presented in Table II, the available study level covariates reduce (or increase) the between study variance in

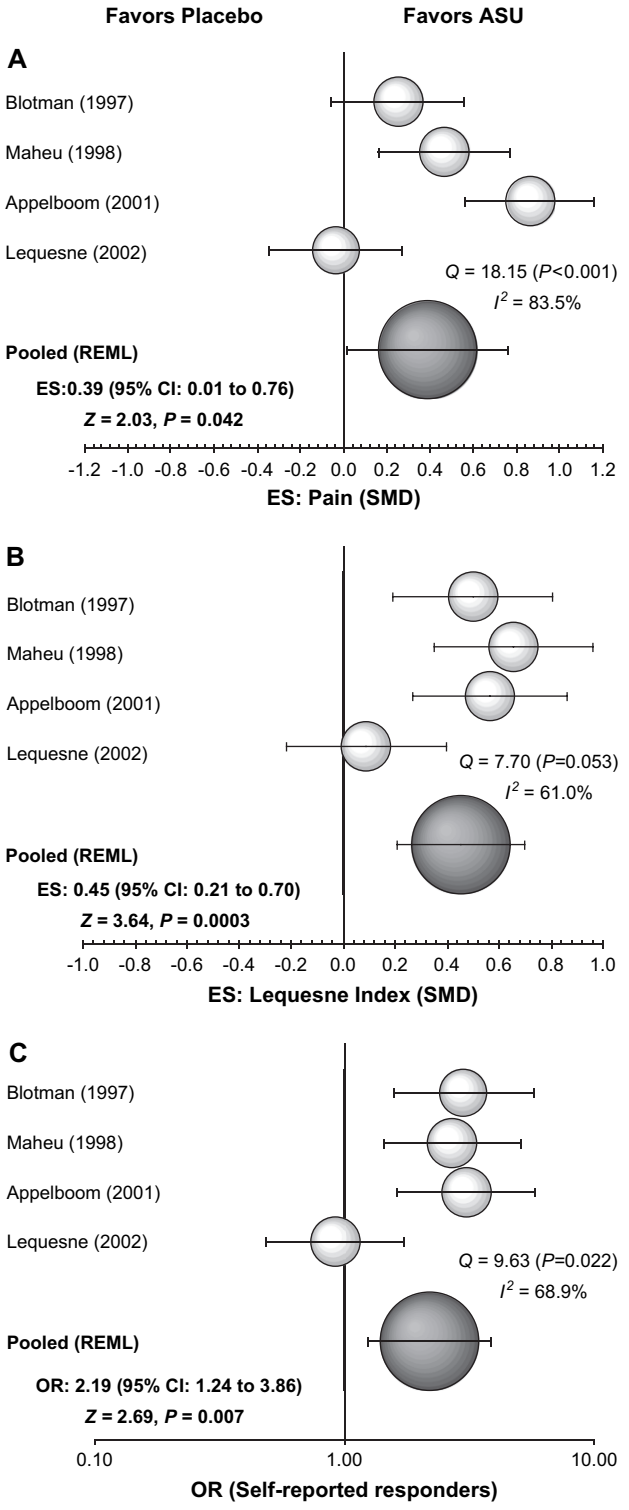


Fig. 2. Forest-plots of trials comparing ASU with placebo on pain, Lequesne, and the number of responders to treatment, respectively; size of every circle is proportional to the precision of each efficacy estimate.

Table II
Statistical data explaining possible clinical reasons for heterogeneity among available study level covariates

Outcome	ES: pain		ES: Lequesne		$\log_e$(OR): responders	
Variable	$\tau^2 = 0.120$	$I^2 = 83.5\%$	$\tau^2 = 0.038$	$I^2 = 61.0\%$	$\tau^2 = 0.232$	$I^2 = 68.9\%$ (%)
%Hip OA	≤0	≤0	≤0	≤0	≤0	≤0
Jadad QS	0.039	27.1	0.061	98.4	0.324	96.2
Duration	0.074	51.1	0.004	6.4	≤0	≤0
Age	≤0	≤0	0.010	16.6	0.019	5.5
%Females	0.011	7.8	≤0	≤0	≤0	≤0
BMI	0.015	10.7	0.051	82.2	0.315	93.5
KL score	0.160	>100	0.056	89.4	0.398	>100
Pain	0.010	68.2	≤0	≤0	0.065	19.3
Lequesne	0.187	>100	0.068	>100	0.331	98.0

