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Medical Care Costs Associated with Rheumatoid Arthritis in the US: A Systematic Literature Review and Meta-analysis

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Abstract

Background—Rheumatoid arthritis (RA) is a morbid, mortal and costly condition without a cure. Treatments for RA have expanded over the last two decades and direct medical costs may differ by types of treatments. There has not been a systematic literature review since the introduction of new RA treatments, including biologic disease modifying anti-rheumatic drugs (bDMARDs).

Methods—We conducted a systematic literature review with meta-analysis of direct medical costs associated with RA cared for in the US since the marketing of the first bDMARD. Standard search strategies and sources were used and data were extracted independently by two reviewers. The methods and quality of included studies were assessed. Total direct medical costs as well as RA-specific costs were calculated using random effects meta-analysis. Subgroups of interest included Medicare patients and those using bDMARDs.

Results—We found 541 potentially relevant studies and 12 papers met the selection criteria. The quality of studies varied: 1/3 were poor, 1/3 were fair, and 1/3 were good. Total direct medical costs were estimated at $12,509 (95% CI $7,451-21,001) for all RA patients using any treatment regimen and $36,053 (95% CI $32,138-40,445) for bDMARD users. RA-specific costs were $3,723 (95% CI $2,408-5,762) for all RA patients using any treatment regimen and $20,262 (95% CI $17,480-23,487) for bDMARD users.

Conclusions—The total and disease-specific direct medical costs of patients with RA is substantial. Among bDMARD users, cost of RA care is over half of all direct medical costs.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic, progressive autoimmune systemic disease affecting roughly 0.7% of the population. (1) Treatment for RA was transformed in the late-1990s with the advent of biologic disease modifying anti-rheumatic drugs (bDMARDs) targeting specific immunologic pathways. As a disease with early adoption of bDMARDs, RA serves

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as a model for biologic drug use, where the treatment costs vary substantially based on therapeutic strategy.

Biologic DMARDs offer alternatives for patients unresponsive to traditional synthetic DMARDs, but the drugs carry an increased financial burden, with annual costs between $25,000 – $40,000. Thus, a detailed understanding of the cost of care for patients with RA since the advent of bDMARDs will be of importance to policy makers, administrators, and physicians; the high cost of RA treatments impacts the use of limited medical resources.

There is a body of primary literature examining the cost of RA since the introduction of bDMARDs, but a current critical review of these studies is lacking. The most recent reviews on cost-of-care research for RA in the US were both published before the advent of biologics. (2) (3) (4) Several more recent reviews have been published looking at costs outside of the US, (5) (6) but these studies have limited relevance to the US given the difficulties of comparing costs across health care systems with different payment structures and social priorities.

The question of direct medical costs for patients with RA is further complicated by the complexities and lack of standardization in methodology of cost-of-care analyses. When conducting a cost-of-care analysis, researchers must make decisions about the best source of data, the case definition for RA, the financial measure to refer to as “costs,” the elements of medical costs to be included, and the assignment of costs to RA versus other concurrent morbid diseases. Given the need for better understanding of cost of care for RA in the US and the need for standardization in cost-of-care analysis, we undertook a systematic literature review and meta-analysis with the following PICOS assignments: P (patients) – RA patients in the US since 1999; I (interventions) – any treatment regimen for RA; C (comparator) – no comparison group was included; O (outcomes) – direct medical costs; and S (study design) – all study types were included. We also examined the methodology employed by relevant studies.

METHODS

Study Selection

Studies were identified through a search of Medline using the following MeSH search terms: cost of illness; health care costs; expenditures; expenditures, direct; expenditures, health; expenditures, indirect; rheumatoid arthritis; and arthritis, rheumatoid (full search strategy available in Supplement 1). Because this analysis was meant to consider only studies assessing costs after the introduction of biologic DMARDs in 1999, the search was limited to studies published in 2000 and after. The last search we performed was on June 16, 2016.

Citations were screened by one reviewer for eligibility criteria to select articles for full text review. Criteria for inclusion were English language, focus on a US population, analysis of post-1999 data, and consideration of total direct costs of treatment for RA from a provider, insurer, or societal perspective. Studies were excluded if they were non-English language, focused on musculoskeletal or rheumatologic disorders other than RA, did not analyze cost as an outcome, were review papers or conference abstracts, focused on a population outside

the US, focused on indirect costs, failed to analyze key elements of total direct cost, studied a non-generalizable population (e.g. only patients with a specific comorbidity), were economic evaluations of specific drugs or therapies, relied on pre-1999 data, or provided an insufficient description of their cost-analysis methodology. Reference lists of studies deemed potentially relevant were examined for papers not identified by the Medline search. Full text review of potentially relevant studies was performed independently by two reviewers (AH and DHS) to confirm eligibility.

