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J.H. Salmon, A.C. Rat, J. Sellam, M. Michel, J.P. Eschard, Francis Guillemin, D. Jolly, Bruno Fautrel

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JH Salmon[1,2], AC Rat[3,4], J Sellam[5], M Michel[1], JP Eschard[1], F Guillemin[4], D Jolly[2,6], B Fautrel[7]

[1] Rheumatology Department, Maison Blanche Hospital, Reims University Hospitals, Reims, F-51092, France.

[2]University of Reims Champagne-Ardenne, Faculty of Medicine, EA 3797, REIMS, F-51095, France.

[3]Rheumatology Department, CHU de Nancy, Hôpitaux de Brabois, Vandoeuvre-lès-Nancy, France.

[4]Université de Lorraine, Université Paris Descartes, Apemac, EA4360, 54000 Nancy, France; INSERM, CIC-EC 1433, 54000 Nancy, France.

[5]Rheumatology Department, Saint-Antoine Hospital, Inserm UMR S_938, Sorbonne Universités UPMC Univ Paris 06, Assistance Publique - Hôpitaux de Paris (AP-HP), DHU i2B, Paris, France.

[6]Department of Research and Innovation, Robert Debré Hospital, Reims University Hospitals, Reims, F-51092, France.

[7]Rheumatology Department, Université Pierre et Marie Curie Curie - Paris 6, GRC08, Institut Pierre Louis de d'Epidémiologie et Santé Publique, Pitié-Salpêtrière Hospital, 47-83 Boulevard de l'Hôpital, 75013, Paris, France.

jhsalmon@chu-reims.fr, ac.rat@chu-nancy.fr, jeremie.sellam@sat.aphp.fr, mmichel@chu-reims.fr, jpeschard@chu-reims.fr, francis.guillemin@chu-nancy.fr, djolly@chu-reims.fr, bruno.fautrel@psl.aphp.fr

Correspondence and reprint requests to: Pr Bruno FAUTREL, Service de Rhumatologie, Groupe Hospitalier Pitié-Salpêtrière, 83 boulevard de l'Hôpital, 75651 Paris cedex 13. Tel: +33 1 421 77801, Fax: +33 1 421 77802. Email: bruno.fautrel@psl.aphp.fr.

Running title: Costs of hip and knee osteoarthritis

Introduction

Many studies have explored the economic burden of rheumatic diseases, mainly inflammatory arthritides and musculoskeletal disorders such as back problems (1–3). OA is the most frequent or prevalent chronic joint disease and a major contributor to functional disability and loss of autonomy in older adults (4). According to the World Health Organization in 2010, among 289 diseases, OA has become the 11th leading cause of years lived with disability, an increase from 16th to 11th within only 10 years (5). Moreover, OA has become a research priority in the European Community (Horizon 2020 Framework Programme) (6).

For a long time, OA, corresponding to a whole-joint disease involving cartilage, subchondral bone and synovium, was considered only a consequence of aging (7). Hip and knee OA causes the greatest burden to the population in terms of pain, stiffness and disability, thereby leading to the need for prosthetic joint replacement for the most severe cases (8). The disease may have various personal, social and economic consequences for patients, their environment and society: reduced productivity or premature exit from the workplace, autonomy loss, need for help, as well as increased healthcare use and sometimes institutionalization (9).

OA prevalence is expected to increase because of several concomitant factors: population growth and aging due to increasing life expectancy, increased overweight and obesity prevalence, and lack of disease-modifying OA drugs able to modify the progression of the disease. Thus, the burden to society is expected to increase substantially, at least for hip or knee replacement surgery (10). In addition, OA prevalence could result in increased cardiovascular morbidity as an indirect consequence of reduced physical activity and increased need for nursing home facilities for the elderly population (11)**.**

The economic consequences of OA need to be investigated, especially those related to hip and knee OA. The present study aimed to provide, via a systematic review of the literature, an

overview of the economic consequences – overall costs as well as cost breakdown – of hip and knee OA worldwide.

Methods

Research question and literature search

We performed a systematic search of articles in EMBASE, MEDLINE via PubMed, Scopus and Cochrane databases across the period from 1966 to December 2014. We used the Participants, Interventions, Comparisons and Outcomes (PICO) strategy for the research question as follows: population, OA; intervention, analysis of costs of illness; control, different treatments and no treatment OA; and outcome, direct and indirect costs (12). The algorithm used to search article titles, abstracts and key words in EMBASE, MEDLINE and Scopus was ("Osteoarthritis"[Mesh]) AND "Cost of Illness"[Mesh]), (Direct cost AND Osteoarthritis), (Indirect cost AND Osteoarthritis). To optimize our research, we used only one keyword, “osteoarthritis,” in the search equation for the Cochrane database.