several ways. This is why we focused solely on covariates that are able to reduce the impact of heterogeneity for all outcome measures (pain, Lequesne, and number of responders) simultaneously: %patients with hip OA, duration of the individual trial, average patient age, %females in the included population, and finally the average level of pain at baseline. The covariates: "average patient age" and the "average level of pain" in the four existing trials had very similar values; hence they would probably be irrelevant to explain the heterogeneity between trials, except for possible cases where individual patient data (IPD) meta-analysis is applicable. Based on these *post hoc* statistical considerations, details on the joint affected and study duration were considered applicable for clinical practice. These were included in the explicit *post hoc* meta-regression analyses presented in Fig. 3. Please see the Appendix for a detailed description of EB estimates after inclusion of both covariates simultaneously.

Discussion

Trials applying the ASU preparation from Laboratoires Expanscience (PIASCLEDINE®300) for knee or hip OA collectively demonstrated small to moderate treatment effects on symptoms (i.e., pain and Lequesne index). Patients receiving ASU were twice as likely to respond to treatment than patients allocated to placebo. The pooled ES for pain reduction comparing ASU to placebo was 0.39, which according to current European standards represents a modest but clinically significant treatment benefit from ASU[6,7]. Translated into an average European knee and hip OA patient[72,73], this estimate would correspond to a 6.3 (10.7%) and 6.4 (11.3%) mm visual analog scale (VAS) pain reduction, respectively. Our secondary analysis showed that patients prescribed ASU will be more likely respond to therapy, than patients treated with placebo. These data indicate that on a major public health scale[2], one patient of six treated with ASU will benefit from the treatment.

Clinical trials and meta-analyses have mostly addressed the question of how well a treatment works overall. Both these approaches, while useful in estimating a population effect, do not show how to treat individuals[26]; patients often respond differently to treatment. To address this diversity, meta-analyses need to evolve from simple pooling to multidimensional exploration, creating response surface models to summarize evidence along multiple covariates of interest[74]. As presented in the Appendix, EB estimates indicated that after 6 months' ASU treatment, knee OA patients would experience a large clinical effect on pain reduction (ES: 0.99 [0.54−1.44]), whereas the same statistical model revealed that hip OA patients might not experience any pain relief after ASU therapy (ES: −0.44 [−1.05−+0.17]). The clinician will typically be interested in the target joint rather than the sex of the patient. We admit though that knee OA may be associated with female gender in contrast to hip OA in males[75].

How is this diversity possible? The majority of rigorously selected individual trial data available to date, suggests that ASU is effective for the symptomatic treatment of OA[57,58,61] even though the only long-term (hip OA only) trial[63] had a largely negative result[18]. To assess the clinical question we might turn to the study by Maheu *et al.*[58] − which we have categorized as a high quality study (Table I), and it presented detailed joint specific summary statistics for both knee and hip OA patients after 6 months' ASU treatment. The observed *post hoc* calculated clinical improvement with regard to pain reduction after 6 months' ASU therapy corresponded to a significant moderate to large clinical improvement (ES = 0.69 [95% CI: 0.13−1.26]; $P = 0.02$) in hip OA patients, whereas the borderline significant improvement in knee OA patients corresponded to a small to moderate efficacy (ES = 0.35 [−0.02−0.72]; $P = 0.07$). Compared to our empirical prediction model, we interpret this contradictory result as a consequence of having the only long-term study (≥1 year) by Lequesne *et al.*[63] providing the meta-analysis model with the only 100% hip OA population. From a statistical viewpoint, trial duration would be characterized as a detailed trial feature (without any error around the estimate, as a consequence of the original RCT study protocol); accordingly, predictive inference based on meta-regression would be considered sufficient[26]. Conversely, the clinical efficacy × joint interaction might lead to a better statistical model on average (i.e., reducing the between trial variability), whereas the predictive model most certainly calls for an IPD meta-analysis[76]. In general, meta-regression − which we used − can be used to estimate such interactions using detailed published data, but it lacks statistical power, and is prone to bias, whereas the use of IPD can improve estimation of such interactions, among other benefits, but it can be laborious to collect and analyze[77].

