THE UNIVERSITY OF QUEENSLAND

AUSTRALIA

Formulating a complete epidemiological profile of major depressive disorder: Investigating the global distribution, risk factors, outcomes, and burden of major depressive disorder

Alize Juliette Ferrari

BPsySc (Hons)

A thesis submitted for the degree of Doctor of Philosophy at

The University of Queensland in 2014

School of Population Health

Abstract

Background

Major depressive disorder (MDD) has been previously recognized as a severely impacting disorder. Although effective intervention strategies exist, access to treatment remains low, particularly in low- to middle-income countries. The purpose of this thesis was to formulate a complete epidemiological profile for MDD. This involved investigating (1) the global distribution of MDD; (2) the global burden of MDD in terms of disability-adjusted life years (DALYs), years lived with disability (YLDs) and years lost to premature mortality (YLLs) for the Global Burden of Disease Study 2010 (GBD 2010); (3) the contribution of MDD as a risk factor to the distribution and burden of suicide and ischemic heart disease; and (4) the risk factors of MDD and related avenues for further research. Such an epidemiological profile assists in identifying the size of the population who may need intervention for MDD. It provides policy-makers with information that can, along with considerations of cost-effectiveness and equity, be used in resource allocation within the health sector. For researchers, it identifies where the gaps in the literature exist regarding the epidemiology of MDD which need to be addressed with future research.

Methods

A systematic literature review was conducted to capture studies of the prevalence, incidence, duration, and excess-mortality associated with MDD. Data points were integrated into a statistical disease model using DisMod-MR, a Bayesian meta-regression tool. DisMod-MR predicts epidemiological data for parameters and parts of the world with no raw data and also accommodates known methodological and ecological determinants of MDD.

To estimate burden, disability weights measuring the severity of health loss from MDD were obtained from population survey data. These were combined with DisMod-MR prevalence data to calculate YLDs for MDD by age, sex, year, and country. To calculate YLLs, comparative risk assessment methodology was used to explore MDD as a risk factor for both suicide and ischemic heart disease. Data from additional systematic literature reviews and meta-analyses were used to obtain the pooled relative-risk of (1) ischemic heart disease in those exposed to MDD, and (2) suicide in those exposed to select mental and substance use disorders including MDD. For each risk factor-outcome pairing, population attributable fractions were calculated from the pooled relative-risks and DisMod-MR prevalence data. These were then used to calculate the proportion of DALYs originally allocated to ischemic heart disease and suicide in GBD 2010 which could be re-assigned

to MDD. Finally, an investigation into the risk factors for MDD was presented, with a working example of how two previously established risk factors, child sexual abuse (CSA) and intimate partner violence (IPV), can impact on the distribution of MDD.

Results

The literature search for epidemiological data identified 116 prevalence, 4 incidence, 5 duration, and 11 excess-mortality studies. DisMod-MR estimated over 298 million point prevalence cases of MDD globally in 2010. The global point prevalence was very similar across time, although higher in low- to middle-income countries and females aged 25 to 34 years. The annual incidence of an episode of MDD followed a similar age and regional pattern to prevalence but was about one and a half times higher; consistent with an average duration of 37.7 weeks.

When compared to the 290 other diseases and injuries in GBD 2010, MDD was ranked as the second leading cause of YLDs; accounting for 8.2% (5.9%–10.8%) of global YLDs in 2010. MDD was also a leading cause of DALYs, accounting for 2.5% (1.9%–3.2%) of global DALYs. Additionally, MDD explained 4 million ischemic heart disease DALYs and 16 million suicide YLLs. Out of 22.5 million (14.8-29.8 million) suicide YLLs attributable to all mental and substance use disorders identified as risk factors for suicide, MDD was responsible for the largest proportion (46.1%, 28.0%-60.8%).

Data on the risk factors of MDD were sparse and incomplete however there was sufficient evidence to quantify the respective effect of conflict, CSA and IPV on MDD. CSA and IPV had the potential to explain up to 63·7% (46·2%-80·2%) of the sex difference in MDD however this finding was deemed preliminary given uncertainty and omissions in this data. Further research is required to investigate this further, particularly around how the observed effect of CSA and IPV on the sex difference of MDD interacts with other risk factors and changes across age, place and time.

Conclusion

MDD is a common and disabling disorder which imposes significant disease burden on the population. It also contributes substantially to the burden allocated to suicide and ischemic heart disease. These findings emphasize the importance of including MDD as a public-health priority and implementing cost-effectiveness interventions to reduce its burden. There was a paucity of data exploring the risk factors for MDD. However, data that were available underlined the importance of investigating how interventions to ameliorate the increased risk of MDD from abuse, war, and violence can be incorporated into prevention programs.

Declaration by author

This thesis is composed of my original work, and contains no material previously published or written by another person except where due reference has been made in the text. I have clearly stated the contribution by others to jointly-authored works that I have included in my thesis.

I have clearly stated the contribution of others to my thesis as a whole, including statistical assistance, survey design, data analysis, significant technical procedures, professional editorial advice, and any other original research work used or reported in my thesis. The content of my thesis is the result of work I have carried out since the commencement of my research higher degree candidature and does not include a substantial part of work that has been submitted to qualify for the award of any other degree or diploma in any university or other tertiary institution. I have clearly stated which parts of my thesis, if any, have been submitted to qualify for another award.

I acknowledge that an electronic copy of my thesis must be lodged with the University Library and, subject to the policy and procedures of The University of Queensland, the thesis be made available for research and study in accordance with the Copyright Act 1968 unless a period of embargo has been approved by the Dean of the Graduate School.

I acknowledge that copyright of all material contained in my thesis resides with the copyright holder(s) of that material. Where appropriate I have obtained copyright permission from the copyright holder to reproduce material in this thesis.

Publications during candidature

Peer reviewed papers

Ferrari AJ, Saha S, McGrath JJ, Norman R, Baxter AJ, Vos T, et al. Health states for schizophrenia and bipolar disorder within the Global Burden of Disease 2010 Study. Population Health Metrics. 2012; 10(1):16.

Ferrari AJ, Somerville AJ, Baxter AJ, Norman RE, Patten SB, Vos T, et al. Global variation in the prevalence and incidence of major depressive disorder: A systematic review of the epidemiological literature. Psychological Medicine. 2013; 43(3):471-81

Ferrari AJ, Charlson FJ, Norman R, Flaxman AD, Patten SB, Vos T, et al. The epidemiological modelling of major depressive disorder: Application for the Global Burden of Disease Study 2010 PLoS One. 2013;8(7):1-14.

Ferrari AJ, Charlson FJ, Norman RE, Patten SB, Freedman G, Murray CJL, et al. Burden of depressive disorders by country, sex, age and year: Findings from the Global Burden of Disease Study 2010. PloS Medicine. 2013;10(11):e1001547.

Ferrari AJ, Norman RE, Freedman G, Baxter AJ, Pirkis JE, Harris MG, et al. The burden attributable to mental and substance use disorders as risk factors for suicide: findings from the global burden of disease study 2010. PLoS One. 2014;9(4):e91936.

Murray CJL, Vos T, Lozano R, Naghavi M, Flaxman AD, Michaud C, et al. Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet. 2012; 380:2197-223.

Vos T, Flaxman AD, Naghavi M, Lozano R, Michaud C, Ezzati M, et al. Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet. 2012; 380:2163-96.

Lim SS, Vos T, Flaxman AD, Danaei G, Shibuya K, et al. A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990–

2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet. 2012; 380:2224-60.

Whiteford HA, Degenhardt L, Rehm J, Baxter AJ, **Ferrari AJ**, Erskine HE, et al. The Global Burden of Mental and Substance Use Disorders, 2010. Lancet. 2013;382 (9904):1575-86.

Whiteford HA, **Ferrari AJ**, Baxter AJ, Charlson FJ, Degenhardt L. How did we arrive at burden of disease estimates for mental and illicit drug use disorders in the Global Burden of Disease Study 2010? Current Opinion in Psychiatry. 2013;26(4):376-83.

Degenhardt L, Whiteford HA, **Ferrari AJ**, Baxter AJ, Charlson FJ, Hall WD, et al. The global burden of disease attributable to illicit drug use: Results from the GBD 2010 study. The Lancet. 2013; 382 (9904):1564-74.

Degenhardt L, **Ferrari AJ**, Calabria B, Hall WD, Norman RE, McGrath J, et al. The Global Epidemiology and Contribution of Cannabis Use and Dependence to the Global Burden of Disease: Results from the GBD 2010 Study. PLoS One. 2013;8(10):e76635.

Charlson FJ, **Ferrari AJ**, Somerville AJ, Norman R, Patten SB, Vos T, et al. The epidemiological modelling of dysthymia: Application for the Global Burden of Disease 2010 Study. Journal of Affective Disorders. 2013;151:111-20.

Erskine HE, **Ferrari AJ**, Nelson P, Polanczyk G, Flaxman AD, Vos T, et al. Research Review: Epidemiological modelling of attention-deficit/hyperactivity disorder and conduct disorder for the Global Burden of Disease Study 2010. Journal of Child Psychology and Psychiatry. 2013;54(12):1263-74.

Erskine HE, **Ferrari AJ**, Polanczyk GV, Moffitt TE, Murray CJ, Vos T, et al. The global burden of conduct disorder and attention-deficit/hyperactivity disorder in 2010. Journal of child psychology and psychiatry. 2014;55(4):328-36.

Baxter AJ, **Ferrari AJ,** Erskine HE, Charlson FJ, Degenhardt L, Whiteford HA. The global burden of mental and substance use disorders: changes in estimating burden between GBD1990 and GBD2010. Epidemiology and psychiatric sciences. 2014;23(3):239-49.

Baxter AJ, Scott KM, **Ferrari AJ**, Norman R, Vos T, Whiteford HA. Challenging the myth of an "epidemic" of common mental disorders: trends in the global prevalence of anxiety and depression between 1990 and 2010. Depression & Anxiety. 2014;31(6):506-16.

Baxter AJ, Vos T, Scott KM, **Ferrari AJ**, Whiteford HA. The global burden of anxiety disorders in 2010. Psychological medicine. 2014:1-12.

Whiteford HA, **Ferrari AJ**, Degenhardt L, Feign V, Vos T. The Global burden of Neuropsychiatric disorders in 2010: An Analysis from the Global Burden of Disease Study 2010. PLoS One. 2014; Under review.

Book chapters

Whiteford HA, **Ferrari AJ**. The burden of mental disorders in the Global Burden of Disease Study 2010 and the World Mental Health Survey: Similarities, differences and implications for mental health research. In: Alonso J, Chatterji S, Yanling H, editors. The burdens of mental disorders in the WHO World Mental Health Surveys: WMH surveys series Volume IV. Cambridge: Cambridge University Press; 2013. p. 221-9.

Flaxman A, **Ferrari AJ**, Whiteford HA, Vos T. Expert priors in compartments models: bipolar disorder. In: Flaxman A, Vos T, Murray CJL, editors. An integrative meta regression framework for descriptive epidemiology. Washington: University of Washington. 2014; In Press.

Whiteford HA, **Ferrari AJ**, Degenhardt L, Feign V, Vos T. The Global burden of Neuropsychiatric disorders in 2010: An Analysis from the Global Burden of Disease Study 2010. In: Patel V, Chisholm D, Dua T, Laxminarayan R, Medina-Mora M, Vos T, editors. 3rd Edition of Disease Control Priorities in Developing Countries Volume 8: Mental Neurological and Substance use Disorders. 2014; Under review.

Conference abstracts

Ferrari, A.J. (July 17-22, 2012). Depressive disorders in the Global Burden of Disease 2010 Study: A case study. Oral presentation, WHO World Mental Health Survey Initiative Annual Collaborators' Meeting. Brussels, Belgium.

Ferrari, A.J. (October 18, 2013). The Global Burden of Depressive Disorders: Findings from the Global Burden of Disease Study 2010. Oral presentation. The 4th Annual West Moreton Hospital and Health Services Research Day, Ipswich, Australia.

Publications included in this thesis

Ferrari AJ, Somerville AJ, Baxter AJ, Norman RE, Patten SB, Vos T, Whiteford HA. Global variation in the prevalence and incidence of major depressive disorder: A systematic review of the epidemiological literature. Psychological Medicine. 2013; 43(3):471-81.

Incorporated as Chapter Three

Contributor	Statement of contribution
Ferrari AJ (Candidate)	Responsible for 95% of the conceptualization of the manuscript; 60% of the preparation of the dataset; 85% of the statistical design, 100% of the statistical analyses; 70% of the interpretation of findings; 80% of the drafting and writing of the manuscript.
Somerville AJ	Responsible for 40% of the preparation of the datasets.
Baxter AJ	Responsible for 5% of the conceptualization of the manuscript; 5% of the statistical design; 5% of the drafting and writing of the manuscript.
Norman RE	Responsible for 10% of the statistical design; 5% of the drafting and writing of the manuscript.
Patten SB	Responsible for 10% of the interpretation of findings.
Vos T	Responsible for 10% of the interpretation of findings; 5% of the drafting and writing of the manuscript.
Whiteford HA	Obtained funding for the work undertaken by AJF. Responsible for 10% of the interpretation of findings; 5% of the drafting and writing of the manuscript.

**All authors read and approved the final manuscript.*

Ferrari AJ, Charlson FJ, Norman R, Flaxman AD, Patten SB, Vos T, Whiteford HA. The epidemiological modelling of major depressive disorder: Application for the Global Burden of Disease Study 2010. PLoS One. 2013;8(7):1-14.

Incorporated as Chapter Four

Contributor	Statement of contribution
AJ Ferrari (Candidate)	Responsible for 100% of the conceptualization of the manuscript; 100% of the preparation of the dataset for analysis; 30% of the statistical design, 85% of the statistical analyses; 75% of the interpretation of findings; 80% of the drafting and writing of the manuscript.
FJ Charlson	Responsible for 5% of the drafting and writing of the manuscript.
RE Norman	Responsible for 5% of the statistical analyses; 5% of the drafting and writing of the manuscript.
SB Patten	Responsible for 5% of the interpretation of findings.
AD Flaxman	Responsible for 40% of the statistical design.
T Vos	Responsible for 30% of the statistical design; 10% of the statistical analyses; 10% of the interpretation of findings; 5% of the drafting and writing of the manuscript.
HA Whiteford	Obtained funding for the work undertaken by AJF. Responsible for 10% of the interpretation of findings; 5% of the drafting and writing of the manuscript.

**All authors read and approved the final manuscript.*

Ferrari AJ, Charlson FJ, Norman RE, Patten SB, Freedman G, Murray CJL, Vos T, Whiteford, HA. Burden of depressive disorders by country, sex, age and year: Findings from the Global Burden of Disease Study 2010. PloS Medicine. 2013;10(11):e1001547.

Incorporated as Chapter Five

Contributor	**Statement of contribution**
AJ Ferrari (Candidate)	Responsible for 100% of the conceptualization of the manuscript; 60% of the preparation of the dataset; 80% of the statistical design, 80% of the statistical analyses; 70% of the interpretation of findings; 80% of the drafting and writing of the manuscript.
FJ Charlson	Responsible for 40% of the preparation of the dataset; 10% of the statistical analyses.
RE Norman	Responsible for 5% of the interpretation of findings; 5% of the drafting and writing of the manuscript.
SB Patten	Responsible for 5% of the interpretation of findings.
Freedman G	Responsible for 10% statistical analyses.
CJL Murray	Responsible for 5% drafting and writing of the manuscript.
T Vos	Responsible for 20% of the statistical design; 10% of the interpretation of findings; 5% of the drafting and writing of the manuscript.
HA Whiteford	Obtained funding for the work undertaken by AJF. Responsible for 10% of the interpretation of findings; 5% of the drafting and writing of the manuscript.

**All authors read and approved the final manuscript.*

Ferrari AJ, Norman RE, Freedman G, Baxter AJ, Pirkis JE, Harris MG, Page A, Carnahan E, Degenhardt L, Vos T, Whiteford HA. The burden attributable to mental and substance use disorders as risk factors for suicide: findings from the global burden of disease study 2010. PLoS One. 2014;9(4):e91936.

Incorporated as Chapter Six

Contributor	Statement of contribution
AJ Ferrari (Candidate)	Responsible for 85% of the conceptualization of the manuscript; 80% of the preparation of the datasets; 80% of the statistical design, 80% of the statistical analyses; 70% of the interpretation of findings; 85% of the drafting and writing of the manuscript.
RE Norman	Responsible for 10% of the statistical design, 5% of the statistical analyses; 5% of the drafting and writing of the manuscript.
G Freedman	Responsible for 5% of the statistical analyses.
AJ Baxter	Responsible for 5% of the conceptualization of the manuscript.
JE Pirkis	Responsible for 5% of interpretation of findings
MG Harris	Responsible for 5% of interpretation of findings
A Page	Responsible for 10% of the preparation of datasets.
E Carnahan	Responsible for 5% of the statistical analyses.
L Degenhardt	Responsible for 10% of the preparation of datasets.
T Vos	Responsible for 5% of the conceptualization of the manuscript; 10% of the statistical design, 5% of the statistical analyses; 10% of the interpretation of findings; 5% of the drafting and writing of the manuscript.
HA Whiteford	Obtained funding for the work undertaken by AJF. Responsible for 5% of the conceptualization of the manuscript; 10% of the interpretation of findings; 5% of the drafting and writing of the manuscript.

**All authors read and approved the final manuscript.*

Contributions by others to the thesis

Some of the work presented in this thesis went on to inform the Global Burden of Disease Study 2010. As such, the work was conducted in collaboration with the Institute for Health Metrics and Evaluation (IHME), University of Washington (responsible for coordinating the study) and other collaborators who provided expert or technical guidance. These individuals have been recognized as authors or in the acknowledgement.

I worked as a member of the study's mental and substance use disorder research group to estimate the burden of a number of disorders such as major depressive disorder, bipolar disorder, schizophrenia, attention-deficit/hyperactivity disorder, and cannabis dependence. Whilst I contributed to the epidemiological inputs required for the estimation of burden for major depressive disorder, I did not personally calculate the disability weights and burden estimates as these required the application of a central approach to estimate burden for all diseases and injuries in the study simultaneously and machinery located at IHME. After being estimated, all relevant estimates were returned to me for evaluation and for all further analyses included in this thesis.

Statement of parts of the thesis submitted to qualify for the award of another degree

None

Acknowledgements

First I would like to acknowledge the support of my thesis advisors, Prof Harvey Whiteford, Prof Theo Vos and Dr Rosana Norman. The knowledge and guidance they have shared have been invaluable and I am a better researcher because of it. Thank you.

I would like to acknowledge the funding I received from my position as a research associate as part of the Psychiatric Epidemiology and Burden of Disease (PEABOD) Group. PEABOD is based at the Queensland Centre for Mental Health Research (QCMHR) which receives core funding from the Queensland Department of Health. Many thanks to the support of past and present members of PEABOD, Ms Holly Erskine, Ms Fiona Charlson, Ms Adele Somerville, Mr Roman Scheurer, and Dr Amanda Baxter with whom I've shared the many highs and few lows of working on the Global Burden of disease Study. I would also like to thank the administrative team at QCMHR, Carmel Meir, Carol Cottell, Duncan Mclean and Ray Hilko, who have kept me organized these past few years.

I would like to acknowledge the leadership of Prof Christopher Murray and other members of the burden of disease team at IHME, University of Washington. IHME receives funding from the Bill and Melinda Gates Foundation. Thanks to all IHME researchers and other GBD 2010 collaborators, particularly Mr Greg Freedman, Ms Emily Carnahan, Prof Louisa Degenhardt, Dr Abraham Flaxman, Dr Jon Paul Khoo and, Dr Scott Patten who provided both technical and expert assistance throughout the course of my PhD. A full list of collaborators has been provided in the appendix.

I would like to acknowledge the postgraduate team at the School of Population Health, University of Queensland, particularly Ms Mary Roset who has been a constant source of support during my candidature.

Most importantly, I must thank my family. My parents Basil and Therese, my brother Mathieu, and my partner Fabby who support what I do to the fullest and have kept me sane and grounded throughout my PhD. This would not have been possible without them.

Keywords

depression, mental and substance use disorders, epidemiology, burden, risk, outcome, suicide, abuse, violence

Australian and New Zealand Standard Research Classifications (ANZSRC)

ANZSRC code: 111706, Epidemiology, 50%

ANZSRC code: 111714, Mental Health, 50%

Fields of Research (FoR) Classification

FoR code: 1117, Public Health and Health Services, 100%

Table of contents

List of Figures & Tables

List of abbreviations used in the thesis

CIDI	Composite International Diagnostic Interview
CRA	Comparative risk analysis
CSA	Child sexual abuse
DALY	Disability-adjusted life year
DCP3	3rd Edition of Disease Control Priorities in Developing Countries Project
DSM	Diagnostic and statistical manual of mental disorders
GBD	Global burden of disease
GBD 1990	Global Burden of Disease Study 1990
GBD 2000/05	Global Burden of Disease Study 2000 and 2005
GBD 2010	Global Burden of Disease Study 2010
ICD	Internal Classification of Diseases
IHD	Ischemic heart disease
IHME	Institute for Health Metrics and Evaluation
IPV	Intimate partner violence
MDD	Major depressive disorder
MDE	Major depressive episode
MEPS	US Medical Expenditure Panel Survey 2000–2009
NESARC	US National Epidemiological Survey on Alcohol and Related Conditions 2000–2001 and 2004–2005
NOS	Not otherwise specified
NSMHWB	The Australian National Survey of Mental Health and Wellbeing of Adults 1997
PAF	Population attributable fraction
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RR	Relative-risk
SE	Standard error
SF-12	Short Form 12-item
SMR	Standardised mortality ratio
WHO	World Health Organization
WMHS	World Mental Health Survey
YLD	Years lived with disability
YLL	Years lost to premature mortality
QCMHR	Queensland Centre for Mental Health Research

Chapter One: Relevance, aims, and outline of the thesis

Context for the thesis

Major depressive disorder (MDD) has been previously recognised as a severely impacting disorder (1). However, although effective intervention strategies exist (2, 3), access to treatment remains exceedingly low; particularly in low to middle income countries. Even in high income countries, those receiving treatment typically do so many years after the onset of the disorder and few receive optimal treatment strategies (2-4). This has important implications for both national and global health agendas, given that increased life expectancy due to better reproductive health, nutrition and control of communicable diseases means that more of the population are living to the age where MDD is most prevalent (5, 6).

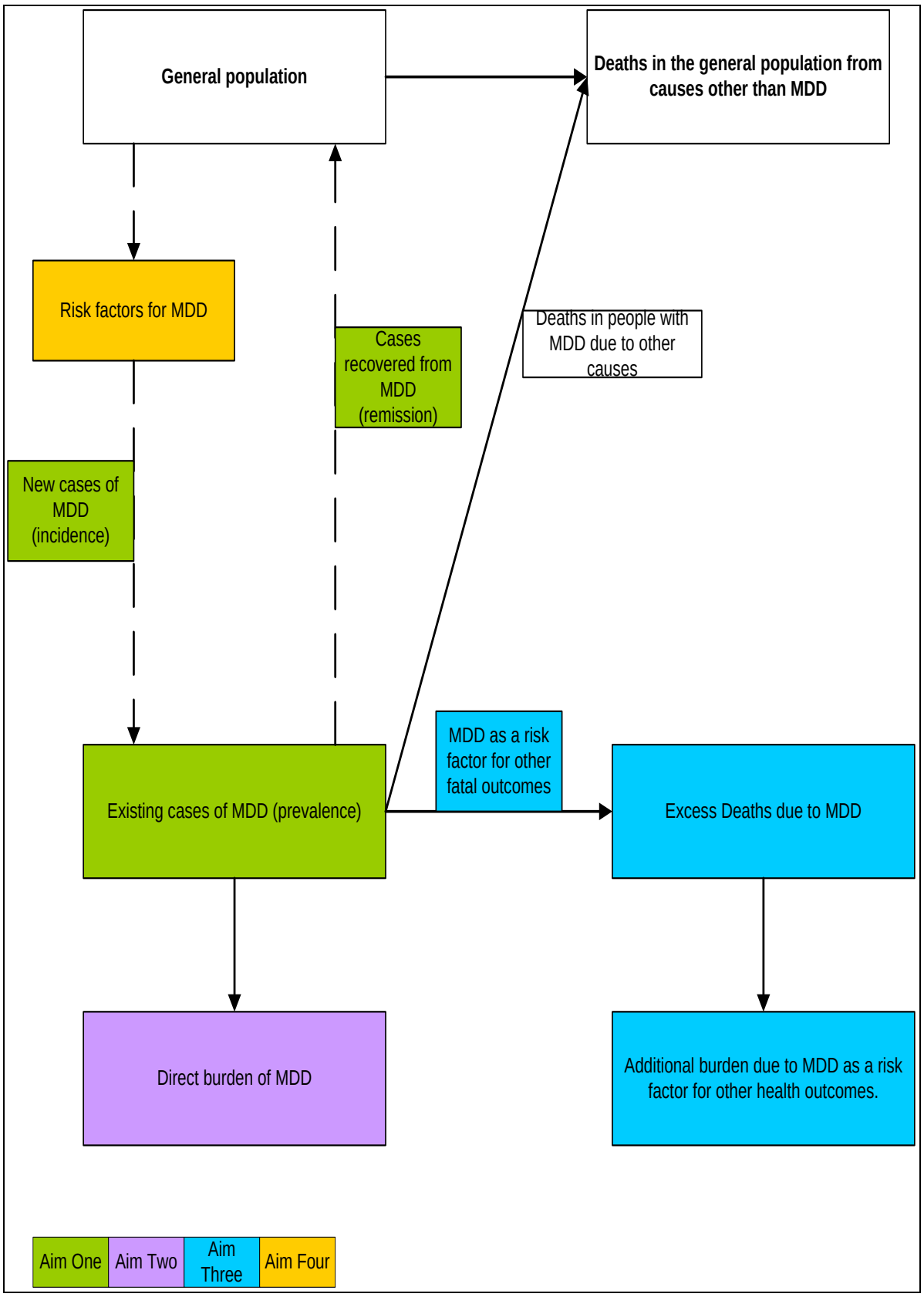
The purpose of this PhD was to formulate an epidemiological profile for MDD. Epidemiology is the study of the distribution and determinants of diseases and injuries in a given population, and the application of this study to regulate these diseases and injuries (7). By extension, an epidemiological profile of MDD describes and quantifies who in the general population has the disorder, has recovered, and died as a result of MDD. It identifies characteristics of those with and without MDD, behaviours that place people at risk, and their health outcomes. This information assists in the identification of people in need of prevention and care services, and ultimately facilitates the setting of health policies and service planning for MDD.

Whilst there is considerable literature on the different elements of the epidemiology of MDD, there has been little effort placed in integrating these into a comprehensive global epidemiological profile for the disorder (8). For the purposes of this PhD, this involved investigating the following areas;

- The global distribution of MDD in terms of the prevalence, incidence, duration, and excess mortality associated with the disorder.
- The extent to which the distribution of MDD impacts on the health of the population compared to other diseases and injuries.
- The contribution of MDD to other diseases and injuries, namely suicide and ischemic heart disease (IHD).
- The risk factors of MDD and related avenues for further research.

Figure 1 illustrates the epidemiological profile of MDD formulated in this thesis. Due to certain exposures or risk factors (many of which have yet to be fully understood), people in the general population meet diagnostic criteria for MDD and contribute to the incidence of the disease. Incident cases go on to inform the number of prevalent cases. Cases are removed from the prevalence pool as they recover (and contribute to the remission rate) or as they die due to MDD (and contribute to the cause-specific mortality rate) or other causes (9).

To reliably quantify the extent to which MDD impacts on the health of the population in its own right, as well as in comparison to other diseases, the epidemiological data generated here were used to estimate the burden of MDD in the Global Burden of Disease (GBD) Study 2010 (GBD 2010) (5, 6, 10-13). GBD 2010 estimated the burden associated with 291 diseases (including 20 mental and substance use disorders) and 63 risk factors, in terms of disability-adjusted life years (DALYs). DALYs provide a consistent unit of measurement to compare the fatal and non-fatal health loss associated with different diseases and injuries, across different populations, settings, and years. They can directly inform priority setting exercises in national and global health agendas; as well as provide the basis from which the effectiveness of existing intervention strategies for MDD and other diseases can be monitored over time (5).



Note. Figure adapted from an existing incidence-prevalence-mortality model (9). Colours correspond to thesis aims.

Figure 1. Illustration of the epidemiological profile of MDD formulated in this thesis.

Thesis aims, relevance, and applicability

Aim One

Aim one was to formulate a comprehensive model of the global distribution of MDD. This task was separated into two parts;

- First, it involved conducting a systematic review of the literature to establish the global prevalence, incidence, duration and excess mortality associated with MDD; and from this, identifying sources of heterogeneity in the data that were 'real' versus heterogeneity due to differences in study methodology and design.
- Second, it involved the application of Bayesian meta-regression techniques to model the distribution of MDD and adequately adjust for the established sources of heterogeneity in the data.

Relevance and applicability

Information on the epidemiological distribution of a given disease typically forms the empirical underpinning for investigating the public health and clinical impact of the disease in the population (14). In this case, it provided the basis for investigating all subsequent thesis aims. That said, interpretation and generalizability of the available literature on the distribution of MDD (as captured in the first part of aim one) was restricted by significant variability in the data obtained between studies, missing data, or unequally distributed data across settings, age groups, years and, parameters. Bayesian meta-regression statistical modelling techniques (13) were used here (for the second part of aim one) to address these limitations and model the prevalence, incidence, duration and excess mortality of MDD for males and females, 20 age groups, 187 countries, 21 world regions and, 3 time points.

Aim two

Aim two was to quantify the global burden of MDD. This aim was conducted as a GBD 2010 deliverable and involved the use of epidemiological output from aim one.

Relevance and applicability

The first global burden of disease study in 1990 (GBD 1990) (1) and its updates by the World Health Organization (WHO) between 2000 and 2005 (GBD 2000/05) (15, 16) identified depression as the leading cause of disability. Although this made notable contributions to shifting international focus onto depression as a leading cause of burden, the global prevalence of MDD remains high (8, 17) and treatment rates remain low (4).

To respond to this, it is important to make available comparable estimates of burden, reflective of recent statistical and epidemiological advancements in mental health research. This provides us with an empirical basis to;

- Compare and contrast burden due to MDD with burden due to other diseases.
- Compare and contrast burden due to MDD between countries, regions, sex, age and year.
- Further explore the status of MDD as a leading cause of disease burden and the extent to which MDD intervention strategies need to be prioritized in health management plans.
- Evaluate the effectiveness of existing health policies and services in improving the health of individuals with MDD and ultimately reducing its burden.

Aim three

Aim three was to quantify the burden attributable to MDD and other mental and substance use disorders as risk factors for suicide. This involved conducting a literature review to assess and compile evidence for mental and substance use disorders as risk factors for suicide. Then, estimating (using GBD 2010's comparative risk assessment (CRA) methodology) the proportion of suicide DALYs from GBD 2010 that could be re-assigned to these mental and substance use disorders as a result. This work also used the output from aims one and two.

Relevance and applicability

In spite of evidence showing excess mortality attributable to the majority of mental and substance use disorders (18), this cannot be entirely reflected in burden of disease estimations. Mental and substance use disorders are rarely identified as primary causes of death in vital registrations (used to estimate deaths in GBD 2010) as this typically involves the problematic task of unraveling the effect of multiple mental, substance and physical disorders to find the primary cause of death. Investigating mental and substance use disorders as risk factors for fatal outcomes like suicide allows us to circumvent this problem (10, 19).

Furthermore, GBD 2010 estimated 'direct burden' where mental and substance use disorders were the direct cause of health loss, but excluded the excess (attributable) burden resulting from the increased risk of mortality and disability due to subsequent health outcomes associated with the disorders (19). Here, we expand on the published GBD 2010 findings by estimating the additional burden attributable to MDD as well as other mental and substance use disorders as risk factors for suicide. Simultaneously considering the direct and the attributable burden of mental and substance

use disorders provides a more comprehensive estimation of total burden. It quantifies the relationship between these disorders and their health outcomes which is imperative to the identification of the leading (and potentially modifiable) drivers of disability and mortality.

Aim four

Aim four was to explore the risk factors of MDD, an area of unexplained variability in the epidemiological profile of MDD proposed in the thesis. A key constraint in any form of mental health research is dealing with missing (or incomplete) data and sources of unexplained variability (14). To deal with missing data in this thesis, methods were put into place to explore gaps in the literature, estimate where possible missing data, correct for any inconsistencies due to missing data and, incorporate the effect of missing data within the bounds of uncertainty estimated for all high level findings. In spite of this, it was not possible to quantify all sources of unexplained variability. One of the key areas of unexplained variability pertained to the risk factors of MDD and how these impact its global distribution. Although there is considerable literature on the risk factors of mental disorders, for most of these risk factors there are insufficient data to fully quantify their association with MDD (20-25). The aim here was to identify risk factors for which there was sufficient data to quantify their association with MDD, discuss how these risk factors can impact on the global distribution of MDD, and highlight areas of this literature requiring further research.

Relevance and applicability

Quantifying the risk factors of MDD can make key contributions towards the prevention and treatment of MDD in vulnerable populations. Effective intervention strategies targeting reductions in the duration, severity and deaths associated with MDD exist but can only reduce burden by 10% to 30% (3, 26, 27). Although this highlights MDD as a condition where disease prevention can be critical, there is also much left to establish by way of effective prevention strategies (28). Aside from highlighting opportunities for the further development of the epidemiological model of MDD proposed in this thesis, this aim also responds to the lack of research on preventative strategies for MDD.

Thesis outline

This thesis is partly comprised by publications. It includes four chapters, each made up of one peer reviewed publication attending to aims one to three, and a discussion chapter attending to aim four. It also includes a series of additional publications designed to complement this work. Primary collection of data was not required. Instead, a series of systematic reviews of the literature was conducted to capture studies reporting on the epidemiology of MDD. The thesis is structured as follows (see Figure S1 in Appendix One for an illustration of this):

- Chapter One summarizes the context, aims, relevance and, outline of the thesis.

- Chapter Two presents a literature review of the epidemiology of MDD, highlighting the gaps and limitations in the literature addressed in the thesis.

- Chapters Three to Seven present the original work conducted as part of the thesis. Chapter Three summarizes available data on the global distribution of MDD; Chapter Four makes use of this data to model the distribution of MDD by country, region, age, sex and year; Chapter Five quantifies the global burden of MDD for GBD 2010; Chapter Six investigates suicide as an outcome of MDD and quantifies the additional burden that can be re-assigned to MDD as a result of this; and Chapter Seven explores the available literature on the risk factors of MDD, investigates how two of these risk factors can impact on the global distribution of MDD, and highlights areas of this literature requiring further research.

- Chapter Eight presents a conclusion for the thesis, highlighting the strengths, limitations and implications of the findings, as well as areas for further research.

Chapter Two: Literature review

Chapter summary

This literature review is divided into 5 sections pertaining to the aims of the thesis. It provides the standard definition for MDD used; then reviews the available literature on the global distribution, burden, risk factors, and outcomes of MDD. It also highlights the gaps in the literature which will be addressed in the thesis.

Case definition

For many diseases, the presence of underlying pathogens has been identified and as a result, disease definitions and diagnostic tests have been established. Unfortunately, for mental disorders like MDD underlying mechanisms are complex and remain difficult to operationalise. In Western classificatory systems, a diagnosis of MDD is derived by formulating a prognosis based on a set of behavioural symptoms and one's interpretation of associated levels of impairments. Although there has been much debate around the generalisability of these definitions to non-Western cultures, it is largely accepted that psychological and behavioural disturbances in human populations are present in almost all cultures (29, 30). What tends to differ between cultures is the manifestation of these psychological and behavioural disturbances as this is reliant on the individual or cultural interpretation (31). A relevant example here would be the fact that although some cultures have a word to describe 'sadness', the concept of depression as a disorder does not exist. As such, individuals are more likely to interpret MDD symptoms as a physical illness (32-35).

For the purposes of this thesis, past conventions (8) were followed in setting a case definition for MDD and 'universalism' was assumed. Universalism in this context refers to the position that although culture may influence their development and display, basic human characteristics such as mental disorders are common across all human societies (36, 37). Had it been possible here, a cross-culturally comparable definition and survey instrument for MDD would have been used to explore its global distribution. Unfortunately, (as demonstrated in the next chapter) although Western diagnostic systems and survey instruments exist, these are not fully validated in non-Western cultures where culturally relevant definitions have yet to be developed (32, 36). Consequently, the definition of MDD used in this thesis was based on diagnostic nomenclature from the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) (38) and the International Classification of Diseases (ICD-10) (39), two established but predominantly Western-based classificatory systems for mental disorders. The alternative would be to exclude from analyses, any country where DSM and ICD diagnostic classifications are suspected to be inadequate. Not only is it unclear which countries would need to be excluded, but this exclusion means that subsequent burden analyses

would essentially assume that the burden due to MDD in these countries is zero, a position considered to be indefensible (8).

According to the DSM-IV-TR, MDD (DSM-IV-TR: 296.2) forms part of the depressive disorders sub-group of mood disorders which also includes dysthymia (DSM-IV-TR: 300.4) and depression not otherwise specified (NOS) (DSM-IV-TR: 311). MDD is an episodic disorder characterized by at least one major depressive episode (MDE). A MDE involves symptoms of depressed mood and/or loss of interest causing clinically significant impairment in the main areas of functioning (38). The equivalence as defined by the ICD-10 is characterized by at least 2 of the following symptoms; depressed mood, loss of interest and /or fatigue (ICD-10: F-32) (39). Dysthymia is also characterized by symptoms of depressive mood but differentiated from MDD by severity, and chronicity. To meet a diagnosis of MDD, depressed mood must be experienced mostly all day and every day for a minimum of 2 weeks. To meet a diagnosis of dysthymia depressed mood must be experienced for some but not necessarily all days over a minimum period of 2 years. Depression NOS is characterized by clinically significant presentations of depressed mood which do not meet criteria for MDD or dysthymia (38).

MDD cases can also be categorized in terms of severity. The DSM-IV-TR defines the severity of MDD in terms of whether the symptoms experienced lead to mild, moderate or severe impairment to occupational and social functioning. Severe episodes can also include psychotic features such as delusions and hallucinations (38). The ICD-10 on the other hand, defines the severity of MDD in terms of both impairment and the number of symptoms experienced. A mild state involves 2 or 3 symptoms with minimal distress to daily activities. A moderate state involves 4 or more symptoms with great difficulty in continuing daily activities. A severe state involves the presence of numerous symptoms which are all distressing to daily activities, with suicidal thoughts and psychosis often present (39).

There are slight differences in how the DSM-IV and ICD-10 define MDD but they were both included here to allow for maximum data inclusion. Restricting data inclusion to either one of these diagnostic sources would significantly reduce the global representativeness of findings. However, to further ensure comparability, the effect of diagnostic criteria (i.e. DSM vs. ICD diagnoses) on prevalence was investigated.

Differences in definition aside, both ICD and DSM make use of relatively precise and homogenous criteria (based on the presenting clinical features of a given disorder) to diagnose a mental disorder

(38, 39). Although this categorical approach to defining depression has made significant contributions towards formulating an adequate nosological system for the disorder (40), some limitations exist. It's been argued that in diagnosing MDD, DSM/ICD criteria attempt to impose boundaries upon what is essentially a continuum of depressive symptoms. Applying artificial cutoffs to dimensional features such as symptom frequency, severity and duration may lead to measurement error (40-42). This can have important implications to establishing the epidemiology of MDD. For instance, it affects whether a proportion of what is currently classified as 'substhreshold cases' of depression by DSM and ICD classifications should be considered while quantifying the global distribution, risk factors and outcomes of MDD.

Another challenge with DSM and ICD definitions of MDD is that they change over time. In 2014, DSM-5, the updated version of DSM-IV was published (43). Although the same categorical approach to diagnosing depression was used in DSM-5, some key changes to the criteria were made. Notably, the 'bereavement exclusion' criterion present in DSM-IV was omitted in DSM-5. This criterion stipulated that a diagnosis of MDD could only be made following bereavement if symptoms were present for longer than two months, included significant functional impairment, suicide ideation, psychotic symptoms, or psychomotor retardation (38). Instead of making use of this criterion, the text in DSM-5 seeks to differentiate between a MDE and a normal or expected response to a significant loss, but essentially, individuals diagnosed with severe depression in response to bereavement can be treated as having a mental disorder (43). The clinical and epidemiological impacts of this change in criteria have already been subjected to much debate (44) but new population surveys of prevalence, incidence, remission, duration of MDD using DSM-V rather than DSM-IV criteria are required before they can be included in the present thesis. Similarly, a new version of ICD-10 is also underway (45). The extent to which the definition of MDD will differ from the current ICD-10 definition has yet to be determined.

Although limitations to DSM-IV and ICD-10 definitions of MDD exist, their use ensured a level of consistency and comparability between the definitions of MDD used between studies. That being said, it is important to acknowledge here that the concept of MDD as a disease entity may be more heterogeneous than what has been investigated in the thesis. As more data are made available on the distribution of MDD following DSM-5 or alternative culturally-sensitive definitions of MDD, the baseline estimates presented here using DSM-IV and ICD-10 can be expanded upon.

The global distribution of major depressive disorder

Aim one of this thesis was to formulate a comprehensive model of the global distribution of MDD. The distribution of a disease in the population is typically quantified in terms of its prevalence, incidence, duration and associated excess-mortality (7, 14). Table 1 describes each of these epidemiological parameters in relation to MDD.

Table 1. Summary of parameters investigated for the global distribution of MDD

Parameter	Definition
Prevalence	The proportion of the population with MDD at a specific point in time (point/current/past month prevalence) or during a specified time period (6-, 12-month prevalence) (14)
Incidence	The number of new cases of MDD in the population in one year (7).
Duration	The average length of a MDE (46).
Excess mortality rate	The rate of dying in people with MDD compared to the general population. This can be presented as a relative-risk (RR, ratio of observed death in the sample to expected death in the population) or a standardised mortality ratio (SMR, ratio of observed deaths in the sample to expected death in a population of standard composition in terms of age, sex, etc.) (14).

A review of the literature on the global distribution of MDD revealed that although there are numerous publications on MDD epidemiology, the global representativeness and quality of the data were limited. Interpretation and synthesis of the data were difficult given variations in the choice of instruments used to capture MDD in the population, sampling methodology and statistical analyses used between studies. Gaps in data availability also limited interpretation.

For instance, a review by Paykel and collaborators reported that the pooled 12-month prevalence of MDD in Europe (Spain, Italy, France, Belgium, Netherlands, Germany, Finland, and United Kingdom) was 5%. Although a set of inclusion criteria enforced a minimum quality on the studies included, limitations remained. The geographic representativeness, age range, survey instrument and prevalence type used to capture the data varied between studies, introducing heterogeneity in the pooled prevalence estimate. Another major obstacle was the paucity of data, particularly from Eastern European countries, limiting representativeness (47). Another survey of the prevalence of MDD in Belgium, France, Germany, Netherlands, Spain, and United Kingdom reported that the pooled 6-month prevalence of MDD was higher at 6.9% (48). It too was restricted to a Western European sample.

A review of MDD in the Asia Pacific region (Australia, China, Hong Kong, Japan, Malaysia, Singapore, Taiwan, Thailand and Korea) reported that point prevalence ranged between 1.3% and 5.5%, 12-month prevalence ranged between 1.7% and 6.7%, and lifetime prevalence ranged between 1.1% and 19.9%. The availability of data from Asian countries was poor and the data available often used very different definitions of MDD (49). A more global review summarizing the prevalence of MDD in the United States, Canada, Puerto Rico, France, West Germany, Italy, Lebanon, Taiwan, Korea, and New Zealand reported that the 12-month prevalence varied between 0.8% in Taiwan and 5.8% in New Zealand. Although there were significant cross-national differences in prevalence, females consistently had higher prevalence than males and the mean age of onset was consistently in the mid to late twenties (50). Again, the age range, sample size, and response rate varied substantially between survey sites.

In most cases, the epidemiological studies reviewed were not designed to be systematically compared with one another, but instead, to inform local decisions in priority setting and evaluation (51). Consequently, it remained unclear whether the differences in prevalence reported were 'real' or whether they were driven by between-study differences in methodology and design. A solution to this would be to carry out a cross-national survey which captured the prevalence of MDD using consistent methodology for data collection and assessment. The closest we have to this gold standard for MDD is the World Mental Health Survey (WMHS) Consortium, which conducted representative population surveys of common mental disorders in 28 countries (17). That said, the variability in the prevalence of MDD between WMHS sites is far from trivial (19). For instance, the 12-month prevalence of MDD ranged from 1.1% of adults in Nigeria to 10.4% of adults in Brazil - São Paulo. Women had higher prevalence than men and the mean duration of a MDE ranged from 23.1 to 33.8 weeks depending on the sample (17, 52). It is possible that these represented true variability in the global distribution of MDD however despite using a standard cross-national study protocol, differences remained in the methodology used to capture data between sites (17). The national representativeness of samples varied between survey sites. For instance, surveys conducted in Brazil, India, Japan, Nigeria, and the People's Republic of China used regionally- rather than nationally-representative samples. The amount of missing data and response rates were also different between sites. The WMHS relied on the WHO Composite International Diagnostic Interview (CIDI) to capture cases of MDD. Although the CIDI has been extensively used in Western countries, its reliability and validity in non-Western countries remains unclear. It has been argued that the prevalence of MDD, as captured by the CIDI is likely to be underestimated in non-Western countries as the CIDI is not sensitive to cross-cultural presentations of this disorder (53-55). Furthermore, in the WMHS, the CIDI was administered by lay as opposed to clinically trained

interviewers, the latter of which has been found to be more sensitive to capturing non-Western presentations of mental disorders (56-58). This has also been found to the case for other diagnostic instruments which like the CIDI, can be mapped to DSM/ICD definitions but have yet to be fully validated in non-Western contexts (32). As previously explained, due to limitations in the available definition for MDD, a standard case definition was derived using DSM and ICD classifications and only diagnostic tools which could map to these definitions were considered in the thesis. To further ensure comparability, differences in the surveyed prevalence of MDD between countries, instruments, classificatory systems, and interviewer type were investigated.

The problem of heterogeneity between studies (or survey sites) is also apparent while comparing literature on the excess mortality of MDD. Evidence for an increased risk of death for those with MDD compared to the risk of death in the general population has been based on aggregated data from studies with considerably different methodology (18, 59-62). For instance, previous meta-analyses of all-cause mortality due to MDD in community-based samples reported pooled effect sizes ranging from 1.56 to 1.81 [36, 38, 40]. The definition of depression used also varied between studies, with estimates derived from both clinically defined depression (i.e. MDD based on DSM/ICD criteria) and sub-clinical MDD captured through symptom scales (59). Assuming that the severity of MDD has a significant effect on the risk mortality, the inclusion of sub-clinical MDD may bias findings (59).

A search for studies on the incidence and duration of MDD introduced the issue of inconsistent data. Paykel and collaborators concluded that the overall incidence of MDD was unclear because of a lack of longitudinal follow-up of cases available (47). The few longitudinal studies that do report incidence data (63-67) suggest that MDD has an annual incidence rate of between 1.6 and 7.4 per 100 person years. As many of these surveys excluded those diagnosed with MDD at baseline, new episodes of MDD in people with previous episodes were not counted. Given that the DSM-IV-TR and ICD-10 define MDD as an episodic disorder, where the individual can experience more than one MDE, the incidence of MDD would have been underestimated in these studies. As the data on how long depressive episodes persist is also limited, this also makes it difficult to derive globally representative estimates of the duration of a MDE (46, 68). Expert consensus sets the average duration of MDE at approximately 0.50 of a year (46, 68). Although this is useful, it does not replace high quality raw data.

Overall, we can conclude from the literature that there are more data available on the prevalence of MDD compared to its incidence, duration and excess mortality. There are less data available from

low to middle income countries and the data available are unequally distributed between age, sex, and year or, are limited in terms of study methodology and design (17, 48, 69, 70). These limitations would restrict the epidemiological profile of MDD formulated for this thesis. As such, measures needed to be put in place to supplement them, in the absence of more reliable data. These measures are discussed in greater detail in Chapters Three and Four.

The global burden of major depressive disorder

Aim two of the thesis was to quantify the global burden of MDD. In order to improve the health outcomes of people with MDD, we must understand not only the distribution of those with MDD between countries but also its 'disease burden' i.e. the extent of the health loss caused by MDD in a given population compared with health loss due to other diseases and injuries. Historically, decisions around which diseases and injuries to prioritise in global and national health agendas were informed by mortality statistics. Although this enhanced our understanding of diseases and injuries causing premature mortality, the lack of emphasis on morbidity underestimated the contribution of prevalent and disabling diseases associated with lower rates of mortality (such as MDD) (71, 72). As a result, our understanding of the comparative global epidemiology as well as the identification of the cost effective interventions strategies for MDD (and other mental and substance use disorders) has been considerably limited compared to other diseases.

The initiative to quantify and compare the global burden of diseases in terms of both mortality and morbidity was introduced by the World Bank in their 1993 World Development Report (71). The report proposed a new generic summary measure of health - the DALY- to capture the burden attributable to diseases and injuries. DALYs represent a 'health gap'. They quantify the current state of a population's health compared to a gold standard, which is for the entire population to live with perfect health for the duration of the standard life expectancy. One DALY corresponds to the loss of one healthy year of life. They are calculated by summing years lost to premature mortality (YLLs) and years lived with disability (YLDs) (5, 72).

$$DALY = YLD + YLL$$

In order to calculate YLDs, the prevalence or incidence of a given disease in the population is multiplied by the average disability associated with the disease. Disability is limited to 'within the skin' decrements in functioning (such as body functions, senses, cognition and ambulation) and is quantified using a 'disability weight' ranging from 0 (perfect health) to 1 (death) (12, 13).

$$YLD = P/I \times DW$$

P= number of prevalent cases; I=number of incident cases
DW = disability weight

To estimate YLLs, the number of deaths attributable to the disease is multiplied by the standard life expectancy at the age at which death occurs. The standard life expectancy reflects the lowest death rates recorded in a given year (11).

$$YLL = N \times L$$

N = number of deaths attributable to the disease
L = standard life expectancy at age of death (in years).

The first GBD study (GBD 1990) estimated DALYs for 107 diseases and injuries for 8 world regions (1). This included the burden of 'unipolar depression', an amalgamation of single-episode depression (ICD-10: F 32; DSM IV TR: 296.2), recurrent depression (ICD 10: F 33; DSM IV TR: 296.3) and dysthymia (ICD 10:F34.1; DSM IV TR: 300.4) (1, 38, 39, 73). Unipolar depression explained 3.7% of global DALYs, making it the 4th leading cause of burden worldwide (1, 38, 39). GBD 1990 was followed by a series of updates with partial revisions of the data inputs between 2000 and 2005 (GBD 2000/05), by the WHO. GBD 2000/05 was however still largely based on the GBD 1990's methodology. It provided us with burden estimates for 135 diseases and injuries for 6 world regions and 14 sub regions (16). Unipolar depression explained 4.3% of DALYs, elevating itself to the 3rd leading cause of burden worldwide from the GBD 1990 results. It was also the primary cause of disability, explaining 13.4% of YLDs in women and 8.3% in men (15).

Both GBD 1990 and 2000/05 highlighted unipolar depression as a leading contributor of disease burden, with its burden exceeding that of diseases such as cerebrovascular disease and cancer (1, 15). This finding made notable contributions to shifting international focus onto depression in public health agendas and the addition of mental health interventions to health management plans (74). That said, in spite of this effort, treatment rates remain low for depression, particularly in low- to middle income countries (4). For this reason, it remains important to make available comparable

estimates of burden, which incorporate current statistical and epidemiological advancements in mental health research.

Furthermore, a review of the literature for responses to GBD 1990 and 2000/05 findings revealed parts of the burden estimation methodology in need of further improvement. Unipolar depression, as defined by GBD 1990 and 2000/05 was found to be too heterogeneous. Recent investigation into the presentation of depressive disorders shows that the illness occurs across of wide spectrum of severity and course. Consequently a 'one-size-fits-all' approach as used in GBD 1990 and 2000/05 is not suitable (75). There is also debate around the suitability of epidemiological data used in the estimation of YLDs for unipolar depression in GBD 1990 and 2000/05. Datasets were based on selected 'best' data sources rather than from a systematic review of the literature (1, 15). Brhlikova and collaborators argued that the epidemiological studies included in the GBD 2000/05 study for unipolar depression were limited in study design and methodology and in some instances violated GBD inclusion criteria (69). Disability weights for unipolar depression were derived by health professionals using the person trade off method. This involved a trade-off exercise where target individuals traded off years lived with and without different disabilities first individually, then as a group consensus. This exercise was purposefully designed to be deliberative so that participants could be as comprehensive as possible in their evaluations (1). Kruijshaar and collaborators argued that this was not the most informed method to make complex comparisons about the disability attributable to depression. Health professionals likely made judgments based on the clinical presentation of depression which is typically more severe than the presentation of depression in the general population, thereby inflating disability and subsequently burden (76).

In late 2012, high-level findings from GBD 2010, the latest iteration of the GBD studies were released. GBD 2010 included an all-inclusive re-analysis of burden for 291 diseases and injuries and 63 risk factors, across 187 countries, 21 world regions, males and females, 1990, 2005, 2010, and 20 different age groups. It represented the most comprehensive analysis of disease burden to date (5, 6, 10-13). Aim two of the thesis focused on estimating the global burden of depressive disorders. Analysis of data for this thesis aim was conducted concurrently to GBD 2010 and served as a deliverable for the study. The methodology for estimating the burden of MDD was re-evaluated with considerations given to the mentioned limitations. Chapter Five presents the method used and burden findings for both MDD and dysthymia. The inclusion of the latter disorder enabled comparison of the extent to which MDD contributes to disease burden to other forms of depression.

The health outcomes of major depressive disorder

Aim three of the thesis was to quantify the burden attributable to MDD as a risk factor for other fatal health outcomes. The term 'risk factor' in this thesis refers to an entity (in this case MDD) that increases the likelihood of disease, injury or death (10).

Two pathways have been proposed in explaining health outcomes associated with MDD. The first relates to an increased likelihood of adverse health behaviors in individuals with MDD compared to the general population (59). For instance, depression has been linked with an increased risk of substance use (77-81) and other life threatening behavior (82, 83). The second pathway relates to individuals with MDD having a biological predisposition to certain health outcomes (84). For instance, depression has been linked to an increased risk of cancer (84) and IHD (85).

A literature review by Baxter and collaborators investigating the adequacy of available data required to establish causality (as per Bradford Hill's criteria (86, 87)) between mental and substance use disorders and other health outcomes concluded that although there was a broad array of literature linking MDD to other health consequences the quality and representativeness of this literature was lacking. For most health outcomes (cancers, diabetes, injuries), data were restricted in terms of inconsistent definition of cases, risk factors and outcomes, poor generalizability of findings, and little or no consideration given to confounding factors (88). There was however sufficient evidence to confidently infer an association between (1) MDD and IHD and (2) a selection of mental and substance use disorders (including MDD) and suicide.

Charlson and collaborators' systematic review quantifying the association between MDD and IHD concluded that pooled relative-risk (RR) of developing IHD in those with depression was 1.56 (1.30- 1.87). There was sufficient data to establish a temporal and dose–response relationship between depression and IHD, as well as plausible behavioral and biological pathways (85, 89).

The relationship between mental and substance use disorders and suicide has also been well studied (18, 74, 82, 83, 88, 90-92). Studies using a case cohort/series design have consistently shown an increased risk of suicide in those with mental and substance use disorders compared to the general population. Although it varies by sex and disorder type, this association remains significant after adjusting for the presence of other risk factors such as adverse marital and employment status. Overall, the pooled RR of suicide has been found to be approximately 7.5 (6.2-9.0) times higher in males and 11.7 (9.7-14.1) times higher in females with a mental disorder compared to males and females with no mental disorder (83). Mood disorders such as MDD are typically associated with

greater risk than other disorders such as schizophrenia, substance abuse, anxiety disorder and personality disorders (82, 83).

In spite of the evidence for MDD as a risk factor for IHD and suicide, only substance use disorders, anorexia nervosa, and schizophrenia are documented as causes of death in the ICD-10 cause of death guidelines (39). ICD-10 stipulates that deaths can only be assigned to a given condition when the disorder is considered as the direct cause of death. As such, IHD or suicide deaths occurring as a result of MDD are coded to cardiovascular disease and self-imposed injuries respectively. Even for those few mental and substance disorders recognised as direct causes of death, vital registrations typically assign very few deaths due to them as it is not always possible to separate the effect of various mental, substance and physical disorders to ascertain the principal cause of death. Given that the estimation of deaths and YLLs in GBD studies are derived from vital registry data, previous GBD studies as well as GBD 2010 presented no YLLs for MDD and very few for other mental and substance use disorders. Instead, deaths due to mental and substance use disorders were captured elsewhere in the GBD's mutually exclusive list of diseases and injuries (11, 19).

Investigating mental and substance use disorders as risk factors for fatal outcomes allows us to circumvent this problem by making use of a CRA methodology (10). Rather than rely on certification and coding practices in mortality registration systems, this method quantifies the difference in population health given a counterfactual with a theoretical minimum level of exposure (10). In addition to estimating the burden of diseases and injuries as a 'direct' cause of health loss, GBD studies make use of this CRA methodology to quantify the excess (attributable) burden resulting from diseases and injuries being risk factors for other health outcomes. However, despite the fact that GBD 2010 presented on the direct burden of 20 mental and substance use disorders, only substance use disorders were investigated as risk factors (10).

The purpose of aim three of the thesis was to estimate the additional burden attributable to MDD as a risk factor for other fatal health outcomes. This work was intended to (1) supplement the lack of deaths and YLLs recorded for MDD in spite of evidence of excess-mortality associated with the disorder, for instance in the form of suicide and IHD; and (2) estimate the additional burden due to MDD as a risk factor for other health outcomes. These are useful as they offer an estimation of the putative causal relationships between MDD and other health outcomes. They also help explain the disability and mortality that potentially can be modified by interventions to prevent and treat MDD.

Although both IHD and suicide were investigated as outcomes of MDD and went on to inform the epidemiological profile being formulated in this thesis, MDD as a risk factor for IHD was not considered a core PhD deliverable as the work undertaken was shared between multiple researchers (85, 89). Instead (1) the magnitude of the risk of suicide due to all mental and substance use disorders; and (2) the contribution of MDD on suicide within this group, were investigated. Other mental and substance use disorders were included here as it is important from a public health perspective to not only estimate the burden attributable to MDD as a risk factor for other health outcomes, but also to consider the relative impact of MDD compared to other mental and substance use disorders.

The risk factors of major depressive disorder

Aim four was to explore the risk factors of MDD. One of the key areas of unexplained variability in mental health research pertains to the risk factors of mental disorders. Diseases (such as HIV/AIDs) are diagnosed based on the presence of a virus or pathogen regardless of symptoms or their impact on the individual. Mental disorders on the other hand, are diagnosed (to date) based on a set of behavioural symptoms and our interpretation of associated levels of impairment. This makes the risk factors of mental disorders more difficult to assess and quantify (93).

Nonetheless, a complete epidemiological profile of MDD also requires an understanding of how ecological factors (e.g. environmental, cultural and biological factors) influence the distribution of the disorder. This has enabled better understanding of causal pathways for other disorders like schizophrenia, cancers, auto-immune diseases, and infectious diseases (93). It has also contributed to both clinical and public health domains by providing evidence based rationale for explaining and controlling the occurrence of diseases in the population (94).

Although there have been a number of ecological variables identified as risk factors for MDD (20-25), for most of these risk factors there are insufficient data to fully quantify their association with MDD and/or establish causality (88). GBD 2010's review of the published and unpublished literature for risk factor-outcome pairings concluded that there was sufficient evidence to estimate attributable burden for two accepted risk factors of MDD — child sexual abuse (CSA) and intimate partner violence (IPV) (10). Merits for inclusion of these risk factors were assessed using criteria (e.g. (1) relevance of the risk factor to disease burden or policy; (2) availability of data to estimate the global distribution of the risk factor and effect sizes; (3) availability and strength of the evidence for causal effects) which were in line with accepted frameworks for establishing causality in epidemiological research (86).

CSA is defined as all forms of sexual abuse occurring before the age of 18. This includes both contact forms (e.g. rape) and non-contact forms (e.g. non-contact exposure of genitalia, threatened sexual violence) (95). IPV is defined as violence where the victim is 15 years or older and the perpetrator is the current or ex-intimate partner of the victim (96). The association between both risk factors and MDD has been well established and includes evidence from longitudinal twin studies (which typically offer robust means of assessing confounding effects between early life risk factors), quantifying the link between traumatic events and an increased risk of MDD (97-99).

In GBD 2010, the previously defined CRA methodology was used to quantify the global proportion of MDD cases attributable to CSA and IPV respectively. In this instance, the proportion of MDD prevalent cases averted given a counterfactual absence of ever having experienced CSA or IPV in the population (10) was investigated. Findings showed that CSA accounted for 5.1% and IPV for 11.4% of MDD DALYs respectively (10). With MDD established as one of the leading causes of burden worldwide by GBD 2010 (5, 13), this has salient implications for effectively reducing its ubiquitous burden.

In many countries, particularly low to middle income countries where there are high levels of gender inequality, women are considerably more likely to be exposed to CSA and IPV than men. Furthermore, women are likely to experience more chronic patterns of abuse and violence, more controlling and threatening behaviour and are more likely to be injured and killed by abuse and violence than men (100-102) .

It is conceivable that the sex difference in exposure to CSA and IPV also impacts on the sex difference in MDD. Females are up to two times more likely to have MDD than males. This finding has been replicated in many cross-national epidemiological surveys (103-107) and has been linked to the incidence of depression rather than its duration or re-occurrence (103, 105, 106). Explanatory models consisting of biological, social and psychological pathways have been proposed but have yet to be fully quantified (103, 107-110). For instance, it has been suggested that women may be more susceptible to depression due to changes in body chemistry and hormonal systems during the reproductive years, gender-role associated stress or, exposure to traumatic life events which activate stress hormones and affect the balance of neurotransmitters in the brain (103, 107).

The purpose of aim four of the thesis was to explore the risk factors of MDD, an area of unexplained variability in the epidemiological profile of MDD proposed. This involved investigating how two established risk factors of MDD (CSA and IPV) can impact on its global distribution. This work can contribute further to quantifying the heterogeneity within the epidemiology of MDD i.e. investigating how much of the variability is 'real' and how much can be explained by methodological factors. Further work on establishing potentially avertable risk factors to MDD will also inform the setting of preventative intervention strategies for MDD which is currently lacking (28).

Chapter review

This chapter reviewed the available literature on the epidemiology of MDD. Despite the many publications on this topic, there remains significant gaps in the literature, with more to be learnt for instance about the risk factors of MDD, differences in its distribution between countries, how it impacts on the population, and how it compares to other diseases and injuries. Upcoming chapters present the original research undertaken in this thesis, focused on responding to these research questions and aims of the thesis. Chapter Three pertains to aim one, which was to review the available data and summarise the global distribution of MDD.

Chapter Three: Global variation in the prevalence and incidence of major depressive disorder: A systematic review of the epidemiological literature

Alize J Ferrari[1,2], Adele J Somerville[3], Amanda J Baxter[1,2], Rosana Norman[1,4], Scott B Patten[5], Theo Vos[1], Harvey A Whiteford[1,2]

[1]The University of Queensland, School of Population Health, Herston, Queensland, Australia
[2]Queensland Centre for Mental Health Research, The Park Centre for Mental Health, Wacol, Queensland, Australia
[3] The University of Queensland, Institute of Social Science Research, St Lucia, Queensland, Australia
[4]The University of Queensland, Queensland Children's Medical Research Institute, Herston, Queensland, Australia
[5]Department of Community Health Sciences, University of Calgary, Calgary, Canada.

Published in Psychological Medicine, 2013; 43(3):471-81.

Chapter summary

Background

Summarising the epidemiology of MDD at a global level is complicated by significant heterogeneity in the data. The aim of this study is to present a global summary of the prevalence and incidence of MDD, accounting for sources of bias, and dealing with heterogeneity. Findings are informing MDD burden quantification in GBD 2010.

Method

A systematic review of prevalence and incidence of MDD was undertaken. Electronic databases Medline, PsycInfo and EMBASE were searched. Community-representative studies adhering to suitable diagnostic nomenclature were included. A meta-regression was conducted to explore sources of heterogeneity in prevalence and guide the stratification of data in a meta-analysis.

Results

The literature search identified 116 prevalence and 4 incidence studies. Prevalence period, sex, year of study, depression subtype, survey instrument, age and region were significant determinants of prevalence, explaining 57.7% of the variability between studies. The global point prevalence of MDD, adjusting for methodological differences was 4.7% (4.4%-5.0%). The pooled annual incidence was 3.0% (2.4%-3.8%), clearly at odds with the pooled prevalence estimates and the previously reported average duration of 30 weeks for an episode of MDD.

Conclusion

Our findings provide a comprehensive and up-to-date profile of the prevalence of MDD globally. Region and study methodology influenced the prevalence of MDD. This needs to be considered in the GBD 2010 study and in investigations into the ecological determinants of MDD. Good quality estimates from low/middle income countries were sparse. More accurate data on incidence are also required.

Introduction

Depressive disorders as defined by the DSM-IV-TR typically present in adolescence or early adult life, can be chronic or episodic and are frequently recurrent and comorbid with substance abuse or other mental and physical health conditions (38). The burden attributed to depressive disorders worldwide is a major public health concern. The GBD study measures disease burden in terms of the DALY. This is the sum of YLLs and YLDs (1). The GBD 1990 study reported that depressive disorders were the 4th leading cause of burden, accounting for 3.7% of DALYs in 1990 (1). By 2000/05 they were the 3rd leading cause of burden accounting for 4.3% of DALYs, and the leading cause of disability, accounting for 13.4% of YLDs in women and 8.3% in men (15).

Our understanding of the public health importance of mental disorders, including their impact on other health conditions (74, 111) will be enhanced by the GBD 2010 study currently underway (112). This will quantify burden for over 220 diseases (including 11 mental disorders) by country and 21 world regions for the years 1990, 2005 and 2010. It will use significantly improved methodology compared to the GBD 1990 study, including more representative disability weight estimations (see: http://www.globalburden.org/). In the GBD 2010 study, a dimensional approach is being taken, with burden being calculated for major MDD i.e. one or more MDEs using three severity levels, and dysthymia separately. This will enable burden estimates to encapsulate differences in morbidity within and between depressive disorder subtypes (113-115).

To quantify the morbidity (i.e. YLD) attributable to MDD in the GBD 2010 study, epidemiological data were required to describe the disease occurrence and course of illness (see Table S1, Appendix Two for definitions of the data required). Although there is a wealth of literature on the different epidemiological parameters of MDD, this has yet to be systematically summarised at a global level. Aside from informing the GBD 2010 study, such an integrated summary has both clinical and public health applications (116-118). However, this task is complicated by the presence of significant heterogeneity in the data. Heterogeneity refers to both the variability in epidemiological estimates resulting from true differences in the epidemiology of MDD and the variability produced by differences in the methodology used to capture data (51, 52)

Literature reviews on the prevalence and incidence of MDD have consistently raised the issue of heterogeneity. The GBD 2000/05 update estimated that the 12-month prevalence of a MDE was 1.6% in males and 2.5% in females. Predicted (from prevalence estimates) annual incidence was 3.2% in males and 4.9% in females (15). An analytical review of the GBD 2000/05 update

concluded that there was a lack of data on unipolar depression and significant heterogeneity across epidemiological estimates (69).

Paykel and collaborators' review of MDD in Europe reporting a 12-month prevalence of 5% also revealed significant gaps in the literature. The incidence of MDD was unclear because of the lack of longitudinal follow-up of cases and there was limited data from Eastern Europe (47). Another review investigating the prevalence of MDD in the United States, Canada, Puerto Rico, France, West Germany, Italy, Lebanon, Taiwan, Korea, and New Zealand revealed significant regional variation in prevalence. The 12-month prevalence of MDD ranged from 0.8% in Taiwan to 5.8% in New Zealand (50). Explaining this regional variation is difficult given differences in the methodology used by the different studies (51).

In an attempt to control for this, the WMHS Consortium conducted population surveys in 28 countries using a standard protocol for data collection and assessment. The CIDI was used to diagnose cases of MDE (52) Results revealed regional variation in the 12-month prevalence of a MDE, ranging from 2.2% in Japan to 10.4% in Brazil with similar averages of 5.5% in developed and 5.9% in developing countries. The average duration of an episode estimated from WMHS ranged from 23.1 to 33.8 weeks (17, 52, 119).These differences may reflect true regional variability in the epidemiology of MDE. However, despite WMHS' standardised procedure, some limitations were reported. Notably, validation exercises involving the CIDI have been completed almost entirely in Western countries; hence its cross-cultural reliability and validity remains unclear (4, 52, 120).

The aim of this paper is to summarise the global prevalence and incidence of MDD exploring the global distribution and sources of heterogeneity and, where feasible, adjusting for variability caused by differences in study methodology and design. This will help identify true differences in the global distribution of MDD that need to be considered in the integration of the epidemiological data. This work was undertaken by the GBD Mental Disorders Research Group (http://www.qcmhr.uq.edu. au/ BODP).

Methods

Literature review

The systematic review adhered to guidelines recommended by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (121). Electronic databases Medline (via CSA), PsycInfo and EMBASE were used. Search strings were derived in consultation with a research librarian. For more information on the search strings, see http://www.gbd.unsw.edu.au/gbdweb.nsf/resources/MD_Pt2_SearchStrings/$file/MDSearch+strings_2.pdf. Publications in languages other than English were included. Although the search was limited to studies published between 1980 and 2007, continuing perusal of the literature and correspondence with experts in the field allowed us to capture additional studies up to 2011.

Inclusion and exclusion. Population based surveys representative of the community, region or country were included. Non-representative subsets of the population such as samples based on in-patient admissions or treatment trials were excluded. Studies adhering to DSM or ICD diagnostic classifications were preferred to allow for better consistency in the measurement of MDD; however studies using symptom scales that only broadly map on to DSM/ICD diagnostic thresholds were included for comparison. Where the same data were reported across different papers the most informative paper was selected.

For prevalence, we included studies reporting point (i.e. current or past-month prevalence), 6- and/or 12-month prevalence. Lifetime estimates were excluded as these are more prone to recall bias (122-125). Estimates of MDD were the focus; however if studies reported estimates of depression NOS these were included for comparison. Studies reporting incidence hazards were included (i.e. those with person years of follow-up in the denominator). Estimates of probability such as cumulative incidence based on longer risk intervals were excluded.

Extraction. Data extracted included information on the country and year of study, parameter value and type (e.g. point or 12-month prevalence), sample coverage (community, regional, national), sample urbanicity (rural, urban, mixed), sex (male, female, persons), age range, case ascertainment period (recorded as the midyear time point), response rate, depression subtype (MDD or MDD + depression NOS), diagnostic criteria (ICD, DSM) and survey instrument (diagnostic instruments, symptom scales). Countries were stratified into regions based on the GBD categorisation of regions (see http://www.globalburden.com.au/project-description). Forced entry of key variables was required for quality assurance. A random sample of papers was reviewed by two researchers to

check consistency of data extraction. Where differences occurred, reviewers discussed these with the study's primary investigator (HAW) to arrive at a consensus.

Uncertainty (standard error (SE) or confidence interval) pertaining to each prevalence or incidence estimate was extracted if reported or otherwise calculated. If the denominator (sex- and/or age-specific sample size) was reported, SE was calculated using $SE = \sqrt{2.1*(P*(1–P)/N}$ where P is the proportion of cases reported, 2.1 is the average design effect and N is the denominator. The average design effect accounted for any increase in uncertainty produced by a study's sampling methodology. It was calculated based on a sample of 110 design effects from the GBD Mental Disorders Research Group's affective disorders dataset. If the denominator was not reported by age and sex, the United Nation's country-, sex-, age- and year-specific population size was used to distribute the overall sample size across age and sex categories (126).

Analysis

Prevalence. For prevalence, Stata II.2 software (http://www.stata.com/) was used to conduct a meta-regression (127) to help explain the variability between studies. We based our statistical methodology on previous applications of meta-regression to explore the effect of methodological and ecological variables on prevalence (127-129). Since the distribution of prevalence estimates was positively skewed, logarithmic transformation (natural log) was applied to meet the parametric assumption of normality (130).

Results from the meta-regression guided the stratification of pooled prevalence estimates in the subsequent meta-analysis (127). As it is essential for GBD purposes to avoid any overestimation in burden estimates, point prevalence is considered as the gold standard as it is less susceptible to recall bias compared to estimates of period prevalence (113-115). For this reason, it was also set as the primary summary measure here as well as in the upcoming GBD disease modelling of MDD for which this literature review was undertaken.

Statistical heterogeneity was quantified using the I^2 statistic, which indicates the total variation in the data attributable to heterogeneity (131). A random effects model was selected over the fixed effects model to accommodate for heterogeneity (132, 133). We used the post-estimation 'predict' command to estimate overall prevalence by region, accommodating for methodological factors. This command fitted a value to each reported prevalence estimate and the associated SE based on the coefficients from the meta-regression (134).

Incidence. Similar methods of pooling incidence were used as described for prevalence. However, the paucity of incidence estimates did not permit us to conduct a meta-regression.

Results

Out of 32,579 data sources on the epidemiology of MDD only 120 studies fitted the inclusion criteria for prevalence and incidence. The search and main reasons for exclusion are summarised in figure 2. A summary of the studies included for each parameter is given in Tables S2 and S3, Appendix Two.

Prevalence

One hundred and sixteen studies reporting the prevalence of MDD were included, the majority of which were from Western countries i.e. Europe and North America (n=74). We identified 11 studies reporting both MDD and depression NOS and 22 studies using a symptom scale. There was considerable variability between estimates. Point prevalence ranged from 0.05% in males from Japan aged 65 years or older (135) to 73% in females from Afghanistan aged 15 years or older (136).

To maximise inclusion, potential outliers in the dataset with no salient methodological limitation were retained and investigated further through the meta-regression. To ensure independence of observations, where person as well as sex-specific estimates were reported by the same study only the latter were included in analyses. Where age-specific and overall-age estimates were reported, only the latter were included. Where only age-specific estimates were reported, these were combined to calculate the overall-age prevalence i.e. the summed number of cases across each age group was divided by the summed denominator across each age group. This reduced the final dataset from 783 to 274 prevalence estimates. To investigate the effect of age on prevalence, estimates were grouped into 4 broad categories: whole age range (e.g. 0 to 99 years), <18 years, 18-65 years and >65 years. Where reported age ranges could fit into more than one category they were allocated to the most representative one on a case-by-case basis.

