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Economics of Medically Unexplained Symptoms: A Systematic Review of the Literature

Alexander Konnopka[a] Rainer Schaefert[b] Sven Heinrich[a] Claudia Kaufmann[b]
Melanie Luppa[c] Wolfgang Herzog[b] Hans-Helmut König[a]

[a]Department of Medical Sociology and Health Economics, University Medical Center Hamburg-Eppendorf, Hamburg,
[b]Clinic for Psychosomatic and General Internal Medicine, University of Heidelberg, Heidelberg, and
[c]Institute of Social Medicine, Occupational Health and Public Health, University of Leipzig, Leipzig, Germany

Key Words
Somatization disorder · Medically unexplained symptoms · Economic evaluations · Cost of illness · Cost-effectiveness

Abstract
Objective: To review cost-of-illness studies (COI) and economic evaluations (EE) conducted for medically unexplained symptoms and to analyze their methods and results. ***Methods:*** We searched the databases PubMed, PsycINFO and National Health Service Economic Evaluations Database of the University of York. Cost data were inflated to 2006 using country-specific gross domestic product inflators and converted to 2006 USD purchasing power parities. ***Results:*** We identified 5 COI and 8 EE, of which 6 were cost-minimization analyses and 2 were cost-effectiveness analyses. All studies used patient level data collected between 1980 and 2004 and were predominantly conducted in the USA (n = 10). COI found annual excess health care costs of somatizing patients between 432 and 5,353 USD in 2006 values. Indirect costs were estimated by only one EE and added up to about 18,000 USD per year. In EE, educational interventions for physicians as well as cognitive-behavioral therapy approaches for patients were evaluated. For both types of interventions, effectiveness was either shown within EE or by previous studies. Most EE found (often insignificant) cost reductions resulting from the interventions, but only two studies explicitly combined changes in costs with data on effectiveness to cost-effectiveness ratios (ratio of additional costs to additional effects). ***Conclusions:*** Medically unexplained symptoms cause relevant annual excess costs in health care that are comparable to mental health problems like depression or anxiety disorders and which may be reduced by interventions targeting physicians as well as patients. More extensive research on indirect costs and cost-effectiveness is needed.

Background

Patients with medically unexplained symptoms suffer from patterns of persistent bodily complaints indicating no sufficiently explanatory physical pathology despite frequent intensive diagnostic efforts. Such patients present a substantial portion of patients in all health care sectors, particularly in primary care, where prevalence rates between 16 and 32% have been reported [1–3]. Multiple medical symptoms found in medically unexplained symptoms are associated with negative treatment outcomes in other disorders, e.g. depression or anxiety dis-

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Alexander Konnopka
University Medical Center Hamburg-Eppendorf
Department of Medical Sociology and Health Economics
Martinistrasse 52, DE–20246 Hamburg (Germany)
Tel. +49 40 741 059 048, E-Mail a.konnopka@uke.de

orders [4], and are connected to high health care utilization [5, 6], causing substantial costs. Health care utilization and costs are two different measures of resource usage. While health care utilization is easier to interpret for clinicians, costs are easier to interpret for economists. Presenting resource usage as costs rather than utilization allows summing cost from different cost areas to total costs, enabling more compressive analysis than for utilization data. For this reason, resource use should be presented as cost data. The costs of medically unexplained symptoms have two origins: resources utilized for health care (direct costs) and productivity losses arising primarily from morbidity-related sickness absence (indirect costs). The question about relevance of single cost categories strongly depends on the perspective taken by the study. From a societal perspective, all costs (including indirect costs) are relevant, whereas from a payer's perspective only direct medical costs may be relevant. Direct and indirect costs together constitute the economic burden of medically unexplained symptoms, which can be quantified via cost-of-illness studies (COI). In COI, the costs of an illness are estimated by measurement and monetary valuation of health care utilization and lost productivity in patient samples or by extraction of this information from routine data. As health care systems are confronted with limited resources and a large proportion of medical health care utilization of patients with medically unexplained symptoms can be regarded as 'misspent', several economic evaluations (EE) investigated how the costs of medically unexplained symptoms can be reduced by specific interventions [7, 8]. There are different types of EE: cost-minimization analyses (CMA) address the question whether an intervention results in lower health care costs. However, treatment decisions should not be based on cost considerations alone. Instead, cost data should always be combined with data on effectiveness in order to create cost-effectiveness analyses (CEA), which use clinical parameters like gained life years or recovered cases as a measure of effectiveness [9]. Health economists even prefer so-called cost-utility analyses with quality-adjusted life years (QALYs) as the measure of effectiveness. In order to calculate QALYs, life years are weighted with a preference-based index of their health-related quality of life, normally estimated from questionnaire-based assessments of a patient's health-related quality of life. Typically, cost-effectiveness refers to the ratio of the differences in costs and differences in health effects when two or more treatment strategies are compared (e.g. intervention vs. control). This ratio is called 'incremental cost-effectiveness ratio' and can be interpreted as the cost of one effect unit resulting from performing the intervention rather than the control [10]. Whereas COI present information only on the economic burden of a disease, EE can assist decision makers in the allocation of scarce resources by providing information about the input-output ratio of a health care technology.