Data Abstraction and Quality Rating

Two independent reviewers abstracted data from included studies using a standardized form (see Supplement 2). Information abstracted from each study included: the characteristics of study participants, such as age, gender, comorbidities, and health insurance coverage; the study's inclusion and exclusion criteria; cost-analysis methodology; and cost of care findings. Specific aspects of the cost-analysis examined were the definition of RA, methods for comparisons with costs of non-RA patients, the overall costing methodology, and adjustment for inflation. Regarding costing methodology, some papers used the frequency of utilization of specific services and multiplied this by a pre-defined dollar amount; we defined this as the "utilization × standardized cost." All abstracted costs were converted to 2015 dollars using the consumer price index medical care component.

Additionally, we developed a quality rating form based on the Newcastle-Ottawa Quality Assessment Form for Cohort Studies (7), modified to facilitate assessment of RA cost-of-illness analyses (see Supplement 3). The quality rating included assessment of the representativeness of the studied cohort to assess for risk of selection bias. The same two reviewers who abstracted data also independently rated the quality of included studies. Disagreements regarding data abstraction or quality ratings were resolved by discussion between the two reviewing authors.

Meta-Analysis

The description of the meta-analysis followed the PRISMA checklist (see Supplement 4). The analysis of costs utilized a pooled estimate from random-effects models. The variance of the pooled estimates was stabilized by the double arcsine transformation. This method was found to produce less bias and mean squared error than the traditional log transformation. (8) We assessed heterogeneity among studies using the Cochran Q test and quantified inconsistencies across studies and their impact on the analysis by using the I^2 statistic (28). All analyses were done by MetaXL 1.4 package (http://www.epigear.com).

RESULTS

Study Selection

The Medline search yielded 541 citations and all abstracts were reviewed. Of these, 523 were discarded because they did not meet inclusion criteria (see Figure 1). Of those citations excluded based on abstracts, 364 were excluded because they were not cost-of-illness analyses, 68 because they examined non-US data, 62 because they focused on indirect costs or only a subset of total costs, 18 because they used data from years prior to 1999, and 11

because they focused on a population that could not be generalized to a national sample, such as only patients with a specific comorbidity or using a specific drug. After full text review of the remaining 18 articles, 6 did not meet the inclusion criteria: 2 were excluded because they did not describe their costing methodology sufficiently for comparison to other included articles, 2 because their populations could not be generalized, and 2 because on further inspection their sample included data from years prior to 1999. A total of 12 studies were identified for inclusion in the review.

Data Sources, Populations, and Quality Assessment

Table 1 displays the data sources and patient characteristics of the 12 studies included in final analyses. The included studies used a total of 16 different sources of patient data for their cost analyses. Only one database, the Medical Expenditure Panel Survey, was used in more than one of the included studies. The included studies analyzed costs within a number of different medical insurance settings; 6 studies reported costs for privately insured patients (9) (10) (11) (12) (13) (14), 3 studies reported costs for patients enrolled in Medicaid programs (15) (16) (11), and 1 study reported costs for patients enrolled in Medicare (17). Additionally, 3 studies utilized patient data from large, national databases and used weighting to generalize their findings to be representative of the entire US population (18) (19) (20). One paper (11) incorporated costs from multiple insurance settings in the same set of analyses.

Identification of ICD-9-CM codes in the 714.xx series in medical claims was the most common method for identifying RA patients in claims databases; only one study (18) did not rely on ICD-9-CM codes in some capacity for patient identification. However, there was considerable variability in which codes were used and the number of instances of an RA code required for inclusion. Of the 11 studies using ICD-9-CM codes, 4 identified a narrow subset of codes to define RA (9) (15) (16) (14), while the rest accepted any code within the 714.xx series (10) (11) (12) (13) (17) (19) (20). Eight (73%) studies required only one instance of an RA code for inclusion; the remaining 3 (27%) required more than one instance of an RA code, or a combination of one RA code with either a claim for at least one DMARD or self-reported RA diagnosis.

Most studies included all patients with RA in their chosen database; however, 4 studies limited their population to only those patients using bDMARD medications. All studies, by design, analyzed costs incurred after 1999, but none analyzed costs later than 2010. There was an even distribution in the quality of included studies according to our established quality assessment framework – 4 studies were judged to be of poor quality, 4 were fair quality, and 4 were good quality. However, in all studies the observed cohort was deemed to be adequately representative of a national sample, indicating little risk of selection bias.

