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2021

BRIDGING THE MENTAL HEALTH GAP IN THE DIGITAL AGE

ZHONGFANG FU



Bridging The Mental Health Gap In The Digital Age

© Zhongfang Fu



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Bridging the mental health gap in the digital age

ACADEMISCH PROEFSCHRIFT

ter verkrijging van de graad van doctor
aan de Universiteit van Amsterdam
op gezag van de Rector Magnificus
prof. dr. ir. K.I.J. Maex

ten overstaan van een door het College voor Promoties ingestelde
commissie,

in het openbaar te verdedigen in de Agnietenkapel
op dinsdag 23 november 2021, te 12.00 uur

door Zhongfang Fu
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To those who were deceived by life but still believe in the future

Chapter 1

Introduction

There are 195 countries in this world, and all with different habits and cultures. A consensus has gradually been reached, specifically in the global mental health field, that “mental disorders affect people in all cultures and societies, and no longer a figment of the ‘Western’ imagination” (Patel, Minas, Cohen, & Prince, 2013). However, sizable ethnic and socioeconomic disparities shape the availability of access to care, the help-seeking patterns, and therapeutic outcomes for mental disorders across the world (Cohen, Patel, & Minas, 2014). Common mental health problems are highly prevalent globally and have become a significant burden in many countries. However, the under-resourced regions are affected disproportionately due to the tremendous lack of mental health care service. The current thesis seeks to explore potential accessible routes that might improve the impact of mental disorders in low resourced settings.

Common mental disorders

Definition and prevalence

Common mental disorders (CMD) refer to those mental disorders that are most prevalent in the population. Three main diagnostic categories (based on ICD-10 code, World Health Organization, 1992) are regarded as CMD: depressive disorders, anxiety disorders, and substance use disorders, which can be delineated from more severe but less common mental illnesses such as schizophrenia and bipolar disorders. Detailed prevalence of these three CMDs by World Bank income levels (World Bank, 2020) are presented in Table 1. The prevalence of these disorders in high income countries are relatively higher than those in the other countries. With income level decreasing, the prevalence of CMDs also decreases. Though globally, all countries are affected alike by CMD in terms of prevalence. Approximately one in five persons had lived with these disorders in the previous twelve months in low to high income countries (Steel et al., 2014).

Disease burden

Disease burden is defined as “the total, cumulative consequences of a defined disease or a range of harmful diseases with respect to disabilities in a community” (Hessel, 2008). These consequences include health, social aspects, and costs to society. An estimate as US\$2.5-8.5 trillion in lost output worldwide in 2010 can be attributed to mental, neurological and substance use disorders (Bloom et al., 2012). These disorders can pose enormous challenges to communities and society due to the foregone production and increasing demands of mental health care capacities.

Disease burden is commonly quantified using the disability-adjusted life year (DALY) which aggregates the time lost in years due to premature mortality and the time living in a

Table 1: The point prevalence and disease burden (DALYs) of (common) mental disorders by income level of countries in 2019

Mental disorder	Income level	Prevalence (%) (95% CI)	DALYs (%) (95%CI)
Depressive disorders	Global	3.76 (3.38, 4.17)	1.84 (1.36, 2.38)
	High income	4.36 (3.95, 4.82)	2.39 (1.82, 3.02)
	Upper Middle	3.83 (3.45, 4.24)	2.08 (1.55, 2.67)
	Lower Middle	3.51 (3.13, 3.93)	1.65 (1.20, 2.16)
	Low income	3.60 (3.13, 4.12)	1.34 (0.92, 1.84)
Anxiety disorders	Global	4.05 (3.39, 4.78)	1.13 (0.83, 1.48)
	High income	5.52 (4.65, 6.60)	1.65 (1.24, 2.13)
	Upper Middle	4.36 (3.72, 5.08)	1.40 (1.04, 1.81)
	Lower Middle	3.40 (2.85, 4.05)	0.90 (0.65, 1.19)
	Low income	3.37 (2.67, 4.24)	0.69 (0.47, 0.97)
Substance use disorder	Global	2.17 (1.95, 2.43)	1.38 (1.17, 1.60)
	High income	3.80 (3.48, 4.16)	3.44 (3.05, 3.83)
	Upper middle	2.45 (2.19, 2.75)	1.72(1.44, 1.99)
	Lower Middle	1.51 (1.35, 1.72)	0.77 (0.63, 0.91)
	Low income	1.37 (1.18, 1.59)	0.44(0.34, 0.55)

DALY = Disability adjusted life year; CI = Confidence interval.

limited healthy state (Homedes, 1996). Anxiety, depressive disorders, and substance use disorders rank highest amongst mental disorders as measured by DALYs according to the global estimates of the Global Burden of Disease Study from 1990 onwards (GBD, 2019).

LMICs and HICs

Despite of the universal nature of CMD, variations exist in the capacity to handle CMD across the globe and the income level is regarded as an important index to map this heterogeneity onto different countries/regions. According to the calculation by the World Bank in 2020, a gross net income (GNI) per capita of \$12,535 has been set as the threshold with above it as high-income countries and below as low- and middle-income countries (LMICs). The latter category can be translated into 70% of countries (135) in this world. These countries, the home to nearly 80% of the population, are mainly distributed across Asian, African, and Latin American regions.