Though theoretical standards and guidelines for COI or EE exist, general methods, data sources and analytical techniques in the literature are heterogeneous. One reason may be that health economic studies are often conducted 'piggy back' to clinical studies or as secondary analyses, enforcing compromises in study design. Systematic reviews of the literature may help to structure methods used in COI and EE and to facilitate the interpretation of their results.

While reviews about economic aspects of specific single disorders like fibromyalgia [11] or irritable bowel syndrome [12] already exist, to our knowledge, this is the first systematic review of health economic literature in the field of medically unexplained symptoms in general. The aim of our study is to provide the first systematic review of COI and EE in medically unexplained symptoms.

Methods

Data Sources and Search Strategy

We conducted a chronological unlimited literature search (until January 2010) in the databases PubMed, PsycINFO and the National Health Service Economic Evaluations Database of the University of York as well as in the reference lists of identified studies. According to the current development process of the S3-guideline (guideline with all components of a systematic development: logical structure of clinical algorithms, consensus, evidence base, decision analyses and outcome analyses) for nonspecific, functional and somatoform bodily complaints (http://www.awmf.org/leitlinien/detail/anmeldung/1/ll/051-001.html) of the Association of the Scientific Medical Societies in Germany (AWMF), we used the following search terms: ('somatoform disorder' OR somatiz* OR somatis* OR 'conversion disorder' OR multisomatoform* OR 'medically unexplained symptoms' OR 'medically unexplained illness' OR psychogen* OR nonorgan* OR (psychosom* syndrome) OR 'functional somatic syndrome' OR 'functional syndrome' OR hypochondri* OR 'illness phobia' OR 'health anxiety' OR 'body dysmorphic disorder' OR dysmorphophobia) and (cost OR economic OR expenditure). Search terms were adjusted to meet the formal specifications of the databases.

Selection Criteria

Studies were included if they reported original cost or cost-effectiveness data for medically unexplained symptoms. We excluded reviews, studies reporting results of other studies, studies not meeting diagnostic criteria, studies that used economically relevant parameters (e.g. being a 'high utilizer') as inclusion criteria and studies which were not in the English language.

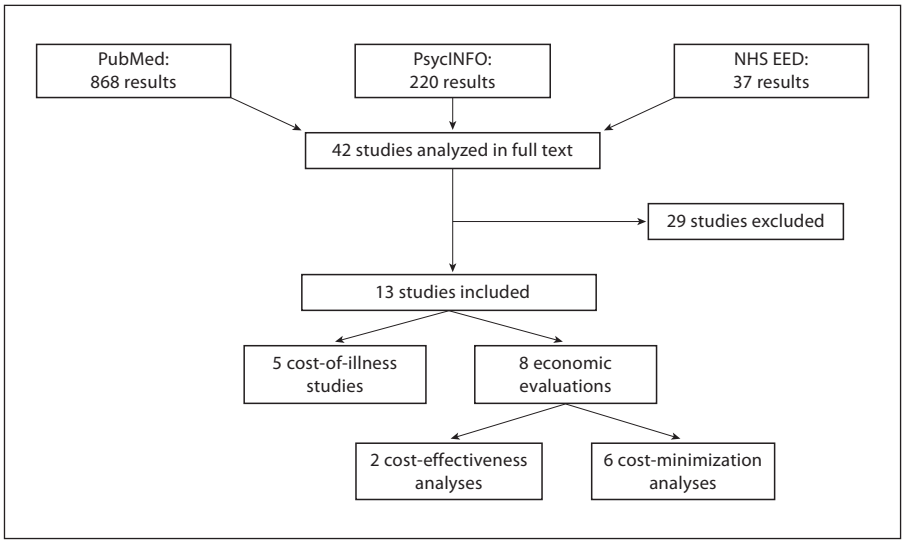

Fig. 1. Flow chart of search results, study inclusion and study exclusion.

Methodological Assessment, Extraction and Analysis of Cost Data

We analyzed general methodological issues (e.g. study type, recruitment setting, diagnostic criteria, sample size, sources of cost data) and minimal quality (e.g. calculation and presentation of cost data and effectiveness) as well as cost results. If necessary, cost data were transformed to annual values, inflated to the year 2006 using country-specific price indices of gross domestic products and converted to USD using purchasing power parities to account for differences in purchasing power between countries [13]. Given sufficient data, we estimated excess costs (see Appendix) for COI and cost differences (e.g. before and after intervention) for CMA and CEA.