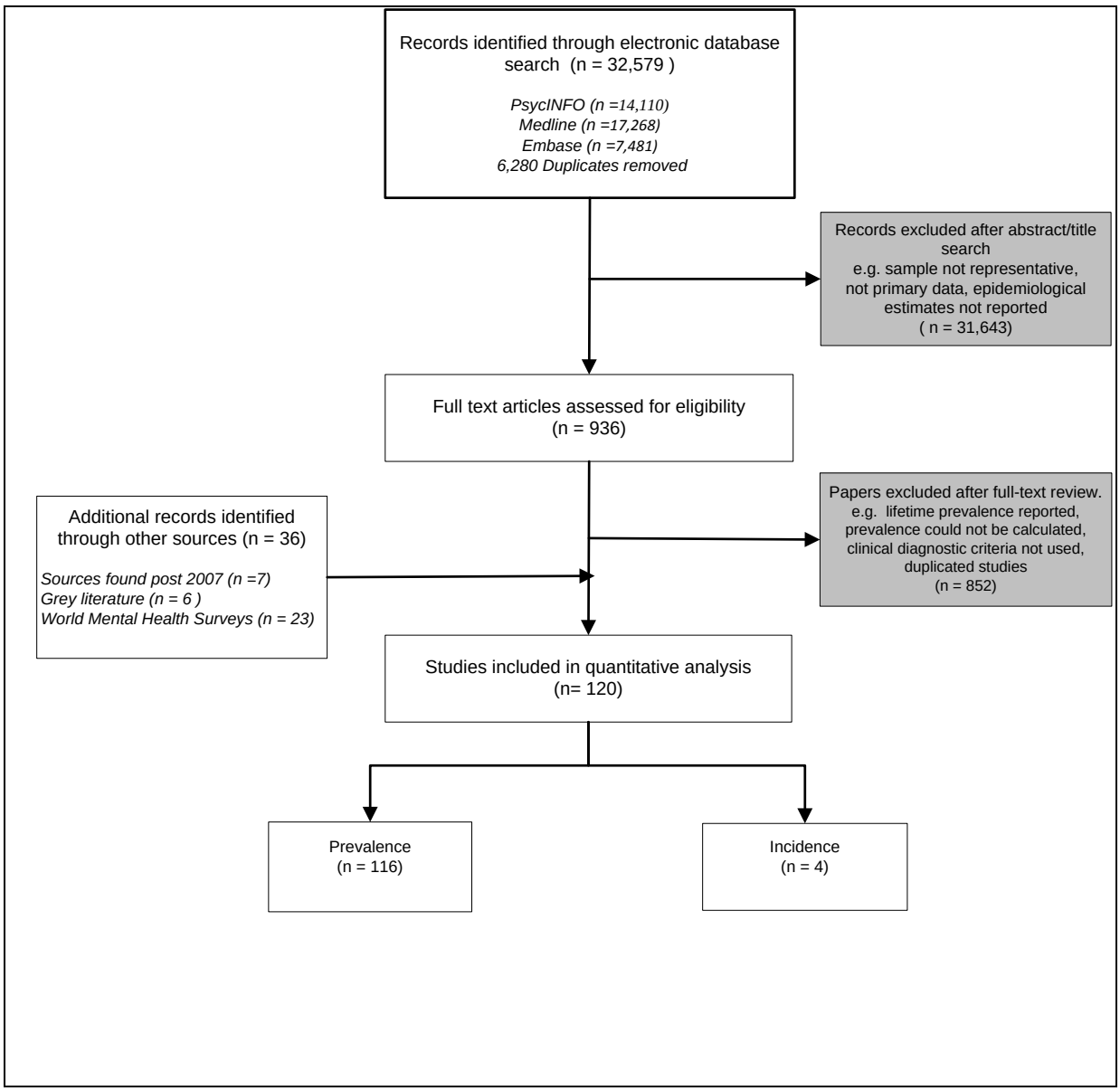


Figure 2. Flowchart showing results of the systematic review for the prevalence and incidence of MDD.

In the meta-regression, study-level variables were inserted in the model first (model 1), and the country-level variable (region) second (model 2). Coverage and urbanicity variables were excluded from both models as they were signficantly correlated with the majority of other variables, particularly with the region variable, which is a major focus of this paper. Model 1 explained 43.1% of the between study variance (Adjusted R^2 43.1%, $F(11, 265)= 16.9$, $p<0.001$). Prevalence type, sex, midyear of case ascertainment, age range, depression subtype and survey instrument were statistically significant determinants of reported prevalence (table 2). Diagnostic criteria were not significantly associated with prevalence.

Prevalence was statistically higher for past year prevalence compared to point, in females compared to males and persons, in studies capturing MDD and depression NOS compared to MDD alone, and in studies with more recent case ascertainments. Persons under 18 years had lower prevalence than persons across the overall age group and studies that used symptom scales reported a higher prevalence than studies where DSM or ICD criteria were used. The survey instrument variable was originally made up of 8 categories, summarising the most frequent instruments in the dataset. The CIDI was used as the reference as it was the most commonly reported. This variable was dichotomised in the final model because symptom scales were the only instruments to yield signicantly different prevalence estimates at $p<0.001$. Results were similar when clinical interview (interviews conducted by a clinician) were used instead of the CIDI as the reference, with only symptoms scales ($p<0.001$) and the Geriatric Mental State Schedule ($p<0.041$) yielding statistically significant results.

The inclusion of the region variable in model 2 explained an additional 14.6% of the between study variance. The overall variance explained by study- and country-level variables combined was 57.7% (Adjusted R^2 57.7%, $F(19, 257)=16.5$, $p<0.001$). Prevalence period, sex, midyear of case ascertainment, depression subtype, survey instrument and age range remained statistically significant determinants of reported prevalence in model 2. When Western Europe, the region with the most data, was set as the reference, a statistically significant effect of region emerged such that prevalence from South America, South Asia and Africa/Middle East was statistically higher than prevalence from Western Europe. Estimates from East/Southeast Asia and Asia Pacific, High Income were statistically lower. Similar results were obtained when North America was used as the reference, except that South America and North Africa/Middle East no longer yielded statistically higher prevalence.

Table 2. Results of meta-regression models showing odds ratios for reported prevalence by study- and country-level determinants.

Determinant	Unadjusted[a] Odds ratio (95% uncertainty)	*p* value <	Adjusted (Model 1)[b] Odds ratio (95% uncertainty)	*p* value <	Adjusted (Model 2)[c] Odds ratio (95% uncertainty)	*p* value <
Prevalence period	**Reference: Point**					
12 month prevalence	1.02 (0.79-1.32)	0.853	1.2 (1.0-1.5)*	0.048*	1.3 (1.1-1.6)	0.007*
Sex	**Reference: Female**					
Male	0.6 (0.5-0.7)*	0.001*	0.6 (0.5-0.7)*	0.001*	0.6 (0.5-0.7)	0.001*
Total	0.7 (0.5-0.9)*	0.009*	0.7 (0.6-0.9)*	0.012*	0.7 (0.6-0.9)	0.008*
Midyear of case ascertainment[d]	1.03 (1.01-1.05)*	0.003*	1.02 (1.00-1.03)*	0.036*	1.02 (1.01-1.04)	0.002*
Age (years)	**Reference: Overall age groups (0-99 years)**					
18-65	1.02 (0.78-1.34)	0.864	1.2 (0.9-1.5)	0.145	1.2 (0.9-1.5)	0.067
<18	0.7 (0.5-1.0)*	0.025*	0.6 (0.4-0.7)*	0.001*	0.6 (0.4-0.7)	0.001*
>65	0.5 (0.4-0.7)*	0.001*	0.98 (0.73-1.33)	0.913	1.1 (0.8-1.4)	0.568
Depression subtype	**Reference: MDD only**					
MDD + Depression NOS	0.6 (0.4-0.8)*	0.002*	1.96 (1.47-2.62)*	0.001*	2.1 (1.6-2.8)	0.001*
Diagnostic criteria	**Reference: DSM**					
ICD	0.8 (0.6-1.2)	0.281	0.95 (0.72-1.25)	0.697	0.9 (0.7-1.2)	0.390
Not specified	3.3 (1.9-5.8)*	0.001*	1.5 (0.9-2.5)	0.145	1.5 (0.9-2.5)	0.106
Survey instrument	**Reference: DSM/ICD tools**					
Symptom scale	3.4 (2.6-4.6)*	0.001*	3.6 (2.6-5.0)*	0.001*	2.9 (2.1-4.0)	0.001*
Region	**Reference: Western Europe**					
Central/Eastern Europe	1.5 (0.9-2.4)	0.132			1.3 (0.9-2.0)	0.143
North America	0.9 (0.6-1.3)	0.563			1.2 (0.9-1.6)	0.200
South America	1.3 (0.9-1.9)	0.148			1.6 (1.5-2.1)*	0.004*
Australasia	0.8 (0.5-1.2)	0.281			0.9 (0.6-1.3)	0.580
East/Southeast Asia	0.4 (0.3 -0.6)	0.001*			0.4 (0.3-0.6)*	0.001*
South Asia	3.3 (1.8-6.2)	0.001*			2.1 (1.2-3.6)*	0.006*
Asia Pacific, High Income	0.6 (0.3-1.0)	0.045*			0.4 (0.3-0.7)*	0.001*
Africa/Middle East	1.9 (1.4-2.7)	0.001*			1.4 (1.1-1.8)*	0.042*

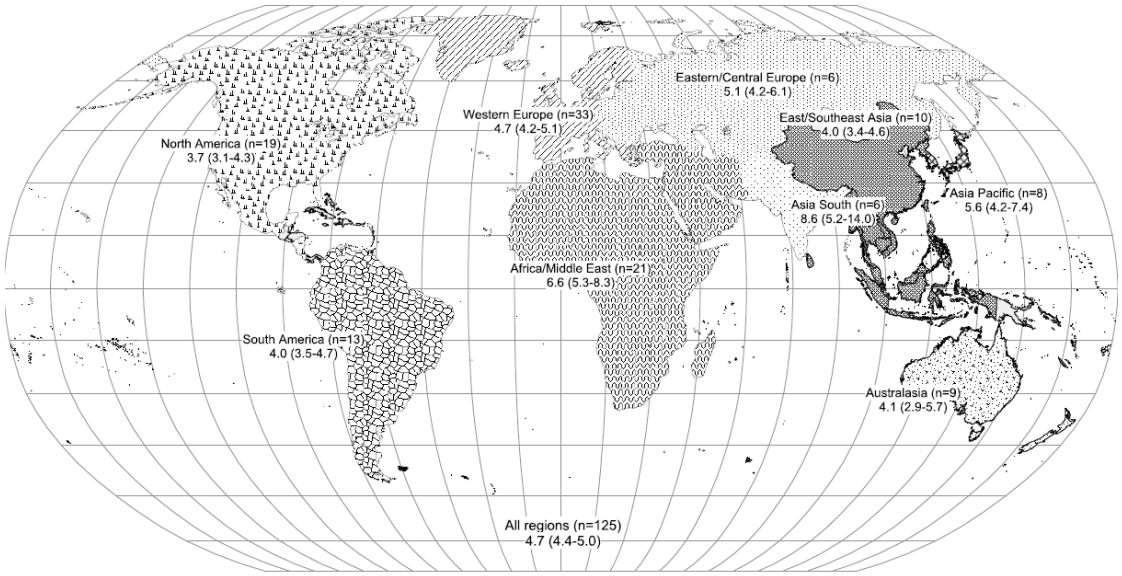
Note. The response rate variable was exlcuded from the model as it did not contribute to the overall variance explained. [a]*Unadjusted results represent meta-regression ran on indiviual variables without countrolling for the effect of others.* [b]*Adjusted model 1 results represent meta-regression ran on study-level variables only.* [c]*Adjusted model 2 results represent meta-regression ran on study- and country-level variables.* [d]*Midyear of case ascertainment modelled as a continuous variable. *Statistical significance at p<0.05.*

A series of meta-analyses was used to further illustrate the effect of statistically significant determinants of prevalence. Reported prevalence was pooled according to each statistically significant study-level determinant (table 3). For each determinant, reported prevalence was also pooled by sex, but there was insuffient data to simultaneously stratify prevalence by all other determinants. To address this limitation, prevalence was also predicted for each region while adjusting for the effects of study-level determinants in model 2 (figure 3). Although reduced, cross-national differences in prevalence persisted after adjusting for study-level determinants of prevalence. Notably, although adjusted downwards, estimates from South Asia and Africa/Middle East remained the highest in the dataset, and although adjusted upwards, estimates from East/Southeast Asia remained amongst the lowest. Estimates from Asia Pacific were no longer amongst the lowest. The adjusted and unadjusted prevalence by region is summarised in Table S4, Appendix Two.

Table 3.Pooled reported prevalence stratified by study-level determinants statistically associated with prevalence.

	Female (n= 82)	**Male (n=79)**	**Person (n=34)**
Determinant	Prevalence (95% CI)	Prevalence (95% CI)	Prevalence (95% CI)
Prevalence period			
Point (n=82)	5.9 (4.7-7.5)	3.8 (3.2-4.5)	4.7 (3.7-5.5)
12 months (n=47)	7.2 (6.0-8.9)	3.9 (3.0-5.1)	3.7 (2.7-5.0)
Depression subtype			
MDD only (n=105)	5.8 (4.7-7.1)	3.5 (2.9-4.2)	4.2 (3.4-5.2)
MDD + depression NOS (n=11)	10.2 (8.9-12.1)	6.4 (5.2-7.9)	7.2 (4.3-11.8)
Survey instrument			
DSM/ICD tool (n=94)	5.4 (4.9-6.1)	3.1 (2.7-3.6)	3.8 (3.1-4.6)
Symptom scale (n=22)	17.03 (11.46-25.28)	11.6 (7.5-18.0)	12.1 (9.3-15.7)

Note. For each determinant, prevalence was additionally pooled only by sex hence did not account for the effect of all other determinants of prevalence. All I^2 statistics were >90%; n: number of studies in each group; CI:Confidence interval.



Note. Map derived using MapInfo Professional. Version 10.5.2. (2010) Pitney Bowes Software Inc. Troy, New York; Map Projection: Robinson WGS84.

Figure 3. Predicted point prevalence by region, adjusted for study level determinants.

Incidence

Only 4 studies (64-67) reporting annual incidence rates of MDD from USA, Canada and Ethiopia were identified. Estimates ranged from 1.6% in females aged 18 years or above to 7.1% in females aged 15 to 19 years, from the USA. Male and female estimates across overall age groups were pooled to calculate an overall estimate of annual incidence (table 4). Total estimates were only included if sex-specific estimates were not reported. Although pooled female estimates were higher than pooled male estimates, there was no statistically significant effect of sex. Since there were only 3 estimates in each group, more data is required to make a definitive statement on whether a difference exists.

Table 4. Pooled estimates of annual incidence.

Sex	Incidence (95% CI)	Weight (%)[a]
Female (n=3)	3.4 (1.9-6.3)	48.0
Male (n=3)	2.7 (2.0-3.7)	49.1
Total (n=1)	2.4 (0.7-8.4)	2.9
Overall (n=7)	**3.0 (2.4-3.8)**	**100.00**

Note. All I^2 statistics were >86%; n is the number of estimates in each group; CI:Confidence interval; [a]Random effects weights.

Discussion

The majority of the literature on prevalence was from Western Europe and North America with much less from non-Western regions. Prevalence data were highly sensitive to elements of study design and methodology. Consistent with existing literature, prevalence in females was higher than

in males (107, 137, 138) and 12-month prevalence was higher than point prevalence (139-141). Given these results, it would be reasonable to assume that when pooled by gender and prevalence type simultaneously, pooled 12-month prevalence would be higher than pooled point prevalence; however this was not the case. For persons pooled 12-month prevalence was lower than pooled point prevalence although this result was not statistically significant. Pursuing the reason for this finding was outside the scope of this study however, similar unanticipated results have been reported in literature pertaining to the prevalence of schizophrenia (142). It must also be noted that prevalence was pooled by prevalence type and sex only due to lack of data. Controlling for the other significant study-level determinants of prevalence as was done in the meta-regression may have yielded different results.

Symptom scales were the only survey instruments significantly associated with prevalence, suggesting adequate consistency between the other diagnostic tools in the MDD literature. There has been continuous debate as to whether symptom scales are better suited to measuring mental disorder symptoms or psychological distress (143-145) . In this case, we found that symptom scales inflated the overall prevalence of MDD. That said, they were often the only tools used to capture prevalence, particularly in conflict settings where epidemiological data is sparse (146). In order to maximize the global representativeness of our findings we chose to include prevalence estimates derived from symptoms scales. We adjusted for any inflation to pooled prevalence by specifying that prevalence derived from diagnostic tools was the gold standard. This is consistent with the methodology used by other authors specifying that data from symptoms scales need to be 'recalibrated' relative to data from diagnostic tools (145, 147, 148). Despite some differences in the DSM and ICD definitions of MDD, diagnostic criteria did not have a statistically significant effect on prevalence.

We detected a time effect suggesting that the prevalence of MDD had increased over time. This was based on an ecological comparison of the midpoint of the case ascertainment period, as a continuous variable. It's possible that this finding represented a true increase in prevalence. Alternatively, it could be due to other methodological or ecological differences across time that we were unable to capture. More in-depth investigation is required to confirm this finding. The only age effect found was from the <18 years age group, which yielded lower estimates compared to estimates across the entire lifespan. This was likely due to estimates from very young children (e.g. 8-9 years) in the <18 year old group. However, drawing conclusions from this variable is also problematic given that we could only categorize age using 4 broad age categories and some age ranges could be allocated to multiple categories. We used broad as opposed to age-specific

estimates as the latter would violate the parametric assumption of independent observations required in a meta-regression. A more detailed comparison of prevalence across the lifespan is required for better conclusions

We detected considerable regional differences in the prevalence of MDD, some of which were reduced when study-level sources of variability were controlled for. Although our finding of higher prevalence of MDD in developing regions (except for Asia East/Southeast) compared to developed regions corresponded to WMHS results, our overall adjusted point prevalence of 4.7% was higher than the WMHS finding of 1.8% point prevalence in developed countries and 2.6% in developing countries. Instead, it was closer to the 5.5% 12-month prevalence in developed countries (52). The higher point prevalence obtained here may be due to the adjustments made for differences in study methodology. Despite WMHS efforts to enforce a standardised methodology, differences still occurred. Response rates and the amount of missing data varied substantially across countries which may have reduced the representativeness of some samples (4, 52, 120). The WMHS used data collected by the CIDI only. Our broader focus allowed us to include data from countries that were not part of the WMHS, using other diagnostic instruments. That said, our inclusion of prevalence derived from symptom scales must be treated with caution given the possibility of inflating final results with presentations of MDD symptoms rather than diagnoses.

Estimates from East/Southeast Asia remained much lower than other regions even after adjusting for methodological differences. This may reflect a true difference in the global distribution of MDD. Alternatively, it may be due to unidentified sources of measurement bias that we were unable to control for. One possibility is that DSM/ICD diagnostic criteria are not sensitive to cross cultural presentations of MDD (4, 52, 120). Another is that MDD may be mis-coded as depression NOS in less developed countries (53, 55), underestimating prevalence. We recommend that in upcoming GBD burden calculation this limitation be addressed through the inclusion of estimates of depression NOS as was done here.

Ecological factors may also contribute to regional differences in prevalence. Consistently high prevalence in Africa/Middle East and South Asia raises the possibility that conflict in countries such as Afghanistan, Iraq and Sudan increase the prevalence of MDD. This is consistent with literature suggesting that exposure to torture and other trauma in conflict settings increase the prevalence of depression and post-traumatic stress disorder (148). Based on this, we also recommend that the effect of conflict status be investigated further.

Whilst we found numerous naturalistic studies of the annual incidence of MDD, very few follow-up studies using representative community samples were available. The GBD 2000/05 update predicted an average incidence of 3.2% in males and 4.9% in females (15, 73) which was higher than our results of 2.7% in males and 3.4% in females. If a duration of 30 weeks for an episode of MDD (27) is taken into account, there is a clear inconsistency between the few incidence estimates we obtained and our adjusted prevalence estimate, in that incidence was lower than prevalence instead of higher. This problem illustrates the importance of internal consistency between epidemiological parameters. While summaries of individual epidemiological parameters of MDD are useful, they may be inaccurate, particularly where data are limited. In this case, parameters need to be considered simultaneously for an internally consistent epidemiological profile of MDD. The upcoming GBD disease modelling of the epidemiology of MDD will help clarify this (149). In the meantime, our incidence findings are indicative only. More cross-national data are required for stronger conclusions. Although more data were available for prevalence, there were few good quality estimates from less developed parts of the world. This prevented us from conducting region-specific analyses of variance. We were also unable to control for all sources of variability in prevalence. Further investigation into other determinants of prevalence, for instance human development indicators outside the scope of this review, is required.

Our literature review addressed a range of issues central to the epidemiology of MDD. It identified the data sources required for burden estimation in the GBD 2010 study. It also provided an epidemiological summary of MDD, considering, where feasible, sources of heterogeneity in the data. We recommend that the statistically significant study-level determinants of prevalence identified be considered when generating other ecological models of MDD prevalence. We were also able to identify salient gaps in the literature that need further consideration. There were very little incidence data and very few studies from non-developed parts of the world across all parameters. We were also unable to comprehensively assess the effect of age on prevalence. Further investigation of these limitations is required for a clearer epidemiological profile of MDD.

Acknowledgments

Special thanks to Angela Higginson from the Institute for Social Science Research, University of Queensland for providing us with statistical advice. We are also grateful to the contribution of Holly E Erskine, An Pham and Amanda Brown to data collection and to Roman Scheurer for assistance in generating maps.

Chapter review

Chapter Three focused on reviewing the available data on the global distribution of MDD (Thesis aim one, part one). The focus was primarily on analysing the available prevalence and incidence data, although duration and excess-mortality data were also discussed and will be presented in greater detail in the next chapter.

The summary of prevalence data presented in Chapter Three was incomplete given missing data, as well as considerable variability between data points from different studies. An analysis of incidence data revealed inconsistency between reported incidence, prevalence and duration data, likely due to restrictions in how incidence was surveyed. Rather than rely on these data points to inform the epidemiological profile of MDD, in Chapter Four, statistical modelling was used to assemble them into an internally consistent disease model. This made is possible to estimate epidemiological data for ages, years and countries for which raw data was not available, while adjusting for the sources of variability identified in Chapter Three.

Chapter Four: The epidemiological modelling of major depressive disorder: Application for the global burden of disease study 2010.

Alize J Ferrari[1,2], Fiona J Charlson[1], Rosana E Norman[1,3], Abraham D Flaxman[4], Scott B Patten[5], Theo Vos[1,4], Harvey A Whiteford[1,2].

[1]University of Queensland, School of Population Health, Herston, Queensland, Australia
[2]Queensland Centre for Mental Health Research, Wacol, Queensland, Australia
[3]University of Queensland, Queensland Children's Medical Research Institute, Herston, Queensland, Australia
[4]University of Washington, Institute for Health Metrics and Evaluation, Seattle, Washington, USA
[5] University of Calgary, Department of Community Health Sciences, Calgary, Canada

Published in PloS One, 2013, 8(7):e69637

Chapter summary

Background

Although the detrimental impact of MDD at the individual level has been described, its global epidemiology remains unclear given limitations in the data. Here we present the modelled epidemiological profile of MDD dealing with heterogeneity in the data, enforcing internal consistency between epidemiological parameters and making estimates for world regions with no empirical data. These estimates were used to quantify the burden of MDD for GBD 2010.

Method

Analyses drew on data from our existing literature review of the epidemiology of MDD. DisMod-MR, the latest version of the generic disease modelling system redesigned as a Bayesian meta-regression tool, derived prevalence by age, year and sex for 21 regions. Prior epidemiological knowledge, study- and country-level covariates adjusted sub-optimal raw data.

Results

There were over 298 million cases of MDD globally at any point in time in 2010, with the highest proportion of cases occurring between 25 and 34 years. Global point prevalence was very similar across time (4.4% (95% uncertainty: 4.2-4.7%) in 1990, 4.4% (4.1-4.7%) in 2005 and 2010), but higher in females (5.5% (5.0-6.0%) compared to males (3.2% (3.0-3.6%) in 2010. Regions in conflict had higher prevalence than those with no conflict. The annual incidence of an episode of MDD followed a similar age and regional pattern to prevalence but was about one and a half times higher, consistent with an average duration of 37.7 weeks.

Conclusion

We were able to integrate available data, including those from high quality surveys and sub-optimal studies, into a model adjusting for known methodological sources of heterogeneity. We were also able to estimate the epidemiology of MDD in regions with no available data. This informed GBD 2010 and the public health field, with a clearer understanding of the global distribution of MDD.

Introduction

Quantitative summaries of disease epidemiology are essential inputs to generating health indicators such as burden of disease estimates. They have also made significant contributions to health policy, service planning, and funding priorities in public-health (116-118). That said, epidemiological data can be costly and difficult to assemble. As a result global data are limited and sometimes unreliable, in which case supplementary measures to accurately compile the data are required.

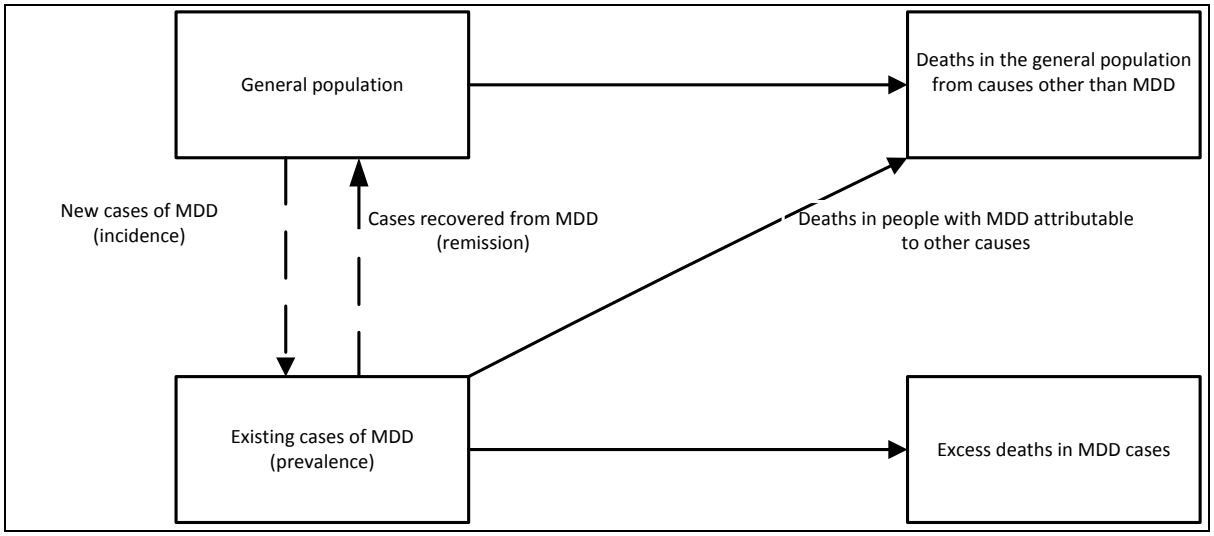
GBD 1990 and its update in 2000/05 quantified burden in terms of DALYs which are the sum of YLDs and YLLs (1, 16). In 1990, depressive disorders were the 4th leading cause of burden (1). In 2000, they were the 3rd leading cause of burden as well as the leading cause of disability (15). This has made the estimation of burden for depressive disorders a critical component of the GBD 2010 study. GBD 2010 is a comprehensive re-assessment of disease burden and draws on a wide range of data sources and expertise to quantify burden for 291 diseases and injuries, 21 world regions and the years 1990, 2005 and 2010. Main findings from this study were published in 2012 in a series of publications (5, 6, 10-13).

The GBD 2010 mental disorders research group (see: http://www.globalburden.com.au/) oversaw the burden quantification process for 20 mental disorders, including MDD and dysthymia. For each mental disorder, this involved: (1) conducting a literature review of the disorder's epidemiology; (2) evaluating the extracted data in a disease model; and (3) producing estimates of prevalence for calculating disease burden (13). A major point of difference of GBD 2010 from previous versions is that results were presented without discounting, without the previously used age weights and with prevalent rather than incident YLDs (13). This paper follows our literature review of the raw global epidemiological data for MDD(150), representing step 1 of the burden calculation process. Here, we present an integrated and complete epidemiological model of MDD (step 2). The epidemiological review and modelling of dysthymia is being reported separately (151).

For GBD purposes, epidemiological data on prevalence, incidence, remission, duration and excess mortality are required (13). Summarising these parameters for MDD: (1) there are more data available for prevalence than for other parameters; (2) there are sparse data from low and middle income countries; and (3) there is considerable between-study variability in the epidemiology of MDD(27, 59, 150). This epidemiological variability may be an artefact of differences in data collection and assessment or, alternatively, due to 'real' differences in the disorder's epidemiology (51, 152, 153). The aim is to correct for the former and to retain the latter in order to present an accurate epidemiological profile of the burden of MDD.

Existing reviews of the global prevalence of MDD suggest that the 12-month prevalence ranges between 0.8% and 5.8% (50) or between 2.2% and 10.4% (17), depending on study methodology and sampling. Given that GBD focuses on capturing people who are experiencing disability within the year of interest, period prevalence is not the ideal measure for quantifying disease burden(13). Our review estimated that the global point (defined as current or past-month) prevalence of MDD was 4.7% (4.4%-5.0%) ranging from 3.7% (3.1%-4.3%) in North America to 8.6% (5.2%-14.0%) in South Asia, a region which included prevalence from countries in conflict. Study methodology and geographic location explained 57.7% of the variability in prevalence, noting that lack of data for certain parts of the world limited findings (150). Our pooled estimate of annual incidence derived from studies identified in the systematic review was 3.0% (2.4%-3.8%). As the estimated average duration of a MDE is less than a year (27), it is clear that the prevalence and incidence findings were 'inconsistent' as logically, incidence of MDD episodes should be higher than prevalence.

Internal consistency can be achieved by making use of an incidence-prevalence-mortality model (Figure 4) to check for, and force consistency between epidemiological parameters. This is when final prevalence, incidence, duration and excess-mortality estimates simultaneously adhere to the generic relationships in the incidence-prevalence-mortality model for a single time, place, and sex (9, 13, 154). More specifically, people in the general population are at risk of becoming ill and after incidence, become prevalent cases of MDD. They are then at risk of dying as a result of MDD and contributing to the cause-specific mortality rate or they may recover, contributing to the remission rate. People with and without MDD are also at risk of dying from other causes. Internal consistency is met if there is a corresponding incident case for every prevalent case of MDD; and if the total number of prevalent cases for MDD reflects not only prevalent and incident cases but also individuals that have died (as a result of MDD or other causes) and individuals that have recovered from MDD.



Note. Figure adapted from an existing incidence-prevalence-mortality model (9).

Figure 4. Incidence-prevalence-mortality model

Supplementing this model with expert knowledge also helps address other limitations in the empirical data. For instance, identifying relevant covariates from study design and methodology (e.g. prevalence period) helps to adjust sub-optimal data. Making predictions based on the raw data and identifying relevant ecological covariates (e.g. conflict status) enables us to estimate data for parameters and world regions with no available data. Excluding these parts of the world from GBD estimations would assume no burden from those countries hence exclude them from the global priority setting exercises intended for GBD 2010 findings. Conscious of the importance of accurately representing all world regions in global health agendas, the GBD 2010 approach was not only to predict epidemiological data for parts of the world with missing data but to also ensure that the resulting uncertainty around these predicted estimates was incorporated into final burden results.

In this paper we present an internally consistent epidemiological profile of MDD generated by DisMod-MR, a Bayesian meta-regression tool (13, 154) that predicts epidemiological data for parameters and parts of the world with no raw data and accommodates known methodological and ecological determinants of MDD through the use of covariates. Aside from informing GBD 2010 burden estimates, this work contributes to the wider MDD literature by providing a more accurate and complete depiction of the global distribution of MDD.

Methods

Case definition

The DSM-IV-TR characterises MDD by one or more MDEs, lasting for at least 2 weeks (38), a definition resembling that of recurrent depressive disorder in the ICD-10 (39). A MDE involves symptoms of depressed mood and/or loss of interest or pleasure in all or almost all activities occurring most of the day and nearly every day. Consistent with the methodology proposed by Vos and collaborators (155, 156) as well as Ustun and collaborators (46), we modelled MDD as an episodic disorder, with the incidence and average length (i.e. duration) of an episode specified. We also incorporated prevalence estimates of depression NOS. This was in response to literature suggesting that MDD is often coded as depression NOS in non-Western regions because DSM/ICD diagnostic criteria are less sensitive to non-Western presentations of the disorder (52, 53, 55).

Search strategy

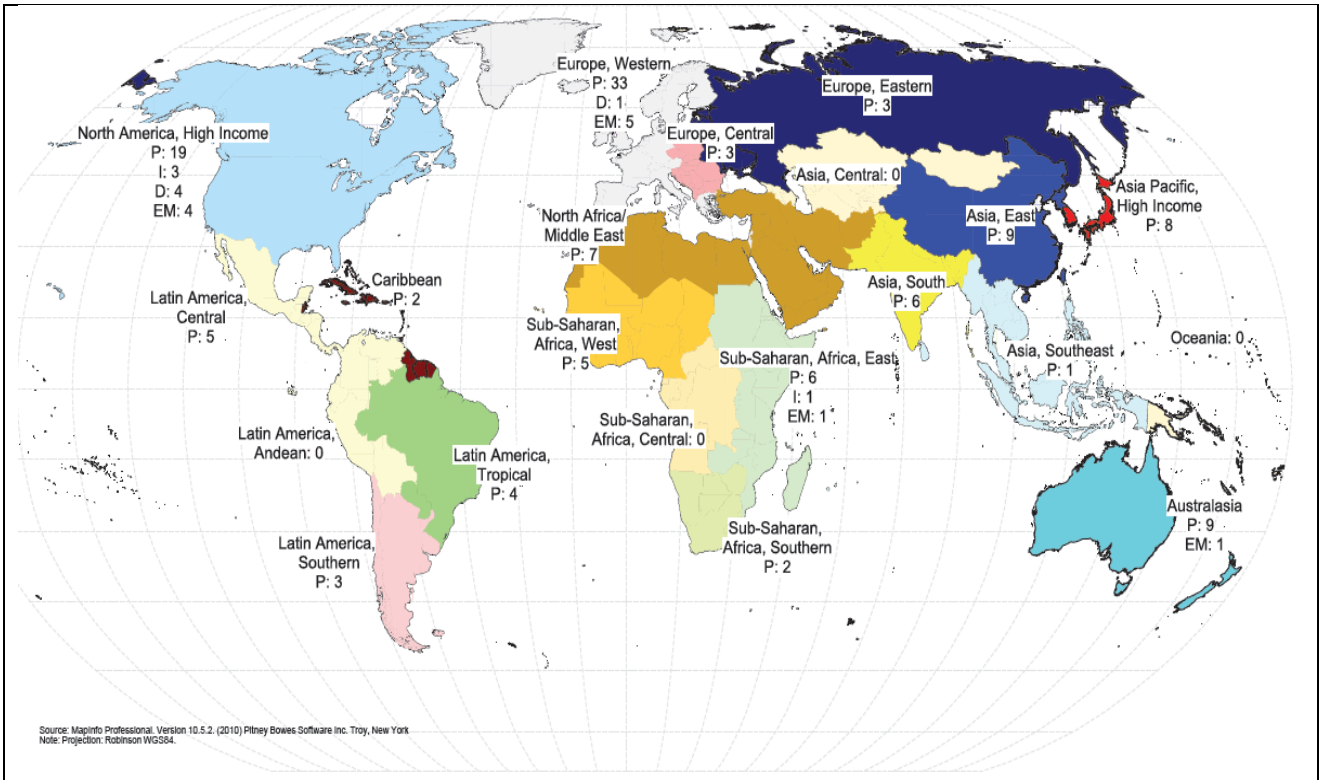
Estimates of prevalence, incidence, duration and excess mortality were searched for in a systematic review of the literature. This methodology has been outlined in greater detail elsewhere (27, 59, 150) with the PRISMA checklist and flowchart (121) summarised in supporting Text S1, Appendix Three. In summary, electronic databases Medline, PsycInfo and EMBASE were searched from 1980 onwards and studies were included if prevalence, incidence, duration and/or excess mortality of MDD were reported and if they were representative of the community, region or country. DSM or ICD diagnostic categorisations were required although if studies used symptom scales that broadly mapped to DSM/ICD thresholds, these were also included for prevalence due to lack of data in low to middle income regions. For prevalence we also required past year or point estimates. Even though point prevalence is the more representative measure for GBD purposes as it measures actual disability, 12-month prevalence was accepted to maximise inclusion. Lifetime estimates were excluded as they are most susceptible to recall bias (122-125). Given these allowances made to the inclusion criteria, we then looked at ways to adjust sub-optimal estimates (e.g. estimates derived from symptom scales and based on 12-month prevalence) towards optimal estimates (e.g. estimates derived from diagnostic instrument and based on point prevalence) to minimise the methodological heterogeneity in the dataset (see covariates section). For incidence we used hazard rates, with person years of follow-up in the denominator; for duration we used estimates based on follow-up studies reporting the natural history of MDD in community samples; for excess mortality we used RR (i.e. deaths in people with MDD compared to people without MDD) or standardized mortality ratio (SMRs, i.e. deaths in people with MDD compared to deaths in the general population).

Epidemiological data were extracted into a Microsoft Excel spreadsheet. Along with information pertaining to the study methodology, design, parameter type and value, an estimate of uncertainty SE or 95% confidence interval) was extracted if reported. If not reported, uncertainty was calculated using SE = $\sqrt{2.1*(P*(1–P)/N)}$ where P is the proportion of cases reported and 2.1 is an average design effect calculated using 110 design effects from the GBD Mental Disorders Research Group's affective disorders dataset. N is the age- and sex-specific denominator which, if not reported, was estimated using United Nation's country-, sex-, age- and year-specific population size to apportion the study sample size across age and sex categories (126).

The country in which each study was conducted was coded according to the 21 world regions (see: http://www.globalburden.com.au/project-description) used for GBD 2010. This regional grouping was based on broad geographic regions or continents where each region comprised of no fewer than two countries, grouped according to country-specific child/adult mortality levels and major causes of death (13, 154). Seven 'super-regions' were also defined which grouped regions according to cause of death patterns (Super-region 0: high income regions-Asia Pacific High Income, Australasia, Western Europe, Latin America South and North America High Income; Super-region 1: Central and Eastern Europe and Central Asia; Super-region 2: West, East, Central and Southern Sub-Saharan Africa; Super-region 3: North Africa and Middle East; Super-region 4: Asia South; Super-region 5: East and Southeast Asia and Oceania; Super-region 6: Central, Andean and Tropical Latin America and Caribbean). The aim of this was to categorise countries into regions and regions into super regions approximating more epidemiologically homogeneous groups. These were used to guide the estimation of missing data informed by data from surrounding countries and/or regions (13, 154).

Empirical data

The systematic literature review identified 136 relevant studies covering 17 GBD world regions. Epidemiological estimates were reported for males, females and/or persons, across broad and/or specific age groups. Sex- and age-specific estimates were preferable. Figure 5 summarises the raw epidemiological data used as inputs in the disease modelling process. A more comprehensive summary of the included studies has been reported elsewhere (27, 59, 150).



Pooled prevalence, incidence, duration and excess mortality data									
Overall prevalence (%)	4.7 (4.4-5.0)								
Point prevalence by region (%)	North America: 3.7 (3.1-4.3)	South America: 4.1 (3.5-4.7)	Western Europe: 4.7 (4.2-5.1)	Eastern/Central Europe: 5.1 (4.2-6.1)	Australasia: 4.1 (2.9-5.7)	Africa/Middle East: 6.6 (5.3-8.3)	East/Southeast Asia: 3.96 (3.4-4.6)	Asia South: 8.6 (5.2-14.0)	Asia Pacific: 5.6 (4.2-7.4)
Overall incidence (per 100 person years)	3.1 (2.4-3.8)								
Average duration of an episode	37.7 weeks								
Excess risk of mortality	1.9 (1.7-2.2)								

Note: This figure summarises findings from previous work (27, 59, 150) and represents the raw data included in DisMod-MR analyses; The map shows the number of studies available for each world region where P: Prevalence; I:Incidence; D: Duration; EM: Excess-mortality; Although the literature review found 136 studies overall, some studies have been counted more than once in the map as they reported data for multiple countries/regions.

Figure 5. Summary of the raw data on prevalence (P), incidence (I), duration (D) and excess mortality (EM) of MDD

For prevalence, we found 116 studies (556 data points) from 53 countries and 17 regions. After further consideration, 3 prevalence studies were excluded as outliers in the dataset (157-159). Estimates from these studies were well over 2 times higher than other estimates from the same country and/or region, and stood out as outliers in the initial stages of the modelling process. This reduced the prevalence dataset to 113 studies (544 data points). For incidence we found 4 studies (19 data points) on annual incidence from 3 countries and 2 regions (150). For duration, we found 4 studies from USA (65, 160-163) and 1 study from the Netherlands (68) reporting a median duration of between 6 to 12 weeks. We replicated the methodology used by Vos and collaborators to estimate an average duration from a best fit curve between the data points available from all 5 studies reporting on time to end of an episode (27). For excess-mortality we found 11 studies (14 data points) from 7 countries and 4 regions as compiled by Baxter and collaborators (59).

Analyses

DisMod-MR was used to model the epidemiology of MDD. DisMod-MR is the latest iteration of the generic disease modelling system (9) but redesigned as a Bayesian meta-regression tool (13, 154). The Bayesian approach is one of several interpretations of statistical probability in which existing data is used to inform the probability of a given hypothesis i.e. the data is considered as fixed and the hypothesis as random. This is different to the frequentist approach for instance which quantifies the probability (or frequency) of the data given the hypothesis i.e. the data is considered random and the hypothesis fixed (164); A meta-regression can be understood as an extension of a meta-analysis whereby data from different studies are pooled into a weighted average, adjusting for sources of variability between studies (165). DisMod-MR has the capability to combine epidemiological data from multiple sources, reconcile data that are inconsistent and forecast data for regions and parameters with no or little data. It applies a negative-binomial model of disease prevalence, incidence, remission, and case-fatality rates and fits models with a randomized Markov-Chain Monte Carlo algorithm (13, 154). Non-fatal burden estimates for all disorders in GBD 2010 were calculated using DisMod-MR with the exception of a few conditions for which a customised model had to be created (13).

DisMod-MR works in two stages. At stage 1 it pools raw data for each parameter while incorporating prior expert knowledge of the disease (based on empirical evidence and expert knowledge of the distribution of MDD in the population). In the absence of sufficient data to show age-pattern variation, DisMod-MR imposes a common age pattern based on evaluating age-specific input data available for the disorder. This stage also includes a first consistency check at the global level. At stage 2, DisMod-MR simultaneously integrates the input data from all parameters as well

as the output from stage 1 to derive internally consistent epidemiological estimates for 187 countries, 21 GBD world regions for 1990, 2005 and 2010, carrying forward uncertainty from primary data sources (13, 154). These 3 time periods were chosen to enable analysis of time trends and enable comparisons between different time periods using the same methodology. It would not be possible to compare time trends using GBD 1990 estimates from the original study as methodology is different. If the period of data collection was before and including 1997 (the midpoint between 1990 and 2005) then those studies contributed to the 1990 estimates. Studies with data collected after 1997 contributed to the 2005 and 2010 estimates. Although the year 2000 would have also been a sensible alternative to categorise estimates as it is the midpoint between 1990 and 2010, there was insufficient data to detect any difference in the current findings if the latter option had been used. Where relevant, year-specific country-level covariates informed the difference between 1990, 2005 and 2010 estimates. Regions without primary data borrowed strength from other regions in a super-region through random effects. If a whole super-region had no data, epidemiological estimates defaulted to the global average unless country-level covariates were specified (13, 154)

Adjustments to the data

As per the Bayesian approach, a range of adjustments were implemented during the modelling phase to account for prior knowledge of disease patterns. A mimimum age of onset of 3 years was selected based on literature and expert advice suggesting that despite difficulties in diagnosing early childhood depression, cases of MDD manifest as early as 3 years (166). Adjustments were also used to supplement gaps in the raw data. After running sensitivity analyses with and without the incidence data included in the DisMod-MR model (see results section), it was deemed necessary to exclude the few data points showing low rates of MDD incidence in the population. MDD was modelled as an episodic disorder (as per how it's defined in DSM-IV-TR)/ICD-10), as such we required data on the incidence and duration of a MDE in the DisMod-MR modelling of MDD. In our review of the literature, we found that the average duration of a MDE was less than a year. Based on this, we would expect the incidence of a MDE to be higher than the prevalence of MDD. In the four studies we had available for incidence, new MDEs in people with previous episodes were either excluded at baseline (66, 67), discussed but not included in the final incidence estimate (64), or alternatively reported but limited to a narrow teenage sample where the incidence of new episodes comes close to total incidence (previous plus current episodes) (65). This meant that for our purposes, incidence was underestimated and 'inconsistent' with prevalence and duration data. Given this limitation, we excluded the few incidence estimates available and instead, allowed DisMod-MR to predict incidence based on the data from all other parameters. The estimate of

average duration was applied equally to all regions, sex and years given that there were only 5 follow-up studies available with information on time to end of an episode and none of those 5 studies found statistically significant sex differences in episode duration.

Covariates

Study-level covariates. The prevalence dataset included estimates of point and past-year prevalence based on varying survey instruments, response rates and sample coverage (150). Study-level covariates were applied to adjust sub-optimal estimates to the desired level of each of these variables (Table 5). Our meta-regression of the raw prevalence data outside of DisMod-MR (150) guided the selection of these study-level covariates.

Table 5. Study-level covariates used in the statistical modelling of MDD.

Study-level covariates		
Covariate	**Gold-standard**	**Rationale**
Prevalence type	Point prevalence	GBD methodology requires point rather than 12-month prevalence. Given their structure, diagnostic interviews capturing 12-month prevalence may also be insensitive to past MDEs, leading to the underestimation of prevalence.
Survey intrument	Instruments using DSM/ICD diagnostic thresholds	Symptom scales are likely to over-estimate prevalence relative to diagnostic instruments using DSM/ICD thresholds (150). Prevalence estimates based on symptom scales are adjusted to the level of those using DSM/ICD diagnostic thresholds
Sample coverage:	National coverage	This study level covariate adjusts prevalence ascertained from a local community sample to the level of prevalence from a more representative regional or national sample.
Study response rate	response rate ≥60%	This study level covariate adjusts prevalence from samples with poor response rate (<60%) to the level of those with better response rate (≥60%).
Country-level covariates		
Covariate	-	**Definition**
Conflict	-	The natural log of mortality due to war or conflict in any country and year.
Post conflict	-	The natural log of mortality due to war or conflict in the past ten years, in any country and year.

Country-level covariates. Country-level covariates guided the DisMod-MR estimation of prevalence, particularly in the prediction of missing data. As described in previous work (147, 148, 167, 168), conflict status is associated with an increase in the incidence (and therefore prevalence) of MDD. We also found evidence for this while comparing pooled prevalence across regions including countries in current or past conflict(150). To improve the predictive power of the model for regions with no data, we included conflict and post conflict covariates in the modelling of prevalence. These covariates used the natural log of GBD 2010 mortality rates due to war or conflict in any country and year (Table 5).

Results

To demonstrate the effect of the DisMod-MR modelling process on the epidemiological data, the first section of results compares the input data to the final DisMod-MR output. In spite of being limited by data on the incidence, duration, and excess-mortality of MDD, we discuss the DisMod-MR output for all parameters here in the interest of illustrating internal consistency. The next section focuses exclusively on the prevalence output given that the majority of our data was for prevalence and GBD 2010 calculated prevalent YLDs. More information on the DisMod-MR output can be obtained by contacting the corresponding author (AJF).

Comparing data points with final DisMod-MR output

Figure 6 shows the adjustments made to prevalence based on the effect of covariates. Study-level covariates for data points of past-year prevalence and using symptom scales had statistically significant positive values. Those data points were adjusted downwards to reflect an equivalent value if the studies would have measured point prevalence, using formal diagnostic instruments. The study response rate and community coverage covariates did not significantly impact on prevalence. There was however a positive effect of conflict whereby prevalence from countries in current conflict was higher than prevalence from countries in no conflict. This effect guided the prediction of prevalence for regions with missing data.

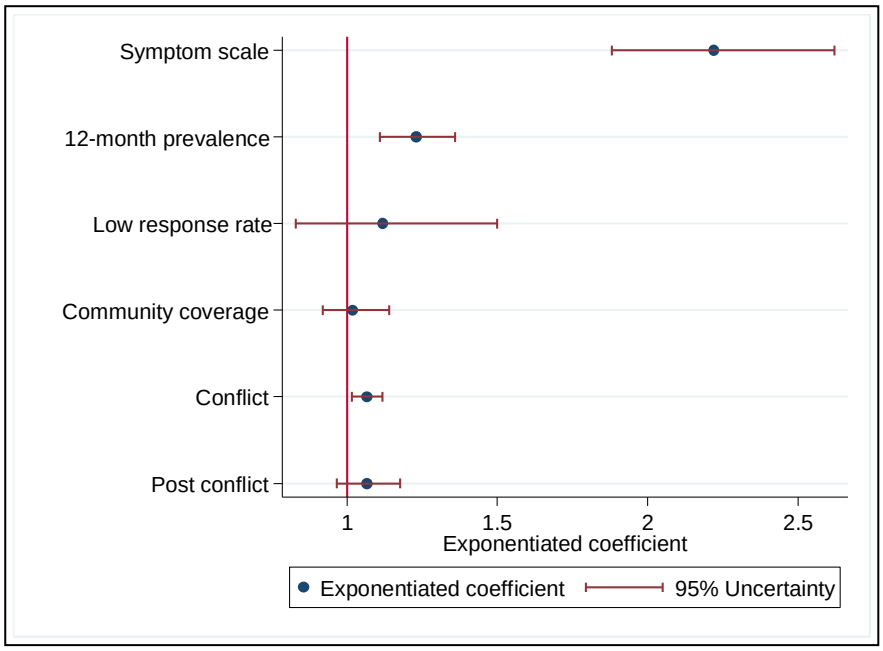
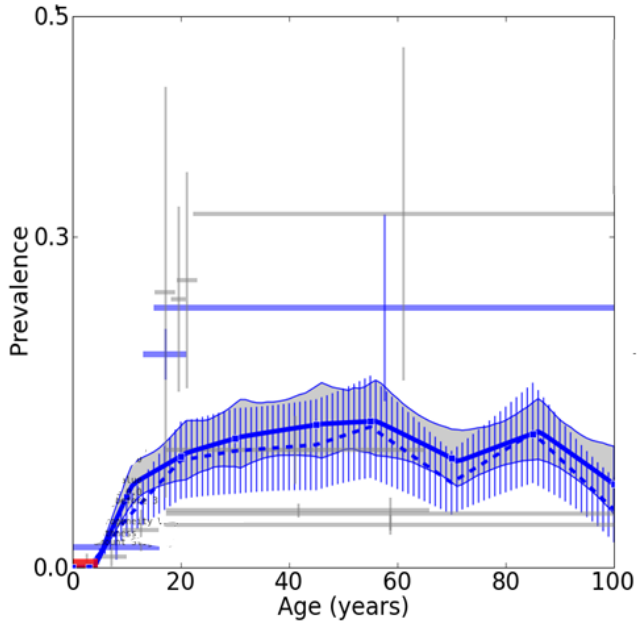


Figure 6. Country- and study-level covariate adjustments for MDD

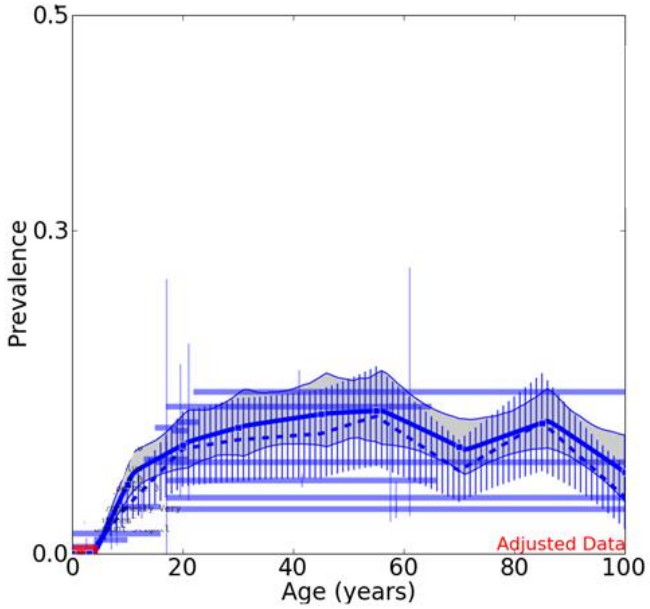
Figures 7 and 8 further illustrate the adjustments applied to the input data by summarising the input data and DisMod-MR output for females in 2010 from North Africa/Middle East (figure 7) and North America, High income (figure 8), regions for which we had few and considerable data points, respectively. Similar plots for all 21 GBD regions have been included in supporting table S1, Appendix Three. Each plot in figure 7, shows the minimum age of onset of 3 years (solid red line), the prevalence data points (blue crosses) and the final pooled prevalence output (solid blue line) before (plot 1) and after (plot 2) they were adjusted by study-level covariates. The difference between the two plots reflects adjustments made by study level covariates. Note how the prevalence data points were adjusted downwards (from plot 1 to plot 2) to reflect an equivalent value if the studies would have measured point prevalence, using formal diagnostic instruments.

The first plot in figure 8 shows the prevalence data and the second plot shows the incidence data with their respective pooled DisMod-MR output. As previously explained, incidence data points (pink crosses) in plot 2 were not included in the modelling process. However, it is worth noting here how much lower they were in comparison to the incidence calculated by DisMod-MR (solid pink line), using data from all other parameters. In dealing with the previously noted inconsistency between incidence, prevalence and duration data, the final incidence output was also greater than the final prevalence output in plot 1. Incidence was greater by a fixed amount as we applied the same estimate of average duration across all regions, sex, age and year. The third plot from figure 8 shows the single duration data point used (grey cross). The last plot shows prevalence by excess mortality which represents the mortality rate at the population level due to the (all-cause) excess mortality experienced by people with MDD.

Plot 1. Prevalence before covariate adjustments



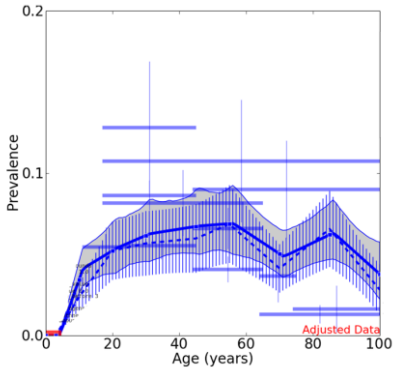
Plot 2. Prevalence after covariate adjustments



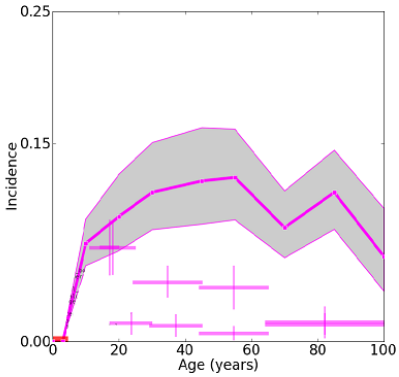
Note. Blue crosses show the individual, sex-specific data points available for that region, with the horizontal line showing the age range for the data point and the vertical line showing the range of uncertainty around the data point; grey crosses in the first plot show non sex-specific data points which are converted into sex-specific data points in the second plot as per a sex-ratio of 0.59 (0.54-0.64); the dotted line shows prevalence output from stage 1 of the modelling process. This is the line of best fit based on data for that parameter only; the numerous blue vertical lines show uncertainty around stage 1 estimates; the solid blue line shows output from stage 2 of the modelling process. This is the line of best fit based on data from all parameters and represents the final output for that parameter; the grey area shows uncertainty around stage 2 estimates; the solid red line represents ages below the minimum age of onset applied.

Figure 7. Prevalence of MDD before and after covariate adjustments for females from North Africa/Middle East, 2010.

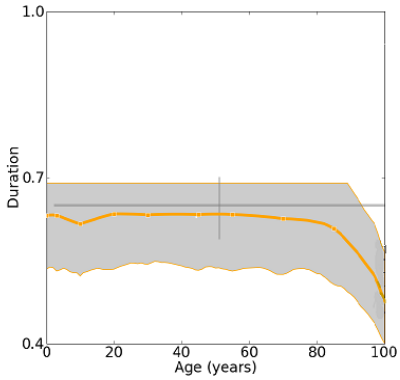
Plot 1. Prevalence



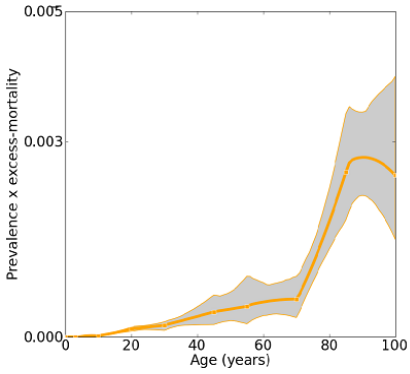
Plot 2. Incidence



Plot 3. Duration



Plot 4. Prevalence times excesss mortality



Note. Crosses show the individual data points available for that region, with the horizontal line showing the age range for the data point and the vertical line showing the range of uncertainty around the data points; solid lines show output from stage 2 of the modelling process. This is the line of best fit based on data from all parameters and represents the final output for that parameter; grey areas represent the range of uncertainty around the final output.

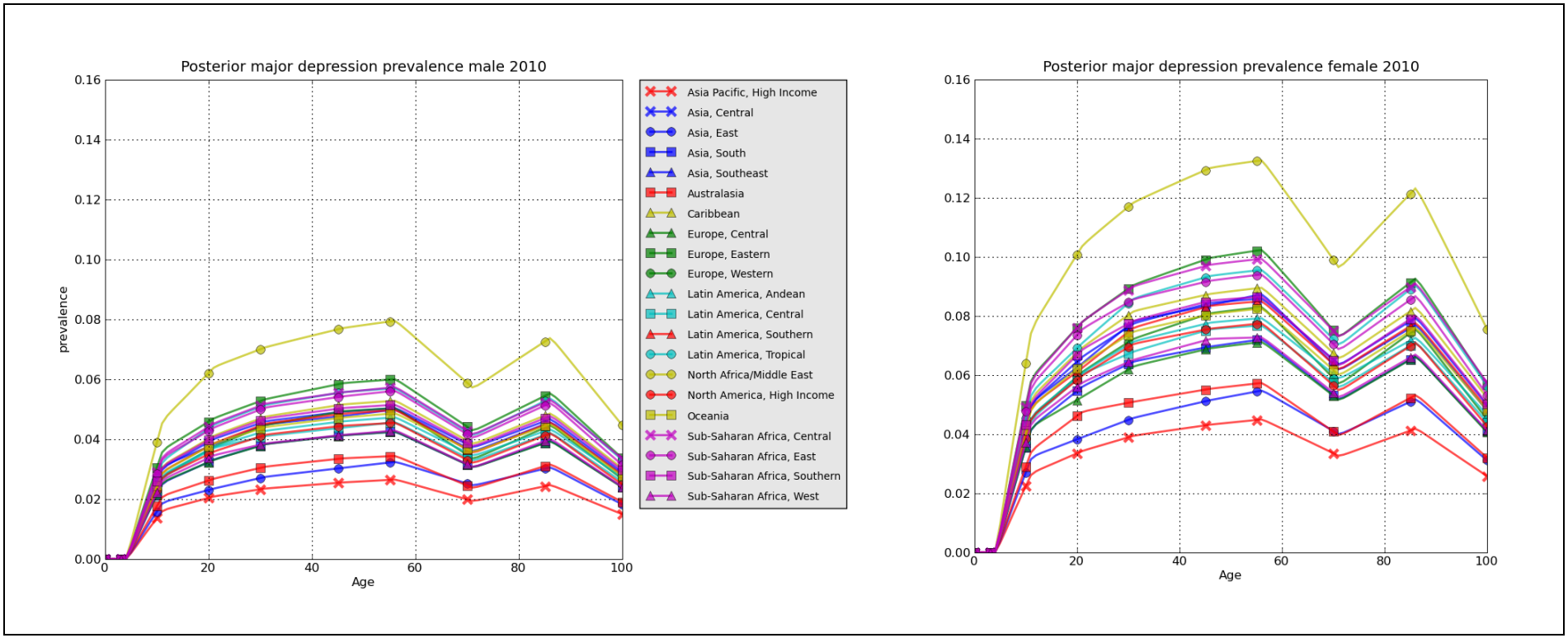
Figure 8. Prevalence, incidence, duration and excess-mortality of MDD in females from North America, High income, 2010.

Final prevalence output

Figure 9 shows the final prevalence estimates by age, sex and region, for 2010. The equivalent data for 2005 and 1990 are summarised in supporting figures S1 and S2, Appendix Three. When prevalence was aggregated by year (standardised by population age and sex (169)), the prevalence of MDD was very consistent between 1990 (4.4% (95% uncertainty: 4.2-4.7%)), 2005 (4.4% (4.1-4.7%) and 2010 (4.4% (4.1-4.7%)). Given the lack of time trend, the rest of the results will focus on the 2010 DisMod-MR output.

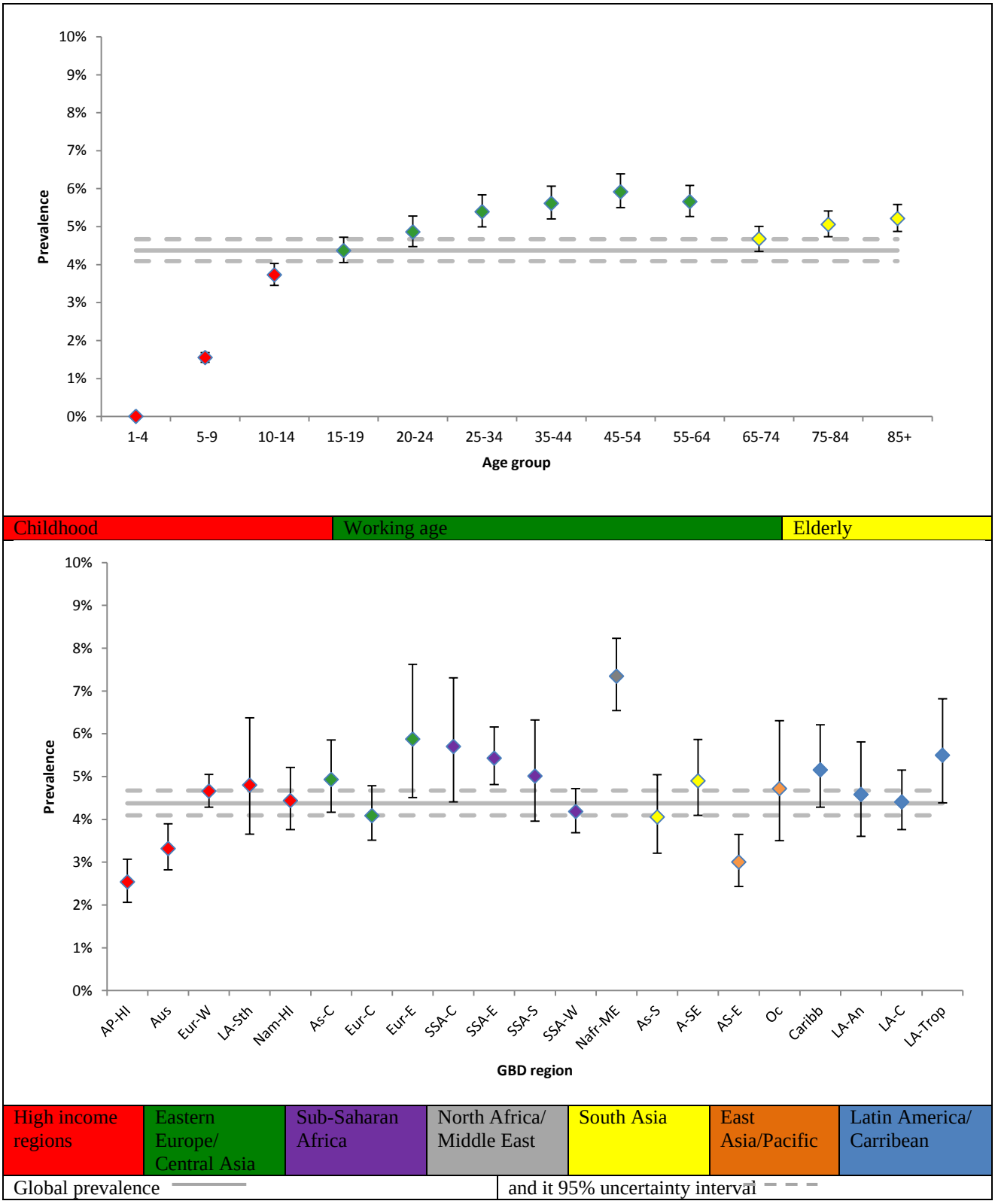
Prevalence in 2010 was higher in females at 5.5% (5.0-6.0%) compared to males at 3.2% (3.0-3.6%), equivalent to a male: female prevalence ratio of 0.59 (0.54-0.64). When observed across the lifespan, prevalence increased steadily between 3 and 19 years; peaked between 20 and 64 years; decreased between 65 to 74 years; and showed a smaller increase in the oldest age group. Plot 1 in figure 10 summarises the age differences in the global prevalence of MDD. Note, for most age groups, estimates were within overlapping bounds of uncertainty. Plot 2 summarises the regional differences in the global prevalence of MDD. There was a 3-fold difference between North Africa/Middle East, the region with the highest prevalence and Asia Pacific, High income, the region with the lowest prevalence. Although this suggests considerable regional differences, the overlap in uncertainty intervals across regions is worth noting.

When multiplied with United Nation's region-, sex-, year- and age-specific population size (170), the overall prevalence of MDD in 2010 corresponded to over 111 million male and 187 million female prevalent cases of MDD. The majority of cases appeared between 25 and 34 years at over 57 million cases and the least number of cases between 1 and 4 years at 19 thousand cases. Given their population size, Asia East and Asia-South yielded the highest number of prevalence cases at over 44 million and 62 million cases respectively. Prevalent cases by age and region have been summarised further in figure 11.



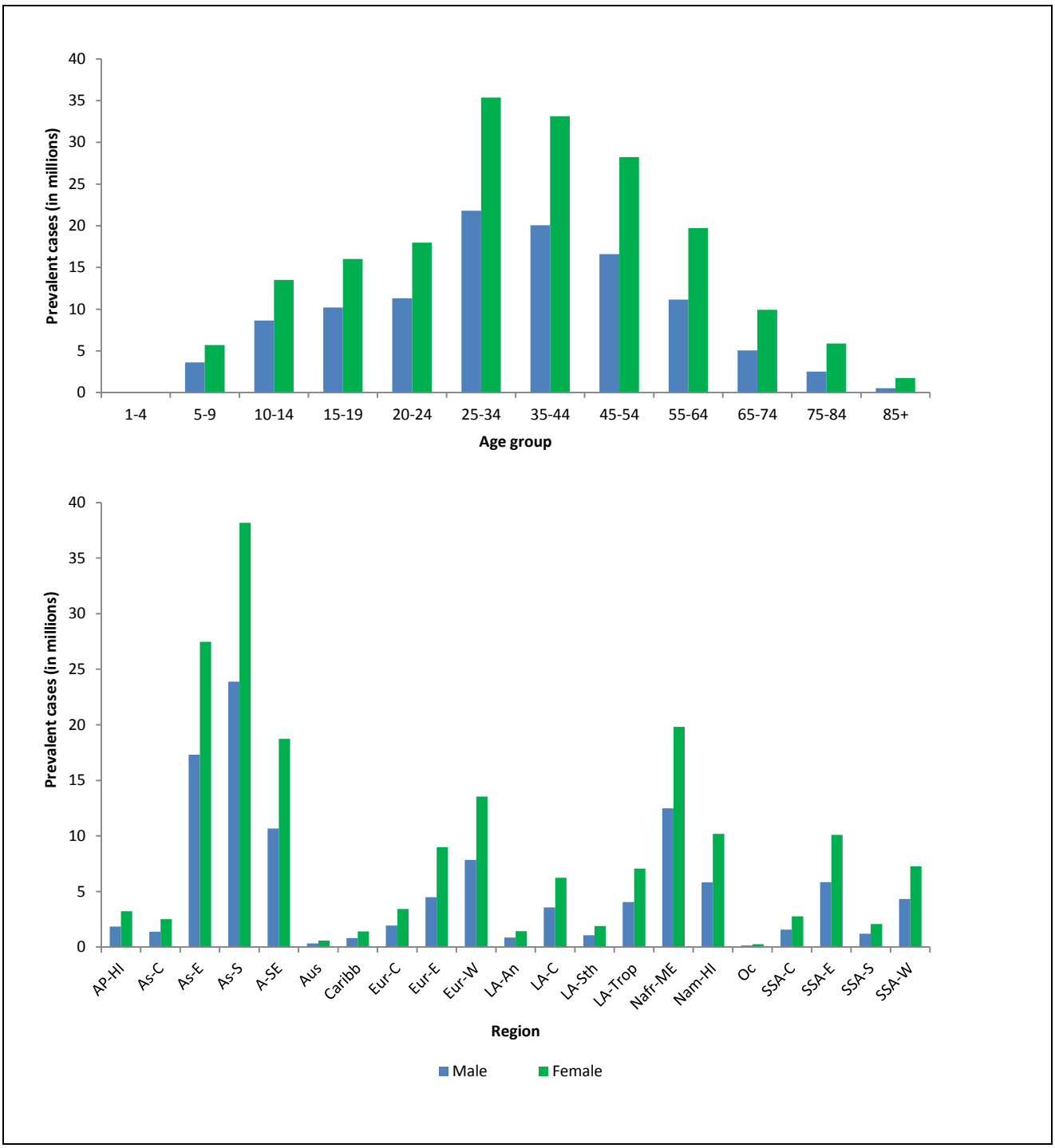
Note. Prevalence interpreted as a proportion where 0.01 equates to 1%

Figure 9. Regional point prevalence of MDD by age and sex, 2010.



Note. Global and regional prevalence estimates have been standardised by population age and sex; AP-HI: Asia Pacific, High Income, As-C: Asia Central, AS-E: Asia East, AS-S: Asia South, A-SE: Asia Southeast, Aus: Australasia, Caribb: Caribbean, Eur-C: Europe Central, Eur-E: Europe Eastern, Eur-W: Europe Western, LA-An: Latin America, Andean, LA-C: Latin America, Central, LA-Sth: Latin America, Southern, LA-Trop: Latin America, Tropical, Nafr-ME: North Africa/Middle East, Nam-HI: North America, High Income, Oc: Oceania, SSA-C: Sub-Saharan Africa, Central, SSA-E: Sub-Saharan Africa, East, SSA-S: Sub-Saharan Africa Southern, SSA-W: Sub-Saharan Africa, West

Figure 10. The overall point prevalence of MDD and 95% uncertainty by region and age, 2010.



Note. All prevalent cases where divided by 1000000 to facilitate presentation; AP-HI: Asia Pacific, High Income, As-C: Asia Central, AS-E: Asia East, AS-S: Asia South, A-SE: Asia Southeast, Aus: Australasia, Caribb: Caribbean, Eur-C: Europe Central, Eur-E: Europe Eastern, Eur-W: Europe Western, LA-An: Latin America, Andean, LA-C: Latin America, Central, LA-Sth: Latin America, Southern, LA-Trop: Latin America, Tropical, Nafr-ME: North Africa/Middle East, Nam-HI: North America, High Income, Oc: Oceania, SSA-C: Sub-Saharan Africa, Central, SSA-E: Sub-Saharan Africa, East, SSA-S: Sub-Saharan Africa Southern, SSA-W: Sub-Saharan Africa, West.

Figure 11. The number of point prevalent cases (in millions) of MDD by region, age and sex, 2010.

Discussion

Consistent with previous reports, the prevalence of MDD (as estimated by DisMod-MR) was higher in females compared to males (107, 137, 138). However, unlike our meta-regression outside of DisMod-MR which found that prevalence increased significantly over time (150), our findings differed; suggesting that the former could have been an artefact of measurement bias rather than a 'real' difference in the disorder's epidemiology.

The pooled prevalence estimate derived by DisMod-MR was also more conservative than that from our meta-regression (4.4% (4.1-4.7%) vs., 4.7% (4.4-5.0%)). This difference was likely due to the differences in the age range for which estimates were pooled. In the meta-regression we aggregated data from different studies all using different age ranges (from 0-9 through to 65 to 99 years). DisMod-MR was much more versatile in this respect as it was able to aggregate estimates with different age ranges into the most plausible age pattern for the entire lifespan. This allowed us to more consistently measure differences in prevalence across the lifespan which was not possible in our analyses outside of DisMod-MR where we could only classify age using 4 broad age groups with some age ranges fitting into several groups. According to DisMod-MR findings, prevalence was lowest, but still evident in early childhood and highest between 20 and 64 years. There was an increase in prevalence between 75 and 85 years (5.1%(4.7-5.4%) and onwards (5.2%(4.9-5.6%), well within the prevalence range (4.6 to 9.3%) obtained by Luppa and collaborators' in their recent review and meta-analysis of the prevalence of MDD in those aged 75 years or above (171). This age group is not always represented in population surveys as they tend to exclude people in residential care or non-private households (70, 172, 173). Consequently, this finding has important implications for the burden calculation of MDD which as a result incorporated prevalent cases of MDD across the entire lifespan.

Also important for burden calculations was the ability to estimate prevalence (and therefore burden) for all 21 GBD regions, including regions like Oceania, Sub-Saharan-Africa Central, Latin America-Andean and Asia Central from where we had no empirical data. The regional pattern of prevalence was similar to that derived in our meta-regression (150), where prevalence from high income regions was lower than prevalence from low to middle income regions, particularly regions in conflict. Calculating the number of prevalent cases across world regions helps to emphasize the challenge confronting health services in responding to MDD. For instance, Asian regions which do not have the highest prevalence in comparison to other regions have the most prevalent cases due to their population size. That said, the low prevalence rate of MDD, in all Asian regions needs to be

noted. Although the inclusion of depression NOS cases helped capture non-Western presentations of MDD likely missed by DSM/ICD diagnostic criteria, it could be that it did not completely account for this limitation. This is especially true for studies where lay rather than clinically trained interviewers were used to diagnose cases (55). Further investigation into the cross-cultural validity of DSM/ICD diagnostic criteria is required for clearer conclusions.

The process of modelling epidemiological parameters by GBD region necessarily dilutes the effects of conflict on prevalence of mental disorders which may otherwise be clearly demonstrated in country or local level surveys. Despite this, and combined with the fact that we found very few data points from populations in current or past conflict, we were still able to detect an increase in prevalence in those settings. Prevalence was highest in North Africa/Middle East which includes conflict countries such as Afghanistan, Iraq and Lebanon. This highlights the importance for future mental health research to provide comparable assessments of mental disorders in conflict-affected populations. The conflict covariates together with the survey instrument and prevalence type study-level covariates allowed us to accommodate for some, but not all of the variability in the epidemiological data available for MDD as DisMod-MR assumes the same level of adjustment for covariates across regions. The data presented here is reflective of the current state of this literature. With ongoing work on the global epidemiology and determinants of this disorder, we hope to explain more of the uncertainty around our final estimates.

With the emphasis on providing a 'data driven' epidemiological profile of MDD, we would have preferred to have incidence data inform our DisMod-MR output. Our search for data on the incidence of MDD revealed very low rates of MDD incidence in the population. An explanation for this is that the few longitudinal studies reporting on the incidence of MDD typically focused on capturing the incidence of MDD, rather than the incidence of MDEs (63-67). Given that MDD is being modelled as an episodic disorder for GBD, this means that new episodes in people with previous episodes were not counted and incidence was underestimated. By relying on prevalence, duration and excess-mortality data to calculate incidence, DisMod-MR derived incidence estimates which were higher than prevalence, illustrating much better internal consistency between the prevalence, incidence and duration output.

We used an average duration of 37.7 weeks which was higher than the 30.1 weeks reported by Vos and collaborators (27, 67). This difference was due to the inclusion of data from the Netherlands (68) previously excluded by Vos and collaborators on the basis that it included cases of subsyndromal depression and dysthymia. Given the lack of available duration data for all parts of

the world except USA and that the median duration yielded by this study (12 weeks) was comparable to the median duration from other included studies (6-12 weeks) (160-163), we chose to include it. However, even with this inclusion, we did not have enough data to investigate and adjust for any age, sex and cross-national differences in the duration of a MDE. This highlights the need for more studies following up community identified cases of MDD and measuring course of episode, particularly in low to middle income countries.

Rather than rely solely on sub-optimal estimates of prevalence, incidence, duration and excess mortality, we were able to model these into an internally consistent epidemiological profile of MDD. This will contribute to GBD 2010 and the MDD literature at large by providing global estimates for MDD which go beyond mere tabulation and pooling of epidemiological data. For some parameters, DisMod-MR had to rely on data from only a small number of studies, limiting the accuracy and generalisability of findings. This has been represented through large and at times, overlapping bounds of uncertainty which need to be considered while interpreting DisMod-MR estimates. As more evidence accumulates, the approach taken here will become increasingly sophisticated in its ability to synthesize available information and to project intelligent estimates into areas where data are not available.

Acknowledgments

We would like to acknowledge members of the GBD mental and drug use disorders expert group and other international experts who provided us with feedback on our DisMod-MR models. We would also like to thank Adele J Somerville, Amanda J Baxter, Holly E Erskine and Jed Blore for their support in the initial stages of data collection and disease modelling and Roman Scheurer for his assistance in generating maps.

Chapter review

Chapter Four made use of the raw data on the distribution of MDD to estimate prevalence, incidence, remission, duration and excess-mortality by location, age, sex, year (thesis aim one, part two). This data on the distribution of MDD is useful in its own right. For instance, it can assist in establishing groups in the population most at risk for MDD and which type of intervention strategy (treatment, rehabilitation, prevention, and promotion) should be prioritized. That said, it is also important for decision makers to know how health losses due to MDD compares to other diseases and injuries.

