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ADULT MENTAL HEALTH

Comorbid physical health burden of serious mental health disorders in 32 European countries

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ABSTRACT

Background Mental health disorders (MHDs) are associated with physical health disparities, but underlying excess risk and health burden have not yet been comprehensively assessed.

Objective To assess the burden of comorbid physical health conditions (PHCs) across serious MHDs in Europe.

Methods We estimated the relative prevalence risk of PHCs associated with alcohol use disorders (AUD), bipolar disorder (BD), depressive disorders (DD) and schizophrenia (SZ) across working-age populations of 32 European countries in 2019 based on a targeted literature review. Excess physical health burden was modelled using population-attributable fractions and country-level prevalence data.

Findings We screened 10 960 studies, of which 41 were deemed eligible, with a total sample size of over 18 million persons. Relative prevalence of PHCs was reported in 54%, 20%, 15%, 5% and 7% of studies, respectively, for SZ, DD, BD, AUD or mixed. Significant relative risk estimates ranged from 1.44 to 3.66 for BD, from 1.43 to 2.21 for DD, from 0.81 to 1.97 for SZ and 3.31 for AUD. Excess physical health burden ranged between 27% and 67% of the total, corresponding to 84 million (AUD), 67 million (BD), 66 million (DD) and 5 million (SZ) PHC diagnoses in Europe. A 1% reduction in excess risk assuming causal inference could result in two million fewer PHCs across investigated MHDs.

Conclusions This is the first comprehensive study of the physical health burden of serious MHDs in Europe. The methods allow for updates, refinement and extension to other MHDs or geographical areas.

Clinical implications The results indicate potential population health benefits achievable through more integrated mental and physical healthcare and prevention approaches.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ People with mental health disorders experience worse physical health compared with the general population and have an increased risk for physical comorbidity; however, the magnitude of the associated physical health burden remains unknown.

WHAT THIS STUDY ADDS

⇒ This study provides the first comprehensive synthesis, estimation and visualisation of the excess physical health burden associated with alcohol use disorders (AUD), bipolar disorder (BD), depressive disorders (DD) and schizophrenia (SZ) across all International Statistical Classification of Diseases and Health Related Problems 10th Revision categories in the European working-age population.

⇒ Excess physical health diagnoses associated with AUD, BD, DD and SZ were estimated at 84 million, 67 million, 66 million and 5 million among those aged 20–64 years in Europe in 2019, respectively.

⇒ Any 1% reduction in the identified excess annual prevalence risks of physical health conditions could lead to overall two million fewer physical health diagnoses associated with AUD, BD, DD and SZ.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The estimates unequivocally demonstrate the potential value and broader population health benefits of investing into improved and closely integrated mental and physical healthcare approaches.

⇒ The study reveals major limitations in the existing epidemiological evidence and the key areas needing improvement for refined, fully Europe-specific estimates.

BACKGROUND

Mental health disorders (MHDs) are considered among the leading causes of disease burden globally. Within the working-age population, the disease burden attributed to depressive disorders and alcohol use disorders, as well as schizophrenia, has been on the rise since 1990 and these were within the 25 largest causes of disability-adjusted life years in 2019.[1] Recent studies even suggest these estimates for the burden of mental illnesses to be underestimated.[2] Moreover, it has been established that people with MHDs have worse physical health than the general population and that MHDs are associated with an increased risk of onset of chronic physical health conditions (PHCs).[3] A recent meta-analysis showed a higher incidence of cardiovascular diseases in patients with severe mental illnesses versus controls.[4] Another study found that the prevalence of many physical disorders was higher in individuals with MHDs.[5] However, physical diseases themselves also increase the incident

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risk of MHDs.[6] This reciprocal association further contributes to the multimorbidity of MHDs and PHCs.[7]

Individuals with MHDs also experience excess mortality, which constitutes a major public health challenge.[8] In Scandinavia, for example, reductions in life expectancy from age 15 were estimated to be 20 and 15 years less for male and female patients, respectively.[9] These excess deaths are primarily driven by more frequent and potentially preventable PHCs.[5 10] A recent large umbrella review demonstrated that MHDs increase the risk of poor clinical outcomes for PHCs, including all-cause and disease-specific mortality, particularly for alcohol use disorders, depressive disorders and schizophrenia.[11] Poor mortality-related outcomes are further explained as comorbid PHCs are associated with increased risks for suicidal ideation[12] and suicide attempts[13] in people with MHDs.

The underlying reasons for such physical health disparities vary by physical comorbidity disease area and MHD. One of the most influential psychological and biological factors in the bidirectional pathophysiology of comorbid MHDs and PHCs is distress/stress, for instance linked to immune-mediated inflammation.[14 15] Other factors are lifestyle-related, with tobacco dependency and low levels of physical activity considered widely problematic across individuals with MHDs.[16] Several medications commonly prescribed to individuals with MHDs have further adverse effects on physical health. For example, several second-generation antipsychotics may contribute to the risk of developing metabolic syndrome and cardiovascular comorbidities.[17] Further disparities may be explained by physical health needs among patients with severe MHDs being frequently ignored by themselves and healthcare providers, leading to reduced access to and utilisation of physical healthcare. For example, while cancer mortality is increased in patients with mental disorders, cancer screening is used less frequently, leading to potential suboptimal diagnosis of cancer cases.[18] The fragmentation of mental health services and other medical services is another major factor worsening these disparities.[19] In addition, another cause of ill physical health may be genetic cosegregation.[20] Physical health disparities are further associated not only with diagnosed disorders, but psychiatric symptoms.[20] Another recent large report summarised common physical comorbidity areas across different MHDs and highlighted the lack of systematic meta-analytic research across several specific disease areas, for example infectious diseases or respiratory comorbidities.[21]