In the recent years, the absolute number of individuals in these countries suffering from common mental disorders is rapidly increasing given their population growth and aging (Richter, Wall, Bruen, & Whittington, 2019). However, given that the disparities appear in various facets between HICs and LMICs in terms of economy, social inequalities, structural violence, and priority of mental health, people in LMICs may be affected by CMDs disproportionately.

Mental health gap

Common mental disorders can have substantial impairment on the quality of life of affected persons. Unfortunately, not every sufferer is able to get access to care. Indeed, the mental health gap, i.e. the gap between available treatment and the number of people with mental disorders in need of treatment, has become a global issue (World Health Organization, 2008). In a recent systematic review (Chisholm et al., 2016), it was observed that 79%-95% sufferers of depression and anxiety do not receive evidence-based treatments in LMICs, and 72%-80% in HICs. Thus, although the intervention coverage in HICs is moderately larger than that in LMICs, the authors stated that overall, there is a greater need for improvement on the recognition and investment of evidence based mental health care.

The broad mental health gap means that large proportions of the population with mental disorders are left untreated. Given the relative paucity of research on treatment strategies for people living in LMICs, WHO continuously calls for action to fill in the mental health gap in terms of expenditure, human workforce, and policy priority (see review Patel

et al., 2018). On top of this, WHO has provided some guidelines to address the mental health gap, especially in LMICs (World Health Organization, 2008, 2013, 2015).

One of the strategies to reduce the mental health gap is the utilization of digital technology (Bockting, Williams, Carswell, & Grech, 2016). The advances of technology have offered unique opportunities to deliver mental health care service remotely and has been making prevailing difference globally to improve access of health care. Reasonable inclusion of lay person in the task sharing process is another possible strategy to handle the shortage of health professionals. Attempts have been made in the recent years to examine the feasibility and effectiveness of these promising strategies, including the combination of both strategies (Arjadi et al., 2018), but an overview on the overall effectiveness of these intervention in LMICs is missing.

Therefore, the current dissertation will set out to provide more insights into the etiology of CMD, and effectiveness and working mechanisms of digital treatment for CMD that is mostly remotely delivered. Given the fact that depressive disorders contribute most to the losses in health and functioning (indicated by DALYs and prevalence) compared to anxiety disorder and substance use disorder, in this thesis our primary attention will be on depression.

Depression

Depression, as characterized by its core symptoms being sadness and/or loss of interest or pleasure (American Psychiatric Association, 2013). The total number of people living with depression in the world is 322 million (World Health Organization, 2017). Nearly half of these people live in the South-East Asia Region and Western Pacific Region, where most of LMICs are distributed. Among them, China and India are two most populated countries, home to one third of population on this planet with young population growing in the recent years.

Psychological theories of onset of depression

Generally, the risk for developing major depressive disorder (MDD) is fairly low until the early teens, then rises in a linear fashion, and reaches its peak in young adulthood (Rohde, Lewinsohn, Klein, Seeley, & Gau, 2013). An alarming finding is that the incidence of depression seems to be steadily increasing these decades partly because of an aging population and the drastic change of lifestyle in modern society (Hidaka, 2012; World Health Organization, 2017). Comorbid with most of the mental disorders, suicide most likely occurred when a person has comorbid depression (Angst, Stassen, Clayton, & Angst, 2002). The risk of completed suicide, which is the worst possible outcome of MDD, is 20-fold

compared with the normal population (Holma et al., 2010). Therefore, it is essential to identify factors that precede onset of MDD which often originate from etiological models and theories in order to improve the effect of (preventative) interventions (Cuijpers, 2017).

Substantial work has been done in the biological, psychological, and societal domain to uncover possible etiological factors/theories of depression. Biologically, MDD has been assumed associated with alterations in brain structure and function, gastrointestinal factors, immunology, endocrinology (including neurotransmitters), neurotrophic factors, hormones, and oxidative stress (see review in Kennis et al., 2019). In this thesis we will, however, focus on psychological theories. Psychologically, there are five leading theories about the potential pathway to MDD, including behavioral, cognitive, psychodynamic, personality-based, and (overarching) diathesis-stress theories. Current well-received psychological interventions for depression are rooted in one or more of these five theories.

Therefore, we will assess the evidence for the validity of these psychological etiological theories in order to refine future preventive intervention strategies to improve their effectiveness. This is important because the current interventions have been shown to reach a plateau with a limited increase in the effectiveness with only half patients can benefit from the treatments in the past four decades (Holmes et al., 2018). A recent meta-analysis even found a significant decline since 1960 of the effectiveness of psychological interventions for MDD for youth (Weisz et al., 2019). Hence, a step backward to scrutinize where the therapies derived from may assist with the future adaptation or innovation of psychological (preventive) intervention on MDD.

This dissertation (*Chapter 2*), therefore, will provide a comprehensive review on the current status of these leading theories and investigate to what extent the theory-derived factors can predict the first onset of MDD.

Treatment effectiveness for depression

Evidence of psychological intervention for depression has massively accumulated in HICs in the past four decades. Several psychotherapies, such as cognitive behavior therapy, interpersonal psychotherapy, problem-solving, and behavioral activation, have been found to be effective for treatment of depression (Cuijpers, Karyotaki, Reijnders, & Ebert, 2018). Accumulation of evidence for the effectiveness of psychological intervention for depression in LMICs has been found in the recent years. A comprehensive systematic review reported that 32/253 randomized controlled trials on depression with face-to-face psychological intervention were conducted in LMICs and these therapies are found at least as effective as they are in Western countries (Cuijpers et al., 2018). However, it remains largely unknown

what the overall effect is of digital interventions for depression in LMICs and for specific vulnerable groups, e.g. young adults like university students. Moreover, effectiveness of digital psychological interventions in LMICs for any other mental disorders than depression is largely unknown either. Therefore, two special case scenarios that investigated the effectiveness of minimally adequate psychological intervention will be reported in this thesis as below.