Results

Search results are shown in figure 1. We identified 42 studies that were analyzed in full text, of which 13 studies were included: 5 COI, 6 CMA, and 2 CEA. We excluded 29 studies for several reasons, mainly because they did not meet diagnostic criteria, reported no costs or used economic parameters as inclusion criteria (for details, see online supplementary table 1, www.karger.com/doi/10.1159/000337349).

Study Characteristics

General study characteristics are presented in table 1. The earliest studies came from the year 1986, the most recent one from 2008. The majority of studies (n = 10) were conducted in the USA [7, 8, 14–20], 2 in Great Britain and 1 in Germany. Patients were predominantly recruited in primary care settings (n = 7). The most often included syndromes were 'somatization' (n = 6) and 'somatization disorder' (n = 5). Diagnostic criteria differed largely between studies: half of the studies (n = 6) used DSM criteria (DSM-III or DSM-IV), the remaining studies used either the presence of medically unexplained symptoms assessed by chart reviews (n = 3) or patient self-report questionnaires and symptom checklists (n = 3), or both of them (n = 1). The study design strongly depended on the type of economic analysis (or vice versa): while COI were conducted alongside cohort studies without intervention, EE of interventions were either pre-post cohort studies or randomized controlled trials (RCTs). Sample sizes ranged from 38 to 299, and all studies used patient level data for cost calculations. Except for Seivewright et al. [21], who used a health service perspective, no study explicitly stated the perspective from which the study was conducted. Cost estimates were predominantly based on billing information or medical records obtained from health care providers or payers, often complemented by further investigations to assess costs not covered by payers (table 1).

Online supplementary table 2 displays the cost categories considered. All studies assessed costs of outpatient physicians, and all but one assessed costs of inpatient care. Costs of emergency rooms and outpatient procedures were assessed by 10 and 9 studies, respectively. Ten studies assessed an outpatient diagnostic procedure, most often for laboratory. Surprisingly, only 5 studies assessed costs for drug use. Indirect costs were hardly recorded. Only Hiller et al. [22] assessed productivity losses due to sickness absence.

Table 1. General study characteristics

Study	Country	Recruitment setting	Condition/ syndrome	Diagnostic criteria	Study type	Age, range or mean (SD)	Sample size with cost	Costing year	Sources of cost data
Cost-of-illness studies									
Smith et al. [7], 1986	USA	Primary care physicians	SD	DSM-III	CS	21–73 44	41	1981[a]	Billing information from payers identified by patient interviews and medical records
Labott et al. [16], 1995	USA	Pulmonary clinic	S	Unexplained symptoms	CS	13–59 39	41	1989[a]	Study hospital's database
Barsky et al. [17], 2001	USA	Primary care clinic	S, HA	Hopkins symptom checklist + WI-14	CS	18+	212	1998[a]	Study hospital's database
Barsky et al. [18], 2005	USA	2 primary care practices affiliated with a hospital	S	PHQ-15	CS	18+	299	2001[a]	Study hospital's database
McFall et al. [19], 2005	USA	Veteran affairs primary care clinic	MUPS	Unexplained symptoms	CS	35 (9)	206	1999[a]	Department of veteran affairs database
Economic evaluations									
Smith et al. [14], 1986	USA	Primary care physicians	SD	DSM-III	RCT	45	38	1980	Billing information from payers identified by patient interviews and medical records
Kashner et al. [8], 1992	USA	Primary care physicians	SD	DSM-III R	RCT	35–55	73	1990	Billing information from payers identified by interviews and medical records
Smith et al. [15], 1995	USA	Primary care physicians	S	DSM-III R	RCT	42 (12)	56	1990	Billing information from payers identified by interviews and medical records
Morriss et al. [23], 1998	Great Britain	General practitioners	S	GHQ-12 + unexplained symptoms	PPCS	45 (14)	103	1995	Health care utilization assessed by patient interview and questionnaire and primary care records, monetary valuation by unit costs
Hiller et al. [22], 2003	Germany	Psychosomatic clinic	S, SD	DSM-IV	PPCS	19–72	95	1994[a]	Billing information from payers identified by patient interview
Allen et al. [24], 2006	USA	Medical clinics and advertisements in the community	SD	DSM-IV	RCT	46 (8)	56	2001[a]	Billing information from payers and providers identified by medical records
Luo et al. [20], 2007	USA	Primary care	MUPS	Unexplained symptoms	RCT	50 (8)	189	2001[a]	HMO database and patient interview on costs not covered by HMO
Seivewright et al. [21], 2008	Great Britain	Genitourinary medical clinic	HA	Health Anxiety Inventory	RCT	n.s.	41	2004	Examination of medical records by study staff and monetary valuation of health care utilization by unit costs

CS = Cohort study (i.e. no intervention); GHQ-12 = General Health Questionnaire; HA = health anxiety; MUPS = medically unexplained symptoms; n.s. = not stated; PHQ = Patient Health Questionnaire; PPCS = pre-post cohort study; S = somatization; SD = somatization disorder; WI = Whiteley Index.