The direct economic losses associated with MHDs have been estimated at US$5 trillion globally, ranging from 4% of the national gross domestic products for Sub-Saharan Africa to 8% in North America.[2] Additional economic losses are pertinent due to excess physical comorbidity since the increased physical health burden associated with MHDs contributes to more frequent and intensive use of healthcare resources, and thus costs, as shown by a recent large systematic review, ranging from +6% to +320% and from +14% to +614%, respectively, with profound variations across primary MHDs and types of care.[22]

Objective

Despite the existing evidence for elevated levels of specific physical comorbidities and their costs in people with MHDs, so far little is known about the overall level of physical health burden disparity. The overarching aim of this study was to comprehensively estimate the excess physical health burden associated with selected serious MHDs prevalent within the working-age population in Europe. For this purpose, we conducted a comprehensive evidence synthesis and modelling exercise based on excess risk data from the published literature and baseline population-level prevalence data from the Global Burden of Disease (GBD) 2019 study.

METHODS

Data sources

Relative risks of PHCs for selected MHDs

Evidence on the relative risk (RR) of PHCs in individuals with selected MHDs based on point prevalence (or close approximation up to 1 year) was retrieved from the literature and synthesised quantitatively. Selected MHDs were alcohol use disorders (AUD), bipolar disorder (BD), depressive disorders (DD) and schizophrenia (SZ). International Statistical Classification of Diseases and Health Related Problems 10th Revision (ICD-10) codes reflecting AUD (F10.2–F10.8, G31.2, X65–X65.9, Y15–Y15.9), BD (F30–F31.9, F34.0), DD (F32–F33.9, F34.1) and SZ (F20–F25.9) were used to identify and categorise MHD diagnoses. We conducted a targeted literature review employing MeSH term-based literature searches by the 4 primary MHDs combined with 16 common comorbidity categories and the MeSH term of comorbidity to identify records in PubMed published from January 2000 to November 2022 (online supplemental appendix A). Additionally, we deployed a backward pearl growing approach by reviewing the reference lists of full text-screened studies, including literature reviews and meta-analyses. Included publications were primary studies that had aggregated risk or prevalence measures of PHCs (all ICD-10 chapters except 'V Mental and behavioural disorders') for working-age adults (18–65 years) with a diagnosis of a selected MHD versus those without. Excluded studies had no available full text; focused on paediatric (<18 years) or older age populations (>65 years), or had no extractable risk estimates for the working-age adult population; reported only incidence-based measures; reported only longer (>1 year) or lifetime prevalence estimates; provided no statistical dispersion measures allowing further quantitative synthesis; reported sample sizes deemed too small for the current study (n <1000); included non-random study populations (eg, veterans); reported duplicate estimates from the same study; or reported the PHC as clearly preceding the given MHD. Systematic literature reviews and meta-analyses were retrieved for the pearl growing step. No explicit restrictions were made based on study design or publication language prior to the search. The study selection process was according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[23] Screening and data extraction were carried out by two researchers independently. Discrepancies were resolved by discussion, or in case of no decision through a third reviewer. Inclusion and exclusion criteria were carefully devised to limit the risk of bias. At full-text screening stage, we systematically assessed study quality using the Joanna Briggs Institute's critical appraisal checklist for studies reporting prevalence data to ensure that only studies with a fully positive quality appraisal were included.[24]

Population prevalence of selected MHDs and PHCs per country for the working-age population

We synthesised population-level cross-sectional disease prevalence data retrieved from the 2019 GBD database[25] for the European Union 27 Member States, plus Iceland, Liechtenstein, Norway, Switzerland and the UK, with a total working-age population of 312 528 667 in 2019.[26] The 2019 GBD project is the most comprehensive epidemiological study providing disease burden estimates for 369 different causes linked to ICD-10 codes

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across 204 countries worldwide.[1] GBD data were mapped for all relevant 32 European populations aged 20–64. We obtained population estimates for a given age range per country from the European Statistical Office (EuroStat).[26]

Data analysis

Synthesis of RRs

We categorised RR estimates by ICD-10 categories of PHCs and conducted random-effects meta-analyses, quantitatively synthesising the evidence on the RR of PHCs among persons with a selected MHD compared with matched controls without the given MHD. Where necessary, ORs retrieved from the literature were approximated to RRs.[27]

Estimation of physical health burden at the population level

'Total' PHC diagnoses for the selected MHD populations were modelled at country level in two parts. 'Expected' PHC diagnoses were defined as diagnoses that would occur at similar rates as in the population without the given MHD, and were based on baseline point prevalence rates from the GBD study for year 2019. 'Excess' PHC diagnoses were defined as the difference between the number of diagnoses occurring at rates of the specific RR levels synthesised for the given MHD population and their expected baseline levels, and could be positive or negative. Excess diagnoses were calculated using the population-attributable fractions (PAF) method. PAF is defined as the proportional (%) change in disease burden that may be achievable if the exposure of interest was reduced to an alternative ideal exposure scenario, while other risk factors in the population remain unchanged.[28] We estimated PAFs based on the summary RRs and the corresponding 95% CIs synthesised in the meta-analyses together with obtained working-age population sizes and matching disease prevalence data by PHC groups within each selected MHD population using the formula by Miettinen.[29] Additionally, we modelled scenarios of potential reductions of 5%, 10% and 50% in the excess PHC risk levels of MHDs and their resulting hypothetical population health impacts.