Cost-of-Illness Analysis Methods

Table 2 displays details on the cost analysis methodologies used by the included studies. The vast majority of studies based their cost analysis on actual reimbursements paid by an insurer for medical services or drugs as reported in a claims database. *Michaud et al.* (18) and *Weycker et al.* (9) instead employed a utilization-based method in which they applied a

consistent standardized dollar amount to each instance of utilization of a given medical service or drug as reported in a claims database. For a second database, *Weycker et al.* based their cost analysis on charges billed by a health care institution for medical services and drugs, as opposed to the actual reimbursed amount. *Weycker et al.'s* findings yielded the highest cost estimates in our dataset.

Of the 12 included studies, 10 reported at least one element of cost – such as costs of hospitalizations, ambulatory care, or prescription drugs – specific to care for RA as opposed to other comorbid diagnoses. Of those, 8 reported RA-specific costs across three cost domains and were included in the meta-analysis of total RA costs.

Cost of Care Findings

Among the 8 studies including all RA patients (and not only those using a biologic DMARD) in their analyses (18) (15) (16) (11) (13) (17) (19) (20), findings for annual total cost of care across all conditions ranged from $3,266 to $25,260, with the lowest estimate being in a population of Medicaid enrollees and the highest in a Medicare population (see Table 3). It is worth noting that the low estimate of $3,266 (16) is much lower than any other finding, being only 28% of the next lowest-estimate. Meta-analysis of studies including all RA patients found annual total cost of care to be $12,509 (95% CI $7,451-21,001) (see Figure 2A). Removing the low estimate did not substantially change the total cost of care ($12,458, 95% CI 7,381-21,025). Among studies restricted to RA patients using bDMARDs, annual total cost of care ranged from $26,469 to $52,837, with the lower estimate comprising privately insured working-age adults and the higher estimate privately insured adults over age 65. Meta-analysis found annual total cost of care among patients using biologics to be $36,053 (95% CI $32,138-40,445) (see Figure 2B).

Estimates for annual cost for RA-specific care ranged considerably. Estimates in studies including patients using any treatment regimen (i.e. not limiting to bDMARD users only) ranged from $2,437 to $7,849 (See Table 3), with the lower estimate representing a population modeling the general US population and the higher being comprised of Medicaid enrollees. Meta-analysis determined annual cost for RA-specific care to be $3,723 (95% CI $2,408-5,762) when accounting for patients using any treatment regimen (see Figure 2C), representing 30% of total costs for all care. Estimates of RA-specific costs in studies limiting their population to patients using bDMARDs ranged from $16,716 to $22,445, with both estimates being based on different claims databases comprising privately insured working-age adults. Meta-analysis found annual RA-specific cost within this population to be $20,262 (95% CI $17,480-23,487) (see Figure 2D), representing 56% of total costs for all care.

DISCUSSION

Rheumatoid arthritis is a morbid, mortal, and costly illness. The cost of treating RA has increased over the last two decades with the advent of bDMARDs, however this has not been well studied. We conducted a systematic literature review and analyzed prior cost-of-care studies for RA; the cost of direct medical care for a patient with RA was $12,509 and the costs attributable to RA were $3,725 or 30% of the total costs. Among patients using

bDMARDs, total direct medical costs were $36,053 and costs attributable to RA were $20,262, or 56% of the total.

These findings suggest that costs associated with RA are in line with those for other prominent chronic diseases. Recent studies have reported annual total direct cost of care for diabetes patients as $14,732 (21), multiple sclerosis patients as $23,195 (22), ulcerative colitis between $4,032 and $13,722 (23), and COPD between $1,681 and $10,812 (24) using 2015 dollars. Our findings also suggest that the burden of RA patients on the US health care system may become outsized compared to the disease's relatively small prevalence and compared to patients with these other chronic conditions as more patients use bDMARDs in the future.

In considering the observed costs, it is interesting to note that patients that use bDMARD's had increased cost over typical RA patients. Additionally, bDMARD use had a larger incremental effect on RA-specific costs (444% increase) than on total direct medical costs (188% increase). However in both cases the increment was below the total cost of bDMARDs themselves. This suggests that either the use of bDMARD's may be associated with lower total non-drug direct medical costs or that the patients who receive bDMDARDs have fewer comorbid conditions. Research comparing the characteristics of bDMARD users versus regular DMARD users has shown differences in the demographic and clinical characteristics of bDMARD users compared to regular DMARD users, (25) (26) but this topic is worthy of further examination.