Digital psychological intervention in LMICs

The coverage of internet and mobile phones increases over the years in the LMICs and facilitates the digital delivery of the psychological intervention. Naslund (2017) provided a summary of 49 studies on the use of mobile, online, and other remote technologies for treatment and prevention of mental disorders in LMICs. Most of them were preliminary evaluations of feasibility and acceptability. Three other reviews (Arjadi, Nauta, Chowdhary, & Bockting, 2015; Jimenez-Molina et al., 2019; Martinez, Rojas, Martinez, Lara, & Perez, 2018) could identify no more than four randomized controlled trials (RCT) on digital psychological intervention. Due to the insufficient number of RCTs, these relevant reviews were not able to answer the basic question of effectiveness. Some evidence has been obtained in the HICs whereas the generalizability is of concern. Hence, a meta-analysis based on continued research is still needed to rigorously evaluate the effectiveness of digital psychological interventions for mental disorders, and to carefully consider potential risks introduced by technology, eventually to determine how emerging technologies might facilitate the scale-up of psychological (preventive) intervention across low-resourced settings.

Therefore, in *Chapter 3*, instead of only focusing on depression, we expand our scope to all mental health problems and disorders to achieve a better understanding of the effectiveness of digital interventions.

Psychological intervention on depression in Chinese university students

University students are in a period of life in which they grow from adolescents to adults denoted as ‘emerging adulthood’ (Arnett, 2000). As mentioned earlier, university students are right in the age range vulnerable to the occurrence of MDD. They can experience substantial stress due to academic pressures, interpersonal relationships, and preoccupation with post-graduation life (Bayram & Bilgel, 2008). These accumulated stresses could jeopardize the mental health status of this group in particular.

In China, around 34 million students registered at campus of universities. Studies observed that one in four Chinese university students had experienced depressive

symptoms at some moment (Gao, Xie, Jia, & Wang, 2020). A recent longitudinal survey observed the cumulative incidence of clinical depressive symptoms can be as high as 42% among Chinese university students since the first year of university (Song, Liu, Chen, Guo, & Huang, 2020).

Guided by the local policy of mental health, each university has to install at least one professional psychological counsellor for every 2000 students. According to a survey in 2016, the counsellor-to-student ratio, a ratio recommended to be best maintained as 1 to 250 (American School Counsellor Association), is 1 to 2,363 among Chinese university students in average which performs better than that among communities in China (1 to 10,000; Simple Psychology, 2016), while worse than that in well-developed countries like United States is around 1 to 500 (American School Counselor Association & National Association for College Admission Counseling, 2017). These treatment gaps produced long waitlists in the universities and emphasized the necessity to provide suitable interventions to mitigate depression symptoms among Chinese university students. However, an overview of how effective of interventions for Chinese university students is currently missing. Therefore, in *Chapter 4*, we will provide a systematic overview and meta-analysis of the effectiveness of psychological interventions for Chinese students.

Treatment mechanism for depression

Compared to the other evidence-based psychological interventions, behavioral activation (derived from behavior therapy) is structured and easily implemented and reasoned as a favorable candidate treatment of depression to disseminate. An RCT evaluating the effect of internet-based behavioral activation (BA) to treat depression in 313 patients with major depressive disorder was conducted in Indonesia (Arjadi et al., 2018). In this trial, at ten weeks after baseline, the patients in the BA intervention group guided by lay counselors reported significantly fewer depressive symptoms than those in the control group (with an adjusted effect size as 0.24) and had a 50% higher chance of remission compared to the control group.

Based on this internet-based behavioral activation RCT on depression in Indonesia, in this thesis, we further seek to answer the classical questions in the psychotherapy studies: “how does the treatment work” (*Chapter 5*). To know how the treatment works, that is the working mechanisms, we often examine mediators. A mediator is the variable that statistically explains this process and can be seen as part of the mechanism. Mediation in treatment studies indicates the process that why and through which path the treatment effect occurs.

BA is designed to target and restore activation of patients to reverse the cycle of depression. All the behavior-change strategies it adopts are developed on the basis of a careful examination of the individual behavior analysis for a given patient and to help the patient engage in increased activation (Dimidjian, Martell, Herman-Dunn, & Hubley, 2014). Therefore, activation level is assumed to be the primary mediator of treatment effect of BA.

Previous reviews critically evaluated the current status of research on a variety of psychological mediators in various forms of (preventive) psychotherapy for depression (Lemmens, Müller, Arntz, & Huibers, 2016; Moreno-Peral et al., 2020). Behavioral constructs are rarely examined, and inconsistency still exists regarding the examination of behavioral activation as working mechanism. Therefore, in the current dissertation, we aim to examine activation level as a working mechanism of BA intervention among MDD patients. The field would benefit from a further well-designed investigation of behavioral activation level to elucidate the mechanism of change in behavioral therapy, and in turn to optimize the current intervention and assist to refine the behavioral theory of depression.