Data analyses and visualisations were conducted using Microsoft Excel V.2016 and R V.4.2.2. All study data are available from public sources or provided within this publication.

RESULTS

RR of PHC prevalence associated with selected MHDs

A PRISMA flow chart of the review process is available in online supplemental appendix B. In total, 10 960 records were identified in the initial literature search of risk evidence, of which 213 records were deemed eligible for full-text screening. From the reference list search of these studies, an additional 374 records were included for full-text screening. Following all eligibility checks, 41 records were included for quantitative synthesis to estimate the RRs by given ICD-10 PHC categories, with a total sample size of 18 954 315. Most included studies were from Taiwan (n=11, 27%), the UK (n=8, 20%) or the USA (n=8, 20%). The frequency of assessed primary MHDs was 54% (n=22) for SZ, 20% (n=8) for DD, 15% (n=6) for BD and 5% (n=2) for AUD, while 7% (n=3) reported on multiple MHDs. Most included studies reported point prevalence (n=33, 80%). The risk estimates were most frequently either fully adjusted (n=19, 46%) or unadjusted (n=41%), and fewer adjusted for basic sociodemographic characteristics (n=4, 10%). Details of all included studies are available in online supplemental appendix C, while figure 1 shows the inter-relation of the main study characteristics. An overview of the RR results by ICD-10 chapters is presented in figure 2 and in online supplemental appendix D. The following sections present the main RR findings by individual MHDs.

Alcohol use disorders

For AUD, only one comparison resulted in a significant RR estimate. A risk increase, more than threefold, was obtained for 'XI Diseases of the digestive system' (RR=3.31; 95% CI 1.84

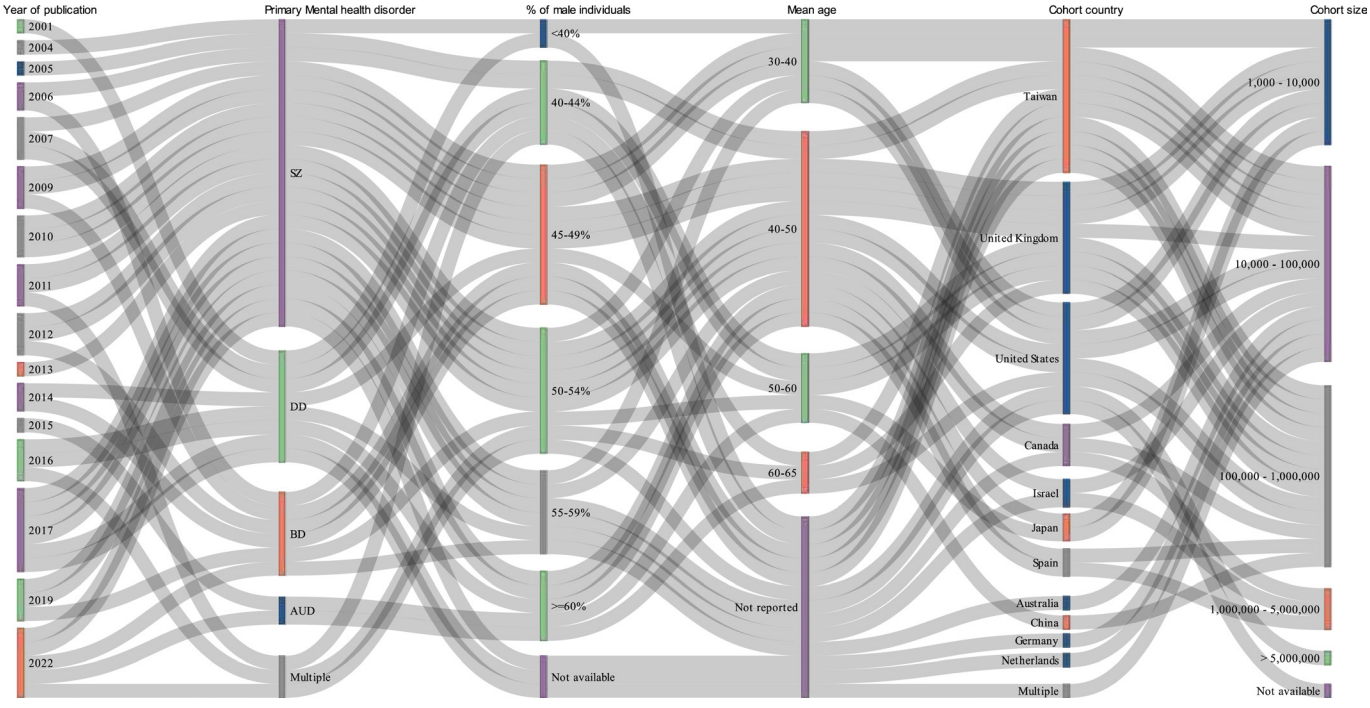

Figure 1 Inter-relation between main study characteristics. AUD: alcohol use disorders; BD: bipolar disorder; DD: depressive disorders; SZ: schizophrenia.

