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The excess costs of depression: a systematic review and meta-analysis

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Original Article

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Abstract

Aims. Major depressive disorders are highly prevalent in the world population, contribute substantially to the global disease burden and cause high health care expenditures. Information on the economic impact of depression, as provided by cost-of-illness (COI) studies, can support policymakers in the decision-making regarding resource allocation. Although the literature on COI studies of depression has already been reviewed, there is no quantitative estimation of depression excess costs across studies yet. Our aims were to systematically review COI studies of depression with comparison group worldwide and to assess the excess costs of depression in adolescents, adults, elderly, and depression as a comorbidity of a primary somatic disease quantitatively in a meta-analysis.

Methods. We followed the PRISMA reporting guidelines. PubMed, PsycINFO, NHS EED, and EconLit were searched without limitations until 27/04/2018. English or German full-text peer-reviewed articles that compared mean costs of depressed and non-depressed study participants from a bottom-up approach were included. We only included studies reporting costs for major depressive disorders. Data were pooled using a random-effects model and heterogeneity was assessed with I^2 statistic. The primary outcome was ratio of means (RoM) of costs of depressed *v.* non-depressed study participants, interpretable as the percentage change in mean costs between the groups.

Results. We screened 12 760 articles by title/abstract, assessed 393 articles in full-text and included 48 articles. The included studies encompassed in total 55 898 depressed and 674 414 non-depressed study participants. Meta-analysis showed that depression was associated with higher direct costs in adolescents (RoM = 2.79 [1.69–4.59], $p < 0.0001$, $I^2 = 87\%$), in adults (RoM = 2.58 [2.01–3.31], $p < 0.0001$, $I^2 = 99\%$), in elderly (RoM = 1.73 [1.47–2.03], $p < 0.0001$, $I^2 = 73\%$) and in participants with comorbid depression (RoM = 1.39 [1.24–1.55], $p < 0.0001$, $I^2 = 42\%$). In addition, we conducted meta-analyses for inpatient, outpatient, medication and emergency costs and a cost category including all other direct cost categories. Meta-analysis of indirect costs showed that depression was associated with higher costs in adults (RoM = 2.28 [1.75–2.98], $p < 0.0001$, $I^2 = 74\%$).

Conclusions. This work is the first to provide a meta-analysis in a global systematic review of COI studies for depression. Depression was associated with higher costs in all age groups and as comorbidity. Pooled RoM was highest in adolescence and decreased with age. In the subgroup with depression as a comorbidity of a primary somatic disease, pooled RoM was lower as compared to the age subgroups. More evidence in COI studies for depression in adolescence and for indirect costs would be desirable.

Introduction

Major depressive disorders have an increasing impact on the global burden of disease and are highly prevalent in the global population (4.4%) (G. B. D. Disease Injury Incidence Prevalence Collaborators, 2016; World Health Organization, 2017). Findings from the Global Burden of Diseases, Injuries and Risk Factors Study in 2015 (GBD 2015) show that major depressive disorders ranked third among the leading causes of disability in the world (G. B. D. Disease Injury Incidence Prevalence Collaborators, 2016). Despite the burden of these disorders, their correlation with other medical conditions like chronic diseases tends to be underestimated (Prince *et al.*, 2007). These findings highlight that depressive disorders are a current issue for public health and will be a future challenge for policymakers.

Although criticised for only considering costs and not effects, information on health care costs as provided by cost-of-illness (COI) studies can be useful to emphasise the economic relevance of a disease (Koopmanschap, 1998; Larg and Moss, 2011). These studies can be classified according to two methodological approaches: In bottom-up studies, costs of patient samples are assessed on basis of individual resource-consumption, whereas in top-down studies, aggregate costs at population-level are combined with relative risk and prevalence rates of a disease. Disease-specific costs can be extracted from bottom-up studies by matching a non-

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diseased comparison group and calculating excess costs (the difference between the costs of diseased and non-diseased patients) (Akobundu *et al.*, 2006; Larg and Moss, 2011).

Previous systematic reviews of COI-studies of depression addressed specific subtypes or age groups or the costs of depression as comorbidity of somatic diseases (Lehnert *et al.*, 2011; Luppa *et al.*, 2012; Molosankwe *et al.*, 2012; Mrazek *et al.*, 2014; Sambamoorthi *et al.*, 2017). The last global systematic review was conducted in 2007 (Luppa *et al.*, 2007). In general, a large number of systematic reviews with cost data are available in the literature, but very few conducted meta-analyses (van der Hilst *et al.*, 2009; Haschke *et al.*, 2012; Zhang *et al.*, 2018). Haschke and colleagues included depression in a meta-analysis of COI-studies of coronary artery disease and coexistent mental disorders, but none was solely focusing on depression. Reasons for comparatively little literature on meta-analyses with cost data could be that combining results across studies is difficult and requires a specific format, namely costs reported for a diseased and non-diseased group.

This study is a systematic review and meta-analysis of bottom-up COI-studies of depression with comparator group, with the objectives to (1) update and provide a global overview of the current state of the literature (2) assess the impact of depression on costs by calculating effect sizes of included studies (3) conduct a meta-analysis and display pooled results of all studies as forest plots (4) draw generalizable conclusions about the relevance of depression.

Methods

We used the 27-item checklist of the PRISMA Statement as guideline for this systematic review and meta-analysis (Liberati *et al.*, 2009). Studies were considered for inclusion if they met the following eligibility criteria: full-text peer-reviewed articles in English or German reporting costs for depression and a comparison group were included. We included bottom-up studies, with no limitation on publication date and study design. Reviews, commentaries, editorials, short reports, and duplicates were excluded. Participants with a diagnosis of depression (e.g. major depressive disorder, mild depression, depressive symptoms) were included. If two patient samples (e.g. in the depressed patient group) were reported, they were pooled to a single patient group (Higgins and Deeks, 2011). Exclusion criteria were participants with bipolar disorders, adjustment disorders or other mental disorders like anxiety disorders. Studies with patient subgroups, but missing information needed for pooling (standard deviation (S.D.), sample sizes) were also excluded. No limitations on age, region or diagnostic instruments were imposed. For the purpose of this study, a depressed group is compared to a non-depressed group. Studies comparing excess costs of depressed and non-depressed among (1) adolescent, adult and elderly participants or (2) participants with a specific primary diagnosis of a somatic disease were included. The outcome of interest was limited to studies reporting mean costs for both groups in monetary units per participant. Outcomes only reported as median, log mean or mean difference, predicted costs and results from two-part models were excluded. If both were reported, unadjusted means were preferred over adjusted means. The reason was that processed data contains the risk of an additional source of variability between studies.

We conducted a systematic literature search in PubMed, PsycINFO, NHS Economic Evaluation Database and EconLit following the search term of the most recent systematic review on COI-studies of depression ('cost*' OR 'economic burden' OR 'cost-of-illness' OR 'burden-of-illness') AND ('depression' OR 'depressive disorder') (Luppa *et al.*, 2007). Additionally, reviews and references in identified articles were screened for more relevant literature. The initial search was conducted by HK and completed on 30/01/2018. Literature was then searched for updates until 27/04/2018. Search results were screened for eligibility by title and abstract and then retrieved for full-text examination. Eligibility assessment was performed by HK and AK and in the case of disagreement the reasons were discussed until agreement on eligibility was achieved. Data were identified and extracted in a piloted Excel sheet by HK and double checked by a second reviewer. Authors were contacted if data were missing or unclear for selection of articles.