Article selection

The titles and abstracts of all articles identified were independently screened by 2 rheumatologists (JHS and MM) who used predefined criteria to identify relevant articles; disagreements were resolved by consensus. Articles without an abstract and those in non-English or -French languages were excluded (Figure 1). Abstracts were excluded if 1) OA was not the main subject, 2) no cost data were reported, 3) no primary data were reported (e.g., literature review), 4) data focused only on surgical procedures, and 5) the abstract was from a society meeting before 2012. The full texts of the remaining articles were then retrieved. We excluded articles that had insufficient, imprecise or incomplete data (e.g., indirect costs only, lack of direct cost breakdown).

Data extraction

Data extracted were the database (insurance- or clinic-based), sample size (population-based or worker sample) and country of the study; patient demographics (gender, occupation profile [i.e., workers only or not]); and disease characteristics (OA definition [i.e., self-reported or based on American College of Rheumatology (ACR) criteria (13,14)], involved joints, clinical expression and symptom intensity, radiologic features and Kellgren & Lawrence stage).

Costs

All costs were extracted from articles that described assessing them from a payer or societal perspective. Direct costs included medical doctor (MD) visits; hospitalizations, including emergency room visits, imaging or biologic work-up; treatment costs that were drug-related or not; joint replacement surgery; and complementary and alternative medicine use (acupuncturist, herbalist, and osteopathy). In addition, non-medical costs (transport, auxiliary devices and temporary caregivers) were included when available. Indirect costs included all types of productivity loss: temporary or long-term sick leave as well as disability status. Total costs were the sum of direct and indirect costs. With incomplete data, the corresponding author of the article was contacted by email to collect additional relevant information.

Extracted or elicited costs were converted to an annual cost and to 2013 euros (€) by using the Consumer Price Index of the relevant countries and the 2013 Purchasing Power Parities (Organization for Economic Cooperation and Development, www.oecd.org) between these countries and the European Union average (15).

Statistics

Costs are presented as mean ± SD and 95% confidence interval (95% CI). Direct and indirect costs per patient per year were summarized separately across studies and countries. Average

costs were weighted by study sample size and were used to calculate the overall mean annual costs induced by hip or knee OA.

Results

Literature search

We obtained 98 article titles with abstracts through the meta-search, and 45 abstracts were selected. The assessment of full texts resulted in 32 articles selected for the review (Figure 1) (16–47).

Selected studies

The 32 articles were heterogeneous (Table 1). Data sources were national surveys (n=18), insurance or administrative databases (n=8), convenience sample from hospital-based cohorts (n=5) or a randomized clinical trial (n=1). Sample sizes varied from 70 to 3,400,000. Seventeen studies focused on the presence of comorbidities in OA patients. Studies were conducted in North America (n=19), Europe (n=10), and Australasia (n=3). Periods of publication were 1995-2000 (n=5), 2000-2005 (n=6), 2005-2010 (n=8), and after 2010 (n=13).

OA characteristics

Most of the articles (n=27) included all types of OA patients, without restriction on age, gender or occupation; 5 focused on workers (< 65 years old). The diagnosis of OA was reported by the patient (n=8) or based on ACR criteria (n=24). In these latter articles, only 5 included radiographic data to assess OA severity based on Kellgren & Lawrence stage. The median patient follow-up was 12 months (interquartile range [IQR] 6–12).

A total of 19 articles estimated the overall OA economic burden without separating OA subtypes (upper limb, lower-limb and spine): 9 reported on only lower-limb OA (knee and/or hip OA) and 4 on general OA, with most lower-limb OA (> 50% [28,46,47] and > 60% [34]). Among these 13 latter articles, the mean age was reported in 9: mean 57 ± 9 years or median 65.8 years (IQR 56.9–69.2). All articles described symptomatic OA patients.

Cost structure

Overall, 31 articles reported annual direct costs per patient with OA. The reported direct cost categories varied (Table 2). Only 16 articles reported indirect costs. Only 4 studies explicitly stated that the human capital approach had been used to estimate the indirect costs of OA (17,25,45,48,49). Absenteeism was reported in 14 articles, and only 2 described absenteeism and presenteeism according to the method of Lofland et al. (39,40,50).

Cost estimates for all OA

The supplemental table provides a summary of mean annual direct costs per patient (in 2013 €). The annual total cost per patient varied from 0.3 to 19.5 k€/year, direct cost per patient from 0.2 to 15.3 k€/year and indirect cost per patient from 0.05 to 9.4 k€/year. The weighted average annual costs per patient were 0.35, 2.4 and 0.06 k€/year for total, direct and indirect costs, respectively. The study by Levy et al. represented a significant weight because of the number of patients (3,400,000) and was an outlier in terms of cost estimates (16), which were far lower than those of other studies. This justified a sensitivity analysis excluding this study to explore the stability of our cost estimates. Consequently, a specific sensitivity analysis was conducted with removal of this paper: the weighted average annual costs per patient were then 8.5, 6.7 and 5.4 k€/year for total, direct and indirect costs, respectively.