While the cost of RA is extremely important to the healthcare system, the methodologies observed and used across the included prior studies varied substantially. The definition of RA differed, what was considered costs and their calculation was not standardized, and the attempt to partition RA costs from non-RA costs differed by study. Two predominant methods were used to identify RA-specific costs: 1) Identification of claims with an RA-related ICD-9-CM diagnosis code and 2) determination of the incremental costs between a population of RA patients versus a population of controls. Both methods have their limitations. Identification of claims with RA-related codes fails to address the possibility that claims may be misclassified as being RA-related or not based on a coding error. Likewise, assessment of incremental cost is subject to error in the nuance of defining a non-RA control population, especially in the consideration of which comorbidities may or may not be related to the pathophysiology of RA. In addition, the quality of reporting in the included studies was inconsistent.

The methods for studying direct medical costs need further standardization. Standardized methods would facilitate comparison across studies with less concern for heterogeneity and would also allow for better temporal trend analyses, ensuring "apples to apples" comparisons. Ideal methods would account for all inpatient, outpatient, prescription medication, and post-acute care costs, rely on actual reimbursement amounts reported in claims as the basis of analysis, define RA patients by requiring multiple instances of an RA-related diagnosis code in claims, assess both total cost for all medical care and RA-specific care, and compare costs between RA patients and similar non-RA patients from the same database.

The current meta-analysis is limited by the literature we included. As noted, the methods across studies were not consistent and this increases the uncertainty of our summarized results. Since we did not have individual patient-level data, we could not examine the associations between individual patient characteristics and cost. As well, the methods for partitioning RA costs were inconsistent making the RA-specific cost analyses more difficult to interpret. Finally, we did not include studies of "indirect" costs of RA, such as work lost and caregiver costs. While indirect costs are substantial (27) (28) (29), the methodologic variability is also significant; thus, we worried about introducing even more heterogeneity in this meta-analysis.

In light of these limitations, we conclude that the direct medical costs of patients with RA are significant. Clearly, medication costs comprise a substantial portion of these costs, especially for patients using bDMARDs. Without considering the health effects, benefits and risks, the current analysis cannot comment on whether specific treatments are of value. Cost-effectiveness analyses comparing different treatment strategies for RA are ongoing and will provide useful information. The studies included in this meta-analysis do not include assessments of RA-outcomes, but our findings may be a valuable resource for future cost-effectiveness analyses that will further understanding of the relative benefits of treatment options available to RA patients. As standards of care evolve in RA, the standards for studying cost of care in RA must also mature and become codified. This will facilitate better comparisons across treatments and across time.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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SIGNIFICANCE AND INNOVATION

- We conducted a systematic literature review with meta-analysis of direct medical costs associated with RA cared for in the US since the marketing of the first bDMARD.
- The 12 papers that met the selection criteria demonstrated that total direct medical costs were $12,509 (95% CI $7,451-21,001) for all RA patients using any treatment regimen and $36,053 (95% CI $32,138-40,445) for bDMARD users.
- RA-specific costs were $3,723 (95% CI $2,408-5,762) for all RA patients using any treatment regimen and $20,262 (95% CI $17,480-23,487) for bDMARD users.
- Among bDMARD users, cost of RA care is over half of all direct medical costs.