Data on (1) study characteristics (study year, country, study perspective and data source) (2) participants (sample sizes, age range, diagnostic instruments, diagnostic criteria and included disorders) (3) characteristics of the depressed and non-depressed group and (4) outcome (year of pricing, currency and time interval for costs) were extracted from included articles. We created cost categories for direct excess costs (inpatient, emergency, outpatient treatment, medication and a category including all other direct costs) and indirect excess costs (reduced/lost productivity). If more than one outcome was reported per cost category, we summed mean values and imputed standard errors (S.E.) in the meta-analysis. The methodological quality of included studies was assessed independently by two reviewers. Since there was no existing standardised checklist for COI, we used the checklist reported by Stuhldreher *et al.* (2012), see online Supplementary material S1.

Costs across studies were adjusted to a 12 month time interval, inflated to the year 2017 using consumer price indices and converted to US dollars using Purchasing Power Parities (US$ PPP). For missing data on the year of pricing, we made assumptions based on the recruitment period or information provided in the text and other sources. We formed four patient subgroups for comparison (depressed *v.* non-depressed in adolescents, adults, old age and depression as comorbidity).

We used Ratio of Means (RoM) as effect measure in the meta-analysis, which is calculated as the mean of the depressed group divided by the mean of the non-depressed group (Friedrich *et al.*, 2008; 2011). Results are interpreted as the percentage change in the depressed group compared to the non-depressed group (e.g. RoM = 1.15 implies that the mean costs of the depressed group are 15% higher than the comparison group) (Fu *et al.*, 2014). RoM and corresponding S.E. were calculated in Excel and log-transformed for pooling. Using Review Manager 5.3, results of studies were combined with the generic inverse variance method (DerSimonian and Laird) using random-effects models (DerSimonian and Laird, 1986). When S.D. was missed, we imputed data using direct substitution of the highest S.E. in the patient subgroup (Fu *et al.*, 2014). Pooled results are back-transformed so that RoM and 95% confidence intervals (95% CI) are presented on a non-logarithmic scale (Friedrich *et al.*, 2008, 2011). Heterogeneity was assessed with I^2 statistic (with $I^2 = 25\%$, $I^2 = 50\%$ and $I^2 = 75\%$ indicating low, moderate, and high heterogeneity) (Higgins *et al.*, 2003). Meta-analyses were performed for direct and indirect total excess costs as well as for all cost categories separately. All eligible studies were included in the systematic review and meta-analysis of total excess costs. In the direct cost categories, meta-analyses were conducted if more than one study was comprised in the patient

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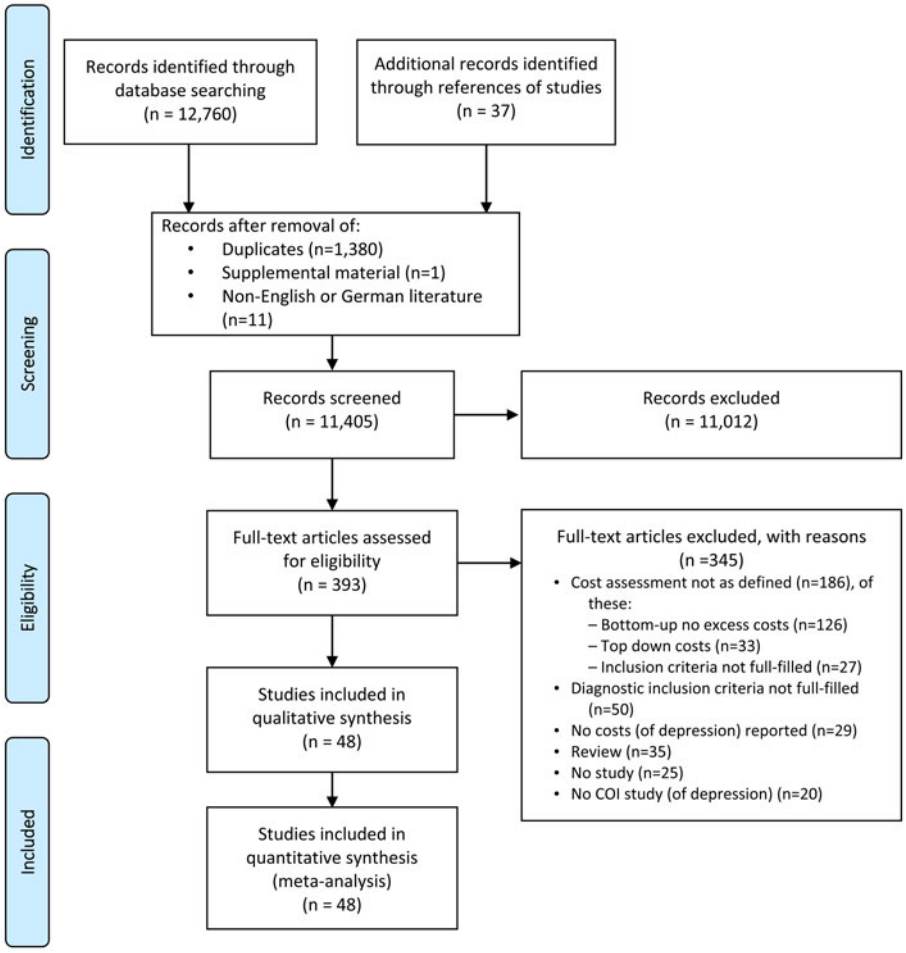

Fig. 1. PRISMA 2009 Flow diagram.

subgroups. Results of meta-analysis are shown as forest plots. Robustness of results was tested by removing studies with extreme values from the analysis.

Results

We identified 12 760 articles and 37 additional articles through references to studies. After exclusion of duplicates, supplemental material and non-English or German literature, we screened 11 405 articles by title and abstract, of which 11 012 were excluded. Of 393 full-text articles assessed for eligibility, 345 were excluded, because they did not meet the inclusion criteria (see Fig. 1). In total, 48 studies were included in the systematic review and meta-analysis.

A total of 20 studies compared excess costs of depression in adults (D *v.* ND) (Simon *et al.*, 1995; Druss *et al.*, 2000; Garis and Farmer, 2002; Carta *et al.*, 2003; Trivedi *et al.*, 2004; Shvartzman *et al.*, 2005; Thomas *et al.*, 2005; Gameroff and Olfson, 2006; Arnow *et al.*, 2009; Bosmans *et al.*, 2010; Hamre *et al.*, 2010; Stamm *et al.*, 2010 , Woo *et al.*, 2011; Carstensen *et al.*, 2012; Brilleman *et al.*, 2013; McTernan *et al.*, 2013; Choi *et al.*, 2014; Greenberg *et al.*, 2015; Chiu *et al.*, 2017; Hsieh and Qin, 2018), 12 studies reported excess depression costs in old age (D-Elderly *v.* ND-Elderly) (Callahan *et al.*, 1994; Callahan *et al.*, 1997; Fischer *et al.*, 2002; Katon *et al.*, 2003; Luppa *et al.*, 2008; Vasiliadis *et al.*, 2013; Bock *et al.*, 2014; Choi *et al.*, 2014; Prina *et al.*, 2014; Alexandre *et al.*, 2016; Bock *et al.*, 2016; Ludvigsson *et al.*, 2018) and two studies examined excess costs of depression in adolescents (D-Adolescents *v.* ND-Adolescents) (Guevara *et al.*, 2003; Wright *et al.*, 2016). In total 16 studies compared comorbid depression excess costs among participants with a somatic disease (CD *v.* NCD) –predominantly diabetes, heart diseases, chronic pain – or after birth (Engel *et al.*, 1996; Frasure-Smith *et al.*, 2000; Egede *et al.*, 2002; Petrou *et al.*, 2002; Rosenzweig *et al.*, 2002; Sullivan *et al.*, 2002; Finkelstein *et al.*, 2003; Gilmer *et al.*, 2005; Williams *et al.*, 2005; Morgan *et al.*, 2008; Arnow *et al.*, 2009; Rutledge *et al.*, 2009; Edoka *et al.*, 2011; Dagher *et al.*, 2012; Rayner *et al.*, 2016; Adam *et al.*, 2017).