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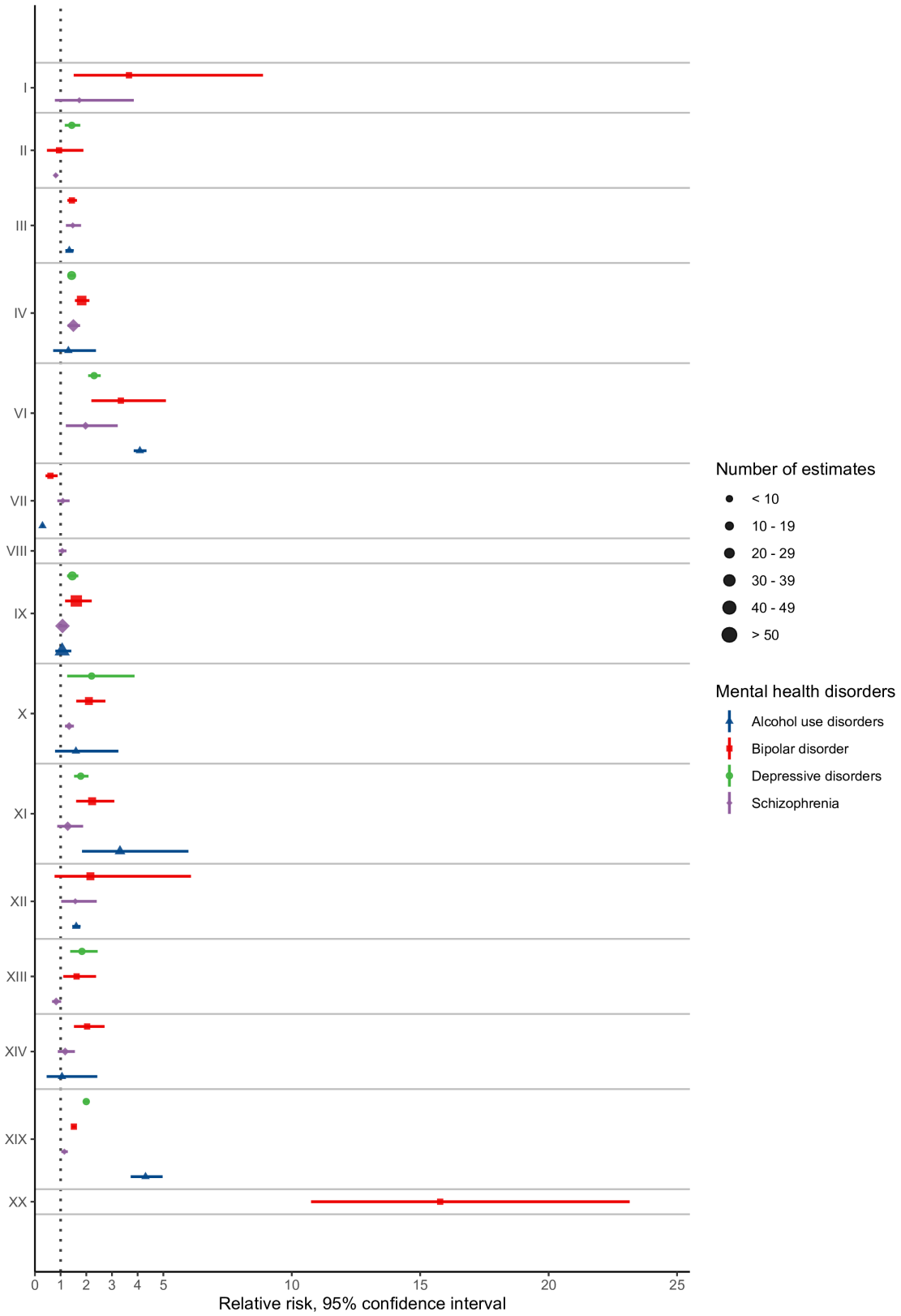

Figure 2 Levels of excess physical health condition risks by ICD-10 chapters. I: certain infectious and parasitic diseases; II: neoplasms; III: diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism; IV: endocrine, nutritional and metabolic diseases; VI: diseases of the nervous system; VII: diseases of the eye and adnexa; VIII: diseases of the ear and mastoid process; IX: diseases of the circulatory system; X: diseases of the respiratory system; XI: diseases of the digestive system; XII: diseases of the skin and subcutaneous tissue; XIII: diseases of the musculoskeletal system and connective tissue; XIV: diseases of the genitourinary system; XV: pregnancy, childbirth and the puerperium; XVII: congenital malformations, deformations and chromosomal abnormalities; XVIII: symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified; XIX: injury, poisoning and certain other consequences of external causes; XX: external causes of morbidity and mortality; XXI: factors influencing health status and contact with health services.

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to 5.97). Small, non-significant increases were estimated for 'X Diseases of the respiratory system', 'IV Endocrine, nutritional and metabolic diseases', 'IX Diseases of the circulatory system' and 'XIV Diseases of the genitourinary system' (figure 2).