Supportive data of a disease-modifying anti-OA activity of ASU have been presented in animal studies. A recent placebo-controlled animal study by Kawcak *et al.* evaluated

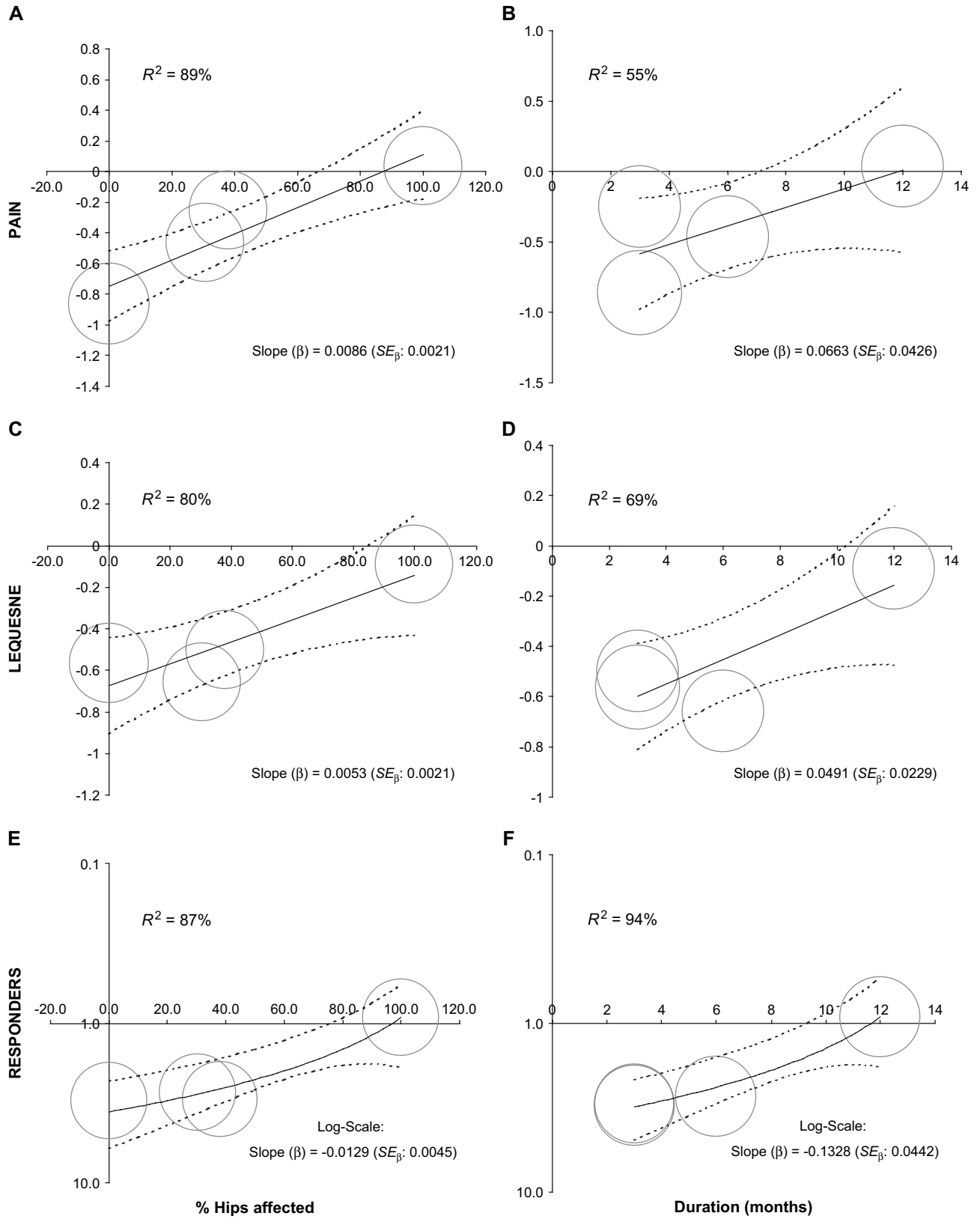


Fig. 3. Meta-regression relations: ESs (ES_{pain}, $ES_{Lequesne}$, and $OR_{responders}$) on the vertical axis are plotted against the %hip OA patients included (A, C, and E) and trial duration (B, D, and F), respectively. Size of every circle is proportional to the precision of each efficacy estimate. The solid line indicates the predicted treatment magnitude and direction, whereas the dashed lines represent 95% CI using a REML based model.

the efficacy of ASU extracts for the treatment of experimentally induced OA in 16 horses[78]. ASU extracts given for 70 days had no effect on signs of pain or lameness; however, there was a reduction in severity of articular cartilage erosion and synovial hemorrhage and increase in articular cartilage glycosaminoglycan synthesis[78]. These objective data lead the authors to conclude that the use of ASU extracts might serve as a disease-modifying treatment for management of OA in horses. Similarly, in an ovine meniscectomy animal model an anabolic effect on chondrocytes was demonstrated, resulting in the stimulation of matrix production[79].

The biochemical pathway associated with the possible efficacy of ASU in OA has not been clarified. In a recent paper by Gabay *et al.* the effect of ASU on chondrocyte intracellular responses was examined, suggesting a novel mechanism of ASU-mediated activity[80]. Their results indicated that ASU might express a unique range of activities, which could counteract deleterious processes involved in OA, such as inflammation. However, as emphasized by the authors more studies are needed to substantiate this possible mode of action in a clinical setting. Since the concentration of ASU in blood and synovial fluid is not known – and ASU is composed of different components – the activity of the various components needs to be determined before defining the optimal ASU concentration for future experiments[80].

Oral non-steroidal anti-inflammatory drugs are widely used in OA without proven long-term efficacy[81]. In this context, the results with ASU indicate a relevant clinical effect with a short term, general ES larger than other medica[7], including paracetamol (acetaminophen)[82]. Four domains – including joint imaging in long-term studies (studies $\geq$ 1 year in duration) – have been identified as core outcome measures[21] that should