[a] No reference year given, reference year assumed from other data (e.g. year of recruiting, time span of study conduction).

Table 2. Mean cost per patient and year in COI

Study	Original currency	Control group	Control group adjusted for	Original cost data			Costs in 2006, USD PPP			Composition of costs in patients
				patients	comparator	excess costs	patients	comparator	excess costs	
Smith et al. [7], 1986	USD	Unpublished data from general population (no number given)	No adjustment	3,256	543	2,713	6,424	1,071	5,353	74% inpatient treatment, 26% outpatient treatment
Labott et al. [16], 1995	USD	Average of 'Health Alliance Plan' patients (n = 210,000)	No adjustment	1,424	109	1,315	2,112	162	1,950	≈41% diagnostic tests, ≈37% professional services, ≈16% room use, ≈3% drugs, ≈2% additional charges
Barsky et al. [17], 2001	USD	Screened patients below the somatization cutoff (n = 664)	Sociodemographic variables and medical comorbidity	1,312	954	358	1,584	1,152	432	≈60% physicians, ≈40% lab and procedures
Barsky et al. [18], 2005	USD	Random patient group without somatization (n = 1,157)	Sociodemographic variables, medical and psychiatric comorbidity	5,678	2,944	2,724	6,465	3,352	3,113	Total costs: 51% inpatient treatment, 49% outpatient treatment; excess costs: 68% inpatient, 32% outpatient
McFall et al. [19], 2005	USD	–	–	3,106			3,699			57% medical treatment, 32% mental treatment, 11% drugs

Cost-of-Illness Studies

Table 2 shows total and excess costs found in COI. In values of 2006, 5 COI found mean annual health care costs ranging from 1,584 to 6,424 USD. Four of these studies calculated excess costs using either data from the general population, average 'Health Alliance Plan' patients, patients below the somatization cutoff used, or a random patient group without somatization as comparator. Excess costs ranged from 432 to 5,353 USD. Reporting of percentages of cost categories in overall costs was limited. Two studies found inpatient costs to account for a substantial part of total direct costs: Smith et al. [14] found inpatient costs of 74% and Barsky et al. [18] of 51%; the latter additionally reported inpatient costs to account for 68% of excess costs. Two further studies reported that diagnostic procedures accounted for about 40% of total direct costs [16, 17]. McFall et al. [19] showed that direct costs were primarily caused by medical treatment (57%) and drugs (11%), while only 32% stemmed from mental treatment.

Economic Evaluations

General study characteristics of EE are shown in table 1, details on intervention, health outcomes and costs in table 3. Studies can be grouped by whether the evaluated interventions are targeting primary care physicians (PCP) [7, 8, 15, 23] or the patients [20–22, 24]. Interventions targeting PCPs intended to strengthen PCPs' abilities to identify and manage patients with medically unexplained symptoms. Interventions targeting patients were all based on cognitive behavioral therapy (CBT). Six studies were based on RCTs and three studies on pre-post cohorts. From the economic perspective, the majority of EE (n = 6) were CMA, questioning whether or not the intervention was cost saving. Two studies were CEA [21, 23], which put changes in costs in relation to changes in a measure of effectiveness.

Interventions Targeting on PCPs

Consultation Letter. In three studies of a study group surrounding G.R. Smith [7, 8, 15], a consultation letter for PCPs was evaluated in terms of cost minimization. The letter informed physicians about clinical characteristics, course and prognosis of medically unexplained symptoms and gave recommendations on clinical patient management. It encouraged physicians to serve as the patient's PCP and suggested regular appointments including physical examination and avoidance of hospitalizations, surgeries, diagnostic procedures and laboratory assessments, unless clearly indicated. In the oldest study [7], the cross-sectional cost data of Smith [5] were longitudinally fol-

Table 3. Specific characteristics and mean (median in italics) cost per patient and year in EE