For this reason, the prevalence output presented in this chapter was used in the estimation of burden (DALYs, YLDs, and YLLs) for MDD in Chapter Five. Although it would have been preferable to make use of high quality raw data for all countries, years and age groups in burden estimation, this was not possible given the limitations in the data discussed in Chapters Three and Four. The estimation of missing data in this chapter made it possible to include countries, years and age groups in the burden estimation which would have otherwise been ignored. A comparison between burden due to MDD and dysthymia was also presented in Chapter Five. This was done to enhance our understanding of how MDD contributes to disease burden compared to other forms of depression.

Chapter Five: Burden of depressive disorders by country, sex, age and year: Findings from the global burden of disease study 2010

Alize J Ferrari[1,2], Fiona J Charlson[1,2],Rosana E Norman[1,3], Scott B Patten[4], Greg Freedman[5], Christopher JL Murray[5], Theo Vos[1,5], Harvey A Whiteford[1,2]

[1] University of Queensland, School of Population Health, Herston, Australia

[2]Queensland Centre for Mental Health Research, Wacol, Australia

[3]University of Queensland, Queensland Children's Medical Research Institute, Herston, Queensland, Australia

[4]University of Calgary, Department of Community Health Sciences, Calgary, Canada.

[5]University of Washington, Department of Global Health, Institute for Health Metrics and Evaluation, Seattle, Washington, USA

Published in PloS Medicine, 2013, 10(11):e1001547

Chapter summary

Background

Depressive disorders were a leading cause of burden in the GBD 1990 and 2000/05 studies. Here, we analyse the burden of depressive disorders in GBD 2010 and present severity proportions, burden by country, region, age, sex, and year, as well as burden of depressive disorders as a risk factor for suicide and IHD.

Methods

Burden was calculated for MDD and dysthymia. A systematic review of epidemiological data was conducted. The data were pooled using a Bayesian meta-regression. Disability weights from population survey data quantified the severity of health loss from depressive disorders. These weights were used to calculate YLDs and DALYs. Separate DALYs were estimated for suicide and IHD attributable to depressive disorders.

Results

Depressive disorders were the second leading cause of YLDs in 2010. MDD accounted for 8.2% (5.9%–10.8%) of global YLDs and dysthymia for 1.4% (0.9%–2.0%). Depressive disorders were a leading cause of DALYs even though no mortality was attributed to them as the underlying cause. MDD accounted for 2.5% (1.9%–3.2%) of global DALYs and dysthymia for 0.5% (0.3%–0.6%). There was more regional variation in burden for MDD than for dysthymia; with higher estimates in females, and adults of working age. Whilst burden increased by 37.5% between 1990 and 2010, this was due to population growth and ageing. MDD explained 16 million suicide DALYs and almost 4 million IHD DALYs. This attributable burden would increase the overall burden of depressive disorders from 3.0% (2.2%–3.8%) to 3.8% (3.0%–4.7%) of global DALYs.

Conclusion

GBD 2010 identified depressive disorders as a leading cause of burden. MDD was also a contributor of burden allocated to suicide and IHD. These findings emphasize the importance of including depressive disorders as a public-health priority and implementing cost-effectiveness interventions to reduce its burden.

Introduction

Depressive disorders are common mental disorders, occurring as early as 3 years of age and across all world regions (150, 151). Previous GBD studies in 1990 (1) and 2000/05 (16, 174) made notable contributions to shifting international focus towards depressive disorders as a leading cause of burden in its own right and also in comparison to more recognized physical disorders.

Using an approach first proposed in the World Development Report of (71), GBD 1990 and 2000/05 used DALYs to quantify the global burden attributable to diseases and injuries. One DALY represents the loss of a healthy year of life and aggregates the YLDs with the YLLs (1, 16, 174). GBD 1990 ranked depressive disorders as the fourth leading cause of burden worldwide (equivalent to 3.7% of all DALYs) after lower respiratory infections, diarrhoeal diseases, and conditions arising during the perinatal period (1). In GBD 2000/05, depressive disorders were the third leading cause of burden (equivalent to 4.3% of all DALYs) after lower respiratory infections and diarrhoeal diseases. It was also the leading cause of disability, responsible for 13.4% of YLDs in women and 8.3% in men (15).

These results have since made significant contributions to prioritising depressive disorders, and mental disorders as a group, in global public health agendas; particularly in promoting the addition of mental health interventions to health management plans (74). For this purpose, it has also become important to provide comparable estimates of burden, reflective of recent statistical and epidemiological advancements in mental health research. This was a focus of the latest iteration of GBD (GBD 2010), which involved a substantial expansion of the GBD framework. GBD 2010 quantified the direct burden of 291 diseases and injuries, in parallel with the quantification of burden attributable to 67 risk factors. It included a complete epidemiological re-assessment of all diseases, injuries, and risk factors, across 187 countries, 21 world regions, males and females, 1990, 2005, 2010, and 20 different age groups. Unlike previous GBD studies, which estimated the burden of "unipolar depression" (i.e., a combination of the DSM (38) and the ICD (39) categories (15, 73)), GBD 2010 quantified burden separately for MDD and dysthymia; this was done to better accommodate differences in burden between the subtypes of depression. Rather than rely on a selective sample of data points (as was the case in previous GBD studies), burden estimation was based on a systematic review of the literature to obtain all available epidemiological data on MDD and dysthymia. Furthermore, revised estimation methods utilized modernized new statistical methods to model these epidemiological disease parameters, quantify disability, adjust for comorbidity between diseases, and propagate uncertainty into final burden estimates (5).

This article follows the GBD 2010 capstone papers on the overarching methodology and findings of the study for all 291 diseases and injuries (5, 6, 10-13), and also the GBD 2010 mental and illicit drug use disorders research group's publication focusing on how mental and substance use disorders performed in comparison to other disease groups in GBD 2010 (see Figure S1, Appendix Four for an illustration of the GBD 2010 publications hierarchy) (19). Here we focus on presenting the burden of MDD and dysthymia specifically. Analyzing burden estimates at the national, regional, and individual characteristic level is important from both a clinical and population-health perspective to identify populations most at risk. We summarise the updated methodology and inputs used for the computation of YLDs, YLLs, and DALYs and present an analysis of country-, region-, age-, sex-, and, year-specific trends in the burden of depressive disorders. We also address a criticism of previous GBD studies (74) by estimating the additional burden attributable to MDD as a risk factor for other health outcomes.

Methods

Case Definition

The DSM-IV-TR (38) describes MDD (296.21–24, 296.31–34), as an episodic disorder with a chronic outcome and an elevated risk of mortality, equivalent to ICD-10's description of recurrent depressive disorder (F32.0–9, F33.0–9) (39). It involves the presence of at least one MDE, which is the experience of depressed mood almost all day, every day, for at least 2 weeks. As dysthymia (DSM-IV-TR: 300.4; ICD-10: F34.1) involves a less severely depressed mood compared to MDD and a duration of at least 2 years, it is described as chronic rather than episodic, with low rates of remission and no elevated risk of mortality (38, 39).

Calculation of Direct Burden-YLDs

The estimation of YLDs for a given disorder can be understood as a synthesis of epidemiological data that not only accommodates the number of people affected but also the severity and disability associated with their symptoms (13). In GBD 2010, prevalent rather than incident YLDs were calculated, without age-weighting and discounting (13). This means that for GBD 2010, YLDs were calculated by multiplying the prevalence of a given disorder by its corresponding severity- and comorbidity-adjusted disability weight. As these choices fundamentally change the metric, YLDs for 1990 were re-estimated using the same methods to allow meaningful comparisons of changes over time.

Epidemiological inputs. For MDD and dysthymia, prevalence, incidence, remission or duration, and excess mortality data were captured through a systematic review of the literature between 1st January 1980 and 31st December 2008 and continued perusal of the literature until 31st December 2011. A search of relevant online databases (Medline, PsycInfo, and EMBASE) was conducted as per the PRISMA statement (121). To be eligible for inclusion studies needed to report estimates: of prevalence, incidence, duration, and/or excess mortality from 1980 onwards; representative of the community, region, or country under investigation; and based on DSM or ICD definitions of MDD and dysthymia. For prevalence, we required point (current/past month) or past year prevalence estimates. Lifetime estimates were excluded as recall bias invalidates them as credible measures of disease burden (27, 59, 151, 175). For incidence, we used hazard rates with person years of follow-up as the denominator. Given the episodic presentation of MDD, we used data on the duration of MDEs from follow-up studies of the natural history of the disorder. For dysthymia we used remission data from follow-up studies capturing cases no longer fulfilling diagnostic criteria for the disorder. For excess-mortality, we used estimates of RR or SMR. Information on this systematic review can be accessed in previous publications (27, 59, 151, 175) with the main findings highlighted in Tables 6 and S1.

Disease modelling. For each disorder, epidemiological estimates from the literature review were pooled using DisMod-MR, a Bayesian meta-regression tool developed specifically for GBD 2010 (154). DisMod-MR is based on a generalized negative binomial model that: (1) uses an Incidence-Prevalence-Mortality mathematical model (9, 154) to enforce internal consistency between estimates from different epidemiological parameters; (2) estimates data for countries and world regions with no or few available input data based on random effects for country, regions, and their corresponding super-region groupings; (3) deals with variability in the data due to measurement bias or alternatively ecological factors through the use of study- and country-level covariates; and (4) propagates uncertainty around the raw epidemiological data through to the final estimates (154). The DisMod-MR output required for YLD estimations were prevalence estimates (including their respective 95% uncertainty intervals) for 187 countries, 21 world regions, males and females, 1990, 2005, and 2010, for 20 age groups. The global point prevalence output has been summarised in Table 6 and the country-level output in Table S2, Appendix Four. Given that the focus of this article was to report on the burden of depressive disorders, we have only summarised the disease modelling process here. More details on the disorder-specific modelling methodology, output, and, sensitivity analyses around final estimates have been reported in separate publications (151, 175).

Disability weights. The GBD 2010 framework describes disability as any short-term or long-term loss of health associated with a given health state (12). Unlike GBD 1990, which estimated disability weights by expert deliberation (1), GBD 2010 captured community-representative data through population surveys in Bangladesh, Indonesia, Peru, Tanzania, and the United States of America (14,710 participants) and an open-access internet survey available in English, Spanish, and Mandarin (16,328 participants). Each survey included lay descriptions of 220 health states, which together parsimoniously described the non-fatal consequences of all diseases and injuries in GBD 2010. These were presented as paired-comparison questions asking participants to decide which of two randomly selected health states they considered the healthier. Responses were anchored on a scale of 0 (healthy) to 1 (death) with some additional "population health equivalence" questions, which compared the overall health benefits of different life saving or disease prevention programs, to derive disability weights (12).

Severity distribution. In order to capture the range of severity in the presentation of MDD, disability weights were estimated for mild, moderate, and severe states of MDD. The choice of health states and their lay descriptions (Table 6) were formulated by members of the GBD mental disorders expert group, under the guidance of the GBD core group. The aim here was to encapsulate the main features of MDD and dysthymia (as described by DSM-IV and ICD-10 (38, 39)), using consistent, brief, and clear wording across each health state. Given the milder and more stable presentation of dysthymia, it was allocated the same disability weight as that for mild MDD.

Information on the distribution of mild, moderate, and severe cases of MDD was obtained from the US Medical Expenditure Panel Survey (MEPS) 2000–2009 (176), the US National Epidemiological Survey on Alcohol and Related Conditions (NESARC) 2000–2001 and 2004–2005 (177), and the Australian National Survey of Mental Health and Wellbeing of Adults (NSMHWB) 1997 (178); these surveys captured the prevalence of multiple mental and physical disorders included in GBD 2010 (156 in MEPS; 32 in NESARC; 20 in NSMHWB) as well as health status information measured by the Short Form 12-item (SF-12) (179).

A crosswalk between a score on the SF-12 and the GBD 2010 disability weights was derived from a convenience sample of participants asked to fill in the SF-12 to reflect 62 lay descriptions of health states of varying severity. From a mathematical relationship between SF-12 summary scores and disability weights, SF-12 values were translated into disability weights for all respondents in the MEPS, NESARC, and NSMHWB reflecting the combined severity of any comorbid condition. Next, a regression with random effects for all comorbid health states was run to parse disability in

each individual to each comorbid health state (13). Once disability attributable to comorbid disorders was portioned out, 14% of MDD cases and 29% of dysthymia cases had no disability (i.e., a disability weight of 0) at the time of the survey. Cases scoring a disability weight of >0 counted as symptomatic. For MDD, symptomatic cases were further disaggregated into mild, moderate, and severe where cases scoring a disability weight of >0 to halfway between a corresponding score of mild and moderate on the SF-12 counted as mild; cases scoring from there to halfway between a corresponding SF-12 score of moderate and severe counted as moderate; and those scoring from there onwards counted as severe. The proportion of cases in each state was then multiplied by its disability weight and summed to obtain an overall disability weight for MDD. Overall, the proportion of cases in asymptomatic, mild, moderate, and severe states over the course of MDD was almost identical across MEPS, NESARC, and NSMHWB for 12-month prevalence. As the NSMHWB was the only survey with one-month diagnoses and the SF-12 questions pertain to severity in the past month we used the distribution of severity from the NSMHWB for one-month diagnoses. Table 6 summarises the resulting health state proportions and disability weights. More details on this methodology have also been provided elsewhere (12, 13).

Comorbidity adjustment. GBD 2010 YLD estimates were adjusted for the effect of comorbidity between diseases. Hypothetical populations by age, sex, year, and country were estimated using microsimulation. For each individual in the hypothetical population: (1) prevalence data for all GBD sequelae were used to estimate the probability of experiencing no, one, or more than one disabling condition (i.e., health state); (2) from this, a combined disability weight capturing disability attributable to each comorbid condition was estimated with a multiplicative function and; (3) re-distributed to individual conditions in a manner that was proportional to the disability weight of each condition in isolation; (4) the decrease between the original disability weights for MDD and dysthymia and the adjusted disability weights was considered as the "comorbidity correction" for YLDs. As we were unable to find sufficiently large datasets to explore and quantify the difference in disability due to comorbidities that were dependent versus independent of each other, only the latter was taken into consideration here. In support for this step, the severity adjustments using MEPS data showed that estimating independent comorbidity (i.e., assuming no correlation between comorbid conditions), using a multiplicative approach, explained most of the modulating effect of comorbidity on disability. The GBD 2010 approach to comorbidity has been discussed in greater detail elsewhere (13).

Table 6. Summary of data used to calculate YLDs for depressive disorders.

Parameter	MDD	Dysthymia	Source
Epidemiological inputs			
Number of data points (and studies)			Systematic review of the literature (150, 151).
Prevalence	544 (116)	141 (36)	
Incidence	19 (4)[a]	3 (2)[a]	
Remission	—	3 (2)	
Duration	1 (5)[b]	—	
Excess-mortality	14 (11)	5 (2)[c]	
DisMod-MR point prevalence % (95% UI) and cases			
Global prevalence	4.4% (4.1%–4.7%); 298 million cases	1.55% (1.5%–1.6%); 106 million cases	DisMod-MR epidemiological modelling (151, 175).
Males	3.2% (3.0%–3.6%); 111 million cases	1.3% (1.2%–1.4%); 44 million cases	
Females	5.5% (5.0%–6.0%);187 million cases	1.8% (1.7%–1.9%); 62 million cases	
Disability weights			
Health state lay descriptions			Derived by GBD core group and mental disorders expert group for the GBD 2010 disability weight survey (12).
Mild	Has constant sadness and has lost interest in usual activities. The person can still function in daily life with extra effort, but sleeps badly, feels tired, and has trouble concentrating		
Moderate	Has constant sadness and has lost interest in usual activities. The person has some difficulty in daily life, sleeps badly, has trouble concentrating, and sometimes thinks about harming himself (or herself).		
Severe	Has overwhelming, constant sadness and cannot function in daily life. The person sometimes loses touch with reality and wants to harm or kill himself (or herself)		
Raw disability weights (95% UI)			
Mild	0.16 (0.11–0.22)	0.16 (0.11–0.22) [d]	GBD 2010 disability weight Survey (12)
Moderate	0.41 (0.28–0.55)		
Severe	0.66 (0.47–0.82)		
Severity distribution %(95% UI)			
Asymptomatic	13.9% (10.2%–17.7%)	29.2% (24.9%–33.6%)	Based on SF–12 data from MEPS, NSMHWB, and NESARC (13).
Mild MDD/Symptomatic dysthymia	58.8% (48.0%–68.5%)	70.8% (66.4%–75.1%)	
Moderate	16.5% (12.1%– 21.0%)		
Severe	10.8% (3.8%–20.3%)		
Average disability weight (95% UI)			
	0.23 (0.18– 0.30)	0.11 (0.07–0.15)	Based on severity proportions from MEPS, NSMHWB, and NESARC data, applied to weights from GBD 2010 disability weights survey (13).

Note. [a]Incidence data were excluded for MDD and dysthymia as they were not consistent with the prevalence and duration/remission data; [b]The one data point for duration of 37.7 weeks was an estimate of average duration calculated from a best fit curve between the data points available from five studies; [c]Both studies reported no elevated risk of mortality in those with dysthymia; [d]The disability weight for mild-MDD was applied to dysthymia; 95% UI: 95% uncertainty interval.

Time trend analysis. We replicated the methodology presented in the GBD 2010 capstone YLD paper (13) to disaggregate the change in YLDs between 1990 and 2010 into changes due to population growth, population age and sex structure, and YLD rates (i.e., the disorder's epidemiology). This process involved estimating the total YLDs anticipated in 2010 if: (1) population growth increased to 2010 levels but the population age/sex structure and YLD rates remained the same as in 1990; and (2) the age/sex-population structure was at 2010 levels but the YLD rates remained the same as in 1990.

Calculation of Direct Burden—DALYs

We calculated DALYs as the sum of YLDs and YLLs. YLLs are calculated by multiplying the number of deaths due to the given disorder at a particular age by the standard life expectancy at that age. However, death records used in GBD 2010 followed ICD-10 rules for categorical attribution of cause of death to a single underlying cause (39) and, therefore, did not document any deaths due to depressive disorders. As such, we were unable to calculate disorder-specific YLLs for depressive disorders. Instead, associated deaths were captured under other causes in the GBD cause list and needed to be re-attributed to depressive disorders.

Calculation of Attributable Burden

The CRA component of GBD 2010 quantified the burden attributable to each risk factor exposure compared to an alternative (counterfactual) exposure distribution (10). Diseases, like MDD, can also be considered risk factors for loss of health if associated with elevated risk of mortality or disability from other diseases or injuries. We replicated the GBD 2010 CRA methodology to investigate the additional burden attributable to depressive disorders as a risk factor for other health outcomes. The burden of disease attributable to depressive disorders was estimated by comparing the current health status with a theoretical-minimum-risk exposure distribution, the optimum exposure distribution with the lowest possible risk. For depressive disorders the theoretical minimum was defined by the counterfactual status of absence of the disease. This process involved (1) the selection of health outcomes attributable to MDD and dysthymia based on data availability and adherence to criteria about causality; (2) conducting systematic reviews of the literature and meta-analyses of effect sizes of the disorder-outcome pairing (the gold standard for effect measure was RR estimates by year and sex derived from prospective cohort studies with a naturalistic follow-up of cases, representative of the general population); (3) combining the pooled RR estimates with the DisMod-MR prevalence output for the disorder to calculate population attributable fractions (PAFs); and (4) multiplying PAFs by the corresponding cause-specific

DALYs for the outcome under investigation to calculate attributable burden. The process allowed us to estimate attributable burden by sex, age, year, region, and country. Out of the comprehensive list of health outcomes originally investigated for mental disorders (88), there was sufficient evidence for causal effects to quantify the burden attributable to MDD as a risk factor for suicide and IHD. These literature searches have been reported in greater detail elsewhere (83, 85) with the main results highlighted in Table 7.

Table 7. Summary of data used to calculate burden attributable to MDD as a risk factor for suicide and ischemic heart disease.

Outcome	Suicide	IHD
Number of data points (and studies)	4 (3)	13 (8)
Number countries	2	2
Pooled RR (95% UI)[a]	19.9 (9.5–41.7)	1.6 (1.3–1.9)

Note. [a]RR estimates were pooled using meta-analytic strategies (83, 85); 95% UI: 95% uncertainty interval.

Where we report comparisons of prevalence, YLDs, or DALYs by country or region we use ISO 3166-1 alpha 3 codes (http://www.iso.org/iso/home/standards/country_codes.htm) and age-standardised values using direct standardisation to the global standard population proposed by the WHO in 2001 (http://www.who.int/healthinfo/paper31.pdf).

Results

Direct Burden of Depressive Disorders

Out of a total of 2.5 billion DALYs generated in the year 2010, mental and substance use disorders accounted for 7.4% (95% uncertainty interval: 6.3%–8.6%), depressive disorders for 3.0% (2.2%–3.8%), MDD for 2.5% (1.9%–3.2%), and dysthymia for 0.5% (0.3%–0.6%). MDD ranked as the 11th and dysthymia as the 51st leading cause of global DALYs in 2010. DALYs for both MDD and dysthymia were based solely on YLDs as there were no disorder-specific deaths (and therefore YLLs) recorded for either disorder. MDD was the second leading cause explaining 8.2% (5.9%–10.8%) of all YLDs, after low back pain. Dysthymia ranked as the 19th leading cause, explaining 1.4% (0.9%–2.0%) of all YLDs in 2010.

Although the global YLD rankings were the same in 1990, depressive disorders caused only 9.3% (6.7%–12.2%) of all YLDs, corresponding with a 37.5% increase in YLDs between 1990 and 2010 (see Table 8). The increase was entirely accounted for by population growth and ageing with no substantial change in age-specific prevalence.

Table 8. Change in depressive disorder YLDs between 1990 and 2010.

Total YLDs in 1990 and 2010	**MDD**	**Dysthymia**	**Depressive Disorders**
Total YLDs in 1990	46,138,600	7,870,700	54,009,300
Total YLDs in 2010	63,179,247	11,084,100	74,261,500
Total YLDs generated from 2010 population, 1990 population age structure, 1990 YLD rates (step 1)	59,904,870	10,067,939	69,972,809
Total YLDs generated from 2010 population, 2010 population age structure, 1990 YLD rates (step 2)	64,537,300	11,061,231	75,598,531
Total change in YLDs between 1990 and 2010	36.9%	40.8%	37.5%
Change in YLDs between 1990 and 2010 due to population growth	*29.8%*	*27.9%*	29.6%
Change in YLDs between 1990 and 2010 due to population aging	*10.0%*	*12.6%*	10.4%
Change in YLDs between 1990 and 2010 due to prevalence increase	*−2.9%*	*0.3%*	−2.5%

Note. The difference between total YLDs in 1990 and YLDs at step 1 represents the change in YLDs due to population growth; the difference between YLDs at step 1 and YLDs at step 2 represents the change in YLDs due to population aging; the difference between total YLDs in 2010 and YLDs at step 2 represents the change in YLDs due to changes in prevalence.

Figure 12 shows the composition of YLDs by age and sex for MDD and dysthymia in 1990 and 2010. YLDs were consistently higher for MDD compared to dysthymia and also in females compared to males. There were changes across the lifespan with YLDs peaking in the twenties and gradually decreasing into the older ages. Globally in 2010, the largest proportion of YLDs from depressive disorders occurred at working ages (15 to 64 years) with 60.4 million YLDs, followed by the 0 to 14 year age group with 7.8 million YLDs, and the 65 and over age group with 6.1 million YLDs.

Figure 13 shows the composition of YLD rates by region for MDD and dysthymia in 1990 and 2010. Although dysthymia YLD rates were consistent between regions, there were differences for MDD. While the focus of GBD 2010 publications so far has largely been on reporting regional and global burden estimates, all analyses were primarily conducted at the country level. On the basis of these country-level analyses, Figure 14 shows the composition of YLD rates in 2010 (with the corresponding 1990 estimates presented in Figure S2, Appendix Four) by country for MDD and dysthymia combined (plot 1) and countries with statistically higher or lower YLD rates than the global mean (plot 2); the latter of which also needs to be considered while interpreting country-level findings. Most of the regional, and country-level differences in YLDs, were within wide and overlapping ranges of uncertainty, with only a few countries with statistically higher or lower YLD rates compared to the global mean. YLD rates were highest in Afghanistan (included in North Africa/Middle East) and lowest in Japan (included in the Asia Pacific, high income).

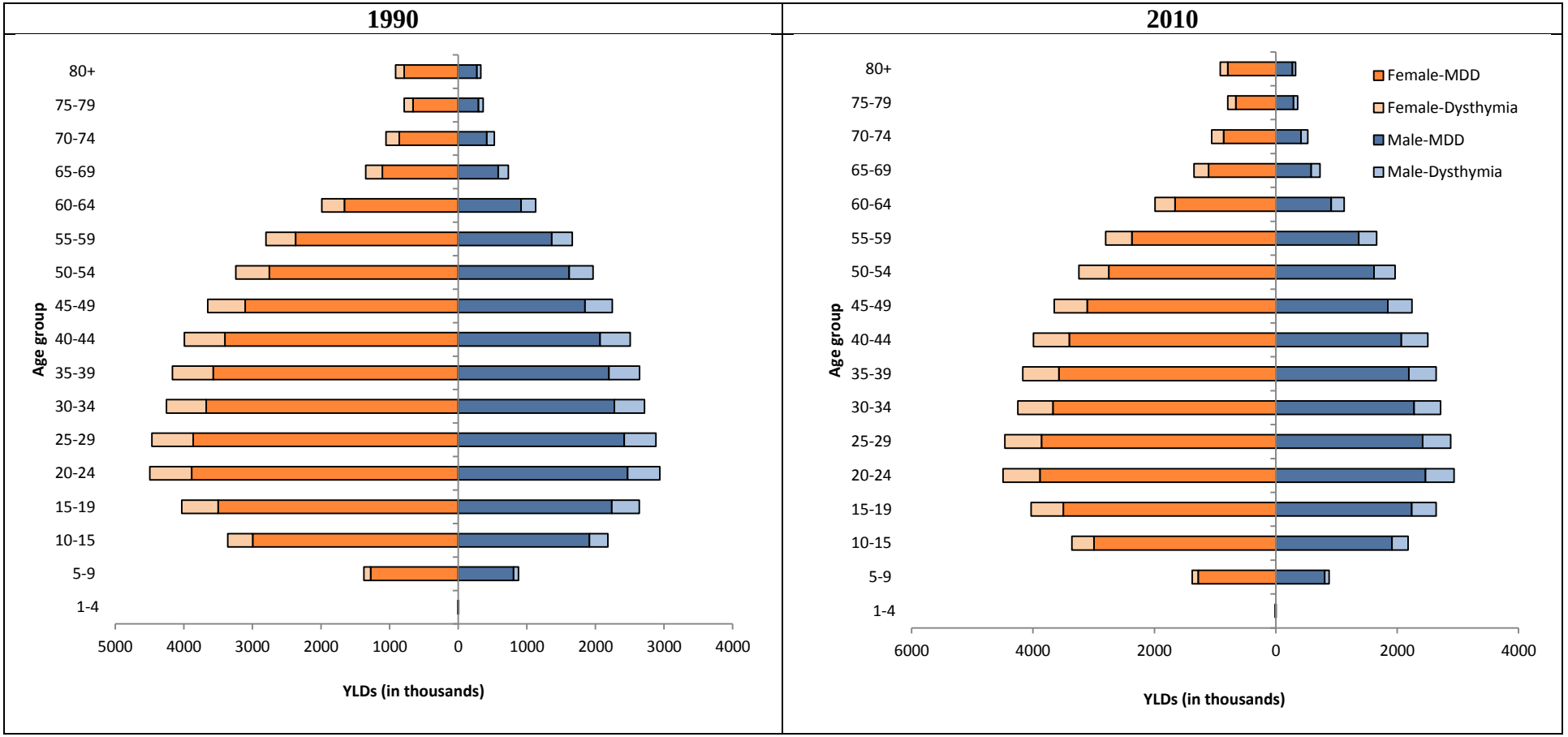
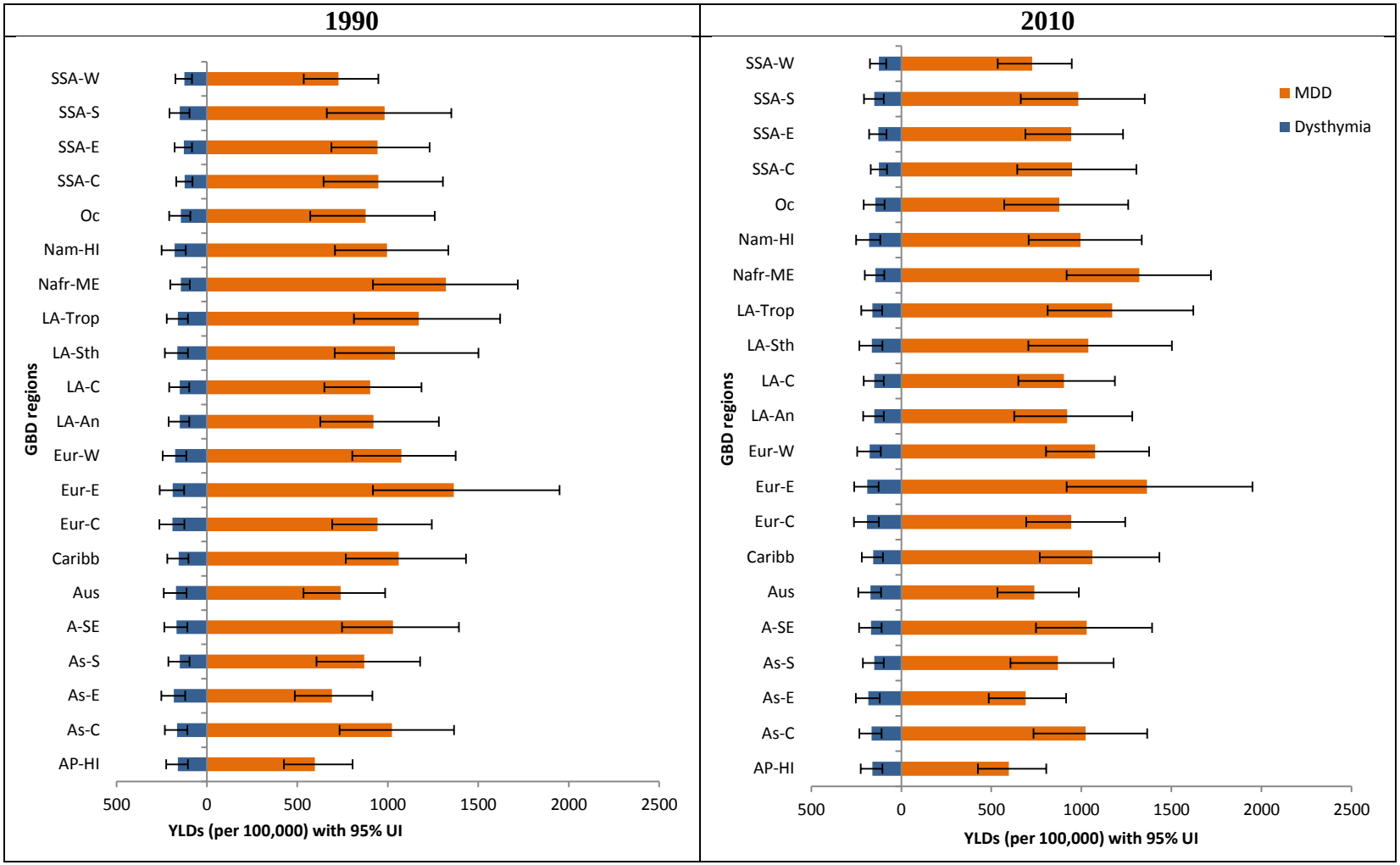


Figure 12. YLDs by age and sex for major depressive disorder and dysthymia in 1990 and 2010.

Table 9 summarises the regional YLD and DALY rankings for MDD and dysthymia in 2010 (with the corresponding 1990 rankings presented in Table S3, Appendix Four). This information highlights how MDD and dysthymia ranked in burden in comparison to other diseases and injuries in GBD 2010. MDD ranked as the 11th leading cause of DALYs globally but was as high as third in North Africa/Middle East and Latin America, Andean, and as low as 19th in sub-Saharan Africa, West. Although these regional rankings differed substantially to their corresponding global ranking, the overlapping 95% uncertainty intervals around some mean ranks also need to be considered.

Attributable Burden

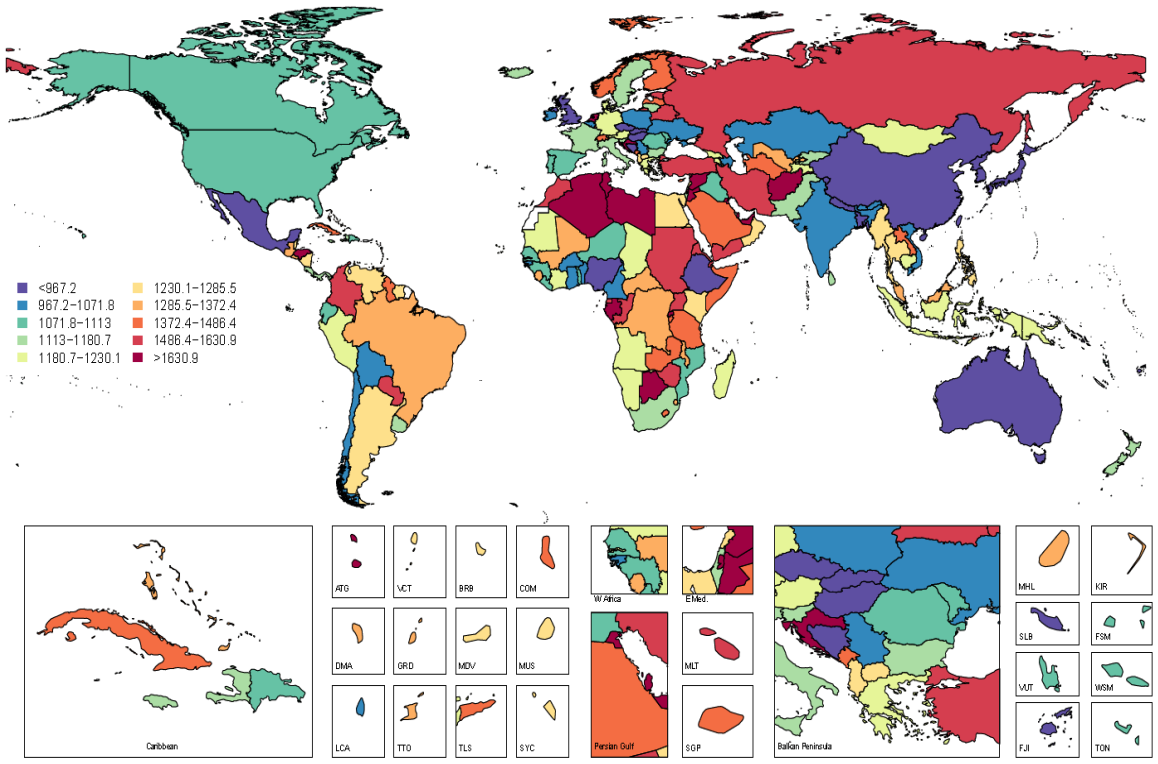
The above estimates reflect direct disability where MDD is selected as the underlying cause but exclude the excess deaths resulting from the increased risk of mortality from suicide and burden from IHD attributed to MDD as a risk factor. In 2010, MDD explained a further 16 million DALYs when it was considered as a risk factor for suicide. Overall, close to half (46.1% [28.03%–60.8%]) of DALYs originally allocated to suicide (included as intentional injuries in the GBD cause list) could be re-attributed to MDD. In addition to this, 2.9% (1.5%–4.5%) of IHD DALYs (3.8 million DALYs of which 93.5% were YLLs) was attributable to MDD. Adding these to MDD would have increased the overall burden of MDD from 2.5% (1.9%–3.2%) to 3.4% (2.7%–4.2%) of global DALYs and the overall burden of depressive disorders from 3.0% (2.2%–3.8%) to 3.8% (3.0%–4.7%) of global DALYs. The global burden rankings of MDD in the GBD cause list would have increased from 11th to eighth place, surpassing road injury, chronic obstructive pulmonary disease, and preterm birth complications.



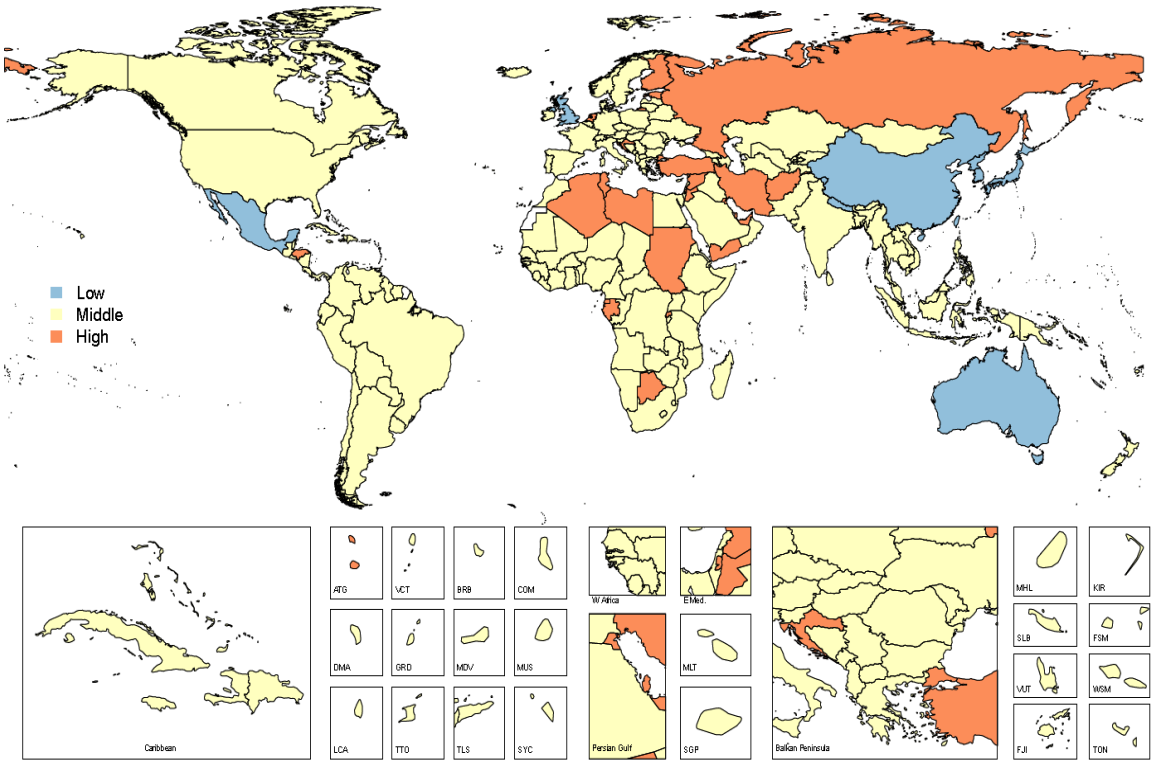
Note. 95% UI: 95% uncertainty interval; AP-HI: Asia Pacific, High Income, As-C: Asia Central, AS-E: Asia East, AS-S: Asia South, A-SE: Asia Southeast, Aus: Australasia, Caribb: Caribbean, Eur-C: Europe Central, Eur-E: Europe Eastern, Eur-W: Europe Western, LA-An: Latin America, Andean, LA-C: Latin America, Central, LA-Sth: Latin America, Southern, LA-Trop: Latin America, Tropical, Nafr-ME: North Africa/Middle East, Nam-HI: North America, High Income, Oc: Oceania, SSA-C: Sub-Saharan Africa, Central, SSA-E: Sub-Saharan Africa, East, SSA-S: Sub-Saharan Africa Southern, SSA-W: Sub-Saharan Africa, West.

Figure 13. YLD rates (per 100,000) by region for major depressive disorder and dysthymia in 1990 and 2010.

Plot 1: World map showing age-standardised YLD rates (per 100,000) by country



Plot 2: World map marking countries with statistically higher or lower YLD rates compared to the global mean



Note. Low: statistically lower YLD rates compared to global mean; Middle: YLD rates not statistically different to global mean; High: statistically higher YLD rates compared to global mean.

Figure 14. YLD rates (per 100,000) by country for depressive disorders in 2010.

Table 9. Regional DALY and YLD rankings with 95% uncertainty intervals for depressive disorders in 2010.

Region	YLDs				DALYs			
	MDD		Dysthymia		MDD		Dysthymia	
	Order	Mean Rank (95% UI)	Order	Mean Rank (95% UI)	Order	Mean Rank (95% UI)	Order	Mean Rank (95% UI)
Global	**2**	**1.9 (1–3)**	**19**	**18.6 (13–26)**	**11**	**10.8 (7–14)**	**51**	**51.2 (42–62.5)**
Asia Pacific, high income	4	4.3 (2–7)	22	21.1 (14–28)	12	11.5 (6–17)	35	35.9 (27–47)
Asia Central	1	1.5 (1–3)	19	19.4 (14–26)	6	7.2 (4–12)	46	46.7 (38–56)
Asia East	2	2.3 (1–3)	16	15.1 (9–21)	8	8.4 (5–12)	33	32.4 (22–42.5)
Asia South	3	2.9 (1–4)	20	19.8 (11–29)	14	13.3 (8–18)	55	54.7 (41–70)
Asia Southeast	1	1.4 (1–2)	19	17.9 (10–26)	6	6.7 (3–11)	44	45.1 (36–57)
Australasia	2	2.9 (2–7)	21	20.8 (14–28)	4	6.1 (3–14)	33	34.5 (23–47)
Caribbean	2	2.3 (1–4)	22	23 (18–33)	7	8.6 (4–13)	52	52.1 (41–65)
Europe Central	2	2.2 (2–4)	20	19.2 (13–26)	5	6.6 (4–10)	36	37.4 (28–52)
Europe Eastern	2	1.8 (1–2)	20	19.3 (14–26)	5	5.6 (3–9.5)	43	45.2 (35–59.5)
Europe Western	2	2.1 (2–3)	20	20.7 (15–28)	4	4.2 (3–8)	36	36.7 (27–51)
Latin America, Andean	1	1.7 (1–3)	22	20.9 (15–28)	3	4.6 (2–10.5)	42	43.5 (35–57)
Latin America, Central	1	1.3 (1–2)	19	19.1 (13–26)	5	5.2 (3–10)	41	40.1 (31–52)
Latin America, Southern	2	1.6 (1–3)	20	20.2 (13–28)	4	3.4 (2–6.5)	41	42.0 (32–58)
Latin America, Tropical	2	1.8 (1–2)	20	20.2 (14.5–27)	6	5 (2.5–7)	42	42.8 (35–53)
North Africa/Middle East	2	1.9 (1–2)	19	19.6 (15–28)	3	3.8 (2–8)	44	42.9 (32.5–55)
North America, high income	2	2.1 (1–4)	21	20.2 (14–27)	5	5.0 (2–10)	38	38.1 (30–50)
Oceania	1	1.6 (1–4)	23	22.4 (15–32)	12	13.4 (6–23.5)	65	63.1 (51–75)
Sub-Saharan Africa, Central	2	2.0 (1–3)	31	28.0 (18–37)	17	17.9 (12–24)	64	61.8 (50–75)
Sub-Saharan Africa, East	2	2.0 (1–3)	20	22.5 (14–35)	13	14.2 (11–18)	54	55.5 (43–75)
Sub-Saharan Africa Southern	2	2.5 (1–5)	22	22.6 (14–32)	10	10.4 (6–16)	52	52.3 (43–64)
Sub-Saharan Africa, West	3	3.1 (2–4)	27	26.1 (18–34)	19	19.7 (14–26)	58	58.4 (46–72)

Note. Mean rank, YLD and DALY ranks were estimated for MDD and dysthymia then simulated 1,000 times to estimate 95% uncertainty ranges. The 95% bounds of uncertainty represent the 25th and 975th value of the 1,000 draws; order, regional YLDs and DALYs for MDD and dysthymia were ordered by their mean rank across 1,000 draws.

Discussion

GBD 2010 has identified depressive disorders as one of the leading causes of YLDs. In spite of the lack of disorder-specific YLLs, it was also a leading cause of DALYs, emphasizing the importance of non-fatal health outcomes in the quantification of disease burden. Within depressive disorders, MDD was the main contributor to burden, accounting for 85% of YLDs and DALYs in 2010. This finding was driven by high prevalence estimates with 298 million MDD cases in 2010 (175) and 106 million cases of dysthymia (151). Discounting and age-weighting in previous GBD studies contributed in part to the high ranking of mental disorders. Despite not discounting (and therefore giving greater weight to mortality than disability) and not age-weighting (and therefore giving less weight to disabling conditions in young and middle aged adults) depressive disorders are still a leading cause of disability.

GBD 2010 quantified burden for 1990, 2005, and 2010 allowing comparisons of estimates over time based on comparable methods. Contrary to recent literature on the topic (180, 181), our findings suggest that the epidemiology of both MDD and dysthymia remained relatively stable over time. There was a slight decrease in the prevalence rate of MDD between 1990 and 2010 but this was too small to allow for any explicit interpretation. As noted earlier there was a 37.5% increase in YLDs between 1990 and 2010 due to population growth and ageing. This has important implications for global health, especially in developing countries where increased life expectancy due to better reproductive health, nutrition, and control of childhood infectious diseases means more of the population are living to the age where depressive disorders are prevalent.

Our findings not only emphasize depressive disorders as a global health priority, but also highlight the importance of understanding the variations both between and within regions when setting global health objectives. Variations in burden rankings between regions can be masked while considering global-level findings. For instance, some regional DALY rankings of MDD and dysthymia were considerably different than their corresponding global ranking. In the case of North Africa/Middle East, conflict in the region increased the prevalence of MDD, leading to a higher burden ranking for MDD. In sub-Saharan Africa on the other hand, the larger burden of communicable diseases such as malaria and HIV/AIDs resulted in a relatively lower ranking of MDD and dysthymia (5).

GBD 2010's capacity to generate country-level burden as well as regional estimates was especially relevant for MDD, which has been linked to risk factors such as conflict (175, 182), IPV and CSA (10), the levels of which vary between countries. Nevertheless, it's important to stress that variation (or in some cases lack of variation) in burden estimates and rankings may reflect the true

distribution of burden, a lack of available epidemiological data, or outliers that can occur by chance in any distribution. The nature of the DisMod-MR modelling strategy used was such that if raw epidemiological data were not available for a given country, prevalence estimates were imputed on the basis of random effects for country, region, and super-region and fixed effects for country-level covariates such as the mortality rate due to conflict. In the case of MDD, as previously stated, our literature review was able to capture prevalence data from conflict countries such as Afghanistan and Iraq. To improve the predictive power of our DisMod-MR model, we included conflict and post conflict status covariates to guide the DisMod-MR estimation of MDD prevalence for regions with no data (175). This strategy does not replace high quality primary data but we preferred computing burden estimates for these countries/regions rather than excluding them entirely from this global health exercise. The global availability of the raw epidemiological data for MDD and dysthymia has been summarised in Table S1, Appendix Four as well as in previous publications (150, 151). Any utilization of GBD country-level estimates will have to take these data into consideration (183-185). As the updating of GBD continues we hope the scrutiny of these country-level findings will promote primary data collection on the epidemiology of depressive disorders, particularly in developing countries where data are sparse.

We found no evidence of deaths attributable to dysthymia; this was consistent with our investigations into the epidemiology of dysthymia, finding no excess mortality attributable to the disorder (151). We found evidence for an elevated risk for mortality in those diagnosed with MDD (59, 175); however, since a health outcome could only occur once in the GBD cause list, MDD related deaths from suicide and IHD were captured under the headings of intentional injuries and cardiovascular disease in the GBD capstone papers (5). In this article, we've attributed a fraction of these DALYs to MDD using counterfactual estimation and GBD 2010 CRA methodology (10). The addition of these outcomes would have shifted MDD from 11th to eighth leading cause of DALYs, further supporting the prioritisation of depressive disorders in the prevention and management of wider aspects of health.

It is worth noting that we were unable to quantify burden for all the outcomes of MDD and dysthymia. As a result, it is likely that the burden estimates presented here still underestimate the true burden of depressive disorders. Although there is literature linking stroke, diabetes, and vascular dementia/Alzheimer's disease to MDD, there was insufficient evidence at the time of our review for a causal relationship and more studies are needed to support these tentative associations (88). For instance, many studies relied on symptom scales rather than DSM/ICD criteria to capture people with MDD and are hence likely to overestimate the strength of these associations. As more

rigorous evidence is made available we aim to quantify the burden due to MDD as a risk factor of other causes. Furthermore, for both suicide and IHD, meta-analyses relied on data from two countries that met our inclusion criteria. There is also uncertainty as to the extent to which these effect sizes are generalizable to different populations and GBD regions; this too is an area for further research.

New to GBD 2010 was the capability of propagating uncertainty from the epidemiological data points through to burden estimates. While this also included uncertainty introduced by the adjustment of data points for study quality variables, the true uncertainty may be larger yet as we did not account for the rather crude nature of the study quality covariates as binary variables applied equally at all ages and both genders. The aim of GBD 2010 was to provide an empirical platform for consistently comparing the global burden attributable to different diseases and injuries. Given that MDD and dysthymia represented only two out of 291 causes included in the study, it was not surprising that some elements of the burden methodology could not be completely tailored to them. With ongoing improvements to the GBD methodology and the growing availability of epidemiological data, we will be able to add to our understanding of the global burden of depressive disorders.

It is also worth acknowledging that our findings were reliant on the validity of the disability weights used. Although the methodology used to quantify disability largely improved on what was used in GBD 1990, some areas could benefit from further refinement. The health state definitions and subsequent lay descriptions for MDD and dysthymia may not have been representative of all participants' experiences of the disorder. Further research is required into whether different health state definitions would change disability weights and, ultimately, burden estimates. Analyses of the disability weight surveys suggested a high degree of consistency between disability weights from the country surveys and the internet survey. In spite of responses coming from a heterogeneous sample of individuals (e.g., a high proportion of highly educated individuals from the internet-based survey and the opposite from the population-based survey from Tanzania), the strength of the correlation between disability weights was at least 0·9 across all surveys except in Bangladesh where it was 0·75 (12). That said, although these high correlations lend support to the argument that the disability weights used can be generalized across countries, replication of the disability weights survey in other settings is required for clearer conclusions.

Our review of the literature also indicated that there was much less reported on the severity of MDD and dysthymia compared to other areas of the disorders' epidemiology. Moreover, the available literature differed vastly in sampling methods and survey instruments hence capturing different conceptualisations of severity with no general consensus in distinguishing between mild, moderate, and severe states of MDD (186). For instance, severity distributions obtained from the WMHS study group indicated the majority of cases with MDD were classified as severe. The skew towards classifying cases as severe was partly due to the algorithm used to group answers to questions from the Sheehan Disability Scale and/or the Quick Inventory of Depressive Symptomatology (17, 187, 188) and partly due to the inclusion of additional criteria related to comorbid health states rendering the classification as unusable for GBD purposes (17, 106, 187, 188). So instead, we turned to data from the MEPS, NESARC, and NSMHWB, which provided a less skewed distribution of cases and allowed us to derive severity distributions while also controlling for comorbidity. However, these three surveys were from two high income countries, limiting the global representativeness of our severity distributions and making it impossible to quantify any effect of treatment on severity. There is a clear need for further investigations with comparable methods into the severity distribution of MDD and dysthymia and the variation thereof between countries and by levels of access to care.

Conclusions

Our findings not only highlight the fact that depressive disorders are a global health priority but also that it is important to understand variations in burden by disorder, country, region, age, sex, and year when setting global health objectives. Furthermore, estimating the burden attributable to MDD as a risk factor for other health outcomes allows for a more accurate estimate of burden and reinforces the importance of implementing cost-effectiveness interventions to reduce its ubiquitous burden. Ongoing improvements to the GBD methodology and access to more epidemiological data will enhance the precision of our burden estimates and add to our understanding of the global burden of depressive disorders.

Acknowledgments

We would like to acknowledge the members of the mental and illicit drug use expert group for their guidance with the burden estimation process. We would also like to thank Abraham Flaxman, University of Washington, for his support and expert guidance with the epidemiological disease modelling of MDD and dysthymia. We are also very grateful to Amanda Baxter, University of Queensland; Adele Somerville, University of Queensland; and Roman Scheurer, Queensland Centre for Mental Health Research, for their invaluable contributions during the course of the study.

Chapter review

Chapter Five estimated DALYs, YLDs, and YLLs due to MDD as part of GBD 2010 (thesis aim two). Given the lack of deaths and YLLs estimated for MDD, burden attributable to MDD but allocated to other diseases and injuries in GBD 2010 was also quantified. Findings showed that MDD was a significant contributor to the burden originally assigned to suicide and IHD.

Given the literature presented in Chapter Two showed that other mental and substance use disorders also lead to an increased risk of suicide, the next chapter estimates the burden attributable to a number of different mental and substance use disorders as risk factors for suicide. It is important from a public health perspective to not only estimate the burden attributable to MDD as a risk factor for other health outcomes, but also to consider the relative impacts of MDD compared to other mental and substance use disorders. With that in mind, the aim of Chapter Six was to investigate the effect of all mental and substance used disorders (as a group) as well as the contribution of MDD (and other individual mental disorders) on suicide burden.

Chapter Six: The burden attributable to mental and substance use disorders as risk factors for suicide: Findings from the global burden of disease study 2010

Alize J. Ferrari, BPsySc Hons[1,2]; Rosana E. Norman, PhD[1,3]; Greg Freedman, BA[4]; Amanda J. Baxter, MPH[1,2]; Jane E. Pirkis, PhD[5]; Meredith G. Harris, MPH[1,2]; Andrew Page, PhD[6]; Emily Carnahan, BA[4]; Louisa Degenhardt, PhD[5,7]; Theo Vos, PhD[1,4], Harvey A. Whiteford, MD[1,2]

[1] University of Queensland, School of Population Health, Herston, Queensland, Australia

[2] Queensland Centre for Mental Health Research, Wacol, Queensland, Australia

[3]University of Queensland, Queensland Children's Medical Research Institute, Herston, Queensland, Australia

[4]University of Washington, Institute for Health Metrics and Evaluation, Seattle, Washington, USA

[5]University of Melbourne, Melbourne School of Population and Global Health, Melbourne, Australia

[6]University of Western Sydney, School of Science and Health, Campbelltown, New South Wales, Australia.

[7]University of New South Wales, National Drug and Alcohol Research Centre, Sydney, Australia

Published in PloS One, 2014, 9(4):e91936

Chapter summary

Background

The GBD 2010 study identified mental and substance use disorders as the 5th leading contributor of burden in 2010, measured by DALYs. This estimate was incomplete as it excluded burden resulting from the increased risk of suicide captured elsewhere in GBD 2010's mutually exclusive list of diseases and injuries. Here, we estimate suicide DALYs attributable to mental and substance use disorders.

Method

RR estimates of suicide due to mental and substance use disorders and the global prevalence of each disorder were used to estimate PAFs. These were adjusted for global differences in the proportion of suicide due to mental and substance use disorders compared to other causes then multiplied by suicide DALYs reported in GBD 2010 to estimate attributable DALYs (with 95% uncertainty).

Results

Mental and substance use disorders were responsible for 22.5 million (14.8-29.8 million) of the 36.2 million (26.5-44.3 million) DALYs allocated to suicide in 2010. Depression was responsible for the largest proportion of suicide DALYs (46.1% (28.0%-60.8%)) and anorexia nervosa the lowest (0.2% (0.02%-0.5%)). DALYs occurred throughout the lifespan, with the largest proportion found in Eastern Europe and Asia, and males aged 20-30 years. The inclusion of attributable suicide DALYs would have increased the overall burden of mental and substance use disorders (assigned to them in GBD 2010 as a direct cause) from 7.4% (6.2%-8.6%) to 8.3% (7.1%-9.6%) of global DALYs, and would have changed the global ranking from 5th to 3rd leading cause of burden.

Conclusion

Capturing the suicide burden attributable to mental and substance use disorders allows for more accurate estimates of burden. More consideration needs to be given to interventions targeted to populations with, or at risk for, mental and substance use disorders as an effective strategy for suicide prevention.

Introduction

There has been growing recognition of the importance of mental and substance use disorders as contributors to health loss in all countries. GBD 2010 is the largest and most recent effort to quantify this by systematically integrating YLLs and YLDs into DALYs for diseases, injuries and risk factors (5, 6, 10-13)

GBD 2010 presented age-, sex-, year-, country-, and region-specific DALYs for 291 diseases and injuries as well as for 67 risk factors (5, 6, 10-13)using improved methodology compared to previous GBD studies (1, 16). Mental and substance use disorders explained 7.4 % (95% uncertainty interval: 6.2-8.6%) of total DALYs in 2010, confirming them as the leading disease category of YLDs, and the 5th leading category of DALYs globally (19, 189, 190). This estimate reflects 'direct burden' where mental and substance use disorders are the direct cause of health loss, but excludes the excess (attributable) burden resulting from the increased risk of mortality and disability due to subsequent health outcomes captured elsewhere in the mutually exclusive disease and injury categories in GBD 2010. Jointly considering the direct and the attributable burden of mental and substance use disorders provides an estimation of the putative causal relationship between the disorders and other health outcomes. This is of clinical and policy relevance as it clearly delineates the disability and mortality that potentially can be modified by interventions to prevent and treat mental and substance use disorders.

Here, we expand on the published GBD 2010 findings by estimating the additional burden attributable to mental and substance use disorders as risk factors for suicide. Suicide, defined as deaths caused by intentional, self-inflicted poisoning or injury (39), was the 13th leading cause of YLLs worldwide in 2010 (5, 11). Nearly 1 million people complete suicide every year with over 50% aged between 15 and 44 years (74, 191). Over 80% of suicides occur in low to middle income countries and close to 50% occur in India and China alone (191, 192). Suicide from firearms, car exhaust and poisoning are more common in high income countries and suicide from pesticide poisoning, hanging and self-immolation are more common in low to middle income countries (193). It is important to consider these differences in the global epidemiology of suicide while quantifying the suicide burden attributable to mental and substance use disorders.

The link between mental and substance use disorders and suicide is well documented (74, 82, 83, 90, 191-193) and authors such as Prince and colleagues argued (74) that failure to include suicide as part of mental and substance use disorder estimates in the previous GBD studies (1, 16) led to an underestimate of the extent of the burden. A literature review and meta-analysis by Harris and Barraclough showed that of the 249 studies and 44 mental disorders assessed, 36 disorders were

associated with an increased risk of suicide (82). Li and collaborators also found that the risk of suicide was 7.5 (6.2-9.0) times higher in males and 11.7 (9.7-14.1) times higher in females with a mental or substance use disorder compared to males and females with no disorder. Depression and bipolar disorder accounted for the highest risk (83). Even when other risk factors such as adverse marital effects, employment and socio-economic status were considered, mental and substance use disorders remain strongly associated with suicide (83, 92)

Quantifying the suicide burden attributable to mental and substance use disorders also corrects for the low burden from premature mortality (YLLs) directly attributed to mental and substance use disorders in GBD 2010. Although mental and substance use disorders were identified as a leading cause of global burden, YLDs contributed to 95% of DALYs (5, 19). In spite of evidence of excess mortality attributable to many mental and substance use disorders, only substance use disorders, anorexia nervosa, and schizophrenia are recognized as underlying causes of death in the ICD-10 cause of death guidelines (39) used in GBD 2010. Even for those disorders, few deaths were captured in the vital registrations used in the estimation of YLLs, as this typically involves the cumbersome task of disentangling the effect of multiple mental, substance and physical disorders to identify primary cause of death.

Investigating mental and substance use disorders as risk factors for fatal outcomes like suicide allows us to circumvent this problem by making use of GBD 2010's CRA methodology (10). Rather than rely on certification and coding practices in mortality registration systems, this method allows quantification of the difference in population health in a counterfactual with a theoretical minimum level of exposure (10). We make use of this method here to calculate the suicide burden attributable to mental and substance use disorders, and examine variations by region, country, age, year and disorder.

Methods

The suicide burden attributable to mental and substance use disorders was estimated by comparing the current health status with a theoretical-minimum-risk exposure defined as the counterfactual status of the absence of mental and substance use disorders. PAFs were determined from the prevalence of exposure to each disorder and the RR of suicide (10). For each disorder this involved:

- Reviewing the strength of the evidence for a causal relationship between the disorder and suicide.

- Expanding on existing systematic reviews of the literature quantifying the effect size for the disorder as a risk factor for suicide. The preferred metric was population-representative RR estimates.
- Pooling all RR estimates using meta-analysis.
- Combining the pooled RR estimate with GBD 2010 prevalence estimates to generate PAFs by age, sex, country, and year.
- Adjusting PAFs for global differences in suicide attributable to mental and substance use disorders versus differences attributable to other causes.
- Multiplying PAFs by suicide YLLs reported in GBD 2010 to estimate attributable burden.

Case definition

GBD methods suggest that for each risk factor-outcome pairing, there should be (1) sufficient data to enable estimation of relative effect sizes as well as (2) sufficient evidence for a causal effect (10). A literature review by Baxter and collaborators (88) as well as other studies summarised in the previous section (74, 82, 83, 90, 191-193) investigating mental and substance use disorders as risk factors for other health outcomes found sufficient evidence to meet these two conditions for suicide. Mental and substance use disorders investigated were those included in GBD 2010 for which there was evidence of an increased risk of suicide (19, 82, 83). These were MDD, bipolar disorder, schizophrenia, anxiety disorder, anorexia nervosa, alcohol dependence, amphetamine dependence, cocaine dependence and opioid dependence. All disorders were defined using the DSM (38) or ICD diagnostic criteria (39). Suicide was defined as cases meeting ICD-10 cause of death codes for intentional self-inflicted poisoning or injury (X60-X84) (39). In some countries a large proportion of injury-related deaths are coded as 'underdetermined intent' for cultural, religious or medico-legal reasons. GBD 2010 developed a method to redistribute these deaths to specific underlying causes, including suicide (5). Although GBD 2010 also considered the effects of attempted suicide as 'non-fatal self-harm' (5), this was not investigated in this paper.

Literature search to identify relative-risk estimates

We used data sources from recent and methodologically comparable systematic reviews of the association between suicide and mental and substance use disorders (83, 194-196), specifically affective disorders, anxiety disorders, schizophrenia (14 studies from these 3 disorder groups) (83), cocaine, opioid, and amphetamine dependence (24 studies) (194, 195), s and alcohol dependence (12 studies) (196). We expanded the Li and collaborators systematic review and replicated the literature search (83) to collect data for bipolar disorder and MDD separately (rather than affective disorders combined), and anorexia nervosa which was not included in the original review. The

search strategy used was in keeping with the PRISMA statement (121) (See Text S1, Appendix Five for the PRISMA checklist and flow diagram). Electronic databases (Medline and Embase) were searched between 1966 and 2010. A secondary search of reference lists and the grey literature was also conducted. Studies were included that; (1) considered mental and substance use disorders as a risk factor associated with suicide; (2) reported a RR with 95% uncertainty, or provided sufficient information for these to be calculated; (3) were individual-level case-control or cohort studies where a clear temporal association between exposure and outcome could be determined; (4) had a minimum follow up period of 1 year and; (5) included disorders based on ICD (39) or DSM (38) nomenclature to ensure consistency in case definitions. Sex-specific data were preferred but non sex-specific estimates were included (e.g. for substance use disorders) where data were sparse. For each study, information on study methodology, quality and findings were extracted into a Microsoft Excel spreadsheet. See Table S1, Appendix Fice for a summary of the study variables extracted.

Meta-analysis of relative-risk estimates

For each disorder (except alcohol dependence for which a pooled estimate was available (196)), MetaXL software, an add-in for Microsoft Excel (197), was used to pool RR estimates from different studies. This was done for males and females separately and also combined. RR estimates were pooled using a random effects model, and if there was sufficient data to do so, a quality effects model (198). Pooled RRs from the quality-effects model were preferred as these gave greater weight to studies of high quality versus studies of lesser quality, and avoided the anomaly of random effects models which revert to equal weighting regardless of sample size if heterogeneity is large (198-200). Study quality was assessed using a quality index which scored studies based on sampling design and representativeness and also the availability of age- and gender-specific estimates. It was limited to these items to reduce potential subjectivity within and between quality scores. To prevent inter-rater bias, all studies were rated by one researcher and a random sample of scores was checked by an independent researcher. The quality index and scores have been summarised in Table S1, Appendix Five.

Prevalence of mental and substance use disorders

We obtained the prevalence distribution of each mental and substance use disorder from the epidemiological disease models used in the calculation of direct burden (i.e. YLDs) in GBD 2010 (19, 189). These were based on a separate literature review (presented in greater detail elsewhere (19, 142, 150, 201-203) conducted between 1980 to 2010 to capture studies reporting prevalence, incidence, remission, duration and all cause-excess mortality associated with mental and substance

use disorders. Point (current or past month) prevalence estimates of DSM/ICD defined disorders were required. Twelve-month prevalence estimates were accepted to maximize inclusion but adjusted towards the level of point prevalence using study-level covariates. Lifetime prevalence was excluded as it is more likely than point or period prevalence to be affected by recall bias (122, 123). GBD 2010's DisMod-MR, a Bayesian meta-regression tool, was used to integrate these estimates into an epidemiological disease model. From the epidemiological inputs, DisMod-MR generated prevalence by sex and age for 187 countries, 21 world regions and 1990, 2005 and 2010 (13, 154). Prevalent cases for each disorder have been summarised in previous publications (13, 19, 189).

Population attributable fractions

PAFs were calculated from the DisMod-MR prevalence output (P) for each disorder and the pooled RR of suicide given exposure to the disorder. PAFs were calculated by age, sex, country, year and disorder (consistent with the format of GBD 2010 estimates) using the following formula (14):

$$PAF = \frac{p(RR-1)}{p(RR-1)+1}$$

Given the presence of comorbidity between mental and substance use disorders, disorder-specific PAFs cannot be summed to obtain the 'joint effect' of combined mental and substance use disorders on suicide. Instead, a joint PAF was estimated using the multiplicative method of adjusting for comorbidity between disorders (204). This can be understood as calculating the complement of the product of the complements of each individual PAF. The following formula was used where i is the individual risk factor, and n is the total number of risk factors (10);

$$Joint\ PAF = 1 - \prod_{i=1}^{n}(1 - PAF_i)$$

Ceiling values for joint population attributable fractions

Although studies from high income countries have consistently shown that up to 90% of suicides occur as a result of an underlying mental or substance use disorder (90-92), there is also evidence to suggest that this proportion is substantially lower in China, Taiwan and India; where symptoms of 'dysphoric affect' and 'impulsivity' (which do not constitute a mental and substance use disorder) are expressed through more lethal methods of self-harming such as pesticide poisoning and self-immolation (205-208). This in turn, increases the number of completed suicides occurring from self-harm behaviours (characteristically instigated as impulsive acts, without the presence of a

mental and substance use disorder or a clear intent to die) in these countries which would have resulted in an "attempted suicide" had such methods not been available (206, 207).

So as not to overestimate the total proportion of suicide burden attributable to mental and substance use disorders, we first portioned out global differences in suicide attributable to mental and substance use disorders from differences attributable to other causes. More specifically, the total proportion of suicide cases attributable to mental and substance use disorders in different countries was calculated and used to set a ceiling value (or upper threshold) for the joint PAFs. We examined reference lists of existing reviews for psychological autopsy studies (90-92) and conducted a supplementary literature search to capture additional data sources up to 2010. The psychological autopsy method is a retrospective assessment of causes of death which involves canvassing the views of individuals closest to the deceased and substantiating evidence from sources such as hospital and police records (209). The overall number of suicide cases attributable to mental and substance use disorders was extracted from these studies if DSM/ICD diagnostic criteria (38, 39) were used and the number of attributable suicide cases was reported for mental and substance use disorders as a group rather than for individual disorders. If gender was not recorded we also accepted combined estimates for males and females. Given that there were insufficient data to calculate ceiling values individually for each country or region, we pooled estimates into 2 broad categories based on the percentage of suicide cases reported to be due to mental and substance use disorders. Meta-analyses based on quality effects models were used to generate separate pooled proportions for Group 1: China, India and Taiwan and Group 2: all other countries.

These calculated proportions of suicide cases due to mental and substance use disorder were used to set the ceiling value of joint PAFs. All quantities of interest in GBD 2010 were calculated a thousand times in order to incorporate all sources of uncertainty. Similarly, we created a thousand draws of the 'ceiling values' based on the pooled estimates of mean and SE. When estimating the joint PAFs of suicide attributed to all mental and substance use disorders we did not allow PAF estimates in any of the one thousand draws to exceed the ceiling value in the corresponding draw. For draws that did exceed the ceiling, we scaled down each of the component mental and substance use disorder PAFs by the ratio of the ceiling to the combined PAF.

Attributable burden

The final step was to multiply PAFs by the corresponding GBD 2010 YLLs for suicide (5, 11) to calculate attributable burden. Since only completed suicides were considered in our analyses, only YLLs were included in attributable DALY estimates. To quantify 95% uncertainty around our final

burden estimate we calculated attributable YLLs and DALYs at the one thousand draw level and bounded the 95% uncertainty interval by the 2.5 and 97.5 centile values. All reporting of DALYs by region and country is based on age-standardised estimates using direct standardization to the global standard population proposed by the WHO in 2001 (169).

Results

Pooled relative-risk estimates

Our search culminated in a dataset of 40 studies and 85 RR estimates covering 14 countries (Table S1 summarizes included studies). There was a statistically significant increased risk of suicide for all selected mental and substance use disorders (table 10). The greatest risk was seen in MDD followed by schizophrenia, and alcohol dependence. The 95% confidence intervals around each pooled RR indicated high levels of uncertainty with statistical heterogeneity (as measured by the I^2 statistic) of up to 90%. A statistically significant sex difference was only observed for alcohol dependence (Table S2, Appendix Five summarizes sex-specific pooled RRs) hence the overall pooled proportions for both sexes combined were used in PAF calculations. Given that the one RR estimate for amphetamine dependence was not statistically different (i.e. occurred within overlapping 95% uncertainty) to the three estimates for cocaine dependence, we combined them to calculate a pooled RR for all psychostimulants. This was used to calculate PAFs for both disorders.

Table 10. Pooled relative-risk of suicide in those diagnosed with a mental or substance use disorder.

Disorder	**Number of studies**	**Pooled relative risk (95% UI)**
Major depressive disorder	4	19.9 (9.5-41.7)
Anxiety disorder	7	2.7 (1.7-4.3)
Schizophrenia	4	12.6 (11.0-14.5)
Bipolar disorder	4	5.7 (2.6-12.4)
Anorexia nervosa	9	7.6 (2.2-25.6)
Alcohol dependence[b]	12	9.8 (9.0–10.7)
Opioid dependence	21	6.9 (4.5-10.5)
Psychostimulant dependence	4	8.2 (3.9-16.9)
Amphetamine dependence[a]	1	4.5(1.1-9.03)
Cocaine dependence[a]	3	16.9(6.01-47.2)

Note. 95% UI: 95% uncertainty interval; [a]Due to lack of data, simultaneously pooled cocaine and amphetamine relative-risk estimates into an overall estimate for psychostimulants which was applied to both disorders; [b]Used reported pooled standardised mortality ratios from Wilcox et al (196) for alcohol dependence.

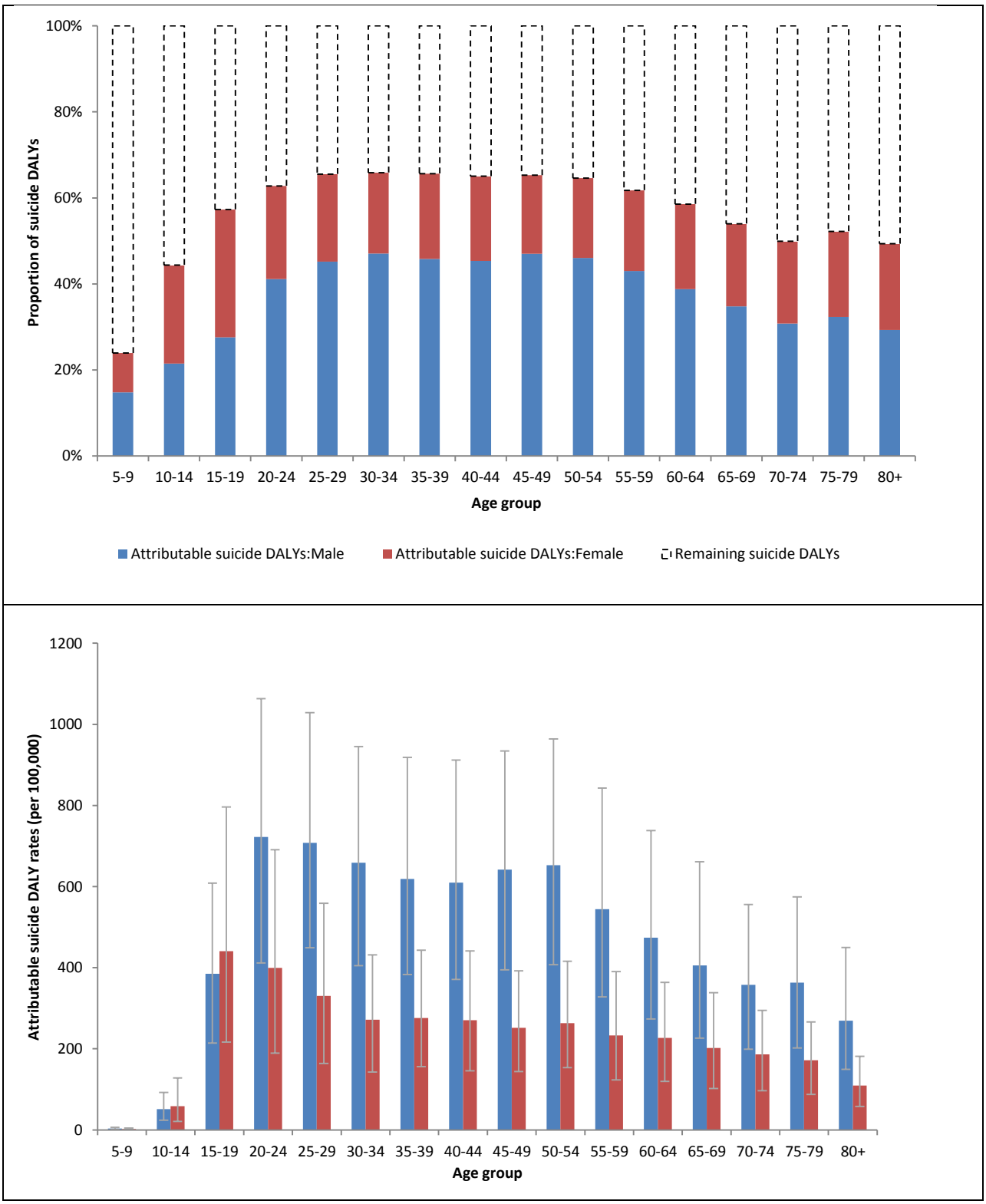
Ceiling values for joint PAFs

Out of 166 psychological autopsy studies reviewed, 43 studies and 57 estimates covering 20 countries were used to calculate ceiling value for joint PAFs (Table S3, Appendix Five summarizes included studies). In China, India and Taiwan (group 1), 68.3% (55.2%-80.0%) of suicide cases was due to mental and substance use disorders which was lower than in all other countries (group 2), where 84.5% (78.6%-89.6%) of suicide cases were due to mental and substance use disorders. These two pooled proportions were used as the ceiling values for joint PAFs from China, India and Taiwan (Group 1) and all other countries (Group 2) respectively. Note that there was considerable heterogeneity between studies. As we found no statistically significant sex difference, the overall pooled proportions were used in PAF calculations (Table S4, Appendix Five summarizes sex-specific pooled proportions).