Bipolar disorder

For BD, the largest increases, more than threefold, were found for diagnoses in the categories 'I Certain infectious and parasitic diseases' (RR=3.66; 95% CI 1.51 to 8.88) and 'VI Diseases of the nervous system' (RR=3.35; 95% CI 2.20 to 5.10). The risks more than doubled for diagnoses of 'XI Diseases of the digestive system' (RR=2.23; 95% CI 1.61 to 3.09), 'X Diseases of the respiratory system' (RR=2.10; 95% CI 1.61 to 2.74) and 'XIV Diseases of the genitourinary system' (RR=2.03; 95% CI 1.52 to 2.71). In the case of 'IV Endocrine, nutritional and metabolic diseases' (RR=1.82; 95% CI 1.56 to 2.12), 'XIII Diseases of the musculoskeletal system and connective tissue' (RR=1.62; 95% CI 1.11 to 2.38), 'IX Diseases of the circulatory system' (RR=1.61; 95% CI 1.18 to 2.21) and 'III Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism' (RR=1.44; 95% CI 1.27 to 1.63), excess risks varied between 44% and 82%, respectively. No significant risk difference was found for 'II Neoplasms' (figure 2).

Depressive disorders

For DD, the RR was more than twofold for 'X Diseases of the respiratory system' (RR=2.21; 95% CI 1.26 to 3.88), and nearly doubled for 'XIII Diseases of the musculoskeletal system and connective tissue' (RR=1.83; 95% CI 1.37 to 2.44), 'IX Diseases of the circulatory system' (RR=1.45; 95% CI 1.25 to 1.69), 'II Neoplasms' (RR=1.43; 95% CI 1.17 to 1.77) and 'IV Endocrine, nutritional and metabolic diseases' (RR=1.43; 95% CI 1.30 to 1.57) (figure 2).

Schizophrenia

For SZ, the largest increase in PHC risks was identified for 'VI Diseases of the nervous system' (RR=1.97; 95% CI 1.21 to 3.22). Further substantially increased risk estimates were found for 'XII Diseases of the skin and subcutaneous tissue' (RR=1.57; 95% CI 1.02 to 2.41), 'IV Endocrine, nutritional and metabolic diseases' (RR=1.50; 95% CI 1.28 to 1.76), 'III Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism' (RR=1.47; 95% CI 1.21 to 1.79) and 'X Diseases of the respiratory system' (RR=1.33; 95% CI 1.17 to 1.51). The risk estimate for 'II Neoplasms' (RR=0.81; 95% CI 0.76 to 0.87) decreased by approximately 19%. For 'I Certain infectious and parasitic diseases', 'XI Diseases of the digestive system', 'XIV Diseases of the genitourinary system', 'VII Diseases of the eye and adnexa', 'IX Diseases of the circulatory system', 'VIII Diseases of the ear and mastoid process' and 'XIII Diseases of the musculoskeletal system and connective tissue', the changes in risks were smaller and inconclusive (figure 2).

Physical health burden at the population level

Based on the latest GBD data, we estimated a total number of 1 416 751 867 PHC diagnoses within the 312.5 million working-age populations of the included 32 European countries in year 2019 (table 1). The number of the total and excess PHC diagnoses associated with the selected MHDs based on the PAF estimates is reported by ICD-10 chapters in table 1. Online supplemental appendix E provides an overview of the mean, minimum and maximum PAFs estimated across the 32 European countries. Furthermore, we provide information on the excess physical health burden by country in online supplemental appendix F. The following is a short summary of the main results.

We estimated 83 965 058 excess PHC diagnoses associated with AUD, 48% linked to 'XI Diseases of the digestive system' and 42% linked to 'VI Diseases of the nervous system' (table 1). For BD, we estimated 66 817 245 excess PHC diagnoses, 45% linked to 'XX External causes of morbidity and mortality', 16% linked to 'VI Diseases of the nervous system' and 12% linked to 'XI Diseases of the digestive system' (table 1). For DD, the number of excess PHC diagnoses across all ICD-10 chapters was estimated at 66 222 801 in the European working-age population in year 2019. Of these, 37% were linked to 'VI Diseases of the nervous system' and 33% were linked to 'XI Diseases of the digestive system' (table 1). The number of excess PHC diagnoses associated with SZ was 4 931 564, 39% linked to 'VI Diseases of the nervous system', 17% linked to 'I Certain infectious and parasitic diseases' and 16% linked to 'XI Diseases of the digestive system' (table 1).

A reduction by 1% in the identified excess prevalence risks of PHCs may lead to a decrease in the physical health disparities by 0.85% for AUD, 0.86% for BD, 0.91% for DD and 0.99% for SZ. When comparing the estimated excess PHC diagnoses with scenarios of potential reductions in the underlying excess risks by 5%, 10% and 50%, excess PHC diagnoses were reduced by 3 590 230, 7 234 468 and 38 511 971 for AUD; 2 900 905, 5 838 423 and 30 821 458 for BD; 3 019 492, 6 066 849 and 31 502 250 for DD; and 244 993, 490 151 and 2 457 410 for SZ, respectively (figure 3). A full overview of the effects of different levels of potential excess risk reductions per ICD-10 chapter is available in online supplemental appendix G.

DISCUSSION

This is the first comprehensive synthesis and estimation of the physical health burden associated with frequent serious MHDs in Europe. We identified elevated risks for almost all available PHC categories based on existing literature, although some of these did not reach statistical significance. A conclusive RR of 3.3 ('XI Diseases of the digestive system') was estimated for AUD, while conclusive ranges of RRs varied on average between 1.4 ('III Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism') and 3.7 ('I Certain infectious and parasitic diseases') for BD, between 1.4 ('IV Endocrine, nutritional and metabolic diseases') and 2.2 ('X Diseases of the respiratory system') for DD, and between 0.8 ('II Neoplasms') and 2.0 ('VI Diseases of the nervous system') for SZ.

