Critical Appraisal: Mental Health Disorders

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Mapping Chronic Non-Communicable Disease Research Activities and their Impact
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Abbreviations

ACI	Academic citation index
ADHD	Attention Deficit Hyperactivity Disorder
CBT	Cognitive behavioral therapy
DALY	Disability-adjusted life year
DBS	Deep brain stimulation
EC	European Commission
ECT	Electro-convulsive therapy
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration (US)
GBD	Global Burden of Disease
ICD-10	International Disease Classifications, 10th revision
ICT	Information and Communication Technologies
IHME	Institute for Health Metrics and Evaluation
IMI	Innovative Medicines Initiative
JPND	EU Joint Programme – Neurodegenerative Disease Research
LSE	London School of Economics
MD	medical device
MENTH	Mental Health Disorders (used in bibliometric analysis)
MHD	Mental Health Disorder
mHealth	Mobile health applications
MS	Member State
MST	Magnetic seizure therapy
NCD	Non-communicable disease
NGO	Non-governmental organization
NIMH	National Institute of Mental Health
OCD	Obsessive compulsive disorder
PPP	Public-Private Partnership
R&D	Research and development
RFO	Research funding organization
rTMS	Repetitive transcranial magnetic stimulation
tDCS	Transcranial direct current stimulation
UB	Università Bocconi

UK	United Kingdom
UPEC	Université Paris-Est Créteil
US	United States
VNS	Vagus nerve stimulation

Executive Summary

Mental health disorders (MHDs) represent an estimated 28% of the non-communicable disease (NCD) burden worldwide, and there is evidence that this proportion will increase as the global population ages (Prince *et al.*, 2007). According to the 2010 Global Burden of Disease Study (GBD), the number of Disability-adjusted life years (DALYs) attributed to MHDs increased 37% between 1990 and 2010 (Murray *et al.*, 2013).

To better understand how the focus of MHD project-based research relates to the burden of disease at the Member State (MS) and European levels, we explored the disease-specific funding priorities of three large MSs – France, Germany and Italy – as well as the types of projects funded by the European Commission (EC) and the Innovative Medicines Initiative (IMI). More than three-quarters of the projects related to three diseases: Alzheimer's disease, schizophrenia and depression. While Alzheimer's disease and depression each represent a high proportion of the disease burden in the three MSs as well as across Europe, the focus on Alzheimer's disease research appears to be disproportionate, accounting for 50% of the MHD projects funded by these countries. The emphasis on schizophrenia appears to be based on the severe impact of this disease on individuals as well as society. Meanwhile, other MHDs, such as anxiety and alcohol abuse, also represent substantial disease burdens but are not the subject of much research among the projects in our sample.

Research in the private sector by pharmaceutical, biopharmaceutical and medical device companies is a critical aspect in mapping the full research landscape for MHDs. Six of the top nine European pharmaceutical companies by research and development (R&D) investment had MHD drugs in their pipelines. Most of these companies had stable to increasing levels of R&D investment, although strategic partnerships and divestments make it more difficult to clearly see trends in that regard. Of the 34 MHD molecules identified as being in the research pipelines of the top European and U.S. pharmaceutical companies, 15 were developed by European companies. As was seen in the project analysis, Alzheimer's disease dominated the R&D investment in MHDs, accounting for nearly half of the molecules (16), followed by schizophrenia with eight. These results must also be considered in light of the massive withdrawal of pharmaceutical companies from R&D in psychopharmacology since the start of the global financial crisis.

The situation with respect to medical devices is murkier, particularly in Europe, where there is no public database of devices that have received the CE mark. A search of clinical trials on MHD medical devices only revealed three trials for two devices, both deep brain stimulation (DBS) systems developed by U.S. medical device companies and designed to treat depression and obsessive compulsive disorder. Recent MHD device-related research efforts have targeted "personal health systems", such as mHealth applications, many of which are developed by smaller companies outside of the traditional medical device industry.

The ten European MHD experts we interviewed agreed that MHD research funding has increased in recent years but still remains far too low given the disease burden. They differed, however, regarding whether research priority should be based upon disease severity or frequency and also whether public health or clinical investigation should be emphasized. The need for better coordination and collaboration was highlighted, with several respondents calling for the creation of

a permanent coordinating structure at the European level devoted to MHDs, similar to the National Institute of Mental Health (NIMH) in the U.S.

In terms of private sector investment in MHDs, the experts we interviewed underscored the diminishing level of investment by the pharmaceutical industry, which will require greater public investment, particularly aimed at identifying biomarkers. There are few private charities focused on MHDs, but it was suggested that they could play a role in addressing stigma, which is seen as an impediment to public support for MHD research.

The impact of research funding investment was explored through bibliometric analysis and revealed that MHD research papers by European researchers accounted for 40% of the worldwide output, with the UK as the clear leader. Not surprisingly, smaller countries had higher levels of international collaboration; Switzerland had both a high level of collaboration and high research output. MHD research more than doubled between 2002 and 2013. In terms of subject matter of the research, depression, Alzheimer's disease and schizophrenia accounted for the largest shares of the MHD research papers. When examined in light of the burden of disease, there was generally poor correlation with the amount of research. For example, the burden of drug addiction and alcoholism are similar, but there is nearly 40% more research on drug addiction.

Each element of this Critical Assessment provides evidence designed to identify the existing MHD research landscape and to suggest what should drive the priorities of the future research agenda.

1 European Research Programs

In this section we present a purposive sample of funded research projects for MHDs. Given the vast number of projects that have been funded in recent years, it would not be feasible to provide or analyze a comprehensive sample. Thus, we sought to identify a maximum of 100 projects that would provide an indication of the focus of mental health disorders (MHD) research at the Member State (MS) and European levels.

1.1 Method: RFO Research Project Selection

We chose to focus on projects that studied one of 10 MHDs for which the disease burden as measured in DALYs has been identified in the 2010 Global Burden of Disease study and that were funded at a minimum of €100 000 for the period 2006-2013. The MHDs included were: addiction, alcohol, Alzheimer's disease, anxiety, bipolar disorder, depression, eating disorders, schizophrenia, ADHD and suicide (Table 1.1).

Our MS sample was drawn from the project funding data we obtained through the Mapping_NCD survey tool (WP1) for three large European countries: France, Germany and Italy. We limited our analysis to this small set of Member States so that we would have a sufficiently large number of projects from each country in order to get a sense of the prioritization among the different MHDs and also to be able to compare it to the burden of disease in these countries as measured by DALYs.

The data from the three MSs was supplemented with data collected regarding large-scale, disease-specific European projects undertaken by the European commission (EC) and the Innovative Medicines Initiative (IMI). We searched the Cordis database to identify a selection of disease-specific projects receiving the highest funding in the time period 2006-2013. IMI projects were identified through its website. Projects that covered multiple diagnoses or MHDs generally were excluded.

We examined the disease burden in DALYs for the 10 MHDs at the MS-level for the three countries and also for the Western European region in order to compare how the program priorities related to the disease level.

Table 1.1 Codes for MHDs included in project sample

Mental health disorder	*Code*
Drug use and other addictions	**ADD**
Alcohol use	**ALC**
Alzheimer's disease and other dementias	**ALZ**
Anxiety disorder	**ANX**
Bipolar disorder	**BIP**
Unipolar depression	**DEP**
Eating disorder	**EAT**
Attention-deficit hyperactivity disorder	**HYP**
Schizophrenia	**SCH**
Suicide and self-harm	**SUI**

1.2 Results: MHD Research Programs

We identified and analyzed 88 projects sponsored by three MSs (France, Germany and Italy) or by the EC or the IMI at the European level (Figure 1.1) that focused one of 10 MHDs. Overall, projects related to Alzheimer's disease (33), schizophrenia (21) and depression (14) comprised more than three-quarters of the projects (Figure 1.2).

Figure 1.1 Project sample by sponsor (n=88)

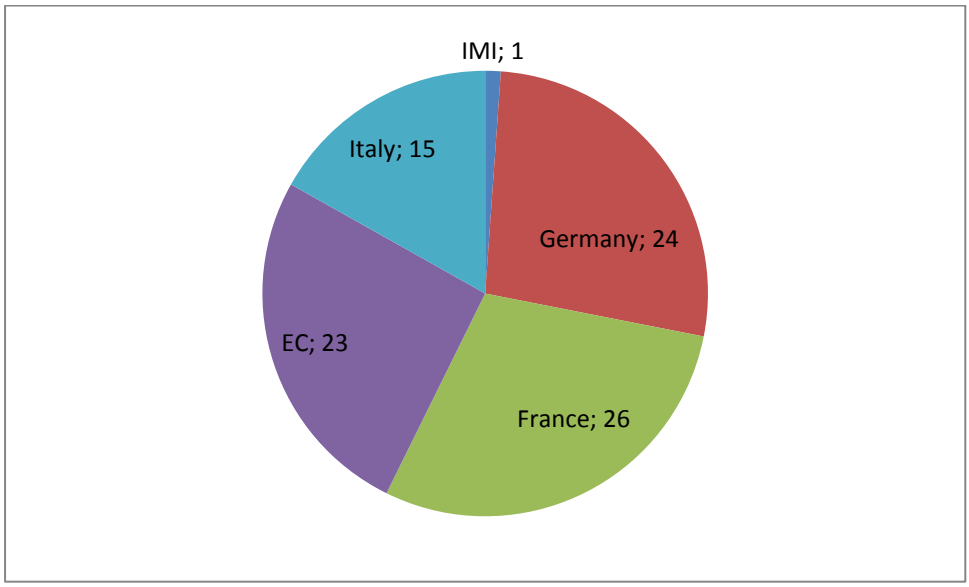
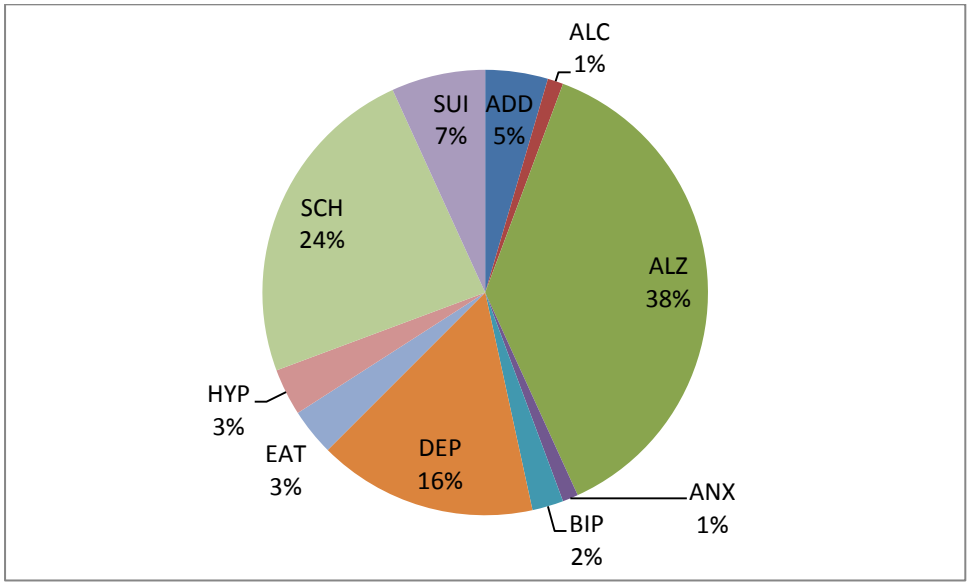


Figure 1.2 Project sample by MHD (n=88)



To provide context, we considered the burden of disease for each of the 10 MHDs by MS and by the Western Europe region (Table 1.2).

Table 1.2 Burden of disease for 10 MHDs in France, Germany, Italy and the Western Europe region

France		Germany		Italy		W. Europe	
MHD	% total DALYs	MHD	% total DALYs	MHD	% total DALYs	MHD	% total DALYs
DEP	4.75	DEP	4.57	DEP	4.82	DEP	4.64
SUI	2.68	ALZ	1.91	ALZ	2.46	ALZ	2.38
ALZ	2.66	ANX	1.79	ADD	1.43	ANX	1.82
ANX	2.6	SUI	1.63	ANX	1.4	SUI	1.61
ALC	1.96	ALC	1.5	SUI	0.88	ADD	1.45
ADD	1.03	ADD	1.12	SCH	0.84	ALC	1.28
SCH	0.84	SCH	0.81	BIP	0.66	SCH	0.85
BIP	0.64	BIP	0.61	ALC	0.4	BIP	0.66
EAT	0.42	EAT	0.29	EAT	0.27	EAT	0.35
HYP	0.019	HYP	0.015	HYP	0.016	HYP	0.018
10 MHDs	17.599	**10 MHDs**	14.245	**10 MHDs**	13.176	**10 MHDs**	15.058

Details of the projects are presented in Tables 1.3 through 1.12 in descending order by funding level.

1.2.1. Addiction (ADD)

Four MS-level projects were identified in France and Italy, three of which focused upon the etiology of substance abuse and one on treatment of cocaine addiction (Table 1.3). Among the 10 MHDs, addiction ranks third in Italy, accounting for 11% of the disease burden.

1.2.2 Alcohol (ALC)

Only one project related to alcohol abuse was included in our sample (Table 1.4). It was an FP7 project in which 14 countries participated, including Germany, Italy and France. Within the Western European region, problematic alcohol abuse contributes 9% to the disease burden of the 10 MHDs, reaching 11% in France.

1.2.3 Alzheimer's disease (ALZ)

Perhaps unsurprisingly, projects related to Alzheimer's disease dominated our sample, both at the MS level, with 13 projects each in Germany and France and six in Italy (Table 1.5). Most of these projects focused on disease etiology or development of new treatments.

The largest project in terms of funding was the IMI's Pharma-Cog project, which is designed to predict the cognitive properties of potential new drug treatments in early clinical development for neurodegenerative diseases. The funding for the five-year project exceeded €30 million, with 31 funding recipients in 12 European countries.

Alzheimer's disease presents a heavy disease burden among the 10 MHDs studied in each of the study countries and in the European region overall, accounting for 13-19% of DALYs for MHDs.

1.2.4 Anxiety (ANX)

Only one project devoted to anxiety was identified in our sample (Table 1.6). It was an EC FP7 project led by France with four other partner countries that researched etiology in terms of

developmental risk factors as well as treatment. The lack of other identified projects was surprising given the heavy burden of disease, ranging from 11-15% of MHD DALYs.

1.2.5 Bipolar Disorder (BIP)

Two projects focusing on bipolar disorder were identified, including one EC FP7 project devoted novel disease management in the form of personalized monitoring systems that included six EU MS partners, including the three MSs in our national project sample (Table 1.7). A French project explored disease progression in patients with bipolar disorder as they age. While the disease burden for this MHD is relatively low (around 4%), the consequences for affected individuals and their families can be significant.

1.2.6 Depression (DEP)

Fourteen depression-related projects were identified in our sample, including four EC FP7 projects and ten MS projects distributed among the three MSs (Table 1.8). The large number of projects reflects the fact that depression constitutes the heaviest disease burden in each of the MSs – from 27% of the MHD DALYs in France to 37% in Italy and 31% across Western Europe. The projects mostly focused on etiology and new treatments, both pharmaceutical and eHealth, which are critical given the fact that there have been few new and innovative treatments for depression in many years.

1.2.7 Eating disorders (EAT)

We found three projects on eating disorders in our sample, including an EC FP6 project with eight EU partners that focused on care for women with these disorders (Table 1.9). At the MS level, two treatment-focused projects were identified, including one using transcranial magnetic stimulation. While the disease burden is relatively low for eating disorders, averaging 2% in the three MSs in our sample, the challenge in identifying effective treatments underscores the importance of research in this area.

1.2.8 Schizophrenia (SCH)

Twenty-one projects studying schizophrenia were identified, including nine EC projects (eight FP7 projects and one FP6 project) and 12 projects mostly in Germany and France, with one in Italy (Table 1.10). These projects largely focused on etiology and treatment, including identification of biomarkers to aid in treatment decisions and a large-scale genome study. While the burden of schizophrenia accounts for 5-6% of DALYs among the 10 MHDs studied – clearly much lower than depression, Alzheimer's and anxiety – this relatively low burden does not capture the true burden of schizophrenia on individuals and their families and society.

1.2.9 Attention Deficit Hyperactivity Disorder (HYP)

Three projects studying ADHD were identified in our sample, including two five-year FP7 projects (Table 1.11). The projects focused on different aspects of the disorder, including aggression subtyping, treatment of adults and effects of drug use. ADHD ranks 10th among the 10 MHDs studied, accounting for less than 1% of the DALY burden in the three MSs and across Western Europe.

1.2.10 Suicide (SUI)

Six projects studying suicide were found in our sample, with three EC FP7 projects and three MS projects (two in France and one in Italy) (Table 1.12). Prevention was the major focus of the studies,

although one of the French studies explored the molecular genetics of suicidality. The burden of suicide varies across the MSs in our sample, from a high of 15% of MHD DALYs in France to less than half that in Italy (7%).

Table 1.3 Research Programs for Addiction (2006-2013)

Funder(s)	Recipient type	Level of collaboration	Partner countries	Project Title	Research area	Timeframe	Funding
Italian MoH	Government / Public	National		Childhood, adolescence and psychopathology: effect of maternal care, psychiatric drugs and substance abuse on brain development	Aetiology	2010	768 810 €
French MoH	Government / Public	National		Study of clinical and genetic factors associated with emergence of psychotic symptoms in cocaine addicts	Aetiology	2010	426 000 €
French MoH	Government / Public	National		Can failures and successes in cocaine withdrawals in hospital settings be predicted?	Treatments, Health and social services	2012	326 598 €
Italian MoH	Government / Public	National		"Techno Cannabis" as a drug of abuse: determining the effect of synthetic cannabinoids on non-biological and biological matrices, both living and cadavers, and forensic-toxicological issues related to the spread of "smart drugs".	Aetiology, Prevention	2009	111 262 €

Table 1.4 Research Programs for Alcohol (2006-2013)

Funder(s)	Recipient type	Level of collaboration	Partner countries	Project Title	Research area	Timeframe	Funding
EC FP7-HEALTH	Government/public; private non-profit; commercial n=33	European	ES, DE, AT, SE, CH, UK, NL, IT, PL, SI, NO, HU, FI, FR	AMPHORA Alcohol Measures for Public Health Research Alliance	Aetiology, Diagnosis/screening, Treatments, Prevention, Policy	2009-2012	2 996 687 €

Table 1.5 Research Programs for Alzheimer's disease (2006-2013)

Funder(s)	Recipient type	Level of collaboration	Partner countries	Project Title	Research area	Timeframe	Funding
Innovative Medicines Initiative (IMI); European Federation of Pharmaceutical Industries and Associations (EFPIA); Other	Government/public, private non-profit; commercial n=31	European	BE, CH, UK, DK, UK, FR, LU, GR, ES, IT, NL, DE	Pharma-Cog Prediction of cognitive properties of new drug candidates for neurodegenerative diseases in early clinical development	Treatments	2010-2014	30 715 556 €
German Federal Ministry of Education and Research	Government / Public	National		Joint project: Dementia Competence Network - Epidemiology	Diagnosis/ Screening	2007	11 276 750 €
German Federal Ministry of Education and Research	Government / Public	National		Joint project: A new concept for the treatment of neuroinflammatory and neurodegenerative diseases	Treatments	2013	5 014 437 €
German Federal Ministry of Education and Research	Government / Public	National		Joint project: Dementia Competence Network	General	2011	4 340 362 €
German Federal Ministry of Education and Research	Government / Public	National		Joint project: A new concept for the treatment of neuroinflammatory and neurodegenerative diseases ; Project: Development of antagonists for the orphanen G Protein - Coupled Receptor GPR17	Treatments	2013	3 941 113 €
French MoH	Government / Public	National		Study of the vascular component in the emergence of Alzheimer's and related diseases	Aetiology	2012	2 273 585 €
French MoH	Government / Public	National		Longitudinal study using multimodal imagery in early Alzheimer's: biomarkers for detection and progression and physiopathological mechanisms	Aetiology		2 246 642 €
German Federal Ministry of Education and Research	Government / Public	National		A 12-week, multicenter, randomized, double-blind, placebo-controlled trial for treatment of apathy in Alzheimer's disease with bupropion	Treatments	2009	1 798 307 €
French MoH	Government / Public	National		Trial to prevent cerebral lesions of vascular origin observed by MRI by reducing blood pressure in individuals with early cognitive deficits	Prevention	2010	1 524 000 €
German Federal Ministry of Education and Research	Government / Public	National		NEURON-composite: neurodengenerativen diseases	General	2009	1 313 102 €