Cost estimates for hip and knee OA

Table 3 provides a summary of mean annual direct costs per patient (in 2013 €). After adjustment to 2013 €, annual total costs per patient varied from 0.7 to 12 k€/year, direct costs per patient from 0.5 to 10.9 k€/year and indirect costs per patient from 0.2 to 12.3 k€/year. The weighted average annual costs per patient were 11.1 k€/year, 9.5 k€/year and 4.4 k€/year

for total, direct (Figure 2a) and indirect costs (Figure 2b), respectively. A sensitivity analysis was conducted because of the substantial weight of the study by Gore et al. (number of patients 112,951) (47). The weighted average annual direct cost without the Gore et al. study decreased from 9.5 to 6.8 k€/year (Figure 2a). Direct costs varied according to consideration of surgery. In fact, the weighted average annual direct costs per patient in populations without surgery, with surgery or awaiting surgery were 6.7, 10.8 (3 k€/year without Gore et al.) and 7.4 k€/year, respectively. The impact of the design of the study on costs was important: the weighted average annual total cost per patient was 10 k€/year for hospital-based cohorts (direct cost 2.1 k€/year and indirect cost 5.5 k€/year); 12 k€ for administrative databases (direct cost 10.2 k€/year and indirect cost 4.2 k€/year) and 6.8 k€/year for national surveys (direct cost 6.2 k€/year and indirect cost 6.4 k€/year).

Discussion

We performed a systematic review of the literature of the economic consequences – overall costs as well as cost breakdown (direct and indirect) – of hip and knee OA worldwide. Depending on the database and the diagnosis, OA articles reported different cost estimates for the disease, with a multiplication factor of 22-fold (hip and knee OA) and 65-fold (all OA) between the lowest and highest estimate. We found a gradient depending on the continent: direct costs in North America were 6.7 k€/year for all OA and 10 k€/year for hip and knee OA. In Europe, direct costs were 0.7 k€/year and 1 k€/year respectively. This situation can be explained by the higher frequency of obesity and related comorbidities in the United States than in European countries (51).

This is the first systematic review of the literature to specifically focus on the costs of hip and knee OA, which are a major contributor to global disability-adjusted life years (5). Puig-Junoy J et al reported recent data on hip and knee osteoarthritis costs (52). However, this paper was a literature review on the cost of osteoarthritis in general, as opposed to a focus on hip and knee osteoarthritis costs in our review. Moreover we have included four new articles (23-25,44). The burden to society is expected to be high (prevalence of 10% to 20%) because of the prevalence of symptomatic disease (53–59). The costs induced could be as high as 408 to 817 billion €/year and 350 to 700 billion €/year for total and direct costs, respectively, in Europe (59).

Our review highlights the substantial heterogeneity in how the cost of OA has been estimated over the world during the last decades. Several sources of heterogeneity could be mentioned and taken into account when interpreting the results of this review. Variable definitions of hip and knee OA have been used – clinical, radiological or both (53) Most studies included symptomatic OA patients and only 5 included patients with a diagnosis by radiographic criteria. OA diagnosis was based on ACR criteria (13,14) or sometimes only on self-reported

information, which is known to feature inadequate sensitivity or specificity as compared with clinical examination for ascertainment (60). Actually, from a public health perspective, a diagnosis based on both clinical and radiological features is recommended (53). In addition, some authors recently suggested separating OA by phenotypes, reflecting different risk factors, comorbidities and potentially pathogenic pathways (7,61). Comorbidities such as obesity are closely related with lower-limb OA (62).

We could not assess this new "view" of OA because the reviewed articles did not provide enough details on medical history or comorbidities. However, integrating these phenotypic specificities in future epidemiological and economic analyses will be interesting; such phenotypes could have substantial impact on both functional outcome (health resource use) and loss of autonomy (due to comorbidities), thereby resulting in major differences in cost estimates (34,37,47).

As another source of heterogeneity, the patient selection method could have affected the results and led to selection bias or recruitment. Populations studied from administrative, hospital and national health survey databases could be substantially different, which questions the external validity of the results. In the same way, different countries or continents are represented by totally different health systems and cultural or genetic backgrounds, which may affect health resource use and productivity loss (48). The characteristics of OA and the severity of structural damage contribute to the heterogeneity. However, these data are often difficult to assess.