Attributable burden

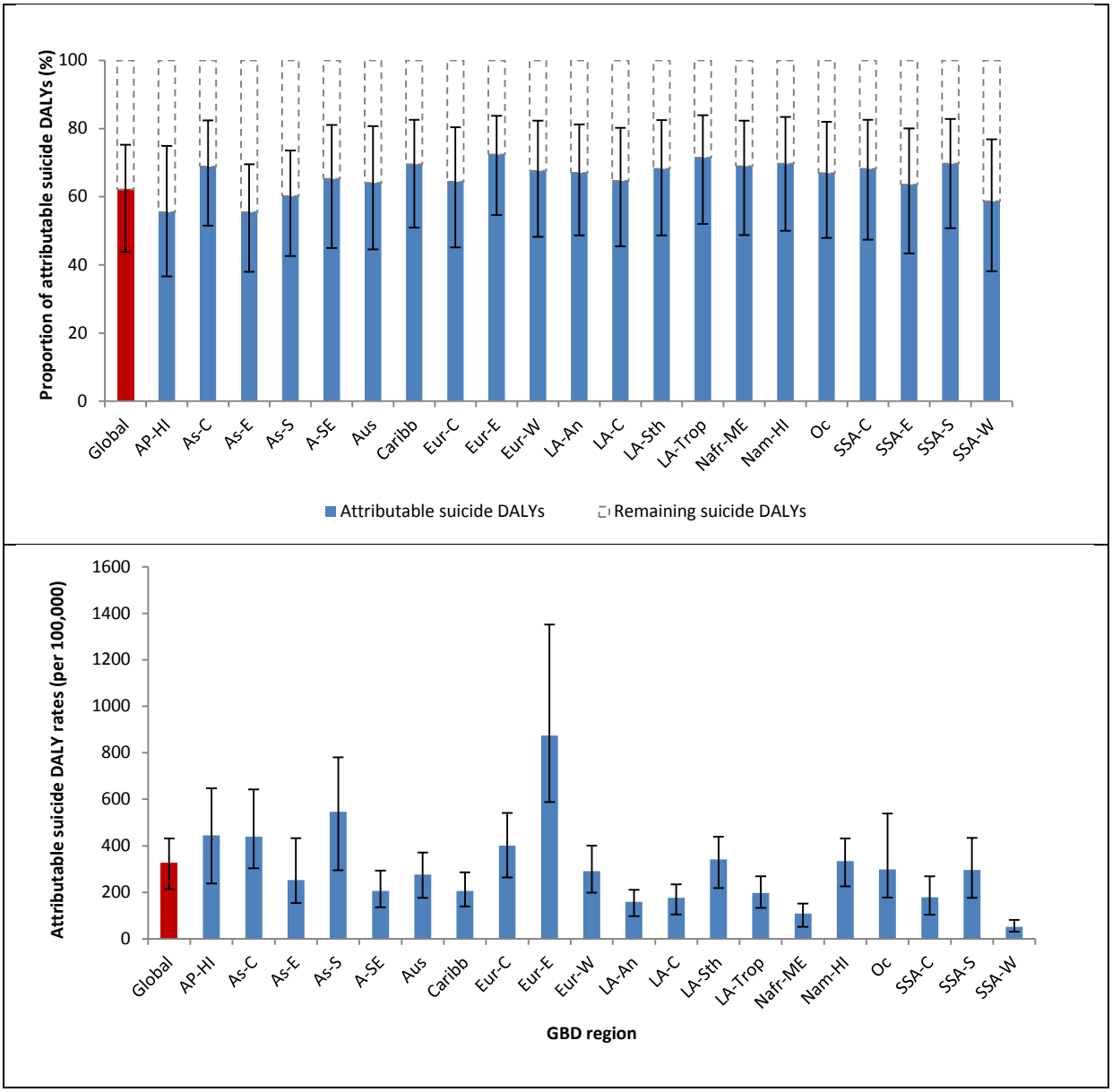
Mental and substance use disorders were responsible for 22.5 million (14.8-29.8 million) of the 36.2 million (26.5-44.3 million) DALYs allocated to suicide in 2010, amounting to 62.1% (43.8%-75.3%) of total suicide DALYs. The proportion of attributable suicide DALYs in 1990 was almost identical to that in 2010 (62.1% (44.5%-75.4%)). The remainder of this section focuses on 2010 estimates with 1990 estimates summarised in Table S5, Appendix Five. There were twice as many mental and substance use disorders attributable suicide DALYs for males (14.9 million (9.5-20.1 million)) compared to females (7.6 million (4.4-10.6 million)). For all disorders, this sex difference was consistent throughout the lifespan. Attributable suicide DALYs were apparent from those aged ≥ 5 years, with the highest proportion occurring between those aged 20-30 years (Figure 15).

The proportion of suicide DALYs explained by mental and substance use disorders was reasonably consistent between regions and within the range of the ceiling values presented in the previous section. When considered in terms of absolute DALYs, Asia South and Asia East had the highest burden attributable to mental and substance use disorders, given their large population size. In terms of age-standardized rates, Europe Eastern had the highest burden (almost 3 times higher than the global mean) and Sub-Saharan Africa West the lowest (6 times lower than the global mean) (Figure 16, Table S5, Appendix Five summarizes attributable DALYs by disorder, region, age and sex).



Note. Plot 1 shows attributable DALYs as proportion of suicide DALYs. Plot 2 shows attributable DALYs as a rate per 100,000

Figure 15. Suicide DALYs attributable to mental and substance use disorders by age and sex, in 2010.

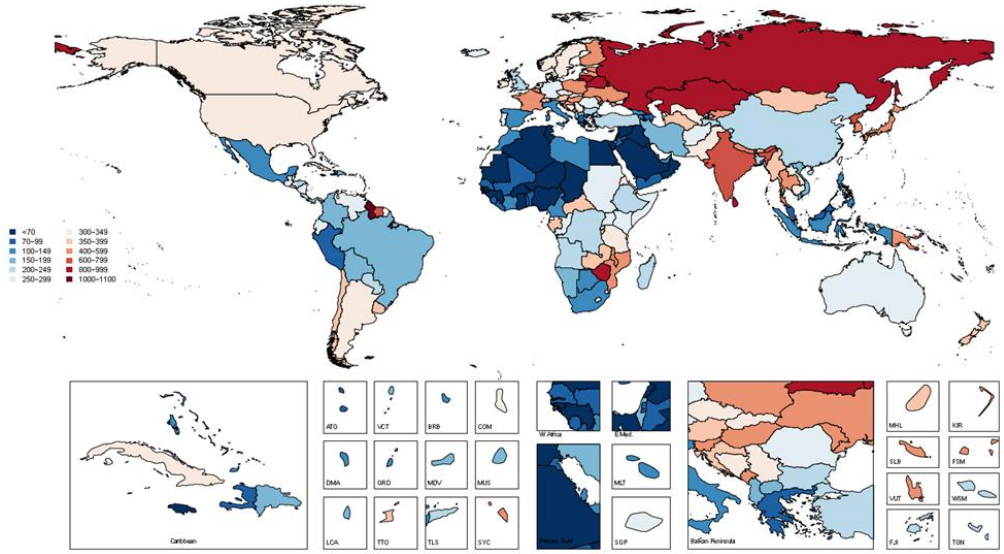


Note. Plot 1 shows attributable DALYs as proportion of suicide DALYs. Plot 2 shows attributable DALYs as a rate per 100,000; AP-HI: Asia Pacific, High Income, As-C: Asia Central, AS-E: Asia East, AS-S: Asia South, A-SE: Asia Southeast, Aus: Australasia, Caribb: Caribbean, Eur-C: Europe Central, Eur-E: Europe Eastern, Eur-W: Europe Western, LA-An: Latin America, Andean, LA-C: Latin America, Central, LA-Sth: Latin America, Southern, LA-Trop: Latin America, Tropical, Nafr-ME: North Africa/Middle East, Nam-HI: North America, High Income, Oc: Oceania, SSA-C: Sub-Saharan Africa, Central, SSA-E: Sub-Saharan Africa, East, SSA-S: Sub-Saharan Africa Southern, SSA-W: Sub-Saharan Africa, West.

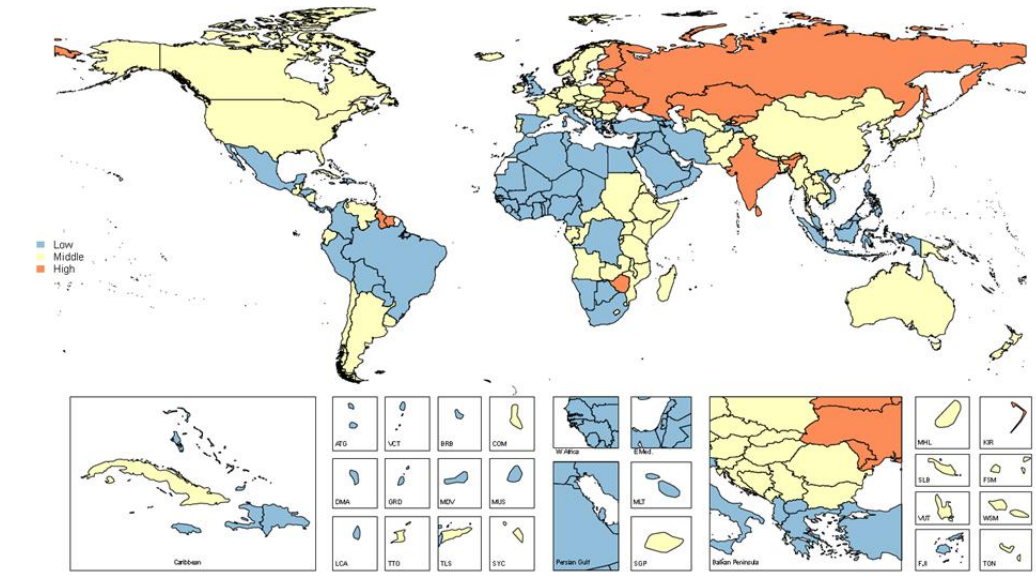
Figure 16. Suicide DALYs attributable to mental and substance use disorders by region, in 2010.

There were also differences in attributable suicide DALYs across countries (plot 1, figure 17). Attributable DALY rates were highest in Kazakhstan and lowest in Saudi Arabia, however many of the country level differences presented in plot 1 were within overlapping ranges of uncertainty (plot 2, figure 17). Except for Guyana, Suriname and Zimbabwe, all countries with statistically higher attributable DALY rates than the global mean were from Eastern Europe and South Asia. Countries with statistically lower DALY rates than the global mean included those from South America, Oceania, Africa and the Middle East and parts of Asia.

Plot 1: Map showing age standardized DALY rates (per 100,000) by country



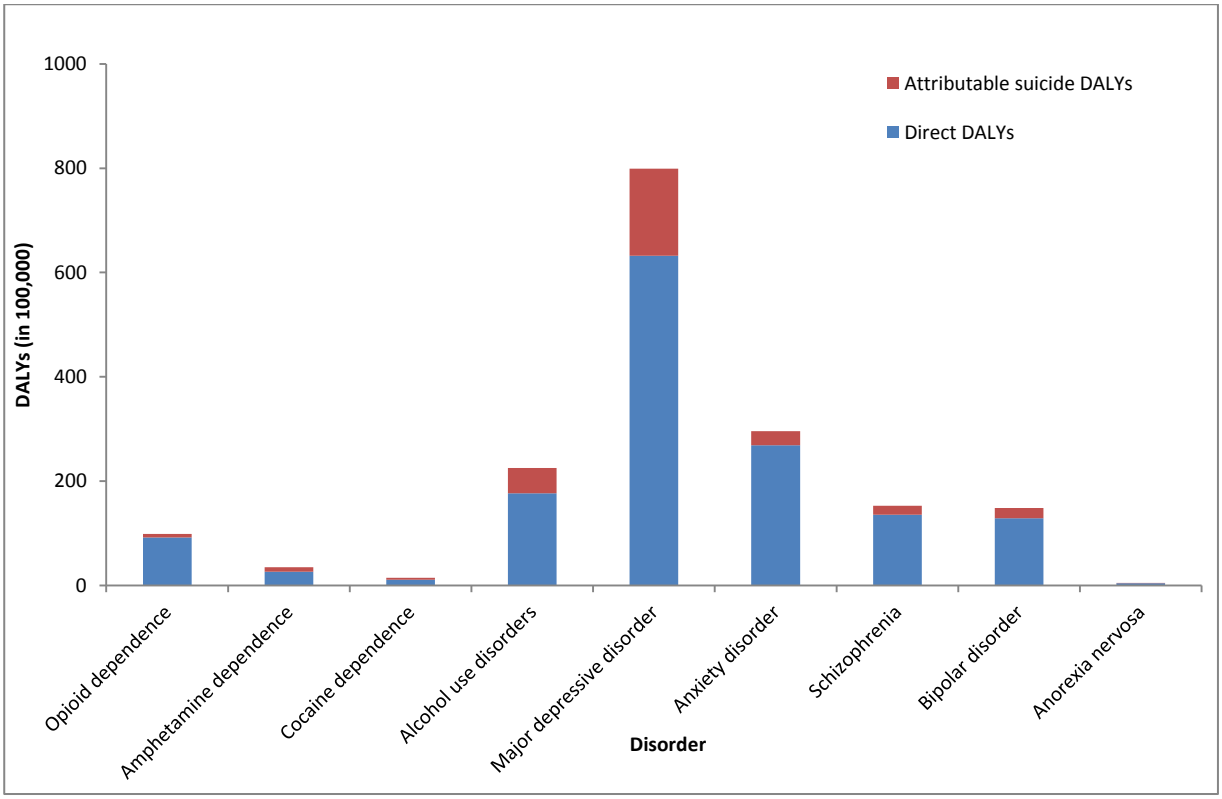
Plot 2: Map comparing country-specific DALY age standardized rates (per 100,000) to the global mean



Note: Low: countries with statistically lower DALY rates than the global mean; middle: countries with statistically similar DALY rates to the global mean; high: countries with statistically higher DALY rates than the global mean.

Figure 17. Suicide DALYs (rates per 100,000) attributable to mental and substance use disorders by country, in 2010.

Of the suicide DALYs attributable to mental and substance use disorders, MDD was responsible for the largest proportion (46.1% (28.0%-60.8%)), followed by alcohol dependence (13.25% (12.0%-15.0%)), anxiety disorder (7.4% (3.0%-12.7%)), bipolar disorder (5.4% (1.8%-10.7%)), schizophrenia (4.7% (4.1%-5.3%)), amphetamine dependence (2.4% (0.9%-4.6%)), opioid dependence (1.9% (1.1%-2.9%)), cocaine dependence (0.9% (0.3%-1.8%)) and anorexia nervosa (0.2% (0.02%-0.5%)) (figure 18). MDD explained the most suicide DALYs and anorexia nervosa the least across all age groups, sex and regions although most of the age and regional differences between disorders remained within wide and overlapping confidence intervals (Table S6, Appendix Five).



Note. Absolute DALYs in 100,000.

Figure 18. Suicide DALYs attributable to mental and substance use disorders by disorder, in 2010.

The additional burden attributable to suicide for each mental and substance use disorder (over and above the DALYs assigned to them as a direct cause) is also illustrated in figure 18. The inclusion of attributable suicide burden increased the fatal burden (YLLs) due to mental and substance use disorders from 0.5% (0.4%-0.7%) (assigned to them as a direct cause) to 1.8% (1.4% - 2.2%) of global YLLs and the overall burden (DALYs) of mental and substance use disorders from 7.4% (6.2%-8.6%) to 8.3% (7.1% - 9.6%) of global DALYs. Out of the 10 leading classes of diseases included in GBD 2010(5), mental and substance use disorders increased from the 5th to the 3rd leading class of disease burden once the burden attributable to suicide was considered; exceeding the burden due to neoplasms (7.6% (7.0%-8.2%) of global DALYs) and neonatal conditions (8.1% (7.3%-9.0%) of global DALYs) but not cardiovascular and circulatory diseases (11.9% (11.1%-12.7%) of global DALYs) and diarrhoea, LRI, meningitis, and other common infectious diseases (11.4% (10.4%-12.8%) of global DALYs). The global DALY ranking of individual disorders (as presented in GBD 2010's publication series (5)) also increased when attributable suicide burden was included (table 11). Although within overlapping ranges of uncertainty, the ranking for alcohol dependence increased the most, from the 35th (29th-45th) to the 28th (26th-37th) leading cause of burden.

Table 11. Global DALY proportions and rankings before and after the addition of attributable suicide burden, in 2010.

	Before addition of attributable suicide burden (95% UI)		**After addition of attributable suicide burden (95% UI)**	
Disorder	**Direct DALYs As a proportion of total DALYs**	**Mean rank**	**Direct plus attributable DALYs As a proportion of total DALYs**	**Mean rank**
Major depressive disorder[a]	2.5% (1.9%-3.3%)	11 (7-14)	3.2% (2.5%-4.0%)	8 (4-11)
Anxiety disorder[a]	1.1% (0.8%-1.5%)	26 (19-33)	1.2% (0.9%-1.6%)	25 (17-30)
Alcohol dependence[a]	0.7% (0.5%-0.9%)	35 (29-45)	0.9% (0.7%-1.1%)	28 (26-37)
Schizophrenia[a]	0.6% (0.4%-0.7%)	43 (36-57)	0.7% (0.5%-0.9%)	39 (30.5-50)
Bipolar disorder[a]	0.5% (0.3%-0.8%)	46 (35-59)	0.6% (0.4%-0.8%)	44 (31-56)
Mental and substance use disorders combined[b]	7.4% (6.2%-8.6%)	5 (3-6)	8.3% (7.1%-9.6%)	3 (3-6)

Note. 95% UI: 95% uncertainty interval; [a]Global ranking of direct burden for <u>each</u> disorder was from the official GBD 2010 disease ranking for 2010 (5). Illicit drug use disorders have not been included here as the GBD 2010 official disease ranking investigated drug use disorders as group (rather than by specific drug types). Similarly, the ranking for anorexia nervosa was presented in addition to bulimia nervosa; [b]The global ranking of direct burden of mental and substance use disorders <u>as a group</u> compares the direct burden of the 11 main classes of diseases in GBD 2010 (19).

Discussion

Mental and substance use disorders are associated with an increased risk of suicide, a finding that is well established in the literature (82, 83, 196) but until now, not quantified in terms of a global comparison of disease burden. DALY rankings in GBD 2010 were based on a classification of mutually exclusive disease and injury categories (5, 19). Considering the additional burden due to mental and substance use disorders as a risk factor for suicide elevated mental and substance use disorders from the fifth to the third leading disease category of global burden in 2010. Few mental and substance use disorders are recognized as a primary cause of death in mortality registrations, and those that are recognised are often under-represented. The data presented here provide a more comprehensive insight into the magnitude of the burden due to these disorders.

Mental and substance use disorders were the cause of two-thirds of all suicide DALYs reported in GBD 2010. Aside from emphasising these as a debilitating group of disorders, our findings highlight the importance of prioritising the prevention, early detection and effective management of mental and substance use disorders – particularly MDD – as a key suicide prevention strategy. Presenting the differences in attributable burden between regions and countries also provides a beginning for developing policies or intervention strategies that are applicable at the national level. Such interventions can be described as 'selective', in the sense that they target subgroups of the population whose members have yet to manifest suicidal behaviours, but exhibit risk factors (in this case, mental and substance use disorders) that predispose them to do so in the future. These can be contrasted with 'universal' interventions, which target whole populations with the aim of favourably shifting proximal and distal risk (and protective) factors across the entire population, and 'indicated interventions' which are designed for individuals already exhibiting suicidal behaviours (210).

Typically, countries that have put in place national suicide prevention strategies have funded a range of universal, selective and indicated interventions, in recognition of the variety of risk and protective factors associated with suicide (211). However our findings suggest that a relatively greater emphasis on selective interventions targeting individuals with mental and substance use disorders may be applicable. By way of example, equipping general practitioners to detect, diagnose and manage MDD is likely to have benefits, particularly because many individuals with MDD will receive care from a general practitioner rather than a specialist mental health provider. This was one of the few interventions for which there was good evidence of effectiveness as a suicide prevention strategy in a recent review by Mann and colleagues (212). That said, ensuring that care from general practitioners is evidence-based requires further consideration, given

findings that rates of minimally adequate treatment for depression are lower among patients treated solely by general practitioners or in the general medical care sector, compared to those treated by specialist mental health providers (213, 214).

However universal and indicated interventions have their place, particularly in low and middle income countries where mental and substance use disorders were associated with a lesser proportion of the burden of suicide. In these countries, universal interventions for example restricting access to means (e.g., pesticides) is worth pursuing given that they are relatively cheap to implement, can have a broad community reach and are known to be effective (212).

Although within overlapping bounds of uncertainty, we found that attributable suicide DALY rates among young people aged 15-19 years were approaching those of the adult age groups. Although males had higher rates of attributable burden in most age groups, female rates were higher between the ages of 10 and 19 years. These age-related findings support the importance of school-based prevention programs which include a focus on mental health targeted to at-risk adolescents. The sex-difference in attributable burden also needs to be considered when formulating prevention strategies for this age group. Although evidence of a reduction in suicide behaviours has not been demonstrated, there is evidence for the effectiveness of school-based programs in reducing the effect of risk factors such as depression (211, 215). A recent systematic review of interventions targeting adolescents or young adults at risk of suicide identified individual cognitive behavioural therapy-based interventions and attachment-based family therapy as promising interventions, requiring further investigation (216).

As there was insufficient data to (1) obtain pooled RR estimates for all countries or regions included in GBD 2010 and (2) clearly detect differences in RR estimates between all countries/regions, the pooled RR estimates used to estimate PAFs were assumed to be constant across age, sex and country. Instead, the variation in attributable DALYs across countries was driven by (a function of both) the prevalence of mental and substance use disorders and the amount of burden accounted for by suicide in each country. In addition, given evidence for differences in the underlying causes of suicide in China, India and Taiwan (205-208), where it has been well documented that the ease of availability of particularly lethal means of self-harm such as pesticides may influence patterns of suicide, we constrained the maximum proportion of suicide attributable to mental and substance use disorders to a ceiling value of 68.3%. In spite of this, some Asian countries were amongst those with the highest rates of attributable suicide burden due to the high rates of suicide in those countries. This emphasizes the fact that although there may be other risk factors for suicide, the

prioritisation of mental and substance use disorders in the prevention of suicide remains a global priority.

The maximum proportion of suicide attributable to mental and substance use disorders in all other countries was constrained to a ceiling value of 84.5%. The studies categorized as "all other countries" were mainly from North America, Western Europe and Australia and, although we had data for three low to middle income countries (Colombia, Pakistan and Indonesia), this pooled proportion might not be appropriate for use in Sub-Saharan Africa where we found no data. It is possible that these countries have a different distribution of suicides attributable to mental and substance use disorders but more cross-national RR data are required before we can incorporate this in our findings. Islamic countries, for instance from North Africa/Middle East, were amongst the countries with the lowest proportion of attributable burden, despite being allocated the higher ceiling value of 84.5%. In contrast to the high rates of depression in the Middle East, rates of suicide were low. The lowest rate of suicide recorded in GBD 2010 was from Saudi Arabia. Stigma around suicide due to religious beliefs and legislative prohibition (i.e. suicide being considered as a criminal offence) can lead to fewer cases of suicide being recorded as a cause of death in countries from the Middle East. For similar reasons, the degree of psychopathology underpinning suicide cannot be as clearly assessed in these countries (217, 218). These issues may have biased our estimates of attributable burden. The large bounds of uncertainty presented reflect this to some extent; however, more data are required on the distribution and aetiology of suicide in these countries to improve estimates.

Like all population-based analyses, a number of methodological limitations need to be considered here. The ceiling values for suicide attributable to mental and substance use disorders were derived from psychological autopsy studies. As these collect retrospective data after the individual had died, they are limited by the accuracy of coroners' reports and systematic bias from interviewees (209). Although the pooled RR estimates used were derived from more representative population-based prospective cohort studies, there were only a few estimates available for most disorders. We applied the same pooled RR across all countries, sex and age groups for each disorder to reduce errors in estimates as a result of paucity in the data. It is possible that this masked differences in the distribution of attributable suicide DALYs. More representative population cohort studies are now emerging from low and middle income countries such as India (192). We hope that the scrutiny of data presented here will encourage more and better quality data collection for mental and substance use disorders as risk factors for suicide. Until then, it is important to consider the uncertainty around our final estimates in interpreting these findings.

CRA methodology assumes a causal relationship between the exposure and outcome (10). In support for this, the RR estimates used here showed that mental and substance use disorders were significantly associated with suicide risk, even when other risk factors such as socio-economic factors (e.g. adverse marital, employment and socio-economic status) were considered (83, 92). Another assumption was that the proportion of suicide burden attributable to mental and substance use disorders was estimated while holding all other independent risk factors constant. We estimated the joint effect of all mental and substance use disorders on suicide while adjusting for comorbidity between these disorders, the next step would be to explore the joint effect of mental and substance use disorder with other risk factors of suicide. Finally, PAF calculations were sensitive to the exposure distribution used. Here we used DisMod-MR to pool the prevalence of each disorder based on the raw epidemiological data that were available (8, 19). Although this provided consistent prevalence estimates by country, region, age, sex, and year, in some cases DisMod-MR was required to adjust for considerable heterogeneity in the raw data. This was, to some extent, incorporated in our analyses through the 95% uncertainty intervals around all prevalence estimates propagated to the final attributable burden estimates.

Conclusions

Mental and substance use disorders were responsible for two thirds of the suicide burden in 2010, adding a further 22 million DALYs to their global burden. More consideration needs to be given to interventions targeted to populations with, or at risk for, mental and substance use disorders as an effective strategy for suicide prevention.

Acknowledgements

We would like to acknowledge members of the mental and illicit drug use expert group and other international collaborators for their assistance with the methodology used in this paper. We would like to specifically thank Abraham D. Flaxman, Institute of Heath Metrics and Evaluation, University of Washington, for his assistance with the DisMod-MR modelling of mental and substance use disorders and suicide and Chiara Stone, National Drug and Alcohol Research Centre, University of New South Wales for her assistance with the literature review for illicit drug use disorders.

Chapter review

Chapter Six estimated the proportion of suicide burden in GBD 2010 that could be allocated to mental and substance use disorders (thesis aim three). MDD explained almost half of all suicide burden, surpassing the impact of all the other mental and substance use disorders investigated. This further contributed to our understanding of MDD as a significant contributor of the world's burden.

This chapter concludes the presentation of published materials in this thesis. The next chapter explores the risk factors of MDD. In the meta-regression of MDD prevalence presented in Chapter Three, variables investigated could only explain 57.7% of variability in prevalence. The aim here was to add to the epidemiological profile of MDD by investigating other potential determinants of its distribution. Efforts to establish potentially avertable risk factors to MDD can also inform the setting of preventative intervention strategies for MDD in the population, which is currently lacking (28).

Chapter Seven: An exploration of the risk factors of major depressive disorder and how they explain its distribution in the population

The contents of this discussion chapter were developed by Alize J Ferrari[1,2,3] in collaboration with Rosana E Norman[1,4], Karen M Devries[5], Jon-Paul Khoo[1,2], Joelle Y Mak[5], Claudia Garcia-Moreno[6], Theo Vos[3], Charlotte H Watts[5], Harvey A Whiteford[1,2,3]

[1]*University of Queensland, School of Population Health, Herston, Queensland, Australia*
[2]*Queensland Centre for Mental Health Research, Wacol, Queensland, Australia*
[3]*University of Washington, Institute for Health Metrics and Evaluation, Seattle, Washington, United States of America*
[4]*University of Queensland, Queensland Children's Medical Research Institute, Herston, Queensland, Australia*
[5]*Gender Violence and Health Centre, London School of Hygiene and Tropical Medicine, London, United Kingdom*
[6]*World Health Organization, Geneva, Switzerland*

Chapter summary

This chapter explores the risk factors of MDD, an area of unexplained variability in the epidemiological profile of MDD proposed in this thesis. Although there is considerable literature on the risk factors of mental disorders, for most of these risk factors there are insufficient data to fully quantify their association with MDD and/or establish causality. The aim here was to identify risk factors for which there are sufficient data to quantify an association with MDD, discuss how these risk factors can impact on the global distribution of MDD and highlight areas requiring further research.

The work presented in Chapters Three and Four illustrated the effect of war or conflict on the prevalence of MDD, whereby countries exposed to conflict had higher rates of MDD. In addition to this, GBD 2010's risk factor analysis published in late 2012 highlighted CSA and IPV as risk factors for MDD. In this chapter, a working example of how CSA and IPV (both of which are globally more common in women) can impact on the sex difference in MDD is presented. Globally, there were 298,000,000 prevalent cases of MDD in 2010 of which 187,000,000 were women. Findings suggest that CSA and IPV have the potential to explain up to 63·7% (46·2%-80·2%) of this sex difference. This finding emphasizes the need to investigate how interventions to ameliorate the increased risk from CSA and IPV can be incorporated into prevention programs for MDD. Nonetheless, given key omissions in the data, these findings are preliminary until further research can be accumulated. Caveats of this work are presented and include lack of data on IPV in males as well as lack of data to quantify how the observed effect of CSA and IPV on the sex difference of MDD interacts with other risk factors.

Introduction

According to the definition proposed in Chapter One, an epidemiological profile of MDD should quantify who in the general population has the disorder, who has recovered, and who has died as a result of MDD. It should also identify characteristics of those with and without MDD, behaviours that place people at risk, and their health outcomes.

Whist the work presented in previous chapters on the prevalence, incidence, duration, mortality and, burden provide us with ample data to explore the distribution and impact of MDD in the population, to complete the epidemiological profile of MDD, there also needs to be a quantification of its risk factors. The systematic review of the global prevalence of MDD and well as the model put in place to identify the methodological determinants of prevalence in Chapter Three began to explore some of the unexplained variability in the prevalence of MDD by quantifying how much of the variability in the prevalence of MDD reported between studies was 'real' and how much could be explained by methodological factors. With only 57.7% of variability in prevalence explained by this model, there is scope to further explore how other ecological factors can impact on the prevalence of MDD. Aside from adding to the epidemiological profile of MDD, this work offers potential and possibilities for the prevention of MDD.

What do we know about the risk factors of major depressive disorder?

Risk factors can be classed into categories such as biological, psychosocial, economic or environmental. Although there have been a number of such variables identified as risk factors for MDD (20-25), for most of them, there are insufficient data to fully quantify their association with MDD. Furthermore, the majority of this research focuses on symptoms of depression (rather than a clinical diagnosis of MDD) from which the association between a risk factor and MDD can be overestimated.

Examples of potential socioeconomic or environmental risk factors for MDD are linked to macro-issues such as economic instability, poverty, war and inequity. Individuals living in poor socioeconomic conditions have been found to have higher levels of psychiatric symptoms including depression (219). However, as these individuals have limited access to resources (e.g. food, shelter, education, health) and often live without the basic liberties (e.g. freedom of speech or choice) found in populations living in higher socio-economic conditions, it is difficult to identify which of these factors are directly associated with MDD (20-25).

Analysis of MDD prevalence in Chapters Three and Four contributed to this work by exploring the extent to which war and conflict impacted on the distribution of MDD. The significant association between exposure to war or conflict and an elevated risk of MDD has been well established (147, 148, 167, 168, 220). Additionally, the work presented in Chapters Three and Four showed that countries containing populations at war or conflict displayed higher rates of MDD compared to other countries. Although this assisted in explaining some of the variability in the prevalence of MDD between countries, the estimation of prevalence at the country level likely diluted the effect of conflict on the prevalence of MDD given the more localised geographical nature of many conflicts. For a more in-depth understanding of the effect of war or conflict on the distribution of MDD, a post-doctoral avenue for research collaboration (discussed in the next chapter) has been developed to investigate the distribution of MDD within specific conflict affected populations.

Examples of biological or psychosocial risk factors can be hereditary, hormonal, interpersonal or related to one's lifestyle (20-25). Imbalances in the production or transmission of neurotransmitters (e.g. serotonin, dopamine, noradrenaline) are postulated in individuals diagnosed with MDD but a biological marker for the occurrence of MDD has yet to be identified (20-25). Similarly, there is literature to suggest that lifestyle factors such as diet, sleep and exercise are associated with MDD although the underpinnings of these risk factor and their association with MDD have yet to be fully quantified (221).

CSA and IPV have also been identified as risk factors for MDD. Longitudinal studies have provided evidence for a statistically significant association between CSA and IPV (respectively) and incident MDD (10, 222-225). This includes evidence from longitudinal twin studies (which typically offer the best means of detecting confounding effects between early life risk factors) showing a causal link between traumatic events and an increased risk of MDD (97-99). GBD 2010's review of the published and unpublished literature for risk factor-outcome pairings for which there was sufficient evidence to estimate attributable burden included only CSA and IPV as risk factors for MDD (10). Merits for inclusion were assessed using criteria (e.g. 1. relevance of the risk factor to disease burden or policy; 2. availability of data to estimate the global distribution of the risk factor and effect sizes; 3. availability and strength of the evidence for causal effects) which were in line with accepted frameworks for establishing causality in epidemiological research (86). CSA was defined as all forms of sexual abuse occurring before the age of 18. This included both contact forms (e.g. rape) and non-contact forms (e.g. non-contact exposure of genitalia, threatened sexual violence) (226, 227). IPV was defined as physical and/or sexual violence perpetrated since the age of 15 by a current or ex-intimate partner (227).

How can abuse and violence impact on the distribution of major depressive disorder?

In GBD 2010, CRA methodology was used to quantify the global proportion of MDD cases attributable to CSA and IPV respectively (10). As explained in Chapter Six, this methodology makes use of a 'hypothetical minimum' as an alternative distribution of exposure against which loss of health can be quantified. In this instance, the proportion of MDD prevalent cases averted given a counterfactual absence of ever having experienced CSA or IPV was investigated (10). Findings showed that CSA accounted for 5.1% and IPV for 11.4% of MDD DALYs respectively (10).

In many countries, particularly low- to middle-income countries where there are high levels of gender inequality, women are considerably more likely to be exposed to CSA and IPV than men. Furthermore, women are likely to experience more chronic patterns of abuse and violence, more controlling and threatening behaviour and are more likely to be injured and killed by abuse and violence than men (100-102). Consequently, it is conceivable that the sex difference in exposure to CSA and IPV also impacts on the sex difference in MDD.

One of the most robust (103-110, 228, 229) and cited (230) findings in mental health epidemiology is that MDD is up to 2 times more prevalent in females compared to males. This sex-difference typically emerges during adolescence, and is driven by incident depression rather than differences across its duration or reoccurrence (103, 105, 106). However, despite the consistency of this finding across countries and ethnicity, we are yet to fully understand why it exists (103, 104, 106). Although there is sufficient evidence to rule out artefactual factors (e.g. differences in help-seeking behaviour and bias in recall and measurement) as the only explanation to the sex difference in depression, the remaining explanations are inconsistent and difficult to interpret (103, 107-110).

Reviews of this literature suggest that the sex difference in the prevalence of MDD can be best explained through an integrated etiological model comprising biological, social and psychological risk factors (103, 107-110). Women have a greater vulnerability to depression during the reproductive years, which could be due to psychosocial or biological factors, or a combination of these factors. Biologically, gonadal hormones and associated biological changes with puberty and/or pregnancy may increase vulnerability to depression. Psychosocially, gender-role stereotypes, discrimination and exposures to traumatic life events differ between men and women. Adverse life events such as trauma activate stress hormones which in turn modulate central neurotransmissions, including serotonin, a neurotransmitter linked to depression (103, 107). Furthermore, women suffer more of the socioeconomic disadvantages associated with depression, which along with role limitations and expectations reduce feelings of mastery and control, further increasing their

likelihood of depression (108, 110, 231-235). That said, causal pathways between these risk factors and the sex difference in depression, or their integration into an etiological model, are far from established. Evaluating the impact of CSA and IPV on MDD can contribute to this work.

CSA and IPV have the potential to alter the sex difference in the distribution of MDD in two ways (1) through sex differences in exposure to CSA and IPV, i.e. more women are exposed to CSA and/or IPV and therefore at greater risk of MDD; and (2) through sex differences in sensitivity to the effects of CSA and/or IPV, for instance women may be more likely than men to develop MDD after being exposed to IPV (236). Although previous endeavours to quantify this association exist, they were typically restricted to sub-clinical presentations of MDD which tend to overestimate the effect of CSA and IPV on clinically diagnosed MDD or, community-level data which were not representative at the national or global level. For instance, Cutler and collaborators' review of the literature showed that in spite of significant variability and data limitations, up to 35% of the sex difference in depression could be explained by CSA alone (237). Dunn and collaborators' investigations of data from 5,692 participants in the US' National Comorbidity Survey Replication, found that adjusting for exposure to sexual assault and rape, led to a 15.2% and 12.6% reduction respectively in effect-size between sex and the distribution of depression (236).

A working example quantifying the impact of abuse and violence on major depressive disorder

In keeping with the analytical approach presented in previous chapters, we make use of GBD 2010 CRA methods (10) here to quantity the potential impact of CSA and IPV on the sex difference in MDD. This work has been titled as a 'working example' because in some instances, we have relied on assumptions or the substitution of less ideal data due to the lack of the required data to derive estimates. Given these caveats, this working example represents a preliminary analysis of the effect of CSA and IPV on the sex difference in MDD. As was the case for conflict as a risk factor for MDD, the work on CSA and IPV as risk factors for MDD highlights a post-doctoral avenue for research to be supplemented as more and better quality data are made available.

In this case, the hypothetical minimum required for CRA analyses was the proportion of MDD prevalent cases averted given a counterfactual absence of ever having experienced CSA and IPV in the population. Given the evidence showing that females who experience CSA are more likely to experience IPV than non-abused females and, those who experience multiple types of abuse including CSA and IPV have a higher risk of MDD than those exposed to only CSA or only IPV (238-242), in the present analysis we chose to investigate the combined effect of CSA and IPV on the sex difference in MDD.

Data sources

Findings from existing reviews of the literature were used to obtain data on the global prevalence of MDD, CSA, and IPV respectively; as well as the effect size of CSA and IPV as risk factors for MDD.

The prevalence distribution of MDD (as estimated by DisMod-MR) was obtained from Chapter Four. Equivalent DisMod-MR prevalence data for CSA and IPV were obtained from published works of GBD 2010 (175, 226, 243). DisMod-MR prevalence was derived using data from published systematic reviews of the literature to capture studies reporting on the point prevalence, incidence, remission, duration, and excess-mortality of MDD (reported in Chapters Three and Four); and the lifetime prevalence of CSA and IPV respectively (150, 175, 226, 243). DisMod-MR, GBD 2010's Bayesian meta-regression tool was used to pool these epidemiological estimates into an internally consistent epidemiological model which also adjusted for study- and country-level variability in the input data and predicted epidemiological estimates for countries with no data (13, 154). The global DisMod-MR prevalence estimates for CSA, IPV and MDD used here have been summarised in table 12.

Table 12. DisMod-MR global prevalence of MDD, CSA and, IPV by sex.

	Prevalence % (95% Uncertainty interval)	
	Female	**Male**
MDD[a]	5.5% (5.0%-6.0%)	3.2% (3.0% 3.6%)
CSA[b]	8.2% (8.0%-8.5%)	5.5% (5.3%-5.6%)
IPV[b]	29.4% (27.7%-31.2%)	-

Note. Prevalence estimates presented for 2010; DisMod-MR modeled the [a]point prevalence of MDD and the [b]lifetime prevalence of CSA and IPV; IPV prevalence was estimated for females only; Source of data: GBD 2010 analysis of DisMod-MR prevalence output by age, country and region (10, 13, 175, 243).

We made use of pooled RR estimates quantifying the risk of MDD in those experiencing CSA and/or IPV from the two published systematic reviews and meta-analyses (222, 224). Devries and collaborators' meta-analysis of CSA as a risk factor for MDD included 16 studies and produced a pooled RR of 1.7 (1.5-1.9) (226). Beydoun and collaborators' meta-analysis of IPV as a risk factor for MDD included 34 studies and produced a higher pooled RR of 2.7 (2.2-3.3) (222). Studies were accepted if they used a case cohort/series design and representative samples of the previous population. Cases of MDD, CSA and IPV were included based on the case definitions previously presented. Final estimates were adjusted for the quality of the definition of CSA/IPV used. Estimates derived from sub-clinical presentations of depression (depressive symptoms rather than DSM/ICD diagnoses) were not included to avoid an overestimation of the effect of CSA and IPV on MDD.

Paucity in the risk data constrained the scope of the rest of the analyses. Although the DisMod-MR prevalence data points were stratified by age, sex, country and region, all analyses were restricted to the global level, for all age groups combined, as there were insufficient data to quantify changes in the risk of MDD after CSA and IPV by country, region, or age. Similarly, the same pooled RR of MDD given exposure to CSA was applied to males and females as there was no statistically significant sex difference detected in the risk of MDD (226). For IPV, the pooled RR estimate was based on data for females (222). For the purposes of this paper, the risk of MDD after IPV in males was set to 1 based on insufficient evidence for a statistically significant association between IPV and MDD in males (100-102). A literature review by Devries and colleagues (224) investigating the effect of IPV on the incidence of depressive symptoms found no clear evidence for a relationship between IPV and depressive symptoms in males, however very few studies reported data for males. In many countries, particularly low to middle income countries where there are high levels of gender inequality, women are considerably more likely to be exposed to IPV than men. Furthermore, whilst both men and women are exposed to IPV, the type of violence experienced and their reactions can be different (100-102). Findings from a self-administered survey among university students from North-East Italy showed that whilst exposure to IPV can lead to a statistically significant increase in depressive symptoms in women, this was not the case in men where the only significant health outcome was an increase in negative self-evaluations of health (101).

Accounting for dual exposure to child sexual abuse and intimate partner violence

To prevent any double counting of females with a history of both CSA and IPV, we estimated the prevalence and risk of MDD after single and after dual exposure to CSA and IPV.

The DisMod-MR prevalence output for CSA and IPV were not adjusted for dual exposure, i.e. the prevalence of CSA also contained those experiencing IPV and vice versa. We made use of data from the WHO multi-country study on women's health and domestic violence (244) which conducted standardised population-based household surveys of women aged 15–49 years from 10 different countries to collect data on their experiences of physical and sexual abuse. Of the 24097 women surveyed, 2387 of them had experienced both CSA and IPV (245). Meta-XL (a meta-analysis add in tool for Microsoft Excel (197)), was used to pool the proportion of women with lifetime experience of IPV or CSA who have dual exposure across the 10 countries surveyed based on a quality-effects model (198-200). The quality-effects model gives greater weighting to estimates of higher quality versus those of lower quality and avoids the limitation in random-effects models of returning to equal weighting irrespective of sample size if heterogeneity is large (198-200). Quality was assessed following a previously established quality index for epidemiological surveys (246), with the quality rankings summarised in table 13. Assuming no differences between world regions, the pooled proportions of cases of IPV also experiencing CSA were used to derive the prevalence of dual exposure to CSA and IPV which was then subtracted from the DisMod-MR CSA and IPV prevalence estimates (presented in Table 12) to derive the prevalence of single exposures (i.e. CSA only and IPV only; see Figure S1, Appendix Six for an illustration of this).

As was the case for prevalence, the previously reported pooled RRs of MDD after exposure to CSA and IPV (222, 224) needed to be adjusted for dual exposure. In a two-step process we estimated the equivalent effect of a change in psychological functioning (mean score of depression) after dual exposure to CSA and IPV on the reported pooled RRs. At step one we made use of data presented by Messman-Moore and collaborators (241) showing differences in women's mean depression scores after no exposure to CSA or IPV (control group), exposure to IPV only, CSA only, or CSA and IPV combined (see table 14). Based on an approach presented in the Australian Burden of Disease Study (247) and the South African Burden of Disease Study (248), the reported mean depression scores and SEs (241) were used to calculate Hedges' adjusted g for the standardized mean difference (an effect size) (249) which were then converted into, first ORs (250, 251) then RRs (252, 253) of depression for each exposure group. At step two, these RRs along with the estimated prevalence of dual exposure to CSA and IPV were used to proportionately redistribute the pooled RR of MDD after CSA (from Devries and collaborators (226)) and after IPV (from Beydoun

and collaborators (222)) into three separate RRs quantifying the risk MDD after CSA only, IPV only and CSA and IPV combined.

Estimating population attributable fractions

The estimated RRs of MDD given CSA only, IPV only, and CSA and IPV combined were paired with their corresponding prevalence estimates to calculate PAFs using the following formula (10, 254)

$$PAF = \frac{P(RR-1)}{P(RR-1)+1}$$

Where, 'P' is the prevalence of exposure to the risk factor and 'RR' is the relative-risk of MDD given CSA and IPV from published meta-analyses, adjusted for dual exposure to CSA and IPV. PAFs were applied to prevalent cases of MDD to estimate male and female MDD cases attributable to CSA and IPV worldwide.

Estimating uncertainty

Monte Carlo simulation–modelling techniques were used to present uncertainty ranges around point estimates reflecting the main sources of sampling uncertainty in the calculations using Ersatz software version 1.2 (255). Beta distributions were specified for prevalence estimates. For the RR input variables we used the Ersatz function "ErRelativeRisk" (255).

Table 13. Proportion of females with lifetime experience of IPV or CSA who also have dual exposure to both CSA and IPV.

Setting	**Sample size**	**CSA cases (% also experiencing IPV, 95% uncertainty interval)**	**IPV cases (% also experiencing CSA, 95% uncertainty interval)**	**Quality score (/1)**
Bangladesh city	1,603	406 (69.4%, 60.5%-79.3%)	733 (38.5%, 34.2-43.5)	0.9
Bangladesh province	1,527	448 (78.1%, 69.1%-87.8%)	820 (42.7%, 38.3-47.2)	0.9
Brazil city	1,172	139 (43.2%, 31.6%-56.4%)	272 (22.1%, 16.4-28.6)	0.9
Brazil province	1,473	179 (57.0%, 45.1%-72.0%)	438 (23.3%, 18.9-28.5)	0.9
Ethiopia province	3,016	1137 (70.9%, 65.5%-76.6%)	1602 (50.3%, 46.9-53.9)	0.8
Japan city	1,371	135 (27.1%, 18.8-38.0)	196 (18.9%, 13.0-26.0)	0.7
Namibia city	1,500	130 (51.5%, 38.1-67.9)	491 (13.6%, 10.6-17.3)	0.8
Peru city	1,414	317 (57.7%, 48.8-68.4)	556 (32.9%, 28.1-38.4)	0.9
Peru province	1,837	292 (69.9%, 59.0-82.2)	1,059 (19.9%, 16.8-22.0)	0.9
Samoa SMA	1,640	56 (50.0%, 30.6-77.7)	555 (5.0%, 3.3-7.0)	1
Serbia & Montenegro city	1,456	34 (38.2%, 19.5-68.6)	282 (4.6%, 2.5-7.4)	0.8
Thailand city	1,536	133 (39.0%, 28.0-53.3)	431 (12.1%, 8.9-15.7)	0.9
Thailand province	1,282	86 (56.9%, 39.8-79.7)	485 (10.1%, 7.4-13.3)	0.9
Tanzania city	1,820	171 (45.5%, 34.7-58.2)	596 (13.1%, 10.3-16.1)	0.9
Tanzania province	1,450	125 (60.5%, 45.3-80.3)	702 (10.8%, 8.5-13.3)	0.9
Total	**24,097**	**3,788 (QE: 58.6%, 51.5-65.5;** RE: 55.3%, 46.9-63.5)[a]	**9,218 (QE: 20.4%, 13.8-27.9;** RE:19.5%, 12.4-27.6)[a]	

Note. [a]Estimates were pooled in a meta-analysis with a quality-effects design (QE) and random-effects design (RE) respectively; Pooled proportions of dual exposure from the quality effects model were used in analyses. Pooled proportions from the random effects model have been included for comparison purposes only. Source of data: WHO's multi-country study on women's health and domestic violence (244, 245)

Table 14. Estimating the difference in risk of depression after single, and dual exposure to CSA and IPV.

Step One								
Exposure group	**Reported mean value[a]**		**Reported SE[a]**		**Hedges' adjusted g (effect size)**		**From effect size to OR**	**From OR to RR**
	control	**exposure**	**control**	**exposure**	**Hedges' g**	**SE**	**OR (95% uncertainty)**	**RR (95% uncertainty)**
Child sexual abuse only	0.79	1.03	0.04	0.1	0.35	0.15	1.89 (1.37-2.54)	1.80(1.34-2.36)
Intimate partner violence only	0.79	1.04	0.04	0.05	0.36	0.09	1.92 (1.61-2.28)	1.83 (1.56-2.16)
Child sexual abuse and intimate partner violence	0.79	1.27	0.04	0.09	0.69	0.14	3.52(2.67-4.58)	3.13 (2.45-3.92)

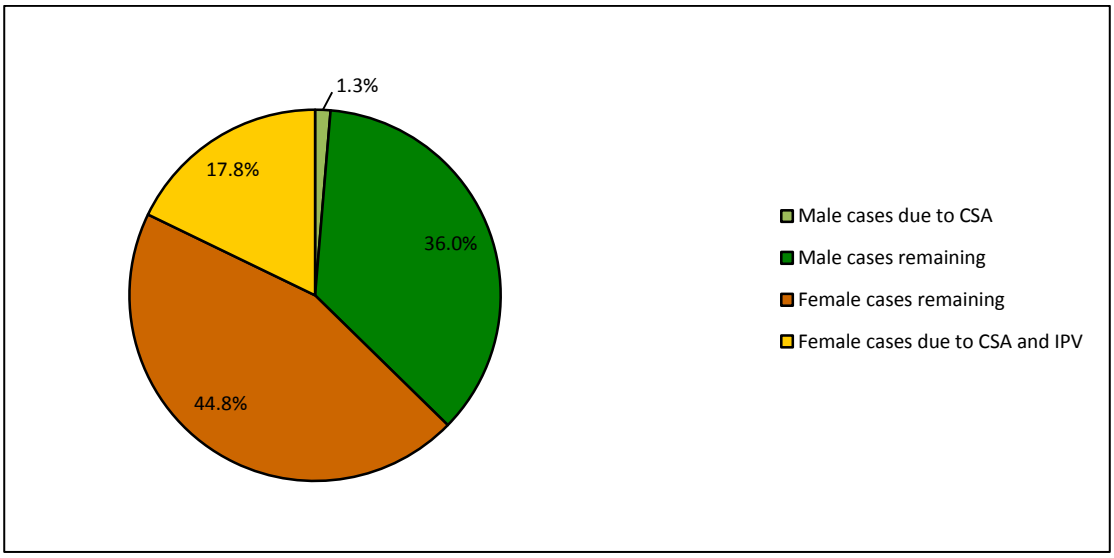
Step Two		
Exposure group	**Reported RR of MDD (not adjusted for dual exposure to CSA and IPV)**	**Adjusted RR of MDD (adjusted for dual exposure to CSA and IPV)**
Child sexual abuse	1.7(1.5-2.0)	1.1 (1.0-1.3)
Intimate partner violence	3.1(2.5-3.9)	2.2 (1.9-2.8)
Child sexual abuse and intimate partner violence	-	3.0 (2.7-3.7)

Note. OR: odds ratio; [a]Source of data: Reported mean differences of depression score (and standard error) (241)

Findings

Globally, there were 298,000,000 prevalent cases of MDD in 2010 of which 187,000,000 were women and 111,000,000 men (175). This was equivalent to 67.9% (95% uncertainty: 59.0%-77.3%) more females diagnosed with MDD than males in 2010.

CSA and IPV explained an estimated 57,000,000 prevalent cases of MDD, equivalent to 19·2% (14·9%-23·2%) of total MDD cases. The majority of cases occurred in females, with CSA and IPV resulting in 53,000,000 females with MDD (equivalent to 28·4% (21·7%-34·9%) of all females with MDD). CSA alone resulted in an additional 4,000,000 males with MDD (equivalent to 3·6% (3·5%-3·7%) of all males with MDD). As previously explained, MDD cases explained by IPV in males was set to 0. Figure 19 illustrates the proportion of MDD cases explained by CSA and IPV.

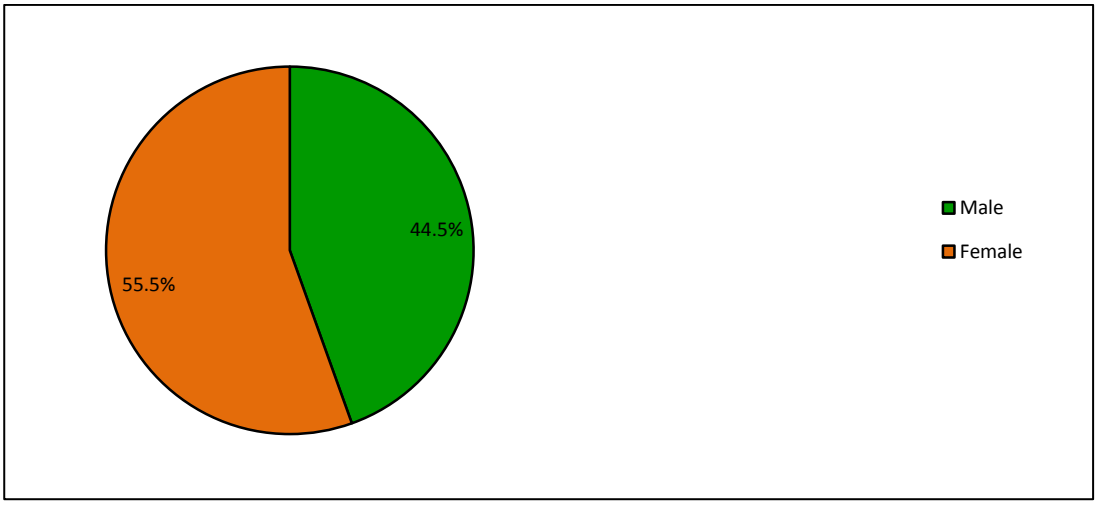


Note. CSA: Child sexual abuse; IPV: intimate partner violence; Cases presented as a proportion of males and female cases of MDD combined.

Figure 19. Global prevalence of MDD in 2010 by sex and the proportion in males and females attributed to CSA and IPV.

In the counterfactual of no exposure to IPV and CSA over the lifetime of the 2010 global population, there would have been 134,000,000 females and 107,000,000 males with MDD (i.e. after accounting for MDD cases attributable to CSA and IPV). There were 24·6% (13·5%-36·5%) more females with MDD than males in this counterfactual of no exposure to IPV and CSA over the lifetime. This was a statistically significant decrease from the baseline estimate of 67·9% (59·0%-77·3%) more females with MDD than males (before accounting for cases due to CSA and IPV). Overall, this translated to CSA and IPV explaining 63·7% (46·2%-80·2%) of the sex difference in

MDD. Figure 20 illustrates the sex difference in MDD after accounting for cases due to CSA and IPV.



Note. This distribution of MDD cases has now been adjusted for the proportion of cases explained by child sexual abuse and intimate partner violence.

Figure 20. Sex distribution in the global prevalence of MDD in 2010, adjusted for CSA and IPV.

Limitations of this work and requirements for more concrete conclusions

Although our findings suggest a statistically significant decrease in the sex difference in MDD after accounting for cases with CSA and IPV, the 95% uncertainty intervals around these estimates were large. Measuring exposures to abuse and violence in the population is challenging and particularly sensitive to methodological factors that impact on the accuracy of participant responses. As such, key limitations and areas of uncertainty need to be considered and explored in further analysis before definite conclusions can be drawn surrounding the extent to which CSA and IPV explain the sex difference in MDD.

- As has been the case in previous publications (224), we found a paucity of data on the health impacts of CSA and IPV in males. There was insufficient evidence to detect a significant sex difference in the association between CSA and MDD. Additionally, there was no clear evidence in the literature to suggest an association between IPV and MDD in males (224). The gaps in the current research base required the use of past conventions (10) in setting the number of male cases of MDD explained by IPV to 0 which may have overestimated the extent to which IPV explained the sex difference in MDD. That said, the literature that is available suggests that although IPV can affect both males and females, globally, it is more common in females. Females are also more likely to experience more severe forms of IPV. For instance, they are likely to experience more chronic patterns of violence, more

controlling and threatening behavior and are more likely to be injured and killed by their intimate partners (256, 257). In view of this, it is plausible that females are disproportionately at risk for MDD from IPV. There is also evidence to suggest that males and females respond differently to experiences of IPV (100-102), which may further explain the lack of an association between IPV and MDD in males. However, until more research investigating the association between IPV and MDD in males is made available, these remain hypothetical and our findings need to be interpreted with caution.

- We investigated the combined (rather than individual) effect of CSA and IPV on the sex difference in MDD. This was in response to evidence showing that females who experience CSA are more likely to experience IPV than non-abused females (238-242), and those who experience multiple types of abuse, including CSA and IPV, have a higher risk of MDD than those exposed to only CSA or only IPV. Based on previously outlined definitions, individuals are first exposed to CSA during early childhood and IPV from 15 years onwards. As such, it may be argued that CSA rather than IPV is the critical risk factor to the sex difference in MDD. On the other hand, we found that IPV (1) had a higher global prevalence compared to CSA (29.4% vs. 8.2% in females) and (2) led to a higher risk of MDD after exposure compared to CSA (RR of 2.9 vs 1.8). As these prevalence and RR estimates served as inputs in our CRA analyses, overall IPV would have likely explained a larger proportion of the sex difference in MDD than CSA. More data on differences between the combined and individual health impacts of CSA and IPV by age, is required for us to clarify the impact of only CSA or IPV on the sex difference in MDD.

- The majority of our prevalence data on dual exposure to CSA and IPV came from developing countries and we assumed that the proportion of dual exposure to lifetime experiences of CSA and IPV in females, was globally applicable. Similarly, the data used to estimate the added risk of MDD after dual exposure to CSA and IPV were collected from a single study of psychological functioning among college women in the USA which may not be fully representative of the impact of dual exposure to CSA and IPV on MDD. Though admittedly data were sparse, these adjustments to account for the combined exposure state of having experienced both CSA and IPV were key to avoid overestimating the proportion of MDD cases explained when both of these risk factors are present.

- Finally, the impact of CSA and IPV in females with MDD may be mediated by any number of biological, psychosocial, or cultural factors. There is a need for more integrative models

as it is unlikely the CSA and IPV impact on the sex difference of MDD in isolation. It is conceivable that across cultural settings or the life span, other risk factors (e.g. child physical abuse, emotional abuse and neglect; community violence including adult sexual assault by acquaintances or strangers; and bullying in childhood and adolescence) may impact on the sex difference in MDD. In further elucidating the mechanisms behind sex differences in MDD, future research should also attempt to control for the confounding effect of comorbidity (e.g. the confounding or mediating effects of post-traumatic stress disorder or the excess of anxiety disorder in women, both of which are also associated with IPV (77, 235, 258)), differences in psychological coping styles (259, 260), gendered division of labor, gender roles, socioeconomic status, and sex discrimination (108, 110, 231-234, 260). Integrated stress-diathesis models of depression are favored, as the sex gradient in the prevalence of MDD is likely multifactorial and the factors inter-dependent. The present study provides the template from which this work can be done. As more data on the relationship between CSA, IPV and MDD are made available, we can quantify when these two risk factors begin to alter the sex pattern in MDD, how their effect changes across place and time, and how they interact with other risk factors.

Conclusion

Although CSA and IPV are established risk factors for MDD, the present findings also highlight their potentially significant contribution to the sex difference in MDD; an observation which although well cited (230) has yet to be fully explained in the literature. Given the size of the global burden of MDD (190), particularly in females, there is a need to investigate how interventions to ameliorate the increased risk from CSA and IPV can be incorporated into prevention programs for MDD; and also how interventions for the treatment of MDD in women exposed to CSA and IPV can be improved. That said, given the caveats discussed, these findings are preliminary until further research on this topic is accumulated, particularly around how the observed effect of CSA and IPV on the sex difference of MDD interacts with other risk factors and changes across age, place and time. The work presented here provides a template from which such further work can be done. It also adds to the epidemiological model of MDD formulated in this thesis by illustrating how risk factors of MDD can impact on its global distribution and by extension, burden in the population.

Acknowledgements

We would like to acknowledge the work of all GBD 2010 collaborators who participated in the study's epidemiological modelling and comparative analysis work for MDD, CSA and IPV. Dr

Abraham Flaxman, Institute of Health Metrics and Evaluations for his work on DisMod-MR and Roman Scheurer for his assistance is reviewing the literature on CSA and IPV.

Chapter review

Chapter Seven explored risk factors for which there are sufficient data to quantify an association with MDD, discussed how two of these risk factors can impact on the global distribution of MDD and highlighted areas of this literature requiring further research. The data presented here calls for more consideration to be given to experiences of abuse, war and violence when setting intervention and prevention strategies for MDD, particularly for women.

This chapter also concluded the presentation of original data in this thesis. Chapter Eight amalgamates findings across all previous chapters and illustrates how they contribute to the epidemiological profile of MDD. Other implications, limitations and areas for future research are also discussed.

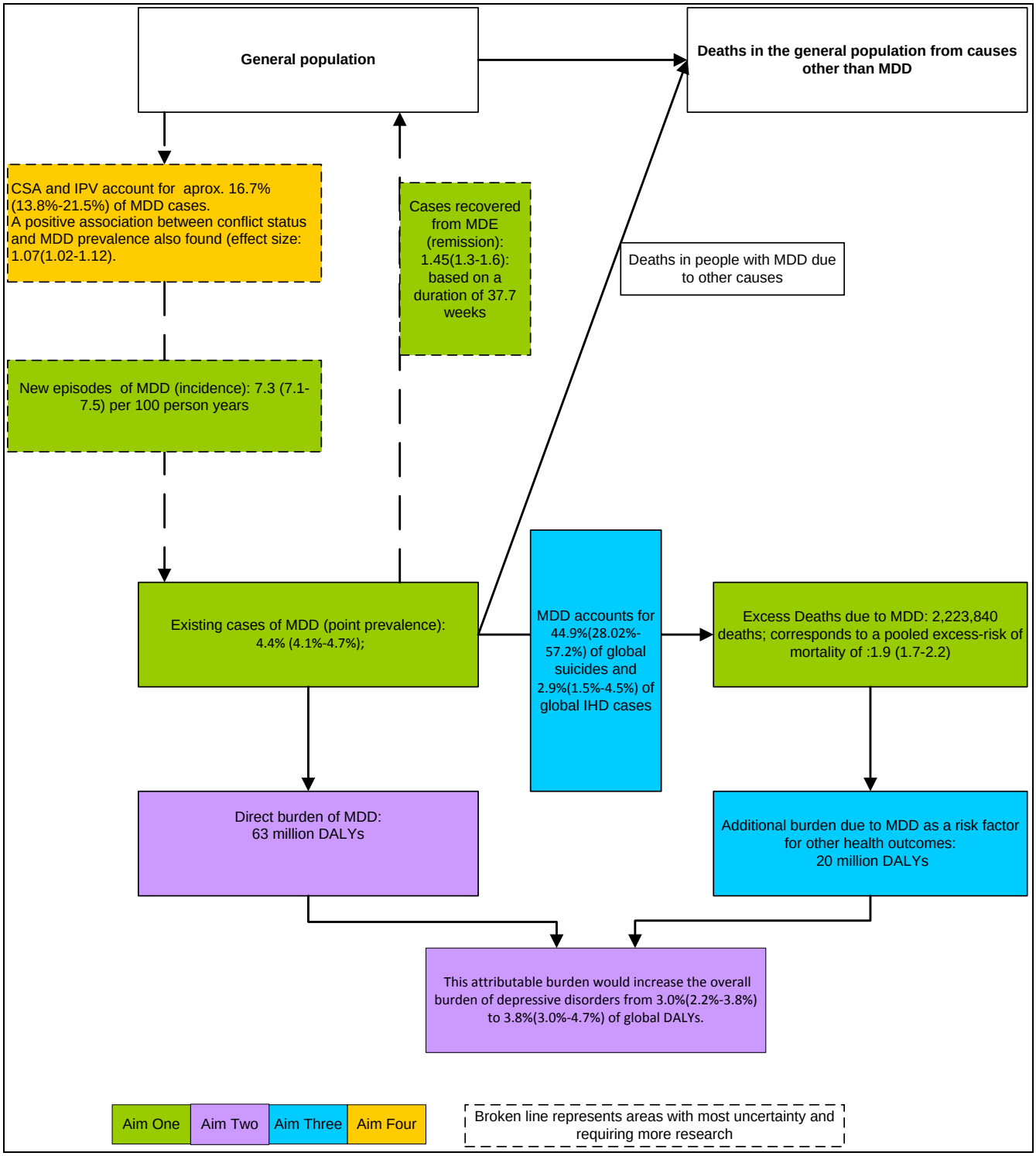
Chapter Eight: Discussion

Chapter summary

The research presented in this thesis focused on formulating a complete epidemiological profile for MDD. Although there is considerable literature on the different elements of the epidemiology of MDD, until now, there has been little effort placed in integrating these into a comprehensive global profile. Such a profile assists in the identification of people in need of prevention and treatment services for MDD. Additionally, policy-makers need to be provided with complete and current information about the nature of the disorder in order to distribute health funds adequately between (1) MDD and other diseases and (2) between the treatment, rehabilitation, prevention, and promotion of MDD (28).

By making use of a systematic review with strict inclusion criteria it was possible to capture data on the prevalence, incidence, duration, and excess-mortality associated with MDD from high quality epidemiological surveys (Chapter Three). Bayesian meta-regression statistical modelling techniques were used to integrate these epidemiological estimates into an internally consistent disease model for MDD and estimate data for parts of the world with little or no raw data available (Chapter Four). This made it possible to quantify the burden of MDD (in terms of DALYs, YLDs, YLLs) by sex, year, age, country and region (Chapter Five). To supplement vital registry data which can only assign deaths due to MDD to the direct physical cause (restricting the estimation of YLLs in Chapter Five), the additional burden attributable to MDD as a risk factor for suicide was also estimated (Chapter Six). To complete the epidemiological profile of MDD, an investigation into the risk factors of MDD was presented, with a working example of how two established risk factors ― CSA and IPV― can impact on the distribution of MDD.

Figure 21 expands on the epidemiological profile presented in figure 1 (Chapter One) using the data compiled in Chapters Three to Seven.



Note. Figure adapted from an existing incidence-prevalence-mortality model (9).

Figure 21. Illustration of the completed epidemiological profile of MDD.

Summary of findings and contributions to the literature

Chapter Three presented on the state of the literature on the global distribution of MDD. A systematic literature review identified 116 prevalence and 4 incidence studies. The majority of the data for prevalence was from Western Europe and North America with much less from Non-Western regions. Overall, 57.7% of the variability between prevalence estimates could be explained by elements of study design and methodology. Whilst there were various naturalistic studies estimating the annual incidence of MDD, very few were follow-up studies based on representative community samples. Although MDD has been defined as an episodic disorder, most incidence studies excluded participants with past episodes of MDD at baseline (63-67). Consequently, annual incidence estimates presented in the litertaure tended to underestimate the true incidence of MDD.

Understanding the global distribution of MDD is central to investigating its health impacts in the population. The analysis of heterogeneity across prevalence highlighted variables that need to be considered in future research involving collection, analysis and interpretation of prevalence data. It also highlighted variability in the prevalence of MDD that was an artefact of differences in data collection and assessment and, alternatively due to 'real' differences in the disorder's epidemiology. The aim of the next chapter was to correct for the former and to retain the latter in order to present a more accurate summary of the global distribution of MDD.

Chapter Four made use of Bayesian meta-regression techniques to model the distribution of MDD while (1) adjusting for known sources of variability and (2) dealing with missing data. Using the data presented in Chapter Three, this model produced estimates of prevalence, incidence, duration, remission and excess-mortality for MDD for 187 countries, 21 regions, males and females, 20 age groups and 3 time points. There were 298 million cases of MDD globally at any point in time in 2010. The global point prevalence was very similar across time (4.4%, 4.2-4.7% in 1990, 4.4%, 4.1-4.7% in 2005 and 2010), challenging previous claims of an 'epidemic' of depression (261). In regards to age and sex differences, females had higher prevalence of MDD (5.5%, 5.0-6.0%) compared to males (3.2%, 3.0-3.6%) and prevalence was lowest, but still evident in early childhood and highest between 20 and 64 years. There was a second peak in prevalence between 75 and 85 years, which further added to our understanding of the distribution of MDD across the lifespan. Historically, individuals aged 75 years or over were not well represented in population surveys which typically excluded people living in aged-care facilities or non-private households (70, 172, 173). As such, the prevalence of MDD in this age group has not always been accurately reflected in summary estimates of prevalence. Prevalence from high-income regions was lower than prevalence from low- to middle-income regions, particularly regions in conflict. Analyses revealed a significant

effect of conflict, whereby populations at war or conflict displayed higher rates of MDD. This further contributed to our knowledge of the risk factors of MDD and drivers of the global differences in its distribution. Modelled prevalence by country also provided the basis from which further research of this effect of conflict could be conducted (182).

To address limitations to the raw incidence data highlighted in Chapter Three, incidence was estimated using data available for the prevalence, duration and excess mortality of MDD. When compared to the raw incidence data, the estimated annual incidence of an episode of MDD was about one and a half times higher, consistent with an average duration of 37.7 weeks (27). Although estimating missing data was less optimal than using high quality raw data, the work presented in Chapter Four enabled all countries and age groups to be included in Chapter Five's burden calculations. This strategy was preferred as not quantifying prevalence would be equivalent to assuming 0% prevalence (and therefore burden) of MDD in countries or age groups where no raw data was available.

Chapter Five identified MDD as the second leading cause of YLDs in 2010, when compared to 290 other diseases and injuries. Although previous estimation of burden exists for MDD, regular updating provides policy makers with a way to keep track of the size of the burden and how it compares with other diseases and injuries. Findings reinforced depression as both a current and future public health priority. Despite of the lack of direct YLLs computed for MDD, it remained a leading cause of DALYs, emphasizing the importance of non-fatal health outcomes in quantifying disease burden. Although the rate of MDD was not increasing between 1990 and 2010, increasing life expectancy due to better reproductive health, nutrition and control of communicable diseases means that more of the population are reaching the age where MDD is most prevalent (5, 6).

A comparison of burden between MDD and dysthymia highlighted MDD as the leading contributor to the burden of depressive disorders, accounting for 85% of its YLDs and DALYs in 2010. This was driven by the high prevalence estimates reported in Chapter Three, and high levels of disability found to be associated with MDD (13). MDD DALY and YLD rates followed the same sex and age pattern seen in the prevalence data, with estimates highest in Afghanistan and lowest in Japan. The capacity to compare burden by country was especially relevant for MDD, which has been linked to risk factors such as conflict (148), IPV (222, 224) and, CSA (224), the levels of which vary between countries. Country-level differences in prevalence and burden estimates for a given disease may also be driven by differences in access and quality of prevention and treatment strategies available. Although it was not possible to fully assess this in the thesis, it is unlikely that differences in prevention and treatment would have considerably impacted on the prevalence and burden of MDD

given that access to treatment remains exceedingly low in low to middle income countries and, even in high income countries, current intervention strategies can only reduce the burden of MDD between 10% to 30% (3, 26, 27).

In addition to burden that can be directly attributed to MDD, Chapter Six quantified the surplus burden due to MDD and other mental and substance use disorders as risk factors for suicide. Mental and substance use disorders were responsible for 22.5 million (14.8-29.8 million) of the 36.2 million (26.5-44.3 million) DALYs allocated to suicide in 2010. This surplus burden elevated them from the 5th to 3rd leading cause of global burden (DALYs). Within mental and substance use disorders, MDD explained almost half of all suicide DALYs (46.1%, 28.0%-60.8%), the highest proportion when compared to all other mental and substance use disorders. Aside from emphasising MDD as a debilitating disorder, findings emphasized the importance of prioritising the prevention, early detection and effective management of MDD as a key suicide prevention strategy. They also illustrated how the lack of direct YLLs estimated for mental and substance use disorders in GBD 2010 should not be interpreted as having little or no excess risk of mortality in those with these disorders.

Chapter Seven explored the risk factors of MDD, an area of this disorder's epidemiology for which there is a paucity of high quality, quantitative data. War or conflict, CSA, and IPV (all potentially avertable risk factors) were discussed as risk factors for which there was sufficient evidence to infer a positive association with MDD. A working example investigating the impact of CSA and IPV on the sex difference in MDD showed that these two risk factors combined had the potential to explain up to 63·7% (46·2%-80·2%) of the sex difference in MDD however this estimate is preliminary and subject to change as further research is accumulated. Nonetheless, having presented on the ubiquitous burden associated with MDD in previous chapters, the data presented here provides an opening for the further development of prevention and intervention strategies for MDD. They also add to existing aetiological models for MDD (103, 107-110) by further elucidating mechanisms behind its occurrence.

Translating research into practice

Having established the global distribution and size of the burden associated with MDD, the next logical question is how can we use this data to reduce the burden of MDD? Reduction in disease burden can be reached by: (1) decreasing incidence, (2) decreasing duration, (3) reducing disorder severity, and (4) reducing the number of deaths due to the disorder (19, 28). Although a

comprehensive service system should be equipped to provide evidence-based interventions targeting each of these avenues for burden reduction, this is rarely, if ever, the case for MDD.
Cost-effectiveness analysis is typically used for comparing the cost of a given health intervention against its associated health gains (262). In this case, it can also help inform the allocation of resources between the different approaches (1 to 4 above) to the burden reduction of MDD. In cost-effectiveness analysis, the DALY can be used as a unit of measurement to quantify the proportion of disease burden that can be averted (i.e. the number of DALYs that can be gained) from a given intervention. From this, a dollar value per DALY averted can also be estimated provided there is sufficient cost data available for a given intervention. Such cost-effectiveness analyses of intervention strategies targeting reductions in the duration, severity and deaths associated with MDD exist but as previously mentioned, depending on the population coverage of these strategies, can only reduce burden by 10% to 30% (3, 26, 27). Although this highlights MDD as a condition where disease prevention can be critical, there is also much left to establish by way of effective prevention strategies (28).

In regards to prevention strategies, this thesis highlighted the importance of investigating how interventions to ameliorate the increased risk from abuse and violence can be incorporated into prevention programs for MDD. These could include parenting, social and gender norm change interventions to reduce violence against children and women (263). Findings also highlighted the importance of considering the role of CSA and IPV in the clinical formulation and treatment planning of MDD. There is evidence linking a history of childhood trauma and abuse to earlier onset and more chronic forms of depression, longer episode duration (264-267) and, poorer response to psychological and pharmacological treatments (268, 269). As such, for women diagnosed with MDD, there may be value in considering their lived experience and social context when delivering depression-focused psychotherapies to address not just their symptoms but also their response to any specific contributing adverse life event.

In regards to reducing the number of deaths associated to MDD, Chapters Four and Five highlighted the importance of prioritising the prevention, early detection and effective management of MDD as suicide and IHD prevention strategies. Such strategies can be ‘selective’ and target those in the population who have yet to display suicidal behaviour or symptoms of IHD but have been diagnosed with MDD hence are at risk to do so; ‘universal’ and target the entire population with the aim of favourably shifting proximal and distal risk (and protective) factors across the entire population; or ‘indicated’ which specifically targets individuals already exhibiting suicidal behaviours or symptoms of IHD (210).

Presenting findings at the age, sex, and country level facilitated the selection and tailoring of intervention strategies for MDD. For instance, by estimating prevalence and disease burden for the entire lifespan, ages at which intervention would be most beneficial can be elucidated. The prevalence of MDD was evident from the ages of three onwards, but peaked during early adulthood. This provided further rationale for setting early intervention strategies for MDD. There is evidence to suggest that the integration of stress, anxiety and depression management courses into high school curriculums can be effective in preventing depression but further research is needed for clearer conclusions (270). The impact of conflict on MDD also highlighted populations most in need of global resources for MDD. Using data from Chapter Four, Charlson and collaborators estimated the required service response to severe presentations of MDD and PTSD in a post conflict Libyan population. Based upon service coverage targets, approximately 154 full-time equivalent staff would be required; an amount which would involve substantially more resources to be designated to mental health in the region than what is currently available (182).

Strengths and limitations of the evidence

A key constraint in this thesis was the lack of raw epidemiological data available for MDD. Bounds of uncertainty were estimated for all high level findings in the thesis. It is important to consider these when interpreting findings, particularly where missing data were most apparent. For instance, when interpreting the modelled incidence output in Chapter Four which was entirely estimated using data from other epidemiological parameters; when comparing differences in prevalence and burden between countries, particularly from less developed parts of the world; and when examining the risk factors of MDD. Although there were a number of ecological variables linked with the occurrence of MDD, there were sufficient data to quantify an association between war or conflict, CSA, and IPV (respectively) and MDD. Although a working example of the extent to which CSA and IPV could impact on the sex difference in MDD was presented, this work needs to be interpreted with caution given the lack of data available for (1) CSA and IPV in males and (2) the impact of other risk factors which are yet to be established.