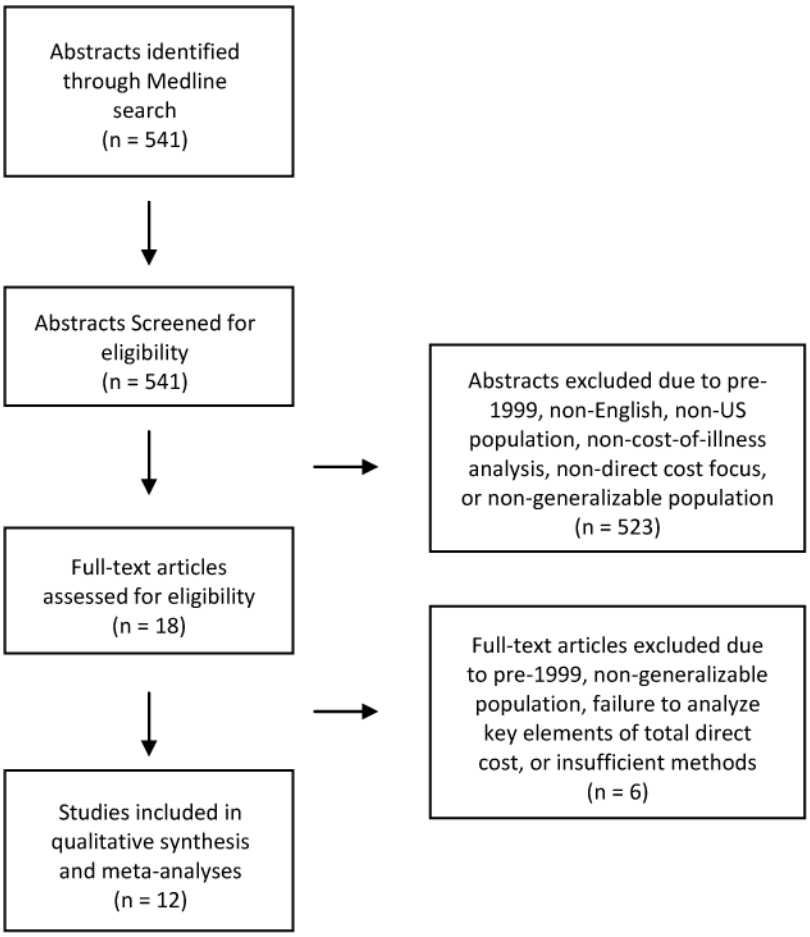
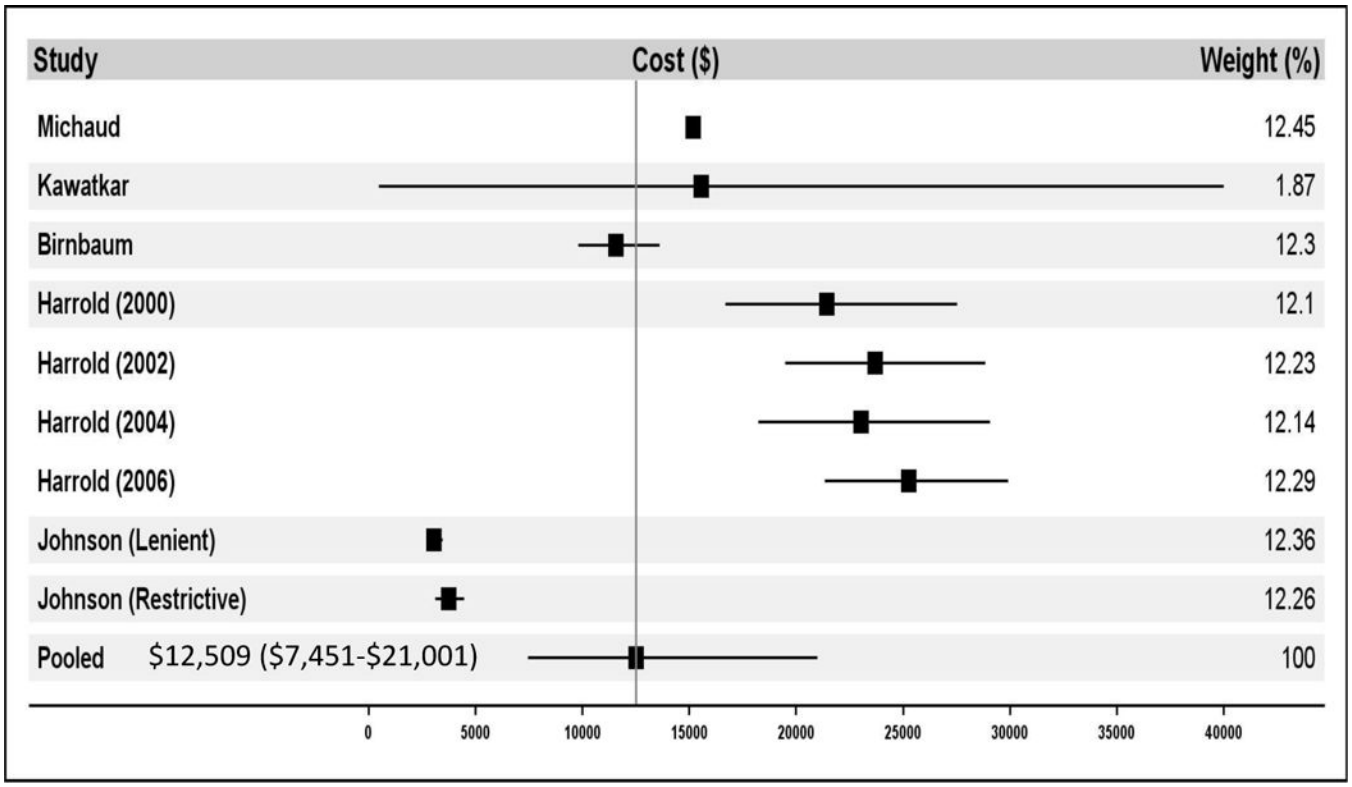