German Federal Ministry of Education and Research	Government / Public	National		NorChlor-fluoro-HomoEpiBatidin - a potential positron emission tomography (PET) marker of early Alzheimer's dementia,	Aetiology	2008	1 150 405 €
French MoH	Government / Public	National		Use of targeted quantitative proteomics and stable isotope markers for diagnosis and study of neurological diseases, particularly Alzheimer's	Aetiology	2010	966 000 €
German Federal Ministry of Education and Research	Government / Public	National		Joint project: Dementia Competence Network	General	2012	898 612 €
Italian MoH	Government / Public	National		Synaptic alterations in Alzheimer's disease: the new generation of in vitro models for the identification of new targets (Synad)	Aetiology	2010	808 543 €
French MoH	Government / Public	National		Co-lesions in Alzheimer's and related diseases	Aetiology	2012	782 008 €
German Federal Ministry of Education and Research	Government / Public	National		Composite "NSAIDS" in disease-related Dementia Competence Network	Treatments	2007	717 354 €
French MoH	Government / Public	National		Role of central and peripheral anti-amyloid inflammatory and immune reactions in early Alzheimer's	Aetiology	2010	710 000 €
German Federal Ministry of Education and Research	Government / Public	National		Joint project: Dementia Competence Network	General	2011	650 863 €
German Federal Ministry of Education and Research	Government / Public	National		NEURON composite nano Brain: Transport of Alzheimer drugs across the blood-brain barrier by nanoparticles	Treatments	2010	637 700 €
German Federal Ministry of Education and Research	Government / Public	National		Collaborative project: , Subproject 1: COMPARE - correlation impedimetric measurements with Alzheimer-typical pathological changes in cells and organotypic hippocampal slice cultures	Aetiology	2008	578 465 €
French MoH	Government / Public	National		Neuroinflamation and cognitive decline in Alzheimer's disease: Pilot study of PET imagery of translocator protein TSPO using [18 F] DPA-714 (NICAD)	Aetiology	2013	571 042 €
German Federal Ministry of Education and Research	Government / Public	National		NEURON composite: development of new chemical and optical tools for the study and manipulation of lateral diffusion of glutamate receptors and synaptic transmission in different models of neuronal degeneration	Aetiology	2010	538 027 €
French MoH	Government / Public	National		Study of imagery markers in the very early phases of dementia in retired agricultural workers living in rural Gironde and	Aetiology	2011	481 000 €

				participating in the epidemiological cohort AMI: a longitudinal study			
French MoH	Government / Public	National		Illiteracy and vulnerability in developing Alzheimer's disease: contribution of PET imagery	Aetiology	2012	360 162 €
French MoH	Government / Public	National		Evaluation of driving abilities in "ecological setting" (time series?) in subjects with mild or moderate Alzheimer's disease	Diagnosis/ screening	2011	319 000 €
French MoH	Government / Public	National		Early affective symptoms in Alzheimer's disease: characterization by TEP F18 AV45	Aetiology	2010	298 000 €
Italian MoH	Government / Public	National		Laboratory medicine, genetic, neuropsychological and clinical assessment for the early detection, prediction of course and response to therapy in subjects at risk for Alzheimer's disease	Aetiology, Diagnosis/ Screening, Treatments	2007	290 000 €
Italian MoH	Government / Public	National		PROGRESSION OF ALZHEIMER'S DISEASE IN THE COURSE OF AGING: GOING BEYOND BETA AMYLOID TO IDENTIFY NEW TARGETS FOR THERAPY	Aetiology	2009	279 660 €
French MoH	Government / Public	National		Plasma tau protein and biomarkers for degradation of the APP (Amyloid precursor protein) for the diagnosis and prognosis in Alzheimer's disease. Ancillary study to BALTAZAR study (Biomarker of Amyloid pepTide and AlZheimer's diseAse Risk).	Aetiology	2013	273 978 €
French MoH	Government / Public	National		Evaluation of non-drug therapies in Alzheimer's disease: Long-term follow up (3 years) of patients treated in the context of a trial	Treatments	2011	272 000 €
Italian MoH	Government / Public	National		Does palmitoietanolamide represent a novel approach for the treatment of Alzheimer's disease? Study of anti-inflammatory and neuroprotective of palmitoylethanolamide in transgenic mouse models of Alzheimer's	Treatments	2009	192 958 €
Italian MoH	Government / Public	National		BETA AMYLOID: THE MAIN CAUSE OF NEURODEGENERATION IN ALZHEIMER'S DISEASE OR A NEW NEUROMODULATOR?	Aetiology	2007	161 868 €
Italian MoH	Government / Public	National		Nitrosative and oxidative damage to mitochondrial proteins in models of cell senescence and in subjects with Alzheimer's disease: preclinical study of natural forms and new synthetic analogues of vitamin E.	Aetiology, Treatments	2007	119 000 €

Table 1.6 Research programs for Anxiety (2006-2013)

Funder(s)	Recipient type	Level of collaboration	Partner countries	Project Title	Research area	Timeframe	Funding
EC FP7-HEALTH	Government/public; private non-profit n=6	European	FR, DE, CH, IE, ES	DEVANX Serotonin and GABA-B receptors in anxiety: From developmental risk factors to treatment	Aetiology, Treatments	2008-2012	2 841 578 €

Table 1.7 Research Programs for Bipolar Disorder (2006-2013)

Funder(s)	Recipient type	Level of collaboration	Partner countries	Project Title	Research area	Timeframe	Funding
EC FP7-ICT	Government/public; private non-profit; commercial n=10	European	IT, CH, DE, ES, FR, IE	PSYCHE Personalised monitoring Systems for Care in mental Health	Disease Management, Treatments, Prevention	2010-2013	2 909 969 €
French MoH	Government / Public	National		Evolution of cognitive and neurobiological aspects in individuals with bipolar disorder as they age	Disease management	2012	801 372 €

Table 1.8 Research Programs for Depression (2006-2013)

Funder(s)	Recipient type	Level of collaboration	Partner countries	Project Title	Research area	Timeframe	Funding
EC FP7-HEALTH	Government/public; private non-profit; commercial n=21	European	NL, DE, AT, BE, UK, IT, BG, IE, FR, SE	MOODINFLAME Early diagnosis, treatment and prevention of mood disorders targeting the activated inflammatory response system	Aetiology, Treatments	2008-2013	10 235 585 €
EC FP7-HEALTH	Government/public; private non-profit n=14	European	NL, SE, DE, UK, ES, IE, CH, PL, PT, FR, BE	E-COMPARED European-COMPARative Effectiveness research on online Depression	Treatments	2014-2016	5 827 000 €
EC FP7-ICT	Government/public; private non-profit; commercial n=10	European	UK, ES, IT, RO	HELP4MOOD A Computational Distributed System to Support the Treatment of Patients with Major Depression	Treatments, Disease management	2011-2013	2 819 993 €
EC FP7-ICT	Government/public; commercial n=7	European	NL, CH, IE, PT, SE	ICT4DEPRESSION User-friendly ICT tools to enhance self-management and effective treatment of depression in the EU	Diagnosis/screening, Disease management, Treatments	2010-2012	2 701 845 €
German Federal Ministry of Education and Research	Government / Public	National		Randomized, multicenter, active-controlled, single-blind clinical trial to compare the "Early Medication Change" (EMC) strategy with "Treatment as Usual" (TAU) in patients with major depression - the EMC trial	Treatments	2009	2 370 341 €
German Federal Ministry of Education and Research	Government / Public	National		Coordinated treatment of senile depression in primary care	Treatments	2013	1 274 660 €
German Federal Ministry of Education and Research	Government / Public	National		NEURON composite : pre-, peri-and postnatal stress in human and non-human offspring: A translational approach to the study of epigenetic effects on depression, sub-projects 1 and 3b	Aetiology	2011	857 876 €
French MoH	Government / Public	National		Evaluation of the role of the interaction between genetic vulnerability and stressful life events in the risk of post-partum depression	Aetiology	2010	672 000 €
French MoH	Government / Public	National		Studies of ribonucleic acid messengers as serum biomarkers in depression	Aetiology	2010	492 000 €

Italian MoH	Government / Public	National		Ketamine as a tool to analyze the nature of the rapid antidepressant. Implications for the treatment of treatment-resistant depression	Treatments	2012	407 521 €
Italian MoH	Government / Public	National		Innovative strategies for depression treatment: novel pharmacological targets and preclinical studies for the personalization of therapy	Treatments	2007	400 000 €
Italian MoH	Government / Public	National		Depressive features in medical (neurological and oncological) patients recruited in the general medical setting: reliability of diagnostic criteria, predictive role of biological markers, and effect of treatment with antidepressants	Aetiology, Diagnosis/ Screening, Treatments	2007	400 000 €
French MoH	Government / Public	National		Acute myocardial Necrosis and Depression: antiplatelet effect of Reuptake inhibition Of Serotonin	Treatments	2011	309 000 €
Italian MoH	Government / Public	National		Implementation of a stepped collaborative care for the treatment of depression in primary and secondary care	Treatments	2007	300 000 €

Table 1.9 Research Programs for Eating Disorders (2006-2013)

Funder(s)	Recipient type	Level of collaboration	Partner countries	Project Title	Research area	Timeframe	Funding
EC FP6-MOBILITY	Government/public; commercial n=9	European	DE, FR, CZ, UK, HU, PT, NL, CH	INTACT Individually Tailored Stepped Care for Women with Eating Disorders	Aetiology, Diagnosis/ Screening, Treatments, Disease Management	2007-2011	3 146 798 €
German Federal Ministry of Education and Research	Government / Public	National		Joint project: composite Psychotherapy: Eating Disorders Diagnostic and Treatment Network“ : Project 0, Project 3, Project 11	Treatments	2006	1 833 609 €
Italian Bank F	Government / Public	National		Transcranial Magnetic Stimulation in persons affected by food problems	Treatments	2012	102 312 €

Table 1.10 Research Programs for Schizophrenia (2006-2013)

Funder(s)	Recipient type	Level of collaboration	Partner countries	Project Title	Research area	Timeframe	Funding
EC FP7-HEALTH	Government/public; commercial n=26	Global	NL, UK, DE, TR, ES, FR, BE, GR, AT, CH, HK, IE, IT, AU	EU-GEI European Network of National Schizophrenia Networks Studying Gene-Environment Interactions	Aetiology	2010-2015	11 616 855 €
EC FP7-HEALTH	Government/public; private non-profit; commercial n=21	Global	NL, UK, FR, DE, DK, ES, AT, IL, PL, CH, IT, RO, CZ, BG	OPTIMISE OPtimization of Treatment and Management of Schizophrenia in Europe (OPTiMiSE)	Treatments, Disease management, Health and social services	2010-2016	11 187 685 €
EC FP7-HEALTH	Government/public; commercial n=11	Global	DE, CH, UK, FI, IT, AU	PRONIA Personalised Prognostic Tools for Early Psychosis Management	Diagnosis/screening, prevention	2013-2018	6 000 000 €
EC FP7-HEALTH	Government/public; commercial n=10	European	UK, IS, DE, DK, NL	CRESTAR Pharmacogenomic biomarkers as clinical decision making tools for clozapine treatment of schizophrenia	Aetiology, diagnosis/screening, treatments	2011-2015	6 000 000 €
EC FP7-HEALTH	Government/public; commercial n=11	European	IT, GR, DE, CH, FR	TRIMAGE A dedicated trimodality (PET/MR/EEG) imaging tool for schizophrenia	Diagnosis/ Screening, Treatments	2013-2017	5 994 380 €
EC FP7-HEALTH	Government/public; private non-profit; commercial n=21	European	NL, DE, UK, FR, ES, IT, BE	PERS Paediatric European Risperidone Studies	Treatments	2010-2015	5 600 000 €
EC FP7-HEALTH	Government/public; commercial n=10	European	ES, SE, DE, IE, FR, IT	MINDVIEW Multimodal Imaging of Neurological Disorders	Diagnosis/screening	2013-2017	5 381 872 €
EC FP7-HEALTH	Government/public; commercial n=8	European	DK, FI, DE, ES, UK	METSY Neuroimaging platform for characterisation of metabolic co-morbidities in psychotic disorders	Aetiology, diagnosis/screening, prevention, treatments	2013-2017	4 233 869 €

EC FP6-LIFESCIHEALTH	Government/public; private non-profit; commercial n=7	European	IS, UK, FI, DE	SGENE A large scale genome-wide association study of schizophrenia addressing variation in expressivity and contribution from environmental factors	Aetiology	2006-2010	2 499 958 €
German Federal Ministry of Education and Research	Government / Public	National		A randomized controlled trial to investigate the efficacy of antipsychotic combination treatment of olanzapine and amisulpride in acutely ill patients with schizophrenia	Treatments	2012	2 495 807 €
German Federal Ministry of Education and Research	Government / Public	National		Testing the efficacy of olanzapine and aripiprazole Quentiapin compared to conventional antipsychotics	Treatments	2009	1 953 017 €
German Federal Ministry of Education and Research	Government / Public	National		Evaluate the effectiveness of the conversion against the continuation of antipsychotic treatment in patients with schizophrenia who have not responded adequately after 2 weeks on treatment	Treatments	2009	1 603 496 €
German Federal Ministry of Education and Research	Government / Public	National		NEURON composite development of novel strategies for the treatment of schizophrenia based on the genetic variability of the neural cell adhesion molecule NCAM and its post-translationally modifying enzymes, TP1	Treatments	2011	709 110 €
German Federal Ministry of Education and Research	Government / Public	National		Collaborative project: Social action, sub-projects 1, 2, 4: A look behind the mirror: Neurocognitive mechanisms of social actions and their dysfunction in schizophrenia	Aetiology	2008	626 983 €
German Federal Ministry of Education and Research	Government / Public	National		Collaborative project: research network "Psychotherapy of positive symptoms of psychotic disorders"	Treatments	2006	601 448 €
Italian MoH	Government / Public	National		Multicenter study on factors that affect the real life social functioning of people with diagnosis of schizophrenia	Aetiology, Diagnosis/ Screening	2010	596 107 €
French MoH	Government / Public	National		Cognitive remediation and professional reintegration in schizophrenia patients	Treatments	2012	469 689 €

French MoH	Government / Public	National		Effectiveness of a joint crisis plan in preventing relapses in patients with schizophrenia and schizoaffective problems	Prevention, Disease management	2013	453 562 €
French MoH	Government / Public	National		Influence of environmental factors on the prevalence, risk and clinical manifestations of schizophrenia	Aetiology	2010	420 000 €
French MoH	Government / Public	National		Validation study of the use of multimodal MRI-guided repetitive transcranial magnetic stimulation in the treatment of drug-resistant complex hallucinations in children and adults	Treatments	2011	327 000 €
French MoH	Government / Public	National		Evaluation and validation of a social cognitive battery to characterize the functioning of patients with schizophrenia	Diagnosis/ screening	2011	308 000 €

Table 1.11 Research Programs for ADHD (2006-2013)

Funder(s)	Recipient type	Level of collaboration	Partner countries	Project Title	Research area	Timeframe	Funding
EC FP7-HEALTH	Government/public; private non-profit; commercial n=23	Global	NL, UK, ES, DE, NO, US, EE, IS, FR, CH, IT	AGGRESSOTYPE Aggression subtyping for improved insight and treatment innovation in psychiatric disorders	Aetiology, prevention, treatments	2013-2018	6 000 000 €
German Federal Ministry of Education and Research	Government / Public	National		A randomized controlled multicenter trial on the multimodal treatment of adult attention-deficit hyperactivity disorder	Treatments	2006	3 454 680 €
EC FP7-HEALTH	Government/public; private non-profit; commercial n=16	European	UK, NL, DE, IE, BE, IT, FR, HU	ADDUCE Attention Deficit Hyperactivity Disorder Drugs Use Chronic Effects	Treatments	2010-2015	2 999 559 €

Table 1.12 Research Programs for Suicide (2006-2013)

Funder(s)	Recipient type	Level of collaboration	Partner countries	Project Title	Research area	Timeframe	Funding
EC FP7-HEALTH	Government/public; private non-profit; commercial n=16	Global	UK, NL, DE, FR, ES, IT, CA	STOP Suicidality: Treatment Occurring in Paediatrics	Diagnosis/screening, Disease management, Treatments	2010-2014	3 000 000 €
EC FP7-HEALTH	Government/public; private non-profit; commercial n=14	European	DE, EE, UK, BE, NL, IE, HU, SI, PT, AT	OSPI-EUROPE Optimizing suicide prevention programs and their implementation in Europe	Diagnosis/screening, Prevention, Treatments	2008-2013	2 991 727 €
EC FP7-HEALTH	Government/public; private non-profit; commercial? n=12	European	SE, AT, EE, FR, DE, HU, IE, IL, IT, RO, SI, ES	SEYLE Saving and Empowering Young Lives in Europe: Promote health through prevention of risk-taking and self-destructive behaviors	Prevention, Treatments	2009-2011	2 983 941 €
French MoH	Government / Public	National		Evaluation of the effects of ketamine in emergency treatment of suicidal ideation: Multicentric randomized double-blind study	Treatments	2013	357 459 €
French MoH	Government / Public	National		Molecular genetics in suicidality: study of the association between aggressive impulsivity and genes in the serotoninergic system	Aetiology	2011	295 000 €
Italian MoH	Government / Public	National		Prevention of suicide risk in psychiatric patients during and after the discharge	Prevention	2008	151 740 €

1.3 Discussion and Conclusion

Our purposive sample of recent disease-specific projects in three large MSs and the EC and IMI provided insights into the MHD priorities at the national and European levels and allowed us to compare the relative project focus to the disease burden at both levels. By selecting MS projects that had been identified in the survey phase of the Mapping_NCD project, we were able to deepen and extend the analysis undertaken in the Impact Assessment.

While depression accounts for the heaviest disease burden among MHDs in France, Germany and Italy, as well as across the Western European region, only 16% of the projects studied depression. Alzheimer's disease dominated the project portfolios in all three MSs, comprising half of the projects identified for each country. No EC FP6 or FP7 Alzheimer's projects were included in our sample, but the EC is part of the governance structure of the public-private partnership (PPP) IMI, which has a very large and well-funded project focused on treatments for neurodegenerative diseases in early clinical development. IMI2 will include additional projects focusing on MHDs.

It was surprising that there were so few projects related to anxiety and alcohol use given their respective disease burdens. Anxiety is widely under recognized and undertreated according to several European studies. (Lecrubier, 2007). Moreover, drug addiction accounts for almost 40% more research than alcoholism despite having roughly the same disease burden (Rajendram *et al.,* 2006).

Overall, the national level projects tended to be more focused on clinical investigation of etiology and treatments than on provision of health services, and none of them were collaborative. However, EU-level platforms, including the Joint Programming Initiative (JPI) for neurodegenerative disease research (JPND) or ERA-Net NEURON, which includes MHD research but covers a much broader range of disorders, have facilitated international collaborations among MS researchers. Because the projects included in our sample were disease-specific, they did not include multi-disorder projects or those that addressed MHDs generally (e.g., financing of mental health care systems). Obviously, such projects constitute an important part of the research picture. However, because we wanted to explore research project focus in light of the disease burden of specific disorders, we limited inclusion to the 10 MHDs.

Among the EC-funded projects, it is interesting to note the MS affiliations for the lead partners of the identified FP6 and FP7 projects because it may provide insight into the areas of particular interest and research focus for the MS. The Netherlands dominated as lead partner on seven of the 23 projects, followed by the UK with four. Among the MSs whose national projects were included in the sample, Germany led three EC projects (one FP6 and two FP7), while Italy led two FP7 projects and France one.

In the next phase of the Mapping_NCD project, the disease-level synthesis for MHDs will allow us to explore the characteristics of research funding through in-depth country case studies.

2 Private Sector Investments

The Mapping_NCD survey of research funding organizations (RFOs) found that government entities financed the vast majority of NCD research activity in Europe. However, the survey did not include the research undertaken by private sector companies to develop pharmaceutical treatments and medical devices because we knew that these companies were unlikely to provide the detailed research funding data we sought. Thus, we searched the publicly-available documentation in order to measure industry responses in terms of research and development (R&D) of pharmaceutical treatments and medical devices to address NCDs in Europe. Because of the global market reach of these private sector companies, we focused on the top pharmaceutical and medical device companies worldwide, all of which are based either in Europe or the U.S. These data collection efforts were led by our partners at the London School of Economics (LSE) with respect to the pharmaceutical industry and Università Bocconi (UB) with respect to the medical device industry.

2.1 Background

Among the world's top 100 companies in terms of R&D investment, the pharmaceuticals and biotechnology sector is one of the largest investors, with a 24% share of total R&D investment for 2013 (Table 2.1). Nonetheless, the European Commission's 2014 *EU Industrial R&D Investment Scoreboard* found that the poor R&D performance of EU companies in high-tech sectors such as pharmaceuticals (+0.9% in fiscal year 2013-2014) weighed down the total R&D increase of the EU sample. Indeed, the overall amount invested in R&D by EU companies in high-tech sectors represented 40% of the amount invested by their US counterparts and the gap between the two company samples is increasing over time. Moreover, the pharmaceuticals and biotechnology sector accounts for a relatively small share of the patents to R&D investment ratios. For perspective, the electronic and electrical equipment sector has the highest patents to R&D investment ratio, which is about ten times that of the pharmaceuticals and biotechnology sector. This is due in part to the substantial upfront investment required to ensure safety and effectiveness of the molecules developed (Hernández *et al.*, 2014).