Study	Original currency	Study design	Postintervention observation, months	Intervention	Health outcome measured by	Effectiveness (significant only)	Group	Mean cost data in 2006, USD PPP			p value
								preintervention	postintervention	cost difference	
CMA											
Smith et al. [14], 1986	USD	RCT	18	Consultation letter for PCP (n = 19) vs. no consultation letter (n = 19)	RAND health status measure	No significant changes	Intervention Control	*4,373* *2,881*	*846* *1,377*	*–3,527* [a] *–1,504* [a]	<0.05 <0.05
Kashner et al. [8], 1992	USD	RCT	12	Consultation letter for PCP (n = 40) vs. no consultation letter (n = 33)	RAND health status measure	Physical subscale improved (interaction effect)	Total mean Medical Psychiatric	5,441 *1,659* [b] *490* [b]	– – –	– *–752* [b] *+101* [b]	– <0.001[b] n.s.[b]
Smith et al. [15], 1995	USD	RCT	12	Consultation letter for PCP (n = 27) vs. no consultation letter (n = 29)	RAND health status measure	Physical subscale improved (interaction effect)	Medical mean Medical Psychiatric[d]	4,551 *1,255* [b] *1,022* [c]	– – –	– *–413* [b] *–74* [c]	– 0.02 n.s.
Hiller et al. [22], 2003	EUR	PPCS	24	Individual and group CBT for patients vs. no CBT (n = 28–209)[e]	WI, DAQ, CABAH, SOMS, BDI	All scales improved (pre-post effect)	Direct cost Indirect cost Cost of Int	3,779 23,623	3,056 15,287	–723 –8,336 9,112	n.s. <0.05
Allen et al. [24], 2006	USD	RCT	15	CBT for patients and consultation letter for PCP (n = 28) vs. consultation letter alone (n = 28)	CGI-SD, SF-36 physical subscale, SSD	All scales improved (interaction effect)	Intervention Control	*2,214* *2,150*	*1,372* *1,873*	*–842* *–277*	0.01[d]
Luo et al. [20], 2007	USD	RCT	12	CBT and drug management for patients (n = 94) vs. usual care (n = 95)	SF-36	SF-36 mental subscale improved (odds ratio Int vs. control)	Intervention Control Cost of Int[f]	9,046 9,975	7,582 9,027	–1,464 –948 +455[f]	n.s.[d]

Study	Original currency	Study design	Postintervention observation, months	Intervention	Health outcome measured by	Effectiveness (significant only)	Group	Intervention group	Control group	Cost difference	p value
CEA											
Morriss et al. [23], 1998	GBP	PPCS	3	Training package for GP (n = 103) vs. no training package (n = 111)	GHQ-12	More successful treatments (χ^2 p = 0.058)	Cost of Int	2,122	2,700	–578 +30	n.s.
Seivewright et al. [21], 2008	GBP	RCT	12	CBT and supplementary manual (n = 18) for patients vs. usual care (n = 23)	HAI, BAI, HADS	HAI and HADS improved (interaction effect)	Cost of Int	794	1,040	–246 +700	n.s.

BAI = Beck Anxiety Inventory; BDI = Beck Depression Inventory; CABAH = Cognitions about Body and Health Questionnaire; CGI-SD = clinical global impression for somatization disorder; DAQ = Dysfunctional Analysis Questionnaire; GHQ-12 = General Health Questionnaire; GP = general practitioner; HADS = Hospital Anxiety and Depression Scale; HAI = Health Anxiety Inventory; Int = intervention; n.s. = not significant; PCP = primary care physician; PPCS = pre-post cohort study; SOMS = screening for somatoform symptoms; SSD = somatic symptom diary; WI = Whiteley index.

[a] Difference of medians. [b] Authors reported baseline costs for the total sample and effect of intervention on costs estimated by regression analysis. [c] Median psychiatric costs of 26% of all patients with psychiatric health care utilization and statistically estimated cost reductions due to the intervention letter. [d] Significance of between group difference of cost reduction in the intervention group compared to cost reduction in the control group. [e] Sample sizes for pre-post comparisons differed between single cost categories from n = 28 for 'other expenditures' to n = 209 for 'hospital treatment', according to data availability from payers. [f] Per patient cost for training of study nurse, calculated with the assumption the study nurse treats 15 patients per year for 5 years.

lowed using a cost minimization approach. In the two younger studies, Smith and colleagues [8, 15] recruited patients with medically unexplained symptoms and analyzed different subsamples of patients with somatization and somatization disorder. All three studies found significant reductions of median medical or total costs in patients after the intervention. In the younger studies [8, 15], cost changes for psychiatric services were analyzed and not found to change significantly. Health outcome was uniquely assessed using the 'RAND health status measure' (table 3). Whereas Smith et al. [7] found no significant changes in health outcome, Kashner et al. [8] and Smith et al. [15] found significant improvements on the 'physical health' axis of the RAND health status measure.

PCP Training Program. One study evaluated a training package for PCPs 'how to encourage patients with somatized mental disorder to reattribute and relate physical symptoms to psychosocial problems' in the sense of incremental cost-effectiveness [23]. Effectiveness was measured as number of patients that were no longer psychiatric cases according to the general health questionnaire. The authors found an insignificant overall cost reduction and an improved effectiveness, which slightly missed significance ($p = 0.058$).