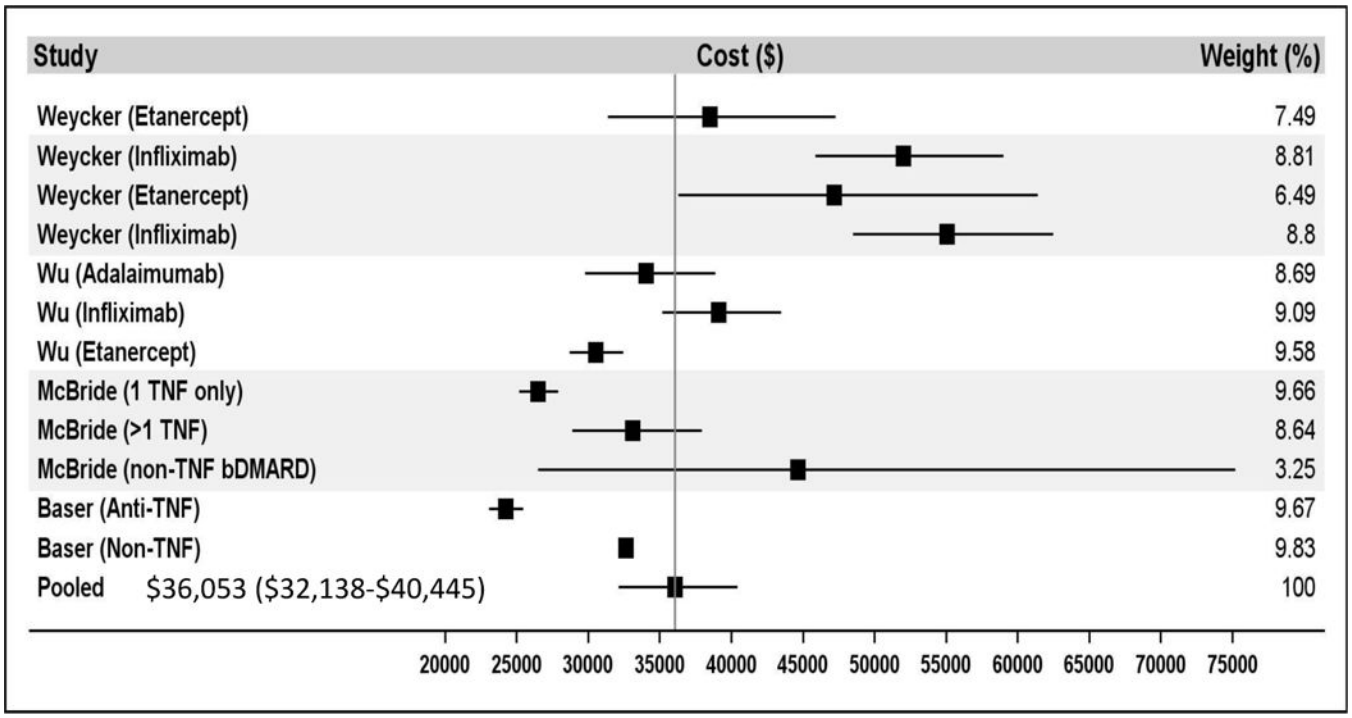


