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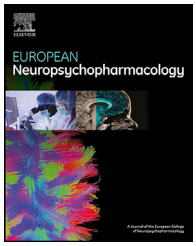

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Excess resource use and costs of physical comorbidities in individuals with mental health disorders: A systematic literature review and meta-analysis

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Abstract
Individuals with mental health disorders (MHDs) have worse physical health than the general population, utilise healthcare resources more frequently and intensively, incurring higher costs. We provide a first comprehensive overview and quantitative synthesis of literature on the magnitude of excess resource use and costs for those with MHDs and comorbid physical health conditions (PHCs). This systematic review (PROSPERO CRD42017075319) searched studies comparing resource use or costs of individuals with MHDs and comorbid PHCs versus individuals without comorbid conditions published between 2007 and 2021. We conducted narrative and quantitative

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syntheses, using random-effects meta-analyses to explore ranges of excess resource use and costs across care segments, comparing to MHD only, PHC only, or general population controls (GPC). Of 20,075 records, 228 and 100 were eligible for narrative and quantitative syntheses, respectively. Most studies were from the US, covered depression or schizophrenia, reporting endocrine/metabolic or circulatory comorbidities. Frequently investigated healthcare segments were inpatient, outpatient, emergency care and medications. Evidence on lost productivity, long-term and informal care was rare. Substantial differences exist between MHDs, with depressive disorder tending towards lower average excess resource use and cost estimates, while excess resource use ranges between +6% to +320% and excess costs between +14% to +614%. PHCs are major drivers of resource use and costs for individuals with MHDs, affecting care segments differently. Significant physical health gains and cost savings are potentially achievable through prevention, earlier identification, management and treatment, using more integrated care approaches. Current international evidence, however, is heterogeneous with limited geographical representativeness and comparability.

1. Introduction

Individuals with mental health disorders (MHD) have worse physical health than the general population. The prevalence of physical health conditions (PHC) in individuals with MHDs is known to be elevated (De Hert et al., 2009; Mitchell et al., 2013; Prince et al., 2007). Furthermore, the presence of MHDs has been associated with increased onset of PHCs (Christoph U Correll et al., 2017; Prince et al., 2007; Scott et al., 2016). A large international study revealed that 1.5% to 13.3% of incidences of physical illness are linked to MHDs (Scott et al., 2016), contributing to a strong overlap between individuals with MHDs and long-term PHCs (Naylor et al., 2012). In turn, these observed health disparities cause substantial reductions in life expectancy. Life expectancy from age 15 has been found to be 20 years less for men and 15 years less for women with mental disorders even in affluent regions such as Scandinavia (Wahlbeck et al., 2011). Considering the public health implications, comorbidities of mental and physical illnesses have been pointed out as one of the most important challenges for medicine in the 21st century (Sartorius, 2018).

Potential reasons for these disparities are manifold, including inadequate access to and uptake of healthcare (Chan et al., 2022; De Hert et al., 2011; Lawrence and Kisely, 2010; Solmi et al., 2021; Solmi et al., 2020) as well as treatment side effects (Barnett et al., 2007; McKnight et al., 2012), while further influences are related to lifestyle (Lê Cook et al., 2014; Sarris et al., 2015) or genetic mechanisms (Moreno et al., 2013). The recent negative impacts posed by the COVID-19 pandemic, which caused substantial harm to mental health and major disruptions to mental health services across the globe (Kawohl and Nordt, 2020; Li et al., 2020; Penington et al., 2022; Pfefferbaum and North, 2020), mean employing timely measures to protect physical health in individuals with MHDs will be even more pressing. In addition, previous studies have found that individuals with MHDs accrue higher physical healthcare costs compared to those without. For instance, individuals with comorbid MHDs and PHCs have longer lengths of stay in hospitals and higher risks of rehospitalisation (Christoph U. Correll et al., 2017; Jansen et al., 2018). Additional costs accrue outside the hospital sector. For example, an Australian study found substantial costs associated with informal care provided to adults with mental illnesses (Diminic et al., 2021). Further major excess burden is caused by productivity losses, both related to excess morbidity and premature mortality. In case of the former, absenteeism, presenteeism or unemployment are considered substantial contributors to economic losses (Knapp et al., 2011; McDaid and Park, 2015).

A recent report by the Lancet Psychiatry Commission has further stressed the importance of protecting physical health in people with mental illnesses while reducing physical health inequalities in the context of multimorbidity. Firth and colleagues highlighted the importance of adding up the costs of physical comorbidities in patients with MHDs. (Firth et al., 2019)

To date, however, no comprehensive international review exists on the excess resource use and costs of physical comorbidities in individuals with MHDs.

The aim of the current systematic review was two-fold; to provide a a) comprehensive narrative overview and b) quantitative synthesis of the existing international evidence on the excess economic burden of physical comorbidities of mental health disorders. This includes the identification of commonly researched mental health and physical comorbidity patterns, as well as quantitative exploration of the magnitude of excess resource utilisation and costs by different care segments plus productivity losses and informal care based on all evidence across different MHDs.

2. Methods

2.1. Search strategy and selection criteria

This systematic literature review with a focus on MHDs was part of a broader, non-disease specific comorbidity review registered on the PROSPERO database (CRD42017075319) and conducted in full accordance with PRISMA guidelines (Page et al., 2021). It aimed to identify and synthesise available evidence with a focus on excess healthcare resource consumption and costs due to physical comorbidities in individuals with MHDs.

Literature published since January 2007 was searched without any language restrictions in August 2017 in six bibliographic databases (MEDLINE, PsycINFO, CINAHL, Econlit, Econpapers, NHS EED). An update of the search was conducted to include literature published until and including June 2021. In addition to peer-reviewed publications, several channels were searched for grey literature, including policy documents of national (e.g. the UK's National Institute for Health and Care Excellence) and international (e.g. World Health Organization, (WHO)) institutions, and grey literature databases (e.g. OpenGrey).

Inclusion criteria were defined using the PICOS framework: All institutionalised and non-institutionalised individuals (P) with a MHD diagnosis and a physical comorbidity (I) versus individuals with no comorbid conditions. Outcomes of interest were excess healthcare utilisation and/or additional costs (O), while including longitudinal, cross-sectional, model-based or cost-of-illness studies (S). We excluded non-original studies or studies with a focus on a paediatric or geriatric population, studies only reporting mental health comorbidities, or where the conceptualisation of comorbidity deviated from the WHO's definition (Cohen, 2017). In addition, studies were excluded where the PHC was confirmed to precede the MHD. Due to the broad scope of the review, we did not restrict the search by study designs. Further, no restrictions were made regarding language, geographical regions, study sample, or type of MHD or physical comorbidities. Details of the search strategy are available in Appendix A.