Aims of this dissertation

This dissertation aims to expand our understanding on the current status of psychological treatment for CMDs, particular for depression, in low- and middle-income countries. We will unfold this thesis from the psychological etiological theories of depression, through the potential of digital psychological intervention for all mental health problems and conditions, and end with the possible mechanism of therapeutic change.

In *Chapter 2*, the results of a comprehensive systematic overview and meta-analysis is described of the current empirical evidence for leading psychological theories of depression (from which most of psychotherapies derived). In *Chapter 3*, a systematic review and meta-analysis was conducted in order to examine the effectiveness of digital psychological interventions in LMICs for mental health problems and conditions. In *Chapter 4*, another systematic review was conducted to provide an overview of the different types of psychological interventions being studied amongst Chinese university students.

Subsequently, knowing the effectiveness of a properly designed and delivered internet intervention in LMICs, we are interested in further exploration on the mechanism of change in treatment. In *Chapter 5*, driven by the behavioral theory of depression, we will examine whether change in activation level is a mediator of change of the effect on reduction of depressive symptomatology using latent growth model and simplex mediation model in the structural equation modelling framework.

Finally, in the Discussion, the findings from the studies above will be integrated and some potential research directions will be discussed. Ultimately, we hope that the studies described in this thesis will lead to accessible routes to reduce the burden of CMDs and hopefully to close the mental health gap globally.

Reference

- American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders (DSM-5)*. American Psychiatric Pub.
- American School Counselor Association, & National Association for College Admission Counseling. (2017). *State-by-state student-to-counselor ratio report: 10-year trends, 1–60*. Retrieved from <https://www.schoolcounselor.org/asca/media/asca/Publications/ratioreport.pdf>
- Angst, F., Stassen, H. H., Clayton, P. J., & Angst, J. (2002). Mortality of patients with mood disorders: follow-up over 34–38 years. *Journal of Affective Disorders*, 68(2-3), 167–181.
- Arjadi, R., Nauta, M. H., Chowdhary, N., & Bockting, C. L. H. (2015). A systematic review of online interventions for mental health in low and middle income countries: a neglected field. *Glob Ment Health (Camb)*, 2, e12. <https://doi.org/10.1017/gmh.2015.10>
- Arjadi, R., Nauta, M. H., Scholte, W. F., Hollon, S. D., Chowdhary, N., Suryani, A. O., ... Bockting, C. L. H. (2018). Internet-based behavioural activation with lay counsellor support versus online minimal psychoeducation without support for treatment of depression: a randomised controlled trial in Indonesia. *Lancet Psychiatry*, 5(9), 707–716.
- Arnett, J. J. (2000). Emerging adulthood: A theory of development from the late teens through the twenties. *American Psychologist*, 55(5), 469.
- Bayram, N., & Bilgel, N. (2008). The prevalence and socio-demographic correlations of depression, anxiety and stress among a group of university students. *Social Psychiatry and Psychiatric Epidemiology*, 43(8), 667–672.
- Bloom, D. E., Cafiero, E., Jané-Llopis, E., Abrahams-Gessel, S., Bloom, L. R., Fathima, S., ... Mowafi, M. (2012). The global economic burden of noncommunicable diseases. *Program on the Global Demography of Aging*.
- Bockting, C. L. H., Williams, A. D., Carswell, K., & Grech, A. E. (2016). The potential of low-intensity and online interventions for depression in low-and middle-income countries. *Global Mental Health*, 3.
- Chisholm, D., Sweeny, K., Sheehan, P., Rasmussen, B., Smit, F., Cuijpers, P., & Saxena, S. (2016). Scaling-up treatment of depression and anxiety: a global return on investment analysis. *Lancet Psychiatry*, 3(5), 415–424. [https://doi.org/10.1016/S2215-0366\(16\)30024-4](https://doi.org/10.1016/S2215-0366(16)30024-4)
- Cohen, A., Patel, V., & Minas, H. (2014). A brief history of global mental health. *Global Mental Health: Principles and Practice*, 3–26.
- Cuijpers, P. (2017). Preventing the onset of depressive disorders an overview. *Public Health Perspectives on Depressive Disorders*, 411–430.
- Cuijpers, P., Karyotaki, E., Reijnders, M., & Ebert, D. D. (2018). Was Eysenck right after all? A reassessment of the effects of psychotherapy for adult depression. *Epidemiology and Psychiatric Sciences*, 1–10. <https://doi.org/10.1017/S2045796018000057>
- Dimidjian, S., Martell, C. R., Herman-Dunn, R., & Hubble, S. (2014). Behavioral activation for depression.