Finally, although some methodological consensus has been reached to determine the reference case for economic assessment in rheumatic diseases (63,64), we lack standardized methods for homogeneous estimates of the economic burden of such diseases. Some costs such as physiotherapy, emergency room visits, and complementary and alternative medicine use are not systematically included in direct cost estimates. Yet, the rates of use and expenditures for

alternative therapies by adults with OA were high and can underestimate direct costs (30). Only 4/13 articles of hip and knee OA included surgery in direct costs, even though joint surgery is considered an important cost driver in hip and knee OA (65) because of the costs of the procedure and the increasing use of knee and hip replacement in the recent and coming years (66,67). This trend could result in a four-fold demand for knee arthroplasty in OECD countries by 2030 (68). There are substantial variations in total hip replacement and total knee replacement implant costs within and across hospitals. For example, the average implant cost per case ranged from $1797 to $12,093 for knee and from $2392 to $12,651 for hip (69). These differences can be explained by socio-economic determinants and physician prescription patterns, with countries with higher medical expenditures and obesity prevalence having significantly higher utilization rates (68). Substantial costs associated with total joint replacement can be balanced by their expected benefits in the medium or long-term; however, their incremental cost effectiveness ratio varies greatly depending on the studies, ranging from $1026 to 28 100/QALY (70). Out-of-pocket costs may be sometimes substantial (35,71). In addition, costs incurred for caregivers may be included, but only one article provided estimated caregiver costs related to OA (33). Finally, the method commonly used to estimate indirect costs of OA was the human capital approach (17,25,45,48), which often maximizes indirect costs as compared with the friction cost method and induces larger variations in the magnitude of indirect costs estimated (72). All these elements contribute to the difficulty in providing a clear idea of the costs due to OA (37,47).

Conclusions

Despite unstable estimates due to methodological issues in articles, this review confirmed that hip and knee OA induces substantial costs to society. With the aging of the population and the increasing prevalence of obesity in many developed countries, the economic burden of lower-

limb OA could be even higher in the coming years (5). Hence, the disease is considered a public health problem and should be a research priority (6). Additional studies are needed to better assess the economic consequences of OA, especially with long-term studies, taking into account disease phenotypes and multimorbidity.

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Table 1: Characteristics of studies of osteoarthritis (OA) costs

Author (REF)	Country	OA	Diagnosis	Population / Workers	Database	Clinical claims	Radiographic Kellgren & Lawrence criteria	Follow-up (months)	Study population
Levy, 1993 (12)	France	All	ACR	Population	Administratives	+	-	12	3400000
Leardini, 2004 (13)	Italy	Limb	ACR	Population	Health survey	+	+	12	254
Rabenda, 2006 (14)	Belgium	All	SR	Workers	Health survey	+	-	6	617
Nunez, 2007 (15)	Spain	Limb	ACR	Population	Hospital based	+	+	6	100
Loza, 2009 (16)	Spain	Limb	ACR	Population	Health survey	+	+	6	1071
Sabariego, 2011 (17)	Germany	All	ACR	Population	Hospital based	+	-	6	97
Hermans, 2012 (18)	Netherland	Limb	ACR	Workers	Health survey	+	+	12	117
Rolfson, 2012 (19)	Sweden	Limb	ACR	Population	Hospital based	+	-	12	2635
Bertin, 2014 (20)	France	Limb	ACR	Population	Health survey	+	-	12	4229
Salaru, 2014 (21)	Moldova	Limb	ACR	Population	Sectional study	+	-	12	256
Gabriel, 1995 (23)	US	All	ACR	Population	Administratives	+	-	12	7889
Gabriel, 1997 (22)	US	All	SR	Population	Administratives	+	-	12	6742
Lanes, 1997 (24)	US	All	ACR	Population	Health survey	+	-	12	10101
Maclean, 1998 (25)	US	All	SR	Population	Health survey	+	-	24	20000
Ramsey, 2001 (26)	US	All	ACR	Population	RCT	+	-	5	122
Maetzel, 2004 (27)	Canada	All	ACR	Population	Health survey	+	-	6	140
Mapel, 2004 (28)	US	All	ACR	Population	Administratives	+	-	12	5129
Gupta, 2005 (29)	Canada	Limb	SR	Population	Health survey	+	-	3	1258
White, 2008 (30)	US	Limb	SR	Workers	Administratives	+	-	24	32043
Dunn, 2009 (32)	US	All	ACR	Population	Health survey	+	-	12	1116437
Kotlarz, 2009 (31)	US	All	SR	Population	Health survey	+	-	12	1423
Berger, 2011 (34)	US	All	ACR	Population	Administratives	+	-	12	2399
Berger, 2011 (33)	US	Limb	ACR	Population	Health survey	+	-	24	16527
Dibonaventura, 2011 (36)	US	All	SR	Workers	Health survey	+	-	6	2173
Gore, 2011 (43)	US	Limb	ACR	Population	Administratives	+	-	12	112951
Dibonaventura, 2012 (35)	US	All	SR	Workers	Health survey	+	-	6	4876
Kim Le, 2012 (37)	US	All	ACR	Population	Administratives	+	-	12	258237
Kim Le, 2012 (38)	US	All	ACR	Population	Health survey	+	-	12	258237
Tarride, 2012 (39)	Canada	All	ACR	Population	Health survey	+	-	12	1474
Lapsley, 2001 (40)	Australia	Limb	ACR	Population	Health survey	+	-	12	70
Woo, 2003 (41)	Hong Kong	All	ACR	Population	Hospital based	+	+	12	509
Xie, 2007 (42)	Singapore	Limb	ACR	Population	Hospital based	+	-	12	574