A total of 30 studies were conducted in the region of the Americas, 14 in the European region and four in the Western Pacific region. The studies were published from the year 2000 onwards, with four exceptions (Callahan *et al.*, 1994; Simon *et al.*, 1995; Engel *et al.*, 1996; Callahan *et al.*, 1997). In total, 55 898 depressed and 674 414 non-depressed participants were encompassed by the studies, whereas study samples and sample sizes varied widely. Depression status was either assessed with disease-specific instruments or retrieved from medical diagnoses. For details, see Table 1.

Since we only included studies reporting excess costs from a bottom-up approach, cost assessment was based on the individual resource utilization per participant. The main data source was the primary data. Alternative data sources were claims data from healthcare providers, physician's electronic medical records or a

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Table 1. General characteristics

General information						Characteristics of depressed			Characteristics of non-depressed	Sample sizes	
Reference	Country	Perspective	Data source	Study sample	Age range	Diagnostic Instruments	Diagnostic Criteria	Included disorders	Comparison group	Depressed	Non-depressed
Depressed and non-depressed in adults											
Arnow *et al.* (2009)[a]	USA	–	Primary data	Members of a HMO in northern California	21–75	PHQ-8 (without suicidal ideation)	DSM-IV	MDD	No MDD + No chronic pain	142	3048
Bosmans *et al.* (2010)	NL	–	EMR	Primary care	–	Physicians diagnosis	ICPC-2 + AM or referral to MH care	Feeling depressed Depressive disorder (ICPC-2 codes P03, P76)	Matched controls	7128	23 772
Brilleman *et al.* (2013)	UK	–	EMR	Primary care	⩾20	Physicians diagnosis	QOF condition depression + chronic status	'Depression'	No chronic illness[b]	12 811	47 400
Carstensen *et al.* (2012)	SWE	–	Claims data	Population of the County Östergötland	20–75	Physicians diagnosis	ICD-10	ICD-10 codes F32-F39	Total population (incl. Depressed)	7712	266 354
Carta *et al.* (2003)	IT	–	Primary data	General population from 2 Sardinian areas	⩾18	CIDI 'Simplified'	ICD-10	Major depressive episode	Matched healthy controls	51	–
Chiu *et al.* (2017)	CAN	–	Claims data	Population-based sample of a nationally representative community MH survey	⩾15	WMH-CIDI	DSM-IV	MDD	No MDD + no psychological distress	409	8905
Choi *et al.* (2014)[a]	USA	–	Primary data	Non-institutionalised US population	18–64	Patients self-report	ICD-9-CM	ICD-9-CM 311	ND	1582	11 625
Druss *et al.* (2000)	USA	PAY	Claims data	Employees	18–77	Physicians diagnosis	ICD-9	ICD-9 296.2, 296.3, 300.4, 296.9	Health claims, without MDD, DM, Heart disease, hypertension, back problems	312	12 785
Gameroff and Olfson (2006)	USA	–	Primary data, EMR	Primary care patients from an urban practice	18–70	PRIME-MD PHQ	DSM-IV	MDD	ND	207	821
Garis and Farmer (2002)	USA	–	Claims data	Medicaid patients in Oklahoma (high	all age groups	Physicians diagnosis +	ICD-9-CM	'Depression'	Age-stratified random	4077	963

				proportion of women + children)		drug-evidence indicator			sample, ⩾1 health care claim + absence of chronic illness		
Greenberg *et al.* (2015)	USA	SOC	Claims data	Private insurance with beneficiaries from 69 large, self-insured US-companies	18–64	At least 2 claims	ICD-9-CM	ICD-9 CM 296.2, 296.3	Matched controls with ND + no AM/ psychotic/ manic drugs	44 241/9,990[c]	44 241/9,990[c]
Hamre *et al.* (2010)	GER	SOC	Primary data	Starting anthroposophic therapy of >6 months duration	17–70	Physicians diagnosis CES-D	+⩾2 DSM-IV symptoms of dysthymic disorder CES-D ⩾ 24	Main disorder depression/ Depressive symptoms	CES-D < 24, other main disorder	81	303
Hsieh and Qin (2017)	CHN	–	Primary data	Persons from approx. 15 000 households in China	16–99	CES-D	CES-D ⩾ 28	Depression/ Depressive symptoms	CES-D < 20	1607	24 883
McTernan *et al.* (2013)	AUS	–	Primary data	Randomly selected employed participants, weighted by age and gender proportions for the state population	⩾18	PHQ-9	PHQ-9 ⩾ 5	Mild, moderate, moderately severe, severe depression	PHQ-9 < 5	664	1410
Shvartzman *et al.* (2005)	ISR	–	Primary data, Claims data	Random sample of patients in 3 primary care clinics of large HMO	21–65	MINI	Screen-positive	MDD	Screen-negative	543	1949
Simon *et al.* (1995)	USA	–	Claims data	Primary care patients in a large staff-model HMO	⩾18	Physicians diagnosis	Outpatient visit diagnoses or AM prescription	'Depression'	Age + gender matched control, ND, no AM	6257	6257
Stamm *et al.* (2010)	GER	PAY	Claims data	Members of a health insurance company for a large chemical trust	–	Physicians diagnosis	ICD-10 + absence from work	ICD-10 codes F32, F33	Matched controls with absence from work (due to somatic illness)	591	591
Thomas *et al.* (2005)	USA	–	Claims data	Patients in a Medicaid HMO	18–98	Physicians diagnosis	ICD-9	ICD-9 296.2–296.36, 300.4, 311	No psychiatric diagnosis	950	3903
Trivedi *et al.* (2004)	USA	SOC	Primary data	Non-institutionalised US population	All age groups	Patients self-report	ICD-9-CM + record of prescribed medicine	Primary diagnosis ICD-9 311	Record of prescribed medicine + No primary diagnosis of depression	–	–
Woo *et al.* (2011)	KOR	–	Primary data		20–60	SCID	DSM-IV + no AM	MDD	Matched healthy	102	91

(*Continued*)

Table 1. (*Continued.*)