When extrapolating the synthesised levels of risk to the European working-age adult population with the given MHDs in year 2019, the number of PHC diagnoses associated with AUD, BD, DD and SZ was estimated at around 84 million, 67 million, 66 million and 5 million across all ICD-10 categories, respectively. These estimates reflect risk associations and not causality; therefore, we separately modelled potential partial % risk reductions and their expected population-level physical health effects. A 1% reduction in the excess prevalence risk across all comorbid physical conditions would yield an overall 1 941 775 fewer diagnoses for the four investigated MHDs in Europe.

The results of our study correspond to the findings of previous studies focusing on specific individual PHC areas. For example, previous meta-analyses estimated comparable increases in risks in patients with DD, BD and SZ for cardiovascular diseases.[4] We were further able to compare our results for endocrine/metabolic diseases and found them similar to previous meta-analyses.[30]

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Table 1 Estimated physical health burden of serious mental health disorders in the working-age European population by ICD-10 chapters for year 2019

	Diagnoses of physical health conditions in the working-age population, 2019	Depressive disorders			Bipolar disorder			Schizophrenia			Alcohol use disorders		
ICD-10 chapters	**Total (n)**	**Total (n)**	**Excess (n)**	**Excess (%)**	**Total (n)**	**Excess (n)**	**Excess (%)**	**Total (n)**	**Excess (n)**	**Excess (%)**	**Total (n)**	**Excess (n)**	**Excess (%)**
I Certain infectious and parasitic diseases	118 887 332	11 947 957	–	–	9 628 877	6 878 989	71.4	1 985 577	833 355	42.0	8 188 946	–	–
II Neoplasms	38 531 983	5 555 533	1 632 286	29.4	842 684	−54 158	−6.4	302 892	−70 425	−23.3	2 481 453	–	–
III Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism	81 510 304	8 399 187	–	–	2 793 153	844 934	30.3	1 162 856	372 827	32.1	7 174 483	1 784 454	24.9
IV Endocrine, nutritional and metabolic diseases	93 922 502	13 474 362	3 926 503	29.1	3 995 566	1 780 389	44.6	1 357 726	449 309	33.1	8 277 158	1 887 720	22.8
V Mental and behavioural disorders	69 615 633*	–	–	–	–	–	–	–	–	–	–	–	–
VI Diseases of the nervous system	207 840 085	45 969 041	24 550 233	53.4	15 940 697	10 988 190	68.9	3 936 636	1 930 210	49.0	49 437 721	35 390 802	71.6
VII Diseases of the eye and adnexa	18 391 729	1 842 517	–	–	251 720	−167 091	−66.4	193 791	15 285	7.9	319 235	−932 756	−292.2
VIII Diseases of the ear and mastoid process	54 195 811	5 430 141	–	–	1 247 899	–	–	559 497	34 275	6.1	3 764 547	–	–
IX Diseases of the circulatory system	21 399 373	3 086 963	934 863	30.3	797 021	299 900	37.6	223 454	15 444	6.9	1 515 840	86 785	5.7
X Diseases of the respiratory system	37 015 617	7 977 691	4 123 285	51.7	1 860 310	962 224	51.7	474 265	118 350	25.0	4 090 492	1 485 776	36.3
XI Diseases of the digestive system	296 715 801	51 878 502	21 799 590	42.0	15 230 388	8 282 132	54.4	3 662 667	794 377	21.7	60 249 624	40 000 570	66.4
XII Diseases of the skin and subcutaneous tissue	70 591 781	7 347 094	–	–	3 620 801	1 919 920	53.0	1 064 703	385 406	36.2	7 524 383	2 769 035	36.8
XIII Diseases of the musculoskeletal system and connective tissue	110 293 218	20 217 626	8 756 993	43.3	4 289 439	1 630 445	38.0	876 249	−185 608	−21.2	7 474 534	–	–
XIV Diseases of the genitourinary system	134 886 696	13 900 878	–	–	6 424 088	3 223 892	50.2	1 532 031	231 046	15.1	9 644 247	483 614	5.0
XV Pregnancy, childbirth and the puerperium	483 807	48 265	–	–	11 082	–	–	4655	–	–	34 853	–	–
XVI Certain conditions originating in the perinatal period	2 748 310	279 550	–	–	64 333	–	–	26 581	–	–	187 730	–	–
XVII Congenital malformations, deformations and chromosomal abnormalities	1 716 836	176 977	–	–	41 284	–	–	16 539	–	–	119 431	–	–

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Table 1 Continued

	Diagnoses of physical health conditions in the working-age population, 2019	Depressive disorders			Bipolar disorder			Schizophrenia			Alcohol use disorders		
XVIII Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified	–	–	–	–	–	–	–	–	–	–	–	–	–
XIX Injury, poisoning and certain other consequences of external causes	5 456 980	1 050 714	499 050	47.5	192 291	64 862	33.7	60 470	7713	12.8	1 389 932	1 009 059	72.6
XX External causes of morbidity and mortality	121 966 770	12 018 227	–	–	32 907 626	30 162 617	91.7	1 182 320	–	–	8 546 908	–	–
XXI Factors influencing health status and contact with health services	–	–	–	–	–	–	–	–	–	–	–	–	–
XXII Codes for special purposes	196 930	21 770	–	–	4863	–	–	1893	–	–	15 399	–	0.0
Total ICD-10	1 416 751 867	210 622 996	66 222 801	31.4	100 144 123	66 817 245	66.7	18 624 801	4 931 564	26.5	180 436 916	83 965 058	46.5

*Not considered for calculation of total cases by the International Statistical Classification of Diseases and Health Related Problems 10th (ICD-10).