be evaluated in Phase III clinical trials of knee, hip, and hand OA[22]. Unfortunately, only one of the included studies could be considered a long-term study in this respect[63], the primary end point in the study was a change of the joint space width (JSW) on plain anteroposterior radiographs of the pelvis in the standing position after 2 years' treatment. The overall comparison of the evolution of JSW showed no difference between the ASU and placebo. However, in a subgroup analysis with patients dichotomized according to the median value of the baseline JSW, the joint space loss in the most severely affected subgroup of patients was significantly greater in the placebo group than in the ASU group. In the less severely affected subgroup of patients the JSW decrease was identical with no difference in ASU and placebo groups[63]. The authors had no explanation for this unexpected result of their *post hoc* analysis.

The possibility of publication bias with a preference for positive results cannot be excluded[83]. However, we found no indication of congress abstracts not being published (as a peer reviewed paper) and non-significant results of ASU have been published as well[55,63]. The total number of studies included in the present meta-analysis seemed too sparse to include a formal graphic test for publication bias[84,85]. In our opinion, the most important limitation associated with the present meta-analysis is the fact that all the included studies were industry funded, which may augment the risk of bias mentioned above: there is evidence suggesting that trials funded by for-profit organizations may be more positive due to biased interpretation of trial results[86,87]. Likewise, there is evidence that industry supported reviews of drugs should be read with caution as they have more favorable conclusions than corresponding Cochrane reviews[88]. We declare that we have no conflicts of interest in regard to ASU and OA; this critical review was initiated based on (local) medical considerations discussed in Denmark[19].

As a conclusion of this meta-analysis, we suggest that ASUs are no worse and no better for treatment of OA than other medications. As there is no evidence of significant adverse effects of ASU, patients may be recommended to give ASU a chance for e.g., 3 months, after which a balanced review of the individual effect is necessary. The health professional should be aware that the combined evidence behind such advice supports a better chance of success in patients with knee OA than in those with hip OA.