Figure 1.
shows the assembly of literature for the systematic literature review.





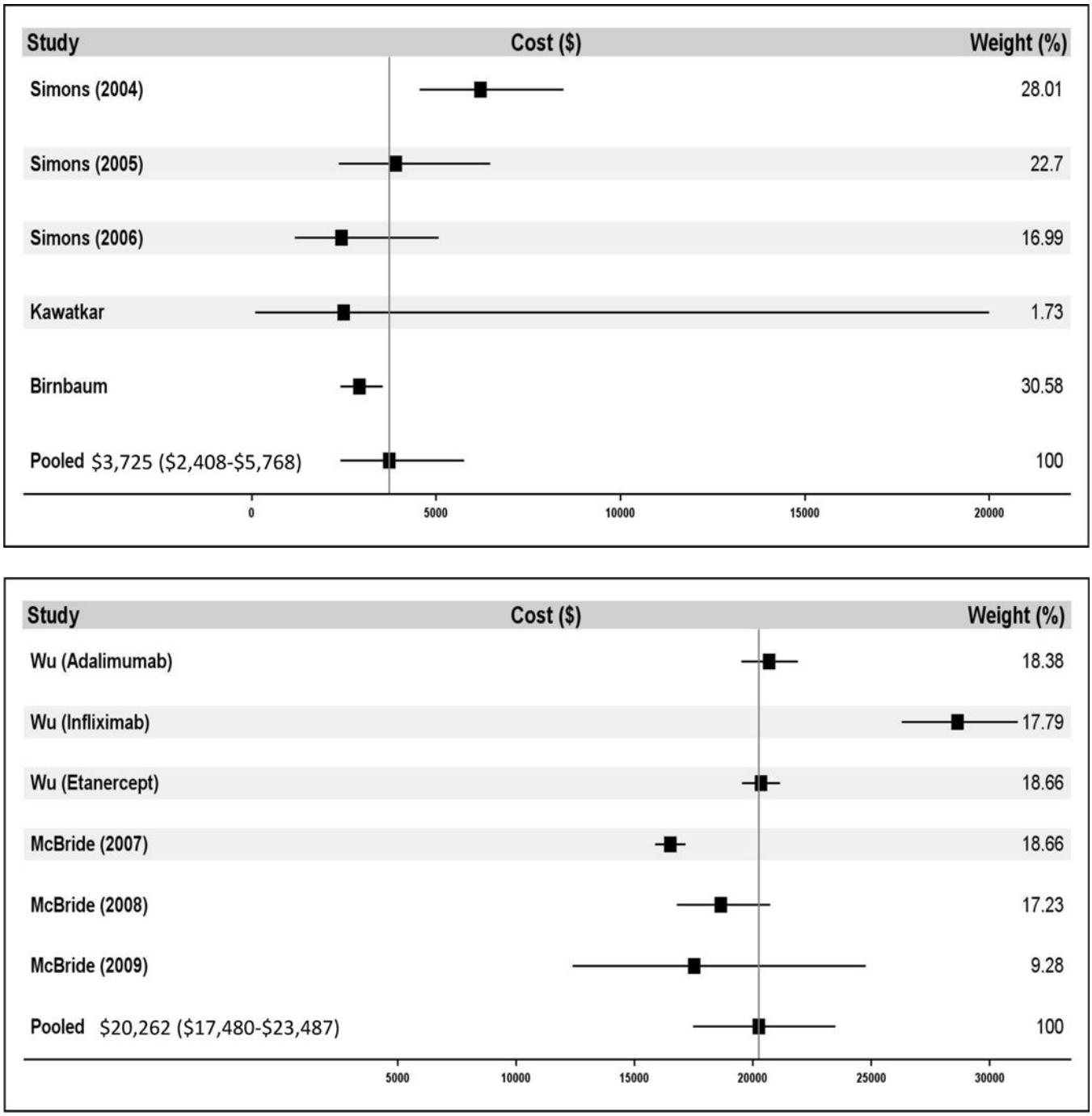


Figure 2.

shows the meta-analysis results for the direct medical costs. Panel A demonstrates the total cost of care for all patients. Panel B demonstrates the total cost of care for biologic DMARD users only. Panel C demonstrates rheumatoid arthritis-specific costs of care for all patients. Panel D demonstrates rheumatoid arthritis-specific costs of care for biologic DMARD users only. Multiple papers included in these meta-analyses reported cost of care findings for several distinct patient populations. These distinct populations are each treated as individual

contributors to the meta-analysis and are listed with the identifying characteristic of the patient population studied (e.g. individual year or specific drug treatment regimen).

Table 1

Included Studies and Populations

Author, Year	Data Source	Population	Patients, N	Mean Age, years	Female, %
Michaud, 2003	National Databank for Rheumatic Diseases	RA patients enrolled by rheumatologists across the US	7527	62	76.8
Weycker, 2005	Constella COMPASS database, Ingenix LabRx database	TNF-antagonist biologic users age 65 and older in private health plans across the US	Constella: 166 Ingenix: 114	71	76.0
Khanna, 2007	West Virginia Medicaid claims	Medicaid enrollees with RA in West Virginia	1157	47	77.4
Wu, 2007	Private insurance claims database	TNF-antagonist biologic users among employees, spouses, and dependents from 31 large employers across the US	997	50	73.9
Johnson, 2008	Arizona HealthQuery (AZHQ) database	Medicaid enrollees in Maricopa County, AZ	1492	56	83.3
Birnbaum, 2010	Ingenix Enployer Database, Medicare SAF, Florida Medicaid claims	Beneficiaries from 37 large employers across the US, 5% sample of Medicare enrollees, Medicaid enrollees in Florida	Private: 14317 Medicaid: 6415	Private: 50 Medicaid: 45	Private: 70.4 Medicaid: 76.6
McBride, 2011	Private insurance claims database	Employees of 40 large employers across the US	2,545	50	74.7
Birnbaum, 2012	Private insurance claims database	Employees of 40 large employers across the US	837	50	31.9
Harrold, 2012	Medicare Current Beneficiary Survey	Medicare enrollees	2000: 225 2002: 260 2004: 253 2006: 247	70	77.8
Kawatkar, 2012	Medical Expenditure Panel Survey	Sample of US population	5.8 mil	62	61.1
Simons, 2012	Medical Expenditure Panel Survey	Sample of US population	2004: 34,403 2005: 33,645 2006: 34,145	2004: 57 2005: 58 2006: 59	77.0
Baser, 2015	Truven Health MarketScan Commercial Claims Database	TNF-antagonist biologic users who switched to a new TNF-antagonist or a non-TNF biologic	3497	54	80.5