Identified records were screened by two independent researchers during all screening stages. The first screening stage focused on title and abstracts (JS, DW, ALP, SM, DH, AL, IS, DM) and the second stage focused on full text screening (JS, DW, ALP, CW, DH, DM). Assessing the final eligibility of each record, studies were categorised based on several characteristics (JS, DW, ALP, DH, DM), which included identifying and potentially excluding studies where the PHC preceded the MHD. Following each stage, discrepancies were discussed and if no agreement was found, a third independent researcher was consulted (JS, DW, ALP, DM).

2.2. Data extraction

Data were extracted using a Microsoft Excel spreadsheet specifically developed by the research team following joint group discussions and piloting on a sample of studies. Relevant extraction details focused on primary MHDs, ICD-10 chapters of physical comorbidities, multiple study characteristics, as well as reported quantitative data on excess resource use and costs. Extracted study data were narratively synthesised concerning study and cohort characteristics, primary MHDs and patterns of reported physical comorbidities. For each study, we categorised reports of resource use or costs by segments of care such as inpatient care, outpatient care, accident and emergency (A&E) care, primary care, medication and long-term care. In addition, health economic evidence on excess informal care burden as well as productivity losses due to morbidity or premature mortality were also synthesised.

2.3. Quantitative synthesis

In the quantitative synthesis, the primary objective was to identify the extent of excess resource use and costs, clustered by the underlying primary MHDs, and further categorised by the aforementioned care segments. Finally, estimates were separated and analysed by the main types of reference groups either as 1) individuals with the given MHD only (vsMHD), 2) individuals with the given PHC only (vsPHC), or 3) matched controls from the general population (vsGPC).

For all established subgroups with two or more estimates, random-effects meta-analyses were conducted (Balduzzi et al., 2019). Estimates without dispersion measures (e.g. confidence intervals) were excluded due to non-suitability for quantitative pooling. For the meta-analyses of continuous data (e.g. annual costs, length of stay or healthcare visits), the ratio of means (RoM) approach was applied (Friedrich et al., 2011). RoMs may be interpreted as a factor of excess resource use and costs compared to the reference groups. One of the advantages of utilising the RoM approach is that resource use and cost information is comparable across different studies regardless of differences in currencies or purchasing powers. Mean results, their standard deviations and number of individuals were used to calculate RoMs and the variance of their natural logarithms; these were used to obtain 95% confidence intervals (CI). Dichotomous data (e.g. utilisation rates for specific services) were synthesised as odds ratios (OR). Results from the meta-analyses were presented in forest plots alongside the I^2 statistic, to allow for assessing heterogeneity. An I^2 of 25% was considered as an indicator for low heterogeneity, 50% for moderate heterogeneity and 75% or above for high heterogeneity. (Higgins and Thompson, 2002)

3. Results

3.1. Narrative synthesis

3.1.1. Study characteristics

Of the initial 20,075 individual records identified by our literature search, 2,963 full-texts were screened, and 1,048 studies were subject to final eligibility checks following all screening stages. Finally, 228 studies met all inclusion criteria for narrative synthesis, of which 100 studies were subsequently included in the quantitative synthesis (Fig. 1). Details of all included studies are available in Appendices B and H.

The majority of included studies were based on administrative database analyses (n=144, 63%) or self-reported data, such as surveys (n=47, 21%). More than half of all studies were from the United States (n=125, 55%). Fewer studies were from the European Union-27 (n=30, 13%), mostly Germany (n=10, 4%), Sweden (n=4, 2%), Denmark (n=4, 2%), and the Netherlands (n=3, 1%). Another eight studies were from the United Kingdom (4%). A number of studies were from Asian countries (n=20, 9%), mostly Japan (n=7, 3%) and Taiwan (n=7, 3%). (Table 1)

3.1.2. Disease patterns

The most commonly investigated primary MHDs were depressive disorder (n=76, 33%) followed by schizophrenia (n=23, 10%) and substance use disorder (n=19, 8%). Additionally, several studies focused on bipolar disorder (n=8, 4%), post-traumatic stress disorder (PTSD, n=8, 4%) and anxiety disorder (n=8, 4%). The remaining studies mostly covered multiple MHDs rather than single conditions (n=69, 30%). (Table 1)

Endocrine, nutritional and metabolic diseases (E00-E90, n=141, 62%) and diseases of the circulatory system (I00-I99, n=133, 58%) were the most commonly mentioned ICD-10 chapters across all the studies, followed by respiratory diseases (J00-J99, n=95, 42%) and musculoskeletal diseases (M00-M99, n=67, 29%) (Table 2).

Table 1 Characteristics of studies included in the systematic literature review.

	All identified studies		Included in quantitative synthesis	
	n	%	n	%
Number of studies	228	100%	100	44%
Geographical origin of study cohort				
Europe	41	18%	17	17%
European Union-27	29	13%	12	12%
United Kingdom	8	4%	3	3%
North America	145	64%	68	68%
United States of America	125	55%	60	60%
Canada	18	8%	8	8%
Asia	22	10%	6	6%
South America	1	<1%	0	0%
Oceania	9	4%	5	5%
Multiple countries	10	4%	4	4%
Primary mental health disorder(s)				
Depressive disorder	76	33%	33	33%
Schizophrenia	23	10%	10	10%
Substance use disorders	19	8%	7	7%
Bipolar disorders	8	4%	3	3%
Post-traumatic stress disorder	8	4%	5	5%
Anxiety disorder	8	4%	3	3%
Alcohol use disorder	4	2%	0	0%
ADHD	3	1%	3	3%
Insomnia	2	1%	1	1%
Others	8	4%	5	5%
Multiple	69	30%	28	28%
Physical comorbidities by ICD-10 chapters				
I: Certain infectious and parasitic diseases	35	15%	12	12%
II: Neoplasms	58	25%	23	23%
III: Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanisms	15	7%	8	8%
IV: Endocrine, nutritional and metabolic diseases	141	62%	61	61%
V: Mental and behavioural disorders	-	-	-	-
VI: Diseases of the nervous system	53	23%	25	25%
VII: Diseases of the eye and adnexa	12	5%	8	8%
VIII: Diseases of the ear and mastoid process	0	0%	0	0%
IX: Diseases of the circulatory system	133	58%	56	56%
X: Diseases of the respiratory system	95	42%	39	39%
XI: Diseases of the digestive system	56	25%	20	20%
XII: Diseases of the skin and subcutaneous tissue	17	7%	8	8%
XIII: Diseases of the musculoskeletal system and connective tissue	67	29%	31	31%
XIV: Diseases of the genitourinary system	48	21%	20	20%
XV: Pregnancy, childbirth and puerperium	1	<1%	1	1%
XVI: Certain conditions originating in the perinatal period	0	0%	0	0%
XVII: Congenital malformations, deformations and chromosomal abnormalities	2	1%	2	2%
XVIII: Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified	18	8%	9	9%
XIX: Injury, poisoning and certain other consequences of external causes	11	5%	7	7%
XX: External causes of morbidity and mortality	3	1%	3	3%
XXI: Factors influencing Health status and contact with health services	4	2%	3	3%
XXII: Codes for special purposes	0	0%	0	0%