Table 2.1 Top 20 European and US pharmaceutical and biotechnology companies ranked by R&D investment (2013)

Rank	World Rank	Company Name	Country	R&D 2013 (€million)
1	5	NOVARTIS	Switzerland	7173.5
2	6	ROCHE	Switzerland	7076.2
3	8	JOHNSON & JOHNSON	US	5933.6
4	12	MERCK US	US	5165.0
5	14	SANOFI-AVENTIS	France	4757.0
6	15	PFIZER	US	4750.2
7	21	GLAXOSMITHKLINE	UK	4154.3
8	23	ELI LILLY	US	4010.8
9	34	BAYER	Germany	3259.0
10	37	ASTRAZENECA	UK	3202.8
11	38	AMGEN	US	2960.6
12	39	BOEHRINGER INGELHEIM	Germany	2743.0

13	40	BRISTOL-MYERS SQUIBB	US	2705.4
14	52	ABBVIE	US	2059.3
15	65	CELGENE	US	1603.4
16	66	NOVO NORDISK	Denmark	1567.4
17	68	GILEAD SCIENCES	US	1537.1
18	70	MERCK DE	Germany	1504.3
19	95	ABBOTT LABORATORIES	US	1052.9
20	96	BIOGEN IDEC	US	1047.1

Source: 'The 2014 EU Industrial R&D Investment Scoreboard' available at: http://iri.jrc.ec.europa.eu/scoreboard14.html.

New drug discovery is a high-risk and time-consuming process. This is particularly true of drugs treating MHDs, which have longer development times (average 13 years) and a higher failure rates than for other disease areas (Nutt and Goodwin, 2011). Indeed, many psychiatric drugs fail late in the development process – at Phase III or even at registration – resulting in significant financial losses. Additional challenges to the development of MHD drugs include the lack of predictive and prognostic biomarkers. Even after regulatory approval, drugs still must undergo health technology assessments before they may be reimbursed by Member State health systems.

Since the global financial crisis, a number of pharmaceutical companies have withdrawn from research and development in psychopharmacology. Moreover, several major companies, including Johnson & Johnson, Sanofi-Aventis and Abbott Laboratories, are increasingly shifting attention and resources to medical devices, perhaps because of higher returns on investment (Ackerly *et al.*,2009).

The medical device industry constitutes the other major component of private sector investment in NCDs. We identified the top 16 medical device companies worldwide ranked by total revenue (Table 2.2). Neurology devices constitute the smallest of the top 15 device areas in terms of revenues generated, but this area is where the fastest growth is expected (EvaluateMedTech, 2014). Neurology devices are designed to treat or assist diagnosis for a wide range of disorders, including stroke, Parkinson's disease, pain management, as well as certain MHDs.

Table 2.2 Top 16 European and US medical device companies ranked by total revenues (2014)

Medical Device Company Rank	Forbes Global 2000 Rank	Company Name	Country	R&D 2014 ($million)	R&D Rank among top 16 MD Companies
1	34	Johnson & Johnson	US	8494	1
2	9	General Electric Co.	US	4233	2
3	249	Medtronic Inc.	US	1477	5
4	54	Seimens AG	Germany	4065	3
5	346	Baxter International Inc.	US	1421	6
6	283	Fresenius Medical Care AG & Co. KGaA	Germany	369	14
7	472	Koninklijke Philips NV	Netherlands	1635	4
8	327	Cardinal Health Inc.	US	NA	16*

9	52	Novartis AG (Alcon)	Switzerland	903	8
10	349	Covidien PLC	Ireland	546	13
11	719	Stryker Corp.	US	614	11
12	610	Becton, Dickinson and Co.	US	550	12
13	1047	Boston Scientific Corp.	US	817	9
14	732	Essilor International SA	France	188	15
15	753	Allergan Inc. (Actavis)	Ireland	1086	7
16	957	St. Jude Medical Inc.	US	692	10

Mapping the Private Sector Research Pipeline

Mapping private sector investment in NCD research funding involves unique challenges. While the details and strategic focus of public and non-profit NCD RFOs are generally readily accessible and in some cases a matter of public record, the research activities of the private sector are less transparent. Nonetheless, publicly-traded companies must disclose their revenues and expenditures, including R&D investment, as part of their financial reporting obligations. Their annual reports also generally include summaries of their development pipelines. Reporting requirements for clinical trials also provide an important source of data.

To measure and compare the commitment of European and U.S. pharmaceutical companies to R&D investment in MHDs, including the specific disease focus, we examined the general trends in R&D expenditure of the top 20 European and American pharmaceutical companies and then explored their research pipelines in terms of molecules in Phase I, Phase II, Phase III, Submission and Approval. Data was collected from the four most recent annual reports available on the companies' global websites (2014-2011), supplemented by additional research on clinicaltrials.gov. The total amount of R&D expenses for the period and the percentage of sales or revenues allocated to R&D are reported for each company. Pipeline data are expressed in terms of phases of development for individual molecules targeting MHDs.

To explore the commitment of European and U.S. medical device companies to R&D investment for MHDs, data were obtained from clinicaltrials.gov for ongoing or completed trials undertaken by the top 16 companies from 2011-2015. Terminated trials and those for whom trial status was unknown/not verified were excluded. Data for medical devices with FDA pre-market approval were also searched for the 2011-2015 period using the following disease-specific keywords: mental, depression, schizophrenia, dementia, Alzheimer's, brain, behavior/behavioral, anxiety and eating disorder. FDA data were also searched for de novo medical devices, an alternate pathway for classification of novel devices with low-to-moderate risk. The search was performed for the same time period and disease areas as for the FDA pre-market approval, and only devices with no 510(k) clearance were included. In Europe, a database of CE marked products called EUDAMED has existed since 2009. However, this database is only accessible to government agencies charged with market surveillance in each country. Thus we relied upon the EuroScan database, which was developed by the International Information Network on New and Emerging Health Technologies, a collaborative network of member HTA agencies for the exchange of information on important emerging new drugs, devices, procedures, programmes and settings in health care. The EuroScan database was searched for the period 2011-2015 based on the following keywords: mental health, addiction and learning difficulties.

In order to provide critical context for the R&D investment and drug and device pipelines, we first describe the unmet need for treatments of MHDs.

2.2 Unmet Need in the Disease Area

MHDs remain a leading cause of morbidity and mortality and account for 37% of healthy life years lost due to NCDs. A large proportion of individuals with MHDs remain untreated, with estimates as high as 74% in Europe and 67% in the U.S. (Thornicroft, 2007). Despite this burden, major pharmaceutical companies have shifted drug R&D away from MHDs towards diseases with identified biological targets.

Psychotropic drugs include antipsychotic drugs or neuroleptics; antidepressants, the use of which has increased dramatically over the past three decades; and other drugs such as anxiolytics, tranquillizers and hypnotics. Development of SSRI (Selective serotonin reuptake inhibitors) antidepressants and atypical antipsychotics for schizophrenia has made pharmaceutical treatment safer by reducing the risk of overdose. However, development of new drug treatments for MHDs has slowed in recent years as pharmaceutical companies have de-emphasized or abandoned psychiatry R&D (Hyman, 2012). Indeed, as of 2012 no mechanistically novel psychiatric drug had reached the market in more than 30 years (Fibiger, 2012). Fibiger points out that the three major classes of psychiatric drugs were developed through clinical observation, while the mechanisms by which they produce their effects were only discovered later. This implicates greater investment in fundamental neuroscience, which is largely driven by clinical and basic scientists in academia.

The situation with respect to development of drugs designed to treat Alzheimer's disease is a bit different. Over the past two decades, considerable effort has been made to understand the etiology and pathophysiology of Alzheimer's disease in both pre-clinical and clinical studies (Geldenhuys and Darvesh, 2015). While the understanding of pathogenesis in Alzheimer's disease has increased, providing targets for therapies, drug development has been difficult and often disappointing. Some drugs have been shown to slow disease progression, but to date none has provided a cure to dementia in Alzheimer's disease. Nonetheless, research in this area remains high, which may be attributable to the visibility of this disease in an aging population (Amara *et al.*, 2011).

The use of medical devices is an interesting case with respect to MHDs. The use of electroconvulsive therapy (ECT) was particularly controversial in part because of depictions in the media and film but also because of serious associated side effects. Coupled with the increase in antidepressant treatment, the use of ECT declined until the 1980s, when its effectiveness in treating severe depression was recognized. Over the past 15 years, there has been a resurgence of interest in the use of weak direct current stimulation delivered transcranially both as a research tool and as a potential treatment for several MHDS, including major depressive disorder, schizophrenia and obsessive compulsive disorder (Tortella *et al.*, 2015).

Another development in device-based treatment of MHDs has come about as a result of the shift from hospital-centered care for MHDs towards more personalized care. The concept of "Personal Health Systems" includes a broad range of devices that may be wearable, implantable or portable, allowing monitoring, assessments and patient feedback (Riva *et al.*, 2011). In terms of regulation, Information and Communication Technologies (ICT), particularly mobile health applications (mHealth apps), remain a grey area. European and American regulators are working to strike the

right balance to encourage development of technologies that allow for timely and appropriate individualized care, particularly to patients who might otherwise be reluctant to seek treatment due to stigma, while ensuring patient safety and data privacy.

2.3 European Pharmaceutical Companies: Research Pipeline for MHDs

We report on the 2011-2014 R&D spending and pipeline data for the top nine European pharmaceutical companies in terms of R&D spending (Table 2.1.) in order to better understand this important aspect of private research investment in MHDs.

Novartis International AG

Novartis is a Swiss multinational pharmaceutical company based in Basel, Switzerland. It was formed in 1996 through the merger of Sandoz and Ciba-Geigy. In 2003, Novartis reintroduced the Sandoz brand as a single subsidiary in which it consolidated its generic drugs businesses. Today, Novartis focuses its business on three leading divisions: pharmaceuticals (Novartis), eye care (Alcon) and generics (Sandoz). Novartis is currently expanding its presence in the emerging markets of Asia, Africa and Latin America, where there is fast-growing demand. The company has more than 119 000 employees in more than 150 countries.

Table 2.3 Novartis International AG R&D Investment (2011-2014)

$ million	2014		2013		2012		2011	
Total R & D Expense	Amount	% of Sales	Amount	% of Sales	Amount	% of Sales	Amount	% of Sales
	9900	17.1	9640	16.6	9120	16.1	9240	15.8
% Change	+2.7		+5.7		-1.3			

Since 2012, Novartis has marginally increased its commitment to R&D activities. The company is consistently rated as having one of the industry's most respected development pipelines, with more than 200 projects in clinical development, including 135 in the Pharmaceuticals Division, as of December 2014. Though Novartis is heavily invested in oncology, its large portfolio also encompasses Alzheimer's disease and ADHD drugs. Its pipeline includes two MHD molecules in development.

Table 2.4 Novartis MHD Research Pipeline (2011-2014)

Year	Product Name	Indication	Phase
2012	AQW051	Schizophrenia	II
2014	CAD106	Alzheimer's disease	II

Roche

Roche is Swiss pharmaceutical company headquartered in Basel, Switzerland. Founded by Fritz Hoffmann-La Roche in 1896, the company is controlled by his descendants, who own close to half of the company's bearer shares with voting rights (45%). Roche owns several important biotechnology

companies, including Genentech and Ventana in the US and Chugai Pharmaceuticals in Japan. In its early years, Roche gained a reputation for being the first company to mass-produce synthetic vitamin C in 1934. Today, it is a market leader in cancer research.

Table 2.5 Roche R&D Investment (2011-2014)

$ million	2014		2013		2012		2011	
Total R & D Expense	Amount	% of Sales	Amount	% of Sales	Amount	% of Sales	Amount	% of Sales
	8900	18.6	8700	18.6	8500	18.6	8100	19.0
% Change	+2.30		+2.35		+4.94			

Since 2011, Roche's R&D investment in has increased an average 3.2% per year. Roche mostly concentrates in the field of oncology followed by neuroscience, with five MHD drugs in its pipeline including three for Alzheimer's disease.

Table 2.6 Roche MHD Research Pipeline (2011-2014)

Year	Product Name	Indication	Phase
2011	RO4995819	Major Depressive disorder	II
2013	RO5545965	Schizophrenia	I
2013	Crenezumab	Alzheimer disease	II
2014	RG1577	Alzheimer's disease	II
2014	Gantenerumab	Alzheimer's disease	III

Sanofi-Aventis

Sanofi-Aventis is headquartered in Paris, France and was formed in 2004 when Sanofi-Synthélabo acquired Aventis in a hostile takeover, which the French government played a major role in resolving. Today, the company is focused on seven strategic growth platforms: diabetes, vaccines, consumer healthcare, rare diseases and multiple sclerosis, other innovative products, animal health and emerging markets. The company has 45 000 employees in 40 countries.

Table 2.7 Sanofi-Aventis R&D Investment (2011-2014)

€ million	2014		2013		2012		2011	
Total R & D Expense	Amount	% of Sales	Amount	% of Sales	Amount	% of Sales	Amount	% of Sales
	4824	14.3	4770	14.5	4922	14.1	4811	14.4
% Change	+1.13		-3.09		+2.31			

In terms of R&D investment, Sanofi-Aventis' commitment has remained relatively steady since 2011. The company concentrates mainly on diabetes and vaccines, but has two molecules in its pipeline for Alzheimer's disease.

Table 2.8 Sanofi-Aventis MHD Research Pipeline (2011-2014)

Year	Product	Indication	Phase
2013	SAR110894	Alzheimer's disease	II
2014	SAR228810	Alzheimer's disease	I

GlaxoSmithKline

GlaxoSmithKline (GSK) is a British multinational pharmaceutical company headquartered in Brentford. It was established in 2000 by the merger of Glaxo Wellcome and SmithKline Beecham. GSK has a portfolio of products for major disease areas such as asthma, cancer, infections, mental health, diabetes and digestive conditions. In March 2015, GSK acquired Novartis's vaccines business (excluding influenza). Today the company has more than 100 0000 employees across 110 countries.

Table 2.9 GlaxoSmithKline R&D Investment (2011-2014)

£ million	2014		2013		2012		2011	
Total R & D Expense	Amount	% of Sales	Amount	% of Sales	Amount	% of Sales	Amount	% of Sales
	3100	13.5	3400	12.8	3500	13.2	4000	14.6
% Change	-8.82		-2.86		-12.5			

GSK's commitment to R&D activities has steadily decreased over the period. The company works in partnership with other institutions and companies for areas such as Alzheimer's disease, for which it currently has one molecule in the pipeline.

Table 2.10 GlaxoSmithKline MHD Research Pipeline (2011-2014)

Year	Product Name	Indication	Phase
2013	Rilapladib	Alzheimer's disease	II

Bayer AG

Founded in 1863, Bayer is a multinational chemical and pharmaceutical company headquartered in Leverkusen, Germany. Its first and best-known product is acetylsalicylic acid, the active ingredient in aspirin. Bayer HealthCare Pharmaceuticals is the company's pharmaceutical division, which was formed by the 2006 merger of Bayer and Schering AG and was named Bayer Schering Pharma until it was renamed in 2011. Bayer HealthCare Pharmaceuticals concentrates on over-the-counter consumer health care products and prescription drugs and has around 40 000 employees and 100 subsidiaries worldwide.

Table 2.11 Bayer AG R&D Investment (2011-2014)

€ million	2014		2013		2012		2011	
Total R & D Expense	**Amount**	**% of Sales**	**Amount**	**% of Sales**	**Amount**	**% of Sales**	**Amount**	**% of Sales**
	3574	8.5	3406	8.5	3013	7.6	2932	8.0
% Change	+4.9		+13		+2.8			

Bayer HealthCare Pharmaceuticals concentrates in five core areas – oncology, cardiology, hematology, ophthalmology and gynecology – but is not active in the field of neuroscience. Its commitment to R&D investment has progressively increased.

AstraZeneca PLC

AstraZeneca PLC is a British-Swedish company with its headquarters in London. Founded in 1999 by the merger of Astra AB (Swedish) and the Zeneca Group (British), the company's activity is focused in the following healthcare areas: cardiovascular and metabolic disease, oncology, respiratory, inflammation and autoimmunity. AstraZeneca is also active in infection, neuroscience and gastrointestinal disease and collaborates with other leading companies in the sector. In 2012, it announced a collaboration with the U.S. company Amgen on inflammatory disease treatments. The same year, it announced a joint acquisition of the biotechnology company Amylin Pharmaceuticals with U.S. company Bristol-Myers Squibb. AstraZeneca has 57 500 employees across 100 countries.

Table 2.12 AstraZeneca PLC R&D Investment (2011-2014)

$ million	2014		2013		2012		2011	
Total R & D Expense	**Amount**	**% of Sales**	**Amount**	**% of Sales**	**Amount**	**% of Sales**	**Amount**	**% of Sales**
	5579	21.4	4821	18.8	5243	18.7	5523	16.4
% Change	+15.7		-8.0		-5.1			

In 2014, the company was the third-largest European investor in R&D, after significantly increasing its commitment following two years of diminished investment. The increase may be related to its joint acquisition of Amylin Pharmaceuticals. Its pipeline currently includes four molecules targeting MHDs.

Table 2.13 AstraZeneca PLC MHD Research Pipeline (2011-2014)

Year	Product	Indication	Phase
2011	AZD6765	Major depressive disorder	II
2011	AZD3293	Alzheimer's disease	II/III
2012	AZD5213	Alzheimer's disease	II
2014	MEDI1814	Alzheimer's disease	I

Boehringer-Ingelheim

Boehringer-Ingelheim was founded in 1885 by Albert Boehringer in Ingelheim am Rhein, Germany, where it is still headquartered today. The company's key assets of interest target respiratory diseases, metabolism, immunology, oncology and diseases of the central nervous system. A family-owned company, Boehringer-Ingelheim has 47 700 employees across 146 affiliates.

Table 2.14 Boehringer-Ingelheim R&D Investment (2011-2014)

€ million	2014		2013		2012		2011	
Total R & D Expense	Amount	% of Sales	Amount	% of Sales	Amount	% of Sales	Amount	% of Sales
	2654	19.9	2743	19.5	2795	19	2516	19.1
% Change	-3.24		-1.9		+11			

Boehringer-Ingelheim focuses mainly on the field of diabetes. Among MHDs, its portfolio includes treatments for Alzheimer's disease and schizophrenia. As of 2014, it had one MHD molecule in its pipeline and is currently recruiting patients for phase II trials of the same molecule in treating Alzheimer's disease.

Table 2.15 Boehringer-Ingelheim MHD Research Pipeline (2011-2014)

Year	Product	Indication	Phase
2014	BI 409306	Schizophrenia	II

Novo Nordisk

Novo Nordisk is a Danish pharmaceutical company headquartered in Bagsvaerd, Denmark, that was founded in 1989 through the merger of two smaller Danish companies, Nordisk Insulinlaboratorium and Novo Terapeutisk Laboratorium. The company's major product lines address the disease areas of diabetes and hemostasis as well as growth hormone and hormone replacement therapies. Novo Nordisk has 39 000 employees across 75 countries.

Table 2.16 Novo Nordisk R&D Investment (2011-2014)

DKK million	2014		2013		2012		2011	
Total R & D Expense	Amount	% of Sales	Amount	% of Sales	Amount	% of Sales	Amount	% of Sales
	13800	15.5	11700	14.0	10900	14.0	9300	14.5
% Change	+17.94		+7.33		+17.2			

While Novo Nordisk has substantially increased its R&D investments since 2011, the company does not focus on MHDs.

Merck KGaA

Founded in 1668 in Darmstadt, Merck is the world's oldest pharmaceutical and chemical company. The 1887 establishment of an office in New York gave rise to the subsidiary Merck & Co. four years later. Since the end of World War I in 1917, the two companies have been separate. The original company, Merck of Darmstadt, Germany, holds the global rights to the name and the trademark MERCK, except in North America, where the company's brand is EMD ("Emanuel Merck Darmstadt"). The Merck family still controls a majority 70.3% of the company's shares. In 2006, Merck KGaA acquired Serono, which since January 2007 has operated as Merck Serono International SA, with headquarters in Darmstadt. Merck Serono's therapeutic focus is on oncology, immune-oncology, immunology, multiple sclerosis, fertility, endocrinology, biosimilars and neglected diseases.

Table 2.17 Merck KGaA R&D Investment (2011-2014)

€ million	2014		2013		2012		2011	
Total R&D Expense	Amount	% of Sales	Amount	% of Sales	Amount	% of Sales	Amount	% of Sales
	1704	15.0	1504	14.0	1511	14.0	1517	15.3
% Change	+13.30		-0.50		-0.40			

In May 2013, Quintiles, the largest contract research organization (CRO), signed a five-year deal as Merck Serono's sole clinical development provider, and the significant increase in R&D expenditure in 2014 may be attributable to this partnership. Merck KGaA/Merck Serono are not active in MHDs.

2.4 U.S. Pharmaceutical Companies: Research Pipeline for MHDs

We report on the 2011-2014 R&D spending and MHD pipeline data for the top 11 U.S. pharmaceutical companies in terms of R&D spending (Table 2.1.) for purposes of comparison with the European-based companies and to better understand private research investment in MHDs in this global marketplace.