The definition of MDD used in this thesis was restricted to cases meeting clinical diagnosis using DSM and ICD criteria (38, 39). This was done to ensure consistency and comparability between estimates. That said, DSM and ICD definitions of MDD are predominantly based on Western presentations of the illness and may not be sensitive to its cross-cultural presentations (4, 52, 120). For instance, some languages do not include words to describe concepts such as ‘sadness’ or ‘depression’. As such, it is likely that epidemiological surveys in these cultures attributed cases of

MDD to other illnesses (8, 32, 271), which would have underestimated its occurrence and burden. Further research into the cross-cultural validity of DSM/ICD diagnostic criteria is essential for clearer conclusions. Furthermore, included epidemiological data were based on either DSM-IV-TR, ICD-10 or earlier versions of DSM and ICD. As new population surveys of MDD using DSM-5 diagnoses are made available, the impact of DSM-5 diagnostic criteria (43) on the epidemiological profile of MDD presented here will require further investigation.

The accuracy of burden estimates relied on the representativeness of disability weights estimated for MDD by GBD 2010's disability weights survey (12). This pairwise comparison of health states required lay vignettes of no more than 35 words in length for each condition which may not have been sufficient to capture all participants' experiences of MDD. Furthermore, disability and health states in GBD 2010 intended to capture 'within the skin' loss to health, welfare loss was not considered. This is a significant omission for MDD where effects of the illness extend to economic, social, and academic functioning. Although it is outside the scope of GBD studies to consider welfare loss to health as this largely obscures the comparability of burden estimates between settings; replication of the disability weights survey, testing the effect of different lay descriptions of health states, as well as their validity between countries is required.

The effect of MDD on suicide and IHD and similarly, the effects of CSA and IPV on MDD were quantified using CRA methodology which stipulates that attributable burden is estimated while holding all other independent risk factors constant (10). In reality, the effect of CSA and IPV on MDD and similarly, MDD on suicide and IHD may be multifactorial and the factors inter-dependent. In further elucidating the epidemiological profile of MDD, future research should explore the effects of other biological, psychosocial, environmental or economic factors. This thesis makes available a template from which this work can be done.

Avenues for future research

This thesis brought together data on the epidemiology of MDD, including the estimation of burden for MDD. Responses to findings thus far have been positive with several avenues for further research already underway. Prevalence output from Chapters Three and Four have facilitated further investigation into the global availability of epidemiological data for mental disorders and how this changes across the lifespan (272, 273); time trends in the prevalence of common mental disorders (261); and the distribution of MDD in conflict affected populations (182). The published systematic review of prevalence and incidence data from Chapter Three was ranked as one of the most cited papers published in Psychological Medicine for the year 2013 (274).

Burden estimates from Chapter Five also received considerable interest from the media (see Text S1, Appendix Seven) and are currently being used in the 3rd Edition of Disease Control Priorities in Developing Countries (DCP3) Project. DCP3 is aimed at evaluating the cost and effectiveness of interventions for leading causes of disease burden which will also facilitate the calculation of up to date estimates of dollars per DALY averted for MDD (273). The work presented in Chapter Seven provided post-doctoral avenues for research pertaining to the quantification of other risk factors of MDD and the extent to which they impact on its distribution. For example, other forms of abuse are now being investigated as risk factors for MDD (275), an area of research which can further contribute to the working example of CSA and IPV as risk factors for MDD and ultimately, the setting of effective prevention strategies for MDD.

In order to remain up to date with the literature and provide decision-makers with the most representative picture of their population's health, the process of estimating disease burden is constantly evolving. For instance, burden of disease inputs presented in Chapters Three to Five also featured in WHO's recently published global burden of disease estimates (also termed 'global health estimates') for 2002-2011 (276). WHO's iteration of burden of disease estimates drew on data and methodology used in GBD 2010 with some key revisions made to GBD 2010's method for a number of causes. Although final DALY rankings changed given changes made to other causes, estimated DALYs for depressive disorders were derived using GBD 2010 inputs and hence were very similar to the DALYs reported here (Chapter Five reported 74.3 million DALYs in 2010 and WHO reported 74.9 million DALYs in 2011 due to depressive disorders) (276).

IHME which lead the GBD 2010 initiative has also endeavoured to make available yearly burden of disease estimates. The next update to burden estimates will be published in late 2014 (GBD 2013). For MDD, this work has been focused on improving some of the issues raised in this thesis. For instance, it will incorporate new data on the distribution of MDD, thereby providing the opportunity to further validate the modelled epidemiological data presented in this thesis, particularly for regions were no raw epidemiological data were available. It will also expand upon the disease modelling strategy to investigate other unexplained sources of variability in the model and ultimately reduce the uncertainty around the prevalence and burden estimates.

Conclusion

The research presented in this thesis reviewed the literature on the global distribution of MDD from which (1) a statistical model of the prevalence, incidence, duration and excess mortality associated with MDD and (2) YLDs due to MDD were generated. CRA methodology was then used to investigate (1) YLDs and YLLs that could be re-assigned to MDD as a risk factor for suicide and IHD and (2) the proportion of MDD prevalent cases that could potentially be explained by CSA and IPV. The epidemiological model compiled as a result of this work showed that MDD is a highly prevalent disorder, leading to an increased risk of mortality. It is present across the lifespan but is more common in females aged 20 to 64 years, from conflict affected populations. High prevalence estimates and disability associated with MDD culminated in it being identified as a significant contributor to the world's disease burden. It was the second leading global cause of non-fatal burden in 2010 and was also a significant contributor the burden assigned to suicide and IHD. These findings emphasize the importance of including MDD as a public-health priority. They also provide several opportunities to set intervention strategies to reduce its ubiquitous burden. For instance, presenting MDD prevalence and burden estimates by age, sex, year, and country facilitates the selection and tailoring of intervention strategies for MDD. Research on the risk factors of MDD also revealed that abuse, war, and violence have the potential to play a significant role in the distribution of MDD. This highlighted the importance of investigating how interventions to ameliorate the increased risk from abuse, war, and violence can be incorporated into prevention programs for MDD. In regards to reducing the number of deaths associated to MDD, findings also highlighted the importance of prioritising the prevention, early detection and effective management of MDD, as suicide and IHD prevention strategies. A key constraint in this thesis was the lack of raw epidemiological data available. Furthermore, the definition of MDD used was restricted to cases meeting clinical diagnosis as per DSM and ICD criteria which may not be fully representative of non-Western presentations of MDD. As more data are made available, the epidemiological profile presented here can be expanded upon to investigate other unexplained sources of variability in the model and, ultimately reduce the uncertainty around estimates presented. This thesis provides the template from which this work can be done.

List of References

1. Murray CJL, Lopez AD, editors. The Global Burden of Disease: a comprehensive assessment of mortality and disability from diseases, injuries, and risk factors in 1990 and projected to 2020. Cambridge: Harvard University Press; 1996.
2. Chisholm D, Diehr P, Knapp M, Patrick D, Treglia M, Simon G. Depression status, medical comorbidity and resource costs. Evidence from an international study of major depression in primary care (LIDO). Br J Psychiatry. 2003;183:121-31.
3. Chisholm D, Sanderson K, Ayuso-Mateos JL, Saxena S. Reducing the global burden of depression: population-level analysis of intervention cost-effectiveness in 14 world regions. Br J Psychiatry. 2004;184:393-403.
4. Wang PS, Angermeyer M, Borges G, Bruffaerts R, Tat Chiu W, G DEG, et al. Delay and failure in treatment seeking after first onset of mental disorders in the World Health Organization's World Mental Health Survey Initiative. World Psychiatry. 2007;6(3):177-85.
5. Murray CJL, Vos T, Lozano R, Naghavi M, Flaxman AD, Michaud C, et al. Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet. 2012;380:2197-223.
6. Salomon JA, Wang H, Freeman MK, Vos T, Flaxman AD, Lopez AD, et al. Healthy life expectancy for 187 countries, 1990–2010: a systematic analysis for the Global Burden Disease Study 2010. Lancet. 2012;380:2144-62.
7. Last JM, editor. A dictionary of epidemiology 4ed. New York: Oxford University Press; 2001.
8. Whiteford1 HA, Ferrari AJ, Baxter AJ, Charlson FJ, Degenhardt L. How did we arrive at burden of disease estimates for mental and illicit drug use disorders in the Global Burden of Disease Study 2010? Current Opinion in Psychiatry. 2013;26(4):376-83.
9. Barendregt JJ, Van Oortmarssen GJ, Vos T, Murray CJ. A generic model for the assessment of disease epidemiology: the computational basis of DisMod II. Popul Health Metr. 2003;1(1):4.
10. Lim SS, Vos T, Flaxman AD, Danaei G, Shibuya K, et al. A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet. 2012;380:2224-60.
11. Lozano R, Naghavi M, Foreman K, Lim S, Shibuya K, Aboyans V, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet. 2012;380:2095-128.
12. Salomon JA, Vos T, Hogan DR, Gagnon M, Naghavi M, Mokdad A, et al. Common values in assessing health outcomes from disease and injury: disability weights measurement study for the Global Burden of Disease Study 2010. Lancet. 2012;380(9859):2129-43.
13. Vos T, Flaxman AD, Naghavi M, Lozano R, Michaud C, Ezzati M, et al. Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet. 2012;380:2163-96.
14. Bonita R, Beaglehole R, Kjellstrom T. Basic Epidemiology. 2nd ed. Geneva: World Health Organization; 2006.
15. Ustun TB, Ayuso-Mateos JL, Chatterji S, Mathers C, Murray CJ. Global burden of depressive disorders in the year 2000. British Journal of Psychiatry. 2004;184:386–92.
16. World Health Organization. The global burden of disease: 2004 update. Geneva: World Health Organization, 2008.
17. Kessler RC, Ustun TB, editors. The WHO World Mental Health Surveys: global perspectives on the epidemiology of mental disorders. New York: Cambridge University Press; 2008.
18. Harris EC, Barraclough B. Excess mortality of mental disorder. British Journal of Psychiatry. 1998;173(JULY):11-53.

19. Whiteford HA, Degenhardt L, Rehm J, Baxter AJ, Ferrari AJ, Erskine HE, et al. The Global Burden of Mental and Substance Use Disorders, 2010. The Lancet. 2013;382(9904):1575-86.
20. Beard JR, Tracy M, Vlahov D, Galea S. Trajectory and socioeeonomic predictors of depression in a prospective study of residents of New York City. Annals of Epidemiology. 2008;18(3):235-43.
21. Colman I, Ataullahjan A. Life Course Perspectives on the Epidemiology of Depression. Can J Psychiatry. 2010;55(10):622-32.
22. Gilman SE, Kawachi I, Fitzmaurice GM, Buka SL. Socioeconomic status in childhood and the lifetime risk of major depression. Int J Epidemiol. 2002;31(2):359-67.
23. Koster A, Bosma H, Kempen GI, Penninx BW, Beekmanb AT, Deegc DJ, et al. Socioeconomic differences in incident depression in older adults: the role of psychosocial factors, physical health status, and behavioral factors. Journal of Psychosomatic Research. 2006;61:619-27.
24. Wang JL, Schmitz N, Dewa CS. Socioeconomic status and the risk of major depression: the Canadian National Population Health Survey. J Epidemiol Community Health. 2010;64(5):447-52.
25. Zimmerman FJK, Katon W. Socioeconomic status, depression disparities, and financial strain: what lies behind the income-depression relationship? . Health Ecconomics. 2005;14:1197-215.
26. Andrews G, Sanderson K, Corry J, Lapsley HM. Using epidemiological data to model efficiency in reducing the burden of depression. The journal of mental health policy and economics. 2000;3(4):175-86.
27. Vos T, Haby MM, Barendregt JJ, Kruijshaar M, Corry J, Andrews G. The burden of major depression avoidable by longer-term treatment strategies. Archives of general psychiatry. 2004;61(11):1097-103.
28. Andrews G. Reducing the burden of depression. Can J Psychiatry. 2008;53(7):420-7.
29. Evans K, McGrath J, Milns R. Searching for schizophrenia in ancient Greek and Roman literature: a systematic review. Acta psychiatrica Scandinavica. 2003;107(5):323-30.
30. Okasha A, Okasha T. Notes on mental disorders in Pharaonic Egypt. History of Psychiatry 2000;11:413–24.
31. Bhugra D, Mastrogianni A. Globalisation and mental disorders. Overview with relation to depression. Br J Psychiatry. 2004;184:10-20.
32. Cheng AT. Case definition and culture: Are people all the same? Br J Psychiatry. 2001;179:1-3.
33. Gureje O, Lasebikan VO, Kola L, Makanjuola VA. Lifetime and 12-month prevalence of mental disorders in the Nigerian Survey of Mental Health and Well-Being. Br J Psychiatry. 2006;188:465-71.
34. Henningsen P, Zimmermann T, Sattel H. Medically unexplained physical symptoms, anxiety, and depression: a meta-analytic review. Psychosom Med. 2003;65(4):528-33.
35. Patel V. Cultural factors and international epidemiology. British medical bulletin. 2001;57:33-45.
36. Patel V, Winston M. 'Universality of mental illness' revisited: assumptions, artefacts and new directions. Br J Psychiatry. 1994;165(4):437-40.
37. Segall MH, Lonner WJ, Berry JW. Cross-cultural psychology as a scholarly discipline. Am Psychol 1998;53:1101–10.
38. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR). Fourth Edition, Text Revision ed. Washington DC: American Psychiatric Association; 2000.
39. World Health Organization. The ICD-10 Classification of Mental and Behavioural Disorders. Clinical descriptions and diagnostic guidelines. Geneva: World Health Organization; 1992.
40. Brown TA, Barlow DH. A proposal for a dimensional classification system based on the shared features of the DSM-IV anxiety and mood disorders: implications for assessment and treatment. Psychological assessment. 2009;21(3):256-71.

41. Kendler KS, Gardner CO, Jr. Boundaries of major depression: an evaluation of DSM-IV criteria. The American journal of psychiatry. 1998;155(2):172-7.
42. Moore MT, Brown TA. Are there meaningful differences between major depressive disorder, dysthymic disorder, and their subthreshold variants? The Journal of nervous and mental disease. 2012;200(9):766-72.
43. American Psychiatric Association. Diagnostic and statistical manual of mental disorders : DSM-5. 5 ed. Washington DC: American Psychiatric Association; 2013.
44. Parker G. Opening Pandora's box: how DSM-5 is coming to grief. Acta psychiatrica Scandinavica. 2013;128(1):88-91.
45. World Health Organization. The International Classification of Diseases 11th Revision is due by 2017 2014. Available from: http://www.who.int/classifications/icd/revision/en/.
46. Ustun TB, Kessler RC. Global burden of depressive disorders: the issue of duration. British Journal of Psychiatry. 2002;181:181–3.
47. Paykel ES, Brugha T, Fryers T. Size and burden of depressive disorders in Europe. Eur Neuropsychopharmacol. 2005;15(4):411-23.
48. Lepine J, Gastpar M, Mendlewicz J, Tylee A. Depression in the community: The first pan-European study. DEPRES (Depression Research in European Society). International Clinical Psychopharmacology. 1997;12(1):19–29.
49. Chiu E. Epidemiology of depression in the Asia Pacific region. Australas Psychiatry. 2004;12 Suppl:S4-10.
50. Weissman MM, Bland RC, Canino GJ, Faravelli C, Greenwald S, Hwu HG, et al. Cross-national epidemiology of major depression and bipolar disorder. JAMA: The Journal Of The American Medical Association. 1996;276(4):293-9.
51. Weich S, Araya R. International and regional variation in the prevalence of common mental disorders: do we need more surveys? Br J Psychiatry. 2004;184:289-90.
52. Bromet E, Andrade LH, Hwang I, Sampson NA, Alonso J, de Girolamo G, et al. Cross-national epidemiology of DSM-IV major depressive episode. BMC medicine. 2011;9:90.
53. Chang SM, Hahm BJ, Lee JY, Shin MS, Jeon HJ, Hong JP, et al. Cross-national difference in the prevalence of depression caused by the diagnostic threshold. J Affect Disord. 2008;106(1-2):159-67.
54. Chen R, Hu Z, Qin X, Xu X, Copeland JR. A community-based study of depression in older people in Hefei, China--the GMS-AGECAT prevalence, case validation and socio-economic correlates. Int J Geriatr Psychiatry. 2004;19(5):407-13.
55. Phillips MR, Zhang J, Shi Q, Song Z, Ding Z, Pang S, et al. Prevalence, treatment, and associated disability of mental disorders in four provinces in China during 2001–05: an epidemiological survey. The Lancet. 2009;373:2041–53.
56. Carta MG, Angst J. Epidemiological and clinical aspects of bipolar disorders: controversies or a common need to redefine the aims and methodological aspects of surveys. Clin Pract Epidemiol Ment Health. 2005;1(1):4.
57. Helzer JE, Robins LN, McEvoy LT, Spitznagel EL, Stoltzman RK, Farmer A, et al. A comparison of clinical and diagnostic interview schedule diagnoses. Physician reexamination of lay-interviewed cases in the general population. Archives of general psychiatry. 1985;42(7):657-66.
58. Jorm AF. National surveys of mental disorders: are they researching scientific facts or constructing useful myths? Aust N Z J Psychiatry. 2006;40(10):830-4.
59. Baxter AJ, Page A, Whiteford HA. Factors influencing risk of premature mortality in community cases of depression: a meta-analytic review. Epidemiology Research International. 2011;2011(Article ID 832945):12 pages.
60. Cuijpers P, Smit F. Excess mortality in depression: a meta-analysis of community studies. J Affect Disord. 2002;72(3):227-36.
61. van den Akker M, Schuurman AG, Ensinck KT, Buntinx F. Depression as a risk factor for total mortality in the community: a meta-analysis. Archives of Public Health. 2003;61(6):313-32.

62. Wulsin LR, Vaillant GE, Wells VE. A systematic review of the mortality of depression. Psychosom Med. 1999;61(1):6-17.
63. Alhasnawi S, Sadik S, Rasheed M, Baban A, Al-Alak MM, Othman AY, et al. The prevalence and correlates of DSM-IV disorders in the Iraq Mental Health Survey (IMHS). World Psychiatry. 2009;8(2):97-109.
64. Eaton WW, Kramer M, Anthony JC, Dryman A, Shapiro S, Locke BZ. The incidence of specific DIS/DSM-III mental disorders: data from the NIMH Epidemiologic Catchment Area Program. Acta psychiatrica Scandinavica. 1989;79(2):163-78.
65. Lewinsohn PM, Hops H, Roberts RE, Seeley JR, Andrews JA. Adolescent psychopathology: I. Prevalence and incidence of depression and other DSM-III-R disorders in high school students. J Abnorm Psychol. 1993;102(1):133-44.
66. Mogga S, Prince M, Alem A, Kebede D, Stewart R, Glozier N, et al. Outcome of major depression in Ethiopia: population-based study. Br J Psychiatry. 2006;189:241-6.
67. Patten SB. The duration of major depressive episodes in the Canadian general population. Chronic Dis Can. 2001;22(1):6-11.
68. Spijker J, de Graaf R, Bijl RV, Beekman AT, Ormel J, Nolen WA. Duration of major depressive episodes in the general population: results from The Netherlands Mental Health Survey and Incidence Study (NEMESIS). Br J Psychiatry. 2002;181:208-13.
69. Brhlikova. P, Pollock. AM, Manners R. Global Burden of Disease estimates of depression – how reliable is the epidemiological evidence? Journal of the Royal Society of Medicine. 2010;104:25-35.
70. Copeland JRM, Beekman ATF, Dewey ME, Hooijer C, Jordan A, Lawlor BA, et al. Depression in Europe. Geographical distribution among older people. British Journal of Psychiatry. 1999;174(APR.):312-21.
71. World Bank. World Development Report 1993. Investing in health: World development indicators. New York: World Bank,, 1993.
72. Murray CJL, Salomon JA, Mathers C. A critical examination of summary measures of population health. Bulletin of the World Health Organisation. 2000;78(8):981-94.
73. Ayuso-Mateos JL. Global burden of bipolar disorder in the year 2000: Version 1. World Health Organization, 2000.
74. Prince M, Patel V, Saxena S, Maj M, Maselko J, Phillips MR, et al. No health without mental health. The Lancet. 2007;370:859–77.
75. Patten SB, Bilsker D, Goldner E. The evolving understanding of major depression epidemiology: implications for practice and policy. Can J Psychiatry. 2008;53(10):689-95.
76. Kruijshaar ME, Hoeymans N, Spijker J, Stouthard ME, Essink-Bot ML. Has the burden of depression been overestimated? Bull World Health Organ. 2005;83(6):443-8.
77. Breslau N, Peterson EL, Schultz LR, Chilcoat HD, Andreski P. Major depression and stages of smoking. A longitudinal investigation. Archives of general psychiatry. 1998;55(2):161-6.
78. Dierker LC, Avenevoli S, Stolar M, Merikangas KR. Smoking and depression: an examination of mechanisms of comorbidity. The American journal of psychiatry. 2002;159(6):947-53.
79. Scott KM, McGee MA, Oakley Browne MA, Wells JE, New Zealand Mental Health Survey Research T. Mental disorder comorbidity in Te Rau Hinengaro: the New Zealand Mental Health Survey. Aust N Z J Psychiatry. 2006;40(10):875-81.
80. Roeloffs CA, Fink A, Unutzer J, Tang L, Wells KB. Problematic substance use, depressive symptoms, and gender in primary care. Psychiatric services. 2001;52(9):1251-3.
81. Degenhardt L, Hall W, Lynskey M, Coffey C, Patton G. The association between cannabis use and depression: a review of the evidence. In: D.J. C, Murray R, editors. Marijuana and Madness: Psychiatry and Neurobiology. NY, USA: Cambridge University Press; 2004.
82. Harris EC, Barraclough B. Suicide as an outcome for mental disorders: A meta-analysis. British Journal of Psychiatry. 1997;170:205-28.

83. Li Z, Page A, Martin G, Taylor R. Attributable risk of psychiatric and socio-economic factors for suicide from individual-level, population-based studies: a systematic review. Soc Sci Med. 2011;72(4):608-16.
84. Gross AL, Gallo JJ, Eaton WW. Depression and cancer risk: 24 years of follow-up of the Baltimore Epidemiologic Catchment Area sample. Cancer causes & control : CCC. 2010;21(2):191-9.
85. Charlson FJ, Stapelberg NJC, Baxter A, Whiteford HA. Should Global Burden of Disease Estimates Include Depression as a Risk Factor for Coronary Heart Disease? BMC medicine. 2011;9(47):1-6.
86. Bradford-Hill A. The environment and disease: association or causation? . Proc R Soc Med 1965;58:293-300.
87. Hofler M. The Bradford Hill considerations on causality: a counterfactual perspective. Emerg Themes Epidemiol. 2005;2:11.
88. Baxter AJ, Charlson FJ, Somerville AJ, Whiteford HA. Mental disorders as risk factors: assessing the evidence for the global burden of disease study. BMC medicine. 2011;9(134):1-7.
89. Charlson FJ, Moran AE, Freedman G, Norman RE, Stapelberg NJC, Baxter AJ, et al. The contribution of major depression to the global burden of ischaemic heart disease: a comparative risk assessment. BMC medicine. 2013;11(250):doi: 10.1186/741-7015-11-250.
90. Arsenault-Lapierre G, Kim C, Turecki G. Psychiatric diagnoses in 3275 suicides: a meta-analysis. BMC Psychiatry. 2004;37(4):1-11.
91. Cavanagh JT, Carson AJ, Sharpe M, Lawrie SM. Psychological autopsy studies of suicide: a systematic review. Psychological Medicine. 2003;33:395-405.
92. Yoshimasu K, Kiyohara C, Miyashita K. Suicidal risk factors and completed suicide: meta-analyses based on psychological autopsy studies. Environmental Health and Preventive Medicine 2008;13:243-56.
93. Gluckman P, Beedle A, Hanson M. Principles of evolutionary medicine. Oxford: Oxford University Press; 2009.
94. Brune M, Belsky J, Fabrega H, Feierman HR, Gilbert P, Glantz K, et al. The crisis of psychiatry - insights and prospects from evolutionary theory. World Psychiatry. 2012;11(1):55-7.
95. World Health Organization. Guidelines for medico-legal care for victims of sexual violence. Geneva: World Health Organization, 2003.
96. Chang JC, Cluss PA, Ranieri L, Hawker L, Buranosky R, Dado D, et al. Health care interventions for intimate partner violence: what women want. Women's health issues : official publication of the Jacobs Institute of Women's Health. 2005;15(1):21-30.
97. Hyde JS, Mezulis AH, Abramson LY. The ABCs of depression: integrating affective, biological, and cognitive models to explain the emergence of the gender difference in depression. Psychological review. 2008;115(2):291-313.
98. Kendler KS, Thornton LM, Prescott CA. Gender differences in the rates of exposure to stressful life events and sensitivity to their depressogenic effects. The American journal of psychiatry. 2001;158(4):587-93.
99. Kendler KS, Karkowski LM, Prescott CA. Causal relationship between stressful life events and the onset of major depression. The American journal of psychiatry. 1999;156(6):837-41.
100. Anderson K. Perpetrator or victim? Relationships between intimate partner violence and well-being. Journal of Marriage and Family. 2002;64(4):851–63.
101. Romito P, Grassi M. Does violence affect one gender more than the other? The mental health impact of violence among male and female university students. Soc Sci Med. 2007;65(6):1222-34.
102. Tjaden P, Thoennes N. Prevalence and consequences of male-to-female and female-to-male intimate partner violence, as measured by the national violence against women survey. Violence Against Women. 2000;6(2):142–61.
103. Accortt EE, Freeman MP, Allen JJB. Women and Major Depressive Disorder: Clinical Perspectives on Causal Pathways. Journal of Women's Health. 2008;17(10):1583-90.

104. Bebbington P. The origins of sex differences in depressive disorder: bridging the gap. International Review of Psychiatry. 1996;8:295-332.
105. Essau CA, Lewinsohn PM, Seeley JR, Sasagawa S. Gender differences in the developmental course of depression. J Affect Disord. 2010;127(1-3):185-90.
106. Kessler RC. Epidemiology of women and depression. Journal of Affective Disorders. 2003;74:5-13.
107. Kuehner C. Gender differences in unipolar depression: an update of epidemiological findings and possible explanations. Acta psychiatrica Scandinavica. 2003;108:163-74.
108. Nolen-Hoeksema S. Gender Differences in Depression. Current Directions in Psychological Science 2001;10:173-6.
109. Nolen-Hoeksema S. The Etiology of Gender Differences in Depression. Understanding depression in women: Applying empirical research to practice and policy. Washington, DC: American Psychological Association; US; 2006. p. 9-43.
110. Piccinelli M, Wilkinson G. Gender differences in depression : Critical review. British Journal of Psychiatry. 2000;177:486-92.
111. Collins PY, Patel V, Joestl SS, March D, Insel TR, Daar AS, et al. Grand challenges in global mental health. Nature. 2011;475(7354):27-30.
112. Murray CJL, Lopez AD, Black R, Mathers CD, Shibuya K, Ezzati M, et al. Global Burden of Disease 2005: call for collaborators. The Lancet. 2007;370(9582):109-10.
113. Global Burden of Disease. Global Burden of Diseases, Injuries and Risk Factors Study Operations Manual 2009. Available from: http://www.globalburden.org/gbdops.html.
114. Salomon JA. New disability weights for the global burden of disease. Bulletin of the World Health Organization 2010;88(12):879.
115. Salomon JA, Murray CJ, Ustun B, Chatterji S. Health state valuations in summary measures of population health. In: Murray CJ, Evans DB, editors. Health systems performance assessment: debates, methods and empiricism. Geneva: World Health Organization 2003. p. 408-36.
116. Kessler RC. The World Health Organization International Consortium in Psychiatric Epidemiology (ICPE): initial work and future directions -- the NAPE Lecture 1998. Nordic Association for Psychiatric Epidemiology. Acta psychiatrica Scandinavica. 1999;99(1):2-9.
117. Skapinakis P, Lewis G. Epidemiology in community psychiatric research: common uses and methodological issues. Epidemiol Psichiatr Soc. 2001;10(1):18-26.
118. Wittchen HU. Epidemiological research in mental disorders: lessons for the next decade of research--the NAPE Lecture 1999. Nordic Association for Psychiatric Epidemiology. Acta psychiatrica Scandinavica. 2000;101(1):2-10.
119. Seedat S, Scott KM, Angermeyer MC, Berglund P, Bromet EJ, Brugha TS, et al. Cross-national associations between gender and mental disorders in the World Health Organization World Mental Health Surveys. Archives of general psychiatry. 2009;66(7):785-95.
120. Simon GE, Goldberg DP, Von Korff M, Ustun TB. Understanding cross-national differences in depression prevalence. Psychol Med. 2002;32(4):585-94.
121. Moher D, Liberati A, Tetzlaff J, Altman DG, The PG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA Statement. PLoS Med. 2009;6(7):e1000097.
122. Kruijshaar ME, Barendregt J, Vos T, de Graaf R, Spijker J, Andrews G. Lifetime prevalence estimates of major depression: An indirect estimation method and a quantification of recall bias. European Journal of Epidemiology. 2005;20:103–11.
123. Moffitt TE, Caspi A, Taylor AJ, Kokaua J, Milne BJ, Polanczyk G, et al. How common are common mental disorders? Evidence that lifetime prevalence rates are doubled by prospective versus retrospective ascertainment. Psychological Medicine. 2010;40:899–909.
124. Simon GE, VonKorff M. Recall of psychiatric history in cross-sectional surveys: Implications for epidemiologic research. Epidemiologic Reviews. 1995;17(1):221-7.
125. Susser E, Shrout PE. Two plus two equals three? Do we need to rethink lifetime prevalence? A commentary on 'How common are common mental disorders? Evidence that lifetime prevalence

rates are doubled by prospective versus retrospective ascertainment' by Moffitt et al. (2009). Psychological Medicine. 2010;40:895–7.
126. United Nations. World Population Prospects: The 2006 Revision, Highlights. Working Paper No. ESA/P/WP.202. Department of Economic and Social Affairs, Population Division, 2007.
127. Sterne JAC, Egger M, Sutton AJ. Meta-Analysis Software. Systematic Reviews in Health Care: BMJ Publishing Group; 2008. p. 336-46.
128. Baker WL, White CM, Cappelleri JC, Kluger J, Coleman CI. Understanding heterogeneity in meta-analysis: the role of meta-regression. Int J Clin Pract. 2009;63(10):1426-34.
129. van Houwelingen HC, Arends LR, Stijnen T. Advanced methods in meta-analysis: multivariate approach and meta-regression. Stat Med. 2002;21(4):589-624.
130. Tabachnick BG, Fidell LS, editors. Using multivariate statistics. 5 ed. Boston: Pearson/Allyn & Bacon; 2007.
131. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ. 2003;327(7414):557-60.
132. DerSimonian R, Kacker R. Random-effects model for meta-analysis of clinical trials: An update. Contemporary Clinical Trials. 2007;28:105–14.
133. DerSimonian R, Laird N. Meta-analysis in clinical trials. Controlled Clinical Trials. 1986;7:177-88.
134. Stata: Data Analysis and Statistical Software. Stata 12 help for predict 2011. Available from: http://www.stata.com/help.cgi?predict.
135. Ihara K, Muraoka Y, Oiji A, Nadaoka T. Prevalence of mood disorders according to DSM-III -R criteria in the community elderly residents in Japan. Environmental Health and Preventive Medicine. 1998;3(1):44-9.
136. Lopes Cardozo B, Bilukha OO, Gotway CA, Wolfe MI, Gerber ML, Anderson M. Mental health of women in postwar Afghanistan. Journal of Women's Health. 2005;14(4):285-93.
137. Angst J, Gamma A, Gastpar M, Lepine JP, Mendlewicz J, Tylee A. Gender differences in depression. Epidemiological findings from the European DEPRES I and II studies. Eur Arch Psychiatry Clin Neurosci. 2002;252(5):201-9.
138. Culbertson FM. Depression and gender. An international review. Am Psychol. 1997;52(1):25-31.
139. Bromet EJ, Gluzman SF, Paniotto VI, Webb CPM, Tintle NL, Zakhozha V, et al. Epidemiology of psychiatric and alcohol disorders in Ukraine: Findings from the Ukraine World Mental Health Survey. Social Psychiatry and Psychiatric Epidemiology. 2005;40(9):681-90.
140. Faravelli C, Degl'Innocenti BG, Aiazzi L, Incerpi G, et al. Epidemiology of mood disorders: A community survey in Florence. Journal of Affective Disorders. 1990;20(2):135-41.
141. Stefansson GE, Bjornsson JK, Gudmundsdottir A. Period prevalence rates of specific mental disorders in an Icelandic cohort. Soc Psychiatry Psychiatr Epidemiol. 1994;29:119-25.
142. Saha S, Chant D, Welham J, McGrath J. A systematic review of the prevalence of schizophrenia. PLoS Medicine. 2005;2(5):e141.
143. Hollander AC, Ekblad S, Mukhamadiev D, Muminova R. The validity of screening instruments for posttraumatic stress disorder, depression, and other anxiety symptoms in Tajikistan. The Journal of nervous and mental disease. 2007;195(11):955-8.
144. Horwitz AV, Wakefield JC. The loss of sadness: How psychiatry transformed normal sorrow into depressive disorder. New York: Oxford University Press; 2007.
145. Ventevogel P, De Vries G, Scholte WF, Shinwari NR, Faiz H, Nassery R, et al. Properties of the Hopkins Symptom Checklist-25 (HSCL-25) and the Self-Reporting Questionnaire (SRQ-20) as screening instruments used in primary care in Afghanistan. Soc Psychiatry Psychiatr Epidemiol. 2007;42(4):328-35.
146. Hollifield M, Warner TD, Lian N, Krakow B, Jenkins JH, Kesler J, et al. Measuring trauma and health status in refugees: a critical review. JAMA. 2002;288(5):611-21.

147. Rodin D, van Ommeren M. Commentary: Explaining enormous variations in rates of disorder in trauma-focused psychiatric epidemiology after major emergencies. Int J Epidemiol. 2009;38(4):1045-8.
148. Steel Z, Chey T, Silove D, Marnane C, Bryant RA, van Ommeren M. Association of torture and other potentially traumatic events with mental health outcomes among populations exposed to mass conflict and displacement: a systematic review and meta-analysis. JAMA. 2009;302(5):537-49.
149. Institute for Health Metrics and Evaluation. Burden of Disease 2012. Available from: http://www.healthmetricsandevaluation.org/research/team/burden-disease#/overview.
150. Ferrari AJ, Somerville AJ, Baxter AJ, Norman R, Patten SB, Vos T, et al. Global variation in the prevalence and incidence of major depressive disorder: a systematic review of the epidemiological literature. Psychol Med. 2013;43(3):471-81.
151. Charlson FJ, Ferrari AJ, Somerville AJ, Norman R, Patten SB, Vos T, et al. The epidemiological modelling of dysthymia: Application for the Global Burden of Disease 2010 Study. Journal of Affective Disorders. 2013;151:111-20.
152. Attanayake V, McKay R, Joffres M, Singh S, Burkle F, Jr., Mills E. Prevalence of mental disorders among children exposed to war: a systematic review of 7,920 children. Med Confl Surviv. 2009;25(1):4-19.
153. Fisher J, Tran T, La BT, Kriitmaa K, Rosenthal D. Common perinatal mental disorders in northern Viet Nam: community prevalence and health care use. Bull World Health Organ. 2010;88(10):737-45.
154. Flaxman AD, Vos T, Murray CJL, editors. An integrative metaregression framework for descriptive epidemiology. Washington: University of Washington Press, In press; 2014.
155. Vos T, Mathers C, Herrman H, Harvey C, Gureje O, Bui D, et al. The burden of mental disorders in Victoria, 1996. Soc Psychiatry Psychiatr Epidemiol. 2001;36(2):53-62.
156. Vos T, Mathers CD. The burden of mental disorders: a comparison of methods between the Australian burden of disease studies and the Global Burden of Disease study. Bull World Health Organ. 2000;78(4):427-38.
157. Maharaj RG, Alli F, Cumberbatch K, Laloo P, Mohammed S, Ramesar A, et al. Depression among adolescents, aged 13-19 years, attending secondary schools in Trinidad: prevalence and associated factors. West Indian Med J. 2008;57(4):352-9.
158. Roberts B, Damundu EY, Lomoro O, Sondorp E. Post-conflict mental health needs: a cross-sectional survey of trauma, depression and associated factors in Juba, Southern Sudan. BMC Psychiatry. 2009;9:7.
159. Uwakwe R. The pattern of psychiatric disorders among the aged in a selected community in Nigeria. Int J Geriatr Psychiatry. 2000;15(4):355-62.
160. Eaton WW, Anthony JC, Gallo J, Cai G, Tien A, Romanoski A, et al. Natural history of Diagnostic Interview Schedule/DSM-IV major depression. The Baltimore Epidemiologic Catchment Area follow-up. Archives of general psychiatry. 1997;54(11):993-9.
161. Kendler KS, Walters EE, Kessler RC. The prediction of length of major depressive episodes: results from an epidemiological sample of female twins. Psychol Med. 1997;27(1):107-17.
162. Lewinsohn PM, Clarke GN, Seeley JR, Rohde P. Major depression in community adolescents: age at onset, episode duration, and time to recurrence. J Am Acad Child Adolesc Psychiatry. 1994;33(6):809-18.
163. McLeod JD, Kessler RC, Landis KR. Speed of recovery from major depressive episodes in a community sample of married men and women. J Abnorm Psychol. 1992;101(2):277-86.
164. Howson C, Urbach P. Scientific reasoning : the Bayesian approach. Chicago, IL, US: Open Court Publishing Co; 1989.
165. Thompson SG, Higgins JPT. How should meta-regression analyses be undertaken and interpreted? Statistics in Medicine 2002;21(11):1559–73.

166. Luby JL. Preschool Depression: The Importance of Identification of Depression Early in Development. Curr Dir Psychol Sci. 2010;19(2):91-5.
167. Karam E, Bou Ghosnb M. Psychosocial consequences of war among civilian populations. Current Opinion in Psychiatry. 2003;16:413-9.
168. Karam EG, Mneimneh ZN, Dimassi H, Fayyad JA, Karam AN, Nasser SC, et al. Lifetime prevalence of mental disorders in Lebanon: first onset, treatment, and exposure to war. PLoS Med. 2008;5(4):e61.
169. Ahmad OB, Boschi-Pinto C, Lopez AD, Murray CJL, Lozano R, Inoue M. Age standardization of rates: A new WHO standard. GPE Discussion Paper Series: No.31, World Health Organization, 2001.
170. United Nations. World Population Prospects - The 2010 Revision. New York: United Nations, 2011.
171. Luppa M, Sikorski C, Luck T, Ehreke L, Konnopka A, Wiese B, et al. Age- and gender-specific prevalence of depression in latest-life--systematic review and meta-analysis. J Affect Disord. 2012;136(3):212-21.
172. Beekman ATF, Deeg DJJ, Van Tilburg T, Smith JH, Hooijer C, Van Tilburg W. Major and minor depression in later life: A study of prevalence and risk factors. Journal of Affective Disorders. 1995;36(1–2):65–75.
173. Kurlowicz LH. Depression in later life: dispelling the myths. J Psychosoc Nurs Ment Health Serv. 2005;43(1):16-9.
174. Mathers CD, Stein C, Ma Fat D, C. R, Inoue M, Tomijima N, et al. Global Burden of Disease 2000: Version 2 methods and results. Geneva: World Health Organization, 2002.
175. Ferrari AJ, Charlson FJ, Norman R, Flaxman AD, Patten SB, Vos T, et al. The epidemiological modelling of major depressive disorder: Application for the Global Burden of Disease Study 2010 PLoS One. 2013;8(7):1-14.
176. Agency for Healthcare Research and Quality. United States Medical Expenditure Panel Survey 2000-2009. Rockville, United States: Agency for Healthcare Research and Quality; 2012.
177. U.S. National Institutes of Health National Institute on Alcohol Abuse and Alcoholism. National Epidemiologic Survey on Alcohol and Related Conditions Wave 1 and Wave 2 Bethesda, Maryland, United States: National Institutes of Health; 2013 [22/08/2013]. Available from: http://www.niaaa.nih.gov/.
178. Australian Bureau of Statistics. National Survey of Mental Health and Wellbeing of Adults 1997 Canberra, Australia: Australian Bureau of Statistics; 2008 [22/08/2013]. Available from: http://www.abs.gov.au/AUSSTATS/abs@.nsf/allprimarymainfeatures/D5A0AC778746378FCA2574EA00122887?opendocument.
179. Ware JE, Kosinski M, Keller SD, QualityMetric Incorporated, New England Medical Center Hospital. Health Assessment Lab. SF-12 : how to score the SF-12 physical and mental health summary scales. Lincoln, R.I, Boston, Mass: QualityMetric Inc, Health Assessment Lab; 2002.
180. Eaton WW, Kalaydjian A, Scharfstein D, Mezuk B, Ding Y. Prevalence and incidence of depressive disorder: the Baltimore ECA follow-up, 1981–2004. Acta psychiatrica Scandinavica. 2007;116:182–8.
181. Fu TS, Lee CS, Gunnell D, Lee WC, Cheng AT. Changing trends in the prevalence of common mental disorders in Taiwan: a 20-year repeated cross-sectional survey. Lancet. 2012;381:235-41.
182. Charlson FJ, Steel Z, Degenhardt L, Chey T, Silove D, Marnane C, et al. Predicting the Impact of the 2011 Conflict in Libya on Population Mental Health: PTSD and Depression Prevalence and Mental Health Service Requirements. PLoS One. 2012;7(7):e40593.
183. GBD 2010 Country Collaboration. GBD 2010 country results: a global public good. Lancet. 2013;381:965-70.
184. Jessop EG. Health in the UK: could do even better? Lancet. 2013;381:970-2.
185. Murray CJL, Richards MA, Newton JN, Fenton LA. UK health performance: fi ndings of the Global Burden of Disease Study 2010. Lancet. 2013;381:997-1020.

186. McKnight PE, Kashdan TB. The importance of functional impairment to mental health outcomes: a case for reassessing our goals in depression treatment research. Clin Psychol Rev. 2009;29(3):243-59.
187. Sheehan DV, Harnett-Sheehan K, Raj BA. The measurement of disability. International Clinical Psychopharmacology. 1996;11(Suppl 3):89−95.
188. Sheehan KH, Sheehan DV. Assessing treatment effects in clinical trials with the discan metric of the Sheehan Disability Scale. Int Clin Psychopharmacol. 2008;23(2):70-83.
189. Degenhardt L, Whiteford HA, Ferrari AJ, Baxter AJ, Charlson FJ, Hall WD, et al. The global burden of disease attributable to illicit drug use: Results from the GBD 2010 study. The Lancet. 2013;382(9904):1564-74.
190. Ferrari AJ, Charlson FJ, Norman RE, Patten SB, Murray CJL, Vos T, et al. Burden of depressive disorders by country, sex, age and year: Findings from the Global Burden of Disease Study 2010. PloS Medicine. 2013;10(11):e1001547. doi:10.1371/journal.pmed.
191. Phillips MR, Cheng HG. The changing global face of suicide. Lancet. 2012;379(9834):2318-9.
192. Patel V, Ramasundarahettige C, Vijayakumar L, Thakur JS, Gajalakshmi V, Gururaj G, et al. Suicide mortality in India: a nationally representative survey. Lancet. 2012;379(9834):2343-51.
193. Vijayakumar L. Suicide and mental disorders in Asia. International Review of Psychiatry. 2005;17(2):109–14.
194. Degenhardt L, Singleton J, Calabria B, McLaren J, Kerr T, Mehta S, et al. Mortality among cocaine users: A systematic review of cohort studies. Drug and Alcohol Dependence. 2011;113:88-95.
195. Singleton J, Degenhardt L, Hall W, Zabransky T. Mortality among people who use amphetamines: A systematic review of cohort studies. Drug & Alcohol Dependence. 2009;105:1-8.
196. Wilcox HC, Conner KR, Caine ED. Association of alcohol and drug use disorders and completed suicide: an empirical review of cohort studies. Drug Alcohol Depend. 2004;76 Suppl:S11-9.
197. Epigear. MetaXL 2012 [15/08/2013]. Available from: http://www.epigear.com/index_files/metaxl.html.
198. Doi SA, Thalib L. A quality-effects model for meta-analysis. Epidemiology 2008;19(1):94-100
199. Barendregt JJ, Doi SA. MetaXL User Guide: Version 1.0. Wilston, Australia: EpiGear International Pty Ltd; 2010. Available from: http://www.epigear.com/index_files/metaxl.html
200. Doi SA, Barendregt JJ, Mozurkewich EL. Meta-analysis Of heterogenous clinical trials: An empirical example. . Contemporary Clinical Trials. 2011;32:288-98.
201. Baxter AJ, Scott K, Vos T, Whiteford HA. Global prevalence of anxiety disorders: A systematic review and meta-regression Psychological Medicine. 2012;43(5):897-910.
202. Degenhardt L, Bucello C, Calabria B, Nelson P, Roberts A, Hall W, et al. What data are available on the extent of illicit drug use and dependence globally? Results of four systematic reviews. Drug Alcohol Depend. 2011;117(2-3):85-101.
203. Ferrari AJ, Baxter AJ, Whiteford HA. A systematic review of the global distribution and availability of prevalence data for bipolar disorder. Journal of Affective Disorders. 2010;34(1-3):1-13.
204. Haagsma JA, van Beeck EF, Polinder S, Toet H, Panneman M, Bonsel GJ. The effect of comorbidity on health-related quality of life for injury patients in the first year following injury: comparison of three comorbidity adjustment approaches. Popul Health Metr. 2011;9:10.
205. Conner KR, Phillips MR, Meldrum S, Knox KL, Zhang Y, Yang G. Low-planned suicides in China. Psychol Med. 2005;35(8):1197-204.
206. Phillips MR. Rethinking the role of mental illness in suicide. The American journal of psychiatry. 2010;167(7):731-3.

207. Yang GH, Phillips MR, Zhou MG, Wang LJ, Zhang YP, Xu D. Understanding the unique characteristics of suicide in China: national psychological autopsy study. Biomedical and environmental sciences : BES. 2005;18(6):379-89.
208. Zhang J, Xiao S, Zhou L. Mental disorders and suicide among young rural Chinese: A case-control psychological autopsy study. American Journal of Psychiatry. 2010;167:773-81.
209. Isometsa ET. Psychological autopsy studies – a review. European Psychiatry. 2001;16:379-85.
210. Silverman MM, Maris RW. The prevention of suicidal behaviors: an overview. Suicide & life-threatening behavior. 1995;25(1):10-21.
211. Scott A, Guo B. For which strategies of suicide prevention is there evidence of effectiveness? Copenhagen: World Health Organization, 2012.
212. Mann JJ, Apter A, Bertolote J, Beautrais A, Currier D, Haas A, et al. Suicide prevention strategies: a systematic review. JAMA. 2005;294(16):2064-74.
213. Briffault X, Morvan Y, Rouillon F, Dardennes R, Lamboy B. [Use of services and treatment adequacy of major depressive episodes in France]. L'Encephale. 2010;36 Suppl 2:D48-58.
214. Gabilondo A, Rojas-Farreras S, Rodriguez A, Fernandez A, Pinto-Meza A, Vilagut G, et al. Use of primary and specialized mental health care for a major depressive episode in Spain by ESEMeD respondents. Psychiatric services. 2011;62(2):152-61.
215. Katz C, Bolton SL, Katz LY, Isaak C, Tilston-Jones T, Sareen J. A Systematic Review of School-Based Suicide Prevention Programs. Depression and anxiety. 2013.
216. Robinson J, Hetrick SE, Martin C. Preventing suicide in young people: systematic review. Aust N Z J Psychiatry. 2011;45(1):3-26.
217. Khan MM. Suicide prevention and developing countries. J R Soc Med. 2005;98(10):459-63.
218. Pritchard C, Amanullah S. An analysis of suicide and undetermined deaths in 17 predominantly Islamic countries contrasted with the UK. Psychol Med. 2007;37(3):421-30.
219. Saxena S, Jane-Llopis E, Hosman C. Prevention of mental and behavioural disorders: implications for policy and practice. World Psychiatry. 2006;5(1):5-14.
220. Karam EG, Friedman MJ, Hill ED, Kessler RC, McLaughlin KA, Petukhova M, et al. Cumulative traumas and risk thresholds: 12-month PTSD in the World Mental Health (WMH) surveys. Depression and anxiety. 2014;31(2):130-42.
221. Lopresti AL, Hood SD, Drummond PD. A review of lifestyle factors that contribute to important pathways associated with major depression: diet, sleep and exercise. J Affect Disord. 2013;148(1):12-27.
222. Beydoun HA, Beydoun MA, Kaufman JS, Lo B, Zonderman AB. Intimate partner violence against adult women and its association with major depressive disorder, depressive symptoms and postpartum depression: a systematic review and meta-analysis. Soc Sci Med. 2012;75(6):959-75.
223. Chen LP, Murad MH, Paras ML, Colbenson KM, Sattler AL, Goranson EN, et al. Sexual abuse and lifetime diagnosis of psychiatric disorders: systematic review and meta-analysis. Mayo Clinic proceedings Mayo Clinic. 2010;85(7):618-29.
224. Devries KM, Mak JY, Child J, Falder G, Bacchus L, Astbury J, et al. Is childhood sexual abuse associated with incident depression? A systematic review of twin and longitudinal studies. Submitted for review. 2014.
225. Maniglio R, Maniglio R. Child sexual abuse in the etiology of depression: A systematic review of reviews. Depression & Anxiety. 2010;27(7):631-42.
226. Devries KM, Mak JY, Bacchus L, Lim S, Petzold M, Child J, et al. The global prevalence of childhood sexual abuse. In preparation. 2014.
227. World Health Organization, London School of Tropical Hygiene and Medicine, South African Medical Research Council. Global and regional estimates of violence against women: Prevalence and health effects of intimate partner violence and non-partner sexual violence. Geneva, Switzerland: World Health Organization, 2013.
228. Nolen-Hoeksema S. Sex Differences in Unipolar Depression: Evidence and Theory. Psychological Bulletin. 1987;101(2):259-82.

229. Weissman MM, Klerman GL. Sex differences and the epidemiology of depression. Archives of general psychiatry. 1977;34(1):98-111.
230. Lipsman N, Lozano AM. The most cited works in major depression: the 'Citation classics'. J Affect Disord. 2011;134(1-3):39-44.
231. Cyranowski JM, Frank E, Young E, Shear MK. Adolescent onset of the gender difference in lifetime rates of major depression: a theoretical model. Archives of general psychiatry. 2000;57(1):21-7.
232. Hankin BL, Abramson LY. Development of gender differences in depression: an elaborated cognitive vulnerability-transactional stress theory. Psychol Bull. 2001;127(6):773-96.
233. Maier W, Gansicke M, Gater R, Rezaki M, Tiemens B, Urzua RF. Gender differences in the prevalence of depression: a survey in primary care. J Affect Disord. 1999;53(3):241-52.
234. Nolen-Hoeksema S, Girgus JS. The emergence of gender differences in depression during adolescence. Psychol Bull. 1994;115(3):424-43.
235. Parker G, Hadzi-Pavlovic D. Is any female preponderance in depression secondary to a primary female preponderance in anxiety disorders? Acta psychiatrica Scandinavica. 2001;103(4):252-6.
236. Dunn EC, Gilman SE, Willett JB, Slopen NB, Molnar BE. The impact of exposure to interpersonal violence on gender differences in adolescent-onset major depression: results from the National Comorbidity Survey Replication (NCS-R). Depression and anxiety. 2012;29(5):392-9.
237. Cutler SE, Nolen-Hoeksema S. Accounting for sex differences in depression through female victimization: Childhood sexual abuse. Sex Roles. 1991;24(7-8):425-38.
238. Carlson BE, McNutt LA, Choi DY. Childhood and adult abuse among women in primary health care: effects on mental health. Journal of interpersonal violence. 2003;18(8):924-41.
239. Follette VM, Polusny MA, Bechtle AE, Naugle AE. Cumulative trauma: the impact of child sexual abuse, adult sexual assault, and spouse abuse. Journal of traumatic stress. 1996;9(1):25-35.
240. McGuigan WM, Middlemiss W. Sexual abuse in childhood and interpersonal violence in adulthood: a cumulative impact on depressive symptoms in women. Journal of interpersonal violence. 2005;20(10):1271-87.
241. Messman-Moore TL, Long PJ, Siegfried NJ. The revictimization of child sexual abuse survivors: an examination of the adjustment of college women with child sexual abuse, adult sexual assault, and adult physical abuse. Child maltreatment. 2000;5(1):18-27.
242. Mouzos J, Makkai T. Women's experiences of male violence, findings from the Australian component of the International Violence Against Women Survey (IVAWS). Canberra: Australian Institute of Criminology, 2004.
243. Devries KM, Mak JYT, García-Moreno C, Petzold M, Child JC, Falder G, et al. The global prevalence of intimate partner violence against women. Science. 2013;340(6140):1527-8.
244. Garcia-Moreno C, Jansen HA, Ellsberg M, Heise L, Watts CH, Health WHOM-cSoWs, et al. Prevalence of intimate partner violence: findings from the WHO multi-country study on women's health and domestic violence. Lancet. 2006;368(9543):1260-9.
245. Devries KM, Garcia-Moreno C. Co-occurence of CSA and IPV in women: Data from the World Health Organization's multi-country study on women's health and domestic violence (Personal Communication). 2013.
246. Hoy D, Brooks P, Woolf A, Blyth F, March L, Bain C, et al. Assessing risk of bias in prevalence studies: modification of an existing tool and evidence of interrater agreement. Journal of clinical epidemiology. 2012;65(9):934-9.
247. Begg SJ, Vos T, Barker B, Stanley L, Lopez AD. Burden of disease and injury in Australia in the new millennium: measuring health loss from diseases, injuries and risk factors. The Medical journal of Australia. 2008;188(1):36-40.
248. Norman R, Bradshaw D, Lewin S, Cairncross E, Nannan N, Vos T, et al. Estimating the burden of disease attributable to four selected environmental risk factors in South Africa. Reviews on environmental health. 2010;25(2):87-119.

249. Egger M, Smith GD, Altman DG, editors. Systematic reviews in health care: meta-analysis in context London: BMJ Publishing Group; 2001.
250. Borenstein M, Hedges LV, Higgins JPT, Rothstein HR. Converting Among Effect Sizes. In: Borenstein M, Hedges LV, Higgins JPT, Rothstein HR, editors. Introduction to Meta-Analysis Chichester, West Sussex, U.K. ; Hoboken: John Wiley & Sons; 2009.
251. Hasselblad V, Hedges LV. Meta-analysis of screening and diagnostic tests. Psychol Bull. 1995;117(1):167-78.
252. Epigear. OR2RR 2013. Available from: http://www.epigear.com/index_files/or2rr.html.
253. Zhang J, Yu KF. What's the relative risk? A method of correcting the odds ratio in cohort studies of common outcomes. JAMA. 1998;280(19):1690-1.
254. Greenland S, Robins JM. Conceptual problems in the definition and interpretation of attributable fractions. American journal of epidemiology. 1988;128(6):1185-97.
255. Barendregt JJ. Ersatz Version 1.2 Brisbane, Australia2012. Available from: http://www.epigear.com.
256. Abrahams N, Mathews S, Martin LJ, Lombard C, Jewkes R. Intimate partner femicide in South Africa in 1999 and 2009. PLoS Med. 2013;10(4):e1001412.
257. Krug EG, Mercy JA, Dahlberg LL, Zwi AB. The world report on violence and health. Lancet. 2002;360(9339):1083-8.
258. Goodwin RD. Anxiety disorders and the onset of depression among adults in the community. Psychol Med. 2002;32(6):1121-4.
259. Nolen-Hoeksema S. Responses to depression and their effects on the duration of depressive episodes. J Abnorm Psychol. 1991;100(4):569-82.
260. Parker G, Brotchie H. Gender differences in depression. Int Rev Psychiatry. 2010;22(5):429-36.
261. Baxter AJ, Scott KM, Ferrari AJ, Norman R, Vos T, Whiteford HA. Challenging the myth of an "epidemic" of common mental disorders: trends in the global prevalence of anxiety and depression between 1990 and 2010. Depression & Anxiety. 2014;31(6):506-16.
262. Musgrove P, Fox-Rushby J. Cost-Effectiveness Analysis for Priority Setting. In: Jamison D, Breman JG, Measham AR, Alleyne G, Claeson M, Evans DB, et al., editors. Disease Control Priorities in Developing Countries. 2 ed. New York: Oxford University Press; 2006. p. 271-85.
263. Heise LL. What works to prevent partner violence ?: An evidence overview. London: Strive, London School of Hygiene and Tropical Medicine 2011.
264. Heim C, Newport DJ, Mletzko T, Miller AH, Nemeroff CB. The link between childhood trauma and depression: insights from HPA axis studies in humans. Psychoneuroendocrinology. 2008;33(6):693-710.
265. Kaplan MJ, Klinetob NA. Childhood emotional trauma and chronic posttraumatic stress disorder in adult outpatients with treatment-resistant depression. The Journal of nervous and mental disease. 2000;188(9):596-601.
266. Lara ME, Klein DN, Kasch KL. Psychosocial predictors of the short-term course and outcome of major depression: a longitudinal study of a nonclinical sample with recent-onset episodes. J Abnorm Psychol. 2000;109(4):644-50.
267. Weiss EL, Longhurst JG, Mazure CM. Childhood sexual abuse as a risk factor for depression in women: psychosocial and neurobiological correlates. The American journal of psychiatry. 1999;156(6):816-28.
268. Asarnow JR, Emslie G, Clarke G, Wagner KD, Spirito A, Vitiello B, et al. Treatment of selective serotonin reuptake inhibitor-resistant depression in adolescents: predictors and moderators of treatment response. J Am Acad Child Adolesc Psychiatry. 2009;48(3):330-9.
269. Lewis CC, Simons AD, Nguyen LJ, Murakami JL, Reid MW, Silva SG, et al. Impact of childhood trauma on treatment outcome in the Treatment for Adolescents with Depression Study (TADS). J Am Acad Child Adolesc Psychiatry. 2010;49(2):132-40.
270. Andrews G, Szabo M, Burns J. Preventing major depression in young people. Br J Psychiatry. 2002;181:460-2.

271. Yang LH, Link BG. Comparing diagnostic methods for mental disorders in China. Lancet. 2009;373(9680):2002-4.
272. Baxter AJ, Patton G, Scott KM, Degenhardt L, Whiteford HA. Global epidemiology of mental disorders: what are we missing? PLoS One. 2013;8(6):e65514.
273. Erskine HE, Baxter AJ, Ferrari AJ, Patton G, Whiteford HA, Scott J. Will somebody thing of the children?;The coverage of epidemiological data for mental disorders in youth. In progress. 2014.
274. Psychological Medicine. Most-cited papers from 2013 2014. Available from: http://view.emarketing.cambridge.org/?j=fe8b1779746600747d&m=fe9f15707765037974&ls=fdf210707361037b73117073&l=fed417717561057c&s=fe241779726d057e711172&jb=ffcf14&ju=fe501377766d01787113&r=0.
275. Norman RE, Moore SE, Ferrari AJ, Scott JG, Dunne M, Erskine H, et al. Burden attributable to child maltreatment in Australia. In progress. 2014.
276. World Health Organization. WHO methods and data sources for global burden of disease estimates 2000-2011. Global Health Estimates Technical Paper WHO/HIS/HSI/GHE/2013.4. Geneva, Switzerland: Department of Health Statistics and Information Systems, WHO, 2013.

Appendices

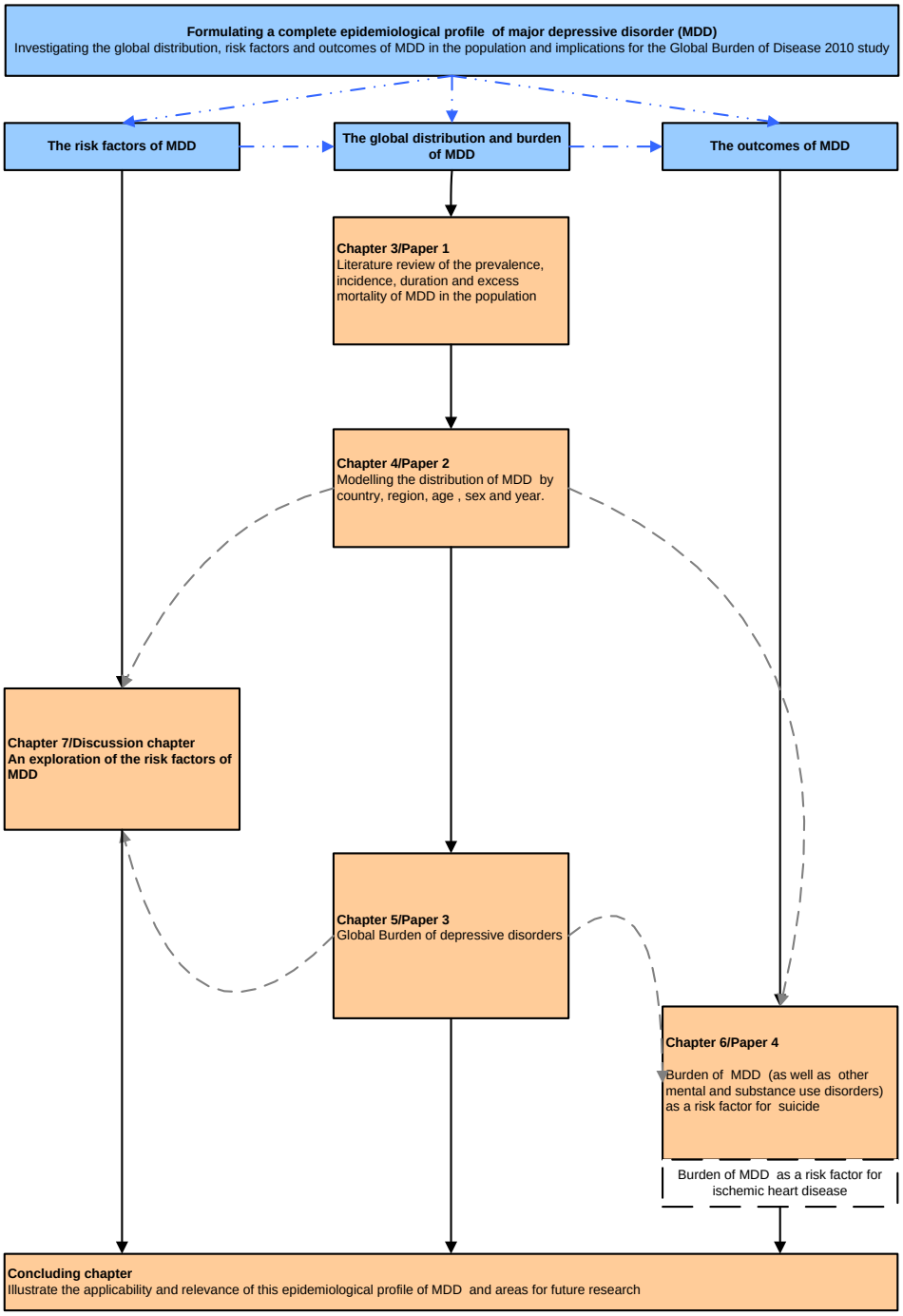
Appendix One

Supplementary text to the Acknowledgements section

As this thesis also included the estimation of burden estimates for the Global Burden of Disease Study 2010 (GBD 2010), I would like to acknowledge all core and collaborating members of the GBD 2010 expert group for mental and substance use disorders who provided advice and assistance during the course of the study.

The mental and illicit drug use disorder expert group was made up of the following core members: Louisa Degenhardt, Harvey A Whiteford, John McGrath, Wayne Hall, Guilherme Polanczyk, Martin Prince, Shekhar Saxena, Oye Gureje, Ronald Kessler, Cille Kennedy, and Maria Elena Medina-More. The alcohol use disorders expert group was made up of the following core members: Guilherme Borges, Gerhard Gmel, Kate Graham, Charles Parry, Vladimir Poznyak, Jürgen Rehm, Robin Room.

I would also like to acknowledge all other collaborating members who provided assistance to the mental and substance use disorder expert group, particularly James Scott, Jon-Paul Khoo, Jed Blore, Amanda Brown, Chiara Bucello, Bianca Calabria, Georgia Carstensen, Bianca Garcia, Yong Yi Lee, Bradley Mathers, Jennifer McLaren, Keryl Mitchener, Paul Nelson, Jayadeep Patra, An Pham, Svetlana Popova, Anna Roberts, Roman Scheurer, Adele Somerville, and Allison Ventura for their assistance in conducting the systematic reviews and/or the provision of expert advice. I would also like to acknowledge the World Mental Health Surveys Consortium for their contribution, led by Ronald Kessler and the following collaborators: Koen Demyttenaere, Ronny Bruff aerts, José Posada-Villa, Jean-Pierre Lepine, Viviane Kovess-Masfety, Matthias Angermeyer, Herbert Matschinger, Daphna Levinson, Giovanni de Girolamo, Norito Kawakami, Elie Karam, Maria Elena Medina Mora, Hans Ormel, Peter de Jonge, Ron de Graaf, Kate Scott, Elisabeth Wells, Oye Gureje, David Williams, Jordi Alonso, Josep Maria Haro Abad, and Evelyn Bromet.



Note. *Blue boxes represent PhD aims. Orange boxes represent PhD deliverables. The white box represents work that was not part of the PhD but was informed by PhD outputs.*

Figure S1. Outline of PhD.

Appendix Two

Supplementary text to Chapter Three

Table S1. Summary of epidemiological parameters required for the burden estimation of MDD.