(*continued on next page*)

Table 1 (*continued*)

	All identified studies		Included in quantitative synthesis	
	n	%	n	%
Study design				
Administrative data based	144	63%	63	63%
Patient reported data/survey based	47	21%	25	25%
Administrative and patient reported data	23	10%	10	10%
Other	14	6%	2	2%
Cohort sizes				
1 – 1000	29	13%	11	11%
1,001 - 10,000	51	22%	24	24%
10,001 - 100,000	74	32%	36	36%
100,001 - 1,000,000	41	18%	17	17%
1,000,001 - 10,000,000	14	6%	6	6%
More than 10,000,000	4	2%	4	4%
Not reported/not applicable	15	7%	2	2%
Year of publication				
2007	6	3%	3	3%
2008	1	<1%	0	0%
2009	9	4%	4	4%
2010	6	3%	3	3%
2011	10	4%	5	5%
2012	8	4%	4	4%
2013	12	5%	3	3%
2014	9	4%	3	3%
2015	10	4%	3	3%
2016	10	4%	4	4%
2017	18	8%	9	9%
2018	29	13%	13	13%
2019	33	14%	16	16%
2020	53	23%	24	24%
2021 (until June)	14	6%	6	6%
Sources of funding				
No funding reported	30	13%	15	15%
Government	81	36%	33	33%
Industry	40	18%	22	22%
University/Hospital	16	7%	7	7%
Non-profit/charity/NGO	4	2%	2	2%
Multiple	29	13%	11	11%
Not reported	28	12%	10	10%

3.1.3. Type of resource use and costs

Three-quarter of all included studies (n=172, 75%) reported information at resource utilisation level. Resource use was mainly investigated for the inpatient care (n=131, 57%) and outpatient care segments (n=80, 35%), followed by A&E (n=74, 32%) and primary care (n=59, 26%). Fewer studies (n=119, 52%) reported cost. Costs were most frequently assessed for inpatient care (n=96, 42%), outpatient care (n=70, 31%) and medication expenditures (n=68, 30%). Overall, four studies (2%) reported resource use and/or costs related to informal care. Information on productivity losses were reported in 12% of all studies (n=27), all of which focused on unemployment or morbidity-related productivity losses such as absenteeism and presenteeism. No study reported excess productivity losses related to premature mortality. (Fig. 2)

3.2. Quantitative synthesis

3.2.1. Study characteristics

Across the 100 studies, which were deemed suitable for quantitative synthesis, 316 comparative estimates for excess resource use and costs could be extracted and synthesised. The characteristics of the studies included in the quantitative synthesis were similar to the full narrative sample including geographical origin, reported MHDs and comorbid PHCs, study designs or cohort sizes (Table 1). The following sections present summary estimates of excess resource use and costs for predefined healthcare segments, informal care and productivity losses according to the identified underlying comparison groups: 1) vsMHD, 2) vsPHC, and 3) vsGPC. Forest plots and supporting tables are available for all analyses in Appendices C-E.

Table 2 Number and proportion of studies reporting physical comorbidities by ICD-10 chapter and primary mental health disorder.

		Any mental health disorder		Depressive disorder		Schizophrenia		Substance use disorder		Bipolar disorder		Post-traumatic stress disorder		Anxiety disorder		Alcohol use disorder	
		n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
I	Certain infectious and parasitic diseases	35	15.4%	6	7.9%	2	8.7%	11	57.9%	..	..	1	12.5%	..	..	..	..
II	Neoplasms	58	25.4%	16	21.1%	..	..	4	21.1%	1	12.5%	..	..	2	25%	1	25%
III	Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanisms	15	6.6%	4	5.3%	..	..	..	..	..	..	..	..	..	..	..	..
IV	Endocrine, nutritional and metabolic diseases	141	61.8%	52	68.4%	13	56.5%	8	42.1%	8	100.0%	1	12.5%	4	50%	3	75%
V	Mental and behavioural disorders	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
VI	Diseases of the nervous system	53	23.2%	18	23.7%	2	8.7%	6	31.6%	1	12.5%	4	50%	1	12.5%	1	25%
VII	Diseases of the eye and adnexa	12	5.3%	9	11.8%	..	..	..	..	..	..	..	..	..	..	..	..
VIII	Diseases of the ear and mastoid process	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
IX	Diseases of the circulatory system	133	58.3%	47	61.8%	11	47.8%	9	47.4%	7	87.5%	2	25%	3	37.5%	3	75%
X	Diseases of the respiratory system	95	41.7%	29	38.2%	2	8.7%	6	31.6%	4	50.0%	1	12.5%	3	37.5%	3	75%
XI	Diseases of the digestive system	56	24.6%	16	21.1%	1	4.3%	4	21.1%	..	..	1	12.5%	3	37.5%	3	75%
XII	Diseases of the skin and subcutaneous tissue	17	7.5%	4	5.3%	..	..	2	10.5%	..	..	..	..	4	50%	1	25%
XIII	Diseases of the musculoskeletal system and connective tissue	67	29.4%	21	27.6%	..	..	5	26.3%	2	25.0%	2	25%	2	25%	2	50%
XIV	Diseases of the genitourinary system	48	21.1%	18	23.7%	1	4.3%	4	21.1%	..	..	..	..	..	..	1	25%
XV	Pregnancy, childbirth and puerperium	1	0.4%	..	..	..	..	..	..	..	..	..	..	..	..	..	..
XVI	Certain conditions originating in the perinatal period	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
XVII	Congenital malformations, deformations and chromosomal abnormalities	2	0.9%	..	..	..	..	..	..	..	..	..	..	..	..	..	..
XVIII	Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified	18	7.9%	5	6.6%	..	..	2	10.5%	1	12.5%	1	12.5%	..	..	..	..
XIX	Injury, poisoning and certain other consequences of external causes	11	4.8%	4	5.3%	..	..	1	5.3%	..	..	..	..	1	12.5%	..	..
XX	External causes of morbidity and mortality	3	1.3%	1	1.3%	..	..	2	10.5%	..	..	..	..	..	..	..	..
XXI	Factors influencing Health status and contact with health services	4	1.8%	2	2.6%	..	..	..	..	..	..	..	..	..	..	..	..
XXII	Codes for special purposes	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..