Johnson & Johnson

Founded in 1886, Johnson & Johnson is a U.S. medical devices, pharmaceutical and consumer healthcare products company headquartered in New Brunswick, New Jersey. The corporation includes around 250 subsidiary companies with operations in more than 57 countries. The Janssen Pharmaceutical Companies of Johnson & Johnson focus on cardiovascular and metabolism, immunology, infectious diseases and vaccines, neuroscience and oncology. Johnson & Johnson Pharmaceutical Research and Development (J&JPRD) is a subsidiary of Johnson & Johnson that is responsible for discovering and developing pharmaceutical drugs. The company is expanding its activities in joint research projects within the framework of the Innovative Medicines Initiative and the European Commission.

Table 2.18 Johnson & Johnson R&D Investment (2011-2014)

$ million	2014		2013		2012		2011	
Total R & D Expense	Amount	% of Sales	Amount	% of Sales	Amount	% of Sales	Amount	% of Sales
	8494	11.4	8183	11.5	7665	11.4	7548	11.6
% Change	+3.8		+6.8		+1.6			

The company has steadily increased its commitment to R&D investment since 2011. Its current pipeline includes a three-month injectable treatment for schizophrenia that was approved in 2015 and a molecule in late-stage development for treatment-resistant depression.

Table 2.19 Johnson & Johnson MHD Research Pipeline (2011-2014)

Year	Product	Indication	Phase
2013	Paliperidone palmitate IM long-acting injectable	Schizophrenia	IV
2014	Esketamine	Depression	III

Merck & Co.

Merck & Co., one of the largest pharmaceutical companies in the world, is headquartered in Kenilworth, New Jersey. The company was established in 1891 as the US subsidiary of the German company Merck (Merck KGaA is described above under European pharmaceutical companies). During the World War I, the U.S. government confiscated Merck, reestablishing it as an independent American company. Merck has more than 50 prescription products in the following therapeutic areas: cardiovascular disease, respiratory disease, oncology, neuroscience, infectious disease, immunology and women's health. As of August 2014, Merck's research and development effort has led to FDA-approval of more new drugs than that of any other company.

Table 2.20 Merck & Co. R&D Investment (2011-2014)

$ million	2014		2013		2012		2011	
Total R & D Expense	Amount	% of Sales	Amount	% of Sales	Amount	% of Sales	Amount	% of Sales
	7180	16.9	7500	17	8200	17.4	8500	17.7
% Change	-4.30		-8.54		-3.53			

Merck's overall investment level in R&D has progressively fallen over the period, with a major fall of 22.7% in 2011. The company currently has a number of molecules aimed at NCDs in its pipeline, including two for Alzheimer's disease. In addition, asenapine, which has been approved by both the FDA and EMA for bipolar disorder was approved for treatment of schizophrenia by the FDA but not the EMA.

Table 2.21 Merck & Co. MHD Research Pipeline (2011-2014)

Year	Product	Indication	Phase
2013	MK-7622	Alzheimer's Disease	II
2013	MK-8931	Alzheimer's Disease	III
2013	Asenapine	Schizophrenia	Approved (US)

Pfizer

Pfizer is a multinational pharmaceuticals company headquartered in New York City, with research headquarters in Groton, Connecticut. Founded in 1849 by Charles Pfizer and Charles F. Erhart, Pfizer produces medicines for a wide range of disease areas, including oncology, diabetes, cardiovascular disease and neurology. Recently, Pfizer has been the subject of prosecutions for illegal and off-label marketing related to the arthritis drug Bextra and has paid multi-billion dollar settlements to the US government.

Table 2.22 Pfizer R&D Investment (2011-2014)

$ million	2014		2013		2012		2011	
Total R & D Expense	Amount	% of Sales	Amount	% of Sales	Amount	% of Sales	Amount	% of Sales
	8393	16.9	6678	12.9	7870	13.7	8681	14.2
% Change	+25.7		-15.1		-9.34			

Pfizer's commitment to R&D had progressively decreased since 2010, but in 2014 R&D investment increased by over 25%. The company has five MHD molecules in its pipeline, including desvenlafaxine, which has been approved in the U.S. and Spain but not in other European countries.

Table 2.23 Pfizer MHD Research Pipeline (2011-2014)

Year	Product	Indication	Phase
2012	PF-04958242	Schizophrenia	I
2012	SAM-760	Alzheimer's Disease	II
2012	Desvenlafaxine	Depression	Approved (ES only; US in 2008)
2013	PF-02545920	Schizophrenia	I
2014	PF 06372865	Anxiety	II

Eli Lilly

Eli Lilly was founded in 1877 by Colonel Eli Lilly, a pharmaceutical chemist and veteran of the American Civil War, who was company president until his death in 1898. With its headquarters in in Indianapolis, Indiana, Eli Lilly was the first pharmaceutical company to mass produce break-through drugs such as insulin, polio vaccine and penicillin. Today, the company focuses on autoimmune disorders, cardiovascular disease, musculoskeletal disorders, neuroscience, oncology and diabetes. Eli Lilly is the largest manufacturer and distributor in the world of psychiatric medications. In 2009,

the company paid a $515 million fine related to off-label marketing of the dementia drug, Zyprexa. Eli Lilly has approximately 41 000 employees worldwide, including more than 8 000 who are engaged in R&D in six countries.

Table 2.24 Eli Lilly R&D Investment (2011-2014)

$ million	2014		2013		2012		2011	
Total R & D Expense	**Amount**	**% of Sales**	**Amount**	**% of Sales**	**Amount**	**% of Sales**	**Amount**	**% of Sales**
	4734	24.1	5531	23.9	5278	23.4	5021	20.7
% Change	-14.4		+5.0		+5.0			

The company's levels on investment in R&D have steadily increased since 2010, but dropped substantially (14%) in 2014. Eli Lilly previously was more active in neuroscience research, but its focus has turned largely to diabetes, for which it is the world leader in R&D. The company currently has four MHD molecules in its pipeline.

Table 2.25 Eli Lilly MHD Research Pipeline (2011-2014)

Year	Product	Indication	Phase
2011	LY2940094	Major Depressive Disorder	II
2013	LY2216684	Major Depressive Disorder	III
2014	LY2940094	Alcoholism	II
2014	LY2216684	ADHD	II/III

Amgen

Amgen is a multinational biopharmaceutical company headquartered in Thousand Oaks, California, and is the world's largest independent biotechnology firm. Founded in 1980, Amgen focuses on kidney disease, cancer, rheumatoid arthritis, bone disease and other serious diseases.

Table 2.26 Amgen R&D Investment (2011-2014)

$ million	2014		2013		2012		2011	
Total R & D Expense	**Amount**	**% of Sales**	**Amount**	**% of Sales**	**Amount**	**% of Sales**	**Amount**	**% of Sales**
	4297	21.4	4100	22.5	3400	20.4	3200	20.9
% Change	+4.8		+20.6		+6.25			

Since 2011, Amgen's level of R&D investment has increased by over one-quarter. The company largely concentrates in oncology and cardiovascular R&D. Amgen has a new schizophrenia molecule (AMG 581) in the pipeline, with a phase I trial set to start in 2015.

Bristol-Myers Squibb

Founded in New York in 1858 by Edward R. Squibb, Bristol-Myers Squibb is a pharmaceutical company headquartered in New York City. Today, Bristol-Myers Squibb manufactures pharmaceutical products in a number of disease areas, including cancer, HIV/AIDS, cardiovascular disease, diabetes, hepatitis, rheumatoid arthritis, fibrotic diseases and psychiatric disorders. Biologics are expected to constitute 75% of the company's portfolio by 2019.

Table 2.27 Bristol-Myers Squibb R&D Investment (2011-2014)

$ million	2014		2013		2012		2011	
Total R & D Expense	Amount	% of Sales	Amount	% of Sales	Amount	% of Sales	Amount	% of Sales
	4534	28.5	3731	30.3	3904	28.6	3839	21.8
% Change	+21.5		-4.4		+1.7			

Bristol-Myers Squibb currently does not have any MHD-relevant molecules in development, focusing mainly on oncology, particularly immuno-oncology, virology and cardiovascular disease. Since 2010, the company's R&D investment level was relatively steady before increasing by over 20% in 2014.

AbbVie

AbbVie is a biopharmaceutical company headquartered in Chicago, Illinois. AbbVie was formed in 2011 through a divestment from Abbott Laboratories. While Abbott focuses on diagnostic equipment, medical devices and consumer health care products, AbbVie operates as a research-based biopharmaceutical company. The company developed two important breakthrough medications for the treatment of HIV. Today the company's research focus includes immunology, oncology, neuroscience, kidney disease and women's health.

Table 2.28 AbbVie R&D Investment (2011-2014)

$ million	2014		2013		2012		2011	
Total R & D Expense	Amount	% of Sales	Amount	% of Sales	Amount	% of Sales	Amount	% of Sales
	3297	16.5	2855	15.19	2778	15.11	2618	15
% Change	+15.48		+2.77		+6.11			

AbbVie's commitment to R&D investment has been steadily increasing since 2011. The company currently has three MHD molecules in its pipeline.

Table 2.29 AbbVie MHD Research Pipeline (2011-2014)

Year	Product	Indication	Phase
2012	ABT-126	Schizophrenia	II
2012	ABT-436	Alcohol Dependence	II
2014	ABT-957	Alzheimer's Disease	I

Celgene

Founded in 1986, Celgene is a biopharmaceutical company headquartered in Summit, New Jersey. Celgene's major products include thalidomide and lenalidomide, approved by both the FDA and the EMA. Celgene also receives royalties from Novartis Pharma AG on sales of methylphenidate-based drugs, which are widely used to treat Attention Deficit Hyperactivity Disorder (ADHD).

Table 2.30 Celgene R&D Investment (2011-2014)

$ million	2014		2013		2012		2011	
Total R & D Expense	Amount	% of Sales	Amount	% of Sales	Amount	% of Sales	Amount	% of Sales
	2431	32.13	2226	34.99	1724	32	1600	34.04
% Change	+9.2		+29.12		+7.75			

Among the top US pharmaceutical companies, Celgene had the second largest percentage increase in R&D investment – more than 50% since 2011. Major compounds in development concern the treatment of hematological and solid tumor cancers, chronic lymphocytic leukemia, non-Hodgkin's lymphoma, small cell lung cancer and prostate cancer. Celgene has no current ongoing research related to MHDs.

Gilead Sciences

Founded in June 1987 by then 29-year-old Michael Riordan, Gilead Sciences is a biotechnology company headquartered in Foster City, California. Gilead's research focus is on HIV/AIDS, liver diseases, cancer, CRDs and CVDs. The company also boasts the first single pill, once-daily treatment for HIV infection as well as the first oral antiretroviral drug to reduce the risk of acquiring HIV.

Table 2.31 Gilead Sciences R&D Investment (2011-2014)

$ million	2014		2013		2012		2011	
Total R & D Expense	Amount	% of Sales	Amount	% of Sales	Amount	% of Sales	Amount	% of Sales
	2854	11.4	2120	19.6	1760	18.72	1230	15.19
% Change	+34.62		+20.45		+43.08			

Treatments for serious respiratory conditions, such as influenza, cystic fibrosis and other diseases of the lungs, are identified as the principal focus of Gilead's R&D investment, which has more than doubled since 2011, representing the largest percentage increase in R&D investment among US pharmaceutical companies. Gilead is not active in MHD research.

Abbott Laboratories

Abbott Laboratories is a pharmaceuticals and healthcare products company headquartered in Chicago, Illinois. Following its divestment of AbbVie in 2011, Abbott refashioned itself as pharmaceutical company focused largely on consumer healthcare, medical devices and prescription medicines. The company has 72 000 employees and operates in over 130 countries.

Table 2.32 Abbott Laboratories R&D Investment (2011-2014)

$ million	2014		2013		2012		2011	
Total R & D Expense	Amount	% of Sales	Amount	% of Sales	Amount	% of Sales	Amount	% of Sales
	1345	6.6	1452	6.66	1544	7.18	1512	7.06
% Change	-7.37		-5.99		+2.12			

Since 2010, the company's investment in R&D has substantially decreased, likely related to its divestment of AbbVie, which took over R&D on several MHD molecules initially developed by Abbott.

Biogen Idec

Biogen Idec is a global biotechnology company based in Cambridge, Massachusetts that specializes in the development of treatments for neurodegenerative, hematologic and autoimmune diseases. Founded in Geneva in 1978, Biogen became the third largest biotechnology company in the world after merging with San Diego, California-based IDEC Pharmaceuticals in 2003. Biogen Idec has 7 550 employees in 26 countries. Biogen Idec shortened its name to Biogen in 2015.

Table 2.33 Biogen Idec R&D Investment (2011-2014)

$ million	2014		2013		2012		2011	
Total R & D Expense	Amount	% of Sales	Amount	% of Sales	Amount	% of Sales	Amount	% of Sales
	1893	19.5	1444	20.8	1335	24.2	1220	24.2
% Change	+31.1		+8.2		+9.4			

In terms of MHDs, Biogen Idec has focused its research exclusively on Alzheimer's disease, with two molecules currently in its pipeline. Following several years of steady growth in R&D investment, 2014 marked a major increase in research expenditure of 31%. This may be due to the fact that Aducanumab has garnered much interest because it has demonstrated reductions in levels of the amyloid plaques in the brain that are associated with Alzheimer's disease, as well as a significant slowing of cognitive declines. A phase III study of that drug is currently recruiting participants.

Table 2.34 Biogen Idec MHD Research Pipeline (2011-2014)

Year	Product	Indication	Phase
2014	Aducanumab	Alzheimer's Disease	I
2014	E2609	Alzheimer's Disease	II

2.5 Medical Devices Industry: Research Pipeline for MHDs in Europe and the U.S.

In the EU, a "medical device" is defined as any instrument, apparatus, appliance, material or other article, whether used alone or in combination, including the software necessary for its proper application intended by the manufacturer to be used for human beings for the purpose of:
— diagnosis, prevention, monitoring, treatment or alleviation of disease,
— diagnosis, monitoring, treatment, alleviation of or compensation for an injury or handicap,
— investigation, replacement or modification of the anatomy or of a physiological process,
— control of conception,
and which does not achieve its principal intended action in or on the human body by pharmacological, immunological or metabolic means, but which may be assisted in its function by such means (Council Directive 93/42/EEC on Medical Devices).

In the U.S., medical devices are regulated by the Food and Drug Administration (FDA), which defines medical devices as "instruments or apparatus (including components), intended for use when diagnosing, treating or preventing diseases, or medical conditions, or intended to affect the body through non-chemical means" (Federal Food, Drug and Cosmetic Act (FDCA), 21 U.S.C. sec. 321(h)).

In the field of MHDs, medical devices may include different brain stimulation devices, including Repetitive transcranial magnetic stimulation (rTMS), Transcranial direct current stimulation (tDCS) and Vagus nerve stimulation (VNS), as well as other therapies and diagnostic devices, including Magnetic seizure therapy (MST), neurofeedback and neuroimaging. An emerging area that is potentially encompassed by medical device regulation is eHealth, which uses Information and Communication Technologies (ICT) for the provision of health-related services. This area includes mHealth – mobile communication systems for the provision of health-related services – which is an ambiguous area in terms of regulation, and regulatory bodies in both the EU and U.S. are currently exploring how existing regulatory schemes may have to be changed in response to these technologies.

Clinical trials for MHD medical devices

A search of the clinicaltrials.gov database for clinical trials involving MHD medical devices for the period 2011-2015 led to the identification of three trials for devices developed by two of the top 16 medical device companies, both based in the U.S. All three trials involved deep brain stimulation (DBS) systems, two of which targeted depression and one obsessive compulsive disorder (OCD) (Table 2.35).

Table 2.35 Medical Device manufacturers with clinical trials for MHD devices (2011-2015)

MHD	Device	Manufacturer	Phase	Year
Obsessive Compulsive Disorder	Reclaim® Deep Brain Stimulation	Medtronic PLC	Post-market clinical follow-up study	2010-ongoing
Depression	Deep Brain Stimulation	St. Jude Medical Inc.	Completed clinical evaluation of device parameters	2015
Depression	Libra Deep Brain Stimulation System	St. Jude Medical Inc.	Clinical evaluation of Subcallosal Cingulate Gyrus Deep Brain Stimulation	2011-ongoing

Because of the dearth of medical devices in development for MHD among the top device companies, we only describe the R&D investment data for the two companies with devices targeting MHDs.

Medtronic PLC (U.S.)

Formerly known as Medtronic, Inc., the group's principal activities are manufacturing, developing and marketing medical technology and providing device-based medical therapies. It operates in eight areas: cardiac rhythm disease management (CRDM), spinal, cardiovascular, neuromodulation, diabetes, surgical technologies and physio-control. It provides therapeutic and diagnostic devices used for the treatment of diabetes, neurological, gastroenterological, urological, and movement disorders, spinal and neurosurgery, neurodegenerative disorders and ear, nose and throat (ENT) surgery, as well as external and manual defibrillators. Its Reclaim DBS Therapy for OCD uses surgically-placed devices to deliver controlled electrical stimulation to precisely targeted areas of the brain linked to OCD, with the goal of reducing OCD symptoms.

Table 2.36 Medtronic PLC R&D Investment (2011-2014)

$ million	2014		2013		2012		2011	
Total R & D Expense	Amount	% of Sales	Amount	% of Sales	Amount	% of Sales	Amount	% of Sales
	1477	8.7	1557	9.4	1490	9.2	1508	9.5
% Change	-5.1		4.5		-1.2			

St. Jude Medical, Inc. (U.S.)

St. Jude Medical, Inc. develops, manufactures and distributes cardiovascular medical devices for the global cardiac rhythm management, cardiovascular and atrial fibrillation therapy areas and neurostimulation medical devices for the management of chronic pain. It operates through two operating divisions: Cardiovascular and Ablation Technologies and Implantable Electronic Systems Division.

Table 2.37 St. Jude Medical, Inc. R&D Investment (2011-2014)

$ million	2014		2013		2012		2011	
Total R & D Expense	Amount	% of Sales	Amount	% of Sales	Amount	% of Sales	Amount	% of Sales
	692	12.6	691	12.6	676	12.3	705	12.6
% Change	0.1		2.2		-4.1			

St. Jude Medical, Inc. had sought to extend the indication for its Libra DBS devices, which already had been approved for the treatment of Parkinson 's disease in Europe and Australia, to treatment-resistant depression. However, its BROADEN trial resulted in a failed futility analysis in 2013. Nonetheless, its work in this area continues.

FDA pre-market and de novo device approvals

The search of medical devices with FDA pre-market approval in the period 2011-2015 failed to identify any MHD-relevant devices. However, exploration of the FDA de novo device database led to the identification of one device that was approved in 2015 (Table 2.38.).

Table 2.38 FDA de novo devices for MHDs (2011-2015)

MHD	Device	Manufacturer	Phase	Year
Dementia	Cognivue	Cerebral Assessment Systems, LLC	Approved	2015

Cerebral Assessment Systems, LLC (CAS) specializes in therapies for Alzheimer's disease and provides services to patients with neurological disorders. The private company was founded in 2002 by Dr. Charles Duffy and is based in Rochester, New York. In 2015, CAS received FDA approval for Cognivue®, a computer-based tool designed to assess, measure and monitor brain function to detect early signs of dementia.

The search of the EuroScan database failed to identify any MHD devices for the period 2011-2015.

2.6 Discussion: Focus of Private Sector Research Pipelines

Pharmaceutical R&D

Among the European pharmaceutical companies investing in MHD research, all but GlaxoSmithKline had generally positive trends in terms of their R&D investments. Reduced R&D investment over the period 2011 to 2014 was seen in several large U.S. pharmaceutical companies with MHD molecules in their pipelines. In the case of Abbott Laboratories, this appeared to be a strategic decision to shift away from drug development toward a greater focus on medical devices and consumer health care.

In terms of the particular MHDs targeted, research for Alzheimer's disease treatments dominated the pharmaceutical research pipeline, accounting for nearly half (16) of the 34 molecules identified (Table 2.39). This may be due to the fact that biological targets have been identified for this disease, as well as to public awareness of and sympathy for the repercussions of Alzheimer's in an aging population.

Nearly one-quarter (8) of the molecules under study were for the treatment of schizophrenia. While this disease accounts for a relatively small burden among MHDs, the severe consequences to patients, their families and other carers and society in general are significant.

Depression and anxiety comprise a large share of the MHD burden, but research into these areas has slowed in recent years, owing in part to the lack of identified biological targets for treatments as well as to the general downturn in R&D investment for MHDs. Existing drugs for treating depression are effective in only half of patients, which underscores the need to develop new depression treatments. Only one molecule targeting anxiety was in development.

Treatments for alcohol dependence (2) and ADHD (1) were in development by U.S.-based pharmaceutical companies, but no treatments for bipolar disorder, drug addiction, obsessive compulsive disorder or eating disorders were found. Due to the complexity of MHDs, this may to a certain extent reflect the fact that the most effective treatment modalities fall outside of the realm of pharmaceutical treatment (e.g., behavioral therapies).