General information						Characteristics of depressed			Characteristics of non-depressed	Sample sizes	
Reference	Country	Perspective	Data source	Study sample	Age range	Diagnostic Instruments	Diagnostic Criteria	Included disorders	Comparison group	Depressed	Non-depressed
				Employees, screened from outpatient psychiatric clinics					controls from the same region		
Depressed and non-depressed in old age											
Alexandre *et al.* (2016)	USA	–	Claims data	Medicare recipients	⩾65	Centres for Medicare and Medicaid services, DIS	ICD-9-CM	296.2, 296.3	Medicare patients with no history of MDD	59	472
Bock *et al.* (2014)	GER	SOC	Primary data	Patients suffering from multiple chronic conditions	65–85	GDS-15	GDS ⩾ 6	Depressive symptoms	GDS < 6	112	938
Bock *et al.* (2016)	GER	SOC	Primary data	Patients with ⩾1 GP visit during the past 6 months	⩾75	GDS-15	GDS ⩾ 6	Depressive symptoms	GP patients with GDS < 6	198	999
Callahan *et al.* (1994)	USA	–	Primary data, EMR	Patients from an academic primary care group practice at an urban ambulatory care clinic	⩾60	CES-D	CES-D ⩾ 16 at least at one time	Depressive symptoms	CES-D < 16	458	1253
Callahan *et al.* (1997)	USA	–	Primary data, EMR	Patients from an academic primary care group practice at an urban ambulatory care clinic	⩾60	CES-D	CES-D ⩾ 16	Depressive symptoms	CES-D < 16	612	3155
Choi *et al.* (2014)	USA	–	Primary data	Non-institutionalised US population	⩾65	Patients self-report	ICD-9-CM	ICD-9-CM 311	ND	355	2822
Fischer *et al.* (2002)	USA	–	Primary data, claims data	Social HMO at HealthPartners in Minnesota	⩾65	DIS, GDS-30	DIS positive, GDS ⩾ 11 and/ or AM during the previous year	Depressive symptoms	ND	245	271
Katon *et al.* (2003)	USA	–	Claims data	Population-based sample of a staff-model HMO	⩾60	PRIME-MD 2-item depress-sion screen + SCID	Score ⩾ 1 + DSM-IV	Major Depression, Dysthymia	Screen-negative	306	7265
Ludvigsson *et al.* (2018)	SWE	–	Primary data, claims data	Elderly in Linköping, south Sweden	85	GDS-15	GDS ⩾ 6	Syndromal depression	GDS < 6, Subsyndromal D + ND	36	280
Luppa *et al.* (2008)	GER	SOC	Primary data	Primary care patients, ⩾ 1 GP visit	⩾75	GDS-15	GDS ⩾ 6	Depressive symptoms	GDS < 6	63	388

				during the past 12 months							
Prina *et al.* (2014)	AUS	–	Primary data, Claims data	Older men living in urban Western Australia	65–83	GDS-15	GDS-15 ⩾ 7	Depressive symptoms	GDS < 7	339	5072
Vasiliadis *et al.* (2013)	CAN	HCS	Primary data, Claims data	Older adult population living at home in Quebec	⩾65	ESA Diagnostic Questionnaire	DSM-IV	Major and minor depression	ND, no anxiety or severe/ moderate cognitive problems	150	2344
Depressed and non-depressed in adolescents											
Guevara *et al.* (2003)	USA	–	Primary data	Non-institutionalised US population	2–18	Patients self-report	ICD-9	ICD-9 311	Children without mental disorders or physical conditions (asthma, epilepsy, diabetes), weighted	56	3390
Wright *et al.* (2016)	USA	PAY	Primary data, Claims data	Depression screened in a large integrated care system	13–17	PHQ-2 PHQ-9	PHQ-9 ⩾ 10	Mild, moderate, severe depression	PHQ-2 < 2 or PHQ-2 ⩾2, but PHQ-9 < 10	281	3707
Depression as comorbidity											
Adam *et al.* (2017)	USA	–	Cost accounting + EMR from Duke University Health Care system	Patients with Sickle cell disease (SCD) at an outpatient SCD centre 6 months after assessment of D	⩾18	BDI + clinical history	BDI > 14 + BDI < 14, while actively receiving therapy for depression	'Depression'	BDI < 14 + not receiving therapy for D	50	92
Arnow *et al.* (2009)	USA	–	Primary data	Members of a HMO in northern California	21–75	PHQ-8 (without suicidal ideation)	DSM-IV	MDD + Chronic (disabling) pain	Chronic (disabling) pain + No MDD	271	2347
Dagher *et al.* (2012)	USA	–	Primary data	Employed women (⩾ 20 h/week) postpartum	⩾18	Patients self-report, EPDS	EPDS ⩾ 13	Postpartum depression	EPDS < 13	31	607
Edoka *et al.* (2011)	UK	HCS	Primary data	Fathers postpartum	–	SCID, EPDS	DSM-IV EPDS ⩾ 10	MDD	ND fathers, EPDS < 10	31	94
Egede *et al.* (2002)	USA	All-payers	Primary data	National representative sample of the U.S. civilian non-institutionalised population	–	Patients self-report	ICD-9-CM	ICD-9 311 + Diabetes	Diabetes, ND	85	740

(*Continued*)

Table 1. (*Continued.*)

General information						Characteristics of depressed			Characteristics of non-depressed	Sample sizes	
Reference	Country	Perspective	Data source	Study sample	Age range	Diagnostic Instruments	Diagnostic Criteria	Included disorders	Comparison group	Depressed	Non-depressed
Engel *et al.* (1996)	USA	–	Primary data, claims data	Primary care patients with back pain	18–75	SCL-90 depression score	SCL-90 > 1.0	Depressive symptoms	Back pain, SCL-90 ⩽ 1.0	394	664
Finkelstein *et al.* (2003)	USA	–	Claims data	Nationally representative Medicare claimants	⩾65	Physicians diagnosis	ICD-9	ICD-9 296.2, 296.3 + Diabetes	Diabetes, ND	4203	218 245
Frasure-Smith *et al.* (2000)	CAN	–	Claims data + accounting-based average costs	1-year survivors of an acute MI	24–88	BDI	BDI ⩾ 10	at least mild depression symptoms	Patients hospitalised for an acute MI	260	588
Gilmer *et al.* (2005)	USA	PAY	Primary data, Claims data	Patients diagnosed with diabetes, comorbid heart disease, hypertension possible	–	Patients self-report	–	Depression spectrum disorders	ND	413	1281
Morgan *et al.* (2008)	USA	–	Primary data	Women, self-identified physical disability or health condition that limited 1 or more major life activities	⩾18	BDI-II	BDI-II ⩾ 17 at any of the interviews	Depressive symptoms	BDI-II <17, women with physical disability	201	148
Petrou *et al.* (2002)	UK	PAY	Primary data	Mothers with risk for postnatal depression	–	Antenatal predictive index f. postnatal D + SCID-II	Index score ⩾ 24 DSM-III-R	Postnatal depression	Index score ⩾ 24, screened negative with SKID-II	70	136
Rayner *et al.* (2016)	UK	–	Primary data	Patients with chronic pain (>9 months) + disability + no treatment success	–	PHQ-9	Symptoms ⩾ 5 for more than half the days in the last 2 weeks	Mild, moderate, severe depression	symptoms <5 for more than half the days in the last 2 weeks	732	472
Rosenzweig *et al.* (2002)	USA	–	Claims data + EMR	Patients with DM under a capitated managed care program at Joslin Diabetes Centre	–	Physicians diagnoses (EMR)	–	'Depression'	ND in the EMR	92	416
Rutledge *et al.* (2009)	USA	–	Primary data	Women with suspected myocardial ischemia (referred for coronary angiogram)	>18	BDI	BDI ⩾ 10	At least mild depression symptoms	BDI < 10, women with suspected myocardial ischemia	292	362