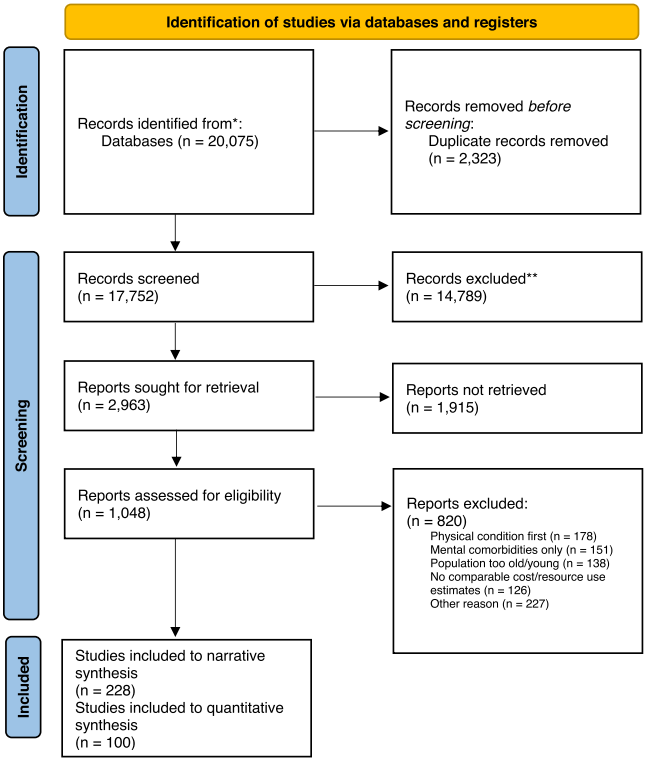

Fig. 1 PRISMA flowchart for study selection.

3.2.2. Excess resource use

Fig. 3a provides an overview of all excess resource use findings based on continuous data expressed as RoMs, while Fig. 3b provides an overview of all dichotomous excess resource use estimates expressed as ORs. Table 3 summarises the variation in of identified estimates based on underlying primary MHDs. A summary of the main findings is given below.

3.2.2.1. Healthcare

Healthcare use was frequently assessed in studies focusing on multiple MHDs (n=26, 32%) or depressive disorder (n=25, 30%). Across the included studies, the highest excess resource use was reported for bipolar disorder [vsGPC, inpatient care, RoM=9.17; 95% CI: 7.60; 11.06] and substance use disorder [vsGPC, inpatient care, OR=36.18; 95% CI: 28.36; 46.15]. The lowest estimates were retrieved from studies focusing on depressive disorder [vsPHC only, primary care, RoM=0.59; 95% CI: 0.35; 1.01] and multiple MHDs [vsMHD only, outpatient care, OR=0.5; 95% CI: 0.27; 0.94].

When comparing the mean resource use of individuals with MHD and PHC versus MHD only, the highest RoM was found in the inpatient care segment [1.36; 95% CI: 1.09, 1.70]. Similarly, high RoMs were calculated for A&E visits [1.34; 95% CI: 1.21, 1.49] and for outpatient care [1.31; 95% CI: 1.17, 1.46]. In terms of the odds of utilising care services, the highest increase was estimated for A&E care [OR=1.94; 95% CI: 1.63, 2.32] followed by inpatient care [OR=1.74; 95% CI: 1.17, 2.58]. Excess resource use in primary care was found less elevated [OR=1.24; 95% CI: 1.17, 1.31], while evidence for outpatient care was not conclusive [OR=1.21; 95% CI: 0.79, 1.85].

Comparing mean resource use data of individuals with MHD and PHCs versus PHC only, the highest excess was estimated for the outpatient care segment [RoM=1.61; 95% CI: 1.25, 2.09]. Further, a RoM of 1.55 was identified for A&E care [95% CI: 1.04, 2.30]. Increased mean resource use

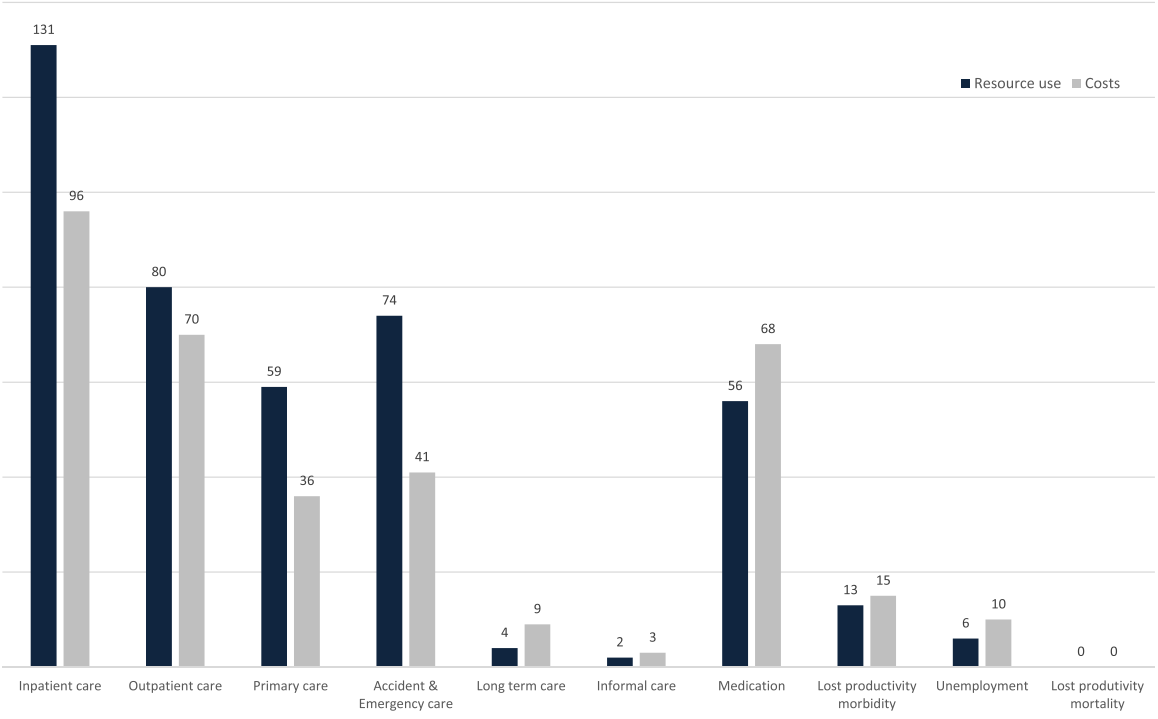

Fig. 2 Number of identified studies reporting excess costs or resource use per healthcare segment.