Interventions Targeting Patients

We identified 4 studies evaluating different CBT approaches: CBT alone [22], CBT combined with a consultation letter for PCPs [24], CBT combined with drug management by nurse practitioners [20] and CBT combined with a patient manual on the principles of CBT [21]. Treatment outcomes were assessed by pertinent questionnaires, which mostly showed superiority for the intervention group (table 3). Three studies [20, 22, 24] were conducted in terms of cost minimization and found reductions in treatment costs which were only significant for median costs in one study [24]. One study assessed indirect costs and found a significant reduction due to the intervention [22]. Three studies reported the costs of the intervention [20–22], which mostly offset the reductions found in treatment costs. Only one study performed a CEA [21] using the Health Anxiety Inventory as measure of effectiveness. From a health service perspective and adjusted for baseline variables, the authors found an incremental cost-effectiveness ratio of 54 USD per Health Anxiety Inventory unit reduced, which can be interpreted as follows: with every unit of Health Anxiety Inventory reduction resulting from conducting the intervention instead of the control, additional overall costs of 54 USD occur (compared to the control).

Discussion

To our knowledge, this is the first systematic review of health economic studies for medically unexplained symptoms. We found two main results: first, medically unexplained symptoms cause relevant excess costs per patient; second, interventions targeting PCPs' diagnostic and patient management skills as well as CBT for patients have the potential to improve patients' health status and to reduce costs.

Strengths

This review has several strengths. We used a broad search strategy and included a wide spectrum of health economic study types leading to a comprehensive overview of existing health economic publications in the field of medically unexplained symptoms. The methodological quality of the studies was described, analyzed and discussed in depth, indicating weaknesses that can be addressed in future research.

Limitations

Our review has some limitations. Due to the heterogeneity and limited methodological quality of studies, it was hardly possible to apply strict quality criteria for the inclusion or exclusion of studies, though we presented all available evidence and tried to discuss important quality issues. Due to restrictions of access to respective literature or languages and to avoid arbitrariness in study inclusion, we did not consider dissertations, unpublished material or studies not in the English language, which makes our review susceptible to publication bias. Four of 13 included studies originated from the same work group, using 2 samples of patients for two studies each, limiting the independence of the data. However, every study had a unique objective, and 3 of the 4 studies had unique patient samples. Comparability of studies was limited due to differences in design, methods and year of study conduction. We used an unlimited search period; but therapeutic possibilities, standards and health care systems change over time, which affects cost estimates. Differences in included cost categories further limited comparability. This was especially true for COI, for which cost comparisons between studies are more relevant than for CMA and CEA, which focus on comparisons of therapeutic alternatives. When comparing different estimates of excess costs, one must also note that these do not only depend on the costs of the disease but also on the comparator used to calculate the excess.

Methodological Quality of Included Studies

The quality of cost measurement and calculation was – as far as assessable – adequate. A majority of cost calculations was based on administrative data from hospital databases or billing information obtained from payers in COI as well as EE. This method tends to underestimate privately paid health care goods, which may be problematic when a societal perspective is used. Further, being a result of individual cost structures and local prices, billing information from specific health care providers may be very inaccurate in reflecting the true economic impact of a disease. But the alternatives of using questionnaires or interviews to assess health care utilization also have disadvantages like underreporting or misreporting due to memory bias. A general problem was the definition of cost categories and the quantity of included cost categories, for which we found large differences between studies, resulting from different scopes and available data sources. This strongly hampered comparison of costs between studies. Labott et al. [16] and Hiller et al. [22] conducted the most comprehensive assessments of cost categories, but no study assessed nonmedical costs (e.g. for transport to physicians), and only Hiller et al. [22] assessed indirect costs.

The quality of presenting the health economic results was sometimes poor. Only one study stated the perspective from which the study was conducted [21]. Yet the perspective of a study (e.g. society or payer) is crucial, because it determines the primary interest group of the study and which costs should or should not be included in the study. From a payer's perspective, for example, indirect costs or private payments are usually irrelevant, but from a societal perspective, these costs are very important. Eight studies [14, 16–20, 22, 24] did not report the year of costing. Due to inflation and changes in prices and health care systems, it is essential for a reader to know the year cost data are referring to. Without this information, inflation adjustment and interpretation of costs are seriously hampered. Four EE reported cost data as median values, due to skewed cost data [7, 8, 15, 24]. From the statistical point of view, medians may be more appropriate than means, but cost data should always also be reported as means for several reasons. Medians cannot be summed or subtracted (hampering the calculation of cost reductions or excess costs, for example) and published cost data are often used as input in mean-based further research (e.g. cost-effectiveness models or budget impact analysis). Methods like bootstrapping [25] can be used to account for skewed data when comparing mean cost data. Related to this issue, there is another problem concerning sample sizes. Due to the large variance and skewed nature of cost data, cost comparisons usually need larger sample sizes than comparisons of clinical effectiveness to detect differences at the significance level. Indeed, sample size was quite low (considerably below 100) in 6 of 9 EE [7, 8, 15, 21, 22, 24]. This presents a general problem in health economics, because EE are often conducted as 'piggy back' studies in clinical trials which often need lower sample sizes due to lower variances of clinical parameters compared to cost data. Finally, RCT-based EE of interventions for physicians were in fact cluster RCTs, but no study indicated that cluster design was taken into account in statistical analyses.