Table 2.39 MHD pharmaceutical pipeline in Europe and US (2011-2014)

MHD	Molecule (company)	Phase	Year
Alcohol Dependence	ABT-436 (AbbVie)	II	2012
	LY2940094 (Eli Lilly)	II	2014
Alzheimer's Disease	MEDI1814 (AstraZeneca)	I	2014
	SAR228810 (Sanofi-Aventis)	I	2014
	ABT-957 (AbbVie)	I	2014
	Aducanumab (Biogen)	I	2014
	E2609 (Biogen)	II	2014
	Rilapladib (GlaxoSmithKline)	II	2013
	MK-7622 (Merck US)	II	2013
	SAM-760 (Pfizer)	II	2012
	CAD106 (Novartis)	II	2014
	AZD5213 (AstraZeneca)	II	2012
	RG1577 (Roche)	II	2014
	Crenezumab (Roche)	II	2013
	SAR110894 (Sanofi-Aventis)	II	2013
	AZD3293 (AstraZeneca)	II/III	2011
	Gantenerumab (Roche)	III	2014
	MK-8931 (Merck US)	III	2013
Anxiety Disorder	PF-06372865 (Pfizer)	II	2014
Attention Deficit Hyperactivity Disorder	LY2216684 (Eli Lilly)	II/III	2014

Depression (unipolar)	RO4995819 (Roche)	II	2011
	AZD6765 (AstraZeneca)	II	2011
	LY2940094 (Eli Lilly)	II	2011
	Esketamine (Johnson & Johnson)	II	2014
	LY2216684 (Eli Lilly)	III	2013
	Desvenlafaxine (Pfizer)	Approved (ES)	2012
Schizophrenia	RO5545965 (Roche)	I	2013
	PF-04958242 (Pfizer)	I	2012
	AQW051 (Novartis)	II	2012
	BI 409306 (Boehringer Ingelheim)	II	2014
	PF-02545920 (Pfizer)	I	2013
	ABT-126 (AbbVie)	II	2012
	Paliperidone palmitate (Johnson & Johnson)	IV	2013
	Asenapine (Merck US)	Approved (US)	2013

Our search strategy focused on the 20 largest European and U.S. pharmaceutical companies, which provided an excellent overview of the place of MHD in these companies' R&D strategies. Nonetheless, it also meant that we did not account for slightly smaller companies that are active in MHD R&D. Indeed, a non-exhaustive analysis of several European pharmaceutical firms that were still highly ranked in terms of R&D investment, including Servier (ranked 21st among European and US pharmaceutical companies with 2013 R&D investment of €895 million), Shire (ranked 24th with R&D investment of €645.5 million) and Lundbeck (ranked 38th with R&D investment of €210.1 million), revealed a high level of activity in MHD-related molecules. For example, in 2014 Lundbeck brought to market a novel antidepressant (vortioxetine) that is effective in some patients with depression for whom existing treatments are ineffective.

Medical device R&D

Our searches revealed very little R&D investment in MHD-related medical devices. Of the two MHD treatment devices undergoing trials, both were deep brain stimulation (DBS) systems, one targeting obsessive compulsive disorder (OCD) and the other depression (Table 2.40). In addition, a diagnostic tool for dementia was approved by the FDA under its de novo process. The identified devices were all developed by U.S. medical device companies. Our failure to identify R&D investment in any MHD-related devices in Europe may be due to the lack of an accessible official European database for medical devices.

Table 2.40 MHD medical device pipeline (2011-2015)

MHD	Device (company)	Phase	Year
Obsessive Compulsive Disorder	Reclaim® Deep Brain Stimulation (Medtronic PLC)	Post-market clinical follow-up study	2010-ongoing
Depression	Libra Deep Brain Stimulation System (St. Jude Medical Inc.)	Completed (clinical evaluation of device parameters)	2015
	Libra Deep Brain Stimulation System (St. Jude Medical Inc.)	Clinical evaluation of Subcallosal Cingulate Gyrus Deep Brain Stimulation	2011-ongoing
Dementia	Cognivue (Cerebral Assessment Systems, LLC)	Approved	2015

The range of identified MHD medical devices may have greater if we had considered smaller medical device companies. Indeed, the newer personalized medicine approaches, including mHealth apps, may be developed by companies that are not medical device manufacturers. The regulatory status of such interventions must be clarified both in Europe and the U.S.

3 Stakeholder Interviews: MHDs

The Mapping_NCD project uses a mixed methods approach in order to describe the current research landscape for five NCDs with the goal of identifying the most promising and potentially fruitful targets and strategies for future research investment. The survey of MHD research funding organizations (RFOs) provided important quantitative and qualitative data that are described in the Impact Assessment. The Critical Appraisal complements that work with an in-depth exploration of the types of research projects that have been funded at the national and European levels (Section 1), an analysis of the research pipelines of top pharmaceutical and medical device manufacturers (Section 2) and a bibliometric analysis of scientific research outputs (Section 4). In order to contextualize the data and knowledge obtained via these methods, we undertook semi-structured interviews with key MHD experts in Europe. In providing their views on the strengths and weaknesses of the MHD research environment specific to Europe, the experts who were interviewed provided critical insights into where future research investment should be directed as well as an indication of the degree of consensus. The interviews also fostered awareness of the Mapping_NCD

project among these key opinion leaders, who likely will have significant roles in shaping future strategies and initiatives in MHD research.

3.1 Methods

Semi-structured interviews are formal interviews in which the interviewer develops and uses an interview guide with the topics and questions to be covered, which may include open-ended questions. Emerging themes may be incorporated into subsequent interviews.

UPEC developed an interview guide (Annex 1) that included questions regarding priorities and funding trends in mental health research; the respective roles and priorities of the public and private entities; the issue of coordination and redundancy; and initiatives beyond funding that could improve MHD research in Europe.

Purposive sampling was used to identify potential interviewees with the goal of interviewing a range of experts with broad knowledge and perspectives on the MHD research landscape in Europe, including RFOs, researchers and policy experts. Twenty-two experts were contacted by email and requested to participate in 20-30 minute telephone interviews. Respondents consented to the interviews, which were anonymous to elicit candid responses and were recorded and transcribed by UPEC team members.

The Framework Method was used for the qualitative analysis of the interviews (Gale *et al.*, 2013). This approach was chosen because it offers a highly systematic method for categorizing and organizing data with a matrix output from which descriptive and explanatory conclusions may be brought out by theme. The Framework Method requires coding of the transcripts, ideally by more than one researcher. As the transcript analysis continues, codes are categorized and incorporated into an evolving analytical framework. The qualitative data is then charted into a framework matrix to allow thematic analysis across the interviews.

3.2 Results

Ten semi-structured interviews were conducted between April and July 2015. Respondents included psychiatrists, researchers and policy analysts from Belgium, Finland, France, Germany, Spain and the UK, most of whom have undertaken work both at the MS and EU levels. The respondents are identified by numbers to facilitate understanding of their different perspectives across the themes.

After coding the interviews and charting them into the framework matrix, four general themes emerged: funding, the role of the private sector, coordination and research priorities.

3.2.1. Funding

Respondents generally agreed that the level of funding for MHD research is increasing and will continue to do so. However, all respondents remained concerned about the level of research funding for MHDs. “[P]eople say that it is a priority, but what is important is to have a look at the figures and in terms of the volume of funding it is not very high.” (4) This was underscored by a respondent who noted that all indicators demonstrate that the “extent of suffering or the extent of need … for mental health is not in proportion to the actual resources put into it.” (6) Another respondent stated that while all MHDs are underfunded, “some are more underfunded than others.” (7) A key question in this regard is which MHDs should be prioritized, and here opinions among the respondents diverged in terms of whether funding should be based upon severity or

frequency of the disorder. “We tend to put a lot of money into serious diseases” such as schizophrenia and less into more “minor diseases, although the burden of illness often lies within the minor diseases rather the major.” (2) Another respondent agreed, explaining that while there has been a shift from hospital to community-based treatment, “there is still old thinking about severe mental illness while the health system does very little for common mental illnesses other than prescribing drugs.” (6) However, another respondent emphasized that “schizophrenia is a major, major social problem that affects a lot of people and has a very negative impact” not only on those with the disorder but also their families and society more generally. (4) This respondent attributed the unwillingness to address schizophrenia to stigmatization, contrasting it with mood disorders which are considered more acceptable because they “affect normal people.” Another area of contention regarding funding centers upon Alzheimer’s disease, which one respondent said has received too much research attention.

In terms of research funding at the European level, a respondent said that although the project-based funding from the EC pursuant to FP7 and Horizon 2020 is substantial, particularly in terms of its strong impact on priorities, it only accounts for 5-10% of total MHD research funding. (4) According to this respondent, MHDs do not appear to be “a very high level priority” in terms of the Horizon 2020 budget. Another respondent agreed, noting that funding for MHDs is low compared to funding for neurological disorders and other areas. (3) This respondent argued that this was due to the lack of a permanent funding structure, because most project-based funding is for a maximum of five years. Several respondents underscored the need for a dedicated ongoing entity to coordinate MHD research, such as the Joint Programming Initiative (JPI) for Neurodegenerative Disease Research (JPND) or ERA-Net NEURON, which includes MHD research but covers a much broader range of disorders. (3, 4, 9) One respondent cited the U.S. National Institute of Mental Health (NIMH) as a model for coordinating research funding. (3) Another respondent completely disagreed, arguing that MHDs are best addressed on a national level. “Patterns of care vary from country to country. Culture varies, so I think that it is a national subsidiarity issue rather than an EU issue.” (2)

The Innovative Medicines Initiative (IMI) is another example of research that is being carried out at the European level. With the advent of IMI 2, a broader range of stakeholders can be involved, and third parties (academics, NGOs, consultants, etc.) can propose potential topics. Strategic groups have been developed within the IMI, for example on metabolic disease, but “unfortunately for psychiatric disorders” no such group exists. (9)

At the international level, large charities that are involved in health care should expand their efforts to include mental health among their activities, according to one respondent, who noted that “the Gates Foundation doesn’t cover mental health.” (10)

The respondents noted that the vast majority of MHD research was funded at the MS level, and several emphasized that funding was too low. “If we look at the sheer burden of disease which is attributable to mental health disorders, it is about one-third of the burden of disease in Europe, and clearly in comparison to this, funding of research regarding mental health is less than 10% of all health research funding in Europe.” (7) Another added: “I think there is still a large stigma around mental health issues and this causes two things. One is that public funding is small. And the second is that private funding is almost non-existent.” (3) This respondent suggested that “we should transmit to society that mental disorders are diseases that are treatable…but if the funding does not increase by many times, we won’t be able to improve [the available treatments].” Another

respondent stated that the issue also concerns the types of research that are funded: “Most funding is focused on basic/translation research with only a small proportion on applied research and implementation science.” (5) This respondent suggested that “advisory groups and funders [should take] a broader view so that the whole of the translational research continuum from most basic to most applied research is reasonably well-funded.”

Finally, several respondents expressed the need for greater transparency in research funding, with one noting that it is “unclear how any literature is actually being funded”. (6) To address this, “we need much more transparency. Researchers should be obliged to disclose their funding, also to avoid conflicts of interest.” (7) Another respondent stated that “I think, in general, the research community is still on its way in terms of transparency, so I’m clearly in favor of open reporting.” (1)

3.2.2. Role of the Private Sector

Private funding, “which usually comes from the pharmaceutical industry in our field, has been diminishing and we have to more and more rely on public funding, which would not be a problem if it were sufficient.” (7) Pharmaceutical manufacturers “have not been duly active in this area in the last 10 years” and “haven’t had any blockbuster drugs coming along in this area for quite a long time.” (2) The same respondent noted that although MHDs clearly represent a “major market” for the pharmaceutical industry, commercial research is “not likely to happen unless there’s potential to make money out of it, ultimately, and that opportunity does not seem to exist at the moment because we don’t have novel therapies coming through." Part of the problem, according to another respondent, is that “industry has to develop drugs based on a clinical model rather than pre-clinical models and most of them are not very satisfying”, which points to the need to focus on the “pharmacology of neuropathy” to better understand this “very important area of modulation of brain function and behavior.” (4)

One respondent cited the Innovative Medicines Initiative (IMI), a public-private partnership designed to bring public researchers and the pharmaceutical industry together, but worried that the research scope has been driven by industry, which has “been able to channel public money” towards research “they would have done anyway with their own money.” (1)

In the case of private research funding from charities, several respondents cited the lack of charity engagement in mental health in Europe, particularly compared to charity involvement in other major NCDs, such as cancer and diabetes. “I think that in areas in cancer, the improvement in research has been driven by similar organizations that have tried to push for increases in funding and also, they have raised a lot of money, but this is not the case in mental disorders.” (3) In addition, private charities generally are less common in certain regions, such as northern Europe. Nonetheless, one respondent suggested that private charities could play a role in addressing the issue of stigma, which is an impediment to “public support for research in this area.” (2)

3.2.3. Coordination

Another prominent theme regarding MHD research in Europe is a lack of coordination, which has resulted in inefficiencies. For example, there “is a lot of research going on that is just a replication of research, which has already been undertaken in some other European country” despite the fact that “the costs and challenges are very much the same everywhere. We can learn so much from each other.” (6) The inefficient use of time and resources can be avoided though “much more

collaboration" among stakeholders and by ensuring that new research is always "based on a systematic review of existing research to avoid replication of efforts." (7)

One respondent said that lack of coordination was also attributable to a "strong disconnection between the research community and the healthcare community" in psychiatry. (4) This respondent said that the lack of an "evidence based culture" impedes "knowledge translation" and the ability "to spread and implement the outcomes of research." In contrast to other disease areas, such as cancer and cardiology, where "there is clearly a community of researchers working together in order to address the optimization of treatments", while "here we have the feeling that the community is still a bit fragmented" and the "culture of cooperation underdeveloped", including at the international level. (4) Another respondent pointed out that "there is little data sharing" and called for an organization that could facilitate "the sharing of information across countries, studies, groups, etc.", perhaps by means of incentives for investigators and standard ways of acknowledging research outputs. (3) Part of the reluctance to share data stems from the fact that MHD researchers view cohort and clinical trial participants as their patients. "You have a cohort that is funded by public money and the patients in this cohort are not your patients. And this is something that has to change and the same with data from clinical trials. The patient data should be made available to the scientific community for reanalysis because opening your data for reanalysis is the best demonstration that you trust your data and trust the statistical analysis of your data." (4)

Comparability of data is another issue that affects coordination. Currently, "even simple measurements are not really comparable sometimes" because there is "not 100% agreement on how to measure" MHDs. (6) However, the need for comparable data is essential in order to address the substantial burden of disease. "We need to have datasets able to say for each EU Member State and across the EU as a whole (a) what is the mental health gap (i.e., the percentage of people with mental illness who receive treatment and care) and (b) whether this gap is changing over time." (5) Existing epidemiological data sources include ESEMeD, which collects data for six countries, and Eurostat, although one respondent noted that the latter provides insufficient detail with respect to diagnoses. A major impediment to standardizing data collection at the national level is institutional inertia: "In each country the data systems have kind of their own structure and they are very heavy bodies to move things and change things and to move away from one way of measuring to another one because other countries have pushed to do so is really not straightforward at all." (6) Another challenge is the lack of agreement regarding which disorders should be included as MHDs. One respondent noted that "some researchers exclude more organic brain disorders, like dementia or intellectual disabilities, which have basis in brain disorders or brain disturbances, and they only include those that have mental and behavioral aspects." (7) This respondent said that "it would be beneficial to have a common standard", particularly "a clear definition of mental health disorders in ICD-11."

3.2.4. Priorities

Respondents differed in their views regarding the priorities for MHD research in Europe, in terms of the process of setting the agenda and the type of research to be emphasized.

At the national level, a respondent described the "very active" process that takes place in setting priorities in one country, which looks at "spending, mortality, morbidity and consultations and we base our priorities partly on those and partly on where the opportunities are to match the negative

implications." (2) This respondent acknowledged that "patterns of morbidity vary from country to country" as do patterns of care. These differences can challenge the transfer of mental health promotion and prevention interventions because they may be "culturally specific, so I don't know how many of them will play in other countries" or even in rural versus urban settings and those areas with much ethnic diversity.

At the European level, several respondents described the consensus-seeking process used in the ROAMER project, which sought to include the broad spectrum of stakeholders to define the mental health research agenda. The project "involves the key research units in Europe and also has input from the patient perspective" and "tries to have connections with the funding stakeholders" with the goal of having "everyone around the table", although it is also "clearly a researcher-driven process." (1) Involving patients is viewed as critical to prioritizing research. "We need deeper collaboration with patients. Patients shouldn't just be subjects for research – they should be agents helping to drive the agenda. Also, carers and family members need to be taken into account." (3)

In terms of the content of the research agenda, there was a divergence among respondents favoring a public health approach versus a medical, individual treatment-oriented approach. One respondent identified the key elements of the public mental health research agenda: mental health promotion, prevention of MHDs, the organization of mental health systems, mental health policy and epidemiology. (7) In particular, improvements are needed in both "prevention and diagnosis" across the different regions and countries in Europe by examining the risk factors for MHDs, which are different between countries and different "in cities than in rural areas." (8) One respondent underscored "youth mental health" as being "neglected in policy practice and academic research. Another area neglected would be the impact of maternal mental health and its consequences on children." (10)

The EC's strategic focus, as set forth in the 2008 European Pact for Mental Health and Well-being and the 2013 Joint Action on Mental Health and Well-being, was described by one respondent as more of a "social vision" of mental health rather than a medical perspective. (3) Nonetheless, it is clear that the two are not mutually exclusive but rather complementary. "We need long-term cohort studies where we also look at risk factors and protective factors to find out the reasons for mental disorders." (7)

Several respondents underscored the importance of identifying biomarkers to better understand prediction, etiology, diagnosis and outcomes of MHDs. One respondent emphasized that "the psychiatric community should really endorse a pragmatic medical approach" because the link with "high credibility neuroscience" is currently missing. (4) There needs to be much more emphasis on "trying to find biomarkers and biomarkers from neuroimages, from neuropsychological assessments, from genes or genomics." (3) To that end, the "construction of biobanks" in Europe is essential to facilitating mental health research. (8) Moreover, it is important to increase the research focus on areas with no or few treatments in addition to "where there are some treatments available." (4)

Regardless of how the priorities are set and which ones are at the top of the research agenda, respondents agreed that the critical elements are ensuring the continuity of research and its translation into mental health care. "It serves nothing to produce a report and then pass to another study." (8) One of the lessons from ROAMER is that "once you stop pushing for change, nothing happens. So we have set a number of recommendations, but what we find now is that we need to continue pushing for those or nothing will happen." (3) Now that the ROAMER Roadmap has

identified research needs and suggested priorities, it is up to "the European Commission to follow this up and steer funding to the most important topics." (7)

3.3 Discussion and Conclusion

The semi-structured interviews highlighted several themes that provide insight into the current state of mental health research in Europe and the areas of consensus and divergence among key opinion leaders. Despite some recent improvements in the mental health research environment in Europe, respondents cited a number of critical concerns that must be addressed to reduce the burden of disease of MHDs.

All respondents expressed concern that while mental health research funding in Europe has increased it remains too low and is not consistent with the burden of disease. These experts disagreed regarding whether disorder-specific MHD research funding should be prioritized based on severity or frequency and also whether the orientation should favor public health initiatives or development individual medical treatments. Several respondents pointed out that EC funding strongly influences priorities but argued that a coordinating structure at the European level specifically devoted to MHDs was needed.

The diminished level of R&D investment in MHDs by the pharmaceutical industry was also cited as a significant challenge. Public institutions likely will have to step into the gap to fund basic research aimed at identifying biological targets because current MHD drug development is based on a clinical rather than pre-clinical model. Compared to major NCDs such as cardiovascular disease and diabetes, the majority of mental health disorders currently lack an independent biological basis that would allow for straightforward diagnosis (Tyrer, 2014). One of the main goals of the IMI PPP is to develop methods and tools that can help the development of new treatments.

In terms of the reasons for underfunding, several respondents mentioned the role of stigma. One way to address the effects of stigma could be through awareness campaigns by private charities, which play a large role in patient advocacy for several major NCDs. However, there is a significant lack of charity engagement for MHDs in Europe, especially compared to other NCDs, such as cancer. A new private mental health charity, the MQ Foundation, has been established in the UK and is currently looking at mental health from a translational science perspective, focusing not only on the biological and psychological aspects of MHDs but also encompassing patient perspectives. Several respondents emphasized the need for inclusion of all stakeholders in setting priorities for MHD research, including patients, caregivers and community members, and this has been a key element in the ROAMER project (Fiorillo *et al.*, 2013).

Policymakers and researchers alike should focus on facilitating coordination of mental health research in order to address redundancy, the disconnect between the research and healthcare communities and the lack of comparability of data and measurements. With respect to the latter, there is a need to improve standard definitions of mental health disorders in order to achieve better diagnosis agreement and treatment (Kendell *et al.*, 2003). Such efforts must include advancements in biomarkers and the use of genomics to help build a better understanding of these complex disorders (Insel, 2009).