+/– cost category explicitly/not explicity reported in the study

Table 2: Direct cost categories reported in articles

Author	Physician visits	ER	Hospit	Non traditional healthcare	Physio	Drugs	Aids Transport	Bio	Radio	Surgery
Levy	+	-	+	-	+	+	-	+	+	+
Leardini	+	-	+	-	+	+	+	+	+	-
Rabenda	+	+	+	+	+	+	-	+	+	-
Nunez	+	-	-	+	+	+	+	+	+	-
Loza	+	-	+	-	-	+	+	+	+	+
Sabariego	+	-	+	-	-	+	+	-	-	-
Hermans	+	-	+	-	-	+	+	+	+	+
Rolfson	+	-	+	-	+	+	+	-	-	-
Bertin	+	-	-	-	-	+	-	-	-	-
Salaru	+	+	+	-	-	+	-	+	+	-
Gabriel	+	-	-	-	+	-	-	+	+	-
Gabriel	+	-	-	-	+	-	-	+	+	+
Lanes	+	+	+	-	+	+	-	-	+	+
Maclean	+	-	-	-	-	+	+	-	-	-
Ramsey	+	+	+	+	+	+	+	-	-	+
Maetzel	+	-	+	+	+	+	+	+	+	+
Mapel	+	+	+	-	-	+	+	+	+	+
Gupta	-	-	-	-	-	-	+	-	-	-
White	+	+	+	-	-	+	+	+	-	-
Dunn	+	+	+	-	-	+	-	+	+	+
Kotlarz	+	-	+	-	-	+	-	+	+	-
Berger	+	+	+	-	-	+	-	-	-	+
Berger	+	+	+	-	-	+	+	-	-	-
Dibonaventura	+	+	+	-	-	-	-	-	-	-
Gore	+	+	+	+	+	+	+	+	+	+
Dibonaventura	+	+	+	-	-	-	-	-	-	-
Kim Le	+	+	+	-	+	+	-	-	+	+
Kim Le	+	+	+	-	+	+	-	-	+	-
Tarride	+	-	+	-	-	-	-	-	-	+
Lapsley	+	+	+	-	-	+	+	+	+	-
Woo	+	-	+	+	+	+	+	-	-	-
Xie	+	-	+	-	-	+	-	+	+	+

ER: emergency room; Physio: physiotherapists; Bio: biology; Radio: radiology

Table 3: Annual costs per patient for hip and knee OA

				Annual costs (k€/year)					
Author	**Country**	**OA**	**n**	**Total**		**Direct**		**Indirect**	
				Mean±SD	**95% CI**	**Mean±SD**	**95% CI**	**Mean±SD**	**95% CI**
Leardini, 2004	Italy	Limb	254	3	2.3–3.6	1.3	1 - 1.5	1.7	1.1–2.3
Nunez, 2007	Spain	Limb	100	-	-	1.8	1.3–2.3	-	-
Loza, 2009	Spain	Limb	1071	1.7 ± 2	1.6–1.9	1.5 ± 1.8	1.4–1.6	0.2 ± 0.7	0.2–0.3
Hermans, 2012	Netherland	Limb	117	10.8 ± 13.2	8.4–13.2	2.4 ± 1.2	2.2–2.6	9.6 ± 13.2	7.2–12
Rolfson, 2012	Sweden	Limb	2635	6.9	6.7–7.7	1.3	-	5.6	-
Bertin, 2014	France	Limb	4429	-	-	0.8	-	-	-
Salaru, 2014	Moldova	Limb	256	0.7	-	0.5	-	0.2	-
Gupta, 2005	Canada	Limb	1258	11.5 ± 11.4	10.9–12.2	2.2 ±2.1	2–2.3	12.3 ± 11.6	11.6–12.9
White, 2008	US	Limb	32043	12	-	7.8	-	4.2	-
Berger, 2011	US	Limb	16527	-	-	8.4	8.2–8.6	-	-
Gore, 2011	US	Limb	112951	-	-	10.9 ± 18.5	10.8–11	-	-
Lapsley	Australia	Limb	70	-	-	0.6	0.5–0.7	-	-
Xie, 2007	Singapore	Limb	574 [a] 80 [b]	6.8 ± 4.4	6.4–7.2	6.2 ± 4.3	5.8–6.5	1.6 ± 2.3	1.5–1.7
	* Europe			5.1		1		3.8	
	* North America			12		10		4.5	
	* Asia			6.8		6.2		1.6	
	* Oceania			-		0.6		-	
	* Total			11.1		9.5		4.4	