Cost-of-Illness Studies

COI showed that medically unexplained symptoms are associated with relevant annual excess costs in health care, ranging from 432 to 5,353 USD per patient in prices of 2006. Recent reviews found comparable annual excess costs per patient of up to 5,871 USD for depression [26], and of up to 3,042 USD for anxiety disorders [27]. Interestingly, excess costs showed much more variability (by factor 12) than total costs (by factor 4), indicating a larger uncertainty in estimating excess costs compared to total costs. This may (in part) result from the diagnostic heterogeneity of the control groups, which showed cost variations by factor 27. The question how to estimate a disorder-specific cost-excess is of general importance in COI, but no general recommendations exist on handling this issue.

The heterogeneity of reported cost categories hampers detailed interpretations or comparisons of single cost categories. Nevertheless, we found two tendencies in the studies. Two studies each found high portions of direct costs for inpatient treatments (68–74% of excess costs [14, 18]) and – using a differing cost stratification – diagnostic procedures (approx. 40% [16, 17]). These findings indicate the potential for cost savings by sufficient treatment of medically unexplained symptoms avoiding unnecessary diagnostics and hospital stays.

Whereas all studies measured direct costs, we found a lack of analyzing indirect costs. Only Hiller et al. [22] estimated indirect costs in an EE. Though restricted to sickness absence from work, the preintervention indirect costs were 3 times the direct costs and were much more reduced by the intervention than direct costs (–35% vs. –19%). It can be suspected that overall indirect costs including costs resulting from reduced productivity at work may even be much higher. This underscores the importance of measuring and analyzing indirect costs connect-

ed to medically unexplained symptoms from a societal perspective.

Economic Evaluations

We identified 9 EE in two waves of studies investigating the management of medically unexplained symptoms. In a first wave of studies, interventions targeted PCPs, evaluating consultation letters [7, 8, 15] and educational training [8, 15, 23]. In a second wave of studies, the focus moved to CBT approaches for patients [20–22, 24]. Almost all studies found cost reductions during follow-up compared to before treatment – yet not always presented as mean differences and often insignificant.

Based on the studies we found, a comparison of interventions for PCPs and CBT is hardly possible. Though intervention costs were hardly stated for PCP trainings, they should be considerably lower than for CBT, because PCP training costs are divided among a couple of patients, whereas CBT costs occur with every patient. If stated, intervention costs for CBT often offset cost reductions resulting from CBT. However, the longest follow-up was 24 months, and one might speculate that CBT may show further cost savings after this time point. Allen et al. [24] found a combination of CBT and a consultation letter to be more effective on a couple of effectiveness measures – a finding that is also provided by the literature [28] – and less costly (on the median level) than consultation letter alone.

In addition to changes in costs, EE of interventions should always relate to changes in effectiveness. In this respect, we found a general lack in methodology in 6 out of 8 EE, which were CMA [7, 8, 15, 20, 22, 24]. CMA are subject to serious criticism, since they ignore differences in the health gain or loss of an intervention [9]. Ignoring health effects is very problematic, because a cost saving intervention might result in adverse health effects. On the other hand, a more costly intervention might result in health gains that are worth the additional costs – depending on a society's economic properties, health preferences and willingness to pay for health care goods. Though not related to cost data, health outcomes of the interventions were either assessed or cited in all CMA. These health outcomes indicate that health status was either improved or unchanged by the interventions. Combined with the reductions found in costs, this can be interpreted in favor of the interventions.

Implications for Clinical Practice

The results of our analysis indicate that two aspects are crucial for patient outcome and to delimit health care costs: first, the sensitization of caregivers for medically unexplained symptoms, and second, provision of effective care models. This affects physicians' knowledge and skills in diagnosis and management of patients with medically unexplained symptoms [29]. Physicians should be skilled in the basic communication techniques to handle functional patients. PCPs are the center of attention, as they are usually the first caregivers who functional patients contact. Instead of unnecessary diagnostic procedures, a 'watchful waiting' strategy should be applied [30]. Physicians' excuses from work should be given very critically; instead, graded activation and exercise should be advised [31]. Instead of poorly prepared referrals to specialists or to hospital, multidisciplinary, stepped and collaborative care models should be established [28, 32]. Premature pension should be avoided and psychotherapy like CBT should be applied when appropriate.