Table 3 Variation by underlying mental health disorders (MHDs) across all analyses.

	vs. Mental Health Disorder only (vsMHD)			vs. Physical Health Condition(s) only (vsPHC)			vs. matched General Population Controls (vsGPC)		
	Summary estimate	Lowest estimate	Highest estimate	Summary estimate	Lowest estimate	Highest estimate	Summary estimate	Lowest estimate	Highest estimate
Resource Use (Ratio of means, continuous outcomes)									
Inpatient Care	1.36 [1.09; 1.7]	1.23 [1.12; 1.34], Schizophrenia	2 [1.23; 3.26], Anxiety	1.23 [1.17; 1.3]	0.91 [0.73; 1.14], Depression	1.79 [1.34; 2.39], Depression	4.2 [2.06; 8.56]	1.53 [1.29; 1.81], PTSD	9.17 [7.6; 11.06], Bipolar disorder
Outpatient Care	1.31 [1.17; 1.46]	0.96 [0.91; 1], Substance use disorder	1.66 [1.48; 1.86], Anxiety	1.61 [1.25; 2.09]	0.68 [0.65; 0.73], Multiple	4 [3.76; 4.25], Autism spectrum disorder	2.49 [2.2; 2.82]	2.17 [2.14; 2.20], Depression	2.84 [2.80; 2.89], Depression
Primary Care	1.06 [0.87; 1.13]	..	..	1.29 [0.95; 1.74]	0.59 [0.35; 1.01], Depression	2.19 [2.15; 2.23], PTSD	2.66 [1.83; 3.85]	2.20 [2.18; 2.22], Depression	3.21 [3.12; 3.30], Depression
A&E Care	1.34 [1.21; 1.49]	1.12 [1.08; 1.16], Substance use disorder	1.67 [1.29; 2.16], Depression	1.55 [1.04; 2.3]	1.00 [0.79; 1.72], Multiple	2.63 [2.21; 3.14], Depression	3.89 [2.33; 6.49]	2.15 [1.99; 2.31], Bipolar disorder	7.27 [5.40; 9.79], Substance use disorder
Long Term Care	..	..	..	..	..	..	3.81 [3.7; 3.92]	..	..
Informal Care	..	..	..	..	..	..	..	..	..
Productivity losses	..	..	..	..	..	..	..	..	..
Resource use (Odds ratios, dichotomous outcomes)									
Inpatient Care	1.74 [1.17; 2.58]	0.66 [0.61; 0.72], Substance use disorder	4.06 [3.51; 4.71], Anxiety	1.83 [1.5; 2.23]	0.84 [0.47; 1.5], Depression	7 [2.98; 16.43], Depression	3.76 [2.56; 5.22]	1.22 [1.12; 1.32], Substance use disorder	36.18 [28.36; 46.15], Substance use disorder
Outpatient Care	1.21 [0.79; 1.85]	0.5 [0.27; 0.94], Multiple	2.83 [1.12; 7.15], Anxiety	1.37 [0.86; 2.19]	0.83 [0.43; 1.41], Depression	2.86 [2.85; 2.86], Multiple	2.47 [1.58; 3.85]	0.89 [0.61; 1.29], Schizophrenia	14.36 [9.04; 22.82], Substance use disorder
Primary Care	1.24 [1.17; 1.31]	0.86 [0.43; 1.71], Depression	3.18 [0.64; 15.92], Anxiety	1.67 [0.8; 3.48]	0.99 [0.96; 1.02], Depression	8.05 [6.22; 10.41], Schizophrenia	3.41 [1.43; 8.14]	0.61 [0.26; 1.42], Gambling disorder	9.57 [8.89; 10.29], Depression
A&E Care	1.94 [1.63; 2.32]	1.68 [1.13; 2.48], Depression	2.29 [3.07; 2.53], Substance use disorder	1.77 [1.29; 2.44]	1.03 [1.03; 1.03], Substance use disorder	6.79 [6.55; 7.03], Substance use disorder	3.3 [2.42; 4.49]	1.67 [1.3; 2.13], Depression	10.19 [8.43; 12.33], Schizophrenia

(*continued on next page*)

Table 3 (*continued*)

	vs. Mental Health Disorder only (vsMHD)			vs. Physical Health Condition(s) only (vsPHC)			vs. matched General Population Controls (vsGPC)		
	Summary estimate	Lowest estimate	Highest estimate	Summary estimate	Lowest estimate	Highest estimate	Summary estimate	Lowest estimate	Highest estimate
Long Term Care	..	..	..	1.75 [1.27; 2.42]	..	..	..	..	..
Informal Care	..	..	..	6.32 [2.59; 15.42]	..	..	..	..	..
Productivity Losses	2.51 [1.44; 4.37]	1.47 [1.35; 1.61], Multiple	17.39 [2.40; 125.81], Depression	1.32 [1.02; 1.71]	0.47 [0.35; 0.64], Depression	4.41 [1.47; 13.21], Depression	..	..	..
Costs (Ratio of means, continuous outcomes)									
Inpatient Care	1.29 [1.1; 1.51]	0.93 [0.82; 1.06], Schizophrenia	2.72 [2.15; 3.45], Schizophrenia	1.37 [1.26; 1.49]	0.65 [0.27; 1.55], Anxiety	2.83 [0.97; 8.23], Depression	3.37 [2.34; 4.87]	1.51 [1.17; 1.94], PTSD	23.25 [16.80; 32.47], Substance use disorder
Outpatient Care	1.4 [1.2; 1.63]	1.07 [0.96; 1.19], Depression	2.35 [1.39; 3.97], Depression	1.63 [1.47; 1.81]	1.11 [0.94; 1.33], Alcohol use disorder	5.12 [4.7; 5.58], Autism spectrum disorder	2.58 [2.14; 3.11]	1.72 [1.56; 1.90], Bipolar disorder	5.52 [4.64; 6.57], Substance use disorder
Primary Care	1.45 [1.12; 1.89]	0.97 [0.9; 1.05], Depression	1.76 [0.81; 3.84], Depression	1.75 [1.59; 1.92]	1.5 [1.29; 1.75], Depression	3.39 [2.43; 4.74], Schizophrenia	3.17 [3.09; 3.26]	..	..
A&E Care	..	..	..	1.87 [1.32; 2.65]	1.26 [1.13; 1.40], Depression	6.13 [5.14; 7.32], Autism spectrum disorder	3.16 [2.63; 3.8]	2.14 [1.95; 2.35], Bipolar disorder	10.46 [6.19; 17.67], Substance use disorder
Long Term Care	1.14 [0.39; 3.33]	..	..	7.14 [1.46; 34.81]	3.22 [1.74; 5.96], Depression	16.22 [7.82; 33.64], Alcohol use disorder	..	..	..
Informal Care	..	..	..	0.41 [0.24; 0.7]	0.31 [0.08; 1.21], Anxiety	0.43 [0.24; 0.77], Alcohol use disorder	..	..	..
Medication	1.96 [1.24; 3.09]	1.04 [0.95; 1.14], Depression	8.12 [7,53; 8.76], Schizophrenia	2.1 [1.76; 2.51]	1.03 [0.09; 11.61], Multiple	4.91 [3.72; 6.49], Schizophrenia	2.77 [1.98; 3.86]	1.08 [0.81; 1.43], Depression	5.27 [4.38; 6.34], Substance use disorder
Productivity losses	..	..	..	2.38 [1.49; 3.81]	0.94 [0.52; 1.70], ADHD	3.88 [1.53; 9.85], Anxiety	..	..	..