* Weighted mean

95% CI, 95% confidence interval

Supplemental table: Annual costs per patient for all OA

				Annual costs (k€/year)					
Author	**Country**	**OA**	**n**	**Total**		**Direct**		**Indirect**	
				Mean ±SD	**95% CI**	**Mean ±SD**	**95% CI**	**Mean ±SD**	**95% CI**
Levy, 1993	France	All	3400000	0.3	-	0.2	-	0.05	-
Rabenda, 2006	Belgium	All	617	2	-	0.6	-	1	-
Sabariengo, 2011	Germany	All	97	-	-	1.8	1.4–2.2	-	-
Gabriel, 1995	US	All	7889 [a] 116 [b]	3.6	-	3.2	-	0.5	-
Gabriel, 1997	US	All	6742	-	-	4.2	-	-	-
Lanes, 1997	US	All	10101	-	-	0.6	-	-	-
Maclean, 1998	US	All	20000	-	-	5.3	-	-	-
Ramsey, 2001	US	All	122	-	-	3.2	2.5–3.9	-	-
Maetzel, 2004	Canada	All	140	3	-	1.9	-	0.9	-
Mapel, 2004	US	All	5129	-	-	4.6 ± 22.4	4–5.3	-	-
Dunn, 2009	US	All	1116437	-	-	5.1	5–5.2	-	-
Kotlarz, 2009	US	All	1423	8.7	-	-	-	-	-
Berger, 2011	US	All	2399	19.5 ± 21.8	18.7 - 20.5	15.3 ± 18.7	15.4–16.9	4.3 ± 7.1	4–4.6
Dibonaventura, 2011	US	All	2173	12.5	-	3	-	9.4	-
Dibonaventura, 2012	US	All	4876	10.9	-	5.5	-	5.4	-
Kim Le, 2012	US	All	258237	-	-	5.6	5.5–5.7	-	-
Kim Le, 2012	US	All	258237	-	-	15.3	15.2–15.4	-	-
Tarride, 2012	Canada	All	1474	-	-	2.1	2–2.2	-	-
Woo, 2003	Hong Kong	All	509	4.1	-	3.4	-	0.6	-
	* Europe			2		0.7		1	
	* North America			8.9		6.7		5.9	
	* Asia			4.1		3.4		0.6	
	* Total			0.35		2.4		0.06	
	* Total without Levy and al.			8.5		6.7		5.4	

* Weighted mean

Table 2: Direct cost categories reported in articles

Author	Physician visits	ER	Hospit	Non traditional healthcare	Physio	Drugs	Aids Transport	Bio	Radio	Surgery
Levy	+	-	+	-	+	+	-	+	+	+
Leardini	+	-	+	-	+	+	+	+	+	-
Rabenda	+	+	+	+	+	+	-	+	+	-
Nunez	+	-	-	+	+	+	+	+	+	-
Loza	+	-	+	-	-	+	+	+	+	+
Sabariego	+	-	+	-	-	+	+	-	-	-
Hermans	+	-	+	-	-	+	+	+	+	+
Rolfson	+	-	+	-	+	+	+	-	-	-
Bertin	+	-	-	-	-	+	-	-	-	-
Salaru	+	+	+	-	-	+	-	+	+	-
Gabriel	+	-	-	-	+	-	-	+	+	-
Gabriel	+	-	-	-	+	-	-	+	+	+
Lanes	+	+	+	-	+	+	-	-	+	+
Maclean	+	-	-	-	-	+	+	-	-	-
Ramsey	+	+	+	+	+	+	+	-	-	+
Maetzel	+	-	+	+	+	+	+	+	+	+
Mapel	+	+	+	-	-	+	+	+	+	+
Gupta	-	-	-	-	-	-	+	-	-	-
White	+	+	+	-	-	+	+	+	-	-
Dunn	+	+	+	-	-	+	-	+	+	+
Kotlarz	+	-	+	-	-	+	-	+	+	-
Berger	+	+	+	-	-	+	-	-	-	+
Berger	+	+	+	-	-	+	+	-	-	-
Dibonaventura	+	+	+	-	-	-	-	-	-	-
Gore	+	+	+	+	+	+	+	+	+	+
Dibonaventura	+	+	+	-	-	-	-	-	-	-
Kim Le	+	+	+	-	+	+	-	-	+	+
Kim Le	+	+	+	-	+	+	-	-	+	-
Tarride	+	-	+	-	-	-	-	-	-	+
Lapsley	+	+	+	-	-	+	+	+	+	-
Woo	+	-	+	+	+	+	+	-	-	-
Xie	+	-	+	-	-	+	-	+	+	+