- Gao, L., Xie, Y., Jia, C., & Wang, W. (2020). Prevalence of depression among Chinese university students: a systematic review and meta-analysis. *Scientific Reports*, 10(1), 1–11.
- GBD. (2019). Global Burden of Disease Collaborative Network. Global Burden of Disease Study 2019 (GBD 2019) Results. Institute for Health Metrics Evaluation. Seattle.
- Hessel, F. (2008). Burden of Disease. https://doi.org/10.1007/springerreference_81582
- Hidaka, B. H. (2012). Depression as a disease of modernity: Explanations for increasing prevalence. *Journal of Affective Disorders*, 140(3), 205–214. <https://doi.org/10.1016/j.jad.2011.12.036>
- Holma, K. M., Melartin, T. K., Haukka, J., Holma, I. A. K., Sokero, T. P., & Isometsä, E. T. (2010). Incidence and predictors of suicide attempts in DSM–IV major depressive disorder: a five-year prospective study. *American Journal of Psychiatry*, 167(7), 801–808.
- Holmes, E. A., Ghaderi, A., Harmer, C. J., Ramchandani, P. G., Cuijpers, P., Morrison, A. P., ... Craske, M. G. (2018). The Lancet Psychiatry Commission on psychological treatments research in tomorrow's science. *Lancet Psychiatry*, 5(3), 237–286. [https://doi.org/10.1016/S2215-0366\(17\)30513-8](https://doi.org/10.1016/S2215-0366(17)30513-8)
- Homedes, N. (1996). The disability-adjusted life year (DALY) definition, measurement and potential use. The World Bank.
- Jimenez-Molina, A., Franco, P., Martinez, V., Martinez, P., Rojas, G., & Araya, R. (2019). Internet-Based Interventions for the Prevention and Treatment of Mental Disorders in Latin America: A Scoping Review. *Frontiers in Psychiatry*, 10(664). <https://doi.org/ARTN 664 10.3389/fpsy.2019.00664>
- Kennis, M., Gerritsen, L., Dalen, M. van, Williams, A., Cuijpers, P., & Bockting, C. (2019). Prospective biomarkers of major depressive disorder: A systematic review and meta-analysis. *Molecular Psychiatry*, 1–18. <https://doi.org/10.1038/s41380-019-0585-z>
- Lemmens, L. H. J. M., Müller, V. N. L. S., Arntz, A., & Huibers, M. J. H. (2016). Mechanisms of change in psychotherapy for depression: An empirical update and evaluation of research aimed at identifying psychological mediators. *Clinical Psychology Review*, 50, 95–107. <https://doi.org/10.1016/j.cpr.2016.09.004>
- Martinez, P., Rojas, G., Martinez, V., Lara, M. A., & Perez, J. C. (2018). Internet-based interventions for the prevention and treatment of depression in people living in developing countries: A systematic review. *J Affect Disord*, 234, 193–200. <https://doi.org/10.1016/j.jad.2018.02.079>
- Moreno-Peral, P., Bellón, J. Á., Huibers, M. J. H., Mestre, J. M., Garcí\`ia-López, L. J., Taubner, S., ... Conejo-Cerón, S. (2020). Mediators in psychological and psychoeducational interventions for the prevention of depression and anxiety. A systematic review. *Clinical Psychology Review*, 76, 101813.
- Naslund, J. A., Aschbrenner, K. A., Araya, R., Marsch, L. A., Unutzer, J., Patel, V., & Bartels, S. J. (2017). Digital technology for treating and preventing mental disorders in low-income and middle-income countries: a narrative review of the literature. *Lancet Psychiatry*, 4(6), 486–500. [https://doi.org/10.1016/S2215-0366\(17\)30096-2](https://doi.org/10.1016/S2215-0366(17)30096-2)
- Patel, V., Minas, H., Cohen, A., & Prince, M. J. (2013). *Global mental health: Principles and practice*. Oxford University Press.
- Patel, V., Saxena, S., Lund, C., Thornicroft, G., Baingana, F., Bolton, P., ... Eaton, J. (2018). The Lancet Commission on global mental health and sustainable development. *The Lancet*, 392(10157), 1553–1598.
- Richter, D., Wall, A., Bruen, A., & Whittington, R. (2019). Is the global prevalence rate of adult mental illness increasing? Systematic review and meta-analysis. *Acta Psychiatrica Scandinavica*, 140(5), 393–407.
- Rohde, P., Lewinsohn, P. M., Klein, D. N., Seeley, J. R., & Gau, J. M. (2013). Key characteristics of major depressive disorder occurring in childhood, adolescence, emerging adulthood, and adulthood. *Clinical Psychological Science*, 1(1), 41–53.

- Song, Y., Liu, Z., Chen, H., Guo, Q., & Huang, Y. (2020). Incidence and risk factors of depressive symptoms in Chinese college students. *Neuropsychiatric Disease and Treatment*, 16, 2449–2457. <https://doi.org/10.2147/NDT.S264775>
- Steel, Z., Marnane, C., Iranpour, C., Chey, T., Jackson, J. W., Patel, V., & Silove, D. (2014). The global prevalence of common mental disorders: a systematic review and meta-analysis 1980–2013. *International Journal of Epidemiology*, 43(2), 476–493.
- Weisz, J. R., Kuppens, S., Ng, M. Y., Vaughn-Coaxum, R. A., Ugueto, A. M., Eckshtain, D., & Corteselli, K. A. (2019). Are Psychotherapies for Young People Growing Stronger? Tracking Trends Over Time for Youth Anxiety, Depression, Attention-Deficit/Hyperactivity Disorder, and Conduct Problems. *Perspectives on Psychological Science*, 14(2), 216–237. <https://doi.org/10.1177/1745691618805436>
- World Bank. (2020). Low & Middle Income. <https://datahelpdesk.worldbank.org/knowledgebase/articles/906519-world-bank-country-and-lending-groups>
- World Health Organization. (1992). The ICD-10 classification of mental and behavioural disorders: clinical descriptions and diagnostic guidelines. World Health Organization.
- World Health Organization. (2008). Mental Health Gap Action Programme - Scaling up care for mental, neurological, and substance use disorders. World Health Organization, 44.
- World Health Organization. (2013). Global action plan for the prevention and control of noncommunicable diseases 2013-2020. World Health Organization.
- World Health Organization. (2015). Update of the mental health gap action programme (mhGAP) guidelines for mental, neurological and substance use disorders, 2015. World Health Organization.
- World Health Organization. (2017). Depression and Other Common Mental Disorders: Global Health Estimates.