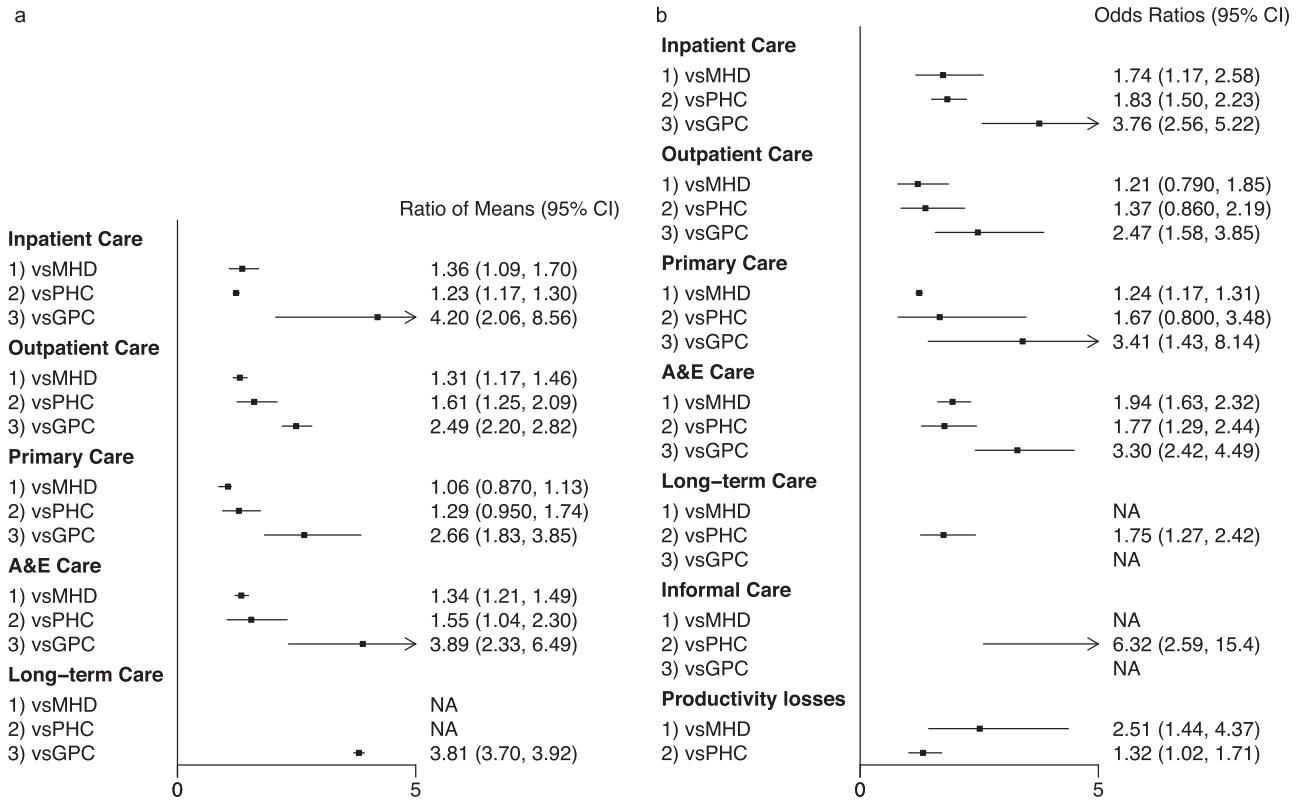

Fig. 3 Summary of meta-analyses: Excess resource use in individuals with mental health disorders and physical comorbidities versus 1) mental health disorder only (vsMHD), 2) physical health condition(s) only (vsPHC), and 3) matched general population controls (vsGPC). A) Ratio of means (RoM) for excess resource use; B) Odds ratios (OR) for excess resource use.

was identified for inpatient care services with a respective RoM of 1.23 [95% CI: 1.17, 1.30], while for primary care the indicative increase was not statistically significant [RoM=1.29; 95% CI: 0.95, 1.74]. The largest increases in the odds of using services were identified in inpatient care [OR=1.83; 95% CI: 1.50, 2.23], followed by A&E care, [OR=1.77; 95% CI: 1.29, 2.44]. Other overall ORs for increased resource use were estimated at 1.67 [95% CI: 0.80, 3.48] in primary care and 1.37 [95% CI: 0.86, 2.19] in outpatient care, but were statistically non-significant.

Analysing mean resource use of individuals with MHD and PHC versus GPC, we found the largest increase, more than four-fold, in inpatient care [RoM=4.20; 95% CI: 2.06, 8.56], followed by A&E care [RoM=3.89; 95% CI: 2.33, 6.49]. More than two-fold increases in mean resource use were further identified in primary care [RoM=2.66; 95% CI: 1.83, 3.85] and in outpatient care [RoM=2.49; 95% CI: 2.20, 2.82]. The largest increase in the odds of utilisation was found for inpatient services [OR=3.76; 95% CI: 2.56, 5.22], while more than three-fold increases were also identified for primary care services [OR=3.41; 95% CI: 1.43, 8.14] and for A&E services [OR=3.30; 95% CI: 2.42, 4.49]. Finally, the odds of outpatient service use was estimated as being nearly two and a half times higher than in the general population [OR=2.47; 95% CI: 1.58, 3.85].

3.2.2.2. Informal care and productivity loss. Excess informal care use was only assessed in studies focusing on depressive disorder (n=3, 100%), while productivity losses were assessed for depressive disorder (n=4, 44%) and multiple MHDs (n=3, 33%) with the range being defined by depressive disorder related studies. [minimum: vsPHC, OR=0.47; 95% CI: 0.35; 0.64; maximum: vsMHD, OR=17.39; 95% CI: 2.40; 125.81].

Informal care data were rarely reported and did not allow quantitative synthesis. We identified only a few studies (n=9) reporting evidence related to excess productivity losses. The odds of unemployment, absenteeism or presenteeism were more than two and a half times higher among individuals with MHD and PHC in comparison to MHD only [OR=2.51; 95% CI: 1.44, 4.37]. Compared to PHC only, an OR of 1.32 [95% CI: 1.02, 1.71] was estimated.