ER: emergency room; Physio: physiotherapists; Bio: biology; Radio: radiology

+/– cost category explicitly/not explicity reported in the study

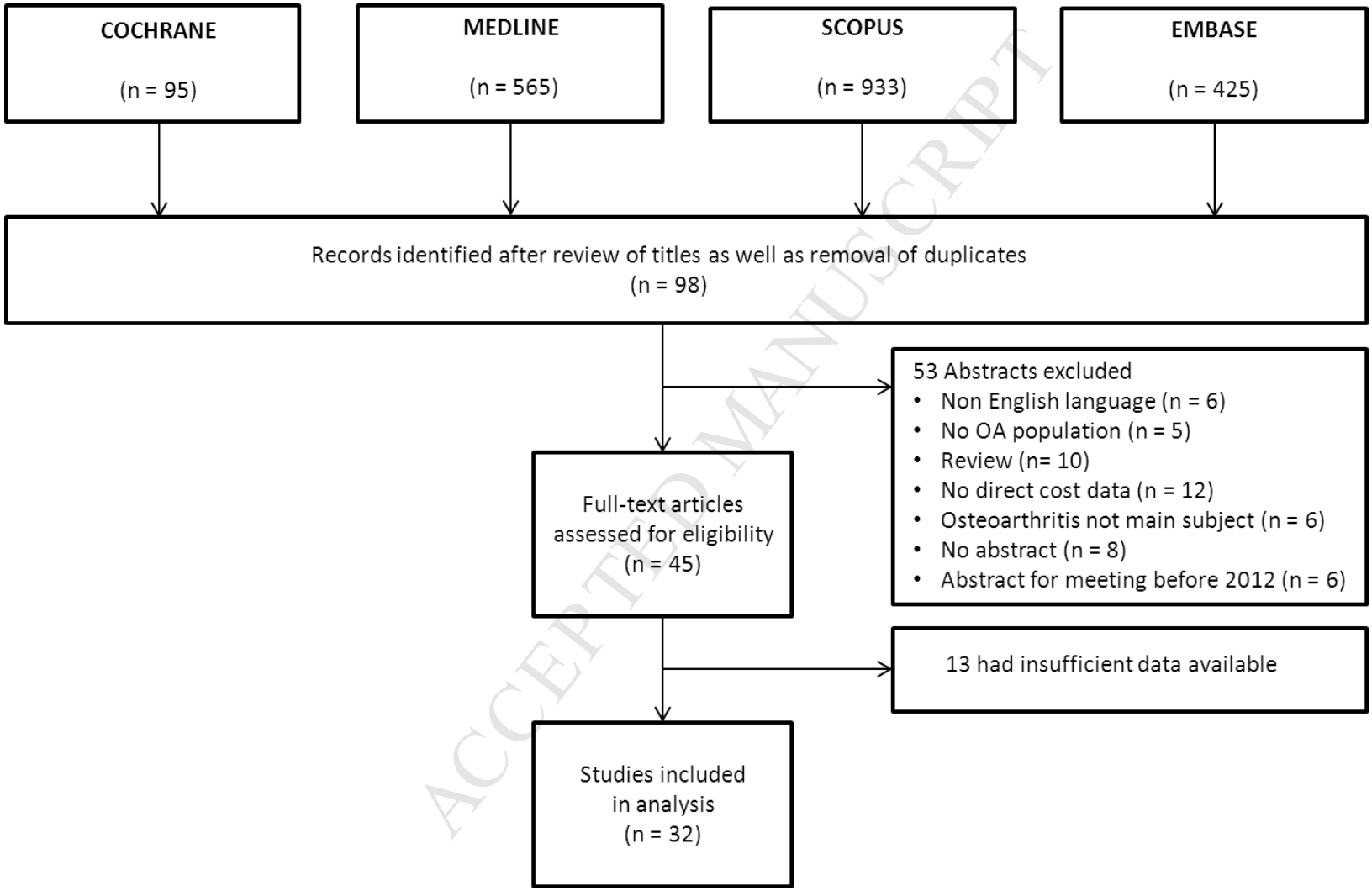