Parameter	**Definition**
Prevalence	The proportion of the population with MDD* at a specific point in time (point prevalence) or during a specified time period (6-, 12-month prevalence)
Incidence	The number of new cases of MDD in the population in one year (rate)
Duration	The average length of a MDE*
Excess mortality rate	The rate of dying in people with MDD compared to the general population. This can be presented as a relative risk (ratio of observed death in the sample to expected death in the population) or a standard mortality ratio (ratio of observed deaths in the sample to expected death in a population of standard composition in terms of age, sex, etc)

Table S2.Summary of included studies for prevalence

Study	Country	Coverage	Age range	Cohort size	Response rate	Midyear	Depression subtype	Diagnostic criteria/tool	Parameter Type	Sex	Prevalence % (95% uncertainty)
Europe, Western											
Aalto-Setala *et al.*, 2001	Finland	National	20-24	647	excellent	1995	MDD	DSM4/SCAN	Point	Female	7.80(2.90-12.70)
										Male	5.40(0.001-11.05)
Almqvist *et al.*, 1999	Finland	National	8-9	5813	excellent	1989	MDD	DSM3R/CDI	Point	Female	4.70(4.66-4.74)
										Male	7.80(7.76-7.84)
Andrade *et al.*, 2003	Germany	Community	14-25	3021	average	1995	MDD	DSM4/CIDI	Point	Total	1.30(0.91-1.69)
	Netherlands	National	18-64	7076	average	1996	MDD	DSM3R/CIDI	Point	Total	2.70(2.31-3.09)
Angst *et al.*, 1990	Switzerland	Community	28-28	4547	average	1988	MDD + dep NOS	DSM3/SPIKE	12 months	Female	18.30(11.09-25.51)
										Male	7.40(2.44-12.36)
Ayuso-Mateos *et al.*, 2001	Finland	Community	18-64	1950	average	2000	MDD	ICD10/SCAN	Point	Female	4.99(3.90-11.00)
	Ireland	Community	18-64	472	average	2000	MDD	ICD10/SCAN	Point	Female	8.01(3.90-43.90)
	Norway	Community	18-64	3050	average	2000	MDD	ICD10/SCAN	Point	Female	9.52(3.80-23.80)
	Spain	Community	18-64	1250	average	2000	MDD	ICD10/SCAN	Point	Female	1.80(1.00-3.10)
	United Kingdom	Community	18-64	2140	average	2000	MDD	ICD10/SCAN	Point	Female	8.14(10.10-39.02)
	Finland	Community	18-64	1950	average	2000	MDD	ICD10/SCAN	Point	Male	2.91(1.20-6.10)
	Ireland	Community	18-64	472	average	2000	MDD	ICD10/SCAN	Point	Male	5.58(1.20-13.90)
	Norway	Community	18-64	3050	average	2000	MDD	ICD10/SCAN	Point	Male	5.17(2.30-8.80)
	Spain	Community	18-64	1250	average	2000	MDD	ICD10/SCAN	Point	Male	2.00(0.70-5.30)
	United Kingdom	Community	18-64	2140	average	2000	MDD	ICD10/SCAN	Point	Male	6.83(2.40-10.00)
Barry *et al.*, 2009	Ireland	National	18-99	10364	average	2007	MDD	DSM4/CIDI	12 months	Female	8.00(7.00-9.00)
								DSM4/CIDI		Male	6.00(4.98-7.02)
Beekman *et al.*, 1995	Netherlands	National	55-85	3056	average	1993	MDD + dep NOS	DSM3/DIS	Point	Female	17.10(14.41-19.79)
										Male	12.40(9.97-14.83)

Study	Country	Coverage	Age range	Cohort size	Response rate	Midyear	Depression subtype	Diagnostic criteria/tool	Parameter Type	Sex	Prevalence % (95% uncertainty)
Bracke and Bracke, 1998	Belgium	National	16-99	8744	average	1992	MDD	RDC/HDL	Point	Female	8.70(7.45-9.95)
										Male	4.30(3.40-5.20)
Carta *et al.*, 2002	France	Community	18-99	2260	average	1995	MDD	ICD10/CIDI	Point	Total	5.90(5.00-7.00)
	Italy	Community	18-99	1040	average	1995	MDD	ICD10/CIDI	Point	Total	6.50(5.10-8.20)
Copeland *et al.*, 1999	Netherlands	Community	65-84	4051	excellent	1993	MDD	DSM3/GMS	Point	Female	2.10(1.54-2.66)
	Germany	Community	70-99	516	poor	1992	MDD	DSM3/GMS	Point	Female	5.80(3.47-8.13)
	Ireland	Community	65-99	936	excellent	1993	MDD	DSM3/GMS	Point	Female	0.30(0.001-0.74)
	Iceland	National	85-87	800	excellent	1983	MDD	DSM3/GMS	Point	Female	4.40(3.64-5.16)
	United Kingdom	Community	65-99	654	excellent	1994	MDD	DSM3/GMS	Point	Female	2.80(1.17-4.43)
	Germany	Community	85-99	358	excellent	1992	MDD	DSM3/GMS	Point	Female	12.30(8.35-16.25)
	Italy	Community	65-99	202	excellent	1991	MDD	DSM3/GMS	Point	Female	8.00(3.26-12.74)
	Spain	Community	65-99	1080	excellent	1989	MDD	DSM3/GMS	Point	Female	5.00(3.22-6.78)
	Netherlands	Community	65-84	4051	excellent	1993	MDD	DSM3/GMS	Point	Male	1.40(0.81-1.99)
	Germany	Community	70-99	516	poor	1992	MDD	DSM3/GMS	Point	Male	5.40(1.61-9.19)
	Ireland	Community	65-99	936	excellent	1993	MDD	DSM3/GMS	Point	Male	1.70(0.23-3.17)
	Iceland	National	85-87	800	excellent	1983	MDD	DSM3/GMS	Point	Male	2.20(0.49-3.91)
	United Kingdom	Community	65-99	654	excellent	1994	MDD	DSM3/GMS	Point	Male	3.10(0.99-5.21)
	Germany	Community	85-99	358	excellent	1992	MDD	DSM3/GMS	Point	Male	5.10(0.001-10.21)
	Italy	Community	65-99	202	excellent	1991	MDD	DSM3/GMS	Point	Male	1.30(0.001-4.21)
	Spain	Community	65-99	1080	excellent	1989	MDD	DSM3/GMS	Point	Male	2.80(1.50-4.10)
Donnelly, 1995	United Kingdom	Regional	11-15	887	average	1993	MDD	NS/CDI	Point	Total	12.00(8.90-15.10)
Faravelli *et al.*, 1990	Italy	Community	15-99	1000	excellent	1987	MDD + dep NOS	DSM3/Clinical IV	12 months	Female	14.34(10.04-18.64)
										Male	7.35(3.91-10.79)
									Point	Female	5.96(3.06-8.86)
										Male	2.60(0.50-4.70)

Study	Country	Coverage	Age range	Cohort size	Response rate	Midyear	Depression subtype	Diagnostic criteria/tool	Parameter Type	Sex	Prevalence % (95% uncertainty)
Frojd *et al.*, 2007	Finland	Community	15-16	3278	excellent	2003	MDD	NS/CDI	Point	Total	9.00(7.58-10.72)
Frojd *et al.*, 2007			17-18	2070	average	2005		NS/CDI			9.00(7.00-10.78)
Goodwin *et al.*, 2007	France	Regional	65-99	7869	average	2000	MDD	DSM4/MINI	Point	Female	2.30(1.68-2.92)
										Male	0.70(0.28-1.12)
Green *et al.*, 2005	United Kingdom	National	5-16	7977	average	2004	MDD	ICD10/DAWBA	Point	Female	1.10(0.62-1.58)
										Male	0.60(0.26-0.94)
Jenkins *et al.*, 1997	United Kingdom	National	16-65	9792	average	1993	MDD	ICD10/CIS-R	Point	Female	2.70(2.30-3.10)
										Male	1.80(1.40-2.20)
Jylha *et al.*, 2006	Finland	Community	20-70	441	poor	2003	MDD	NS/BDI	Point	Total	21.60(16.03-27.17)
Kirby *et al.*, 1997	Ireland	Community	65-99	1232	excellent	1995	MDD	DSM3/GMS	Point	Female	0.50(0.001-1.21)
										Male	0.90(0.001-2.19)
Kringlen *et al.*, 2001	Norway	National	18-65	2066	poor	1996	MDD	DSM3R/CIDI	12 months	Female	9.70(7.94-11.46)
				2066	poor					Male	4.10(2.92-5.28)
Lepine *et al.*, 1997	Belgium	National	18-99	8076	excellent	1995	MDD + dep NOS	DSM3R/MINI	Point	Female	7.90(6.70-9.10)
	France	National	15-99	14517	excellent	1995	MDD + dep NOS	DSM/MINI	Point	Female	13.70(12.56-14.84)
	Germany	National	14-99	16184	excellent	1995	MDD + dep NOS	DSM/MINI	Point	Female	6.60(5.83-7.37)
	Netherlands	National	16-99	7811	excellent	1995	MDD + dep NOS	DSM/MINI	Point	Female	12.30(10.74-13.86)
	Spain	National	15-99	16132	excellent	1995	MDD + dep NOS	DSM/MINI	Point	Female	9.80(8.86-10.74)
	United Kingdom	National	16-99	15743	excellent	1995	MDD + dep NOS	DSM/MINI	Point	Female	12.70(11.68-13.72)
	Belgium	National	18-99	8076	excellent	1995	MDD + dep NOS	DSM3R/MINI	Point	Male	5.10(4.12-6.08)
	France	National	15-99	14517	excellent	1995	MDD + dep NOS	DSM/MINI	Point	Male	7.70(6.81-8.59)

Study	Country	Coverage	Age range	Cohort size	Response rate	Midyear	Depression subtype	Diagnostic criteria/tool	Parameter Type	Sex	Prevalence % (95% uncertainty)
Lepine *et al.*, 1997	Germany	National	14-99	16184	excellent	1995	MDD + dep NOS	DSM/MINI	Point	Male	4.60(3.93-5.27)
	Netherlands	National	16-99	7811	excellent	1995	MDD + dep NOS	DSM/MINI	Point	Male	7.80(6.63-8.97)
	Spain	National	15-99	16132	excellent	1995	MDD + dep NOS	DSM/MINI	Point	Male	5.60(4.87-6.33)
	United Kingdom	National	16-99	15743	excellent	1995	MDD + dep NOS	DSM/MINI	Point	Male	10.30(9.28-11.32)
Levav *et al.*, 1993	Israel	National	24-33	4914	excellent	1985	MDD + dep NOS	RDC/SADS	Point	Female	5.18(2.97-7.39)
										Male	4.55(1.69-7.41)
									12 months	Total	6.15(4.34-7.96)
Meltzer *et al.*, 2000	United Kingdom	National	5-15	10438	excellent	1999	MDD	ICD10/DAWBA	Point	Female	0.70(0.37-1.03)
										Male	0.60(0.30-0.90)
Oldehinkel *et al.*, 1999	Germany	Community	14-17	1395	excellent	1996	MDD	DSM4/CIDI	12 months	Female	4.50(2.74-6.26)
										Male	2.40(1.03-3.77)
Pahkala *et al.*, 1995	Finland	Community	65-99	1022	excellent	1990	MDD	DSM3R/Clinical IV	Point	Female	2.20(0.53-3.87)
										Male	2.00(0.001-4.00)
Pirkola *et al.*, 2005	Finland	National	30-99	6005	excellent	2001	MDD	DSM4/CIDI	12 months	Female	6.30(5.09-7.51)
										Male	3.40(2.42-4.38)
Ponizovsky and Grinshpoon, 2009	Israel	National	21-99	4858	average	2004	MDD	DSM4/CIDI	12 months	Total	5.76(4.81-6.71)
Ritchie *et al.*, 2004	France	Community	65-99	1863	excellent	2000	MDD	DSM4/MINI	Point	Female	4.00(2.90-5.20)
										Male	1.80(0.90-2.80)
Saunders *et al.*, 1993	United Kingdom	Community	65-99	5222	excellent	1990	MDD	DSM3/GMS	Point	Female	3.14(0.55-5.73)
										Male	2.55(0.85-4.24)
Simon *et al.*, 2002	France	Community	18-64	5447	average	2002	MDD	DSM4/CIDI	Point	Total	13.50(10.90-16.00)
	Germany	Community	18-64	5447	average	2002	MDD	DSM4/CIDI	Point	Total	5.30(3.90-6.70)

Study	Country	Coverage	Age range	Cohort size	Response rate	Midyear	Depression subtype	Diagnostic criteria/tool	Parameter Type	Sex	Prevalence % (95% uncertainty)
Simon *et al.*, 2002	Germany	Community	18-64	5447	average	2002	MDD	DSM4/CIDI	Point	Total	9.90(6.60-13.10)
	Greece	Community	18-64	5447	average	2002	MDD	DSM4/CIDI	Point	Total	7.30(4.60-9.90)
	Italy	Community	18-64	5447	average	2002	MDD	DSM4/CIDI	Point	Total	4.60(2.90-6.30)
	Netherlands	Community	18-64	5447	average	2002	MDD	DSM4/CIDI	Point	Total	14.40(11.30-17.60)
	United Kingdom	Community	18-64	5447	average	2002	MDD	DSM4/CIDI	Point	Total	17.10(14.40-19.80)
Singleton *et al.*, 2001	United Kingdom	National	16-74	8580	average	2000	MDD	ICD10/CIS-R	Point	Female	2.80(2.08-3.52)
	United Kingdom	National	16-74	8580	average	2000	MDD	ICD10/CIS-R	Point	Male	2.30(1.65-2.95)
Stefansson *et al.*, 1994	Iceland	National	55-57	862	average	1988	MDD + dep NOS	DSM3/DIS	12 months	Female	6.90(3.39-10.41)
										Male	3.60(1.08-6.12)
									Point	Female	5.10(2.05-8.15)
										Male	2.10(0.16-4.04)
Verhulst *et al.*, 1997	Netherlands	National	13-18	2227	average	1995	MDD	DSM3R/DISC	Point	Total	0.40(0.001-0.99)
Weissman *et al.*, 1996	France	Community	18-64	1746	average	1988	MDD	DSM3/CIDI	12 months	Total	4.50(3.23-5.77)
	Germany	Community	24-64	481	average	1981	MDD	DSM3/CIDI	12 months	Total	5.00(2.79-7.21)
Europe, Central/Eastern											
Aluoja *et al.*, 2004	Estonia	National	15-79	4677	average	1997	MDD	ICD10/EST-Q	Point	Female	14.90(11.37-18.43)
										Male	6.70(0.001-19.83)
Bromet *et al.*, 2005	Ukraine	National	18-99	4725	average	2002	MDD	DSM4/CIDI	12 months	Female	11.34(9.71-12.97)
										Male	4.87(3.93-5.81)
									Point	Female	6.60(5.33-7.87)
										Male	2.61(1.94-3.28)
Pakriev *et al.*, 1998	Russian Federation	Community	18-65	855	excellent	1995	MDD	ICD10/CIDI	12 months	Female	35.40(19.08-51.72)
										Male	14.50(2.09-26.91)
Andrade *et al.*, 2003	Czech Republic	National	18-79	1534	average	1999	MDD	DSM4/CIDI	Point	Total	1.00(0.41-1.59)

Study	Country	Coverage	Age range	Cohort size	Response rate	Midyear	Depression subtype	Diagnostic criteria/tool	Parameter Type	Sex	Prevalence % (95% uncertainty)
Basoglu *et al.*, 2005	Croatia	Community	18-65	256	excellent	2001	MDD	DSM4/SCID	12 months	Total	11.00(5.45-16.55)
									Point	Total	10.00(4.67-15.33)
Szadoczky *et al.*, 1998	Hungary	National	18-64	2953	excellent	1996	MDD	DSM3R/DIS	12 months	Female	9.02(5.30-11.80)
										Male	5.79(2.50-8.10)
									Point	Female	3.15(1.40-5.70)
										Male	1.68(0.50-4.40)
Australasia											
Australian Bureau of Statistics, 2007	Australia	National	16-85	8800	excellent	2007	MDD	ICD10/CIDI	12 months	Female	5.2(4.28-5.92)
										Male	3.10(2.27-3.93)
Feehan *et al.*, 1994	New Zealand	Community	17-19	930	excellent	1991	MDD	DSM3/DISC	12 months	Total	13.30(11.10-15.90)
									Point	Total	3.40(2.30-4.80)
Fergusson *et al.*, 1993	New Zealand	Community	15-15	986	average	1992	MDD	DSM3R/DISC	12 months	Total	2.20(1.30-3.10)
									Point	Total	0.50(0.10-0.90)
Hawthorne *et al.*, 2008	Australia	Regional	15-69	3010	average	1998	MDD	DSM4/PRIME-MD	Point	Female	8.35(6.18-10.52)
										Male	5.56(3.77-7.35)
Hawthorne *et al.*, 2008				3015		2004				Female	10.92(8.46-13.37)
										Male	5.81(3.97-7.65)
Kashani *et al.*, 1983	New Zealand	Community	9-9	641	excellent	1982	MDD	DSM3/K-SADS	12 months	Total	1.10(0.001-2.80)
									Point	Total	1.80(0.001-3.60)
McGee *et al.*, 1990	New Zealand	Community	15-15	943	excellent	1988	MDD	DSM3/DISC	12 months	Total	1.90(1.00-2.80)
									Point	Total	1.20(0.50-1.90)
Sawyer *et al.*, 2007	Australia	National	13-17	1490	average	1997	MDD	DSM4/DISC	12 months	Female	4.40(2.29-6.51)
										Male	3.70(1.72-5.68)
Wells *et al.*, 2006	New Zealand	National	16-99	7435	average	2004	MDD	DSM4/CIDI	12 months	Female	7.10(6.30-7.80)
										Male	4.20(3.50-5.00)
Wilhelm *et al.*, 2003	Australia	National	18-75	10641	average	1997	MDD	ICD10/CIDI	Point	Female	4.20(3.61-4.79)

Study	Country	Coverage	Age range	Cohort size	Response rate	Midyear	Depression subtype	Diagnostic criteria/tool	Parameter Type	Sex	Prevalence % (95% uncertainty)
North America											
Andrade *et al.*, 2003	Canada	Regional	18-99	6902	excellent	1991	MDD	DSM4/CIDI	Point	Total	1.90(1.31-2.49)
Bland *et al.*, 1988	Canada	Regional	18-99	3258	average	1985	MDD	DSM3/DIS	Point	Female	3.90(2.92-4.88)
									Point	Male	2.50(1.72-3.28)
									12 months	Female	5.90(4.72-7.08)
									12 months	Male	3.40(2.42-4.38)
Blazer *et al.*, 1994	United States of America	National	15-54	8098	excellent	1991	MDD	DSM3R/CIDI	Point	Female	5.90(4.72-7.08)
										Male	3.80(2.82-4.78)
Cohen *et al.*, 1993	United States of America	Regional	10-20	776	average	1985	MDD	DSM3R/DISC	Point	Female	4.29(2.53-6.05)
										Male	2.00(0.43-3.57)
Costello *et al.*, 1996	United States of America	Regional	9-13	4500	excellent	1994	MDD	DSM3R/CAPA	Point	Total	1.11(0.67-1.55)
Fleming *et al.*, 1989	Canada	Regional	6-16	2852	excellent	1983	MDD	DSM3/CBCL	Point	Female	1.42(0.59-2.24)
										Male	0.96(0.001-1.95)
Garrison *et al.*, 1992	United States of America	Community	12-14	3283	excellent	1987	MDD	DSM3/K-SADS	12 months	Female	3.22(1.99-4.46)
										Male	1.59(0.71-2.47)
Gum *et al.*, 2009	United States of America	National	18-99	9282	average	2002	MDD	DSM4/CIDI	12 months	Female	8.50(7.72-9.28)
										Male	4.70(4.11-5.29)
Kessler and Walters, 1998	United States of America	National	15-24	1769	excellent	1991	MDD	DSM3R/CIDI	12 months	Female	22.44(17.26-27.62)
										Male	12.81(8.67-16.95)
									Point	Female	8.54(5.33-11.75)
										Male	4.75(2.28-7.21)

Study	Country	Coverage	Age range	Cohort size	Response rate	Midyear	Depression subtype	Diagnostic criteria/tool	Parameter Type	Sex	Prevalence % (95% uncertainty)
Kessler *et al.*, 1993	United States of America	National	25-54	8098	excellent	1991	MDD + dep NOS	DSM3R/CIDI	12 months	Female	11.81(9.26-14.36)
										Male	6.78(4.43-9.13)
Lewinsohn *et al.*, 1993	United States of America	Regional	14-18	1710	average	1988	MDD	DSM3R/K-SADS	Point	Female	3.37(2.19-4.55)
										Male	1.71(0.83-2.59)
			15-19	1508	average	1989	MDD	DSM3R/SADS-LIFE	Point	Female	3.58(2.31-4.85)
										Male	2.80(1.62-3.98)
Mojtabai and Olfson, 2004	United States of America	National	50-99	9747	excellent	1996	MDD	DSM3R/CIDI	12 months	Female	8.50(7.80-9.30)
										Male	4.10(3.50-4.70)
Newman *et al.*, 1998	Canada	Regional	65-99	1119	excellent	1996	MDD	DSM3/GMS	Point	Female	14.10(11.16-17.04)
										Male	7.30(4.56-10.04)
						1994	MDD	DSM4/GMS	Point	Total	0.86(0.27-1.45)
Offord *et al.*, 1996	Canada	Regional	15-64	8115	average	1994	MDD	DSM3R/CIDI	12 months	Female	5.40(4.42-6.38)
										Male	2.80(2.02-3.58)
Patten, 2001	Canada	National	12-99	70538	average	1997	MDD	DSM4/CIDI	12 months	Female	5.24(5.40-8.00)
										Male	2.77(1.90-3.20)
Patten *et al.*, 2003	Canada	Regional	18-99	501	average	2000	MDD	DSM4/CIDI	12 months	Female	13.20(9.10-17.30)
										Male	7.40(4.20-10.60)
Regier *et al.*, 1988	United States of America	Regional	18-99	18571	average	1982	MDD	DSM3/DIS	Point	Female	2.90(2.51-3.29)
										Male	1.60(1.21-1.99)
Simon *et al.*, 2002	United States of America	Community	18-64	5447	average	2002	MDD	DSM4/CIDI	Point	Total	6.40(4.60-8.20)
South America											
Andrade *et al.*, 2003	Mexico	Community	18-54	1734	average	1995	MDD	DSM3R/CIDI	Point	Total	2.20(1.02-3.38)
Benjet *et al.*, 2009	Mexico	Community	12-17	3005	average	2005	MDD	DSM4/CIDI	12 months	Total	4.80(3.90-5.70)
Kohn *et al.*, 2005	Honduras	Community	15-99	800	excellent	1999	MDD	DSM4/Sx Scale	Point	Total	18.09(14.22-21.96)

Study	Country	Coverage	Age range	Cohort size	Response rate	Midyear	Depression subtype	Diagnostic criteria/tool	Parameter Type	Sex	Prevalence % (95% uncertainty)
Medina-Mora *et al.*, 2005	Mexico	National	18-65	5826	average	2002	MDD	DSM4/CIDI	12 months	Total	3.70(3.11-4.29)
Slone *et al.*, 2006	Mexico	Regional	18-92	2509	average	2000	MDD	DSM4/CIDI	12 months	Female	7.60(6.20-9.00)
										Male	4.30(3.10-5.50)
									Point	Female	5.70(4.50-6.90)
										Male	3.30(2.20-4.40)
Andrade *et al.*, 2003	Chile	Regional	15-99	2978	excellent	1996	MDD	DSM3R/CIDI	Point	Total	3.30(2.52-4.08)
Araya *et al.*, 2001	Chile	Community	16-64	3870	excellent	1997	MDD	ICD10/CIS-R	Point	Female	8.00(6.50-9.80)
										Male	2.70(1.40-5.10)
Simon *et al.*, 2002	Chile	Community	18-64	5447	average	2002	MDD	DSM4/CIDI	Point	Total	26.30(16.90-35.80)
Andrade *et al.*, 2002	Brazil	Community	18-99	1464	average	1995	MDD	ICD10/CIDI	12 months	Female	9.20(7.04-11.36)
										Male	4.30(2.54-6.06)
									Point	Female	5.40(4.22-6.58)
										Male	3.20(1.44-4.96)
Costa *et al.*, 2007	Brazil	Community	75-99	392	excellent	1999	MDD	ICD10/SCAN	Point	Female	18.80(12.20-28.00)
										Male	7.90(3.10-18.50)
Fleitlich-Bilyk and Goodman, 2004	Brazil	Community	7-14	1251	excellent	2001	MDD	DSM4/DAWBA	Point	Total	1.00(0.20-1.90)
Simon *et al.*, 2002	Brazil	Community	18-64	5447	average	2002	MDD	DSM4/CIDI	Point	Total	18.30(14.20-22.30)
Canino *et al.*, 1987	Puerto Rico	National	18-64	1513	excellent	1984	MDD	DSM3/DIS	Point	Female	3.30(2.12-4.48)
										Male	2.40(1.22-3.58)
Canino *et al.*, 2004	Puerto Rico	National	4-17	1897	excellent	2000	MDD	DSM4/DISC	12 months	Total	3.00(2.00-4.50)
Maharaj *et al.*, 2008	Trinidad and Tobago	Community	13-19	1290	excellent	2003	MDD	DSM4/BDI	Point	Female	29.70(24.96-34.44)
										Male	19.40(14.55-24.25)

Study	Country	Coverage	Age range	Cohort size	Response rate	Midyear	Depression subtype	Diagnostic criteria/tool	Parameter Type	Sex	Prevalence % (95% uncertainty)
Africa/Middle East											
Afifi *et al*., 2006	Oman	National	14-20	5409	excellent	2004	MDD	NS/CDI	Point	Female	19.40(17.22-21.58)
										Male	14.70(12.78-16.62)
Alhasnawi *et al*., 2009	Iraq	National	18-99	4332	excellent	2007	MDD	DSM4/CIDI	12 months	Total	3.90(3.12-4.68)
Al-Jawadi and Abdul-Rhman, 2007	Iraq	Community	1-15	3079	excellent	2004	MDD	DSM4/Dx IV	Point	Female	1.90(0.86-2.94)
										Male	1.20(0.45-1.95)
Andrade *et al*., 2003	Turkey	National	18-54	6095	average	1996	MDD	DSM3R/CIDI	Point	Total	3.10(2.32-3.88)
Bostanci *et al*., 2005	Turkey	Community	16-99	504	excellent	2000	MDD	NS/BDI	12 months	Female	23.60(15.24-31.96)
										Male	28.00(20.59-35.41)
Ghanem *et al*., 2009	Egypt	National	18-65	14640	excellent	2003	MDD + dep NOS	DSM4/MINI	Point	Total	5.22(4.70-5.74)
Karam *et al*., 2006	Lebanon	National	18-99	2857	average	2003	MDD	DSM4/CIDI	12 months	Total	4.90(3.53-6.27)
Simon *et al*., 2002	Turkey	Community	18-64	5447	average	2002	MDD	DSM4/CIDI	Point	Total	10.70(7.70-13.70)
Bolton *et al*., 2002	Rwanda	Community	18-85	368	excellent	1999	MDD	DSM4/HSCL	Point	Female	17.70(12.90-22.50)
										Male	11.20(5.70-16.70)
Bolton *et al*., 2004	Uganda	Community	18-99	368	excellent	2000	MDD	DSM4/HSCL	Point	Female	21.40(17.10-25.40)
										Male	20.20(14.90-25.40)
Kebede and Alem, 1999	Ethiopia	Community	15-99	10203	average	1994	MDD	ICD10/CIDI	Point	Female	3.40(1.39-5.41)
										Male	1.40(0.19-2.61)
Ovuga *et al*., 2005	Uganda	Community	18-84	939	excellent	2003	MDD	NS/BDI	Point	Female	24.50(17.56-31.44)
										Male	13.90(9.98-17.82)
Roberts *et al*., 2009	Sudan	Community	18-99	1242	excellent	2007	MDD	DSM/HSCL	Point	Female	58.73(55.19-62.18)
										Male	40.85(36.69-45.14)
Shaaban and Baashar, 2003	Sudan	Community	12-19	1107	excellent	2005	MDD + dep NOS	DSM4/PSE	Point	Female	12.90(10.04-15.76)
Bhagwanjee *et al*., 1998	South Africa	Community	18-99	354	excellent	1996	MDD	DSM4/Clinical IV	Point	Total	4.80(1.57-8.03)

Study	Country	Coverage	Age range	Cohort size	Response rate	Midyear	Depression subtype	Diagnostic criteria/tool	Parameter Type	Sex	Prevalence % (95% uncertainty)
Hollifield *et al.*, 1990	Lesotho	Community	19-93	356	average	1987	MDD	DSM3/DIS	Point	Female	14.50(7.76-21.24)
										Male	8.80(1.90-15.70)
Adewuya *et al.*, 2006	Nigeria	Community	15-41	1206	excellent	2004	MDD	DSM4/MINI	12 months	Total	2.70(1.37-4.03)
Adewuya and Ologun, 2006	Nigeria	Community	13-18	1095	average			NS/BDI	Point	Total	9.00(6.54-11.46)
Amoran *et al.*, 2007	Nigeria	Regional	15-99	1105	excellent	2004	MDD	DSM4/SCID	Point	Female	5.70(3.19-8.21)
										Male	4.80(1.82-7.78)
Coleman,2006	Gambia	Regional	15-54	1348	average	1999	MDD	ICD10/PSE	Point	Female	10.30(8.30-12.70)
Gureje,2006	Nigeria	National	18-99	1090	average	2001	MDD	DSM4/CIDI	12 months	Total	1.00(0.80-1.20)
Simon *et al.*, 2002	Nigeria	Community	18-64	5447	average	2002	MDD	DSM4/CIDI	Point	Total	4.00(2.60-5.50)
Uwakwe, 2000	Nigeria	Community	60-99	164	excellent	1995	MDD	DSM3/GMS	Point	Female	21.80(5.99-37.61)
				164	excellent			DSM3/GMS		Male	16.50(6.40-26.60)
Asia, East/Southeast											
Chen *et al.*, 2004	China	Community	65-99	1736	excellent	2001	MDD	DSM3/GMS	Point	Female	2.18(1.34-3.34)
										Male	2.33(1.41-3.61)
Chong *et al.*, 2001	Taiwan	Regional	65-99	1350	excellent	1997	MDD	DSM3/GMS	Point	Total	5.90(4.70-7.30)
Hwu *et al.*, 1996	Taiwan	National	18-99	11004	excellent	1984	MDD	DSM3/DIS	12 months	Female	1.30(0.86-1.74)
										Male	0.60(0.31-0.89)
Keqing *et al.*, 2008	China	Regional	18-95	20716	excellent	2005	MDD	DSM4/SCID	Point	Female	3.15(2.82-3.48)
										Male	2.25(1.96-2.53)
Lu *et al.*, 2008	China	Regional	15-99	5033	excellent	2006	MDD	DSM4/CIDI	12 months	Female	1.47(1.01-1.93)
										Male	0.75(0.41-1.09)
									Point	Female	1.13(0.72-1.54)
										Male	0.62(0.31-0.93)
Phillips *et al.*, 2009	China	Regional	18-99	63004	excellent	2003	MDD	DSM4/SCID	Point	Female	2.6(2.28-2.97)
										Male	1.55(1.29-1.85)
Shen *et al.*, 2006	China	Regional	18-70	5201	average	2002	MDD	DSM4/CIDI	12 months	Total	2(1.412-2.588)
Simon *et al.*, 2002	China	Community	18-64	5447	average	2002	MDD	DSM4/CIDI	Point	Total	2.50(1.60-3.40)

Study	Country	Coverage	Age range	Cohort size	Response rate	Midyear	Depression subtype	Diagnostic criteria/tool	Parameter Type	Sex	Prevalence % (95% uncertainty)
Yang *et al.*, 2004	Taiwan	Community	12-16	2440	excellent	1999	MDD	DSM4/K-SADS	Point	Female	4.30(0-10.50)
										Male	0.50(0-1.40)
Vietnamese survey data, 2006 (personal correspondence from Prof Theo Vos)	Vietnam	National	0-99	78290	average	2006	MDD	ICD10/MINI	12 months	Female	3.68(3.41-3.95)
										Male	1.22(1.06-1.38)
Asia, South											
Lopes Cardozo *et al.*, 2005	Afghanistan	National	15-99	699	excellent	2002	MDD	DSM4/HSCL	Point	Female	73.00(57.03-88.97)
										Male	59(48.04-69.96)
Nisar *et al.*, 2004	Pakistan	Community	18-99	1200	excellent	2000	MDD	ICD10/MINI	Point	Female	7.50(5.34-9.66)
Scholte *et al.*, 2004	Afghanistan	Regional	15-99	1011	average	2003	MDD	DSM4/HSCL	Point	Female	58.4(54.2-62.6)
										Male	16.1(12.8-19.4)
Simon *et al.*, 2002	India	Community	18-64	5447	average	2002	MDD	DSM4/CIDI	Point	Total	8.60(6.10-11.1)
Srinath *et al.*, 2005	India	Community	4-16	2064	excellent	1998	MDD	ICD10/DISC	Point	Total	0.10(0.001-0.33)
Subedi *et al.*, 2004	Nepal	Community	50-99	653	excellent	1997	MDD	DSM3R/Sx Scale	Point	Female	5.1(0.001-11.38)
										Male	3.60(0.001-9.41)
Asia Pacific, High Income											
Cho *et al.*, 2007	Korea	Regional	18-64	6275	average	2001	MDD	DSM4/CIDI	12 months	Female	2.50(1.72-3.28)
										Male	0.80(0.21-1.39)
Fones *et al.*, 1998	Singapore	Regional	13-65	3020	average	1996	MDD	ICD10/CIDI	12 months	Total	5.50(4.32-6.68)
Ihara *et al.*, 1998	Japan	Community	65-99	1965	excellent	1993	MDD + dep NOS	DSM3R/SCID	Point	Female	4.00(2.03-5.97)
										Male	0.05(0.001-0.32)
Kawakami *et al.*, 2004	Japan	Community	20-99	1029	poor	1998	MDD	DSM3R/CIDI	Point	Female	1.40(0.01-2.79)
										Male	0.90(0.001-2.16)

Study	Country	Coverage	Age range	Cohort size	Response rate	Midyear	Depression subtype	Diagnostic criteria/tool	Parameter Type	Sex	Prevalence % (95% uncertainty)
Kawakami *et al*., 2005	Japan	Regional	20-99	1664	poor	2003	MDD	DSM4/CIDI	12 months	Total	2.90(2.10-3.70)
Nakao *et al.*, 2006	Japan	Community	20-65	1066	excellent	2004	MDD + dep NOS	DSM4/HAM-D	Point	Total	11.50(8.72-14.28)
Simon *et al.*, 2002	Japan	Community	18-64	5447	average	2002	MDD	DSM4/CIDI	Point	Total	1.60(0.70-2.50)
Weissman *et al*., 1996	Korea	Regional	18-64	5100	average	1984	MDD	DSM3/CIDI	12 months	Total	2.30(1.87-2.73)

Note. MDD: Major depressive disorder; dep NOS: depression not otherwise specified; DSM: Diagnostic and statistical manual of mental disorders; ICD: International Clarification of Diseases; Clinical IV: Clinical interview; DIS: Diagnostic Interview Schedule; GMS: Geriatric Mental State Schedule; SADS: Schedule for Affective Disorders and Schizophrenia; MINI: **Mini** *International Neuropsychiatric Interview; SCID: Structured Clinical Interview for DSM Disorders; BDI: Beck's depression inventory: CAPA: The child and Adolescent Psychiatric Assessment; CBCL: Child Behaviour Checklist; CDI: Children's Depression Inventory; CIDI: Composite International Diagnostic Interview; CIS-R: Revised clinical interview schedule; DAWBA: Development and Wellbeing Assessment; EST-Q: Emotional State Questionnaire, HAM-D: Hamilton Depression Rating Scale; HDL; Modified version of the global depression scale of the Health and Daily living Form; HSCL: Hopkins Symptoms Check List; PRIME-MD: Primary Care Evaluation of Mental Disorders; PSE:* Present State Examination; SCAN: *Schedule for Clinical Assessment in Neuropsychiatry; SPIKE: Semi-structured diagnostic instrument; Sx Scales: other symptom scales*

Table S3. Summary of included studies for incidence

Study	Country	Coverage	Age range	Cohort size	Response rate	Midyear	Depression subtype	Diagnostic criteria/tool	Sex	Annual incidence % (Standard error)
North America										
Patten, 2001	Canada	National	12-99	70538	average	1997	MDD	DSM4/CIDI	Male	2.46 (0.04)
									Female	3.50 (0.04)
Eaton *et al.*, 1989	USA	Regional	18-99	10861	average	1985	MDD	DSM3/DIS	Male	1.98(0.22)
									Female	1.59(0.57)
Lewinsohn *et al.*, 1993	USA	Regional	15-19	1508	average	1997	MDD	DSM3R/SADS	Male	4.53(0.82)
Africa									Female	7.14(1.05)
Mogga *et al.*, 2006	Ethiopia	Regional	18-52	423	average	2000	MDD	DSM4/CIDI	Total	2.40(1.53)

Note. MDD: Major depressive disorder; dep NOS: depression not otherwise specified; DSM: Diagnostic and statistical manual of mental disorders; DIS: Diagnostic Interview Schedule; SADS: Schedule for Affective Disorders and Schizophrenia; CIDI: Composite International Diagnostic Interview

References

1. Aalto-Setala, T., Marttunen, M., Tuulio-Henriksson, A., Poikolainen, K. & Lonnqvist, J. (2001). One-month prevalence of depression and other DSM-IV disorders among young adults. Psychological Medicine 31, 791-801.
2. Adewuya, A. O., Ola, B. A., Aloba, O. O., Mapayi, B. M. & Oginni, O. O. (2006). Depression amongst Nigerian university students. Prevalence and sociodemographic correlates. Soc Psychiatry Psychiatr Epidemiol 41, 674-8.
3. Adewuya, A. O. & Ologun, Y. A. (2006). Factors associated with depressive symptoms in Nigerian adolescents. J Adolesc Health 39, 105-10.
4. Afifi, M., Al Riyami, A., Morsi, M. & Al Kharusil, H. (2006). Depressive symptoms among high school adolescents in Oman. East Mediterr Health J 12 Suppl 2, S126-37.
5. Al-Jawadi, A. A. & Abdul-Rhman, S. (2007). Prevalence of childhood and early adolescence mental disorders among children attending primary health care centers in Mosul, Iraq: a cross-sectional study. BMC Public Health 7, 274.
6. Alhasnawi, S., Sadik, S., Rasheed, M., Baban, A., Al-Alak, M. M., Othman, A. Y., Othman, Y., Ismet, N., Shawani, O., Murthy, S., Aljadiry, M., Chatterji, S., Al-Gasseer, N., Streel, E., Naidoo, N., Mahomoud Ali, M., Gruber, M. J., Petukhova, M., Sampson, N. A. & Kessler, R. C. (2009). The prevalence and correlates of DSM-IV disorders in the Iraq Mental Health Survey (IMHS). World Psychiatry 8, 97-109.
7. Almqvist, F., Puura, K., Kumpulainen, K., Tuompo-Johansson, E., Henttonen, I., Huikko, E., Linna, S., Ikaheimo, K., Aronen, E., Katainen, S., Piha, J., Moilanen, I., Rasanen, E. & Tamminen, T. (1999). Psychiatric disorders in 8-9-year-old children based on a diagnostic interview with the parents. European Child and Adolescent Psychiatry 8, 17-28.
8. Aluoja, A., Leinsalu, M., Shlik, J., Vasar, V. & Luuk, K. (2004). Symptoms of depression in the Estonian population: prevalence, sociodemographic correlates and social adjustment. Journal of Affective Disorders 78, 27-35.
9. Amoran, O., Lawoyin, T. & Lasebikan, V. (2007). Prevalence of depression among adults in Oyo State, Nigeria: a comparative study of rural and urban communities. Aust J Rural Health 15, 211-5.
10. Andrade, L., Caraveo-Anduaga, J. J., Berglund, P., Bijl, R. V., De Graaf, R., Vollebergh, W., Dragomirecka, E., Kohn, R., Keller, M., Kessler, R. C., Kawakami, N., Kilic, C., Offord, D., Ustun, T. B. & Wittchen, H.-U. (2003). The epidemiology of major depressive episodes: Results from the International Consortium of Psychiatric Epidemiology (ICPE) Surveys. International Journal of Methods in Psychiatric Research 12, 3-21.
11. Andrade, L., Walters, E. E., Gentil, V. & Laurenti, R. (2002). Prevalence of ICD-10 mental disorders in a catchment area in the city of Sao Paulo, Brazil. Soc Psychiatry Psychiatr Epidemiol 37, 316-25.
12. Angst, J., Merikangas, K., Scheidegger, P. & Wicki, W. (1990). Recurrent brief depression: a new subtype of affective disorder. Journal of Affective Disorders 19, 87-98.
13. Araya, R., Rojas, G., Fritsch, R., Acuna, J. & Lewis, G. (2001). Common mental disorders in Santiago, Chile: prevalence and socio-demographic correlates. Br J Psychiatry 178, 228-33.
14. Australian Bureau of Statistics (2008). National Survey of Mental Health and Wellbeing: Summary of results. Australian Bureau of Statistics: Canberra.
15. Ayuso-Mateos, J. L., Vazques-Barquero, J. L., Dowrick, C., Lehtinen, V., Dalgard, O. S., Casey, P., Wilkinson, C., Lasa, L., Page, H., Dunn, G., Wilkinson, G., Ballesteros, J., Birkbeck, G., Borve, T., Costello, M., Cuijpers, P., Davies, I., Diez-Manrique, J. F., Fenlon, N., Finne, M., Ford, F., Gaite, L., Gomez del Barrio, A., Hayes, C., Herran, A., Horgan, A., Koffert, T., Jones,

N., Lehtila, M., McDonough, C., Michalak, E., Murphy, C., Nevra, A., Nummelin, T. & Sohlman, B. (2001). Depressive disorders in Europe: Prevalence figures from the ODIN study. British Journal of Psychiatry 179, 308-316.
16. Barry, M. M., Van Lente, E., Molcho, M., Morgan, K., McGee, H., Conroy, R. M., Watson, D., Shelley, E. & Perry, I. (2009). SLAN 2007: Survey of lifestyle, attitudes and nutrition in Ireland. Mental Health and Social Well-being Report. In Mental Health and Social Well-being Report. Department of Health and Children: Dublin.
17. Basoglu, M., Livanou, M., Crnobaric, C., Franciskovic, T., Suljic, E., Duric, D. & Vranesic, M. (2005). Psychiatric and cognitive effects of war in former Yugoslavia: Association of lack of redress for trauma and posttraumatic stress reactions. JAMA 294, 580-590.
18. Beekman, A. T. F., Deeg, D. J. J., Van Tilburg, T., Smith, J. H., Hooijer, C. & Van Tilburg, W. (1995). Major and minor depression in later life: A study of prevalence and risk factors. Journal of Affective Disorders 36, 65-75.
19. Benjet, C., Borges, G., Medina-Mora, M. E., Zambrano, J. & Aguilar-Gaxiola, S. (2009). Youth mental health in a populous city of the developing world: results from the Mexican Adolescent Mental Health Survey. J Child Psychol Psychiatry 50, 386-95.
20. Bhagwanjee, A., Parekh, A., Paruk, Z., Petersen, I. & Subedar, H. (1998). Prevalence of minor psychiatric disorders in an adult African rural community in South Africa. Psychol Med 28, 1137-47.
21. Bland, R. C., Newman, S. C. & Orn, H. (1988). Period prevalence of psychiatric disorders in Edmonton. Acta Psychiatr Scand Suppl 338, 33-42.
22. Blazer, D. G., Kessler, R. C., McGonagle, K. A. & Swartz, M. S. (1994). The prevalence and distribution of major depression in a national community sample: the National Comorbidity Survey. Am J Psychiatry 151, 979-86.
23. Bolton, P., Neugebauer, R. & Ndogoni, L. (2002). Prevalence of depression in rural Rwanda based on symptom and functional criteria. J Nerv Ment Dis 190, 631-7.
24. Bolton, P., Wilk, C. M. & Ndogoni, L. (2004). Assessment of depression prevalence in rural Uganda using symptom and function criteria. Soc Psychiatry Psychiatr Epidemiol 39, 442-7.
25. Bostanci, M., Ozdel, O., Oguzhanoglu, N. K., Ozdel, L., Ergin, A., Ergin, N., Atesci, F. & Karadag, F. (2005). Depressive symptomatology among university students in Denizli, Turkey: prevalence and sociodemographic correlates. Croat Med J 46, 96-100.
26. Bracke, P. & Bracke, P. (1998). Sex differences in the course of depression: evidence from a longitudinal study of a representative sample of the Belgian population. Social Psychiatry & Psychiatric Epidemiology 33, 420-9.
27. Bromet, E. J., Gluzman, S. F., Paniotto, V. I., Webb, C. P. M., Tintle, N. L., Zakhozha, V., Havenaar, J. M., Gutkovich, Z., Kostyuchenko, S. & Schwartz, J. E. (2005). Epidemiology of psychiatric and alcohol disorders in Ukraine: Findings from the Ukraine World Mental Health Survey. Social Psychiatry and Psychiatric Epidemiology 40, 681-690.
28. Canino, G., Shrout, P. E., Rubio-Stipec, M., Bird, H. R., Bravo, M., Ramirez, R., Chavez, L., Alegria, M., Bauermeister, J. J., Hohmann, A., Ribera, J., Garcia, P. & Martinez-Taboas, A. (2004). The DSM-IV rates of child and adolescent disorders in Puerto Rico: prevalence, correlates, service use, and the effects of impairment. Arch Gen Psychiatry 61, 85-93.
29. Canino, G. J., Bird, H. R., Shrout, P. E., Rubio-Stipec, M., Bravo, M., Martinez, R., Sesman, M. & Guevara, L. M. (1987). The prevalence of specific psychiatric disorders in Puerto Rico. Arch Gen Psychiatry 44, 727-35.
30. Carta, M. G., Kovess, V., Hardoy, M. C., Morosini, P., Murgia, S. & Carpiniello, B. (2002). Psychiatric disorders in Sardinian immigrants to Paris: A comparison with Parisians and Sardinians resident in Sardinia. Social Psychiatry and Psychiatric Epidemiology 37, 112-117.

31. Chen, R., Hu, Z., Qin, X., Xu, X. & Copeland, J. R. (2004). A community-based study of depression in older people in Hefei, China--the GMS-AGECAT prevalence, case validation and socio-economic correlates. Int J Geriatr Psychiatry 19, 407-13.
32. Cho, M. J., Kim, J. K., Jeon, H. J., Suh, T., Chung, I. W., Hong, J. P., Bae, J. N., Lee, D. W., Park, J. I., Cho, S. J., Lee, C. K. & Hahm, B. J. (2007). Lifetime and 12-month prevalence of DSM-IV psychiatric disorders among Korean adults. Journal of Nervous and Mental Disease 195, 203-210.
33. Chong, M. Y., Tsang, H. Y., Chen, C. S., Tang, T. C., Chen, C. C., Yeh, T. L., Lee, Y. H. & Lo, H. Y. (2001). Community study of depression in old age in Taiwan: prevalence, life events and socio-demographic correlates. Br J Psychiatry 178, 29-35.
34. Cohen, P., Cohen, J., Kasen, S., Velez, C. N., Hartmark, C., Johnson, J., Rojas, M., Brook, J. & Streuning, E. L. (1993). An epidemiological study of disorders in late childhood and adolescence--I. Age- and gender-specific prevalence. J Child Psychol Psychiatry 34, 851-67.
35. Copeland, J. R. M., Beekman, A. T. F., Dewey, M. E., Hooijer, C., Jordan, A., Lawlor, B. A., Lobo, A., Magnusson, H., Mann, A. H., Meller, I., Prince, M. J., Reischies, F., Turrina, C., deVries, M. W. & Wilson, K. C. M. (1999). Depression in Europe. Geographical distribution among older people. British Journal of Psychiatry 174, 312-321.
36. Costa, E., Barreto, S. M., Uchoa, E., Firmo, J. O., Lima-Costa, M. F. & Prince, M. (2007). Prevalence of International Classification of Diseases, 10th Revision common mental disorders in the elderly in a Brazilian community: The Bambui Health Ageing Study. Am J Geriatr Psychiatry 15, 17-27.
37. Costello, E. J., Angold, A., Burns, B. J., Erkanli, A., Stangl, D. K. & Tweed, D. L. (1996). The Great Smoky Mountains Study of Youth. Functional impairment and serious emotional disturbance. Arch Gen Psychiatry 53, 1137-43.
38. Donnelly, M. (1995). Depression among adolescents in Northern Ireland. . Adolescence 30, 339-351.
39. Eaton, W. W., Kramer, M., Anthony, J. C., Dryman, A., Shapiro, S. & Locke, B. Z. (1989). The incidence of specific DIS/DSM-III mental disorders: data from the NIMH Epidemiologic Catchment Area Program. Acta Psychiatr Scand 79, 163-78.
40. Faravelli, C., Degl'Innocenti, B. G., Aiazzi, L., Incerpi, G. & et al. (1990). Epidemiology of mood disorders: A community survey in Florence. Journal of Affective Disorders 20, 135-141.
41. Feehan, M., McGee, R., Raja, S. N. & Williams, S. M. (1994). DSM-III-R disorders in New Zealand 18-year-olds. Australian and New Zealand Journal of Psychiatry 28, 87-99.
42. Fergusson, D. M., Horwood, L. J. & Lynskey, M. T. (1993). Prevalence and comorbidity of DSM-III-R diagnoses in a birth cohort of 15 year olds. Journal of the American Academy of Child and Adolescent Psychiatry 32, 1127-1134.
43. Fleitlich-Bilyk, B. & Goodman, R. (2004). Prevalence of child and adolescent psychiatric disorders in southeast Brazil. J Am Acad Child Adolesc Psychiatry 43, 727-34.
44. Fleming, J. E., Offord, D. R. & Boyle, M. H. (1989). Prevalence of childhood and adolescent depression in the community. Ontario Child Health Study. Br J Psychiatry 155, 647-54.
45. Fones, C. S., Kua, E. H., Ng, T. P. & Ko, S. M. (1998). Studying the mental health of a nation: a preliminary report on a population survey in Singapore. Singapore Medical Journal 39, 251-255.
46. Frojd, S., Marttunen, M., Pelkonen, M., von der Pahlen, B. & Kaltiala-Heino, R. (2007). Adult and peer involvement in help-seeking for depression in adolescent population A two-year follow-up in Finland. Soc Psychiatry Psychiatr Epidemiol 42, 945-52.

47. Garrison, C. Z., Addy, C. L., Jackson, K. L., McKeown, R. E. & Waller, J. L. (1992). Major depressive disorder and dysthymia in young adolescents. American Journal of Epidemiology 135, 792-802.
48. Ghanem, M., Gadallah, M., Meky, F. A., Mourad, S. & El-Kholy, G. (2009). National Survey of Prevalence of Mental Disorders in Egypt: preliminary survey. East Mediterr Health J 15, 65-75.
49. Goodwin, R. D., Wickramaratne, P., Nomura, Y. & Weissman, M. M. (2007). Familial depression and respiratory illness in children. Archives of Pediatrics and Adolescent Medicine 161, 487-494.
50. Green, H., McGinnity, A., Meltzer, H., Ford, T. & Goodman, R. (2005). Mental health of children and young people in Great Britain 2004. . Office of National Statistics
51. Gum, A. M., King-Kallimanis, B. & Kohn, R. (2009). Prevalence of mood, anxiety, and substance-abuse disorders for older Americans in the national comorbidity survey-replication. Am J Geriatr Psychiatry 17, 769-81.
52. Hawthorne, G., Goldney, R. & Taylor, A. W. (2008). Depression prevalence: Is it really increasing? . The Australian and New Zealand Journal of Psychiatry 42, 606-616.
53. Hollifield, M., Katon, W., Spain, D. & Pule, L. (1990). Anxiety and depression in a village in Lesotho, Africa: a comparison with the United States. Br J Psychiatry 156, 343-50.
54. Hwu, H. G., Chang, I. H., Yeh, E. K., Chang, C. J. & Yeh, L. L. (1996). Major depressive disorder in Taiwan defined by the Chinese diagnostic Interview Schedule. J Nerv Ment Dis 184, 497-502.
55. Ihara, K., Muraoka, Y., Oiji, A. & Nadaoka, T. (1998). Prevalence of mood disorders according to DSM- III -R criteria in the community elderly residents in Japan. Environmental Health and Preventive Medicine 3, 44-49.
56. Jenkins, R., Lewis, G., Bebbinton, P., Brugha, T., Farrell, M., Gill, B. & Meltzer, H. (1997). The National Psychiatric Morbidity Surveys of Great Britain - initial findings from the Household Survey. . Psychological Medicine 27, 775-789.
57. Jylha, P., Isometsa, E. & (2006). The relationship of neuroticism and extraversion to symptoms of anxiety and depression in the general population. Depression & Anxiety 23, 281-289.
58. Karam, E. G., Mneimneh, Z. N., Karam, A. N., Fayyad, J. A., Nasser, S. C., Chatterji, S. & Kessler, R. C. (2006). Prevalence and treatment of mental disorders in Lebanon: a national epidemiological survey. Lancet 367, 1000-6.
59. Kashani, J. H., McGee, R. O., Clarkson, S. E., Anderson, J. C., Walton, L. A., Williams, S., Silva, P. A., Robins, A. J., Cytryn, L. & McKnew, D. H. (1983). Depression in a sample of 9-year-old children: Prevalence and associated characteristics. Archives of General Psychiatry 40, 1217-1223.
60. Kawakami, N., Shimizu, H., Haratani, T., Iwata, N. & Kitamura, T. (2004). Lifetime and 6-month prevalence of DSM-III-R psychiatric disorders in an urban community in Japan. Psychiatry Res 121, 293-301.
61. Kawakami, N., Takeshima, T., Ono, Y., Uda, H., Hata, Y., Nakane, Y., Nakane, H., Iwata, N., Furukawa, T. A. & Kikkawa, T. (2005). Twelve-month prevalence, severity, and treatment of common mental disorders in communities in Japan: preliminary finding from the World Mental Health Japan Survey 2002-2003. Psychiatry Clin Neurosci 59, 441-52.
62. Kebede, D. & Alem, A. (1999). Major mental disorders in Addis Ababa, Ethiopia. II. Affective disorders. Acta Psychiatr Scand Suppl 397, 18-23.
63. Keqing, L., Ze, C., Lijun, C., Qinpu, J., Guang, S., Haoran, W., Huang, J., Wuwen, Z., Jianguo, X., Yanping, Z., Ben, Z., Jianxun, J., Xueyi, W., Jun, T., Yufu, Z., Haishan, H., Jianping, G. &

Enyi, Z. (2008). Epidemiological survey of mental disorders in the people aged 18 and older in Hebei province. Asian Journal of Psychiatry 1, 51-55.
64. Kessler, R. C., McGonagle, K. A., Swartz, M., Blazer, D. G. & Nelson, C. B. (1993). Sex and depression in the National Comorbidity Survey. I: Lifetime prevalence, chronicity and recurrence. J Affect Disord 29, 85-96.
65. Kessler, R. C. & Walters, E. E. (1998). Epidemiology of DSM-III-R major depression and minor depression among adolescents and young adults in the National Comorbidity Survey. Depress Anxiety 7, 3-14.
66. Kirby, M., Bruce, I., Radic, A., Coakley, D. & Lawlor, B. A. (1997). Mental disorders among the community-dwelling elderly in Dublin. British Journal of Psychiatry 171, 369-372.
67. Kohn, R., Levav, I., Garcia, I. D., Machuca, M. E. & Tamashiro, R. (2005). Prevalence, risk factors and aging vulnerability for psychopathology following a natural disaster in a developing country. Int J Geriatr Psychiatry 20, 835-41.
68. Kringlen, E., Torgersen, S. & Cramer, V. (2001). A Norwegian psychiatric epidemiological study. American Journal of Psychiatry 158, 1091-1098.
69. Lepine, J., Gastpar, M., Mendlewicz, J. & Tylee, A. (1997). Depression in the community: The first pan-European study. DEPRES (Depression Research in European Society). International Clinical Psychopharmacology 12, 19-29.
70. Levav, I., Kohn, R., Dohrenwend, B. P., Shrout, P. E., Skodol, A. E., Schwartz, S., Link, B. G. & Naveh, G. (1993). An epidemiological study of mental disorders in a 10-year cohort of young adults in Israel. Psychological Medicine 23, 691-707.
71. Lewinsohn, P. M., Hops, H., Roberts, R. E., Seeley, J. R. & Andrews, J. A. (1993). Adolescent psychopathology: I. Prevalence and incidence of depression and other DSM-III-R disorders in high school students. J Abnorm Psychol 102, 133-44.
72. Lopes Cardozo, B., Bilukha, O. O., Gotway, C. A., Wolfe, M. I., Gerber, M. L. & Anderson, M. (2005). Mental health of women in postwar Afghanistan. Journal of Women's Health 14, 285-293.
73. Lu, J., Ruan, Y., Huang, Y., Yao, J., Dang, W. & Gao, C. (2008). Major depression in Kunming: Prevalence, correlates and co-morbidity in a south-western city of China. Journal of Affective Disorders 111, 221-226.
74. Maharaj, R. G., Alli, F., Cumberbatch, K., Laloo, P., Mohammed, S., Ramesar, A., Rampersad, N., Roopnarinesingh, N. & Ramtahal, I. (2008). Depression among adolescents, aged 13-19 years, attending secondary schools in Trinidad: prevalence and associated factors. West Indian Med J 57, 352-9.
75. McGee, R., Feehan, M., Williams, S., Partridge, F., Silva, P. & Kelly, J. (1990). DSM-III disorders in a large sample of adolescents. Journal of the American Academy of Child and Adolescent Psychiatry 29, 611-619.
76. Medina-Mora, M. E., Borges, G., Lara, C., Benjet, C., Blanco, J., Fleiz, C., Villatoro, J., Rojas, E. & Zambrano, J. (2005). Prevalence, service use, and demographic correlates of 12-month DSM-IV psychiatric disorders in Mexico: results from the Mexican National Comorbidity Survey. Psychol Med 35, 1773-83.
77. Meltzer, H., R., G., Goodman, R. & Ford, T. (2000). The mental health of children and adolescents in Great Britain. . The Stationery Office London.
78. Mogga, S., Prince, M., Alem, A., Kebede, D., Stewart, R., Glozier, N. & Hotopf, M. (2006). Outcome of major depression in Ethiopia: population-based study. Br J Psychiatry 189, 241-6.
79. Mojtabai, R. & Olfson, M. (2004). Major depression in community-dwelling middle-aged and older adults: prevalence and 2- and 4-year follow-up symptoms. Psychol Med 34, 623-34.

80. Nakao, M., Yano, E., Nakao, M. & Yano, E. (2006). Somatic symptoms for predicting depression: One-year follow-up study in annual health examinations. Psychiatry & Clinical Neurosciences 60, 219-225.
81. Newman, S. C., Bland, R. C. & Orn, H. T. (1998). The prevalence of mental disorders in the elderly in Edmonton: a community survey using GMS-AGECAT. Geriatric Mental State-Automated Geriatric Examination for Computer Assisted Taxonomy. Can J Psychiatry 43, 910-4.
82. Nisar, N., Billoo, N. & Gadit, A. A. (2004). Prevalence of depression and the associated risks factors among adult women in a fishing community. Journal of the Pakistan Medical Association 54, 519-525.
83. Offord, D. R., Boyle, M. H., Campbell, D., Goering, P., Lin, E., Wong, M. & Racine, Y. A. (1996). One-year prevalence of psychiatric disorder in Ontarians 15 to 64 years of age. Can J Psychiatry 41, 559-63.
84. Oldehinkel, A. J., Wittchen, H. U. & Schuster, P. (1999). Prevalence, 20-month incidence and outcome of unipolar depressive disorders in a community sample of adolescents. Psychological Medicine 29, 655-668.
85. Ovuga, E., Boardman, J. & Wasserman, D. (2005). The prevalence of depression in two districts of Uganda. Soc Psychiatry Psychiatr Epidemiol 40, 439-45.
86. Pahkala, K., Kesti, E., Kongas-Saviaro, P., Laippala, P. & Kivela, S. L. (1995). Prevalence of depression in an aged population in Finland. Social Psychiatry & Psychiatric Epidemiology 30, 99-106.
87. Pakriev, S., Vasar, V., Aluoja, A., Saarma, M. & Shlik, J. (1998). Prevalence of mood disorders in the rural population of Udmurtia. Acta Psychiatrica Scandinavica 97, 169-174.
88. Patten, S. B. (2001). The duration of major depressive episodes in the Canadian general population. Chronic Dis Can 22, 6-11.
89. Patten, S. B., Stuart, H. L., Russell, M. L., Maxwell, C. J. & Arboleda-Florez, J. (2003). Epidemiology of major depression in a predominantly rural health region. Soc Psychiatry Psychiatr Epidemiol 38, 360-5.
90. Phillips, M. R., Zhang, J., Shi, Q., Song, Z., Ding, Z., Pang, S., Li, X., Zhang, Y. & Wang, Z. (2009). Prevalence, treatment, and associated disability of mental disorders in four provinces in China during 2001–05: an epidemiological survey. The Lancet 373, 2041–2053.
91. Pirkola, S. P., Isometsa, E., Suvisaari, J., Aro, H., Joukamaa, M., Poikolainen, K., Koskinen, S., Aromaa, A. & Lonnqvist, J. K. (2005). DSM-IV mood-, anxiety- and alcohol use disorders and their comorbidity in the Finnish general population. Results from the Health 2000 Study. Social Psychiatry and Psychiatric Epidemiology 40, 1-10.
92. Ponizovsky, A. M. & Grinshpoon, A. (2009). Mood and anxiety disorders and the use of services and psychotropic medication in an immigrant population: findings from the Israel National Health Survey. Can J Psychiatry 54, 409-19.
93. Regier, D. A., Boyd, J. H., Burke, J. D., Jr., Rae, D. S., Myers, J. K., Kramer, M., Robins, L. N., George, L. K., Karno, M. & Locke, B. Z. (1988). One-month prevalence of mental disorders in the United States. Based on five Epidemiologic Catchment Area sites. Arch Gen Psychiatry 45, 977-86.
94. Ritchie, K., Artero, S., Beluche, I., Ancelin, M. L., Mann, A., Dupuy, A. M., Malafosse, A. & Boulenger, J. P. (2004). Prevalence of DSM-IV psychiatric disorder in the French elderly population. British Journal of Psychiatry 184, 147-152.
95. Roberts, B., Damundu, E. Y., Lomoro, O. & Sondorp, E. (2009). Post-conflict mental health needs: a cross-sectional survey of trauma, depression and associated factors in Juba, Southern Sudan. BMC Psychiatry 9, 7.

96. Saunders, P. A., Copeland, J. R. M., Dewey, M. E., Gilmore, C., Larkin, B. A., Phaterpekar, H. & Scott, A. (1993). The prevalence of dementia, depression and neurosis in later life: The Liverpool MRC-ALPHA study. International Journal of Epidemiology 22, 838-47.
97. Sawyer, M. G., Miller-Lewis, L. R. & Clark, J. J. (2007). The mental health of 13-17 year-olds in Australia: Findings from the National Survey of Mental Health and Well-Being. Journal of Youth Adolescence 36, 185-194.
98. Scholte, W. F., Olff, M., Ventevogel, P., De Vries, G. J., Jansveld, E., Lopes Cardozo, B. & Gotway Crawford, C. A. (2004). Mental health symptoms following war and repression in Eastern Afghanistan. Journal of the American Medical Association 292, 585-593.
99. Shaaban, K. M. & Baashar, T. A. (2003). A community study of depression in adolescent girls: prevalence and its relation to age. Med Princ Pract 12, 256-9.
100. Shen, Y. C., Zhang, M. Y., Huang, Y. Q., He, Y. L., Liu, Z. R., Cheng, H., Tsang, A., Lee, S. & Kessler, R. C. (2006). Twelve-month prevalence, severity, and unmet need for treatment of mental disorders in metropolitan China. Psychological Medicine 36, 257-267.
101. Simon, G. E., Goldberg, D., Von Korff, M. & Ustun, T. (2002). Understanding cross-national differences in depression prevalence. Psychological Medicine 32, 585-594.
102. Singleton, N., Bumpstead, R., O'Brien, M., Lee, A. & Meltzer, H. (2001). Psychiatric morbidity among adults living in private households. The Stationery Office: London.
103. Slone, L. B., Norris, F. H., Murphy, A. D., Baker, C. K., Perilla, J. L., Diaz, D., Rodriguez, F. G. & Gutierrez Rodriguez Jde, J. (2006). Epidemiology of major depression in four cities in Mexico. Depress Anxiety 23, 158-67.
104. Srinath, S., Girimaji, S. C., Gururaj, G., Seshadri, S., Subbakrishna, D. K., Bhola, P. & Kumar, N. (2005). Epidemiological study of child & adolescent psychiatric disorders in urban & rural areas of Bangalore, India. Indian J Med Res 122, 67-79.
105. Stefansson, G. E., Bjornsson, J. K. & Gudmundsdottir, A. (1994). Period prevalence rates of specific mental disorders in an Icelandic cohort. Soc Psychiatry Psychiatr Epidemiol 29, 119-25.
106. Subedi, S., Tausig, M., Subedi, J., Broughton, C. L. & Williams-Blangero, S. (2004). Mental illness and disability among elders in developing countries: the case of Nepal. J Aging Health 16, 71-87.
107. Szadoczky, E., Papp, Z., Vitrai, J., Rihmer, Z. & Furedi, J. (1998). The prevalence of major depressive and bipolar disorders in Hungary. Results from a national epidemiologic survey. Journal of Affective Disorders 50, 153-162.
108. Uwakwe, R. (2000). The pattern of psychiatric disorders among the aged in a selected community in Nigeria. Int J Geriatr Psychiatry 15, 355-62.
109. Verhulst, F. C., van der Ende, J., Ferdinand, R. F. & Kasius, M. C. (1997). The prevalence of DSM-III-R diagnoses in a national sample of Dutch adolescents. Archives of General Psychiatry 54, 329-36.
110. Weissman, M. M., Bland, R. C., Canino, G. J., Faravelli, C., Greenwald, S., Hwu, H. G., Joyce, P. R., Karam, E. G., Lee, C. K., Lellouch, J., LÃ©pine, J. P., Newman, S. C., Rubio-Stipec, M., Wells, J. E., Wickramaratne, P. J., Wittchen, H. & Yeh, E. K. (1996). Cross-national epidemiology of major depression and bipolar disorder. JAMA: The Journal Of The American Medical Association 276, 293-299.
111. Wells, J. E., Oakley Browne, M. A., Scott, K. M., McGee, M. A., Baxter, J. & Kokaua, J. (2006). Prevalence, interference with life and severity of 12 month DSM-IV disorders in Te Rau Hinengaro: The New Zealand Mental Health Survey. Australian and New Zealand Journal of Psychiatry 40, 845-854.

112. Wilhelm, K., Mitchell, P., Slade, T., Brownhill, S. & Andrews, G. (2003). Prevalence and correlates of DSM-IV major depression in an Australian national survey. Journal of Affective Disorders 75, 155-62.
113. Yang, H. J., Soong, W. T., Kuo, P. H., Chang, H. L. & Chen, W. J. (2004). Using the CES-D in a two-phase survey for depressive disorders among nonreferred adolescents in Taipei: A stratum-specific likelihood ratio analysis. Journal of Affective Disorders 82, 419-430.

Table S4. Table showing adjusted(adjusted for study level determinants) and unadjusted point prevalence by region.

Region	Unadjusted[a]		Adjusted(model 2)[b]	
	Prevalence (95% CI)	Weight (%)[c]	Prevalence (95% CI)	Weight[c] (%)
North America (n=19)	4.2(3.5-5.2)	15.5	3.7(3.1-4.3)	14.5
South America (n=13)	6.1(4.4-8.4)	9.5	4.0(3.5-4.7)	9.1
Western Europe (n=33)	5.0(4.6-5.4)	36.4	4.7(4.2-5.1)	37.6
Eastern/Central Europe (n=6)	6.7(4.6-9.9)	5.1	5.1(4.2-6.1)	5.5
Australasia (n=9)	3.8(2.7-4.9)	7.4	4.1(2.9-5.7)	7.2
Africa/Middle East (n=21)	8.6(5.8-12.8)	12.8	6.6(5.3-8.3)	12.1
East/Southeast Asia (n=10)	1.8(1.4-2.3)	7.1	4.0(3.4-4.6)	7.0
Asia South (n=6)	14.5(7.6-27.5)	2.9	8.6(5.2-14.0)	3.2
Asia Pacific (n=8)	2.6(1.6-4.2)	3.4	5.6(4.2-7.4)	4.0
All regions (n=125)	5.0(4.7-5.3)	100	4.7(4.4-5.0)	100

Note. All I^2 statistics >50%; n: number of studies in each group. [a]Unadjusted results represent meta-analysis of reported prevalence estimates without countrolling for the effect of study-level variables. [b]Adjusted model 2 results represent meta-analysis of predicted prevalence estimates contolling for study-level variables. [c]Random effects weights.

Appendix Three

Supplementary text to Chapter Four

Text S1. PRISMA checklist and flow diagram for the literature search to identify epidemiological data.

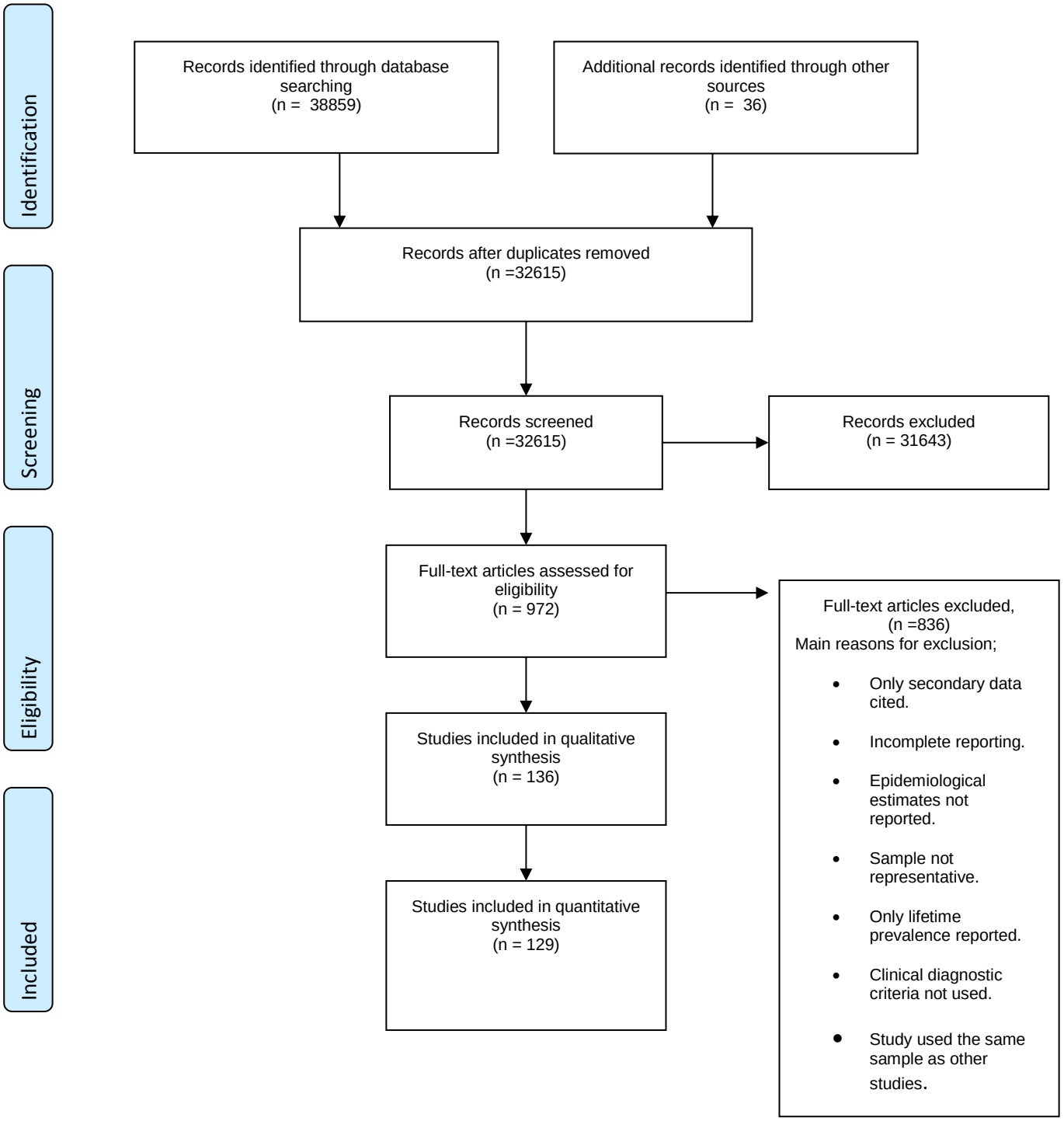
This paper used data from an existing systematic review of the literature which has been published elsewhere (1-3). The PRISMA checklist and flowchart (4), for this systematic review has been summarised below.

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	N/A. This was reported in the specific review papers (1-3).
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	Page 2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	Pages 3-4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	Pages 3-4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	N/A
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	Summary provided on pages 5-6 with more details in specific review papers (1-3).
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	Summary provided on page 5 with more details in specific review papers (1-3).
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Summary provided on page 5 with more details in specific review paper (1-3).
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Summary provided on pages 5-6 with more details in specific review papers (1-3).
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	Summary provided on pages 5-6 with more details in specific review papers (1-3).
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Summary provided on pages 5-6 with more details in specific review papers (1-3).
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	Strategies for adjusting study- and country-level sources of variability discussed on page 8 with additional analyses reported in the specific review papers (1-3).
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	Page 5
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	Summary provided on pages 6-8 with more details in specific review papers (1-3).

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	Strategies for adjusting study- and country-level sources of variability discussed on page 8 with additional analyses reported in the specific review papers (1-3).
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	Pages 7-8 with additional analyses reported in specific review papers (1-3).
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Summary provided on pages 6-7 and figure 2, with more details in specific review papers (1-3).
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Summary provided on pages 5-6 with more details in specific review papers (1-3).
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Results for adjusting study- and country-level sources of variability discussed on page 9 and figures 3-5.
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Summarised in figure 2 with more details in specific review papers (1-3).
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Findings of Bayesian meta regression presented on pages 9-10 and figures 6-8.
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Results for adjusting study- and country-level sources of variability discussed on page 9 and figures 3-5.
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Pages 9-10.
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	Pages 11-12
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	Pages 12-13
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	Page 13
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	See Section 8 of online submission entitled 'Additional Information'

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

PRISMA 2009 Flow Diagram



References

1. Baxter AJ, Page A, Whiteford HA. Factors influencing risk of premature mortality in community cases of depression: a meta-analytic review. Epidemiology Research International. 2011;2011(Article ID 832945):12 pages.
2. Ferrari AJ, Somerville AJ, Baxter AJ, Norman R, Patten SB, Vos T, et al. Global variation in the prevalence and incidence of major depressive disorder: A systematic review of the epidemiological literature. Psychological Medicine. 2013;43(3):471-81.
3. Vos T, Haby MM, Barendregt JJ, Kruijshaar M, Corry J, Andrews G. The burden of major depression avoidable by longer-term treatment strategies. Archives of General Psychiatry. 2004;61(11):1097-103.
4. Moher D, Liberati A, Tetzlaff J, Altman DG, The PG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA Statement. PLoS medicine. 2009;6(7):e1000097.

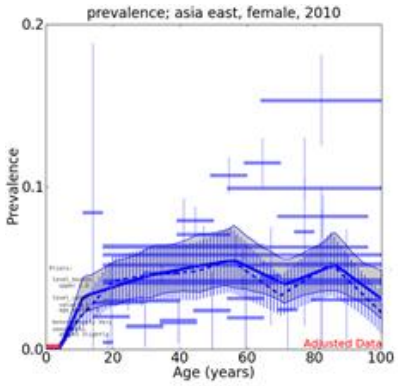
Table S1. Raw and modelled prevalence output for all 21 GBD regions, by sex, 2010

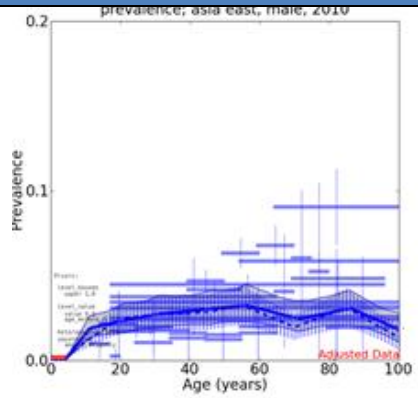
This table compares the modelled prevalence output to the raw prevalence data points for each GBD region. This assists in verifying the level consistency between DisMod-MR's estimated prevalence and reported prevalence estimates obtained from the systematic review of the literature.

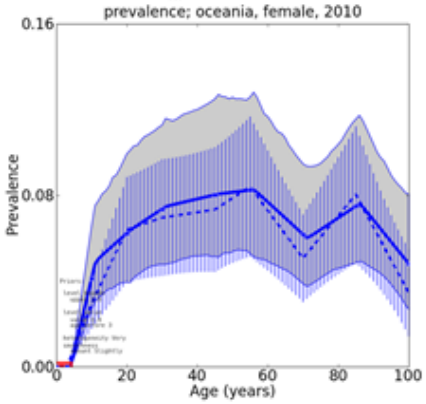
As explained in chapter four, if no data were available for a particular region, then DisMod-MR relied on data points from neighbouring regions in the same GBD super-region to estimate prevalence. Table S1 also groups regions by super-regions so that modelled prevalence and data points can also be compared between regions in the same super region.

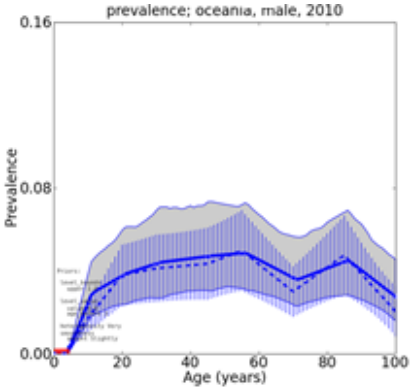
Regional plots are presented separately for males and females, for 2010. In each plot, blue crosses show the individual, sex-specific data points available for that region, with the horizontal line showing the age range for the data point and the vertical line showing the range of uncertainty around the data point. The dotted line shows prevalence output from stage 1 of the modelling process. This is the line of best fit based on data for that parameter only. The numerous blue vertical lines show uncertainty around stage 1 estimates. The solid blue line shows output from stage 2 of the modelling process. This is the line of best fit based on data from all parameters and represents the final output for that parameter. The grey area shows uncertainty around stage 2 estimates. The solid red line represents ages below the minimum age of onset applied.