3.2.3. Excess costs

An overview of all meta-analysis results on excess costs is provided in Fig. 4.

3.2.3.1. Healthcare. Most studies included in the quantitative synthesis reported estimates on costs for depressive disorder (n=26, 43%) or multiple MHDs (n=14, 23%). The highest excess cost estimate was for substance use disorders [vsGPC, inpatient care, RoM=23.25; 95% CI: 16.80; 32.47], while the lowest cost estimate was for anxiety disorder [vsPHC, inpatient care, RoM=0.65; 95% CI: 0.27; 1.55].

We were able to estimate excess costs in five different healthcare segments when compared to MHD only. The highest increase in mean costs was found for medication expenditure with a RoM of 1.96 [95% CI: 1.24, 3.09], followed by primary care costs [RoM=1.45; 95% CI: 1.12, 1.89]. For outpatient and inpatient care, we identified RoMs of 1.40 [95%

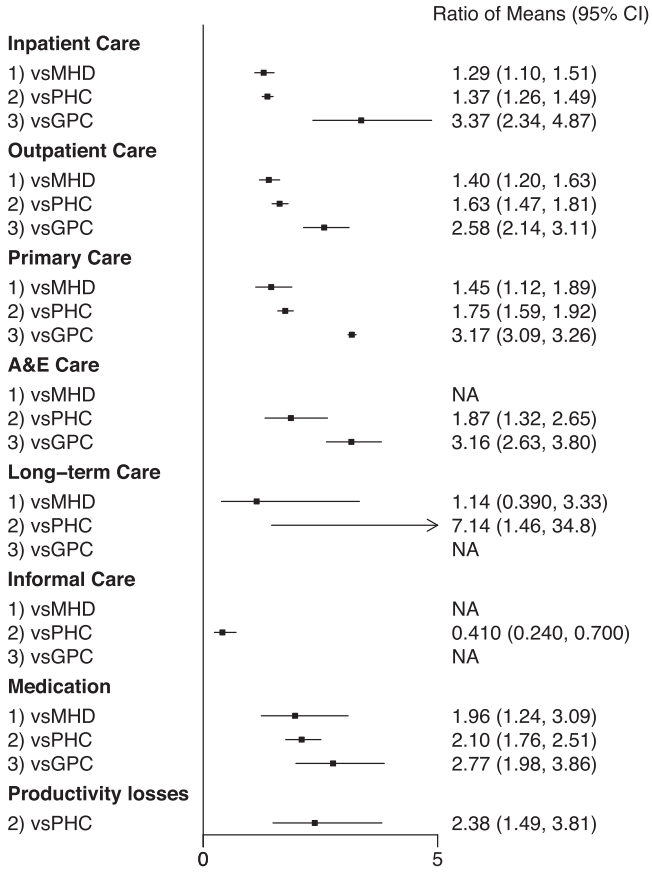

Fig. 4 Summary of meta-analyses: Ratios of mean (RoM) costs in individuals with mental health disorders and physical comorbidities versus 1) mental health disorder only (vsMHD), 2) physical health condition(s) only (vsPHC), and 3) matched general population controls (vsGPC).

CI: 1.20, 1.63] and 1.29 [95% CI: 1.10, 1.51], respectively. The cost of long-term care was non-significantly, marginally increased [RoM=1.14; 95% CI: 0.390, 3.33].

When comparing costs to individuals with PHC only, the largest increase was found for long-term care with a RoM of 7.14 [95% CI: 1.46, 34.81]. Medication costs more than doubled [RoM=2.10; 95% CI: 1.76, 2.51]. Further excess costs were identified in A&E and in primary care, with RoMs of 1.87 [95% CI: 1.32, 2.65] and 1.75 [95% CI: 1.59, 1.92], respectively. Subsequently, a RoM of 1.63 [95% CI: 1.47, 1.81] was found for outpatient and a RoM of 1.37 [95% CI: 1.26, 1.49] for inpatient care related costs.

Comparing healthcare costs to GPC, the largest increase, more than three-fold, was estimated in inpatient care [RoM=3.37; 95% CI: 2.34, 4.87]. We further estimated excess costs of over three-fold for A&E care [RoM=3.16; 95% CI: 2.63, 3.8]. Expenditures more than doubled for medication and outpatient costs [RoM=2.77; 95% CI: 1.98, 3.86 and RoM=2.58; 95% CI: 2.14; 3.11, respectively].

3.2.3.2. Informal care and productivity losses. Two studies reported costs of informal care, with the higher estimate retrieved for alcohol use disorder [vsPHC, RoM=0.43; 95% CI: 0.24; 0.77] and the lower estimate retrieved for anxiety disorder [vsPHC, RoM=0.31; 95% CI: 0.08; 1.21]. Costs of productivity losses were assessed for anxiety disorder, alcohol use, and attention-deficit hyperactivity disorders (ADHD).). The lowest productivity losses were identified for ADHD [vsPHC, RoM=0.94; 95% CI: 0.52; 1.70], and the highest for anxiety disorder [vsPHC, RoM=3.88; 95% CI: 1.53; 9.85].

The only reduction in costs was found for informal care in comparison to PHC only, with an estimated RoM of 0.41 [95% CI: 0.24, 0.70]. Meta-analysis on costs related to productivity losses revealed a more than two-fold increase in individuals with MHD and PHC in comparison to PHC only [RoM=2.38; 95% CI: 1.49, 3.81]. There were no other feasible quantitative comparisons for informal care or productivity loss costs based on the identified literature.

4. Discussion

This is the first systematic review and comprehensive synthesis of existing international evidence on the excess economic burden of physical comorbidities in individuals with MHDs. We found multiple studies with comparisons to MHD only, PHC only or matched GPC. As expected, all except one comparison showed increased resource use and/or cost tendencies. Following quantitative synthesis, pooled excess resource use ranged between +6% (primary care, vsMHD) to +320% (inpatient care, vsGPC) with excess costs between +14% (long-term care, vsMHD) to +614% (long-term care, vsPHC). Excess economic burden tended to be the largest in comparison to matched GPCs, a heterogenous comparison group with no particular disease pattern; and smallest in comparison to those with MHDs only. The excess economic burden of physical comorbidities further varied by primary MHDs with generally higher excess costs identified for schizophrenia and substance use disorder, and higher excess resource use for anxiety disorder. Depressive disorder tended to have the lowest average excess resource use and cost estimates compared to other MHDs across all healthcare segments.