Conflict of interest

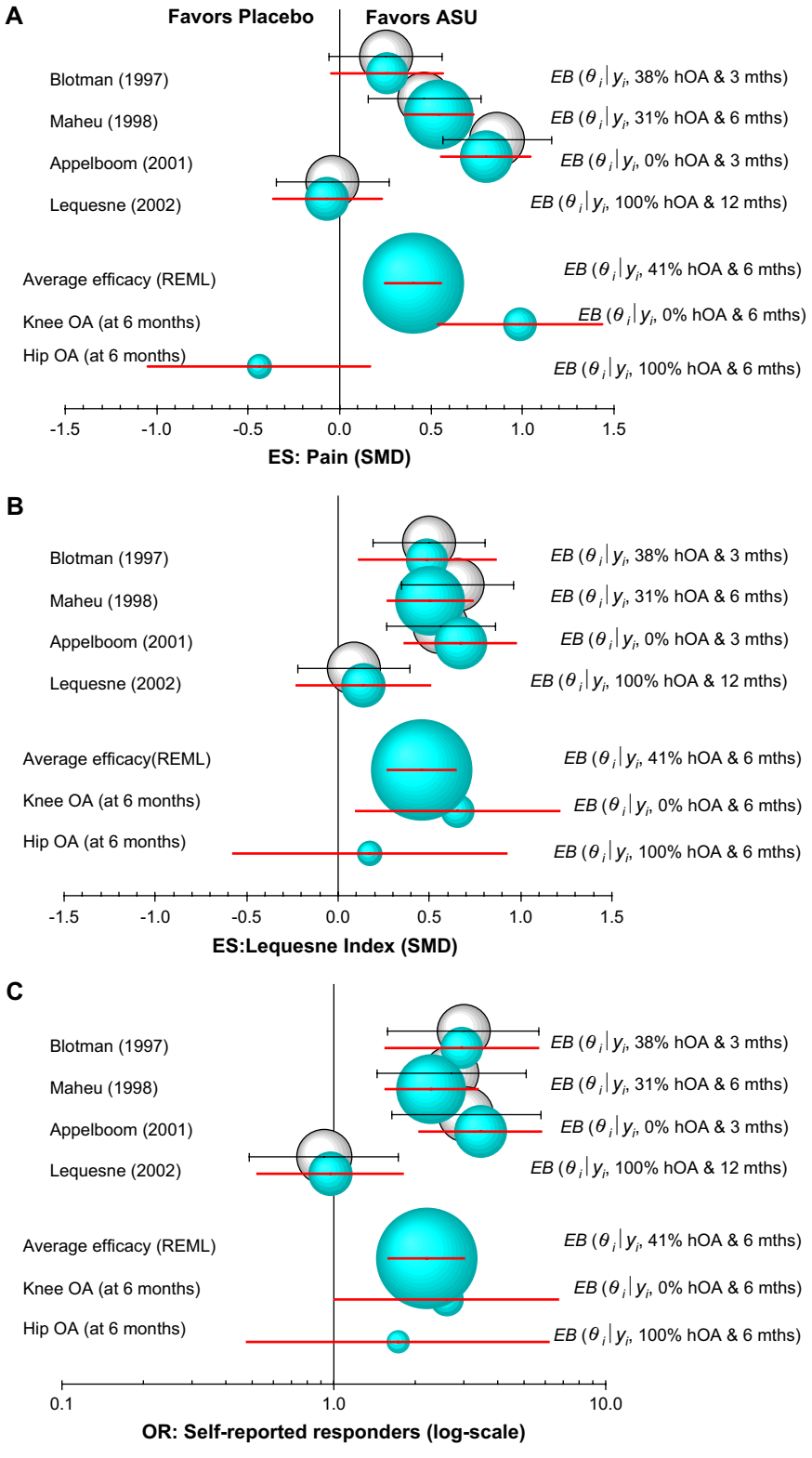
None of the authors have anything to disclose.

Acknowledgments

We acknowledge the personal and scientific support of Professor Bente Danneskiold-Samsøe, M.D., Head of the Parker Institute and the linguistic support of Mette Gad, M.A.