Sullivan *et al.* (2002)	USA	PAY	Claims data	Patients in a large staff-model HMO receiving a first hospitalisation with a primary diagnosis of HF	⩾18	Physicians diagnosis		Primary + secondary outpatient diagnoses of depression	'Depression'	No AM and ND	114	672
Williams *et al.* (2005)	CAN	–	Primary data	Patients with HIV/AIDS	⩾20	CES-D	CES-D ⩾ 21		'Depression'	HIV/AIDS + CES-D < 21	161	136

AM, Antidepressant Medication; BDI, BDI-II, Beck Depression Inventory; BL, Baseline; CES-D, Centre for Epidemiological Studies Depression Scale, German version; CAD, Coronary Artery Disease; CHD, Coronary Heart Disease; CIDI, CIDI-SF, Composite International Diagnostic Interview, short-form; CRC, Colorectal Cancer; DIS, Diagnostic Interview schedule; DM, Diabetes Mellitus; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, 4th edition; EMR, Electronic Medical Record; EPDS, Edinburgh Postnatal Depression Scale; ESA, Étude sur la Santé des Aînés; FUP, Follow-up; GDS, GDS-15, Geriatric Depression Scale, 30-item-scale, 15-item-scale; GP, General Practitioner; HCC, Health Conditions Checklist; HCS, Healthcare System Perspective; HF, Heart Failure; HMO, Health Maintenance Organization; ICD-9, ICD-10, International Statistical Classification of Diseases and Related Health Problems, 9th revision, 10th revision; ICPC-2, International Classification of Primary Care, 2nd edition; MDD, Major Depressive Disorder; MDI, Major Depression Inventory; MH, Mental Health; MI, Myocardial Infarction; MINI, Mini-International Neuropsychiatric Interview; ND, No depression; PAY, Payer Perspective; PHQ-2, PHQ-9, Patient Health Questionnaire, 2 item depression screener, 9 item depression scale; PRIME-MD, Primary Care Evaluation of Mental Disorders; QOF, Quality and Outcomes Framework; SCID, Structured Clinical Interview for DSM-IV; SOC, Societal Perspective; WMH-CIDI, World Mental Health Composite International Diagnostic Interview.

[a]Reports also data in another patient subgroup.

[b]None of the included 17 chronic conditions incentivised within QOF.

[c]Sample sizes of direct/indirect costs.

combination of those. Since Hamre *et al.* (2010) assessed costs after an intervention, we used the excess costs reported for the pre-study year. Table 2 provides details on cost assessment (cost categories reported and total costs). Time interval for costs was mostly 12 months, except for eight studies with time intervals <12 months (Callahan *et al.*, 1994; Katon *et al.*, 2003; Dagher *et al.*, 2012; Bock *et al.*, 2014; Bock *et al.*, 2016; Rayner *et al.*, 2016; Adam *et al.*, 2017; Ludvigsson *et al.*, 2018) and seven studies with time intervals >12 months (Petrou *et al.*, 2002; Gilmer *et al.*, 2005; Rutledge *et al.*, 2009; Bosmans *et al.*, 2010; Carstensen *et al.*, 2012; Prina *et al.*, 2014; Alexandre *et al.*, 2016). Year of pricing had to be assumed for 15 studies (Callahan *et al.*, 1994; Simon *et al.*, 1995; Engel *et al.*, 1996; Callahan *et al.*, 1997; Frasure-Smith *et al.*, 2000; Rosenzweig *et al.*, 2002; Carta *et al.*, 2003; Katon *et al.*, 2003; Shvartzman *et al.*, 2005; Williams *et al.*, 2005; Gameroff and Olfson, 2006; Arnow *et al.*, 2009; Woo *et al.*, 2011; Prina *et al.*, 2014; Adam *et al.*, 2017).

Overall, 82% of the items in the quality assessment were fulfilled, while most studies lagged reporting perspective, sensitivity analysis and information about missing data. Detailed results of the quality assessment are shown in online Supplementary material S1. For nine studies, S.D. was calculated based on 95% CI or S.E. 11 studies did not state measures of variation and one study only reported S.D. for total excess costs. Summary data on mean annual excess costs (in 2017 US$-PPP) are provided in online Supplementary material S2. Results of meta-analyses are shown numerically and graphically as forest plots (Figs 2, 3 and online Supplementary material S3).

Total direct excess costs of depression ranged between $124 and 18 174 in the adults subgroup, between $358 and 14 225 in the elderly subgroup, between $2868 and 2883 in the adolescents subgroup and between $239 and 20 768 in the comorbidity subgroup. Meta-analysis of total direct excess costs was performed with all but seven studies that focused on singular cost categories (Callahan *et al.*, 1994; Engel *et al.*, 1996; Callahan *et al.*, 1997; Fischer *et al.*, 2002; Woo *et al.*, 2011; McTernan *et al.*, 2013; Prina *et al.*, 2014). Depression was associated with significantly higher total direct excess costs in all subgroups. Expressed as point estimate [95% CI], total direct excess costs were higher for depressed *v.* non-depressed adults (2.58 [2.01–3.31], $p < 0.0001$, $I^2 = 99\%$), depression in old age (1.73 [1.47–2.03], $p < 0.0001$, $I^2 = 73\%$), depression in adolescents (2.79 [1.69–4.59], $p < 0.0001$, $I^2 = 87\%$) and depression as comorbidity (1.39 [1.24–1.55], $p < 0.0001$, $I^2 = 42\%$). Total indirect excess costs ranged between $153 and 12 374 in the D *v.* ND subgroup. Meta-analysis was performed with six studies and revealed higher excess costs for D *v.* ND (2.28 [1.75–2.98], $p < 0.0001$, $I^2 = 74\%$) (Druss *et al.*, 2000; Trivedi *et al.*, 2004; Hamre *et al.*, 2010 , Woo *et al.*, 2011; McTernan *et al.*, 2013; Greenberg *et al.*, 2015).

Pooled results of 26 studies showed significantly higher outpatient excess costs for D *v.* ND (1.85 [1.64–2.10], $p < 0.0001$, $I^2 = 91\%$), D-Elderly *v.* ND-Elderly (1.36 [1.18–1.57], $p < 0.0001$, $I^2 = 55\%$) and CD *v.* NCD (1.35 [1.21–1.50], $p < 0.0001$, $I^2 = 43\%$). We included 20 studies in the meta-analysis of medication costs. The pooled results showed significantly higher excess costs for D *v.* ND (2.89 [2.16–3.86], $p < 0.0001$, $I^2 = 99\%$), D-Elderly *v.* ND-Elderly (1.47 [1.24–1.75], $p < 0.0001$, $I^2 = 77\%$), CD *v.* NCD (1.35 [1.04–1.75], $p = 0.02$, $I^2 = 94\%$). Meta-analysis of inpatient costs was conducted with 26 studies. Excess costs were significantly higher for D *v.* ND (2.82 [1.94–4.08], $p < 0.0001$, $I^2 = 89\%$), D-Elderly *v.* ND-Elderly (1.92 [1.63–2.26], $p < 0.0001$, $I^2 = 35\%$), D-Adolescents *v.* ND-Adolescents