Overall, our findings show that physical comorbidities are major drivers of excess resource use and costs for individuals with MHDs, but affect individual care segments differently. These first global estimates indicate a potential excess of over 30% in inpatient, outpatient and emergency care needs, and excess costs in certain healthcare segments of up to 45% when compared to those without physical comorbidities underlining the need for a more integrated care focused approach targeting physical comorbidity disparities for individuals with MHDs. Excess healthcare use was highest in the hospital setting compared to primary or outpatient care, which are likely more deferred and therefore underutilised.

The only identified cost reduction was for informal care, with an almost 60% decrease in comparison to individuals with relevant PHCs only. This finding together with the more than six-fold increase in long-term care costs within the same comparison is likely to be indicative of the more limited informal care opportunities and more excessive formal care use of those with comorbid MHDs, but the evidence remains limited. The odds for unemployment, absenteeism or presenteeism were more than two and a half times as high among individuals with MHD and PHCs versus those with MHDs only. In contrast, compared to individuals with

PHCs only, we estimated an OR of 1.32 [95% CI: 1.02, 1.71]. Although these results suggest that productivity losses are more frequently administered on the basis of PHCs rather than MHDs in individuals with comorbidities, excess productivity losses were shown as substantial in all comparisons.

Despite narratively reviewing over 200 individual studies and quantitatively synthesizing estimates from 100 papers, current evidence remains very heterogeneous and non-representative. More than half of the identified studies were from the United States representing very different healthcare system structures from those in Europe or in Asia. Therefore, the generalisability of many estimates, especially those for costs, is limited within a wider geographical context. This is especially true for evidence about PTSD. Most of the existing evidence also focuses on a few specific combinations of comorbid MHDs and PHCs, with depression and metabolic and cardiovascular diseases being the most frequently investigated. Care segments are also explored disproportionately, with excess inpatient care resource use and costs being the most common, while very few studies currently look at long-term care or impacts beyond healthcare such as informal care and lost productivity. We could not identify a single study estimating lost productivity due to physical comorbidity-related excess mortality.

Our summary estimates commonly have high levels of heterogeneity (I^2 range: 27%-100%) and are often based on small numbers of studies. Pooling estimates for individual MHDs or for long-term care and informal care in general was not feasible due to the lack of multiple relevant studies. Where pooling was feasible, high levels of heterogeneity were expected from the outset even for individual MHDs considering the large geographical scope and the variation of healthcare services definitions internationally (Fischer et al., 2022). Therefore, the aim of our quantitative synthesis differed from the aim of a conventional meta-analysis that is usually designed to detect a simple mean effect and its statistical significance across homogenous randomised controlled studies. We did not pool all estimates claiming to present one 'overall effect' or its statistical significance, but rather to explore the potential ranges of excess resource use and costs across studies and across healthcare systems, similar to the aims of proportional meta-analyses (Barker et al., 2021). As opposed to a simple narrative review, our approach also has the advantage of studies being weighted by their size, which is an important factor when considering that resource use and cost data are often right skewed and individual smaller studies tend to be underpowered to detect significant differences. Furthermore, all existing evidence is comprehensively reported in the Appendix also by individual MHDs allowing additional explorations and future synthesis work once new evidence becomes available.

Nevertheless, considering the high level of heterogeneity pertinent to vastly differing cohort characteristics, study methodologies and diversity in resource use and cost measures, pooling all extracted data was not feasible. We refrained from quantitatively synthesising the use of medications as available estimates were found to represent lines of treatment rather than additional disease burden. Furthermore, the large scope of the review and the broad inclusion criteria considering study types, did not allow for comparative quality assessment of individual studies and further refinement of range estimates according to study quality. We also caution against any aggregation of the current excess economic burden estimates since these do not permit adjusting for the potential co-occurrence of some mental and physical health disorders. Further, we caution against drawing any conclusions regarding causality based on our analyses.

Notwithstanding the carefully designed search strategy, extensive screening of several electronic databases and common grey literature, and rigorous review methods with full double screening and data extraction, we cannot exclude the possibility of missing some relevant specific evidence. It is, however, unlikely, that any potential omission of a few individual studies would have a major impact on the interpretation of the narrative findings or would significantly influence the pooled range estimates. On the other hand, due to the lack of large cohort studies or reliable time series data, the robustness of excess estimates from comparison with the MHD only group remains uncertain based on the current literature. Further, excess resource use is likely underestimated as all studies were based on diagnosed cases, while excess utilisation of services may also present in those without a formal MHD diagnosis (Picco et al., 2018; Schnyder et al., 2017)

In conclusion, existing international health economic evidence systematically synthesised in this study are very heterogeneous with limited geographical representativeness and comparability, and does not allow the comprehensive estimation of the overall excess economic burden associated with physical comorbidities for any single MHD. If physical health gains and cost savings are to be achieved, our study demonstrates that this requires more prevention, earlier identification, management and treatment of MHDs, and more integrated mental and physical healthcare approaches. Future comorbidity research should focus on methodologically sound, epidemiologically harmonised excess cost estimates comparable across comorbidity combinations, care segments and countries.

Contributors

Judit Simon, Guy M. Goodwin and David McDaid conceptualised the study.

Judit Simon and David McDaid acquired funding.

Judit Simon, Susanne Mayer, A-La Park and David McDaid developed and executed the search strategy.

Judit Simon, Dennis Wienand, A-La Park, David McDaid screened records and assessed study eligibility, with assistance from Christoph Wippel, Susanne Mayer, Daniel Heilig, Agata Laszewska and Ines Stelzer.

Dennis Wienand, A-La Park and David McDaid extracted data, with assistance from Christoph Wippel and Daniel Heilig.

Judit Simon and Dennis Wienand planned and conducted the analysis and visualisation.

Judit Simon and Dennis Wienand wrote the original draft of the manuscript.

All authors contributed to the interpretation and subsequent edits of the manuscript and approved the final version for submission.

Declaration of Competing Interest

JS has received academic expert honoraria from the European Brain Council. ALP and DM have received support from the ECNP. GG has received royalties or licenses from Oxford University Press and Oxford University, payment or honoraria for lecture fees from Evopharma and Johnson & Johnson, provided expert testimony for Johnson & Johnson, participated in the advisory board for H Lundbeck, Medscape, Sage, Johnson & Johnson, Novartis, Beckley Psytech, Clerkenwell Health, Ocean neuroscience, and Boehringer Ingelheim, co-chairs the Bipolar Commission of Bipolar-UK, and has stock and/or stock options for P1vital, P1vital products, and Compass pathways. GG is a NIHR Emeritus Senior Investigator and Chief Medical Officer of Compass pathways. All other authors declare no competing interests.

The views expressed are those of the authors and not necessarily those of the ECNP, the NHS, the NIHR or the Department of Health.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.euroneuro.2022.10.001.

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