Previous individual studies identified both increased and decreased risk associations for malignancies depending on the specific diagnosis,[21] which is likely to explain the observed differences and overall less conclusive RR results within our analyses across selected MHDs for the ICD-10 chapter 'II Neoplasms'. We also identified specific PHC areas where reduced risk was suggested for SZ, the same way as previously established, for instance, for musculoskeletal diseases[31] or specific cardiovascular diseases.[4] Furthermore, we estimated highly increased risks for liver diseases across selected MHDs, not only for AUD, likely related to problematic alcohol use and frequently co-occurring AUDs in the case of multiple MHDs.[32] Overall, the excess risk for PHCs associated with BD was considerably higher compared with the other investigated MHDs, likely related to some well-known medication side effects. For instance, the increased risk of genitourinary diseases is in line with a previous study on renal disease related to lithium treatment.[33] While the observation that BD carries higher risks of more comorbid physical diseases than the other selected MHDs is not a new observation, it is reassuring to confirm this and estimate the related health impact at the European population level. Our study does not allow direct estimation of the potential positive impact of potentially reduced PHCs on suicidal behaviour-related outcomes. However, existing literature suggests that reducing the physical health burden of MHDs may also have such added health and societal benefits.[34–36] Therefore, any future extrapolation of the current findings aiming to estimate associated mortality impacts should also incorporate this aspect.

Our methodology has several strengths as compared with previous studies. Comparable studies so far used estimates specific to particular countries, cohorts or disease combinations. Our approach is not only comprehensive across selected disease areas, but also enables international comparability of the estimates across all European countries. Further, we identified risk estimates based on international studies that were appraised to be of sufficient size and good quality, increasing the reliability of the overall RR estimates. For estimation of the excess physical health burden, we solely relied on indicators that are available across countries internationally. Therefore, methods could be easily revised and refined in the future, extended to other disease or geographical areas, or used for comparable economic burden extrapolations.

The present study is not without limitations. First, due to the study's large scope and the available resources, we conducted a targeted literature review that was not preregistered. To limit any potential bias in our estimates due to missed relevant studies, we subjected all full-text study screenings to additional reference searches and screened all identified literature reviews and meta-analyses for further relevant primary studies. The review methods followed a gold standard selection process according to the PRISMA statement, and beyond some specific predefined inclusion criteria (eg, large enough and representative sample, exclusion of duplicate estimates from the same sample) eligible studies were subjected to quality appraisal at the full-text stage. Second, similar to a recent review on the excess economic burden of physical comorbidities of MHDs,[22] we found high levels of heterogeneity of the available risk evidence pertinent to somewhat different disease categorisations (especially for DD), study methodologies, and underlying sociodemographic and country characteristics. While for meta-analyses of specific effect estimates this would limit the reliability of the study results, such heterogeneous findings are not uncommon in epidemiological synthesis