Ultimately, the key question is on what basis research priorities should be set, whether by disease burden (as measured by DALYs, for example), the cost burden of the disease or disease area, the degree of unmet needs or the potential return on investment given the opportunities to address the

negative implications of MHDs. This question will be explored in greater depth in the synthesis phase of the Mapping_NCD project.

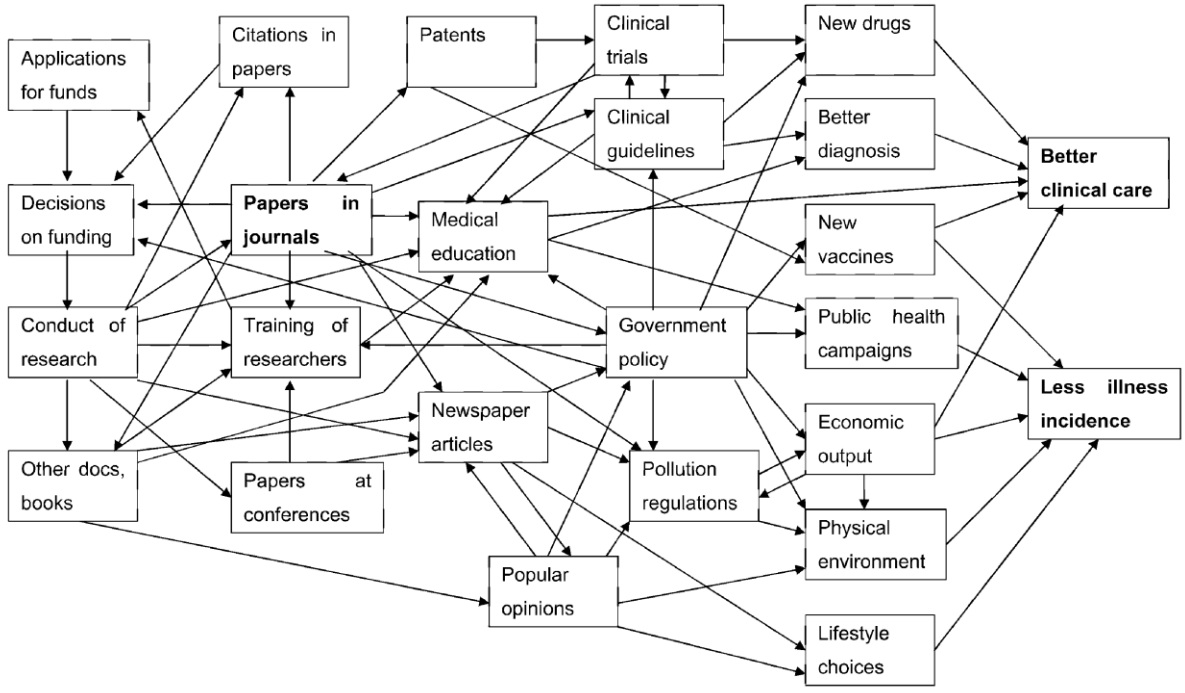
4 Bibliometrics: Impact of MHD Research Funding

A major aim of the MAPPING_NCD project is to establish the impact of funding investment across five key NCDs: cardiovascular disease, chronic respiratory diseases, diabetes, cancer and mental health. To this end, we have undertaken bibliometric analysis of research outputs across the EU and in individual MSs relevant to these disease areas to measure the impact of funding investments. This effort, led by our partners at King's College London (KCL), has resulted in mapping and analyses of the volume, citations, funding sources and influence on clinical guidelines and newspaper stories of research papers and reviews published in EU MSs for the period 2002-2013. Funding is considered to have had 'impact' where the funded research produces scientific papers. Bibliometric analysis further identifies the specific impact of individual research papers through funding acknowledgments and citations in other relevant papers. It also considers the extent to which they have provided the evidence base for clinical guidelines relevant to various NCDs as well as whether they have been cited in newspapers and the broadcast media. Thus, the impact of a paper is associated with the relative values that papers achieve against these measures.

4.1 Measuring Research Impact

Measuring the impact of research is a complex task. Health improvements often depend on a variety of different research discoveries made at different times and in different places. The pathway from the conduct and publication of research to better health is usually indirect. Moreover, the results of research contribute to better health in different ways, from improved diagnosis and treatment to the prevention of illness or reduced incidence. Figure 4.1 depicts some of the links between research funding and health impacts.

Figure 4.1 Some of the links between research and healthcare improvement



Research impacts upon all these linkages and nodes, most of which are not specific to individual disease areas, and different types of research may deliver advances in individual disease areas. Thus, the norms for measuring both the effectiveness of research and its quality can also differ. Nonetheless, the evidence of research impact manifests itself in the paper trails that flow from one node to another. For example, research funding produces research, which results in papers in scientific journals, which in turn lead to citations in other journals and may even result in media stories, all of which may influence clinical practice and policy decisions. Tracking and analyzing these paper trails – and using them as a proxy for research impact – is the fundamental business of bibliometic research.

In this section of the paper, we utilize bibliometric methods to analyze output of scientific research papers in the field of MHDs and their subsequent citation in other papers. These data are then further analyzed in light of the disease burden for ten specific MHDs. Data regarding funding sources, the evidence base of clinical guidelines and news stories reporting on research papers were not available for MHDs at the time of this report but will be included in the Synthesis Report.

4.2 Scientific Research Papers: MHDs

4.2.1 Methodology

The first means by which bibliometric analysis establishes funding impacts is by the number of published scientific papers. This section of the report details the number of articles and reviews for MHDs downloaded from the Web of Science (WoS) for 31 European countries (the EU28 plus Iceland, Norway and Switzerland) for the period 2002-2013. Table 4.1 lists the countries with their digraph ISO codes. The analyses used two overlapping databases, the Science Citation Index Expanded (SCI) and the Social Sciences Citation Index (SSCI).

Table 4.1 List of 31 countries used to limit the downloaded papers

ISO	*Country*	ISO	*Country*	ISO	*Country*	ISO	*Country*
AT	*Austria*	**EE**	*Estonia*	**IS**	*Iceland*	**PL**	*Poland*
BE	*Belgium*	**ES**	*Spain*	**IT**	*Italy*	**PT**	*Portugal*
BG	*Bulgaria*	**FI**	*Finland*	**LT**	*Lithuania*	**RO**	*Romania*
CH	*Switzerland*	**FR**	*France*	**LU**	*Luxembourg*	**SE**	*Sweden*
CY	*Cyprus*	**GR**	*Greece*	**LV**	*Latvia*	**SI**	*Slovenia*
CZ	*Czech Rep.*	**HR**	*Croatia*	**MT**	*Malta*	**SK**	*Slovakia*
DE	*Germany*	**HU**	*Hungary*	**NL**	*Netherlands*	**UK**	*United Kingdom*
DK	*Denmark*	**IE**	*Ireland*	**NO**	*Norway*		

Papers were identified by means of a “filter” for which precision and recall were determined by experts in the subject area who marked sets of papers as relevant or not. Filters were developed for each of the five disease areas:

- Cancer research (oncology): ONCOL
- Cardiovascular research, including stroke: CARDI
- Diabetes research: DIABE
- Mental health disorders research: MENTH, and
- Respiratory disease research: RESPI

Each paper in the combined sheet was given an individual index number, and the following parameters were recorded:

- Names of all authors, in the format SMITH-AB
- Paper title
- Source (journal name, year, volume, issue, pages)
- Journal name
- Document type (article or review)
- Addresses
- Country of publication
- Year of publication
- Month of publication
- Language (almost exclusively English)
- E-mail address(es) of corresponding author, others
- Funders, FU (from late 2008 forward)
- Funding acknowledgement text, FX
- Composite list of authors and their individual addresses (from 2008)
- Authors' full names (where given)
- Whether found in the SCI or SSCI only

From the paper title, a macro was applied to determine whether the paper should be classified as "clinical " or "basic" or "both", based on the presence of one or more words on two lists (Lewison and Paraje, 2004). The research level of the journal was determined from a master list, based on the same scheme, with clinical journals classified as RL = 1, basic journals as RL = 4, and those falling between given an RL value between 1.0 and 4.0. RL values were determined for groups of five years, 2000-04, 2005-09 and 2010-14.

In order to measure the impact of MHDs, a specialized MENTH filter was created, consisting of two main parts: a list of specialist journals and another list of title words. The filter was initially developed in consultation with Professor George Szmukler of the Institute of Psychiatry, KCL in connection with another project and was subsequently updated under his guidance and further updated and calibrated in consultation with Professor Isabelle Durand-Zaleski (UPEC) and her team. The definition of mental disorders excluded mental retardation and autism, but included the following:

> *Alcohol use disorders, Alzheimer's disease and other dementias, Anxiety disorders, Attention-deficit hyperactivity disorder, Bipolar affective disorder, Childhood behavioral disorders, Drug use disorders, Eating disorders, Major depressive disorder, Schizophrenia, Suicide and self-harm, Unipolar depressive disorders*

The calibration gave a **precision, p = 0.729** and a **recall, r = 0.879**.

4.2.2 Outputs for the five NCDs

In order to provide a context and perspective for the MHD research outputs, we first looked at the world and EUR31 outputs for the five NCDs studied in the Mapping_NCD project (Table 4.2). EUR31 outputs for MHDs accounted for 40% of the world output and 5.7% of the total biomedical output for the study period.

Table 4.2 World and EUR31 outputs for the five NCDs compared to overall biomedical research output (2002-2013)

Subject	World output*	EUR31 output*	EUR31 as % world output	% of EUR31 BIOMED output
BIOMED	6075502	2442063	40	
ONCOL	748724	282055	38	11.5
CARDI	508611	211507	42	8.7
MENTH	349027	138666	40	5.7
DIABE	103792	40550	35	1.7
RESPI	33629	18822	56	0.8

**Number of research papers published in the disease area*

4.2.3 Results and analysis of MHD outputs in the EUR31

EUR31 research outputs for MHDs as a group as well as by individual countries were analyzed in multiple ways. The growth in EUR31 research output for MHD papers over the period 2002-2013 was compared to the world output as well as to overall biomedical research output. The output of each EUR31 country was also explored, including the growth rate and the degree of international collaboration. These data were further analyzed by Gross Domestic Product (GDP) to determine variation in expected outputs based on individual countries' economies. We also examined changes in the research levels of the journals (whether clinical, basic or falling between). Finally, we examined the research outputs by individual disorders, both across the EUR31 and by country. These results were also considered in light of the disease burden for 10 specific MHDs.

Unlike the research outputs for other NCDs, a significant number of MHD papers were covered only in the Social Sciences Citation Index (SSCI) and not the Science Citation Index (SCI) (29,617 of a 138,666 or 21%), although many papers were included in both indexes. The papers only included in the SSCI had different citation characteristics: fewer within five years of publication, with a peak between five and seven years following publication rather than two to three. Nonetheless, they were grouped with the other papers for the main analyses. World and European outputs for MHD papers for the period 2002-2013 are shown in Table 4.3.

Table 4.3 EUR31 outputs for MENTH papers in WoS (2002-2013), integer and fractional counts

MENTH						MENTH/BIOMED %	
Year	World	EUR31 int	EUR31 frac	EUR31, % World	Int'l collab, % EUR31	World	EUR31
2002	19830	7700	7041	38.8	8.6	5.33	4.87
2003	20786	8123	7380	39.0	9.1	5.36	4.97
2004	22142	8774	7948	39.6	9.4	5.46	5.20
2005	23779	9396	8446	39.5	10.1	5.59	5.32
2006	25896	10122	9096	39.1	10.1	5.75	5.46
2007	28503	11283	10067	39.6	10.8	5.88	5.70
2008	30189	11831	10496	39.2	11.3	5.79	5.66
2009	32162	12721	11276	39.6	11.4	5.90	5.87
2010	33300	13508	11940	40.6	11.6	5.83	5.99
2011	35252	14176	12486	40.2	11.9	5.82	6.03
2012	37532	15067	13220	40.1	12.3	5.85	6.07
2013	39656	15965	13904	40.3	12.9	5.96	6.22

European MHD research output has remained remarkably constant over the period at nearly 40% of world output. This may be because MHDs have not yet become a major research focus in East Asia. Today, European MHD research represents a larger share of overall biomedical research (6.2% compared with 4.9% in 2002), whereas there has been less of a shift in the worldwide research output (from 5.3% to 6.0%).

For each of the EUR31 countries, we determined the integer and fractional count totals over the 12-year period. We also calculated the annual average percentage growth rate (AAPG) based on fractional counts, which was obtained from a plot of the logarithm of the number of papers each year. Moreover, as we wished to investigate the extent and nature of international collaboration, we recorded the percentage of papers resulting from international collaboration with 11 major countries: Australia, Brazil, Canada, China, Israel, India, Japan, Korea, Turkey, Taiwan and the United States. Bibliometrics may also identify the potential for international collaboration. Indeed, countries with smaller scientific output usually have a greater need to seek partners abroad. Here, bibliometrics can help to identify MSs with lower levels of collaboration in a given subject area than would be expected, which may suggest the need for efforts to encourage such partnerships. The results for the individual European countries are shown in Table 4.4.

The UK had by far the highest output. As expected, smaller countries tended to have higher levels of collaboration, with international contributions exceeding 40% in Bulgaria, Malta, Luxembourg, Iceland, Cyprus, Latvia, Switzerland and Estonia. Switzerland is an outlier in this group, as it has both a high output as well as a high degree of international collaboration.

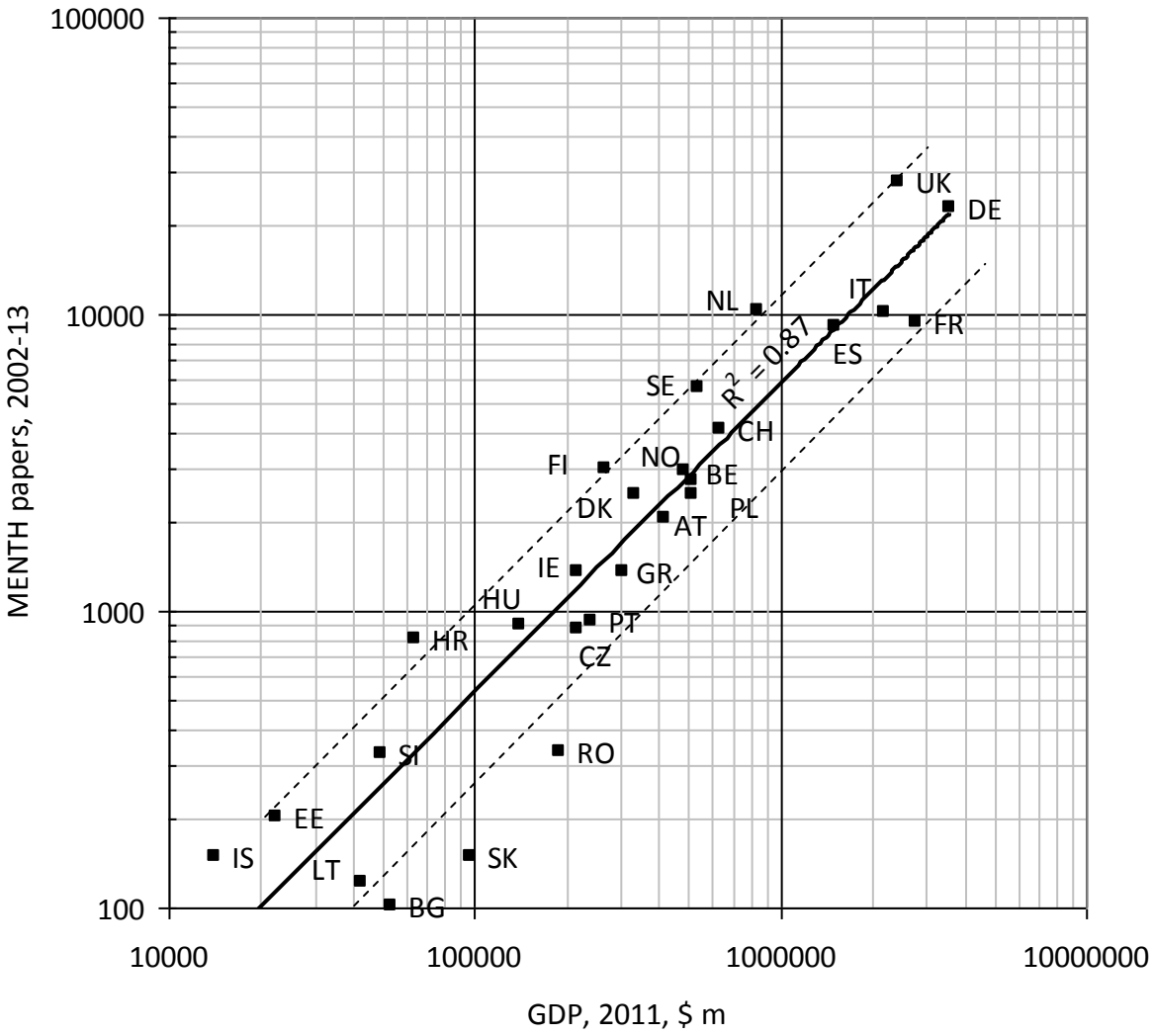
Table 4.4 EUR31 MENTH SCI and SSCI (2002-2013), integer and fractional counts*

Country	Int ct	Frac ct	% Int'l collab	AAPG		Country	Int ct	Frac ct	% Int'l collab	AAPG
UK	38199	28072	26.5	4.7		**PT**	1412	926	34.4	19.9
DE	28903	22945	20.6	4.3		**HU**	1431	898	37.2	5.8
NL	13815	10241	25.9	11.7		**CZ**	1157	869	24.9	12.2
IT	13523	10226	24.4	8.2		**HR**	950	801	15.7	11.4
FR	12202	9468	22.4	6.1		**RO**	516	337	34.7	37.1
ES	11405	9079	20.4	9.4		**SI**	495	329	33.5	15.1
SE	8082	5652	30.1	4.6		**EE**	346	203	41.3	12.1
CH	7055	4128	41.5	4.9		**IS**	300	149	50.2	8.8
FI	4014	3001	25.2	3.0		**SK**	244	149	38.9	9.8
NO	4040	2970	26.5	8.3		**LT**	188	122	34.8	16.2
BE	4617	2773	39.9	7.8		**BG**	236	102	56.7	8.5
PL	3048	2480	18.6	12.0		**LU**	127	63	50.5	15.7
DK	3693	2460	33.4	8.6		**CY**	85	47	44.6	23.5
AT	3304	2045	38.1	1.2		**LV**	36	21	42.4	13.4
GR	1860	1368	26.5	8.2		**MT**	35	17	51.5	5.0
IE	2256	1358	39.8	11.2						

***For the percentage international collaboration and the annual growth rate, the countries are ranked by their fractional count outputs.*

Country outputs were compared with GDP to explore which countries published more than expected and which, less (Figure 4.2). Research output tends to be correlated with GDP rather than population, and we plotted countries' fractional paper counts against GDP for a representative year (2011). In addition to the UK, several other countries published about twice the amount shown by the trend-line: Croatia, Iceland, Finland, Netherlands, Sweden and Estonia. However, France and Lithuania published barely half the expected number of papers, while Slovakia, Romania, Bulgaria published fewer than half.

Figure 4.2 Plot of MENTH paper output (2002-2013) against 2011 GDP for 27 European countries with fractional counts >100 papers*



**CY, LU, LV and MT omitted. Dashed lines show values x2 or x0.5 relative to power trend line.*

MHDs encompass a broad range of disorders, and the extent of the research focus on particular MHDs is quite variable. The 16 MHDs that were investigated are listed in Table 4.5.