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Table 2. Cost assessment

Reference	Year of pricing	Currency	Time interval for costs (months)	Direct costs					Indirect costs	
				Inpatient treatment	Emergency treatment	Outpatient treatment	Medication	Others	Reduced productivity	Lost productivity
Depressed and non-depressed in adults										
Arnow *et al.* (2009)[a]	2001/2002	$	12	✓	✓	✓	✓			
Bosmans *et al.* (2010)	2003	€	36			✓	✓	✓[b]		
Brilleman *et al.* (2013)	2007/2008	£	12			✓	✓	✓[c]		
Carstensen *et al.* (2012)	2007	SEK	24	✓		✓	✓			
Carta *et al.* (2003)	1995	€	12	(✓)			(✓)			
Chiu *et al.* (2017)	2013	$	12	✓	✓	✓		✓[d]		
Choi *et al.* (2014)[e]	2007	$	12	✓	✓	✓	✓	✓[f]		
Druss *et al.* (2000)	1995	$	12	(✓)		(✓)	(✓)		✓	
Gameroff and Olfson (2006)	2002/2003	$	12	(✓)	(✓)	(✓)				
Garis and Farmer (2002)	1995	$	12	✓		✓	✓	✓[g]		
Greenberg *et al.* (2015)	2012	$	12	✓	✓	✓	✓	✓[h]	✓	✓
Hamre *et al.* (2010)	2000	€	12	✓		✓	✓		✓	✓
Hsieh and Qin (2017)	2012	¥	12	(✓)		(✓)				
McTernan *et al.* (2013)	2009	AU $	12						✓	
Shvartzman *et al.* (2005)	1999	€	12	✓		✓	✓			
Simon *et al.* (1995)	1992	$	12	✓	✓	✓	✓	✓[i]		
Stamm *et al.* (2010)	2002	€	12	✓			✓			
Thomas *et al.* (2005)	2000	$	12	(✓)	(✓)	(✓)	✓	(✓)[j]		
Trivedi *et al.* (2004)	1999	$	12	(✓)	(✓)	(✓)	(✓)	(✓)[k]	✓	
Woo *et al.* (2011)	2006	$	12						✓	
Depressed and non-depressed in old age										
Alexandre *et al.* (2016)	2004	$	72	(✓)		(✓)	(✓)			
Bock *et al.* (2014)	2009	€	6	✓		✓	✓	✓[l]		
Bock *et al.* (2016)	2012	€	6	✓		✓	✓	✓[m]		
Callahan *et al.* (1994)	1992	$	9			✓				
Callahan *et al.* (1997)	1994	$	12					✓[n]		
Fischer *et al.* (2002)	1993/1994	$	12			✓				
Katon *et al.* (2003)	1999	$	6	✓	✓	✓	✓	✓[o]		
Ludvigsson *et al.* (2018)	2016	€	1	✓		✓	✓	✓[p]		
Luppa *et al.* (2008)	2004/2005	€	12	✓		✓	✓	✓[q]		
Prina *et al.* (2014)	2003	AU $	24	✓						
Vasiliadis *et al.* (2013)	2009/2010	CAN $	12	✓	(✓)	✓	✓	✓[r]		
Depressed and non-depressed in adolescents										
Guevara *et al.* (2003)	1996	$	12	✓	(✓)	(✓)	(✓)			
Wright *et al.* (2016)	2013	$	12	✓	✓	✓	✓	✓[s]		
Depression as comorbidity										
Adam *et al.* (2017)	2009	$	6	✓	✓	✓				
Dagher *et al.* (2012)	2001	$	2.75	✓	✓	✓				

(*Continued*)

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Table 2. (*Continued.*)

Reference	Year of pricing	Currency	Time interval for costs (months)	Direct costs					Indirect costs	
				Inpatient treatment	Emergency treatment	Outpatient treatment	Medication	Others	Reduced productivity	Lost productivity
Edoka *et al.* (2011)	2008	£	12	✓		✓				
Egede *et al.* (2002)	2001	$	12	✓	✓	✓	✓	✓[t]		
Engel *et al.* (1996)	1990/1991	$	12	(✓)		(✓)	(✓)	(✓)[u]		
Finkelstein *et al.* (2003)	2001	$	12	(✓)		(✓)	(✓)			
Frasure-Smith *et al.* (2000)	1993	CAN $	12	✓	✓	✓				
Gilmer *et al.* (2005)	2002	$	36	(✓)		(✓)	(✓)	(✓)[v]		
Morgan *et al.* (2008)	2002	$	12	(✓)	(✓)	(✓)				
Petrou *et al.* (2002)	2000	£	18	✓		✓				
Rayner *et al.* (2016)	2013/2014	£	3	✓	✓	✓				
Rutledge *et al.* (2009)	2003	$	60	(✓)		(✓)	✓	(✓)[w]		
Rosenzweig *et al.* (2002)	1999	$	12	(✓)		(✓)	✓	(✓)[x]		
Sullivan *et al.* (2002)	1998	$	12	✓	(✓)	✓		(✓)[y]		
Williams *et al.* (2005)	2002	CAN $	12	✓	✓	✓	✓	✓[z]		

✓ Costs reported (✓) Costs considered in calculation of total costs, but not reported as single cost categories.
[a]Reports also data for depression as comorbidity.
[b]Costs reported: Dietician and Physical therapy (physiotherapy, cesar exercise therapy and mensendieck exercise therapy).
[c]Costs reported: Tests and investigations (standard surgery consultation, laboratory testing, GP requested hospital-based tests and investigations).
[d]Costs considered: Outpatient prescriptions for adults aged ⩾65, non-hospital residential care, ambulatory care, home care, medical devices.
[e]Reports also data for depressed and non-depressed in old age.
[f]Costs reported: Home health care and others.
[g]Costs reported: Home health/Medical supply and an all-other-costs category.
[h]Costs reported: Other medical services.
[i]Costs reported: Laboratory/Radiology.
[j]Costs considered: Diagnostic tests (laboratory and radiology).
[k]Costs considered: Home health and other medical equipment and services.
[l]Costs reported: Formal nursing care (Nursing home care, professional nursing care), informal care, medical supplies and dental prostheses.
[m]Costs reported: Nursing care (outpatient nursing care, domestic help, day care/short-term care, informal care).
[n]Costs reported: Diagnostic test charges (special procedures, diagnostic imaging, clinical pathology).
[o]Costs reported: Home health/Medical supply and an all-other-costs category.
[p]Costs reported: Non-pharmaceutical components, private health care.
[q]Costs reported: Medical supply and dentures, home care, assisted living, transportation, non-physician provider.
[r]Costs reported: Physicians fees (not included in any of the unit costs).
[s]Costs reported: Diagnostic tests (laboratory and radiology).
[t]Costs reported: Other medical expenditures (vision aids and other medical equipment and services).
[u]Costs considered: Radiology costs.
[v]Costs considered: Medical supply.
[w]Costs considered: Out-of-pocket for medical devices and alternative therapies, travel costs.
[x]Costs considered: Diagnostic tests (laboratory and radiology) and transportation.
[y]Costs considered: Long-term care costs, ambulance, home equipment costs.
[z]Costs reported: Food banks, house cleaning, outpatient laboratory test, all other, OOP cost.