Figure 1: Flowchart of the study

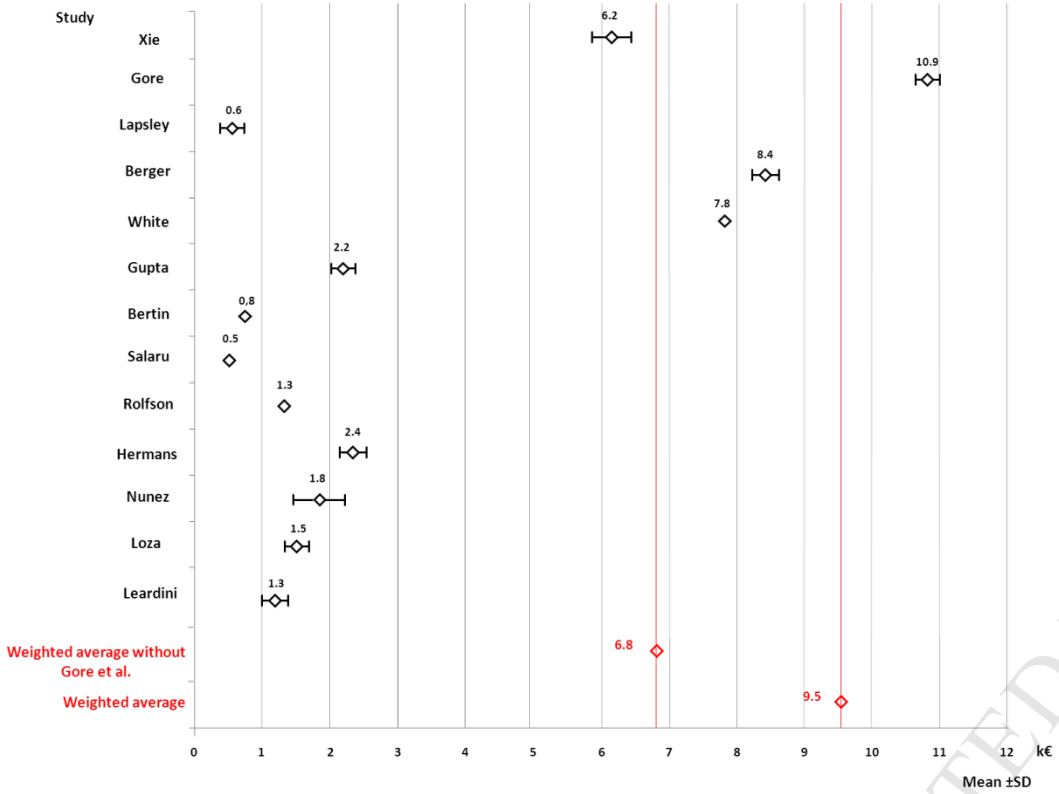

Fig 2a: Annual direct costs per patient

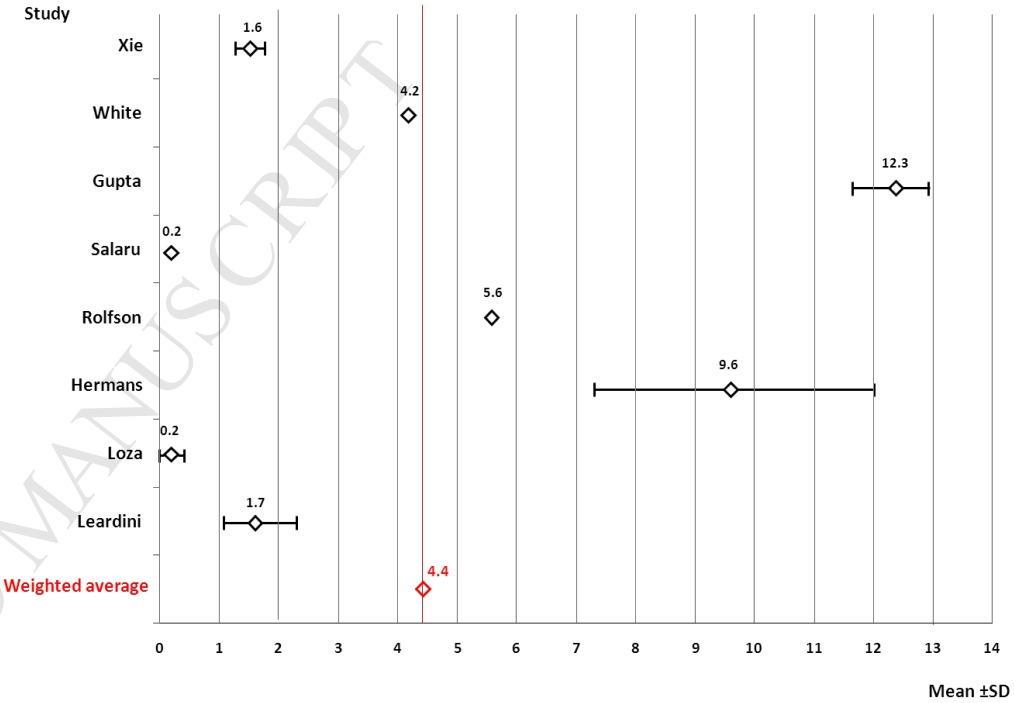

Fig 2b: Annual indirect costs per patient