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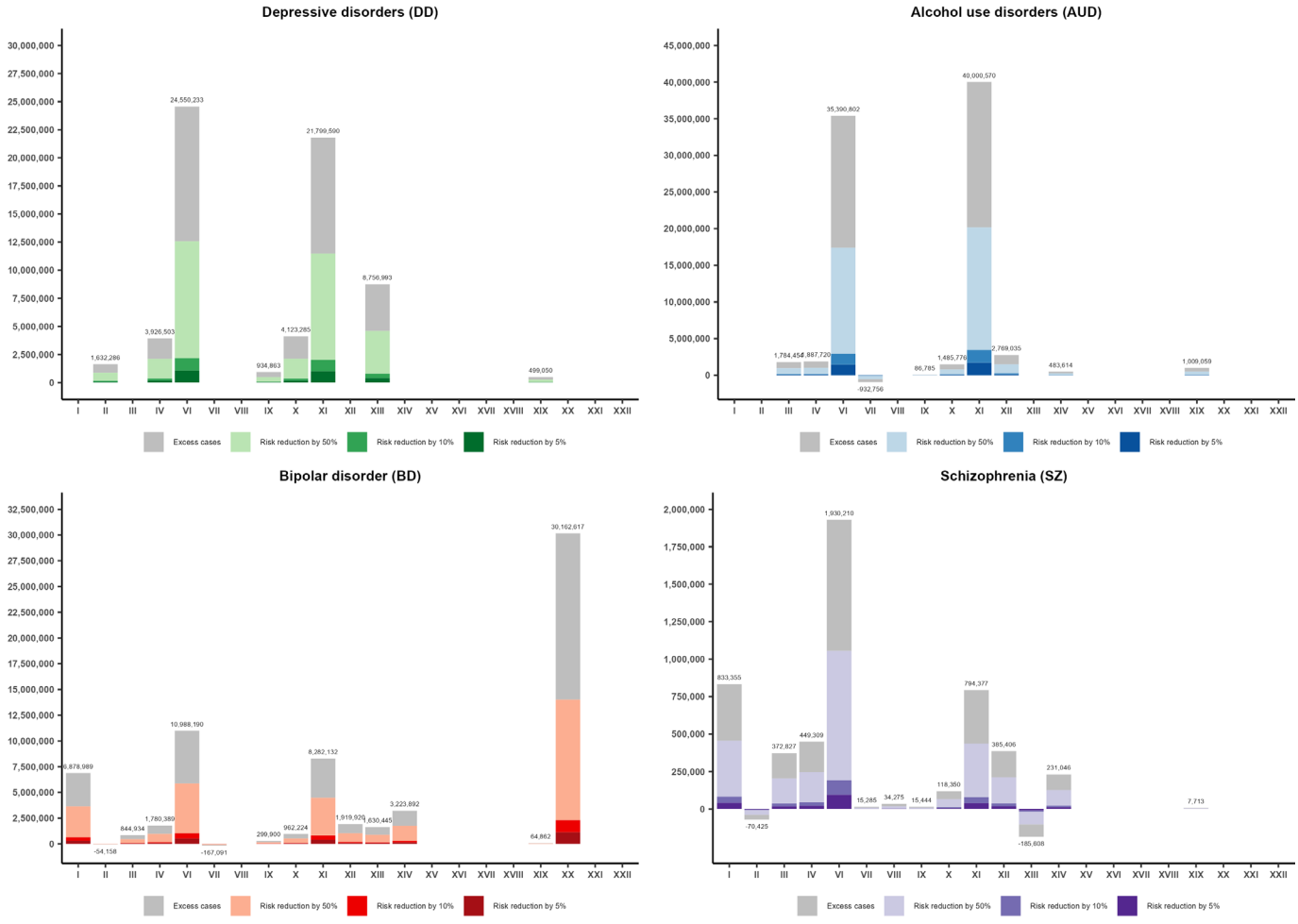

Figure 3 Population health impact of potential reductions in excess physical comorbidity risks by ICD-10 chapters. I: certain infectious and parasitic diseases; II: neoplasms; III: diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism; IV: endocrine, nutritional and metabolic diseases; VI: diseases of the nervous system; VII: diseases of the eye and adnexa; VIII: diseases of the ear and mastoid process; IX: diseases of the circulatory system; X: diseases of the respiratory system; XI: diseases of the digestive system; XII: diseases of the skin and subcutaneous tissue; XIII: diseases of the musculoskeletal system and connective tissue; XIV: diseases of the genitourinary system; XV: pregnancy, childbirth and the puerperium; XVII: congenital malformations, deformations and chromosomal abnormalities; XVIII: symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified; XIX: injury, poisoning and certain other consequences of external causes; XX: external causes of morbidity and mortality; XXI: factors influencing health status and contact with health services.

studies.[24] Estimates retrieved from prevalence studies and included in this synthesis were deemed sufficiently similar for pooling. Third, differences in the prevalence of PHCs were not routinely available by sex/gender, and diagnoses of PHCs were rarely reported according to socioeconomic status or by severity of the underlying MHD in a comparable way across countries. Therefore, no further refinement of the estimates accounting for these potential risk-modifying factors was feasible, or could sex-specific cancer estimates be included. Fourth, our estimates were based on diagnosed PHC cases. It is likely that considerable proportion of the comorbid physical health burden of MHDs is not identifiable in this way and will remain hidden, including those where diagnoses require regular screening attendance or health checks (eg, SZ and cancer). Fifth, a large proportion of the identified RR estimates originate from studies conducted outside Europe, stressing the need for more Europe-specific epidemiological evidence for more refined estimates.

Overall, the results highlight the enormous potential added value and broader population health benefits of any excess comorbid PHC risk reduction efforts for individuals with MHDs through, for example, investments into improved integrated mental and physical healthcare approaches and other targeted policy actions. Developed methods are suitable for systematic updates, extension towards other MHDs or geographical areas and refinement of the estimates once more stratified risk and disease prevalence evidence becomes available. Future epidemiological studies should focus on better definition and reporting of all diseases by ICD categories and present more granulated information by disease severity, disease co-occurrence and socioeconomic status. The provision of detailed information on diagnoses by ICD-10 codes in routine or through text mining of electronic health records will eventually also aid in determining and characterising excess physical health burden more accurately.

CLINICAL IMPLICATIONS

The immediate question posed by the present findings for clinical practice is how far primary or secondary prevention

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of episodes of MHDs can reduce the burden of PHCs[37] and how the delivery of physical healthcare can be improved in established MHDs. The kind of data we present here is essential to making arguments for changing policies towards more effective and efficient systems of care for clinical practice and health policy. The scale of the problem is simply not sufficiently appreciated and the potential for significantly better outcomes than what we currently accept is a promise we should not ignore based on the current findings. Apart from prevention, future research should address the presence of common risk factors achieved early in life, which may not only be genetic.

Contributors DW and JS conceptualised the study. DW, LIW, DH and CW acquired the data. DW analysed and visualised the data, supervised by JS. DW, CA, GMK, GMG and JS interpreted the results. DW and JS wrote the original draft of the manuscript. All authors contributed to the subsequent edits of the manuscript and approved the final version for submission. DW is guarantor.

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