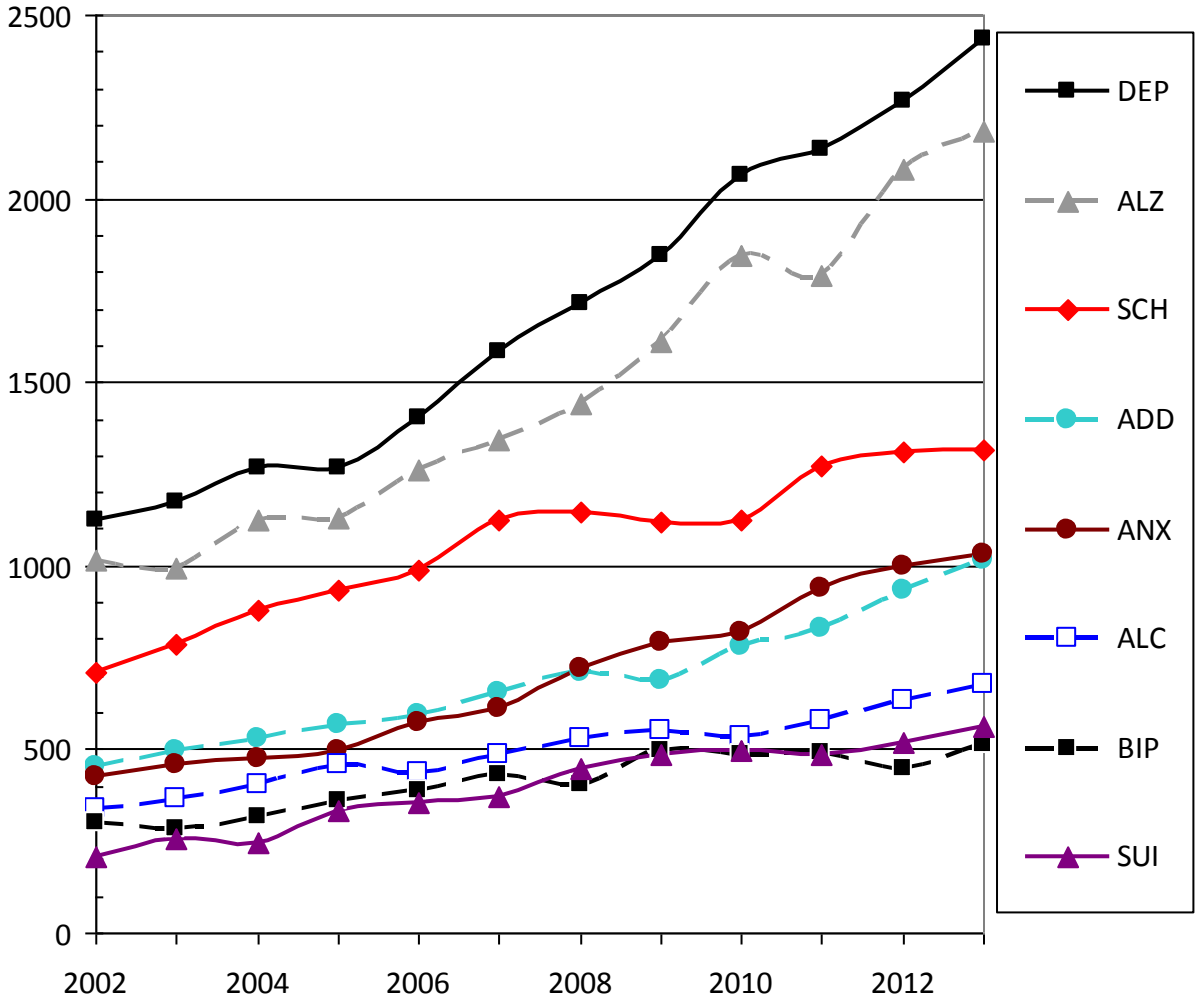
Table 4.5 16 MHDs investigated, with their codes, numbers of papers and % of total MENTH output

Disorder	Code	Papers	%
Depression (unipolar)	DEP	20278	14.6
Alzheimer's & dementia	ALZ	17810	12.8
Schizophrenia	SCH	12706	9.2
Anxiety disorder	ANX	8337	6
Addiction	ADD	8251	6
Alcoholism	ALC	5994	4.3
Bipolar disorder	BIP	4916	3.5
Suicide & self-harm	SUI	4767	3.4

Personality disorder	PER	4221	3
Eating disorders	EAT	3506	2.5
Hyperactivity	HYP	3007	2.2
Post-traumatic stress	PTS	1967	1.4
Obsessive compulsive disorder	OBS	1631	1.2
Sleep disorders	SLE	1430	1
Sexual disorders	SEX	690	0.5
Chronic fatigue syndrome	CFS	199	0.1

The increase in MHD research between 2002 and 2013, which more than doubled (x 2.07), was seen in most individual disorders, particularly hyperactivity (x 4.5), sexual disorders (x 3.7, but from a low base), post-traumatic stress (x 3.4), suicide and self-harm (x 2.7) and eating disorders (x 2.5). However research on certain disorders, while increasing, fared less well, including chronic fatigue syndrome (x 1.1), bipolar disorder (x 1 .7) and schizophrenia (x 1.8) (Figure 4.3).

Figure 4.3 Growth of EUR31 MENTH output in eight disease areas (2002-2013)



Individual countries varied in their relative commitments to research on these individual disorders (Table 4.6).

Table 4.6 MENTH outputs for top 10 MHDs in EUR31 countries (2002-2013), fractional counts

Country	DEP	ALZ	SCH	ADD	ANX	ALC	BIP	SUI	PER	EAT	Total
UK	3250	3065	2371	1493	1617	947	916	1110	944	793	28072
DE	3097	2212	2144	920	1267	915	543	572	728	550	22945
NL	1980	1103	672	518	1037	425	187	159	444	120	10241
IT	1463	2206	847	737	490	325	542	273	293	418	10226
FR	1364	1447	914	768	430	328	339	279	183	241	9468
ES	1137	1486	963	850	572	504	449	161	375	360	9079
SE	723	1071	319	273	385	430	113	318	122	133	5652
CH	497	402	418	367	190	188	122	159	102	66.9	4128
FI	594	354	261	126	127	317	67.5	149	72.3	34.1	3001
NO	453	206	202	223	257	103	102	150	132	84.7	2970
BE	450	387	201	124	165	140	63.6	90	132	87.6	2773
PL	644	276	270	153	140	140	158	50.9	29	91.8	2480
DK	556	179	329	134	110	146	115	126	61.5	42	2460
AT	283	418	203	131	118	56.2	71.4	147	45.1	44.2	2045
GR	287	161	156	80.3	112	45.1	84.5	48.5	34.3	19.3	1368
IE	200	158	173	81	62.6	46.1	54.8	79.1	21	2.26	1358
PT	140	175	55.9	67.1	59	41.2	45.7	16.9	31.2	23.8	926
HU	169	108	103	62	58	25	35.8	76.7	16.4	18.3	898
CZ	149	119	124	58.8	25.4	16.3	39.1	28	23.8	46.8	869
HR	155	75.8	117	22.6	49.7	26.2	31.7	69	14.9	11.6	801
RO	48.2	37.2	17.1	29.1	27.8	8.81	44.8	15	5.7	1.74	337
SI	60.2	26.4	35.2	24.3	21	24.2	9.57	47	7.05	4.27	329
EE	56.3	11.5	2.2	13	27.9	15.8	1.55	26	3.05	5.53	203
IS	22.4	11.4	11.4	8.42	12.8	5.97	0.77	10.8	4.34	3.74	149
SK	26.9	25.1	7.24	14.2	21.6	8.02	3.24	3.95	0	0.75	149
LT	28.3	6.7	7.87	11.2	5.81	13.6	3.67	8.88	0.63	3	122
BG	21	13.4	17.3	9.93	4.64	0.46	8.17	2.23	1.94	0.91	102
LU	2.98	4.32	1.73	6.31	6.87	2.96	3.08	2.66	3.2	3.42	63
CY	6.37	5.88	3.67	3.75	6.78	2.33	0.83	0.58	2.67	2.5	47
LV	0.83	0	0.83	1.67	0	1.13	0	0.67	0.67	0	21
MT	3.17	4.33	0.25	1.7	0.67	0	0	0.84	0	0	17
EUR31	17868	15755	10948	7312	7408	5247	4156	4181	3834	3214	123301

Table 4.7 reveals major variations in countries' research output to what would be expected on the assumption that MHD portfolios would be similar to the output of the EUR31. The individual cells are colored to show particularly high or low relative commitment to research on a particular disorder. Most of the differences between observed and expected values were statistically significant at the 5% level or lower.

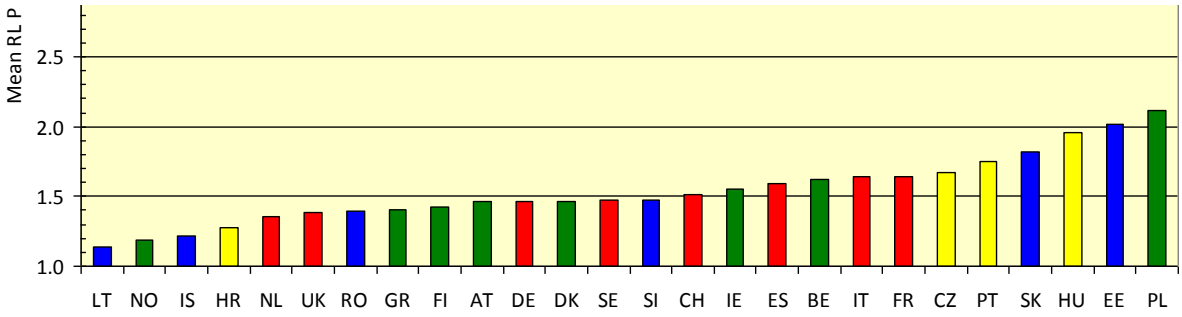
Table 4.7 Ratio of observed to expected numbers of papers relevant to 13 mental disorders for 20 European countries with >800 papers (2002-2013)*

ISO	*DEP*	*ALZ*	*SCH*	*ADD*	*ANX*	*ALC*	*BIP*	*SUI*	*PER*	*EAT*	*HYP*	*PTS*	*OBS*
UK	0.80	0.85	0.95	0.90	0.96	0.79	0.97	1.17	1.08	1.08	0.83	0.99	0.87
DE	0.93	0.75	1.05	0.68	0.92	0.94	0.70	0.74	1.02	0.92	1.37	1.07	1.29
NL	1.33	0.84	0.74	0.85	1.69	0.98	0.54	0.46	1.39	0.45	1.45	1.99	1.45
IT	0.99	1.69	0.93	1.22	0.80	0.75	1.57	0.79	0.92	1.57	0.60	0.46	1.49
FR	0.99	1.20	1.09	1.37	0.76	0.81	1.06	0.87	0.62	0.98	0.56	0.64	0.82
ES	0.86	1.28	1.19	1.58	1.05	1.30	1.47	0.52	1.33	1.52	1.28	0.30	1.29
SE	0.88	1.48	0.64	0.81	1.13	1.79	0.59	1.66	0.69	0.90	1.41	0.91	0.36
CH	0.83	0.76	1.14	1.50	0.77	1.07	0.88	1.14	0.79	0.62	0.77	2.02	0.78
FI	1.37	0.92	0.98	0.71	0.70	2.48	0.67	1.46	0.77	0.44	0.63	0.16	0.14
NO	1.05	0.54	0.77	1.27	1.44	0.81	1.02	1.49	1.43	1.09	1.37	1.44	0.69
BE	1.12	1.09	0.82	0.75	0.99	1.19	0.68	0.96	1.53	1.21	1.24	0.48	0.91
PL	1.79	0.87	1.23	1.04	0.94	1.33	1.89	0.61	0.38	1.42	0.32	0.51	0.36
DK	1.56	0.57	1.51	0.92	0.74	1.39	1.39	1.51	0.80	0.66	0.88	1.59	0.79
AT	0.95	1.60	1.12	1.08	0.96	0.65	1.04	2.12	0.71	0.83	0.39	0.80	0.66
GR	1.45	0.92	1.28	0.99	1.36	0.77	1.83	1.05	0.81	0.54	0.34	1.04	1.24
IE	1.02	0.91	1.43	1.01	0.77	0.80	1.20	1.72	0.50	0.06	1.71	0.15	0.23
PT	1.04	1.48	0.68	1.22	1.06	1.05	1.46	0.54	1.08	0.99	0.32	0.45	0.67
HU	1.30	0.94	1.29	1.16	1.07	0.65	1.18	2.52	0.59	0.78	0.60	0.39	0.68
CZ	1.18	1.07	1.61	1.14	0.49	0.44	1.33	0.95	0.88	2.06	1.07	0.22	0.85
HR	1.34	0.74	1.65	0.48	1.03	0.77	1.17	2.54	0.60	0.56	0.38	9.42	0.32

***Countries are ranked by total output using fractional counts. Mental disorders ranked from left to right by amount of research output based on integer counts.** *Values > 2 tinted bright green; values > 1.41 tinted pale green; values < 0.71 tinted gold; values < 0.5 tinted pink*.

In terms of content, MHD papers tend to be very clinical, as seen in Figure 4.4. For most large countries, the RL is around 1.5 and only exceeds 2.0 for Estonia and Poland, the latter perhaps due to the fact that its clinical mental health journals are in Polish and not covered in the WoS. Over the years, the mean RL declined from 1.60 to 1.47 revealing that the output became somewhat more clinical, although less of a difference was seen compared to the other NCDs.

Figure 4.4 Mean research level of MENTH papers from 26 European countries >100 or more classed papers (2002-2013)



Red bars: > 3000 classed papers (frac. cts); green bars: > 1000 papers; yellow bars: > 300 papers; blue bars: > 100 papers.

The mean research level of the papers on the different disorders is shown in Figures 4.5 and 4.6.

Figure 4.5 Chart of mean Research Level of papers and of journals in which they were published for MENTH papers on eight leading disorders with > 3.1% of papers. ***RL = 1.0 is clinical observation; RL = 4.0 is basic research.***

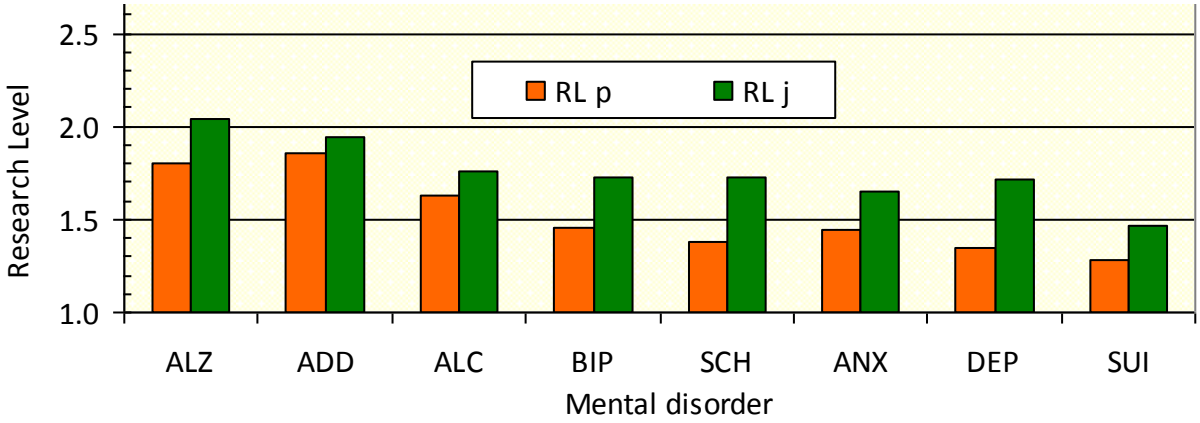
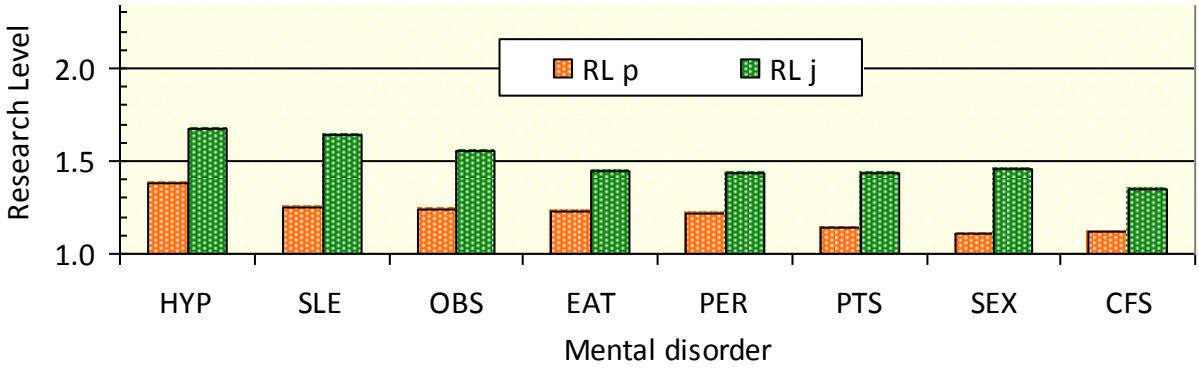


Figure 4.6 Chart of mean Research Level of papers and of journals in which they were published for MENTH papers on eight other disorders with < 3.1% of papers. ***RL = 1.0 is clinical observation; RL = 4.0 is basic research.***



Comparing the MHD outputs against the 2010 Global Burden of Disease data (IHME, 2013) potentially allows identification of where resources are being usefully invested and where savings might be made by deploying resources elsewhere. Conversely, where fewer papers are published in high burden areas, it also holds the potential to identify evidence of research gaps. Using this approach, bibliometric analysis provides an indication of the potential shortfalls, excesses and potential synergies in terms of MHD research funding.

The Global Burden of Disease data gives percentages of all DALYs for 10 MHDs, with a breakdown of certain disorders by sub-category, such as addiction to different classes of drugs. The disease burden in DALYs associated with only 10 of the 16 disorders we investigated were available in the Global Burden of Disease study (Table 4.8).

Table 4.8 List of the 16 individual mental disorders investigated with their codes. Disorders for which the disease burden was available in the 2010 GBD Study are indicated in bold.

Mental disorder	*Code*		*Mental disorder*	*Code*
Drug use and other addictions	**ADD**		**Attention-deficit hyperactivity**	**HYP**
Alcohol use	**ALC**		Obsessive-compulsive disorder	OBS
Alzheimer's and other dementias	**ALZ**		Personality disorder	PER
Anxiety disorder	**ANX**		Post-traumatic stress disorder	PTS
Bipolar affective disorder	**BIP**		**Schizophrenia**	**SCH**
Chronic Fatigue Syndrome	CFS		Sexual disorder	SEX
Unipolar depression	**DEP**		Sleep disorder	SLE
Eating disorder	**EAT**		**Suicide and self-harm**	**SUI**

Table 4.9 reveals both differences and similarities among countries. None of the cells are colored in the columns for schizophrenia or bipolar disease. The bottom row shows which disorders are of most importance, and clearly depression is dominant, followed by dementia, anxiety and suicide & self-harm. There was generally poor correlation between the disease burden of particular diseases and the amount of research, which may suggest grounds for re-balancing some national research portfolios. For example, alcoholism and addiction to prescription drugs may result in a similar burden overall, but drug addiction leads to almost 40% more research than alcoholism, which appears to need more attention, particularly because of its pervasive social effects (Rajendram *et al.,* 2006).

Table 4.9 Percentages of DALYs attributable to MHDs in the EUR31 countries (2010)

ISO	*DEP*	*ALZ*	*SCH*	*ADD*	*ANX*	*ALC*	*BIP*	*SUI*	*EAT*	*HYP*	*MENTH*
UK	3.23	2.30	0.87	2.29	2.10	1.35	0.64	1.28	0.31	0.022	11.54
DE	4.57	1.91	0.81	1.12	1.79	1.50	0.61	1.63	0.29	0.015	11.36
NL	7.76	2.39	0.83	1.02	2.01	1.05	0.67	1.46	0.37	0.020	14.51
IT	4.81	2.46	0.84	1.43	1.40	0.40	0.66	0.88	0.27	0.016	10.50
FR	4.75	2.66	0.84	1.03	2.60	1.96	0.64	2.67	0.42	0.019	13.05
ES	4.82	3.19	0.98	1.88	1.21	0.80	0.76	1.05	0.52	0.019	11.72
SE	4.79	3.04	0.86	1.26	1.83	1.82	0.65	2.00	0.39	0.020	12.35
CH	6.60	2.34	0.95	1.28	1.70	1.19	0.73	2.54	0.44	0.020	13.67
FI	5.58	4.08	0.83	1.24	1.27	2.67	0.61	2.86	0.31	0.018	13.19
NO	5.72	2.52	0.85	2.12	2.83	2.16	0.65	1.77	0.45	0.021	15.55
BE	3.85	2.86	0.80	1.27	1.31	1.21	0.62	2.69	0.46	0.018	10.22
PL	3.49	0.92	0.77	0.99	1.90	2.13	0.63	2.41	0.15	0.014	10.70
DK	4.58	2.27	0.72	1.35	1.35	2.66	0.60	1.73	0.35	0.019	12.31
AT	4.94	1.68	0.84	1.68	1.43	1.60	0.66	2.16	0.55	0.018	12.41
GR	4.65	1.62	0.82	1.18	1.83	0.41	0.65	0.49	0.29	0.017	10.47
IE	4.63	1.66	0.93	2.14	1.81	1.39	0.78	2.13	0.55	0.026	13.10
PT	4.13	1.78	0.81	0.94	1.76	0.92	0.64	1.69	0.19	0.017	10.04
HU	2.58	1.22	0.68	0.62	1.59	1.00	0.53	2.45	0.13	0.011	7.65
CZ	3.15	1.04	0.83	0.72	1.94	0.74	0.67	2.02	0.22	0.013	8.92
HR	5.51	1.09	0.77	0.85	1.69	1.09	0.58	1.83	0.16	0.013	11.36

RO	3.34	0.74	0.71	0.71	0.80	0.97	0.57	1.36	0.08	0.012	7.73
SI	4.39	1.12	0.90	0.86	1.65	1.31	0.70	2.88	0.27	0.014	10.75
EE	5.18	1.09	0.69	1.64	0.91	2.91	0.59	1.94	0.15	0.012	12.66
IS	5.78	2.81	1.06	1.98	2.85	1.44	0.82	1.97	0.55	0.029	15.48
SK	3.33	0.78	0.79	0.82	1.65	1.20	0.66	1.91	0.19	0.015	9.27
LT	3.59	0.87	0.65	1.21	0.92	3.04	0.56	4.01	0.12	0.012	10.64
BG	3.21	0.73	0.64	0.57	0.81	0.49	0.50	1.20	0.09	0.010	6.79
LU	6.51	2.06	0.92	1.89	2.36	1.71	0.70	1.67	1.00	0.021	15.90
CY	6.04	1.64	0.91	1.22	2.00	0.95	0.74	0.57	0.32	0.026	13.03
LV	4.27	0.95	0.62	1.07	0.81	2.32	0.53	2.15	0.10	0.010	10.23
MT	6.64	1.82	0.91	1.53	2.37	0.89	0.70	0.69	0.27	0.022	14.10
EUR31	4.34	2.03	0.82	1.30	1.74	1.32	0.64	1.72	0.30	0.017	11.16

Countries are listed in order of MENTH research output in 2002-13; disorders are listed in order of research output – see Tables25 and 26. Cell tinting in reverse from that of research outputs: where mental disorder DALYs > 2 x European average, cells tinted pink; if DALYs > 1.41 x average, cells tinted gold; if DALYs < 0.71 x average, cells tinted pale green; if DALYs < 0.5 x average, cells bright green.