(4.10 [2.29–7.33], $p < 0.0001$, $I^2 = 0\%$) and CD *v.* NCD (1.44 [1.09–1.90], $p = 0.01$, $I^2 = 25\%$). Meta-analysis of emergency costs was performed with ten studies and revealed significant higher RoM for D *v.* ND (1.88 [1.49–2.37], $p < 0.0001$, $I^2 = 90\%$), D-Elderly *v.* ND-Elderly (1.71 [1.36–2.16], $p < 0.0001$, $I^2 = 0\%$) and CD *v.* NCD (1.62 [1.27–2.08], $p = 0.0001$, $I^2 = 53\%$). Meta-analysis of other direct costs was conducted with 16 studies, with significantly higher excess costs for D *v.* ND (2.31 [1.65–3.24], $p < 0.0001$, $I^2 = 98\%$) and D-Elderly *v.* ND-Elderly (1.75 [1.32–2.31], $p < 0.0001$, $I^2 = 69\%$). Results for CD *v.* NCD were not significant (1.14 [0.88–1.49], $p = 0.32$, $I^2 = 64\%$).

Heterogeneity in direct costs was high for all patient subgroups. Cost data are very sensitive to different framework conditions and settings (e.g. health systems, local prices or target populations), which results in heterogeneity between study results. We tried to cope with this problem using RoM as effect measure, but since costs have high variation by nature, wide statistical variation is to some extent reasonable. Meta-analysis showed that inpatient excess costs for the CD *v.* NCD subgroup scattered close to zero, which is comprehensible since hospitalisation is presumably caused by the primary disease being present in both groups. RoM of the study by Hamre *et al.* (2010) were lower since excess costs were assessed in an anthroposophic setting with alternative therapies. Hence, fewer patients received antidepressant medication or psychotherapy.

Nevertheless, some studies showed considerable deviations whose impact was explored in a sensitivity analysis by excluding the studies as described below. Bosmans *et al.* (2010) limited the depression group to participants with a prescription for antidepressants or a referral to mental health care and compared

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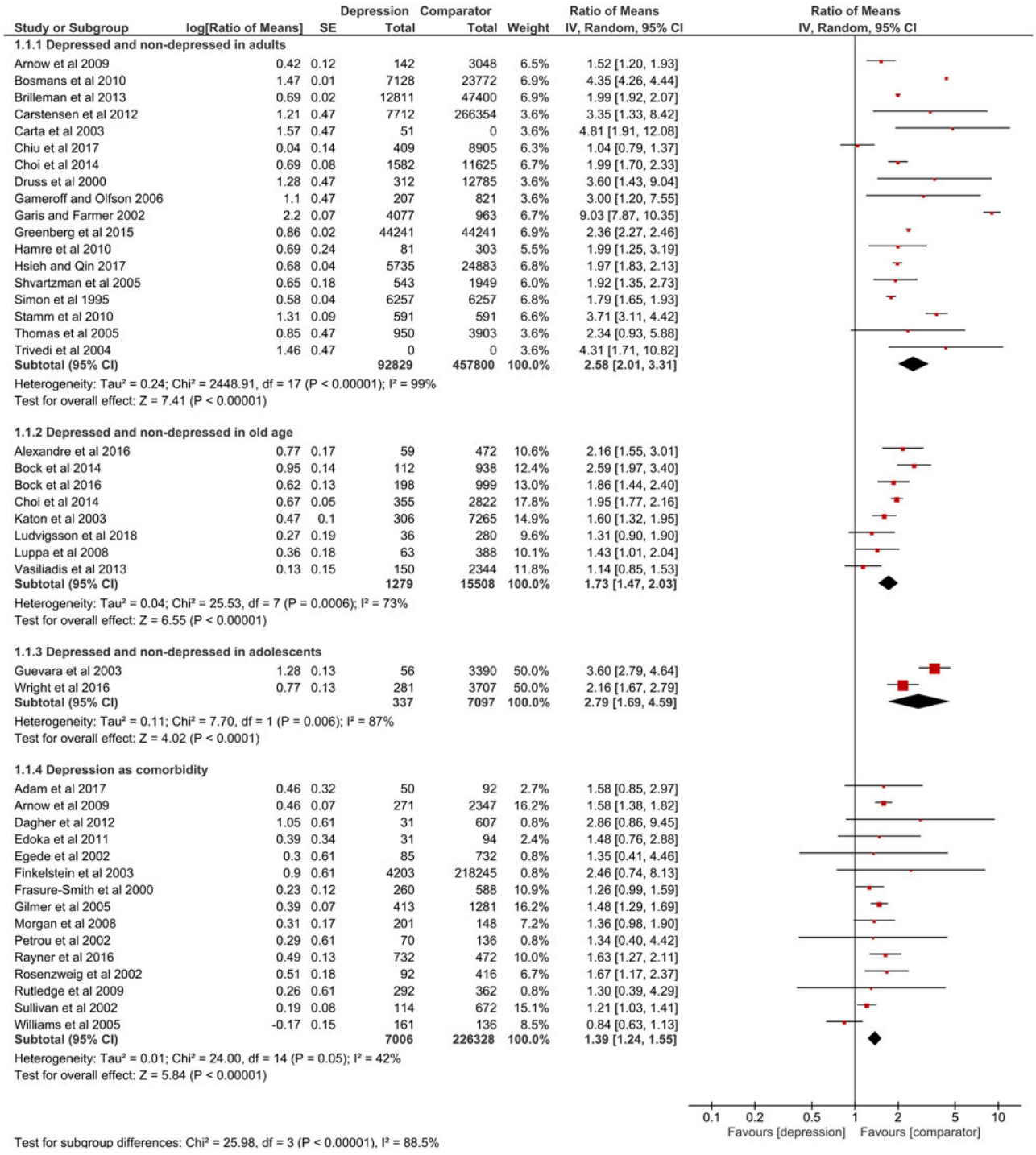

Fig. 2. Forest plot of total direct excess costs (Ratio of means, 95% CI).

those to matched controls that did not meet the criteria, with the effect that RoM in outpatient and medication costs were considerably high. Luppa *et al.* (2008) had a lower RoM in outpatient costs due to high outliers in the comparison group. The analysis of Dagher *et al.* (2012) was based on very small sample sizes, especially in inpatient and emergency costs, leading to high excess costs in these categories. RoM of medication costs among HIV/AIDS patients reported by Williams *et al.* (2005) were extremely low. As depressed patients are found to be less compliant with medication recommendations, fewer participants have taken their HIV/AIDS medication resulting in lower excess costs (DiMatteo *et al.*, 2000). Two studies were removed completely in the sensitivity analysis, because they differed extremely from other studies in length of study time or comparison group, affecting all cost categories: Chiu *et al.* (2017) had extremely lower RoM in all direct cost categories compared to other studies, which could be caused by an outstanding median study time of 10.6 years. RoM of Garis and Farmer, (2002) had higher results in