Appendix. Empirical Bayes estimates

To adjust simultaneously for both relevant covariates: %hips affected and duration of trial, we combined these two in the model, corresponding to a three-dimensional analysis. These multivariate analyses[48] can be illustrated using a conditionally independent hierarchical (i.e., empirical Bayes [EB])[47] modified meta-analysis forest-plot (see Appendix figure)[48]. In the adjusted analyses we included each original study's characteristics (see Table I, %hips affected and duration of trial) in the model, based on the mixing distribution serving as a prior distribution, and resulting in (conditional-) adjusted EB estimates for each study[46–48]. Based on these adjusted estimates, it was evident that the average patient would experience a small to moderate pain reduction (ES = 0.40 [0.25–0.55]) after 6 months' treatment with ASU. Focusing on knee and hip joint separately, these data indicate that knee OA patients would experience a large clinical effect according to pain reduction (ES: 0.99 [0.54–1.44]). However, these theoretical estimates would indicate that patients with hip OA might even experience increased pain after ASU treatment for 6 months (ES: −0.44 [−1.05–0.17]). Similarly, the clinical efficacy according to the Lequesne index was evident, as the average patient experienced a close to moderate improvement (ES: 0.46 [0.27–0.64]). The joint specific efficacy after 6 months' treatment: knee joints showed a moderate to large clinical improvement (ES: 0.65 [0.10–1.21]), whereas patients with hip OA might experience less than a small clinical effect, based on a non-significant test (ES: 0.17 [−0.57–0.92]). Finally, in regard to heterogeneity and *post hoc* adjusted efficacy, data indicated that the average patient is more likely to respond to treatment after ASU as opposed to placebo therapy for 6 months (OR: 2.20 [1.60–3.02]), although this is only evident in knee OA patients (knee OA, ES: 2.60 [1.01–6.70] and hip OA, ES: 1.72 [0.48–6.17], respectively).


A
Favors Placebo
Favors ASU
Blotman (1997)
Maheu (1998)
Appelboom (2001)
Lequesne (2002)
Average efficacy (REML)
Knee OA (at 6 months)
Hip OA (at 6 months)
EB (θi | yi, 38% hOA & 3 mths)
EB (θi | yi, 31% hOA & 6 mths)
EB (θi | yi, 0% hOA & 3 mths)
EB (θi | yi, 100% hOA & 12 mths)
EB (θi | yi, 41% hOA & 6 mths)
EB (θi | yi, 0% hOA & 6 mths)
EB (θi | yi, 100% hOA & 6 mths)
-1.5 -1.0 -0.5 0.0 0.5 1.0 1.5
ES: Pain (SMD)
B
Blotman (1997)
Maheu (1998)
Appelboom (2001)
Lequesne (2002)
Average efficacy(REML)
Knee OA (at 6 months)
Hip OA (at 6 months)
EB (θi | yi, 38% hOA & 3 mths)
EB (θi | yi, 31% hOA & 6 mths)
EB (θi | yi, 0% hOA & 3 mths)
EB (θi | yi, 100% hOA & 12 mths)
EB (θi | yi, 41% hOA & 6 mths)
EB (θi | yi, 0% hOA & 6 mths)
EB (θi | yi, 100% hOA & 6 mths)
-1.5 -1.0 -0.5 0.0 0.5 1.0 1.5
ES:Lequesne Index (SMD)
C
Blotman (1997)
Maheu (1998)
Appelboom (2001)
Lequesne (2002)
Average efficacy (REML)
Knee OA (at 6 months)
Hip OA (at 6 months)
EB (θi | yi, 38% hOA & 3 mths)
EB (θi | yi, 31% hOA & 6 mths)
EB (θi | yi, 0% hOA & 3 mths)
EB (θi | yi, 100% hOA & 12 mths)
EB (θi | yi, 41% hOA & 6 mths)
EB (θi | yi, 0% hOA & 6 mths)
EB (θi | yi, 100% hOA & 6 mths)
0.1 1.0 10.0
OR: Self-reported responders (log-scale)

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