East Asia and Pacific

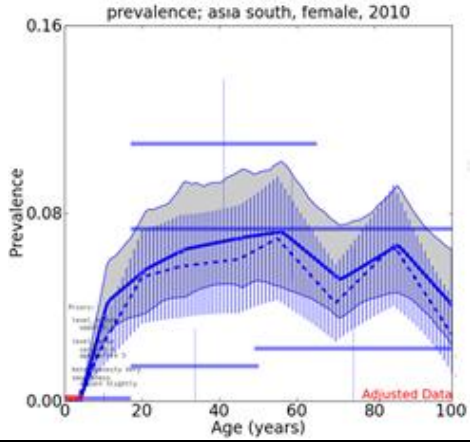


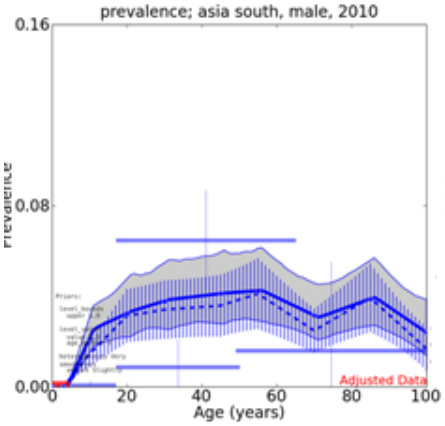


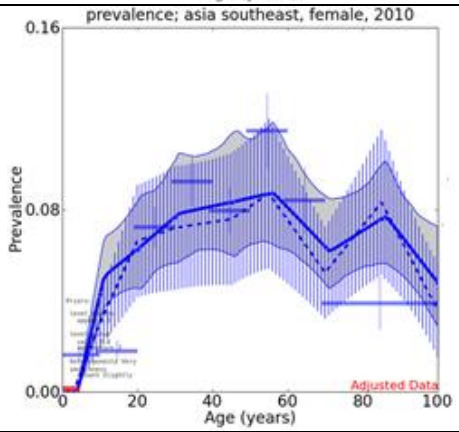


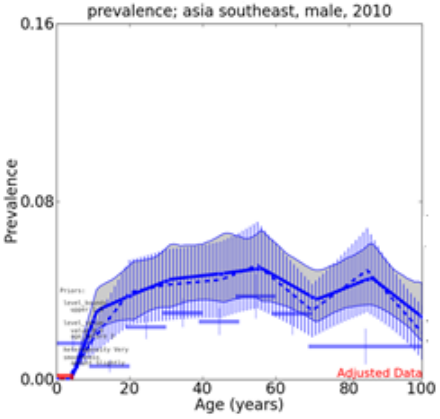


South Asia

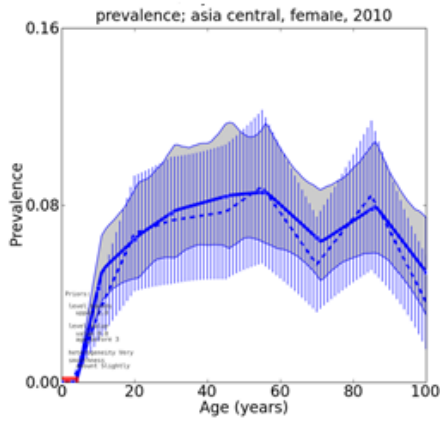


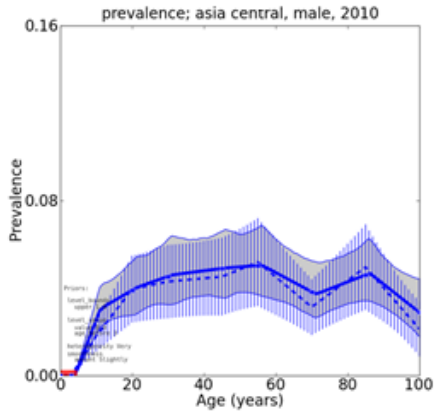


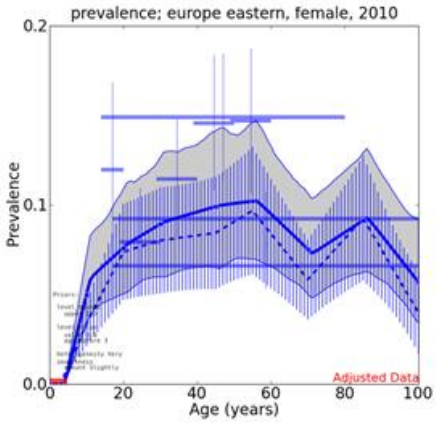


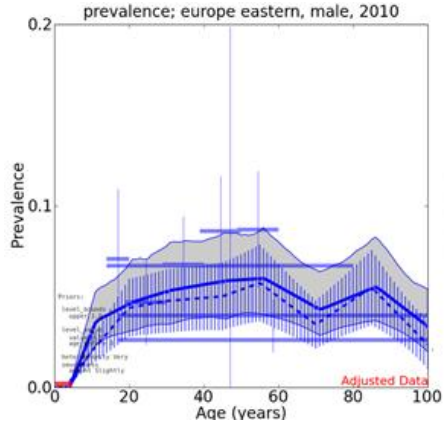


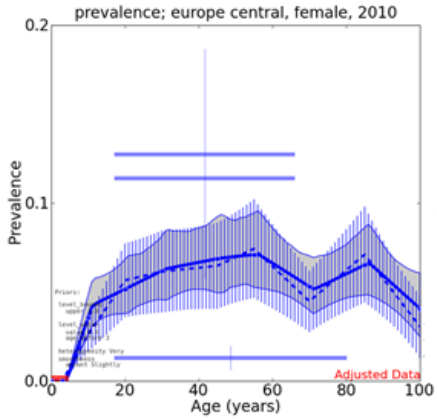
Eastern Europe/Central Asia

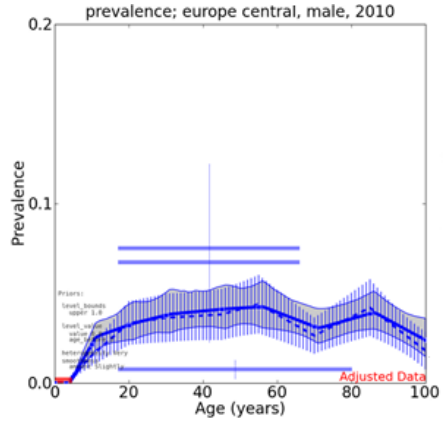




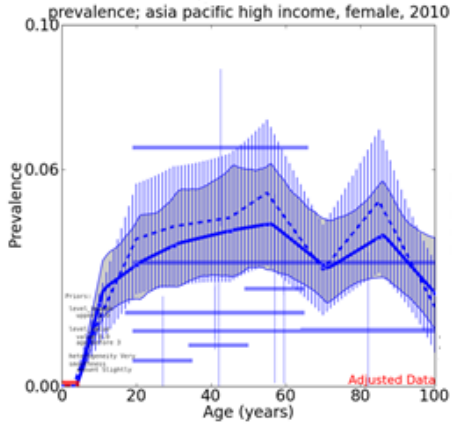


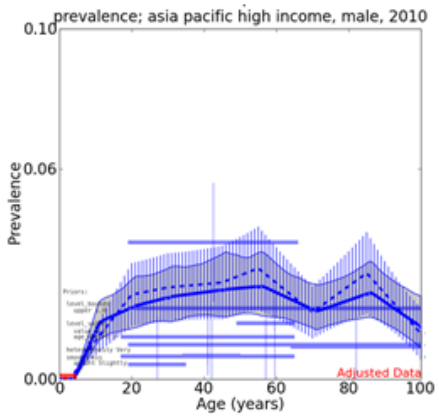


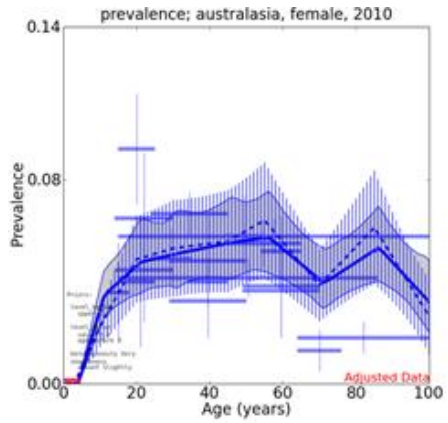


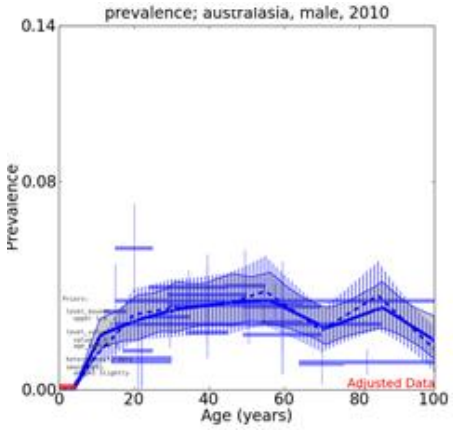


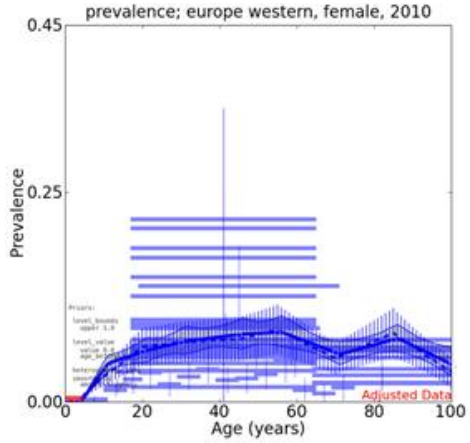
High income

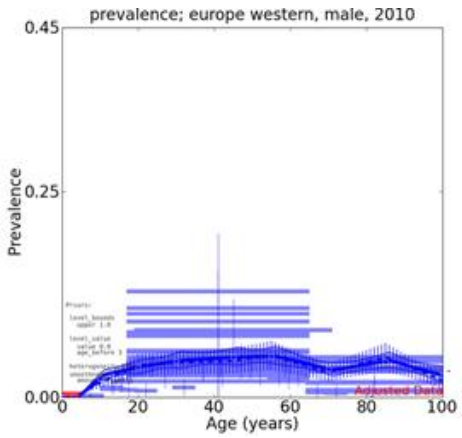

prevalence; asia pacific high income, female, 2010
Prevalence
0.10
0.06
0.00
0
20
40
60
80
100
Age (years)
Adjusted Data

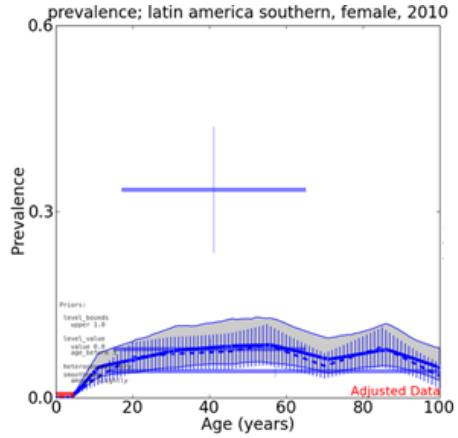

prevalence; asia pacific high income, male, 2010
Prevalence
0.10
0.06
0.00
0
20
40
60
80
100
Age (years)
Adjusted Data

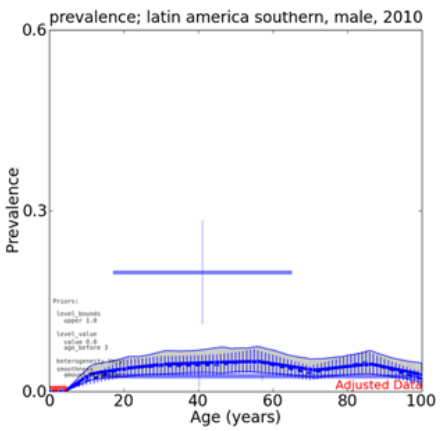

prevalence; australasia, female, 2010
Prevalence
0.14
0.08
0.00
0
20
40
60
80
100
Age (years)
Adjusted Data

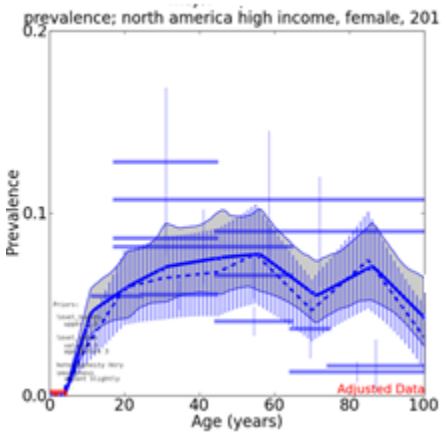

prevalence; australasia, male, 2010
Prevalence
0.14
0.08
0.00
0
20
40
60
80
100
Age (years)
Adjusted Data

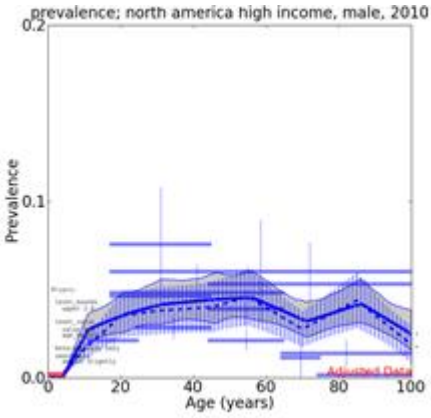

prevalence; europe western, female, 2010
Prevalence
0.45
0.25
0.00
0
20
40
60
80
100
Age (years)
Adjusted Data


prevalence; europe western, male, 2010
Prevalence
0.45
0.25
0.00
0
20
40
60
80
100
Age (years)

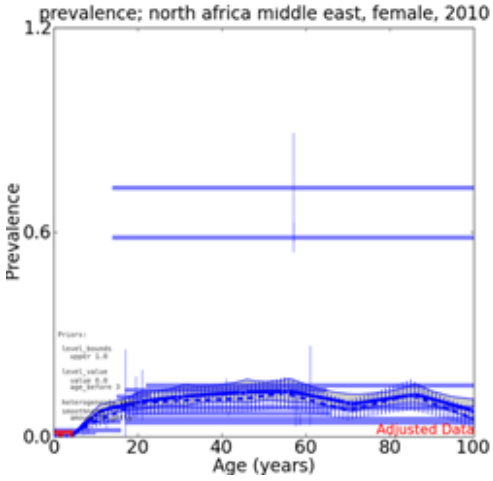


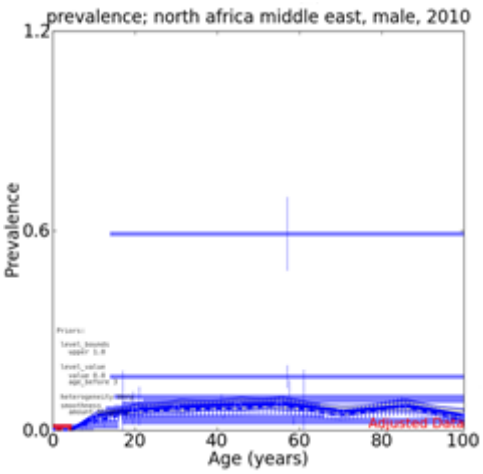




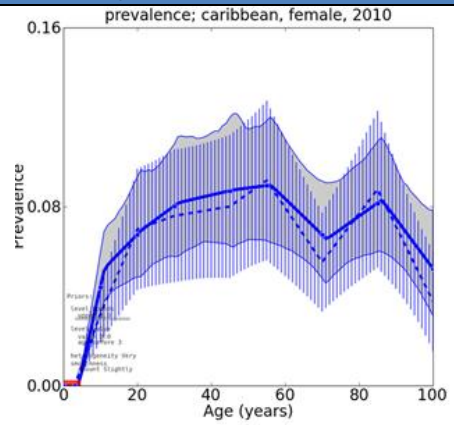


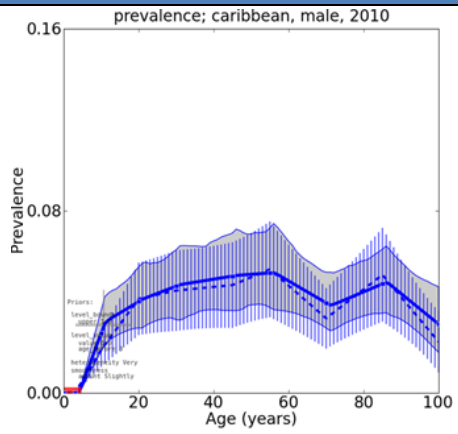
North Africa/Middle East

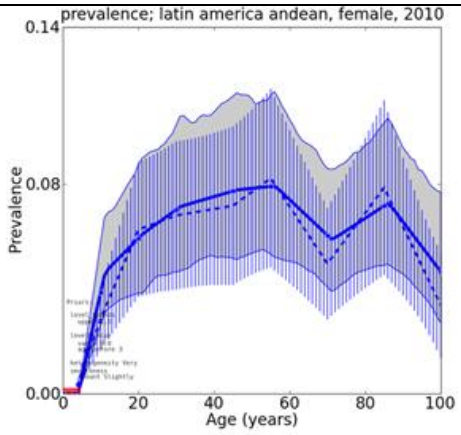


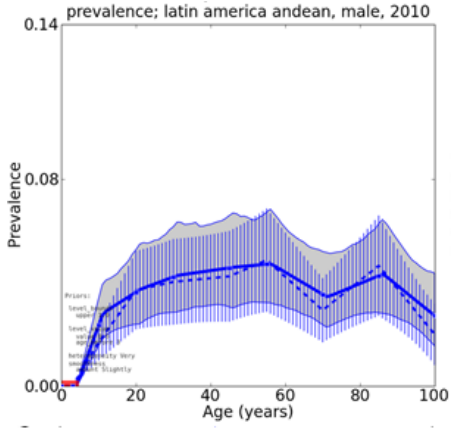


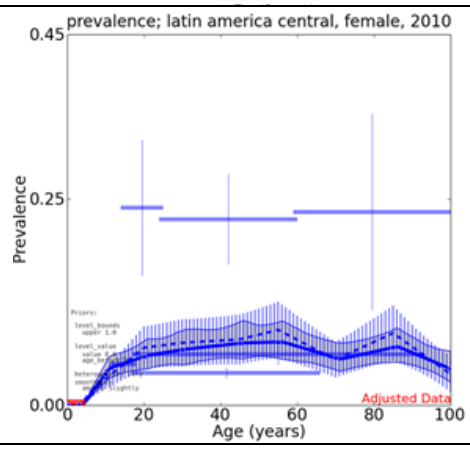
Latin America/Caribbean

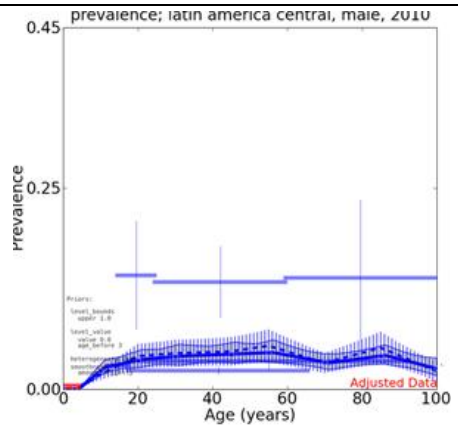


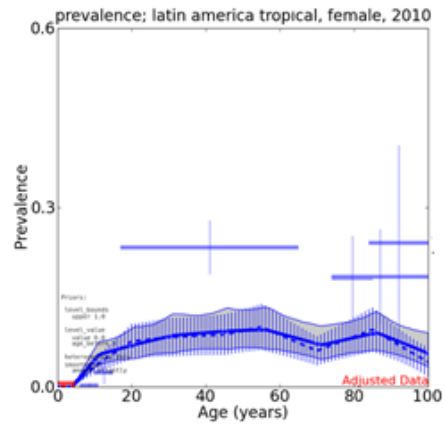


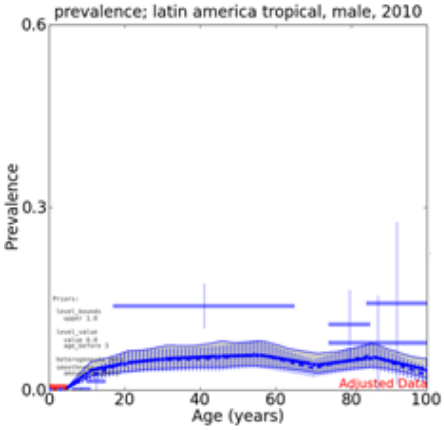




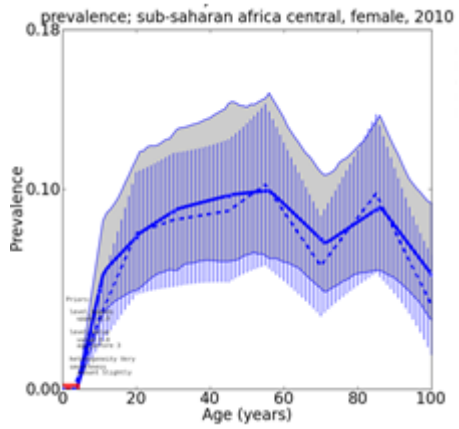


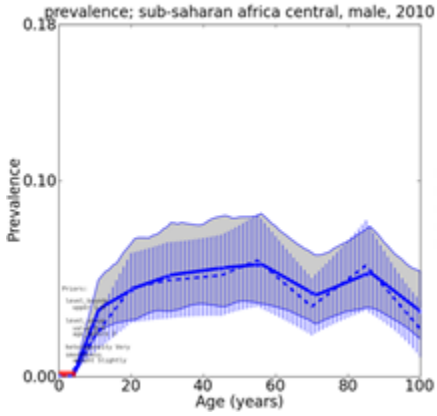


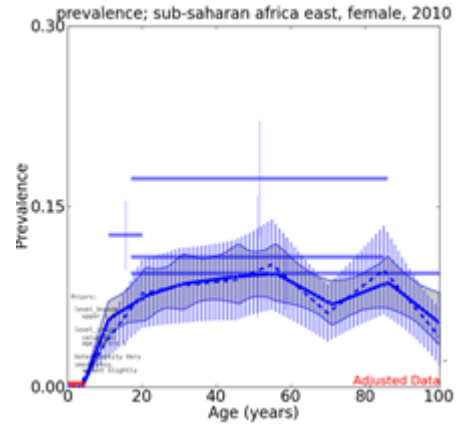


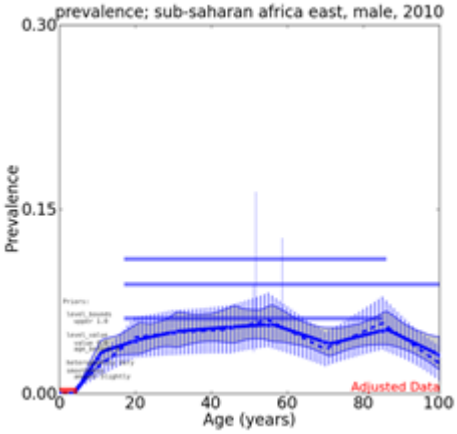


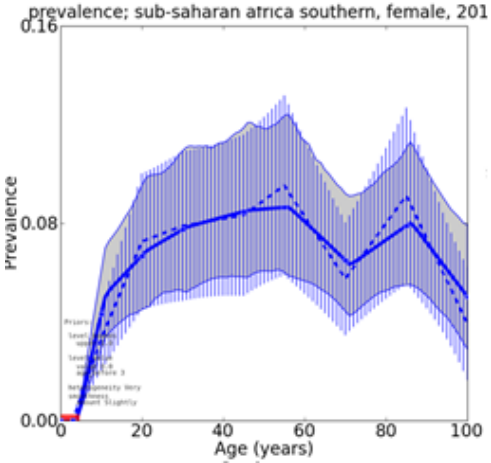
Sub-Saharan Africa

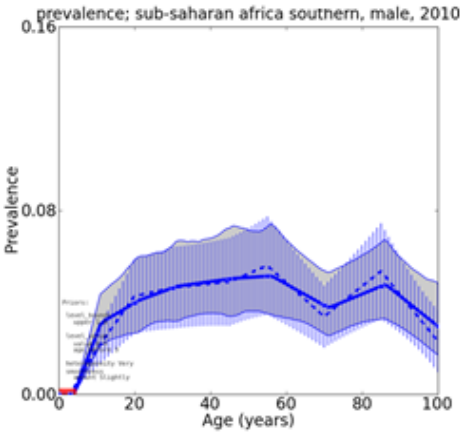


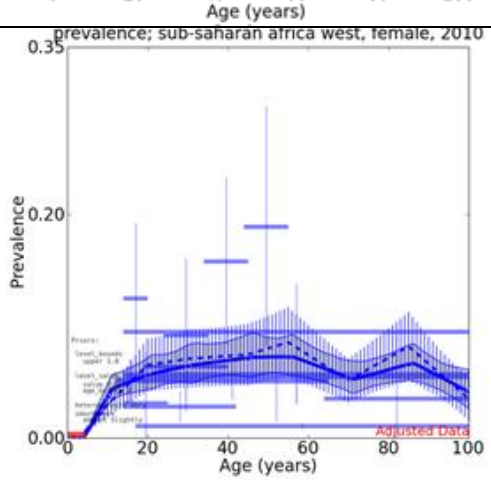


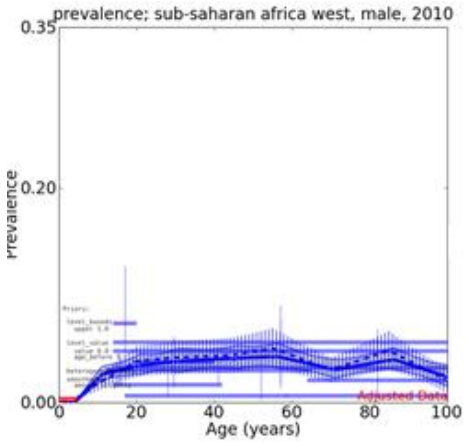


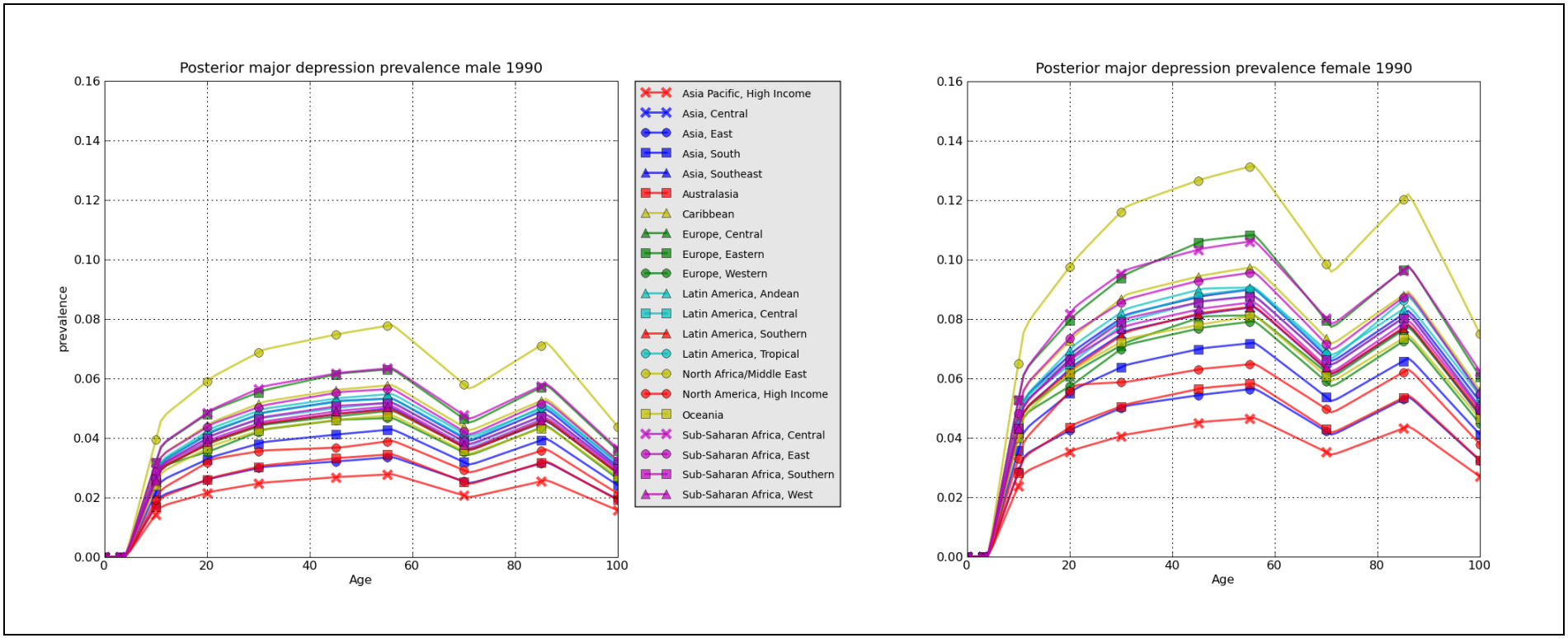






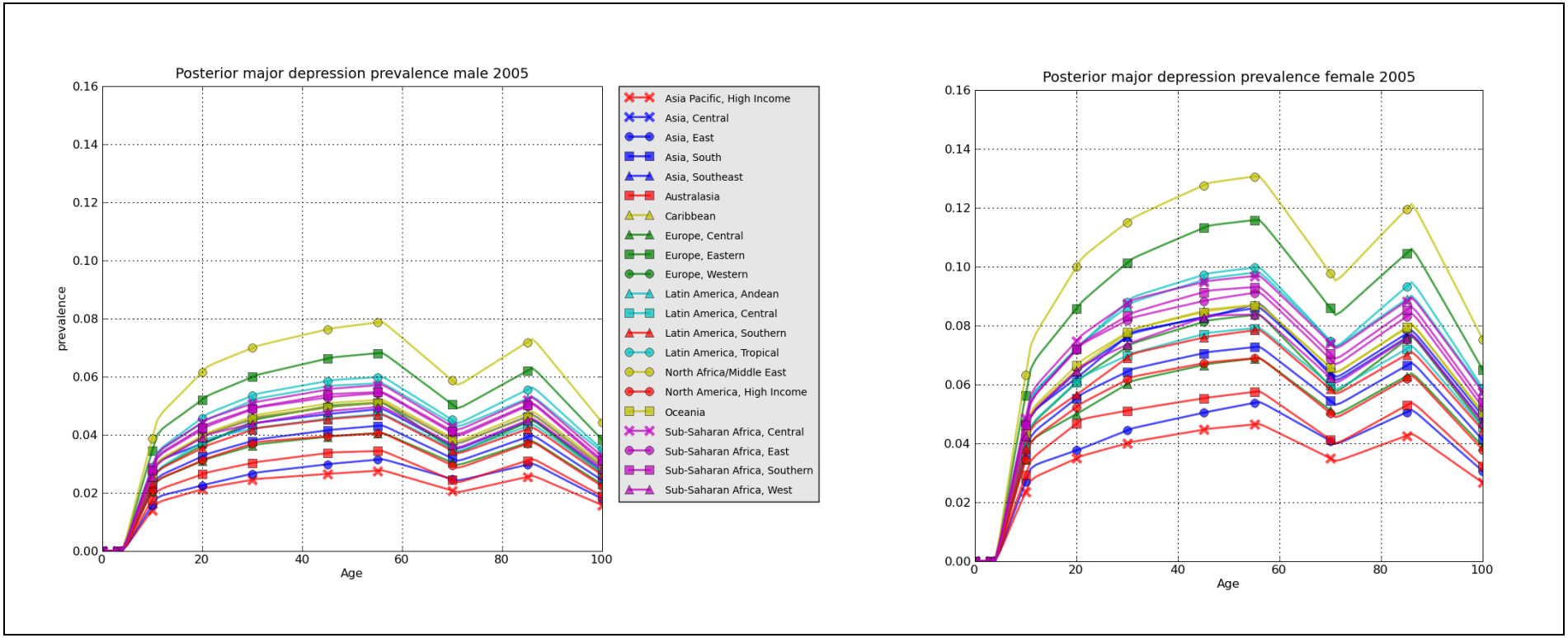






Note. Prevalence interpreted as a proportion where 0.01 equates to 1%

Figure S1. Regional point prevalence of MDD by age and sex, 1990



Note. Prevalence interpreted as a proportion where 0.01 equates to 1%

Figure S2. Regional point prevalence of MDD by age and sex, 2005

Appendix Four

Supplementary text to Chapter Five

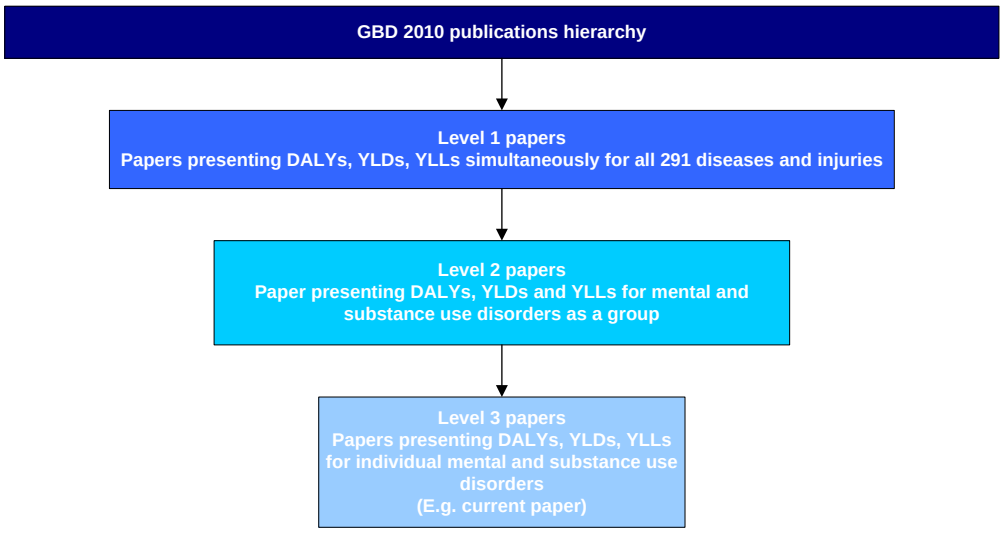
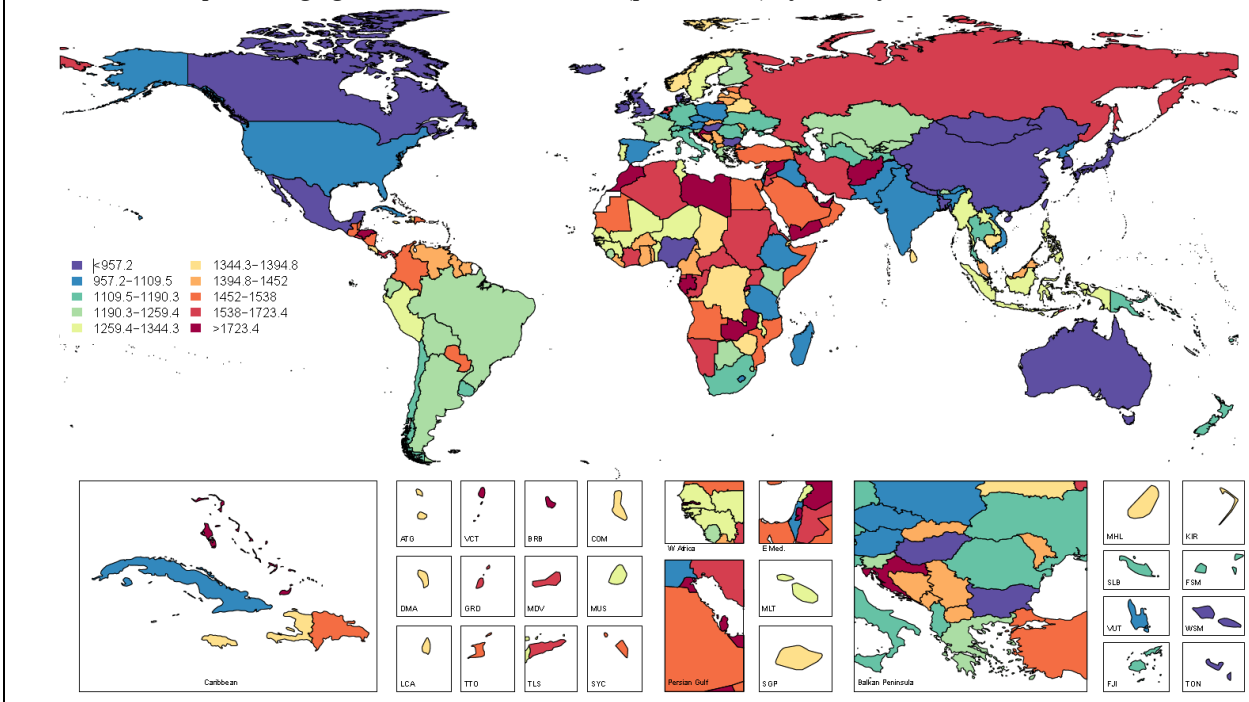
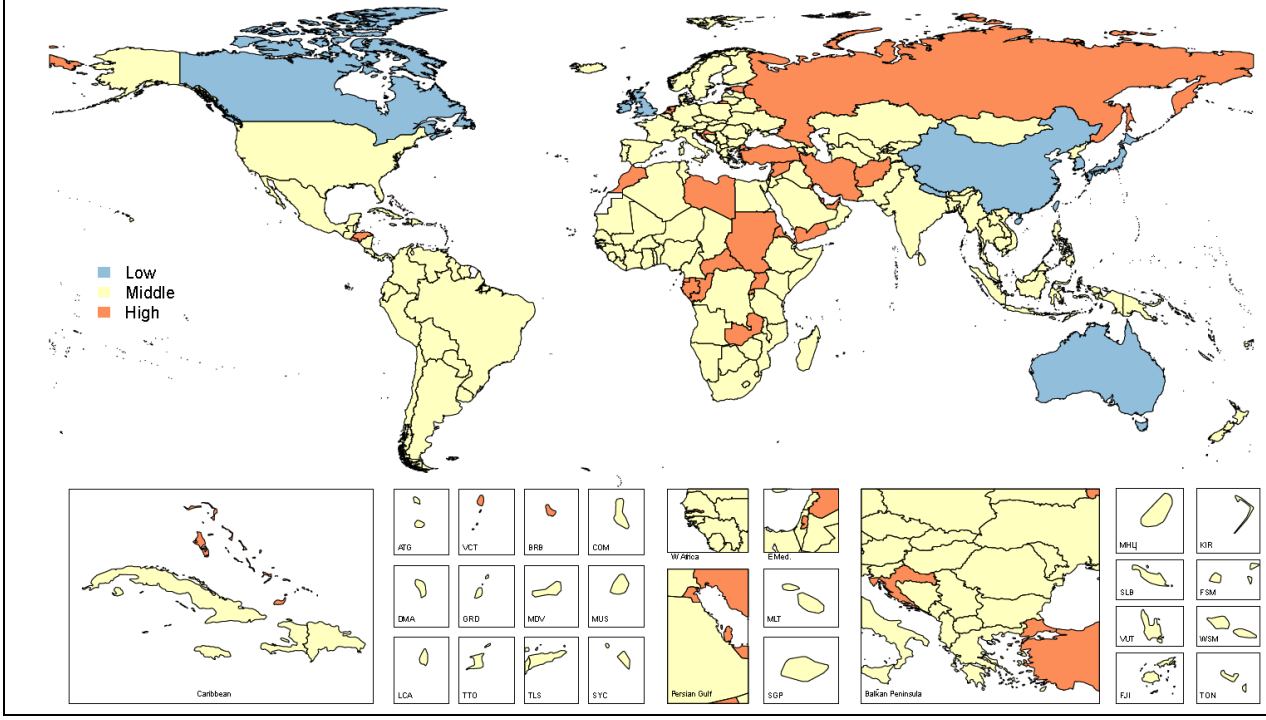


Figure S1: Illustration of the GBD 2010 publications hierarchy

Plot 1: World map showing age-standardised YLD rates (per 100,000) by country



Plot 2: World map marking countries with statistically higher or lower YLD rates compared to the global mean



Note. YLD: years lived with disability; Low: statistically lower YLD rates compared to global mean; Middle: YLD rates not statistically different to global mean; High: statistically higher YLD rates compared to global mean.

Figure S2. YLD rates (per 100,000) by country for depressive disorders in 1990

Table S1: Summary of epidemiological data obtained from the systematic review of the literature and included in the DisMod-MR modelling of major depressive disorder and dysthymia.

	Major depressive disorder					Dysthymia				
Region	**Studies**	**Number of estimates**				**Studies**	**Number of estimates**			
		Prevalence	**Incidence**	**Duration**	**Excess-mortality**		**Prevalence**	**Incidence**	**Remission**	**Excess-mortality**
Asia Pacific, High Income	[1-8]	15	-	-	-	[1-8]	12	-	-	-
Asia, Central	-	-	-	-	-	-	-	-	-	-
Asia, East	[6,9-16]	59	-	-	-	[9-12]	19	-	-	-
Asia, South	[6,17,18 ,19]	6	-	-	-	-	-	-	-	-
Asia, Southeast	[20]	16	-	-	-	-	-	-	-	-
Australasia	[21-30]	41	-	-	1	[21-30]	13	-	-	-
Caribbean	[31,32]	6	-	-	-	[31,32]	1	-	-	-
Europe, Central	[33-35]	23	-	-	-	-	-	-	-	-
Europe, Eastern	[36-38]	13	-	-	-	[36-38]	6	-	-	-
Europe, Western	[6,7,35,39-74]	170	-	1	6	[50,57,61-67,75,76]	35	-	2	0
Latin America, Andean	-	-	-	-	-	-	-	-	-	-
Latin America, Central	[35,77-80]	8	-	-	-	[79,80]	2	-	-	-
Latin America, Southern	[6,35,81]	4	-	-	-	-	-	-	-	-
Latin America, Tropical	[6,82-84]	11	-	-	-	[6,82-84]	8	-	-	-
North Africa/Middle East	[6,35,85-92]	22	-	-	-	{[6,35,85-92]	3	-	-	-
North America, High Income	[6,35,93-116]	122	18	4	6	[94,99,100,102,104, 111,117]	38	3	1	-
Oceania	-	-	-	-	-	-	-	-	-	-
Sub-Saharan Africa, Central	-	-	-	-	-	-	-	-	-	-
Sub-Saharan Africa, East	[118-123]	9	1	-	1	[118-123]	2	-	-	-
Sub-Saharan Africa, Southern	[124,125]	3	-	-	-	[125]	1	-	-	-
Sub-Saharan Africa, West	[6,126-130]	16	-	-	-	[126]	1	-	-	-

Note. Some studies reported more than one estimate

References

1. Cho MJ, Kim JK, Jeon HJ, Suh T, Chung IW, et al. (2007) Lifetime and 12-month prevalence of DSM-IV psychiatric disorders among Korean adults. Journal of Nervous and Mental Disease 195: 203-210.
2. Kawakami N, Shimizu H, Haratani T, Iwata N, Kitamura T (2004) Lifetime and 6-month prevalence of DSM-III-R psychiatric disorders in an urban community in Japan. Psychiatry Research 121: 293-301.
3. Kawakami N, Takeshima T, Ono Y, Uda H, Hata Y, et al. (2005) Twelve-month prevalence, severity, and treatment of common mental disorders in communities in Japan: Preliminary finding from the World Mental Health Japan Survey 2002-2003. Psychiatry and Clinical Neurosciences 59: 441-452.
4. Nakao M, Yano E (2006) Somatic symptoms for predicting depression: One-year follow-up study in annual health examinations. Psychiatry & Clinical Neurosciences 60: 219–225.
5. Ihara K, Muraoka Y, Oiji A, Nadaoka T (1998) Prevalence of mood disorders according to DSM-III-R criteria in the community elderly residents in Japan. Environmental Health and Preventive Medicine 3: 44–49.
6. Simon GE, Goldberg D, Von Korff M, Ustun T (2002) Understanding cross-national differences in depression prevalence. Psychological Medicine 32: 585–594.
7. Weissman MM, Bland RC, Canino GJ, Faravelli C, Greenwald S, et al. (1996) Cross-national epidemiology of major depression and bipolar disorder. JAMA: The Journal of the American Medical Association 276: 293–299.
8. Fones CS, Kua EH, Ng TP, Ko SM (1998) Studying the mental health of a nation: a preliminary report on a population survey in Singapore. Singapore Medical Journal 39: 251–255.
9. Phillips MR, Zhang J, Shi Q, Song Z, Ding Z, et al. (2009) Prevalence, treatment, and associated disability of mental disorders in four provinces in China during 2001–05: an epidemiological survey. The Lancet 373: 2041–2053.
10. Keqing L, Ze C, Lijun C, Qinpu J, Guang S, et al. (2008) Epidemiological survey of mental disorders in the people aged 18 and older in Hebei province. Asian Journal of Psychiatry 1: 51–55.
11. Shen Y, Zhang M, Huang Y, He Y, Liu Z, et al. (2006) Twelve-month prevalence, severity and unmet need for treatment of mental disorders in metropolitan China. Psychological Medicine 36: 257-267.
12. Yang HJ, Soong WT, Kuo PH, Chang HL, Chen WJ (2004) Using the CES-D in a two-phase survey for depressive disorders among nonreferred adolescents in Taipei: A stratum-specific likelihood ratio analysis. Journal of Affective Disorders 82: 419–430.
13. Chen R, Hu Z, Qin X, Xu X, Copeland JRM (2004) A community-based study of depression in older people in Hefei, China – The GMS-AGECAT prevalence, case validation and socio-economic correlates. International Journal of Geriatric Psychiatry 19: 407–413.
14. Hwu H-G, Chang IH, Yeh E-K, Chang C-J, Yeh L-L (1996) Major depressive disorder in Taiwan defined by the Chinese Diagnostic Interview Schedule. Journal of Nervous and Mental Disease 184: 497–502.
15. Lu J, Ruan Y, Huang Y, Yao J, Dang W, et al. (2008) Major depression in Kunming: Prevalence, correlates and co-morbidity in a south-western city of China. Journal of Affective Disorders 111: 221–226.
16. Chong M-Y, Chen C-C, Tsang H-Y, Yeh T-L, Chen C-S, et al. (2001) Community study of depression in old age in Taiwan: Prevalence, life events and socio-demographic correlates. British Journal of Psychiatry 178: 29–35.
17. Nisar N, Billoo N, Gadit AA (2004) Prevalence of depression and the associated risks factors among adult women in a fishing community. Journal of the Pakistan Medical Association 54: 519–525.

18. Srinath S, Girimaji S, S S, Subbakrishna D, Bhola P, et al. (2005) Epidemiological study of child and adolescent psychiatric disorders in urban and rural areas of Bangalore India. Indian Journal of Medical Research 122: 67–79.
19. Subedi S, Tausig M, Subedi J, Broughton CL, Williams-Blangero S (2004) Mental Illness and Disability among Elders in Developing Countries: The Case of Nepal. Journal of Aging and Health 16: 71–87.
20. Nguyen TTN, Long TK, Bui NL, Vos T, Ngo DA, et al. (2011) Viet Nam Burden of Disease and Injury Study. Hanoi.
21. Feehan M, McGee R, Raja SN, Williams SM (1994) DSM-III-R disorders in New Zealand 18-year-olds. Australian and New Zealand Journal of Psychiatry 28: 87–99.
22. Kashani JH, McGee RO, Clarkson SE, Anderson JC, Walton LA, et al. (1983) Depression in a sample of 9-year-old children: Prevalence and associated characteristics. Archives of General Psychiatry 40: 1217–1223.
23. McGee R, Feehan M, Williams S, Partridge F, Silva PA, et al. (1990) DSM-III disorders in a large sample of adolescents. Journal of the American Academy of Child and Adolscent Psychiatry 29: 611-619.
24. Sawyer MG, Miller-Lewis LR, Clark JJ (2007) The mental health of 13-17 year-olds in Australia: Findings from the National Survey of Mental Health and Well-Being. Journal of Youth Adolescence 36: 185–194.
25. Wilhelm K, Mitchell P, Slade T, Brownhill S, Andrews G (2003) Prevalence and correlates of DSM-IV major depression in an Australian national survey. Journal of Affective Disorders 75: 155–162.
26. Hawthorne G, Goldney R, Taylor AW (2008) Depression prevalence: Is it really increasing? . The Australian and New Zealand Journal of Psychiatry 42: 606–616.
27. Wells JE, Oakley Browne MA, Scott KM, McGee MA, Baxter J, et al. (2006) Prevalence, interference with life and severity of 12 month DSM-IV disorders in Te Rau Hinengaro: The New Zealand Mental Health Survey. Australian and New Zealand Journal of Psychiatry 40: 845–854.
28. Australian Bureau of Statistics (2008) National Survey of Mental Health and Wellbeing: Summary of results; ABS, editor. Canberra: Australian Bureau of Statistics.
29. Fergusson DM, Horwood LJ, Lynskey MT (1993) Prevalence and comorbidity of DSM-III-R diagnoses in a birth cohort of 15 year olds. Journal of the American Academy of Child and Adolescent Psychiatry 32: 1127–1134.
30. Jorm A, Henderson A, Kay D, Jacomb P (1991) Mortality in relation to dementia, depression and social integration in an elderly community sample. International Journal of Geriatric Psychiatry 6: 5-11.
31. Canino GJ, Bird HR, Shrout PE, Rubio-Stipec M, Bravo M, et al. (1987) The prevalence of specific psychiatric disorders in Puerto Rico. Archives Of General Psychiatry 44: 727–735.
32. Canino G, Shrout PE, Rubio-Stipec M, Bird HR, Bravo M, et al. (2004) The DSM-IV Rates of child and adolescent disorders in Puerto Rico: Prevalence, correlates, service use, and the effects of impairment. Archives of General Psychiatry 61: 85–93.
33. Basoglu M, Livanou M, Crnobaric C, Franciskovic T, Suljic E, et al. (2005) Psychiatric and cognitive effects of war in former Yugoslavia: Association of lack of redress for trauma and posttraumatic stress reactions. JAMA: The Journal of the American Medical Association 294: 580–590.
34. Szadoczky E, Papp Z, Vitrai J, Rihmer Z, Furedi J (1998) The prevalence of major depressive and bipolar disorders in Hungary. Results from a national epidemiologic survey. Journal of Affective Disorders 50: 153–162.
35. Andrade L, Caraveo-Anduaga JJ, Berglund P, Bijl RV, De Graaf R, et al. (2003) The epidemiology of major depressive episodes: Results from the International Consortium of Psychiatric Epidemiology (ICPE) Surveys. International Journal of Methods in Psychiatric Research 12: 3–21.

36. Pakriev S, Vasar V, Aluoja A, Saarma M, Shlik J (1998) Prevalence of mood disorders in the rural population of Udmurtia. Acta Psychiatrica Scandinavica 97: 169–174.
37. Aluoja A, Leinsalu M, Shlik J, Vasar V, Luuk K (2004) Symptoms of depression in the Estonian population: prevalence, sociodemographic correlates and social adjustment. Journal of Affective Disorders 78: 27–35.
38. Bromet EJ, Gluzman SF, Paniotto VI, Webb CPM, Tintle NL, et al. (2005) Epidemiology of psychiatric and alcohol disorders in Ukraine: Findings from the Ukraine World Mental Health Survey. Social Psychiatry and Psychiatric Epidemiology 40: 681-690.
39. Beekman ATF, Deeg DJJ, Van Tilburg T, Smith JH, Hooijer C, et al. (1995) Major and minor depression in later life: A study of prevalence and risk factors. Journal of Affective Disorders 36: 65–75.
40. Stefansson GE, Bjornsson JK, Gudmundsdottir A (1994) Period prevalence rates of specific mental disorders in an Icelandic cohort. Social Psychiatry and Psychiatric Epidemiology 29: 119–125.
41. Kirby M, Bruce I, Radic A, Coakley D, Lawlor BA (1997) Mental disorders among the community-dwelling elderly in Dublin. British Journal of Psychiatry 171: 369–372.
42. Godin O, Dufouil C, Ritchie K, Dartigues JF, Tzourio C, et al. (2007) Depressive symptoms, major depressive episode and cognition in the elderly: The three-city study. Neuroepidemiology 28: 101–108.
43. Green H, McGinnty A, Meltzer H, Ford T, Goodman R (2005) Mental Health of Children and Young People in Great Britain, 2004. UK National Statistics: 1-156.
44. Pahkala K, Kesti E, Kongas-Saviaro P, Laippala P, Kivela SL (1995) Prevalence of depression in an aged population in Finland. Social Psychiatry & Psychiatric Epidemiology 30: 99–106.
45. Ritchie K, Artero S, Beluche I, Ancelin ML, Mann A, et al. (2004) Prevalence of DSM-IV psychiatric disorder in the French elderly population. British Journal of Psychiatry 184: 147–152.
46. Saunders PA, Copeland JRM, Dewey ME, Gilmore C, Larkin BA, et al. (1993) The prevalence of dementia, depression and neurosis in later life: The Liverpool MRC-ALPHA study. International Journal of Epidemiology 22: 838–847.
47. Jenkins R, Lewis G, Bebbinton P, Brugha T, Farrell M, et al. (1997) The National Psychiatric Morbidity Surveys of Great Britain – Initial findings from the Household Survey. . Psychological Medicine 27: 775–789.
48. Singleton N, Bumpstead R, O'Brien M, Lee A, Meltzer H (2001) Psychiatric morbidity among adults living in private households. London: The Stationery Office.
49. Barry MM, Van Lente E, Molcho M, Morgan K, McGee H, et al. (2009) SLAN 2007: Survey of lifestyle, attitudes and nutrition in Ireland. Mental Health and Social Well-being Report. Dublin: Department of Health and Children.
50. Kringlen E, Torgensen S, Cramer V (2001) A Norwegian psychiatric epidemiological study. American Journal of Psychiatry 158: 1091-1098.
51. Bracke P (1998) Sex differences in the course of depression: evidence from a longitudinal study of a representative sample of the Belgian population. Social Psychiatry & Psychiatric Epidemiology 33: 420–429.
52. Levav I, Kohn R, Dohrenwend BP, Shrout PE, Skodol AE, et al. (1993) An epidemiological study of mental disorders in a 10-year cohort of young adults in Israel. Psychological Medicine 23: 691–707.
53. Frojd S, Marttunen M, Pelkonen M, von der Pahlen B, Kaltiala-Heino R (2007) Adult and peer involvement in help-seeking for depression in adolescent population. A two-year follow-up in Finland. Social Psychiatry and Psychiatric Epidemiology 42: 945–952.
54. Jylha P, Isometsa E (2006) The relationship of neuroticism and extraversion to symptoms of anxiety and depression in the general population. Depression & Anxiety 23: 281–289.
55. Meltzer H, R. G, Goodman R, Ford T (2000) The mental health of children and adolescents in Great Britain. London: The Stationery Office

56. Copeland JRM, Beekman ATF, Dewey ME, Hooijer C, Jordan A, et al. (1999) Depression in Europe. Geographical distribution among older people. British Journal of Psychiatry 174: 312–321.
57. Carta MG, Kovess V, Hardoy MC, Morosini P, Murgia S, et al. (2002) Psychiatric disorders in Sardinian immigrants to Paris: A comparison with Parisians and Sardinians resident in Sardinia. Social Psychiatry and Psychiatric Epidemiology 37: 112–117.
58. Lepine J, Gastpar M, Mendlewicz J, Tylee A (1997) Depression in the community: The first pan-European study. DEPRES (Depression Research in European Society). International Clinical Psychopharmacology 12: 19–29.
59. Angst J, Merikangas K, Scheidegger P, Wicki W (1990) Recurrent brief depression: a new subtype of affective disorder. Journal of Affective Disorders 19: 87–98.
60. Ponizovsky AM, Grinshpoon A (2009) Mood and anxiety disorders and the use of services and psychotropic medication in an immigrant population: Findings from the Israel National Health Survey. Canadian Journal of Psychiatry 54: 409–419.
61. Verhulst FC, Van der Ende J, Ferdinand RF, Kasius MC (1997) The prevalence of DSM-III-R diagnoses in a national sample of dutch adolescents. Archives of General Psychiatry 54: 329–336.
62. Oldehinkel AJ, Wittchen HU, Schuster P (1999) Prevalence, 20-month incidence and outcome of unipolar depressive disorders in a community sample of adolescents. Psychological Medicine 29: 655–668.
63. Pirkola SP, Isometsa E, Suvisaari J, Aro H, Joukamaa M, et al. (2005) DSM-IV mood-, anxiety- and alcohol use disorders and their comorbidity in the Finnish general population. Results from the Health 2000 Study. Social Psychiatry and Psychiatric Epidemiology 40: 1-10.
64. Faravelli C, Degl'Innocenti BG, Aiazzi L, Incerpi G, Pallanti S (1990) Epidemiology of mood disorders: A community survey in Florence. Journal of Affective Disorders 20: 135–141.
65. Almqvist F, Puura K, Kumpulainen K, Tuompo-Johansson E, Henttonen I, et al. (1999) Psychiatric disorders in 8–9-year-old children based on a diagnostic interview with the parents. European Child and Adolescent Psychiatry 8: 17–28.
66. Aalto-Setala T, Marttunen M, Tuulio-Henriksson A, Poikolainen K, Lonnqvist J (2001) One-month prevalence of depression and other DSM-IV disorders among young adults. Psychological Medicine 31: 791-801.
67. Ayuso-Mateos JL, Vazques-Barquero JL, Dowrick C, Lehtinen V, Dalgard OS, et al. (2001) Depressive disorders in Europe: Prevalence figures from the ODIN study. British Journal of Psychiatry 179: 308–316.
68. Bergdahl E, Gustavsson JM, Kallin K, von Heideken Wagert P, Lundman B, et al. (2005) Depression among the oldest old: The Umea 85+ study. International Psychogeriatrics 17: 557–575.
69. Pulska T, Pahkala K, Laippalla P, Kivelä SL (1998) Major depression as a predictor of premature deaths in lderly people in Finland: a community study. Acta Psychiatrica Scandinavica 97: 408-411.
70. Adamson JA, Price GM, Breeze E, Bulpitt CJ, Fletcher AE (2005) Are older people dying of depression? Findings from the Medical Research Council trial of the assessment and management of older people in the community. Journal of the American Geriatrics Society 53: 1128-1132.
71. Penninx BWJH, Geerlings SW, Deeg DJH, van Eijk J, van Tilburg W, et al. (1999) Minor and major depression and the risk of death in older persons. Archives of General Psychiatry 56: 889.
72. Vinkers DJ, Stek ML, Gussekloo J, van der Mast RC, Westendorp RGJ (2004) Does depression in old age increase only cardiovascular mortality? The Leiden 85-plus Study. International Journal of Geriatric Psychiatry 19: 852-857.
73. Donnelly M (1995) Depression among adolescents in Northern Ireland. . Adolescence 30: 339–351.
74. Spijker J, de Graaf R, Bijl RV, Beekman AT, Ormel J, et al. (2002) Duration of major depressive episodes in the general population: results from The Netherlands Mental Health Survey and Incidence Study (NEMESIS). Br J Psychiatry 181: 208-213.

75. Angst J, Wicki W (1991) The Zurich study. XI. Is dysthymia a separate form of depression? Results of the Zurich Cohort Study. European Archives of Psychiatry and Clinical Neuroscience 240: 349–354.
76. Kivela SL, Kongas-Savlaro P, Pahkala K, Kesti E, Laippala P (1993) Five-year prognosis for dysthymic disorder in old age. International Journal of Geriatric Psychiatry 8: 939–947.
77. Slone LB, Norris FH, Murphy AD, Baker CK, Perilla JL, et al. (2006) Epidemiology of major depression in four cities in Mexico. Depression and Anxiety 23: 158–167.
78. Kohn R, Levav I, Garcia ID, Machuca ME, Tamashiro R (2005) Prevalence, risk factors and aging vulnerability for psychopathology following a natural disaster in a developing country. International Journal of Geriatric Psychiatry 20: 835–841.
79. Medina-Mora Icaza ME, Borges-Guimaraes G, Lara C, Ramos-Lira L, Zambrano J, et al. (2005) Prevalence of violent events and post-traumatic stress disorder in the Mexican population. Salud Publica de Mexico 47: 8-22.
80. Benjet C, Borges G, Medina-Mora ME, Zambrano J, Aguilar-Gaxiola S (2009) Youth mental health in a populous city of the developing worlds: results from the Mexican Adolescent Mental health Survey. . The Journal of Child Psychology and Psychiatry 50: 386-395.
81. Araya R, Rojas G, Fritsch R, Acuna J, Lewis G (2001) Common mental disorders in Santiago, Chile: Prevalence and socio-demographic correlates. British Journal of Psychiatry 178: 228–233.
82. Andrade L, Walters E, Gentil V, Laurenti R (2002) Prevalence of ICD-10 mental disorders in a catchment area in the city of Sao Paulo, Brazil. Social Psychiatry and Psychiatric Epidemiology 3: 316–325.
83. Costa E, Barreto SM, Uchoa E, Firmo JOA, Lima-Costa MF, et al. (2007) Prevalence of International Classification of Diseases, 10th Revision common mental disorders in the elderly in a Brazilian community: The Bambui health ageing study. American Journal of Geriatric Psychiatry 15: 17–27.
84. Fleitlich-Bilyk B, Goodman R (2004) Prevalence of child and adolescent psychiatric disorders in southeast Brazil. Journal of the American Academy of Child & Adolescent Psychiatry 43: 727–734.
85. Lopes Cardozo B, Bilukha OO, Gotway CA, Wolfe MI, Gerber ML, et al. (2005) Mental health of women in postwar Afghanistan. Journal of Women's Health 14: 285-293.
86. Scholte WF, Olff M, Ventevogel P, De Vries GJ, Jansveld E, et al. (2004) Mental health symptoms following war and repression in Eastern Afghanistan. Journal of the American Medical Association 292: 585–593.
87. Afifi M, Al Riyami A, Morsi M, Al Kharusil H, Afifi M, et al. (2006) Depressive symptoms among high school adolescents in Oman. Eastern Mediterranean Health Journal 12 Suppl 2: S126–S137.
88. Bostanci M, Ozdel O, Oguzhanoglu NK, Ozdel L, Ergin A, et al. (2005) Depressive symptomatology among university students in Denizli, Turkey: prevalence and sociodemographic correlates. Croatian Medical Journal 46: 96–100.
89. Ghanem M, Gadallah M, Meky FA, Mourad S, El-Kholy G (2009) National survey of prevalence of mental disorders in Egypt: Preliminary survey. Eastern Mediterranean Health Journal 15: 65–75.
90. Karam EG, Mneimneh ZN, Karam AN, Fayyad JA, Nasser SC, et al. (2006) Prevalence and treatment of mental disorders in Lebanon: A national epidemiological survey. The Lancet 367: 1000–1006.
91. Alhasnawi A, Sadik S, Rasheed M, Baban A, Al-Alak MM, et al. (2009) The prevalence and correlates of DSM-IV disorders in the Iraq mental health survey (IHMS). World Psychiatry 8: 97–109.
92. Al-Jawadi A, Abdul-Rhman S (2007) Prevalence of childhood and early adolescence mental disorders among children attending primary health care centres in Mosul, Iraq: A cross-sectional study. BMC Public Health 7: 274–281.

93. Bland RC, Newman SC, Orn H (1997) Age and remission of psychiatric disorders. Canadian Journal of Psychiatry 42: 722–729.
94. Bland R, Newman S, Orn H (1988) Period prevalence of psychiatric disorders in Edmonton. Acta Psychiatrica Scandinavica 77: 33–42.
95. Blazer DG, Kessler RC, McGonagle KA, Swartz MS (1994) The prevalence and distribution of major depression in a national community sample: the National Comorbidity Survey. Am J Psychiatry 151: 979-986.
96. Cohen P, Cohen J, Kasen S, Velez CN, Hartmark C, et al. (1993) An epidemiological study of disorders in late childhood and adolescence – I. Age- and gender-specific prevalence. Journal of Child Psychology and Psychiatry and Allied Disciplines 34: 851–867.
97. Costello EJ, Angold A, Burns BJ, Erkanli A, Stangl DK, et al. (1996) The Great Smoky Mountains Study of youth: Functional impairment and serious emotional disturbance. Archives of General Psychiatry 53: 1137–1143.
98. Fleming JE, Offord DR, Boyle MH (1989) Prevalence of childhood and adolescent depression in the community: Ontario Child Health Study. British Journal of Psychiatry 155: 647–654.
99. Garrison CZ, Addy CL, Jackson KL, McKeown RE, Waller JL (1992) Major depressive disorder and dysthymia in young adolescents. American Journal of Epidemiology 135: 792–802.
100. Gum AM, King-Kallimanis B, Kohn R (2009) Prevalence of mood, anxiety, and substance-abuse disorders for older Americans in the National Comorbidity Survey-replication. The American Journal of Geriatric Psychiatry 17: 769–781.
101. Kessler RC, McGonagle KA, Swartz M, Blazer DG, Nelson CB (1993) Sex and depression in the National Comorbidity Survey: I. Lifetime prevalence, chronicity and recurrence. Journal of Affective Disorders 29: 85–96.
102. Kessler RC, McGonable KA, Zao S, Nelson CB, Hughes M, et al. (1994) Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the United States; results from the National Comorbidity Survey. Archives of General Psychiatry 51: 8-19.
103. Kessler RC, Walters EE (1998) Epidemiology of DSM-III-R major depression and minor depression among adolescents and young adults in the National Comorbidity Survey. Depression and Anxiety 7: 3–14.
104. Lewinsohn PM, Hops H, Roberts RE, Seeley JR, Andrews JA (1993) Adolescent psychopathology: I. Prevalence and incidence of depression and other DSM-III-R disorders in high school students. Journal of Abnormal Psychology 102: 133–144.
105. Mojtabai R, Olfson M (2004) Major depression in community-dwelling middle-aged and older adults: prevalence and 2- and 4-year follow-up symptoms. Psychological Medicine 34: 623–634.
106. Newman SC, Sheldon CT, Bland RC (1998) Prevalence of depression in an elderly community sample: a comparison of GMS-AGECAT and DSM-IV diagnostic criteria. Psychological Medicine 28: 1339–1345.
107. Newman SC, Bland RC, Orn HT (1998) The prevalence of mental disorders in the elderly in Edmonton: a community survey using GMS-AGECAT. Geriatric Mental State-Automated Geriatric Examination for Computer Assisted Taxonomy. Canadian Journal of Psychiatry 43: 910–914.
108. Offord DR, Boyle MH, Campbell D, Goering P, Lin E, et al. (1996) One-year prevalence of psychiatric disorder in Ontarians 15 to 64 years of age. . Canadian Journal of Psychiatry 41: 559–563.
109. Patten SB (2001) The duration of major depressive episodes in the Canadian general population. Chronic Diseases in Canada 22: 6–11.
110. Patten SB, Stuart HL, Russell ML, Maxwell CJ, Arboleda-Florez J (2003) Epidemiology of major depression in a predominantly rural health region. Social Psychiatry and Psychiatric Epidemiology 38: 360–365.
111. Regier DA, Boyd JH, Burke JD, Jr., Rae DS, Myers JK, et al. (1988) One-month prevalence of mental disorders in the United States. Based on five Epidemiologic Catchment Area sites. Archives Of General Psychiatry 45: 977–986.

112. Eaton WW, Kramer M, Anthony JC, Dryman A, Shapiro S, et al. (1989) The incidence of specific DIS/DSM-III mental disorders: data from the NIMH Epidemiologic Catchment Area Program. Acta Psychiatrica Scandinavica 79: 163–178.
113. Gallo JJ, Bogner HR, Morales KH, Post EP, Ten Have T, et al. (2005) Depression, cardiovascular disease, diabetes, and 2-year mortality among older primary care patients. The American journal of geriatric psychiatry: official journal of the American Association for Geriatric Psychiatry 13: 748.
114. Zheng D, Macera CA, Croft JB, Giles WH, Davis D, et al. (1997) Major depression and all-cause mortality among white adults in the United States. Annals of Epidemiology 7: 213-218.
115. Bruce ML, Leaf PJ, Rozal GP, Florio L, Hoff RA (1994) Psychiatric status and 9-year mortality data in the New Haven Epidemiologic Catchment Area Study. The American Journal of Psychiatry 151: 716–721.
116. Murphy JM, Monson RR, Olivier DC, Sobol AM, Leighton AH (1987) Affective disorders and mortality: a general population study. Archives of General Psychiatry 44: 473-480.
117. Klein DN, Shankman SA, Rose S (2006) Ten-year prospective follow-up study of the naturalistic course of dysthymic disorder and double depression. American Journal of Psychiatry 163: 872–880.
118. Bolton P, Neugebauer R, Ndogoni L (2002) Prevalence of depression in rural Rwanda based on symptom and functional criteria. Journal of Nervous and Mental Disease 190: 631–637.
119. Ovuga E, Boardman J, Wasserman D (2005) The prevalence of depression in two districts of Uganda. Social Psychiatry and Psychiatric Epidemiology 40: 439–445.
120. Kebede D, Alem A (1999) Major mental disorders in Addis Ababa, Ethiopia. II. Affective disorders. Acta Psychiatrica Scandinavica 100: 18–23.
121. Bolton P, Wilk CM, Ndogoni L (2004) Assessment of depression prevalence in rural Uganda using symptom and function criteria. Social Psychiatry & Psychiatric Epidemiology 39: 442–447.
122. Shaaban KMA, Baashar TA (2003) A community study of depression in adolescent girls: Prevalence and its relation to age. Medical Principles and Practice 12: 256–259.
123. Mogga S, Prince M, Alem A, Kebede D, Stewart R, et al. (2006) Outcome of major depression in Ethiopia: population-based study. British Journal of Psychiatry 189: 241–246.
124. Hollifield M, Katon W, Spain D, Pule L (1990) Anxiety and depression in a village in Lesotho, Africa: A comparison with the United States. British Journal of Psychiatry 156: 343–350.
125. Bhagwanjee A, Parekh A, Paruk Z, Petersen I, Subedar H (1998) Prevalence of minor psychiatric disorders in an adult African rural community in South Africa. Psychological Medicine 28: 1137–1147.
126. Gureje O, Lasebikan VO, Kola L, Makanjuola VA (2006) Lifetime and 12-month prevalence of mental disorders in the Nigerian Survey of Mental Health and Well-Being. British Journal of Psychiatry 188: 465–471.
127. Adewuya AO, Ola BA, Aloba OO, Mapayi BM, Oginni OO (2006) Depression amongst Nigerian university students. Prevalence and sociodemographic correlates. Social Psychiatry & Psychiatric Epidemiology 41: 674–678.
128. Adewuya AO, Ologun YA (2006) Factors associated with depressive symptoms in Nigerian adolescents. Journal of Adolescent Health 39: 105–110.
129. Amoran O, Lawoyin T, Lasebikan V (2007) Prevalence of depression among adults in Oyo State, Nigeria: A comparative study of rural and urban communities. Australian Journal of Rural Health 15: 211–215.
130. Coleman R, Morison L, Paine K, Powell RA, Walraven G (2006) Women's reproductive health and depression: A community survey in the Gambia, West Africa. Social Psychiatry and Psychiatric Epidemiology 41: 720–727.

Table S2: Age standardised point prevalence (%) by region and country for major depressive disorder(MDD) and dysthymia in 2010.

		MDD			Dysthymia		
Region	**Country**	**Prevalence**	**95% uncertainty interval**		**Prevalence**	**95% uncertainty interval**	
Caribbean		**5.16%**	**4.29%**	**6.21%**	**1.54%**	**1.41%**	**1.71%**
	St Lucia	4.25%	2.82%	6.02%	1.54%	1.31%	1.81%
	Suriname	5.37%	3.54%	7.78%	1.54%	1.31%	1.80%
	Trinidad and Tobago	5.50%	3.64%	7.78%	1.56%	1.31%	1.84%
	Saint Vincent and Grenadines	5.36%	3.66%	7.53%	1.53%	1.30%	1.80%
Europe, Central		**4.09%**	**3.51%**	**4.79%**	**1.62%**	**1.48%**	**1.77%**
	Albania	5.17%	3.48%	7.45%	1.62%	1.37%	1.90%
	Bulgaria	4.58%	3.09%	6.54%	1.62%	1.34%	1.92%
	Bosnia & Herzegovina	3.56%	2.47%	5.17%	1.61%	1.35%	1.88%
	Czech Republic	3.23%	2.28%	4.36%	1.61%	1.36%	1.91%
	Croatia	7.06%	5.06%	9.67%	1.62%	1.38%	1.92%
	Hungary	3.31%	2.59%	4.13%	1.62%	1.38%	1.92%
	Poland	3.91%	2.70%	5.56%	1.62%	1.36%	1.90%
	Romania	4.28%	2.99%	5.99%	1.61%	1.36%	1.88%
	Serbia	4.01%	2.68%	5.76%	1.62%	1.36%	1.90%
	Slovak Republic	3.60%	2.44%	5.13%	1.62%	1.38%	1.91%
	Slovenia	4.52%	3.02%	6.56%	1.62%	1.39%	1.92%
	Macedonia	5.23%	3.57%	7.56%	1.62%	1.35%	1.93%
	Montenegro	6.02%	3.90%	9.07%	1.61%	1.36%	1.90%
Europe, Eastern		**5.88%**	**4.51%**	**7.63%**	**1.59%**	**1.50%**	**1.70%**
	Belarus	6.56%	4.42%	9.49%	1.60%	1.35%	1.87%
	Estonia	6.75%	5.15%	8.79%	1.61%	1.36%	1.90%
	Lithuania	4.79%	3.27%	6.53%	1.60%	1.36%	1.89%
	Latvia	6.21%	4.21%	9.06%	1.61%	1.35%	1.87%
	Moldova	4.39%	2.87%	6.50%	1.60%	1.36%	1.89%
	Russian Federation	6.52%	4.67%	9.05%	1.59%	1.47%	1.71%
	Ukraine	3.91%	2.98%	5.15%	1.61%	1.50%	1.73%
Europe, Western		**4.66%**	**4.28%**	**5.05%**	**1.49%**	**1.40%**	**1.58%**
	Andorra	6.49%	4.15%	9.63%	1.51%	1.29%	1.81%
	Austria	5.01%	3.42%	7.37%	1.51%	1.29%	1.77%
	Belgium	3.98%	3.10%	5.04%	1.51%	1.28%	1.77%
	Switzerland	6.16%	4.26%	8.76%	1.50%	1.37%	1.64%
	Cyprus	5.75%	3.89%	8.21%	1.51%	1.28%	1.77%
	Germany	4.85%	4.05%	5.81%	1.52%	1.39%	1.65%
	Denmark	5.07%	3.45%	7.28%	1.50%	1.28%	1.77%
	Spain	4.33%	3.50%	5.26%	1.48%	1.35%	1.62%
	Finland	5.98%	4.91%	7.15%	1.65%	1.51%	1.79%
	France	4.80%	4.03%	5.65%	1.47%	1.35%	1.60%
	United Kingdom	3.12%	2.70%	3.58%	1.47%	1.34%	1.62%
	Greece	4.87%	3.56%	6.57%	1.51%	1.27%	1.77%
	Ireland	4.05%	3.28%	4.92%	1.49%	1.36%	1.61%
	Iceland	4.74%	3.33%	6.36%	1.50%	1.27%	1.77%
	Israel	4.58%	3.49%	5.73%	1.50%	1.30%	1.74%
	Italy	4.84%	3.97%	5.89%	1.46%	1.33%	1.59%
	Luxembourg	6.55%	4.24%	9.59%	1.51%	1.27%	1.77%
	Malta	6.58%	4.28%	9.68%	1.50%	1.26%	1.78%
	Netherlands	8.03%	6.69%	9.55%	1.47%	1.35%	1.60%
	Norway	5.94%	4.63%	7.57%	1.47%	1.35%	1.60%
	Portugal	4.32%	2.98%	6.11%	1.51%	1.28%	1.77%
	Sweden	4.76%	3.31%	6.75%	1.50%	1.26%	1.75%

Region	Country	MDD			Dysthymia		
		Prevalence	95% uncertainty interval		Prevalence	95% uncertainty interval	
Latin America, Andean		**4.58%**	**3.60%**	**5.81%**	**1.54%**	**1.38%**	**1.71%**
	Bolivia	3.94%	2.73%	5.86%	1.55%	1.32%	1.82%
	Ecuador	4.38%	3.04%	6.26%	1.54%	1.31%	1.81%
	Peru	4.89%	3.36%	7.06%	1.53%	1.29%	1.79%
Latin America, Central		**4.40%**	**3.76%**	**5.15%**	**1.50%**	**1.41%**	**1.61%**
	Colombia	6.31%	4.27%	9.02%	1.51%	1.29%	1.77%
	Costa Rica	4.68%	3.15%	6.48%	1.49%	1.27%	1.74%
	Guatemala	5.35%	3.65%	7.56%	1.51%	1.28%	1.79%
	Honduras	9.22%	6.83%	12.23%	1.50%	1.28%	1.77%
	Mexico	2.96%	2.30%	3.78%	1.50%	1.42%	1.58%
	Nicaragua	5.15%	3.53%	7.51%	1.51%	1.28%	1.77%
	Panama	4.66%	3.13%	6.70%	1.50%	1.27%	1.76%
	El Salvador	5.38%	3.67%	7.66%	1.52%	1.30%	1.80%
	Venezuela	5.06%	3.48%	7.07%	1.51%	1.27%	1.77%
Latin America, Southern		**4.80%**	**3.65%**	**6.37%**	**1.52%**	**1.35%**	**1.71%**
	Argentina	5.16%	3.57%	7.40%	1.53%	1.29%	1.77%
	Chile	3.99%	3.01%	5.19%	1.51%	1.29%	1.76%
	Uruguay	4.65%	3.22%	6.62%	1.52%	1.29%	1.82%
Latin America, Tropical		**5.50%**	**4.39%**	**6.82%**	**1.53%**	**1.44%**	**1.62%**
	Brazil	5.47%	4.34%	6.87%	1.53%	1.44%	1.62%
	Paraguay	6.39%	4.16%	9.63%	1.53%	1.30%	1.77%
North Africa/Middle East		**7.35%**	**6.54%**	**8.23%**	**1.53%**	**1.44%**	**1.62%**
	Afghanistan	22.50%	17.38%	29.32%	1.46%	1.23%	1.73%
	United Arab Emirates	8.12%	5.45%	11.54%	1.36%	1.15%	1.62%
	Bahrain	8.62%	5.88%	12.12%	1.42%	1.20%	1.65%
	Algeria	7.34%	5.12%	10.35%	1.47%	1.25%	1.73%
	Egypt	5.29%	3.91%	7.13%	1.47%	1.35%	1.59%
	Iran (Islamic Republic of)	7.00%	4.97%	9.90%	1.47%	1.24%	1.74%
	Iraq	4.48%	3.42%	5.81%	1.46%	1.35%	1.59%
	Jordan	7.73%	5.24%	10.97%	1.47%	1.25%	1.71%
	Kuwait	7.51%	5.11%	10.72%	1.42%	1.21%	1.67%
	Lebanon	5.27%	3.90%	7.06%	1.49%	1.37%	1.61%
	Libya	9.27%	6.13%	13.42%	1.47%	1.26%	1.72%
	Morocco	6.85%	4.72%	9.60%	1.48%	1.25%	1.73%
	Oman	5.25%	3.77%	7.03%	1.42%	1.21%	1.64%
	Occupied Palestinian Territory	9.01%	6.01%	13.31%	1.47%	1.24%	1.74%
	Qatar	7.99%	5.31%	11.78%	1.35%	1.15%	1.58%
	Saudi Arabia	5.90%	4.10%	8.30%	1.43%	1.21%	1.68%
	Syrian Arab Republic	7.02%	4.57%	10.26%	1.47%	1.26%	1.72%
	Tunisia	7.07%	4.71%	10.48%	1.47%	1.24%	1.73%
	Turkey	6.74%	5.32%	8.54%	1.47%	1.24%	1.72%
	Yemen	7.11%	4.89%	9.96%	1.47%	1.25%	1.73%
North America, High Income		**4.44%**	**3.76%**	**5.21%**	**1.57%**	**1.46%**	**1.69%**
	Canada	4.35%	3.62%	5.22%	1.59%	1.48%	1.72%
	United States	4.45%	3.71%	5.34%	1.57%	1.45%	1.69%
Oceania		**4.72%**	**3.50%**	**6.31%**	**1.62%**	**1.43%**	**1.85%**
	Fiji	3.46%	2.26%	5.07%	1.61%	1.36%	1.89%
	Micronesia (Fed. States of)	4.36%	2.96%	6.21%	1.62%	1.38%	1.91%
	Kiribati	5.73%	3.79%	8.57%	1.62%	1.37%	1.90%
	Marshall Islands	5.71%	3.80%	8.25%	1.62%	1.37%	1.91%
	Papua New Guinea	5.02%	3.41%	7.14%	1.63%	1.38%	1.90%
	Solomon Islands	3.44%	2.25%	5.05%	1.61%	1.36%	1.91%
	Tonga	4.43%	3.08%	6.42%	1.63%	1.37%	1.91%

Region	Country	MDD			Dysthymia		
		Prevalence	95% uncertainty interval		Prevalence	95% uncertainty interval	
Oceania		**4.72%**	**3.50%**	**6.31%**	**1.62%**	**1.43%**	**1.85%**
	Vanuatu	4.40%	2.94%	6.25%	1.61%	1.37%	1.92%
	Samoa	4.37%	2.94%	6.47%	1.62%	1.37%	1.91%
Sub-Saharan Africa, Central		**5.70%**	**4.41%**	**7.31%**	**1.59%**	**1.42%**	**1.78%**
	Angola	5.03%	3.41%	7.09%	1.59%	1.35%	1.87%
	CAF	5.71%	3.92%	8.53%	1.58%	1.34%	1.86%
	Congo, Dem. Rep.	5.79%	3.97%	8.15%	1.59%	1.35%	1.85%
	Congo	6.45%	4.45%	9.21%	1.58%	1.35%	1.84%
	Gabon	7.20%	4.93%	10.31%	1.58%	1.34%	1.87%
	Equatorial Guinea	7.05%	4.79%	10.32%	1.57%	1.33%	1.84%
Sub-Saharan Africa, East		**5.43%**	**4.81%**	**6.16%**	**1.56%**	**1.46%**	**1.66%**
	Burundi	6.06%	4.25%	8.53%	1.57%	1.33%	1.87%
	Comoros	5.78%	3.94%	8.40%	1.56%	1.32%	1.84%
	Djibouti	6.70%	4.58%	9.62%	1.57%	1.34%	1.83%
	Eritrea	6.61%	4.51%	9.73%	1.58%	1.33%	1.86%
	Ethiopia	3.61%	2.65%	4.75%	1.56%	1.47%	1.64%
	Kenya	5.15%	3.61%	7.22%	1.56%	1.31%	1.85%
	Madagascar	5.11%	3.54%	7.39%	1.57%	1.33%	1.85%
	Mozambique	4.58%	3.03%	6.51%	1.58%	1.34%	1.86%
	Malawi	5.77%	3.85%	8.41%	1.56%	1.32%	1.87%
	Rwanda	7.31%	5.43%	9.77%	1.57%	1.31%	1.83%
	Sudan	7.09%	5.19%	9.38%	1.56%	1.33%	1.82%
	Somalia	6.34%	4.40%	9.08%	1.56%	1.31%	1.82%
	Tanzania	6.35%	4.32%	9.25%	1.57%	1.33%	1.82%
	Uganda	6.35%	4.84%	8.31%	1.56%	1.33%	1.82%
	Zambia	5.80%	3.86%	8.65%	1.57%	1.34%	1.84%
Sub-Saharan Africa, Southern		**5.01%**	**3.96%**	**6.33%**	**1.59%**	**1.49%**	**1.69%**
	Botswana	7.42%	4.78%	10.90%	1.59%	1.35%	1.87%
	Lesotho	6.28%	4.38%	8.79%	1.61%	1.36%	1.88%
	Namibia	5.00%	3.38%	7.16%	1.60%	1.34%	1.87%
	Swaziland	5.76%	3.79%	8.47%	1.61%	1.36%	1.87%
	South Africa	4.55%	3.38%	6.06%	1.59%	1.50%	1.68%
	Zimbabwe	6.50%	4.35%	9.54%	1.60%	1.34%	1.89%
Sub-Saharan Africa, West		**4.18%**	**3.69%**	**4.72%**	**1.53%**	**1.44%**	**1.62%**
	Benin	3.92%	2.61%	5.69%	1.54%	1.30%	1.80%
	Burkina Faso	3.95%	2.58%	5.93%	1.55%	1.32%	1.83%
	Cote d'Ivoire	5.05%	3.45%	7.16%	1.52%	1.30%	1.78%
	Cameroon	4.39%	2.99%	6.24%	1.53%	1.28%	1.80%
	Cape Verde	5.02%	3.32%	7.58%	1.54%	1.30%	1.80%
	Ghana	4.38%	2.93%	6.30%	1.52%	1.28%	1.79%
	Guinea	4.45%	3.07%	6.13%	1.53%	1.31%	1.81%
	Gambia	5.07%	3.66%	6.87%	1.54%	1.30%	1.82%
	Guinea-Bissau	3.91%	2.53%	5.62%	1.53%	1.30%	1.81%
	Liberia	4.60%	3.11%	6.65%	1.54%	1.30%	1.80%
	Mali	5.72%	3.79%	8.35%	1.54%	1.31%	1.81%
	Mauritania	4.99%	3.48%	7.01%	1.54%	1.31%	1.80%
	Niger	4.38%	3.08%	6.20%	1.53%	1.30%	1.79%
	Nigeria	3.69%	2.95%	4.65%	1.52%	1.44%	1.61%
	Senegal	4.47%	3.01%	6.38%	1.54%	1.30%	1.81%
	Sierra Leone	5.65%	3.90%	8.01%	1.54%	1.31%	1.80%
	Sao Tome and Principe	6.51%	4.35%	9.46%	1.54%	1.32%	1.82%
	Chad	5.16%	3.49%	7.32%	1.54%	1.30%	1.80%
	Togo	4.49%	3.10%	6.23%	1.54%	1.30%	1.80%

Table S3. Regional DALY and YLD rankings with 95% uncertainty intervals for depressive disorders in 1990

	YLDs				DALYs			
	MDD		Dysthymia		MDD		Dysthymia	
	Order	Mean Rank (95% UI)	Order	Mean Rank (95% UI)	Order	Mean Rank (95% UI)	Order	Mean Rank (95% UI)
Global	**2**	**2.2 (1-3)**	**19**	**19.5 (12-27)**	**15**	**15.2 (11-18)**	**59**	**58.6 (48-69.5)**
Asia Pacific, High Income	4	3.2 (2-5)	20	19.3 (13-27)	10	10.0 (6-15.5)	37	37.8 (29-51)
Asia Central	2	1.8 (1-3)	20	20.4 (14-28.5)	10	10.2 (8-13)	49	49.2 (40-62)
Asia East	2	2.0 (1-3)	20	17.3 (9-24)	12	12.6 (6-19.5)	44	42.2 (30.5-55)
Asia South	3	3.1 (2-4)	24	23 (13-34)	20	20.4 (13-27)	62	61.7 (48.5-79)
Asia Southeast	2	1.8 (1-3)	18	19 (10-30)	11	10.8 (6-16.5)	50	51.5 (43-64)
Australasia	2	2.8 (2-7)	21	20.3 (14-27)	7	8.2 (5-15)	37	37.6 (25.5-52)
Caribbean	2	1.6 (1-3)	23	22.1 (15-29)	7	10 (7-15)	58	55.5 (43-66)
Europe Central	2	2.0 (2-2)	21	19.6 (14-26.5)	7	6.7 (4-10)	46	43.6 (30-57)
Europe Eastern	2	1.7 (1-2)	20	19.4 (14-26.5)	5	5.3 (3-9)	46	45.6 (36-58)
Europe Western	2	2.1 (2-3)	20	20.0 (14-26)	5	5.2 (4-8.5)	37	38.5 (29-54)
Latin America, Andean	1	1.6 (1-3)	24	23.2 (16-32)	10	10.3 (5-16)	50	50.6 (42-65)
Latin America, Central	1	1.1 (1-2)	20	20.2 (13-30)	8	8.4 (5-12)	48	46.6 (37-59)
Latin America, Southern	2	1.6 (1-3)	19	20.6 (14-28)	7	5.9 (3-9)	49	50.5 (38-63)
Latin America, Tropical	2	1.8 (1-3)	22	21.0 (13-28)	10	9.7 (7-13)	47	47.6 (40-58)
North Africa/Middle East	2	1.9 (1-3)	23	22.3 (16-31)	8	8.4 (7-10)	53	53.7 (43-68)
North America, High Income	2	2.7 (1-5)	20	19.4 (13-27)	8	7.5 (3-11)	39	39.3 (31-50)
Oceania	2	2.0 (1-4)	25	23.7 (16-34)	17	18.7 (10-28)	65	64.5 (53-77)
Sub-Saharan Africa, Central	2	2.0 (1-3)	30	28.5 (18-38)	22	22.1 (16-27)	70	67.2 (56-80)
Sub-Saharan Africa, East	2	2.2 (1-3)	23	23.9 (16-37)	21	21.1 (17-26)	66	66.4 (54-81.5)
Sub-Saharan Africa Southern	2	2.0 (1-4)	23	23.1 (14-34)	11	12.2 (7-18)	55	55.1 (45-69)
Sub-Saharan Africa, West	3	2.8 (2-4)	29	26.9 (18-36)	24	23.0 (17-27)	69	66.2 (55-78)

Note. YLDs: years lived with disability; DALYs: Disability adjusted life years; MDD: Major depressive disorder; 95% UI: 95% uncertainty interval; Mean Rank: YLD and DALY ranks were estimated for MDD and dysthymia then simulated 1000 times to estimate 95% uncertainty ranges. The 95% bounds of uncertainty represent the 25th and 975th value of the 1000 draws; Order: Regional YLDs and DALYs for MDD and dysthymia were ordered by their mean rank across 1000 draws.