Table 2

Cost Analysis Methods

Author, year	Definition of RA Cases	Comparison Group	Costing Method(s)	Inflation Adjusted	Analyzed RA Costs	Method for Determining RA Costs
Michaud, 2003	Diagnosed by rheumatologist	No	Utilization × Standard cost	Yes	No	N/A
Weycker, 2005	≥1 claim with dx of ICD-9-CM 714.0, 714.1, 714.2, or 714.81	No	Constella: Utilization × standard costs Ingenix: Charges	No	Yes	Sum of costs in claims with Dx of ICD-9-CM 714.xx in any position, or drug on list of RA-related medications
Khanna, 2007	≥1 claim with primary dx of ICD-9-CM 714.00	No	Reimbursements, Utilization × standard costs	N/A	Yes	Population limited to patients with RA
Wu, 2007	≥1 claim with primary or secondary dx of ICD-9-CM 714.xx	No	Reimbursements	Yes	Yes	Sum of costs in claims with Dx of ICD-9-CM 714.xx in any position, or drug on list of RA-related medications
Johnson, 2008	≥1 claim with primary or secondary dx of ICD-9-CM 714.0	No	Reimbursements	N/A	No	N/A
Birnbaum, 2010	Dx of ICD-9-CM 714.xx	Yes	Reimbursements	Yes	Yes	Incremental costs of RA subjects vs comparison group
McBride, 2011	≥2 claims with dx of ICD-9-CM 714.xx	No	Reimbursements	Yes	Yes	Sum of costs in claims with Dx of ICD-9-CM 714.xx in any position, or drug on list of RA-related medications
Birnbaum, 2012	≥1 claim with dx of ICD-9-CM 714.xx	Yes	Reimbursements	N/A	Yes	Sum of costs in claims with Dx of ICD-9-CM 714.xx in any position, or drug on list of RA-related medications
Harrold, 2012	1) ≥2 dx of ICD-9-CM 714.xx OR 2) Self-reported RA dx and 1 dx of ICD 9-CM 714.xx OR 3) Use of biologic DMARD and self-reported RA dx or 1 dx of ICD-9-CM 714.xx	No	Reimbursements	Yes	Yes	Sum of costs for list of RA-related medications
Kawatkar, 2012	1) Dx of ICD-9-CM 714.xx OR 2) MEPS clinical classification code of 202	Yes	Reimbursements	Yes	Yes	Incremental costs of RA subjects vs comparison group
Simons, 2012	Dx of ICD-9-CM 714.xx	Yes	Reimbursements	No	Yes	Regression analysis
Baser, 2015	≥2 dx of ICD-9-CM 714.0x at least 2 months apart	No	Reimbursements	Yes	Yes	Sum of costs in claims with Dx of ICD-9-CM 714.0x in any position, or drug on list of RA-related medications

Abbreviations: RA, rheumatoid arthritis; Dx, diagnosis; ICD, international classification of diseases; MEPS, Medical Expenditure Panel Survey

Table 3

Reported Cost of Care by Study

Author	Year of Publication	Year(s) of Reported Costs	Total Cost of Care (2015 $)	Cost of RA-Specific Care (2015 $)
Overall US Population				
Michaud	2003	1999-2001	15,189	NR
Simmons	2012	2004	17,159	6,208
Simmons	2012	2005	15,791	3,909
Simmons	2012	2006	12,192	2,437
Kawatkar	2012	2008	15,558	2,493
Privately Insured Patients				
Birnbaum	2010	1999-2005	12,904	7,006
Birnbaum	2012	2006	11,554	2,914
Medicare				
Harrold	2012	2000	21,445	NR
Harrold	2012	2002	23,707	NR
Harrold	2012	2004	23,024	NR
Harrold	2012	2006	25,260	NR
Medicaid				
Khanna	2007	2003	NR	3,486
Johnson	2008	2003	3,266	NR
Birnbaum	2010	1999-2005	19,519	7,849
Biologic DMARD Users Only				
Weycker*	2005	1999-2002	46,567	NR
Weycker†	2005	1999-2002	52,837	NR
Wu	2007	2003-2004	33,308	22,358
McBride	2011	1999-2007	27,373	16,716
Baser	2015	2005-2010	26,469	22,445

*Constella COMPASS database, Util. x Std. Cost method

†Ingenix LabRx database, Charges method

NR, not reported