4.3 Citations of Research Papers

Bibliometric analysis uses five-year cite scores (academic citation index; ACI) to measure of the impact of research papers. For most NCDs, European research was better cited than the world average, although a high degree variation among countries can be seen. There were significant differences among disease areas in terms of their propensity to attract citations. This was due in part to the size of the researcher cohort (*i.e.*, the number of papers) for which the correlation with ACI was $r^2 = 0.49$. The mean five-year citation scores are shown in Figures 4.7 and 4.8.

Figure 4.7 Mean five-year cites for MENTH papers on eight leading disorders with > 3.1% of papers (2002-2009)

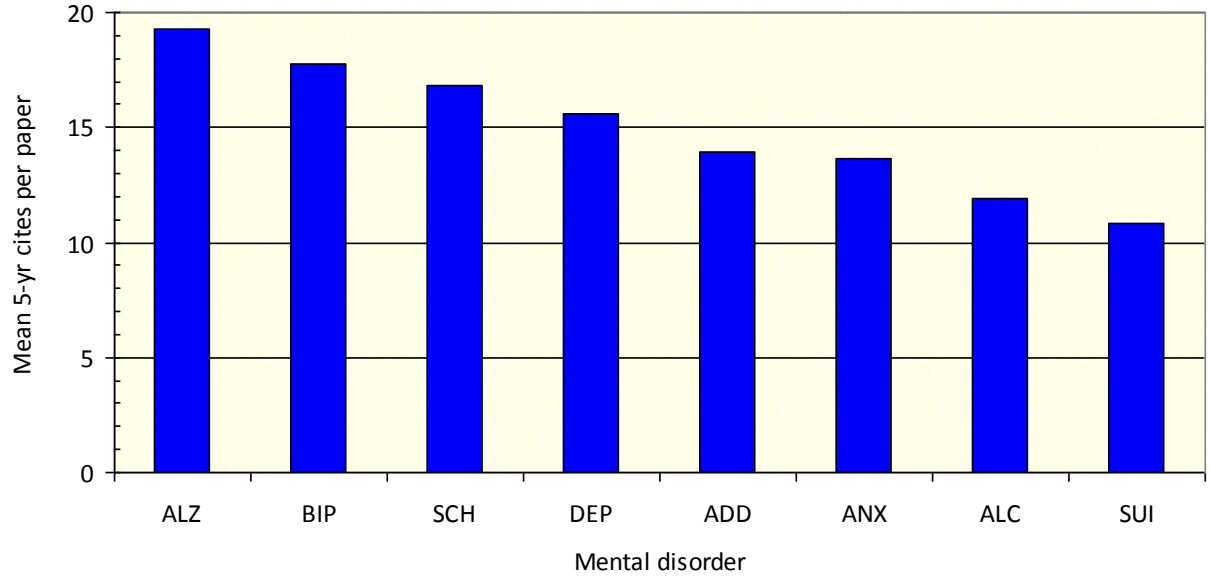
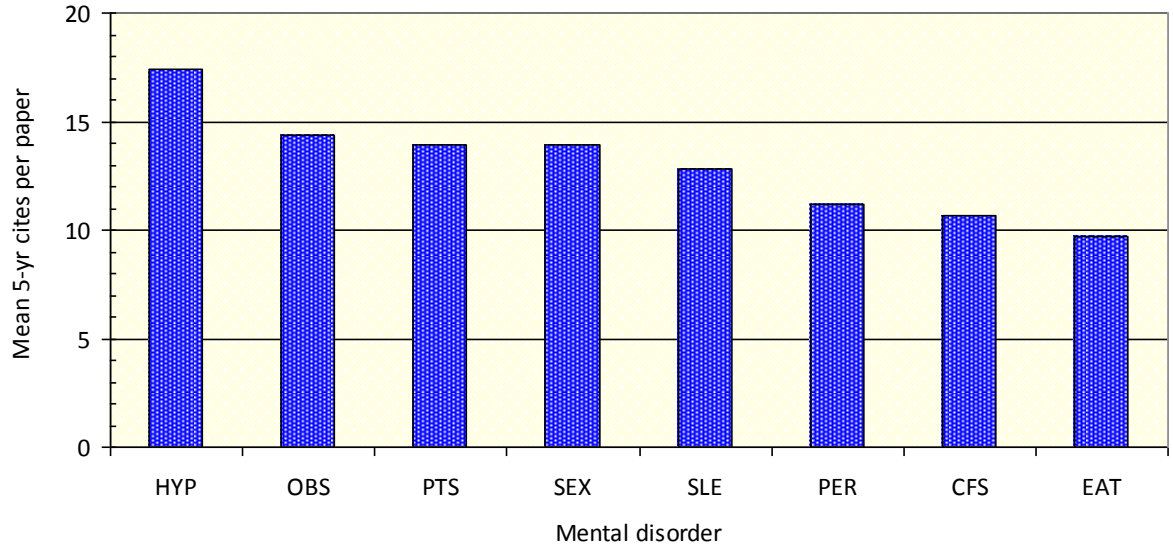


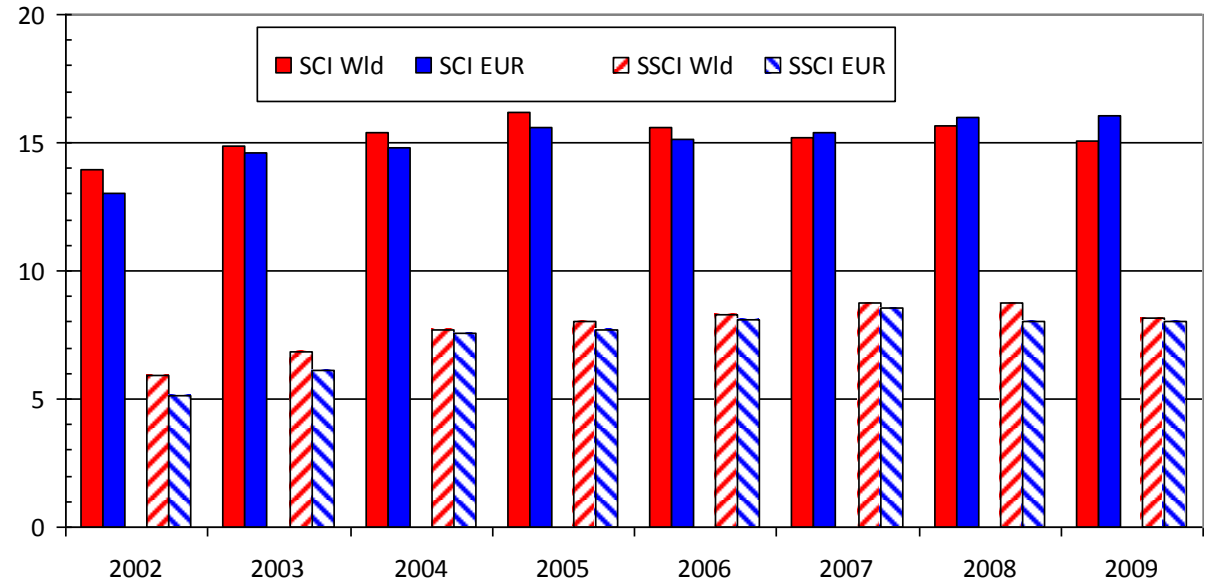
Figure 4.8 Mean five-year cites for MENTH papers on eight other disorders with <3.1% of papers (2002-2009)



There is a two-fold difference between the ACI for the most cited disorder (Alzheimer's and other dementias, 19.3) and the least cited one (eating disorders, 9.7). This is in part due to the numbers of papers identified for the two disease areas, although the correlation is only moderate ($r^2 = 0.28$).

For purposes of citation analysis, MHD papers were divided into two groups: those found in the SCI (some of which were also in the SSCI) and those found exclusively in the SSCI. The citation scores for the world and for the EUR31 countries are shown in Figure 4.9.

Figure 4.9 Increase in mean citations per MENTH paper for world (red), EUR31 (blue), exclusively SSCI (striped, red for world, blue for EUR31) (2002-2009)



The results for the SCI papers show that European papers had fewer citations in 2002-2006 than in 2007-2009. However, for the approximately one-fifth of papers found exclusively in SSCI, the European papers were less cited than the world mean throughout, likely because the world output is

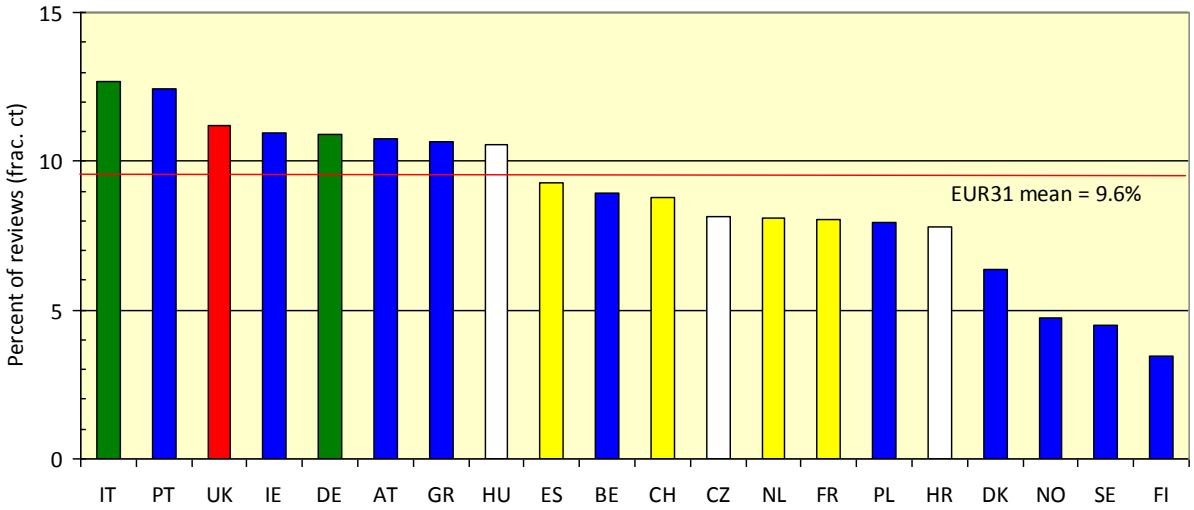
dominated by the USA and the rise of East Asian output has not yet spread into SSCI journals. The citation scores for individual countries in the top 5% of the cohort in terms of citations (minimum 49 cites for SCI and 26 cites for those found exclusively in SSCI) are shown in Table 4.10.

Table 4.10 Citation scores for MENTH papers from 16 European countries in the top 5% of the EUR31 cohort for SCI and exclusively SSCI (2002-2009)

ISO	*SCI ACI*	*Top 5%*	*% of N*		*SSCI ACI*	*Top 5%*	*% of N*
BE	15.52	58.8	5.18		8.92	38.1	8.94
AT	14.50	54.4	5.76		11.17	18.5	7.76
IE	16.62	39.8	6.31		6.67	8.8	5.11
NL	14.01	195.3	4.47		7.86	98.2	6.36
FR	15.08	226.8	5.05		8.51	34.0	5.56
UK	15.07	575.0	5.01		7.68	255.2	5.23
IT	15.66	263.2	5.04		6.47	26.6	4.54
FI	15.51	90.3	5.90		7.14	12.9	3.58
DE	14.61	522.5	5.20		7.63	140.0	4.21
ES	14.95	201.9	4.87		5.72	44.7	4.20
SE	15.47	130.4	5.03		7.91	31.1	3.74
HR	11.68	14.7	4.71		5.80	6.3	4.03
CH	14.71	83.6	4.58		7.12	21.7	3.79
DK	15.12	57.5	4.72		6.30	4.7	1.94
NO	11.52	30.0	2.87		6.54	18.3	3.38
GR	12.94	27.7	4.27		5.61	1.3	0.88

The percentages of countries' papers that were classified as reviews are shown in Figure 4.10 for the 20 countries with at least 50 reviews during the 12-year study period. The European average was 9.6% compared to the world average of 8.6%.

Figure 4.10 Percentage of MENTH papers in 20 European countries > 50 reviews classified as "reviews" in WoS (2002-2013)



Red bars: > 3000 reviews; green bars: > 1000 reviews; yellow bars: > 300 reviews; blue bars: > 100 reviews; white bars: < 100 reviews.

4.4 Discussion and Conclusion

Bibliometric analysis can be used in a variety of ways, from "assessing the growth and utilization of knowledge in the field, to planning how to most effectively use limited resources, and to increasing public support for research" (Pincus *et al.*, 1993). In this section, we have attempted to describe the scientific publication data for the period 2002-2013 to better understand how the knowledge base of MHDs has grown in Europe and been used worldwide and how it relates to the burden of disease for the range of MHDs.

MHD research output more than doubled between 2002 and 2013, and MHD research papers by European researchers accounted for 40% of the worldwide output, with the UK as the clear leader. English language confers an advantage compared to countries where researchers publish their work in other languages, and language barriers may also affect the level of international collaboration (Larivière *et al.*, 2013). Not surprisingly, smaller countries had higher levels of international collaboration, which Switzerland had in addition to its high research output. Indeed, researchers in smaller countries have a higher probability of collaborating with colleagues outside their own borders (Larivière *et al.*, 2013).

In terms of subject matter of the research, depression, Alzheimer's and schizophrenia accounted for the largest shares of the MHD research papers. When examined in light of the burden of disease, there was generally poor correlation with the amount of research. For example, the burden of drug addiction and alcoholism are similar, but there is nearly 40% more research on drug addiction. In terms of the other evidence we explored in the Critical Appraisal, the bibliometric output was inconsistent with our findings regarding the focus of European research projects and the pharmaceutical pipeline for Europe and the U.S. While the bibliometric output showed that Alzheimer's papers were second to those on depression, which accounted for only 16% of the identified research projects and 18% of the molecules in the pharmaceutical pipeline, Alzheimer's research dominated both areas, with around 50% of the output. In terms of impact of research papers by disease area, Alzheimer's disease had the highest mean five-year citations per paper.

The findings presented in this section will be supplemented in the Synthesis report with additional bibliometric analysis regarding news articles and clinical guidelines for MHDs.

5 Conclusion

This Critical Appraisal considered four types of evidence regarding the MHD research environment, including project-based funding, private industry's research pipelines, expert input and bibliometric analysis of research outputs. This evidence was considered and analyzed in light of the disease burden for particular MHDs.

The dominant position of Alzheimer's disease research was clear, accounting for half of the research projects in three large MSs and nearly half of the molecules in the European and U.S. pharmaceutical pipelines. Several experts questioned whether Alzheimer's disease should be included among MHDs. However, it is not clear whether or the extent to which this research has diminished research in other areas. The bibliometric output showed that Alzheimer's papers were second to those on depression, which accounted for only 16% of the identified research projects and 18% of the molecules in the pharmaceutical pipeline. Thus it is unclear which metrics should be considered for purposes of priority setting.

While one can compare disease burden estimates against a variety of research output metrics, it is important to keep in mind that those estimates are only as reliable as the underlying epidemiological surveys, which in many cases do not cover a nationally representative sample, even in Europe (Brhlikova *et al.*, 2011). Ensuring that disease estimates are based on solid epidemiological data is essential, particularly if research priorities are to be established based upon burden of disease. On that point, experts do not agree, with some arguing that severe diseases such as schizophrenia should be prioritized. Indeed, priorities for the research agenda may be considered based on a variety of measures, from DALYs to the cost burden to disease severity to return on investment to unmet needs. In any case, the priority setting process should be transparent and founded on solid evidence.

Beyond the evidence base, one theme that emerged is the need for better coordination so that identified priorities are addressed and redundancies are diminished. Although there are existing platforms to facilitate cross-border research collaboration, including ERA-Net NEURON and JPND, several experts maintained that a permanent platform specifically dedicated to MHD research should be put into place at the European level. Given the withdrawal of a number of pharmaceutical companies from the MHD R&D arena, it would seem that such collaboration is needed now more than ever to facilitate public research aimed at identifying biomarkers and achieving other scientific breakthroughs that may draw pharmaceutical firms back into MHD drug development.

While the Critical Analysis explored research into treatments involving drugs and medical devices, the therapeutic toolbox for some MHDs involves non-drug, non-device therapies, such as cognitive behavioral therapy (CBT). Further exploration into the research targeting such treatments as well as prevention programs/interventions is needed to round out the perspective regarding MHD research.

The Synthesis phase of the Mapping_NCD project will allow us to combine and supplement the evidence gathered to date regarding MHD research.

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Annex 1: Semi Structured Interview Guide

1. **MAPPING_NCD PROJECT Introduction**

Note: The project does not include mental retardation or disorders of psychological development (autism, etc.).

MAPPING_NCD, a project funded by the European Commission (EC) under its 7th Framework programme to map research activities, investment and initiatives for non-communicable diseases (NCDs) across Europe (http://www.ncd-map.eu/). The goal is to quantify the impact of research in five key disease areas: cancer, cardiovascular disease, chronic respiratory diseases, diabetes and mental health. Our unit is responsible for assessing the impact of mental health research in Europe.

- Systematic mapping of mental health research activities at member state, regional and EU level
- Impact assessment of major research initiatives and categorization of impact
- Impact assessment of selected research initiatives and their relation to clinical guidance and policy development
- Critical appraisal of results achieved and future research agenda.

Our work to date has involved surveying public, not-for-profit and private Research Funding Organisations (RFOs) regarding funding levels, practices, impact assessments, collaborations and future research plans. We would like to supplement these data with input from experts in the field of mental health research and policy such as you who have a broad perspective on past and existing funding strategies in Europe, including any gaps and unmet needs or duplicative efforts, to inform recommendations to the EC for future research funding priorities and policies.

2. **RESEARCH STRATEGY IN EUROPE**

2008 Pact for Mental Health and Wellbeing followed by the 2013 Joint Action on Mental Health and Well-being outlined broad areas for the EU's strategic focus on mental health, including:

- Depression and suicide
- Youth and education
- Workplace settings
- Older people
- Combating stigma and social exclusion
- Community-based/socially inclusive settings

In addition, numerous EC-funded projects in recent years have been developed to examine and propose recommendations regarding mental health in Europe, including what the research agenda should be (e.g., ROAMER, MAPPING_NCD).

- Are these the right areas of strategic focus for mental health?
- Is EC the correct (the only?) entity for coordinating the strategic direction of mental health research? Are they doing a good job in this coordination role? A lot of lip service has been paid in last 10 years to MHDs, yet we do not seem to be much closer to addressing them. Do you agree?
- What is the appropriate role of the Member States in defining the strategic agenda?
- What is the appropriate role of research funding entities?

3. **DEFINING AND ADDRESSING MENTAL HEALTH PROBLEMS IN EUROPE**

Mental health disorders encompass a broad range of disorders. Epidemiological data in Europe are not as well-developed as in US/Australia/etc.

- What can/should be done to ensure that the burden of mental disorders in Europe is better recognized and prioritized (both with respect to other diseases, including other NCDs, and also across the range of MHDs)?

4. **RESEARCH FUNDING FOR MENTAL DISORDERS**

- Are there disorders for which research is over- or under-funded relative to the burden of disease?
- Is lack of coordination/duplication of effort a big problem? Any examples you could give?
- How could research be better coordinated?
- What should the relative role of public versus private funding entities be? Any funding trends over past 10-15 years? Should private research have a greater/lesser role?

5. **INITIATIVES OTHER THAN FUNDING THAT COULD IMPROVE MENTAL HEALTH RESEARCH IN EUROPE**

- For example, transparency and reporting requirements to provide a more clear picture of what research is being funding
- Policies, charitable status, etc.