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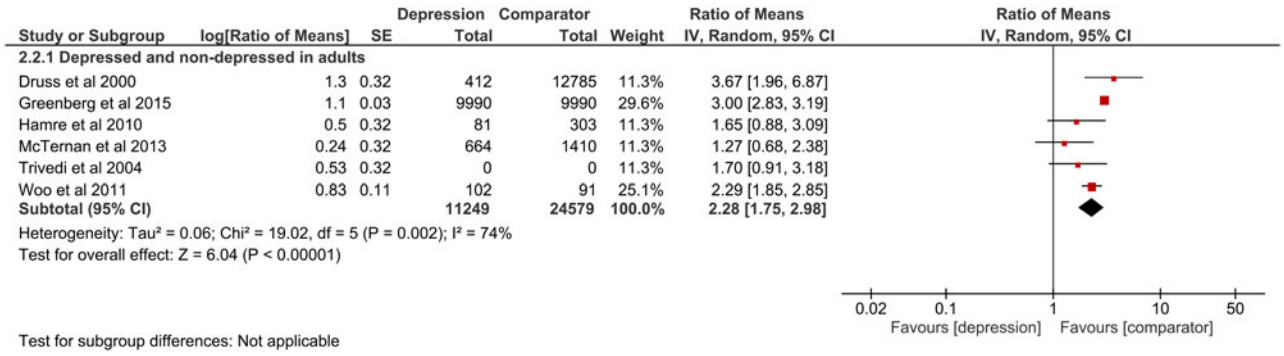

Fig. 3. Forest plot of total indirect excess costs (Ratio of means, 95% CI).

all reported direct cost categories, except for outpatient excess costs. Possible reasons could be an oversampling of young participants combined with a benefit limit for patients over 21 years and the exclusion of chronic illness in the comparison group.

Sensitivity analysis did not reveal significant changes in RoM and heterogeneity (I^2) for total direct costs, inpatient, medication and other direct costs. Detaching outliers reduced heterogeneity in outpatient costs for D-Elderly *v.* ND-Elderly (1.47 [1.36–1.58], $p < 0.0001$, $I^2 = 0\%$). Heterogeneity in emergency costs decreased for D *v.* ND (2.17 [1.94–2.43], $p < 0.0001$, $I^2 = 47\%$) and for CD *v.* NCD (1.57 [1.37–1.80], $p < 0.0001$, $I^2 = 4\%$).

In a second sensitivity analysis, we removed articles in the German language in order to explore whether the inclusion of only one other language besides English biases the results. Only one study (Stamm *et al.*, 2010) was removed and did not reveal significant changes in results. For more details, see online Supplementary material S4.

Discussion

The purpose of this study was to provide a structured overview of the current state of the literature of bottom-up COI-studies of depression with comparison group and to assess the impact of depression on costs. To our knowledge, this study is the first global systematic review combining study results on excess depression costs quantitatively in a meta-analytic framework. We found significantly higher excess depression costs for total direct and indirect costs and all cost categories except for other costs, although with considerable heterogeneity (I^2) in direct costs. Pooled RoM of total direct costs of depressed *v.* non-depressed were 179% higher in adolescents, 158% higher in adults and 73% higher in old age. In depression as comorbidity, pooled RoM of total direct costs was 39% higher. Pooled RoM of total indirect costs of depressed *v.* non-depressed was 128% higher in adults. Meta-analyses in the patient subgroups revealed that RoM decreased with age. As compared to the patient subgroups with participants from different age groups, RoM of comorbid depression was much lower.

The highest levels of RoM in adolescence could have been caused as a result of more resource-intensive treatment of mental disorders at a young age. Nevertheless, calculations were based on only two studies, which is why no generalizable conclusions should be drawn. Another explanation for a decreasing tendency with age could be that comorbidities increase with age, resulting in lower relative excess costs between depressed and non-depressed (Fortin *et al.*, 2005; Schäfer *et al.*, 2012). This would also explain, why RoM in the comorbid depression subgroup was lower as compared to the subgroups with participants from different age groups. Results showed that comorbid depression increased costs, but transferability of results to a specific comorbid disease would need further investigations, since we did not distinguish between the main diseases.

Compared to the findings of preceding reviews (Luppa *et al.*, 2007; Mrazek *et al.*, 2014), this study did not only reveal a positive association between depression and excess costs, but also allows to make precise statements about the amount of excess. In the old age patient subgroup, the review of Luppa *et al.* (2012) also found higher total costs of depressed compared to non-depressed, but of a smaller magnitude than in our findings. A possible explanation could be that only studies with comparable study design were included, resulting in three studies. By contrast, results regarding outpatient excess costs matched with our findings. We found increased excess costs of depression as a comorbidity of other somatic diseases, whereas foregoing reviews of depression as comorbidity found varying results. Another important difference was, that these reviews included also bipolar disorders. Lehnert *et al.*(2011) and Molosankwe *et al.* (2012) found that coexistent depression increased costs of treating diabetes. Sambamoorthi *et al.* (2017) found an increase in costs of treating arthritis when depression coexisted. Baumeister *et al.* (2012) found higher direct, but not indirect costs in the treatment of chronic back pain with comorbid depression.

There might be various reasons for high heterogeneity. First, data originated from 11 different countries of studies published between 1994 and 2018. Second, included studies comprised different degrees of depression severity. On one side, the inclusion of mild depression allows to consider the whole disease pattern. Otherwise, different degrees of severity could have caused variability in results. Additionally, diagnostic instruments, data sources, target populations and sample sizes varied between studies. Furthermore, differences in cost assessment of studies could have caused heterogeneity. Adjusted and unadjusted excess costs were included in our analysis, a potential influencing factor for variability in results. Moreover, in direct costs, included services and monetary valuation were diverse. Since excess costs reported by studies were split according to predefined direct cost categories with one additional category including all other direct costs, heterogeneity in the other direct cost category was to be expected. Indirect excess costs were assessed only in the D *v.* ND patient subgroup. Mainly excess costs of reduced productivity (sickness absence, costs of presenteeism) were assessed,

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resulting in more homogeneity across studies compared to direct excess costs.

This systematic review and meta-analysis of COI-studies of depression were unlimited with respect to region and year of publication, resulting in a sufficiently large number of eligible studies. Another strength of our study was that the literature search and study selection was conducted independently by two reviewers. RoM as a new method for continuous outcomes achieved meaningful results, providing a useful tool for meta-analyses with cost data. When interpreting our results, several limitations should be considered. Overall methodological quality was good, but shortcomings manifested in reporting perspective, missing data and sensitivity analysis. We tried to include all eligible articles in this study and imputed missed S.E. to reduce selection bias. However, studies were restricted to English or German language and bottom-up studies, a potential source of reporting bias. In addition, bottom-up studies tend to involve small sample sizes and more serious cases, leading to an overestimation of excess costs at population-level. Otherwise, few studies assessed indirect excess costs and none quantified costs of reduced productivity due to mortality, although depression is associated with high suicidal risk, which may have underestimated indirect excess costs. Since we focused on studies reporting excess costs of depression, true disease-specific costs were presented, though a large number of COI-studies without a comparison group were ineligible for this study.

In summary, these findings highlight the burden of depression at all ages and as a comorbidity. As a result, screening and prevention programs should be offered for broader target groups. More assessment of indirect costs and methodological uniformity would be highly desirable for future COI research in depression.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S2045796019000180

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Conflict of interest. None.

Ethical standards. Not applicable.

Availability of data and materials. The data supporting the findings of our study cannot be provided online, since the articles included in our systematic review and meta-analysis are protected by copyright. Additional data from our analysis can be requested by the corresponding author.

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