Chapter 2

Psychological factors for the onset of depression: A meta-analysis of prospective studies

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Abstract

Objectives: A comprehensive overview of the evidence for factors derived from leading psychological theories of the onset of major depressive disorder (MDD) that underpin psychological interventions is non-existent. We aimed to systematically investigate the prospective evidence for factors derived from the behavioral, cognitive, diathesis-stress, psychodynamic, and personality-based theories for the first onset of MDD.

Design: Systematic review and meta-analysis.

Methods: Databases PubMed, PsycINFO, Cochrane, and Embase, and published articles were systematically searched from inception up to August 2019. Prospective, longitudinal studies that investigated theory-derived factors before the first onset of MDD, established by a clinical interview, were included. Screening, selection and data extraction of articles were conducted by 2 screeners. The GRADE-criteria were used to estimate level of confidence and risk of bias. Meta-analysis was conducted using random-effects models and mixed-method subgroup analyses.

Primary and secondary outcome measures: Effect size of a factor predicting the onset of MDD (OR, RR, or HR).

Results: From 42,133 original records published to August 2019, 26 studies met the inclusion criteria. Data was only available for the cognitive ($N= 6,585$) and personality-based ($N= 14,394$) theories. Factors derived from cognitive theories and personality-based theories were related to increased odds of MDD onset (pooled OR = 2.12, 95% CI: 1.12 - 4.00; pooled OR = 2.43, 95% CI: 1.41 - 4.19). Publication bias and considerable heterogeneity were observed.

Conclusion: There is some evidence that factors derived from cognitive and personality-based theories indeed predict the onset of MDD (i.e., dysfunctional attitudes, negative emotionality). There were no studies that prospectively studied factors derived from psychodynamic theories and not enough studies to examine the robust evidence for behavioral and diathesis-stress theories. Overall, the prospective evidence for psychological factors of MDD is limited, and more research on the leading psychological theories is needed.

Registration: Protocol was pre-registered at PROSPERO (CRD42017073975).

Introduction

Major depressive disorder (MDD) is a prevalent and highly disabling mental health disorder that has been identified as one of the leading causes of disease burden (Ferrari et al., 2013). There are several preventative interventions and treatment options available for MDD (antidepressants and psychological interventions; Breedvelt et al., 2018; Cuijpers, Karyotaki, Reijnders, & Ebert, 2018). However, their effectiveness raises concerns, with high relapse rates and approximately 50% of patients showing a clinical meaningful reduction in symptoms, or attaining full remission (Holmes, Craske, & Graybiel, 2014). Moreover, there is no indication that the effectiveness of current treatments for MDD improved over the past years (Holmes et al., 2014). A recent meta-analysis found a significant decline since 1960 of the effectiveness of psychological interventions compared to control groups (including active control, waitlist control, usual care, or placebo or antidepressants) for MDD for youth (Weisz et al., 2019). In addition, reported treatment effects may be overestimated due to publication bias and other biases (e.g., bias due to treatment allocation, selective reporting of outcomes; Cuijpers et al., 2018; Driessen, Hollon, Bockting, Cuijpers, & Turner, 2015). The identification of factors that precede and increase the risk of the first onset of MDD might provide points to target with (preventive) interventions. Psychological factors believed to account for the onset of MDD generally originate from psychological models and theories (Cuijpers, 2017). Up to now, a systematic review and meta-analysis of the empirical evidence for the leading psychological theories of the first onset of MDD is non-existent.

Most current psychological interventions for prevention and treatment of MDD, for example Cognitive Therapy (CT; Beck, Rush, Shaw, & Emery, 1979; Beck & Bredemeier, 2016), Behavior Activation (BA; Dimidjian, Barrera, Martell, Muñoz, & Lewinsohn, 2011), Psychoanalytic therapy (Luyten & Blatt, 2012), and Interpersonal Therapy (IPT; Cuijpers et al., 2011), are derived from five psychological theories, which guided our systematic search (see Appendix A): Behavioral, cognitive, psychodynamic, personality-based, and most theories include an overarching diathesis-stress perspective (Fernald, 2008). The core

principles of the five theories are briefly summarized below in reference to the corresponding psychological intervention.

Each theory postulates a hypothesis on specific factors that contribute to the etiology of MDD. For example, cognitive theories emphasize the dominant role of cognitions in the development of MDD, and the way individuals view themselves, others, and the world (Beck & Bredemeier, 2016; Beck et al., 1979). Negative cognitive processing across these domains is proposed to lead to an increased risk of MDD. The factors for the onset of MDD include higher levels of dysfunctional attitudes and beliefs, negative attributional style, rumination, and learned helplessness (Abramson, Metalsky, & Alloy, 1989; Abramson, Seligman, & Teasdale, 1978; Beck & Bredemeier, 2016; Dozois & Rnic, 2015; Gotlib & Joormann, 2010; Hawke & Provencher, 2011; Kircanski, Joormann, & Gotlib, 2012; Nolen-Hoeksema, 1991). Cognitive therapy (often combined with behavioral interventions) is an example of a cognitive theory-based intervention.