Implications for Future Research

The health economic quality of COI and CEA in the field of medically unexplained symptoms should be further improved. This should comprise the use of large enough sample sizes, reporting of sufficient health economic information including mean cost data, perspective, pricing year, and, finally, the calculation of cost-effectiveness or cost-utility rather than cost minimization. Given a societal perspective, indirect costs should be assessed in particular because the strong subjective health impairment of patients with medically unexplained symptoms may substantially impair their productivity. More extensive research on cost-effectiveness is needed. Overall, the study of Seivewright et al. [21] presents the best example of a state-of-the-art EE available in the field of medically unexplained symptoms. For further information, well-accepted literature is available for planning, conducting, analyzing and presenting EE [33].

Conclusions

Medically unexplained symptoms are associated with relevant annual excess costs in health care. Large proportions of these costs seem to be caused by hospital stays, diagnostic procedures and medical treatments. Regarding interventions, we found evidence supporting superiority of training for PCP to recognize and manage patients with medically unexplained symptoms compared to no training from the health economic perspective. Regarding CBT, the health economic evidence remains more uncertain due to the intervention costs – though

favorable cost-effectiveness compared to 'usual care' is indicated. We found a lack of research on indirect costs, which seem to be high in medically unexplained symptoms and should be a focus for further research. EE showed a strong methodological focus on cost reductions with a clear neglect of cost-effectiveness. More effort on (long-term) cost-effectiveness should also be a focus of future research.

Appendix: Glossary of Economic Terms

Cost-effectiveness analysis (CEA): A subtype of *economic evaluations* using clinical measures for medical effectiveness (e.g. life years gained, anxiety-free days, PHQ-15 score, CGI score).

Cost-minimization analysis (CMA): A subtype of *economic evaluations* using no measure of medical effectiveness. As this type compares only costs, it should only be used if medical effectiveness is expected to be identical in the compared alternatives. Because this is mostly not the case, use of CMA is strongly limited.

Cost-of-illness study (COI): In a COI, one estimates the *direct costs* and/or *indirect costs* associated with a disease or disease group (e.g. costs of depression, costs of anxiety disorders) or a risk factor (e.g. costs of smoking).

Cost-utility analysis: A subtype of *economic evaluations* using *quality-adjusted life years* as measure for medical effectiveness.

Direct costs: Monetarily valued resource use resulting from the treatment of a disease. Occur as medical costs (e.g. for hospital use, physician use, pharmaceuticals) and nonmedical costs (e.g. administration costs, travel costs, research costs). Normally direct costs are calculated by multiplying utilization data with costs per unit used.

Economic evaluation (EE): In an EE, one compares an intervention (e.g. a new drug, a new therapy, a prevention program) with an alternative (e.g. gold standard, treatment as usual, no treatment) regarding their costs and their medical effectiveness. Depending on the measure of medical effectiveness *cost-minimization analysis, cost-effectiveness analysis* and *cost-utility analyses* are distinguished as subtypes of EE. The primary outcome of an EE is the so called *incremental cost-effectiveness ratio*.

Excess costs: Costs that can be attributed to a specific disease of interest in addition (excess) to costs that result from other diseases. Can be estimated e.g. by comparing the cost of patients with the disease of interest with 'representative' or matched patients without the disease of interest.

Incremental cost-effectiveness ratio (ICER): This is the ratio of the additional costs (C) to the additional medical effects (E) of an intervention (I) compared to an alternative (A) within an *economic evaluation*. The ICER is calculated as ICER = $(C_I - C_A)/(E_I - E_A)$ and constitutes the costs for an additional medical effect gained by using the intervention instead of the alternative.

Indirect costs: The monetarily valued loss of productivity associated with a disease. Occur primarily as reduced productivity at work, sickness absence, early retirement or premature mortality. Normally indirect costs are calculated by multiplying loss of productivity time with wages.

Perspective: The (economic) perspective determines the cost categories that should be assessed in a *cost-of-illness study* or an *economic evaluation*. If a study is conducted from a payer's perspective only costs relevant for the payer (normally only *direct costs*) are assessed. From a societal perspective (which is recommended in the literature) all relevant costs (including also *indirect costs*) should be assessed. Further possible perspectives are a patient perspective or a provider perspective.

Quality-adjusted life years (QALY): In quality-adjusted life years, time (e.g. lived time or life years gained) is weighted with an index value of a person's health-related quality of life. This index normally ranges from 0 (death) to 1 (full quality of life) and is either calculated from specific quality of life questionnaires (e.g. EQ-5D or SF-6, SF-12) or directly measured via methods like time trade-off or standard gamble. For example, 1 QALY can be 1 year lived with a quality of life index of 1.0, or 2 years lived with a quality of life index of 0.5 (= 2 × 0.5 QALYs). QALYs are the measure of medical effectiveness in *cost-utility analysis* and are recommended as standard measure of medical effectiveness for *economic evaluations*.

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Disclosure Statement

The authors have no conflicts of interest to disclose.

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