Appendix Five

Supplementary text to Chapter Six

Text S1. PRISMA checklist and flow diagram for the literature search to identify relative-risk estimates

We used data sources from recent and methodologically comparable systematic reviews of the association between suicide and mental and substance use disorders (1-5), specifically affective disorders, anxiety disorders, schizophrenia (3), cocaine, opioid, and amphetamine dependence (1, 2, 4) and alcohol dependence (5). We expanded the Li and collaborators systematic review and replicated the literature search (3) to collect data for bipolar disorder and MDD separately (rather than affective disorders combined), and anorexia nervosa which was not included in the original review.

The PRISMA checklist and flowchart (6), for this literature search have been summarised below. The information presented amalgamate the search for data previously reported (1-5), as well as the expansion of the Li and collaborators systematic review (3) to collect data for bipolar disorder and MDD separately.

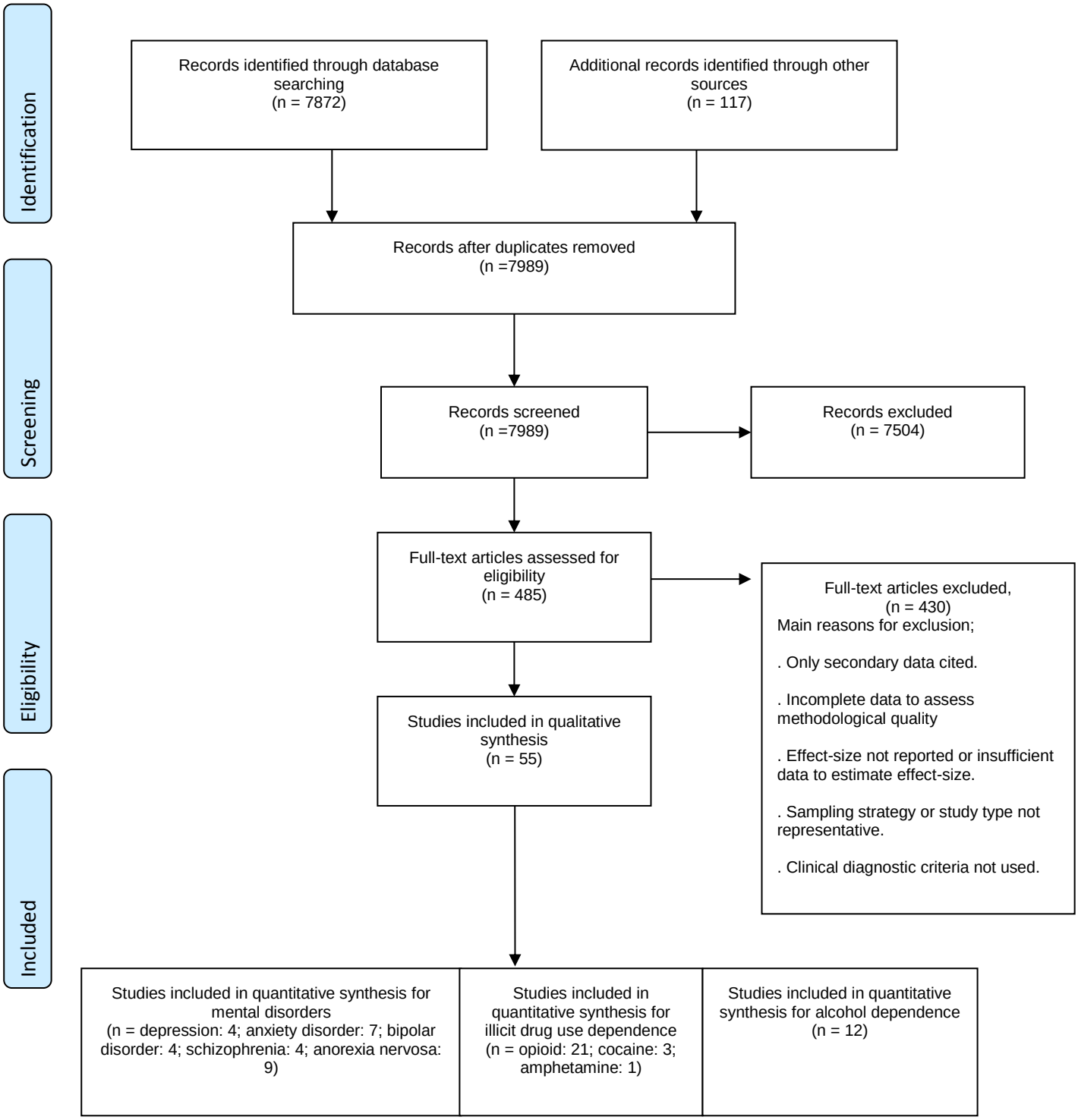
Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	N/A. This was reported in the specific review papers (1-5).
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	Page 2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	Pages 3-4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	Pages 3-4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	N/A
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	Summary provided on pages 5-6 with more details in specific review papers (1-5).
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	Summary provided on page 6 with more details in Text S1 and the specific review papers (1-5).
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Summary provided on page 6 with more details in the specific review papers (1-5).
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Pages 5-6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	Summary provided on page 6 with more details in Table S1 and the specific review papers (1-5).
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Summary provided on pages 5-6 with more details in Table S1.
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	Strategies for adjusting study- and country-level sources of variability through (1) the quality-effects model and (2) ceiling values for joint population attributable fractions discussed on pages 6-8 with more details in Tables S1, S2, S3, S4
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	Page 5
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	Pages 5, 6, 9

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	Strategies for adjusting study- and country-level sources of variability through (1) the quality-effects model and (2) ceiling values for joint population attributable fractions discussed on pages 6-8 with more details in Tables S1, S2, S3, S4. More strategies for addressing publication bias and selective reporting were presented in the specific review papers (1-5)
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	Pages 6-7 discuss the sex-, region, and disorder-specific analyses conducted. As-well as sensitivity analyses around the type of model used to pool estimates in the meta-analysis.
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Summary provided on pages 9-10, Table S1, with a literature search flow diagram in Text S1.
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Summary provided on pages 9-10 with more detail in Table S1.
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Pages 9-10, Tables S2 and S4 compare findings of the meta-analysis conducted using random- and quality-effects models.
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Pages 9-10, and Tables 1, S1, S2, S3, S4
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Pages 9-10, and Tables 1, S1, S2, S3, S4
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Assessments for adjusting study- and country-level sources of variability through (1) the quality-effects model and (2) ceiling values for joint population attributable fractions presented in Tables S1, S2, S3, S4. More strategies for addressing publication bias and selective reporting were presented in specific review papers (1-5)
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Assessments of findings by sex-, region, and disorder presented in Pages 9-10, Tables 1, S2, S4
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	Pages 12-15
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	Pages 14-15
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	Page 12-14

FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	Funding information providing in the 'Additional Information' section of PloS One's online submission form.

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

RISMA 2009 Flow Diagram



References

1. Degenhardt L, Bucello C, Mathers B, Briegleb C, Ali H, Hickman M, et al. Mortality among problematic users of heroin and other illicit opioids: A systematic review and meta-analysis. Addiction. 2011;106:32-51.
2. Degenhardt L, Singleton J, Calabria B, McLaren J, Kerr T, Mehta S, et al. Mortality among cocaine users: A systematic review of cohort studies. Drug and Alcohol Dependence. 2011;113:88-95.
3. Li Z, Page A, Martin G, Taylor R. Attributable risk of psychiatric and socio-economic factors for suicide from individual-level, population-based studies: a systematic review. Social science & medicine. 2011;72(4):608-16.
4. Singleton J, Degenhardt L, Hall W, Zabransky T. Mortality among people who use amphetamines: A systematic review of cohort studies. Drug & Alcohol Dependence. 2009;105:1-8.
5. Wilcox HC, Conner KR, Caine ED. Association of alcohol and drug use disorders and completed suicide: an empirical review of cohort studies. Drug Alcohol Depend. 2004;76 Suppl:S11-9.
6. Moher D, Liberati A, Tetzlaff J, Altman DG, The PG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA Statement. PLoS medicine. 2009;6(7):e1000097.

Table S1: Summary of studies reporting the relative-risk of suicide in those with mental and substance use disorders.

Data source	Country	Disorder	Age Range (years)	Epoch Range	Sex[a]	Relative-risk (95% UI)	Quality score/1[c]
Mental disorders							
Shaffer et al., 1996 [1]	USA	Major Depression Bipolar disorder Anxiety disorders	0-19	1984-1986	M F M F M F	16.1 (2.0-128.1) - - 1.6 (0.1-26.5) 2.6 (1.1-6.0) 0.7 (0.2-3.3)	0.8
Lesage et al., 1994 [2]	Canada	Major depression Major depression with psychotic features Bipolar disorder Bipolar NOS Depression NOS Generalized anxiety disorder Panic Disorder Agoraphobia Obsessive compulsive disorder Social phobia Somatoform disorder Anxiety NOS Schizophrenia Schizoaffective disorder Schizophrenia NOS	18-35	1987-1989	M M M M M M M M M M M M M M M	11.2 (3.7-33.9) - 1.0 (0.2-5.1) 1 (0.1-16.3) - 3.1 (0.3-30.3) - - 2.0 (0.2-22.8) 1.0 (0.1-16.3) 2.0 (0.2-22.8) 3.1 (0.3-30.3) 1.4 (0.3-6.3) - - -	0.6
Waern et al., 2002 [2]	Sweden	Major depression Minor depression Anxiety disorders	65-99	1994-1996	M F M F M F	34.4 (7.5-157.1) 28.7 (6.2-134.1) 5.7 (1.4-22.6) - 2.6 (0.5-12.0) 6.6 (1.7-26.1)	0.8
Dutta et al., 2007 [3]	United Kingdom	Bipolar I disorder	16-99	1965-1999	M F	12.76(5.13-26.29) 4.27(0.11-23.78)	0.9
Brent et al., 1999 [4]	USA	Anxiety disorders	13-19	1989-1994	M F	13.0 (1.7-100.2) 2.8 (0.7-11.9)	0.8
Kreipe et al., 1989 [5]	USA	Anorexia Nervosa	12-19	1979-1984	F	20.41 (0.5-113.7)	0.6
Keel et al., 2003 [6]	USA	Anorexia Nervosa	12-99	1987-2000	F	29.41 (8.0-75.3)	0.8

Data source	Country	Disorder	Age Range (years)	Epoch Range	Sex[a]	Relative-risk (95% uncertainty interval)	Quality score/1[c]
Mental disorders							
Korndofer et al., 2003 [7]	USA	Anorexia Nervosa	10-57	1935-1989	M F	- 10.36 (1.3-37.4)	0.9
Zipfel et al., 2000 [8]	Germany	Anorexia Nervosa	0-99	1974-1998	F	23.81 (2.9-86.0)	0.8
Papadopoulos et al., 2009 [9]	Sweden	Anorexia Nervosa	10-40	1973-2003	F	13.98 (11.2-17.3)	0.8
Moller-Madsen, 1998 [10]	Denmark	Anorexia Nervosa	0-99	1970-1994	M F	31.75 (3.8-114.7) 20.25 (11.6-32.9)	0.9
Signorini et al., 2007 [11]	Italy	Anorexia Nervosa	10-52	1994-2003	F	6.8 (0.2-37.9)	0.8
Qin & Nordentoft, 2005 [12]	Denmark	Schizophrenia	0-99	1981-1997	M F	11.8 (10.9-12.8) 12.6 (11.4-13.9)	0.8
Riala et al., 2007 [13]	Finland	Schizophrenia	0-33	≈1966-2001	M	13.7 (5.2-36.1) 19.5 (4.2-90.8)	0.9
Illicit drug use disorders							
Pavarin, 2008 [14]	Italy	Cocaine dependence	0-99	1989-2004	P	10.3(00.01-32.2)	-
Tyndall et al., 2001 [15]	Canada	Cocaine dependence	14-61	1996-2004	P	15.1(4.01-31.0)	-
Fugelstad et al., 1997 [16]	Sweden	Amphetamine dependence Opioid dependence	0-99	1985-1992	P	4.3(1.1-8.6) 13.9(10.6-30.3)	-
Stenbacka et al., 2007 [17]	Sweden	Opioid dependence	14-47	1967-2003	P	8.03(5.6-10.7)	-
Miller et al., 2007 [18]	Canada	Opioid dependence	0-29	1996-2004	P	10.1(0.01-25.1)	-
Wang et al., 2005 [19]	USA	Cocaine dependence	0-99	1988-2001	P	3.04(0.01-7.8)	-
Goldstein et al., 1995 [20]	USA	Opioid dependence	13-60	1969-1993	P	3.2(1.3-5.1)	-
Soyka et al., 2006 [21]	Germany	Opioid dependence	17-62	1993-1994	P	7.2(0.01-17.8)	-
Fugelstad et al., 1998 [22]	Sweden	Opioid dependence	20-99	1986-1993	P	13.9(0.01-38.5)	-
Antolini et al., 2006 [23]	Italy	Opioid dependence	0-99	1975-1999	P	6.7(4.3-9.5)	-
Brancato et al., 1995 [24]	Italy	Opioid dependence	18-38	1985-1994	P	18.3(0.01-58.04)	-
Galli & Musicco., 1994 [25]	Italy	Opioid dependence	14-57	1980-1991	P	6.7(2.6-11.6)	-
Manfredi et al., 2006 [26]	Italy	Opioid dependence	10-62	1977-2002	P	6.5(2.4-11.6)	-
Eskild et al., 1993 [27]	Norway	Opioid dependence	15-44	1985-1991	P	13.3(5.6-23.6)	-
Odegard et al., 2007 [28]	Norway	Opioid dependence	18-54	1981-2003	P	11.9(6.9-18.5)	-
Rossow., 1994 [29]	Norway	Opioid dependence	16-67	1961-1992	P	16.2(12.3-20.4)	
Risser et al., 2001 [30]	Austria	Opioid dependence	0-99	1995-1997	P	5.7(0.01-16.8)	-
Bartu et al., 2004 [31]	Australia	Opioid dependence	18-50	1985-1998	P	1.5(1.1-1.97)	-

Data source	Country	Disorder	Age Range (years)	Epoch Range	Sex[a]	Relative-risk (95% uncertainty interval)	Quality score/1[c]
Illicit drug use disorders							
Degenhardt et al., 2009 [32]	Australia	Opioid dependence	20-40	1985-2005	P	4.98(4.5-5.5)	-
Digiusto et al., 2004 [33]	Australia	Opioid dependence	0-99	1998-2202	P	13.6(0.01-47.3)	-
Tait et al., 2008 [34]	Australia	Opioid dependence	18-35	1997-2002	P	3.9(1.3-7.3)	-
Vlahov et al., 2005 [35]	USA	Opioid dependence	0-99	1988-2005	P	2.7(0.01-8.2)	-
Vlahov et al., 2008 [36]	USA	Opioid dependence				3.9(1.3-7.3)	-
Oppenheimer et al., 1994 [37]	United Kingdom	Opioid dependence	17-52	1969-1981	P	4.8(0.01-12.6)	-
Alcohol dependence[c]							
Wilcox et al 2004[c] [38]	USA, Kuwait, Sweden Spain, United Kingdom	Alcohol use disorders	-	-	P	9.8 (8.98–10.7)	

Note. NOS: Not otherwise specified; [a]Sex: Males (M), Female (F), Persons(P). [b]Quality scores calculated for mental disorders only due to insufficient data for substance use. Studies scored out of 8 where studies reporting gender specific estimates =2 and person estimates only=1; studies derived from population representative samples= 2 and hospitalised samples=1; studies covering the entire lifespan=2 and only a specific age group=1; studies using a prospective design=2 and a retrospective design=1. RR estimate for alcohol dependence obtained from an existing literature review and meta-analysis of 12 studies [39]. Due to paucity of data estimates based on clinical samples were also included for bipolar disorder and anorexia nervosa. The difference in representativeness of each sample was reflected in the quality indices.

References

1. Shaffer D, Gould MS, Fisher P, Trautman P, Moreau D, et al. (1996) Psychiatric diagnosis in child and adolescent suicide. Archives of General Psychiatry 53: 339-348.
2. Lesage AD, Boyer R, Grunberg F, Vanier C, Morisette R, et al. (1994) Suicide and mental disorders: a case–control study of young men. American Journal of Psychiatry 151: 1063–1068.
3. Dutta R, Boydell J, Kennedy N, J VANO, Fearon P, et al. (2007) Suicide and other causes of mortality in bipolar disorder: a longitudinal study. Psychol Med 37: 839-847.
4. Brent DA, Baugher M, Bridge J, Chen T, Chiappetta L (1999) Age and sex related risk factors for adolescent suicide

Journal of the American Academy of Child Adolescent Psychiatry 38 1497-1505.
5. Kreipe RE, Churchill BH, Strauss J (1989) Long-term outcome of adolescents with anorexia nervosa. Am J Dis Child 143: 1322-1327.
6. Keel PK, Dorer DJ, Eddy KT, Franko D, Charatan DL, et al. (2003) Predictors of mortality in eating disorders. Arch Gen Psychiatry 60: 179-183.
7. Korndorfer SR, Lucas AR, Suman VJ, Crowson CS, Krahn LE, et al. (2003) Long-term survival of patients with anorexia nervosa: a population-based study in Rochester, Minn. Mayo Clin Proc 78: 278-284.
8. Zipfel S, Lowe B, Reas DL, Deter HC, Herzog W (2000) Long-term prognosis in anorexia nervosa: lessons from a 21-year follow-up study. Lancet 355: 721-722.
9. Papadopoulos FC, Ekbom A, Brandt L, Ekselius L (2009) Excess mortality, causes of death and prognostic factors in anorexia nervosa. Br J Psychiatry 194: 10-17.
10. Moller-Madsen SM, Nystrup J, Nielsen S (1998) [Mortality of anorexia nervosa in Denmark 1970-1987]. Ugeskr Laeger 160: 5509-5513.
11. Signorini A, De Filippo E, Panico S, De Caprio C, Pasanisi F, et al. (2007) Long-term mortality in anorexia nervosa: a report after an 8-year follow-up and a review of the most recent literature. European Journal of Clinical Nutrition 61: 119-122.
12. Qin P, Nordentoft M (2005) Suicide risk in relation to psychiatric hospitalization: evidence based on longitudinal registers. Arch Gen Psychiatry 62: 427-432.
13. Riala K, Alaräisänen A, Taanila A, Hakko H, Timonen M, et al. (2007) Regular daily smoking among 14-year-old adolescents increases the subsequent risk for suicide: the Northern Finland 1966 Birth Cohort Study. The Journal of clinical psychiatry 68: 775-780.
14. Pavarin RM (2008) Cocaine consumption and death risk: a follow-up study on 347 cocaine addicts in the metropolitan area of Bologna. Ann Ist Super Sanita 44: 91-98.
15. Tyndall MW, Craib KJ, Currie S, Li K, O'Shaughnessy MV, et al. (2001) Impact of HIV infection on mortality in a cohort of injection drug users. J Acquir Immune Defic Syndr 28: 351-357.
16. Fugelstad A, Annell A, Rajs J, Agren G (1997) Mortality and causes and manner of death among drug addicts in Stockholm during the period 1981-1992. Acta Psychiatr Scand 96: 169-175.
17. Stenbacka M, Leifman A, Romelsjo A (2007) Mortality among opiate abusers in Stockholm: a longitudinal study. . Heroin Addiction and Related Clinical Problems 9: 41-49.
18. Miller CL, Kerr T, Strathdee SA, Li K, Wood E (2007) Factors associated with premature mortality among young injection drug users in Vancouver. Harm Reduct J 4: 1.
19. Wang C, Vlahov D, Galai N, Cole SR, Bareta J, et al. (2005) The effect of HIV infection on overdose mortality. AIDS 19: 935-942.
20. Goldstein A, Herrera J (1995) Heroin addicts and methadone treatment in Albuquerque: a 22-year follow-up. Drug Alcohol Depend 40: 139-150.

21. Soyka M, Apelt SM, Lieb M, Wittchen HU (2006) One-year mortality rates of patients receiving methadone and buprenorphine maintenance therapy: a nationally representative cohort study in 2694 patients. J Clin Psychopharmacol 26: 657-660.
22. Fugelstad A, Agren G, Romelsjo A (1998) Changes in mortality, arrests, and hospitalizations in nonvoluntarily treated heroin addicts in relation to methadone treatment. Subst Use Misuse 33: 2803-2817.
23. Antolini G, Pirani M, Morandi G, Sorio C (2006) [Gender difference and mortality in a cohort of heroin users in the Provinces of Modena and Ferrara, 1975-1999]. Epidemiol Prev 30: 91-99.
24. Brancato V, Delvecchio G, Simone P (1995) [Survival and mortality in a cohort of heroin addicts in 1985-1994]. Minerva Med 86: 97-99.
25. Galli M, Musicco M (1994) Mortality of intravenous drug users living in Milan, Italy: role of HIV-1 infection. COMCAT Study Group. AIDS 8: 1457-1463.
26. Manfredi R, Sabbatani S, Agostini D (2006) Trend of mortality observed in a cohort of drug addicts of the metropolitan area of Bologna, North-Eastern Italy, during a 25-year-period. Coll Antropol 30: 479-488.
27. Eskild A, Magnus P, Samuelsen SO, Sohlberg C, Kittelsen P (1993) Differences in mortality rates and causes of death between HIV positive and HIV negative intravenous drug users. Int J Epidemiol 22: 315-320.
28. Odegard E, Amundsen EJ, Kielland KB (2007) Fatal overdoses and deaths by other causes in a cohort of Norwegian drug abusers--a competing risk approach. Drug Alcohol Depend 89: 176-182.
29. Rossow I (1994) Suicide among drug addicts in Norway. Addiction 89: 1667-1673.
30. Risser D, Honigschnabl S, Stichenwirth M, Pfudl S, Sebald D, et al. (2001) Mortality of opiate users in Vienna, Austria. Drug Alcohol Depend 64: 251-256.
31. Bartu A, Freeman NC, Gawthorne GS, Codde JP, Holman CD (2004) Mortality in a cohort of opiate and amphetamine users in Perth, Western Australia. Addiction 99: 53-60.
32. Degenhardt L, Randall D, Hall W, Law M, Butler T, et al. (2009) Mortality among clients of a state-wide opioid pharmacotherapy program over 20 years: risk factors and lives saved. Drug Alcohol Depend 105: 9-15.
33. Digiusto E, Shakeshaft A, Ritter A, O'Brien S, Mattick RP, et al. (2004) Serious adverse events in the Australian National Evaluation of Pharmacotherapies for Opioid Dependence (NEPOD). Addiction 99: 450-460.
34. Tait RJ, Ngo HT, Hulse GK (2008) Mortality in heroin users 3 years after naltrexone implant or methadone maintenance treatment. J Subst Abuse Treat 35: 116-124.
35. Vlahov D, Galai N, Safaeian M, Galea S, Kirk GD, et al. (2005) Effectiveness of highly active antiretroviral therapy among injection drug users with late-stage human immunodeficiency virus infection. Am J Epidemiol 161: 999-1012.
36. Vlahov D, Wang C, Ompad D, Fuller CM, Caceres W, et al. (2008) Mortality risk among recent-onset injection drug users in five U.S. cities. Subst Use Misuse 43: 413-428.
37. Oppenheimer E, Tobutt C, Taylor C, Andrew T (1994) Death and survival in a cohort of heroin addicts from London clinics: a 22-year follow-up study. Addiction 89: 1299-1308.
38. Wilcox HC, Conner KR, Caine ED (2004) Association of alcohol and drug use disorders and completed suicide: an empirical review of cohort studies. Drug Alcohol Depend 76 Suppl: S11-19.

Table S2: Pooled relative-risk associated to mental and substance use disorders as a risk factor for suicide.

	Pooled Relative-risk (95% UI)		
Disorder	**Overall**	**Male**	**Female**
Major Depressive disorder	QE: 19.9 (9.5-41.7) RE:18.6 (9.02-38.5)	QE: 17.7 (7.6-41.2) RE:16.5 (7.2-37.5)	QE: 28.7 (6.2-133.5) RE:28.7 (6.2-133.5)
Bipolar Disorder	QE: 5.7 (2.6-12.4) RE: 2.9 (0.7-11.7)	QE:6.3 (2.6-15.2) RE: 2.8 (0.4-20.9)	QE: 2.8 (0.1-19.2) RE:2.7 (0.4-18.4)
Anxiety Disorder	QE: 2.7 (1.7-4.3) RE:2.7 (1.7-4.3)	QE:2.8 (1.6-5.2) RE:2.8 (1.6-5.02)	QE: 2.4 (1.0-5.6) RE:2.4 (0.7-8.6)
Anorexia Nervosa	QE: 7.57 (2.24-25.62) RE:6.9 (4.1-11.5)	QE:6.17 (3.00-12.65) RE:6.2 (2.8-11.8)	QE: 8.63 (1.69-43.93) RE:7.7 (3.7-15.9)
Schizophrenia	QE: 12.6 (11.01-14.5) RE:12.1 (11.4-12.9)	QE: 12.04 (10.3-14.03) RE:11.8 (10.9-12.8)	QE: 13.4 (10.6-16.8) RE:12.6 (11.4-13.9)
Alcohol dependence[a]	RE: 9.8 (8.98–10.7)	RE: 4.8 (4.4–5.2)	RE: 16.9 (12.5–22.4)
Cocaine dependence	RE: 16.9 (6.01-47.2)	-	-
Opioid dependence	RE: 6.9 (4.5-10.5)	-	-
Amphetamine dependence	RE: 4.5 (1.1-9.03)	-	-

Note. 95% UI: 95% uncertainty interval; QE: Quality effects model estimate; RE: Random effects model estimate; [a]*Estimates for alcohol dependence were extracted from Wilcox et al [1]; There was sufficient data to calculate quality effects estimates for mental disorders only. There insufficient data to calculate sex specific estimates for illicit drug use disorders.*

References

1. Wilcox HC, Conner KR, Caine ED (2004) Association of alcohol and drug use disorders and completed suicide: an empirical review of cohort studies. Drug Alcohol Depend 76 Suppl: S11-19.

Table S3: Summary of studies reporting the proportion of suicide cases attributable to mental and substance use disorders.

Data source	Country	Epoch range	Age range	Sex[a]	Proportion %[b]	Quality Score[c] /1	Included Disorders
Foster et al., 1997 (1)	Ireland	1992-1993	14-99	M F	82.8 100	0.9	Mood, Substance, Psychotic, Anxiety, Somatoform, Organic Adjustment, Other axis l disorders
Schneider et al., 2005 (2)	Germany	1999-2000	0-99	M F	90.4 88.1	0.7	Mood, Substance, Psychotic disorders
Groholt et al., 1997 (3)	Norway	1990-1992	8-19	M F	74.7 73.3	0.8	Mood, Disruptive, Psychotic, Adjustment, Substance disorders
Henriksson et al., 1993 (4)	Finland	1987-1988	10-89	M F	97.5 100	1.0	Mood, Substance, Psychotic, Organic , Anxiety, Adjustment, Personality disorders
Asgard, 1990 (5)	Denmark	1982-1982	15-99	F	99.0	0.6	Mood, Psychotic , Substance, Anxiety, Adjustment, Organic disorders
Runeson, 1989 (6)	Sweden	1984-1989	15-29	P	98.3	0.4	Mood, Eating, Dementia, Substance, Psychotic , Anxiety, Somatization, Adjustment, Personality disorders
Waern et al., 2002 (7)	Sweden	1994-1996	65-97	P	96.5	0.4	Mood, Substance, Anxiety, Psychotic disorders, dementia
Boardman et al., 1999 (8)	UK	1991-1995	14-89	P	71.2	0.6	Mood, Psychotic, Substance, Organic , Personality disorders,
Cavanagh et al., 1999 (9)	UK	1996-1998	N/S	P	97.8	0.6	Mood, Psychotic, Anxiety, Substance, Personality disorders
Harwood et al., 2001 (10)	UK	1995-1998	60-99	P	77.0	0.6	Mood, Psychotic, Substance-related, Schizophrenia, Sexual, Adjustment, Somatoform, Organic, Personality disorders
Houston et al., 2001 (11)	UK	1993-1995	15-24	P	70.4	0.4	Mood, Psychotic, Substance, Anxiety, Somatoform, Gender identity, Eating disorders
Appleby et al., 1999 (12)	UK	1995-1996	13-35	P	90.5	0.3	N/S

Data source	Country	Epoch range	Age range	Sex[a]	Proportion %[b]	Quality Score[c] /1	Included Disorders
Portzky et al., 2009 (13)	Belgium	1997-2001	15-19	P	100	0.4	Mood, Psychotic, Anxiety, Substance, Adjustment Hyperkinetic, Aspergers, Eating, Impulsive, Gender identity, Conduct, Body dysmorphic disorders
Pompili et al., 2008 (14)	Italy	1994-2004	15-96	P	48.9	0.3	Mood, Substance, other disorders
Isometsa et al., 1997 (15)	Finland	1987-1988	10-89	P	99.1	0.8	Mood, Substance, Psychotic, Organic , Anxiety, Adjustment, Personality, other axis I and II disorders
Almasi et al., 2009 (16)	Hungary	2002-2004	30-62	P	69.1	0.6	Mood, Psychotic, Anxiety, Eating disorders
Arato et al., 1988 (17)	Hungary	1985-1985	0-99	M F	75.7 61.9	0.7	Mood, Somatisation, Psychotic, Substance disorders
Zonda, 2006 (18)	Hungary	N/S-N/S	N/S	P	81.0	0.2	Mood, Substance disorders
Brent et al., 1999 (19)	USA	1989-1991	13-19	M F	82.4 81.0	0.7	Mood, Anxiety, Substance, Conduct/ Antisocial disorders
Shaffer et al., 1996 (20)	USA	1984-1986	0-20	M F	90.4 92.0	0.8	Mood, Psychotic, Anxiety, Substance, Adjustment, Disruptive , Eating disorders
Conwell et al., 1991 (21)	USA	1987-1988	50-92	M F	86.7 100	0.7	Mood, Substance, Anxiety, Dementia/ Delirium disorders
Fowler et al., 1986 (22)	USA	1981-1983	10-29	P	86.5	0.3	Mood, Substance, Conduct, Psychotic, Adjustment, Personality disorders
Rich et al., 1986 (23)	USA	1981-1983	0-99	P	93.5	0.6	Mood, Psychotic, Organic, Substance, Adjustment, Child-adolescent, Axis II disorders
Shafii et al., 1988 (24)	USA	NS-NS	11-19	P	95.2	0.2	Mood, Other disorders
Preville et al., 2005 (25)	Canada	1998-1999	60-99	P	42.1	0.4	Mood, Anxiety, Substance disorders
Lesage et al., 1994 (26)	Canada	1987-1989	18-35	M	88.0	0.7	Mood, Psychotic, Substance, Organic , Anxiety, Sexual, Somatoform, Childhood developmental, Disruptive, Personality disorders
McGirr et al., 2006 (27)	Canada	2000-2005	28-57	M F	93.4 90.5	0.7	Mood, Anxiety, Psychotic, Substance disorders
Palacioa et al., 2007 (28)	Colombia	N/S-N/S	19-42	P	89.8	0.3	Mood, Substance, Psychotic, Adaptive, Personality disorders
Thacore et al., 2000 (29)	Australia	1992-1996	16-86	P	60.1	0.4	Mood, Psychotic, Substance, Other disorders

Data source	Country	Epoch range	Age range	Sex[a]	Proportion %[b]	Quality Score[c] /1	Included Disorders
Graham et al., 1992 (30)	Australia	1986-1988	15-59	P	57.1	0.6	Mood, Psychotic, Organic, Substance, Conduct, Personality, Other disorders
Kurihara et al., 2009 (31)	Indonesia	2007-2007	13-87	P	80.0	0.6	Mood, Psychotic, Anxiety, Substance, Adjustment disorders
Chen et al 2006 (32)	China-Hong Kong	2002-2004	15-59	P	80.7	0.4	Mood, Substance, Other disorders
Chiu et al., 1994 (33)	China-Hong Kong	2000-2001	60-99	M F	87.5 84.2	0.8	Mood, Anxiety, Psychotic, Adjustment, Dementia, Somatoform, Substance disorders
Zhang et al., 2010 (34)	China	2005-2008	15-34	M F	55.1 39.3	0.9	Mood, Psychotic, Anxiety, Substance, Acute stress, Pathological gambling disorders
Zhang et al., 2009 (35)	China	2001-2003	0-99	M F	72.9 55.6	0.8	Mood, Psychotic, Anxiety, Substance disorders
Phillips et a., 2002 (36)	China	1995-2000	10-99	P	62.6	0.7	N/S
Li et al., 2008 (37)	China	1995-2000	15-24	P	44.7	0.6	N/S
Zhang et al, 2004 (38)	China	2001-2002	N/S	P	75.8	0.4	Mood, Anxiety, Psychotic, Substance, Eating disorders
Cheng, 1995 (39)	Taiwan	1989-1991	15-99	P	98.3	0.9	Mood, Organic, Psychotic, Substance, Mental retardation, Adjustment, Pathological gambling disorders
Vijayakumar et al., 1999 (40)	India	1994-1995	14-99	P	88.0	0.6	Mood, Substance, Anxiety, Somatoform, Adjustment, Other disorders
Gururaj et al., 2004 (41)	India	2001-2002	0-99	P	42.8	0.4	N/S
Khan et al., 2005 (42)	India	2003-2003	15-35	P	36.0	0.3	N/S
Khan et al., 2008 (43)	Pakistan	2003-2003	N/S	P	96.0	0.8	Mood, Psychotic , Adjustment, Acute stress reaction, Substance, Mental retardation, Personality disorders

Note. [a]Sex: Males (M), Female (F), Persons(P); [b]Proportion of suicide cases occurring as a result of a mental and substance use disorders; [c] Studies scored out of 9 where studies reporting male and female estimates =2, male or female estimates = 1, person estimates only=0; studies with a clearly reported sample and observation period = 2 and unreported sample and observation period =1; studies using national representative data =3, regionally-representative data =2, community-representative data=1; studies covering the entire lifespan=2 and only a specific age group=1.

References

1. Foster T, Gillespie K, McClelland R. Mental disorders and suicide in Northern Ireland British Journal of Psychiatry. 1997;170 447-52.
2. Schneider B, Schnabel A, Webner B, Frolich L, Maurer K, Wetterling T. Nicotine use in suicide: a case-control study European Psychiatry. 2005;20:129–36.
3. Groholt B, Ekeberg O, Wichstrom L, Haldorsen T. Youth suicide in Norway, 1990–1992: a comparison between children and adolescents completing suicide and age- and gendermatched controls. Suicide and Life Threatening Behavior. 1997;27:250-63.
4. Henriksson MM, Aro HM, Marttunen MJ, Heikkinen ME, Isometsa ET, Kuoppasalmi KI, et al. Mental disorders and comorbidity in suicide American Journal of Psychiatry. 1993;150:935-40.
5. Asgard U. A psychiatric study of suicide among urban Swedish women Acta Psychiatrica Scandinavica. 1990;82:115-24.
6. Runeson B. Mental disorder in youth suicide. DSM-III-R Axes I and II. Acta Psychiatrica Scandinavica. 1989;79:490-7.
7. Waern M, Runeson BS, Allebeck P, Beskow J, Rubenowitz E, Skoog I, et al. Mental disorder in elderly suicides: a case-control study American Journal of Psychiatry. 2002;159:450-5.
8. Boardman AP, Grimbaldeston AH, Handley C, Jones PW, Willmott S. The North Staffordshire Suicide Study: A case-control study of suicide in one health district Psychological Medicine. 1999;29:27-33.
9. Cavanagh JT, Owens DG, Johnstone EC. Life events in suicide and undetermined death in south-east Scotland: a case-control study using the method of psychological autopsy. Social Psychiatry and Psychiatric Epidemiology. 1999;34:645-50.
10. Harwood D, Hawton K, Hope T, Jacoby R. Psychiatric disorder and personality factors associated with suicide in older people: a descriptive and case-control study International Journal of Geriatric Psychiatry. 2001;16:155-65.
11. Houston K, Hawton K, Shepperd R. Suicide in young people aged 15–24: a psychological autopsy study Journal of Affective Disorders. 2001;63:59-170.
12. Appleby L, Cooper J, Amos T, Faragher B. Psychological autopsy study of suicides by people aged under 35 British Journal of Psychiatry. 1999;175:168-74.
13. Portzky G, Audenaert K, Heeringen V. Psychosocial and psychiatric factors associated with adolescent suicide: A caseecontrol psychological autopsy study. Journal of Adolescence. 2009;32:849-62.
14. Pompili M, Innamorati M, Masotti V, Personne F, Lester D, Di Vittorio C, et al. Suicide in the elderly: A psychological autopsy study in a North Italy Area (1994–2004). American Journal of Geriatric Psychiatry. 2008;16(9):727-35.
15. Isometsa ET, Heikkinen ME, Henriksson MM, Marttunen MJ, Aro HM, Lonnqvist JK. Differences between urban and rural suicides Acta Psychiatrica Scandinavica. 1997;95:297–305.
16. Almasi K, Belso N, Kapur N, Webb R, Cooper J, Hadley S, et al. Risk factors for suicide in Hungary: a case-control study. BMC Psychiatry. 2009;9(45):1-9.
17. Arato M, Demeter E, Rihmer Z, Somogyi E. Retrospective psychiatric assessment of 200 suicides in Budapest. . Acta Psychiatrica Scandinavica. 1988;77 454-6.
18. Zonda T. One-hundred cases of suicide in Budapest. A case–controlled psychological autopsy study. Crisis. 2006;27:125–9.
19. Brent DA, Baugher M, Bridge J, Chen T, Chiappetta L. Age and sex related risk factors for adolescent suicide. Journal of the American Academy of Child Adolescent Psychiatry. 1999;38 1497-505.

20. Shaffer D, Gould MS, Fisher P, Trautman P, Moreau D, Kleinman M, et al. Psychiatric diagnosis in child and adolescent suicide. Archives of General Psychiatry. 1996;53:339-48.
21. Conwell Y, Olsen K, Caine ED, Flannery C. Suicide in later life. Psychological autopsy findings International Psychogeriatrics. 1991;3:59–66.
22. Fowler RC, Rich CL, Young D. San Diego Suicide Study II. Substance abuse in young cases. Archives of General Psychiatry 1986;43:962–5.
23. Rich CL, Young D, Fowler RC. San Diego suicide study. I. Young vs old subjects. Archives of General Psychiatry. 1986;43:577-82.
24. Shafii M, Steltz-Lenarsky J, Derrick AM, Beckner C, Whittinghill JR. Comorbidity of mental disorders in the post-mortem diagnosis of completed suicide in children and adolescents. Journal of Affective Disorders. 1988;15 227-33.
25. Preville M, Hebert R, Boyer R, Bravo G, Seguin M. Physical health and mental disorder in elderly suicide: a case-control study. Aging and mental health. 2005;9:576–84.
26. Lesage AD, Boyer R, Grunberg F, Vanier C, Morisette R, Menard-Buteau C, et al. Suicide and mental disorders: a case–control study of young men. American Journal of Psychiatry 1994;151:1063–8.
27. McGirr A, Séguin M, Renaud J, Benkelfat C, Alda M, Turecki G. Gender and risk factors for suicide: evidence for heterogeneity in predisposing mechanisms in a psychological autopsy study. Journal of Clinical Psychiatry. 2006;67(10):1012-617.
28. Palacioa C, García J, Diago J, Zapata C, Lopez G, Ortize J, et al. Identification of suicide risk factors in Medellín, Colombia: A case-control study of psychological autopsy in a developing country. Archives of Suicide Research. 2007;11:297-308.
29. Thacore VR, Varma SL. A study of suicides in Ballarat, Victoria, Australia Crisis 2000;21:26-30.
30. Graham C, Burvill PW. A study of coroner's records of suicide in young people, 1986–88 in Western Australia Australian and New Zealand Journal of Psychiatry. 1992;26:30-9.
31. Kurihara T, Kato M, Reverger R, Tirta IG. Risk factors for suicide in Bali: a psychological autopsy study. BMC Public Health. 2009;9(327):1-7.
32. Chen EY, Chan WS, Wong PW, Chan SS, Chan CL, Law YW, et al. Suicide in Hong Kong: a case- control psychological autopsy study. Psychol Med. 2006;36(6):815-25.
33. Chiu HF, Yip PS, Chi I, Chan S, Tsoh J, Kwan CW, et al. Elderly suicide in Hong Kong – a case controlled psychological autopsy study. Acta Psychiatrica Scandinavica. 2004;109:299-305.
34. Zhang J, Xiao S, Zhou L. Mental disorders and suicide among young rural Chinese: A case-control psychological autopsy study. American Journal of Psychiatry. 2010;167:773-81.
35. Zhang J, Zhou L. A case control study of suicides in China with and without mental disorder. Crisis. 2009;30(2):68-72.
36. Phillips MR, Yang G, Zhang Y, Wang L, Ji H, Zhou M. Risk factors for suicide in China: a national case-control psychological autopsy study Lancet. 2002;360 1728-36.
37. Li XY, Phillips MR, Zhang YP, Xu D, Yang GH. Risk factors for suicide in China's youth: a case- control study. Psychological Medicine. 2008;38:397-406.
38. Zhang J, Conwell Y, Zhou L, Jiang C. Culture, risk factors and suicide in rural China: a psychological autopsy case control study Acta Psychiatrica Scandinavica. 2004;110:430–7.
39. Cheng AT. Mental illness and suicide. A case-control study in east Taiwan. Arch Gen Psychiatry. 1995;52(7):594-603.
40. Vijayakumar L, Rajkumar S. Are risk factors for suicide universal? A case-control study in India. Acta Psychiatrica Scandinavica. 1999;99:407-11.
41. Gururaj G, Isaac MK, Subbakrishna DK, Ranjani R. Risk factors for completed suicide: a case-control study from Bangalore, India International Journal of Injury Control and Safety Promotion. 2004;11(183-191).

42. Khan FA, Anand B, Devi MG, Murthy KK. Psychological autopsy of suicide-a cross-sectional study. Indian journal of psychiatry. 2005;47(2):73-8.
43. Khan MM, Mahmud S, Karim MS, Zaman M, Prince M. Case–control study of suicide in Karachi, Pakistan. British Journal of Psychiatry. 2008;193:402-5.

Table S4: Pooled proportion of suicide cases attributable to mental and substance use disorders

Region	Pooled proportion (95% UI)	Number of studies	Number of countries
Group 1: China, India, Taiwan			
Overall	QE: 68.3% (55.2%-80.0%) RE: 69.4% (53.5%-83.4%)	9	3
Male	QE: 63.4% (46.2%-79.1%) RE: 76.3% (50.1%-90.6%)	1	3
Female	QE: 48.6% (29.1%-68.3%) RE: 61.0% (30.5%-87.9%)	1	3
Group 2: Other countries[a]			
Overall	QE: 84.5% (78.6%-89.6%) RE: 83.8% (76.5%-90.0%)	34	17
Male	QE: 88.8% (84.1%-92.8%) RE: 87.9% (82.9%-92.1%)	12	7
Female	QE: 93.3% (87.2%-97.6%) RE: 94.2% (86.5%-99.0%)	12	8

Note.95% UI: 95% uncertainty interval; QE: Quality effect model estimate, RE: Random effects model estimate; [a]*Group 2 countries: Includes studies from Australia, USA, Canada, Colombia, Hungary, United Kingdom, Belgium, Italy, Germany, Sweden, Ireland, Norway, Finland, Indonesia, Pakistan.*

Table S5: Suicide DALYs (i.e. YLLs) attributable to mental and substance use disorders in 1990 and 2010

	1990			2010		
	YLL	**95% UI**		**YLL**	**95% UI**	
	Mean	*Lower*	*Upper*	*Mean*	*Lower*	*Upper*
By sex						
Male	11,400,000	7,700,000	15,800,000	14,900,000	95000,00	20,100,000
Female	6,800,000	4,000,000	9,900,000	7,600,000	4,400,000	10,600,000
By age						
5-9 years	20,000	10,000	40,000	20,000	10,000	30,000
10-14 years	300,000	200,000	500,000	300,000	100,000	600,000
15-19 years	2,200,000	1,300,000	3,100,000	2,500,000	1,500,000	3,800,000
20-24 years	3,100,000	2,000,000	4,300,000	3,400,000	2,000,000	4,900,000
25-29 years	2,600,000	1,700,000	3,500,000	2,900,000	1,900,000	4,000,000
30-34 years	2,200,000	1,500,000	2,900,000	2,400,000	1,500,000	3,200,000
35-39 years	1,900,000	1,300,000	2,600,000	2,200,000	1,400,000	3,100,000
40-44 years	1,500,000	1,000,000	2,000,000	2,000,000	1,400,000	2,900,000
45-49 years	1,100,000	800,000	1,600,000	1,800,000	1,200,000	2,500,000
50-54 years	1,100,000	800,000	1,600,000	1,600,000	1,000,000	2,300,000
55-59 years	800,000	500,000	1,200,000	1,200,000	700,000	1,800,000
60-64 years	600,000	400,000	900,000	800,000	500,000	1,200,000
65-69 years	400,000	200,000	600,000	500,000	300,000	800,000
70-74 years	200,000	100,000	300,000	400,000	200,000	600,000
75-79 years	200,000	100,000	200,000	300,000	100,000	400,000
80 + years	100,000	100,000	200,000	200,000	100,000	300,000
By region						
Asia Pacific, High Income	600,000	400,000	1,000,000	800,000	400,000	1,200,000
Asia, Central	300,000	200,000	400,000	400,000	200,000	500,000
Asia, East	5,300,000	2,900,000	7,400,000	3,500,000	2,200,000	6,100,000
Asia, South	4,000,000	2,600,000	6,000,000	8,800,000	4,800,000	12,600,000
Asia, Southeast	1,100,000	700,000	1,500,000	1,300,000	800,000	1,800,000

	1990			2010		
	YLL	95% UI		YLL	95% UI	
	Mean	*Lower*	*Upper*	*Mean*	*Lower*	*Upper*
By region						
Australasia	80,000	50,000	100,000	70,000	50,000	100,000
Caribbean	100,000	100,000	100,000	100,000	100,000	100,000
Europe, Central	600,000	400,000	800,000	500,000	300,000	600,000
Europe, Eastern	2,000,000	1,400,000	2,700,000	1,800,000	1,200,000	2,800,000
Europe, Western	1,500,000	1,000,000	2,000,000	1,200,000	800,000	1,700,000
Latin America, Andean	50,000	40,000	70,000	90,000	50,000	100,000
Latin America, Central	200,000	160,000	400,000	400,000	200,000	500,000
Latin America, Southern	200,000	110,000	200,000	200,000	100,000	300,000
Latin America, Tropical	300,000	200,000	400,000	400,000	300,000	500,000
North Africa / Middle East	200,000	100,000	300,000	500,000	200,000	700,000
North America, High Income	1,100,000	700,000	1,400,000	1,100,000	800,000	1,500,000
Oceania	20,000	10,000	30,000	30,000	20,000	50,000
Sub-Saharan Africa, Central	80,000	50,000	100,000	200,000	100,000	300,000
Sub-Saharan Africa, East	400,000	300,000	600,000	800,000	500,000	1,100,000
Sub-Saharan Africa, Southern	100,000	50,000	200,000	200,000	100,000	300,000
Sub-Saharan Africa, West	100,000	60,000	200,000	200,000	100,000	300,000
By disorder						
Alcohol dependence	4,200,000	3,200,000	5,300,000	4,900,000	3,600,000	6,300,000
Amphetamine dependence	700,000	300,000	1,400,000	900,000	300,000	1,700,000
Anorexia nervosa	40,000	10,000	100,000	60,000	10,000	200,000
Anxiety disorder	2,100,000	800,000	3,600,000	2,700,000	1,000,000	4,800,000
Bipolar disorder	1,600,000	500,000	3,300,000	2,000,000	600,000	4,000,000
Cocaine dependence	300,000	100,000	600,000	300,000	100,000	700,000
Major depressive disorder	13,500,000	8,000,000	18,900,000	16,700,000	9,900,000	23,300,000
Opioid dependence	500,000	300,000	800,000	700,000	400,000	1,100,000
Schizophrenia	1,400,000	1,000,000	1,700,000	1,700,000	1,300,000	2,200,000

Note. DALYs: Disability adjusted life years; YLLs: years of life lost; 95% UI: 95% uncertainty interval; Absolute YLLs rounded to 100,000

Table S6: Suicide DALYs (i.e. YLLs) attributable to each mental and substance use disorders in 2010 by region

Region	Alcohol use disorder	Amphetamine dependence	Anorexia nervosa	Anxiety disorder	Bipolar disorder	Cocaine dependence	Major depressive disorder	Opioid dependence	Schizophrenia
Asia Pacific, High Income									
Mean	190,000	30,000	10,000	90,000	70,000	20,000	520,000	30,000	70,000
95% UI: Lower	250,000	70,000	40,000	170,000	160,000	50,000	860,000	70,000	90,000
Upper	110,000	10,000	2,000	30,000	20,000	10,000	240,000	10,000	40,000
Asia, Central									
Mean	120,000	20,000	300	50,000	30,000	4,000	240,000	10,000	30,000
95% UI: Lower	180,000	30,000	1,000	90,000	60,000	10,000	370,000	20,000	50,000
Upper	90,000	10,000	50	20,000	10,000	2,000	140,000	10,000	20,000
Asia, East									
Mean	870,000	100,000	4,000	260,000	330,000	10,000	2,480,000	70,000	340,000
95% UI: Lower	1,450,000	220,000	10,000	520,000	700,000	20,000	4,450,000	140,000	560,000
Upper	590,000	30,000	1,000	90,000	100,000	3,000	1,250,000	30,000	240,000
Asia, South									
Mean	1,820,000	370,000	2,000	1,090,000	770,000	100,000	6,530,000	310,000	600,000
95% UI: Lower	2,630,000	800,000	10,000	2,020,000	1,620,000	220,000	9,730,000	530,000	820,000
Upper	1,020,000	110,000	300	410,000	250,000	30,000	3,280,000	150,000	330,000
Asia, Southeast									
Mean	210,000	90,000	1,000	140,000	120,000	4,000	970,000	30,000	100,000
95% UI: Lower	300,000	180,000	2,000	270,000	250,000	10,000	1,430,000	50,000	150,000
Upper	160,000	30,000	100	50,000	40,000	1,000	570,000	10,000	70,000
Australasia									
Mean	20,000	5,000	1,000	10,000	10,000	2,000	50,000	4,000	10,000
95% UI: Lower	20,000	10,000	2,000	20,000	10,000	4,000	70,000	10,000	10,000
Upper	10,000	2,000	100	5,000	2,000	1,000	30,000	2,000	5,000

Region	Alcohol use disorder	Amphetamine dependence	Anorexia nervosa	Anxiety disorder	Bipolar disorder	Cocaine dependence	Major depressive disorder	Opioid dependence	Schizophrenia
Caribbean									
Mean	20,000	3,000	200	10,000	10,000	5,000	70,000	3,000	10,000
95% UI: Lower	30,000	10,000	1,000	20,000	20,000	10,000	90,000	10,000	10,000
Upper	20,000	1,000	30	4,000	2,000	2,000	40,000	1,000	5,000
Europe, Central									
Mean	110,000	20,000	1,000	70,000	40,000	4,000	340,000	10,000	50,000
95% UI: Lower	150,000	50,000	3,000	130,000	90,000	10,000	490,000	20,000	70,000
Upper	80,000	10,000	200	30,000	10,000	1,000	200,000	10,000	30,000
Europe, Eastern									
Mean	540,000	30,000	2,000	160,000	150,000	10,000	1,410,000	50,000	130,000
95% UI: Lower	850,000	80,000	10,000	360,000	320,000	30,000	2,240,000	110,000	210,000
Upper	400,000	10,000	300	50,000	50,000	5,000	820,000	30,000	90,000
Europe, Western									
Mean	280,000	40,000	10,000	170,000	90,000	20,000	920,000	40,000	70,000
95% UI: Lower	380,000	80,000	40,000	290,000	190,000	50,000	1,330,000	70,000	90,000
Upper	220,000	10,000	2,000	70,000	30,000	10,000	550,000	20,000	50,000
Latin America, Andean									
Mean	30,000	3,000	100	10,000	10,000	4,000	60,000	3,000	10,000
95% UI: Lower	40,000	10,000	200	30,000	10,000	10,000	90,000	10,000	10,000
Upper	20,000	1,000	10	4,000	2,000	1,000	30,000	1,000	3,000
Latin America, Central									
Mean	80,000	20,000	1,000	60,000	40,000	10,000	300,000	10,000	30,000
95% UI: Lower	100,000	50,000	2,000	100,000	80,000	20,000	430,000	20,000	40,000
Upper	60,000	10,000	100	20,000	10,000	3,000	160,000	10,000	20,000

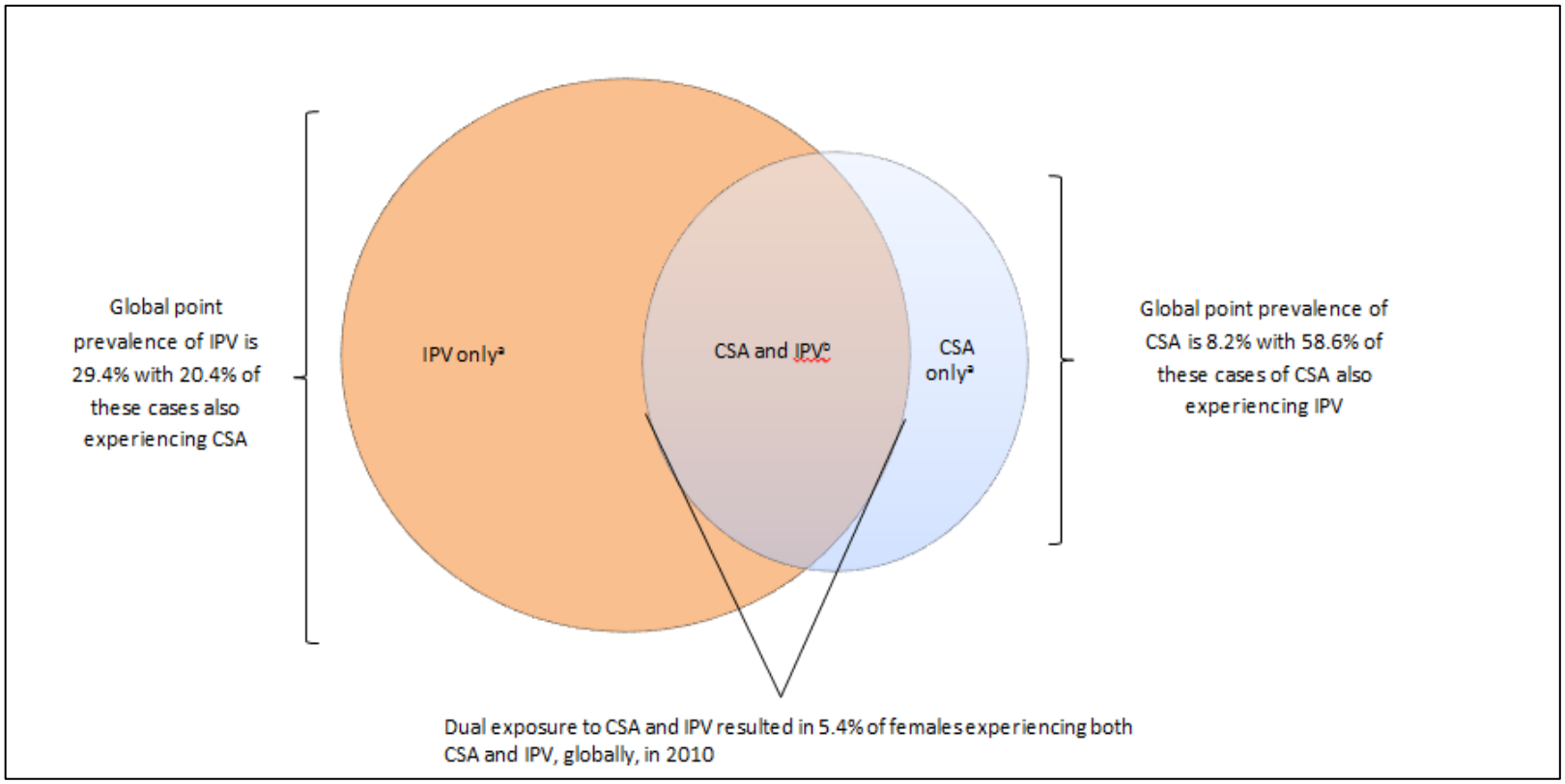
Region	Alcohol use disorder	Amphetamine dependence	Anorexia nervosa	Anxiety disorder	Bipolar disorder	Cocaine dependence	Major depressive disorder	Opioid dependence	Schizophrenia
Latin America, Southern									
Mean	40,000	10,000	1,000	30,000	20,000	10,000	150,000	10,000	10,000
95% UI: Lower	60,000	20,000	2,000	60,000	40,000	20,000	210,000	10,000	20,000
Upper	30,000	3,000	100	10,000	10,000	3,000	90,000	3,000	10,000
Latin America, Tropical									
Mean	80,000	20,000	200	60,000	30,000	20,000	310,000	10,000	30,000
95% UI: Lower	120,000	40,000	1,000	100,000	70,000	40,000	430,000	20,000	50,000
Upper	50,000	10,000	30	20,000	10,000	10,000	190,000	4,000	10,000
North Africa / Middle East									
Mean	40,000	20,000	2,000	80,000	40,000	10,000	400,000	20,000	40,000
95% UI: Lower	50,000	50,000	10,000	160,000	90,000	30,000	580,000	40,000	50,000
Upper	20,000	10,000	300	30,000	10,000	4,000	190,000	10,000	20,000
North America, High Income									
Mean	220,000	30,000	10,000	200,000	100,000	60,000	850,000	30,000	120,000
95% UI: Lower	270,000	70,000	40,000	350,000	200,000	130,000	1,180,000	50,000	150,000
Upper	160,000	10,000	2,000	80,000	30,000	20,000	510,000	20,000	80,000
Oceania									
Mean	10,000	1,000	10	4,000	3,000	200	20,000	1,000	2,000
95% UI: Lower	10,000	3,000	40	10,000	10,000	400	40,000	2,000	10,000
Upper	4,000	300	2	1,000	1,000	40	10,000	300	1,000
Sub-Saharan Africa, Central									
Mean	20,000	10,000	1,000	30,000	20,000	1,000	140,000	3,000	10,000
95% UI: Lower	40,000	20,000	2,000	60,000	30,000	3,000	220,000	10,000	20,000
Upper	10,000	2,000	100	10,000	4,000	400	80,000	1,000	10,000

Region	Alcohol use disorder	Amphetamine dependence	Anorexia nervosa	Anxiety disorder	Bipolar disorder	Cocaine dependence	Major depressive disorder	Opioid dependence	Schizophrenia
Sub-Saharan Africa, East									
Mean	110,000	40,000	100	120,000	70,000	10,000	650,000	20,000	50,000
95% UI: Lower	150,000	80,000	200	220,000	140,000	10,000	930,000	30,000	60,000
Upper	70,000	10,000	10	50,000	20,000	2,000	380,000	10,000	30,000
Sub-Saharan Africa, Southern									
Mean	60,000	10,000	100	20,000	20,000	2,000	160,000	10,000	10,000
95% UI: Lower	90,000	20,000	300	50,000	40,000	5,000	240,000	10,000	20,000
Upper	40,000	4,000	10	10,000	5,000	1,000	80,000	2,000	10,000
Sub-Saharan Africa, West									
Mean	20,000	10,000	10	20,000	20,000	2,000	140,000	4,000	10,000
95% UI: Lower	20,000	20,000	40	50,000	40,000	4,000	220,000	10,000	20,000
Upper	10,000	3,000	2	10,000	5,000	1,000	80,000	2,000	10,000

Note. DALYs: Disability adjusted life years; YLLs: years of life lost; 95% UI: 95% uncertainty interval; Absolute YLLs rounded to 100,000

Appendix Six

Supplementary text to Chapter Seven



Note. Figure has been scaled to approximate prevalence proportions; [a]Prevalence of CSA and IPV in females estimated by DisMod-MR; [b]Prevalence of dual exposure to CSA and IPV in females estimated from WHO's multi-country study on women's health and domestic violence. For the purposes of this paper, single and dual exposures to CSA and IPV in males did not need to be estimated given the lack of evidence for the association between IPV and depression in males.

Figure S1. Illustration of the prevalence of single and dual exposure to lifetime child sexual abuse (CSA) and intimate partner violence (IPV) in females

Appendix Seven

Supplementary text to Chapter Eight

Text S1. Media coverage in response to the data presented in Chapter Three

Source: News article, The Australian, 4th August, 2012
Title: Depression could be Third World disease
Author: Stephen Matchett

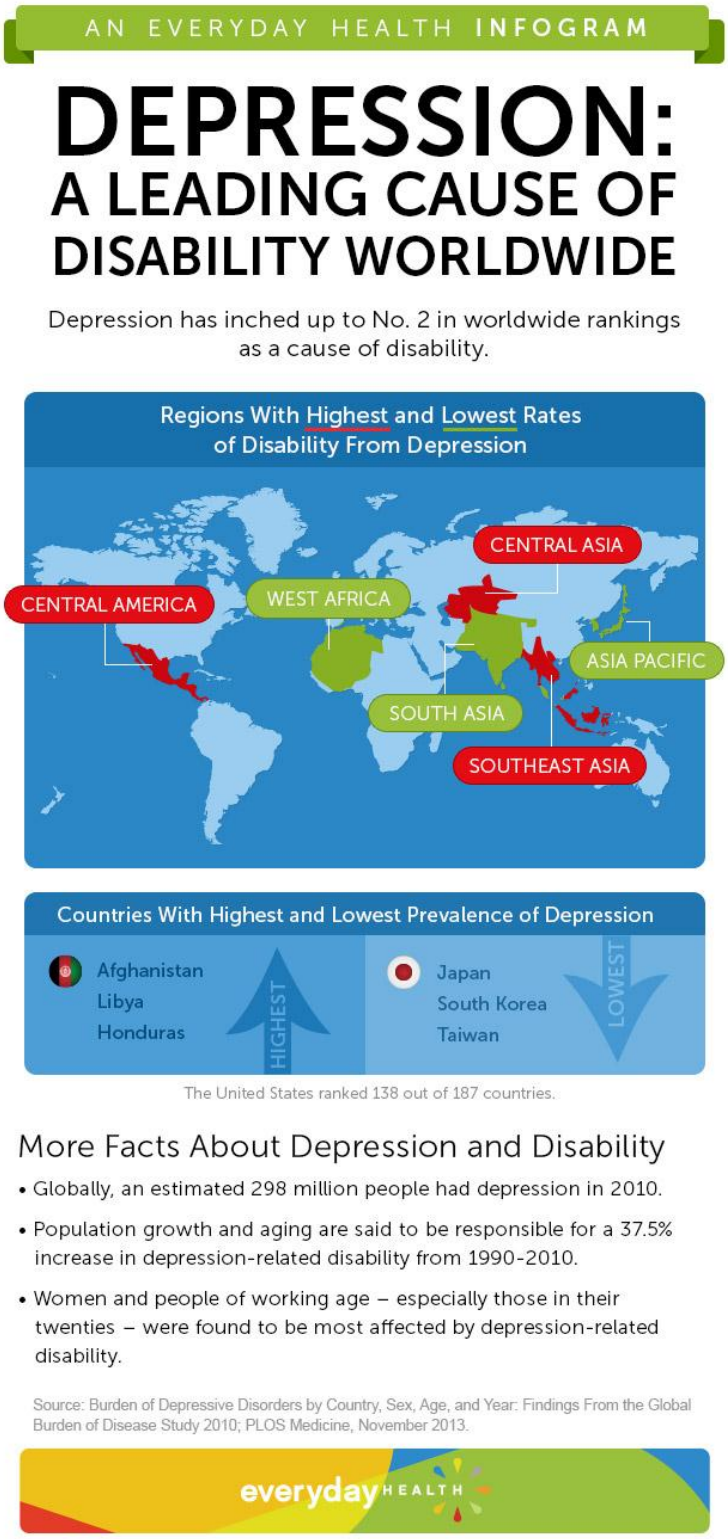
> "DEPRESSION is a disease of developing countries rather than a unique affliction of consumer societies, according to the first global study of worldwide mental illness in a generation.
>
> A statistical analysis by a team led by University of Queensland researcher Alize Ferrari found North America, Western Europe and Australia have the lowest rates of major depressive disorders, while South Asia, Africa and the Middle East lead the world for incidences of major depressive disorders.
>
> However, a separate study by her colleague Amanda Baxter and other researchers identifies anxiety disorders as a disease of affluence, with Africans far less prone to them than Euro and Anglo cultures. The two papers are the first findings of a Bill & Melinda Gates Foundation research project at the University of Queensland led by Harvey Whiteford.
> His team is one of 54 expert groups around the world participating in the Global Burden of Disease project, which follows another World Health Organisation project in 1990. Professor Whiteford said the Gateses' motivation was to discover the effectiveness of 20 years of global health spending.
>
> He said the increase in incidence of major depression in the developing world was a result of an improvement in basic health services. "Better maternal health and better infectious diseases control mean people in the developing world now live into the age group where mental health disorders emerge, which is the late teens and early 20s," he said. But traditional cultures can be better at dealing with anxiety, a sense of disquiet and foreboding out of proportion to real-world risk, thanks to strong systems of family support that encourage resilience among individuals.
>
> However, Professor Whiteford warns the apparent lower level of anxiety in poor and conflict ridden countries than in the West may be more apparent than real, saying Third World surveys show low levels of anxiety but higher incidences of medically unexplained complaints. "People are just as anxious but they report it as physical symptoms," he says. Professor Whiteford is optimistic that identifying the extent of anxiety and major depression will lead to treatments that reduce the social impact and individual burden of these illnesses. While about 20 per cent of depression cases are genetic -- and while both it and anxiety are triggered by factors as diverse as poverty, war and domestic violence – once the symptoms are identified medical treatment becomes possible. The WHO funded programs in the successor states to Yugoslavia to deal with the trauma of the wars in the region a decade ago and Professor Whiteford is in contact with Libyan officials looking to address the impact of the recent conflict. "Wars are like infectious disease. They run their course, with depression rising, and take decades to drop back," Professor Whiteford said. "Our research will show it is possible to measure the disease burden and then come up with ways to reduce it." All 54 teams have filed their data to the Gates Foundation, with publication of their findings scheduled to start in November."

Media coverage in response to the data presented in Chapter Five

Source: News article, BBC News, 6th November 2013 (See: http://www.bbc.co.uk/news/health-24818048)
Title: Depression-'Second biggest cause of disability' in world.
Author: Helen Briggs

> "Depression is a big problem and we definitely need to pay more attention to it than we are now"
>
> Dr Alize Ferrari, University of Queensland
>
> Depression was ranked at number two as a global cause of disability, but its impact varied in different countries and regions. For example, rates of major depression were highest in Afghanistan and lowest in Japan. In the UK, depression was ranked at number three in terms of years lived with a disability.
>
> Dr Alize Ferrari from the University of Queensland's School of Population Health led the study.
>
> "Depression is a big problem and we definitely need to pay more attention to it than we are now," she told BBC News.
>
> "There's still more work to be done in terms of awareness of the disease and also in coming up with successful ways of treating it.
>
> "The burden is different between countries, so it tends to be higher in low and middle income countries and lower in high income countries."
>
> Policy-makers had made an effort to bring depression to the forefront, but there was a lot more work to be done, she added.
>
> "There's lots of stigma we know associated with mental health," she explained.
>
> "What one person recognizes as disabling might be different to another person and might be different across countries as well, there are lots of cultural implications and interpretations that come in place, which makes it all the more important to raise awareness of the size of the problem and also signs and how to detect it."
>
> The data - for the year 2010 - follows similar studies in 1990 and 2000 looking at the global burden of depression.
>
> Commenting on the study, Dr Daniel Chisholm, a health economist at the department for mental health and substance abuse at the World Health Organization said depression was a very disabling condition.
>
> "It's a big public health challenge and a big problem to be reckoned with but not enough is being done."Around the world only a tiny proportion of people get any sort of treatment or diagnosis."
>
> The WHO recently launched a global mental health action plan to raise awareness among policy-makers."

Source: Info graphic, Everyday Health Staff , 7th November 2013 (See: http://www.everydayhealth.com/depression/depression-a-leading-cause-of-disability-worldwide-8061.aspx)
Title: Depression: A Leading Cause of Disability Worldwide.
Author: Janet Kim and Jasmine Kim.



Web links to other media coverage of the data presented in Chapter Five:

- http://www.washingtonpost.com/blogs/worldviews/wp/2013/11/07/a-stunning-map-of-depression-rates-around-the-world/
- http://www.newsinmind.com/general-news/depression-second-biggest-cause-of-disability-in-world
- http://www.everydayhealth.com/depression/depression-a-leading-cause-of-disability-worldwide-8061.aspx
- http://www.cxvascular.com/nn-latest-news/neuro-news---latest-news/depression-was-second-leading-cause-of-global-disability-burden-in-2010?highlight=depression
- http://www.odt.co.nz/lifestyle/health-fitness/280195/depression-leading-cause-global-disability
- http://www.latimes.com/science/sciencenow/la-sci-sn-its-a-sad-sad-sad-sad-world-depression-and-global-disability-20131105,0,1460569.story#axzz2lziRGLkO
- http://www.globalhealthhub.org/2013/11/06/this-week-in-plos-medicine-global-burden-of-depression-syphilis-treatment-in-pregnancy/
- http://www.healthline.com/health-news/mental-depression-a-leading-cause-of-global-disability-110513
- http://historypsychiatry.com/tag/plos-medicine/
- http://www.eurekalert.org/pub_releases/2013-11/plos-a103013.php
- http://inagist.com/all/398395653459423232/
- http://www.medicalnewstoday.com/articles/268367.php
- http://dementianews.wordpress.com/2013/11/06/burden-of-depressive-disorders-findings-from-the-global-burden-of-disease-study-2010-bbc-news-plos-medicine/
- http://depression.about.com/b/2013/11/05/depression-is-second-leading-cause-of-disability-study-says.htm
- http://www.foxnews.com/health/2013/11/06/depression-second-leading-cause-disability-worldwide/
- http://io9.com/which-countries-have-the-highest-rate-of-diagnosed-depr-1461353607
- http://www.globalmentalhealth.org/depression-second-biggest-cause-disability-world
- http://www.hypnotherapy-now.co.uk/depression/bbc-depression-second-biggest-cause-of-disability-in-world/

- http://allafrica.com/stories/201311251248.html
- http://www.insidermedicine.com/archives/Depression_second_leading_cause_of_global_disability_burden_7567.aspx
- http://www.brainphysics.com/news/depression/depression-a-leader-in-global-disability
- http://www.counselheal.com/articles/7548/20131107/experts-call-depression-the-second-leading-cause-of-disability-in-the-world.htm
- http://www.nursinginpractice.com/article/depression-should-be-global-priority
- http://www.torontosun.com/2013/11/07/depression-is-the-second-biggest-cause-of-disability-after-back-pain
- http://sfoxwriting.com/2013/11/08/depression-second-biggest-cause-of-disability-in-world/
- http://www.medscape.com/viewarticle/813896
- http://www.medtiblog.org/2013/11/07/depression-second-largest-cause-of-disability-worldwide/
- http://www.philly.com/philly/health/mental-health/HealthDay681887_20131106_Health_Highlights__Nov__6__2013.html
- http://www.studentnewspaper.org/blog/2013/11/12/recent-report-highlights-global-extent-of-depression/
- http://www.advisory.com/Daily-Briefing/2013/11/07/A-global-health-priority-Depression-among-top-causes-of-disability