Originating from a framework of the learning theory (Skinner, 1957), behavioral theories, that underlie treatments like BA, emphasize the role of the environment and the interaction between individuals and their environment in the development of MDD (e.g., Costello, 1972; Coyne, 1976; Ferster, 1974; Lazarus, 1972; Lejuez, Hopko, LePage, Hopko, & McNeil, 2001; Lewinsohn, Youngren, & Grosscup, 1979; Nezu, 1987). It posited that decline of positive feedback prompts withdrawal behavior (i.e., low rate of response-contingent positive reinforcement) which further leads to depression (Lewinsohn, 1975; Lewinsohn et al., 1979). Examples of behavioral theory-derived factors are classical and operant conditioning, social skills, or behaviors that lack potential reward-value such as withdrawal and inactivity (Lewinsohn, 1975).

The psychodynamic theories were among the earliest to explain mental disorders including MDD and have been used by clinicians and researchers to develop successive, overlapping models (Bibring, 1953; Blatt & Homann, 1992; Bowlby, 1988; Freud, 1994; Jacobson, 1975; Kohut, 1971; MaCkinnon & Andrews, 1993; Sandler & Joffe G, 1965; Stone, 1986). Vulnerability factors derived from these theories include the mother-child relationship, object relations, quality of attachment with caregivers (Bibring, 1953; Blatt &

Homann, 1992; Bowlby, 1988; Freud, 1994), and significant childhood experiences (Freud, 1994; Jacobson, 1975; Kohut, 1971; MaCkinnon & Andrews, 1993; Sandler & Joffe G, 1965; Stone, 1986). Interventions derived from the psychodynamic theories (e.g., psychoanalytic, psychodynamic, and specific forms of interpersonal therapy) often include a focus on attachment and interpersonal relationships (Luyten & Blatt, 2012).

Another longstanding perspective, personality-based theories of MDD, has become an umbrella of multiple personality-based factors that may be related to the onset of MDD. The theories cover various taxonomies (traits/temperament) (Clark & Watson, 1999) and hierarchy (“Big Five”, Goldberg, 2013; “Big Three”, Markon, Krueger, & Watson, 2005). Among these, two major domains can be distilled: Positive emotionality (PE) and negative emotionality (NE), with the assumption that depression-prone individuals experience heightened NE (e.g., neuroticism) and reduced PE (e.g., extraversion; Klein, Kotov, & Bufferd, 2011). Even though these four theories of MDD differ in the proposed vulnerability factors, the majority of these theories underscore the importance of stress in the development of MDD. Diathesis-stress theories underlying these theories propose that vulnerability factors (i.e., the theory-derived vulnerability factors, ‘diatheses’) are activated by stress, or a combination of the vulnerability factor and stress, which leads to the development of MDD (Hankin & Abela, 2005).

Over the past decades, numerous studies and reviews have been conducted to delineate putative factors leading to the onset of MDD (e.g., Klein et al., 2011; Bagby, Quilty, & Ryder, 2008; Beatson & Taryan, 2003; Enns & Cox, 1997; Haaga, Dyck, & Ernst, 1991; Lakdawalla, Hankin, & Mermelstein, 2007; Lewinsohn, Allen, Seeley, & Gotlib, 1999; Mathews & MacLeod, 2005; Miranda, 1992) indicating that cognitive processes such as rumination and a dysfunctional thinking style (Lakdawalla et al., 2007) and personality traits (e.g., neuroticism, Klein et al., 2011; Ormel et al., 2013), increase the risk to develop MDD. Nevertheless, these reviews have not culminated in definitive evidence that supports etiological theories for onset of MDD. Support for the theories is largely based on cross-sectional studies and/or studies that assessed MDD using self-reports instead of clinical interviews, or where relapse and onset were combined (e.g., Lakdawalla et al., 2007; Hong

& Cheung, 2015; Lewinsohn et al., 1999). Clinical interviews are needed to reliably establish whether there is indeed a first onset of MDD, as opposed to (subthreshold and/or self-reported) depressive symptomatology alone since self-report measures are not sufficient. To overcome these limitations, a systematic review of prospective, longitudinal, studies is needed among individuals without a history of MDD, where theory-derived factors are measured before the onset of MDD. This systematic review and meta-analysis investigate and summarize the evidence for factors derived from five leading theories of MDD that underpin most used treatment options.

Methods

The methodology adopted in this meta-analysis and review was in line with the guidelines of Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA). The systematic review and meta-analysis has been pre-registered in PROSPERO (CRD42017073975).

Search strategies

The current study was embedded in a larger project (“My optimism wears heavy boots”, Netherlands Institute for Advanced Study, Bockting et al., 2017) investigating the psychological and biological factors of MDD onset and relapse (Brouwer et al., 2019; Kennis et al., 2019). Therefore, some searches were combined over topics (see Appendix A). PubMed, PsycINFO, Cochrane, and Embase were searched for relevant articles published from inception up to August 2019. The search combined keywords and text words relating to: First onset and studies with a prospective longitudinal design; major depressive disorder; five leading theories. Selection of the search terms indicative of the five psychological theories were guided by prior reviews, books, and an extensive international expert panel (see acknowledgements for the expert panel). Snowballing was conducted by checking inclusions of previous published reviews and articles citing included studies.

Inclusion and exclusion criteria

Studies were eligible if the following criteria were fulfilled: 1) Diagnostic status of MDD was indicated for all participants and was established through a clinical interview at follow-up (i.e. SCID, K-SADS from DSM, CIDI from ICD); 2) At baseline, participants did not meet

criteria for MDD (and did not have depressive symptoms above cut-off scores for MDD), and did not have prior history of MDD ; 3) Participants with first-onset MDD had no comorbidity with other types of depressive disorder, other mental disorders, or physical disease; 4) The study design was prospective/longitudinal; 5) The target variable(s) (theory-derived factors) were assessed before the first onset of MDD; participants needed to be assessed at least twice (baseline and follow-up); 6) The study was original research, published in peer-reviewed journals in the English language. Studies with patients older than 65 years old were excluded because of the heterogeneity introduced by geriatric depression. When multiple publications with data from the same study cohort were available, we included the publication with longest period of follow-up length. When the follow-up period was equal, studies with largest number of total participants were included.

Selection process

The PRISMA flow diagram for all theories is depicted in Figure 1. All records were screened by two screeners in an independent, but not fully blind way; the second screeners could see the decisions from the first screener. All eligible records that met the inclusion criteria during initial screening of the titles and abstracts were further assessed for eligibility by two screeners based on full texts. Any disagreement was resolved by discussion and consulting a senior author. Multiple screeners were included and assigned pairwise during this process, see author contributions and acknowledgements for the full list.

Quality assessment and data extraction

Two researchers assessed the risk of bias and level of confidence for the overall evidence for the psychological theories, using the criteria of the Grading of Recommendations Assessment, Development and Evaluation (GRADE; Langer et al., 2012). Risk of bias was indicated in '+' (low risk of bias = 0), '?' (unclear risk of bias = 1) and '-' (high risk of bias = 2). Score 0 to 6, 6 to 12, and 12 to 18, indicated low, moderate, and high risk of bias respectively. We extracted demographic information, baseline depressive symptoms and its measurement scales, method of MDD diagnosis, psychological factors, and statistical information to calculate the effect sizes. Authors were contacted when a study met the inclusion criteria but reported insufficient data to calculate effect sizes. These authors were

inquired via emails (a reminder was sent two weeks after if no response) on the possibility to provide the relevant statistics within two months. Studies were excluded in the meta-analysis if the necessary data were not provided within this timeframe.

Primary outcome

Primary outcome was the onset of MDD at study follow-up, as established by a clinical interview (e.g., ICD, SCID) or expert opinion (e.g., trained psychiatrist or clinical psychologist).

Statistical analysis

The program Comprehensive Meta-Analysis (CMA version 3.3; Borenstein, Hedges, Higgins, & Rothstein, 2014) was used to enter data of each study and each identified factor, and to calculate pooled effect sizes, forest plots, funnel plots, and heterogeneity. The effect size of each factor reported in the article had to be expressed as an Odds Ratio (OR), Risk Ratio (RR), or Hazard Ratio (HR), with 95% confidence intervals (CIs), to indicate the relationship between the factor and time to, or odds or risk of having an onset of MDD at study follow-up. Alternatively, we calculated the OR, RR or HR by using reported statistics from each study and each factor. For example, the article needed to report means, standard deviations, number of participants, or beta coefficient with standard error. This data was entered and OR, RR, or HR with 95% CIs were then calculated using CMA (Borenstein et al., 2014). If more than one measure from the same main psychological theory was reported in the same study, a combined effect size was calculated in CMA (Borenstein et al., 2014). If a study reported multiple factors derived from different theories, the effect sizes of these factors were allocated to the corresponding theory or theories.

We then calculated pooled effect sizes (HR, RR, and OR) and its 95% CI of each main theory separately using all (combined) factors assigned to that main theory. For example, the pooled effect size was calculated for all factors combined related to the cognitive theory (e.g., dysfunctional attitudes, rumination, automatic thoughts, etc.). Since we expected considerable heterogeneity amongst studies and measures, a random effects model was employed to calculate pooled effect sizes. Second, separate subgroup analyses were conducted for each factor alone, if there were enough studies reporting that factor. To

conduct these subgroup analyses, pooled effect sizes of each (theory-derived) factor were calculated using a mixed-effects model, with a random effects model to summarize the studies within each subgroup, and a fixed effects model to test for differences between subgroups.

The I^2 was calculated to assess heterogeneity between studies for each analysis. In general, heterogeneity is categorized at 0%-40% (low), 30%-60% (moderate), 50%-90% (substantial), and 75%-100% (considerable)(Chandler, Cumpston, Li, Page, & Welch, 2019). The 95% CIs around I^2 were calculated using the non-central chi-squared-based approach within the Heterogi module for Stata (Orsini, Bottai, Higgins, & Buchan, 2006). Funnel plots were visually inspected for publication bias, and investigated with Egger's test and Duval and Tweedie's trim and fill procedure. Trim-and-fill procedure was used to adjust potential publication bias. In this procedure, the asymmetric outlying studies in the funnel plot were firstly trimmed off and the true center of the funnel was estimated with the symmetric remainders. Then the funnel plot was filled with replacement of the trimmed studies and their missing counterparts around the center. A newly pooled overall effect size based on this filled funnel plot indicated the OR after statistically adjusting the publication bias.

A priori, we aimed to conduct a meta-regression if the number of studies was sufficient, including investigating several potential continuous moderators of interest such as age, percentage female, and baseline depressive symptoms were investigated. These variables were considered clinically relevant to major depression (Cuijpers & Smit, 2004; Salk, Hyde, & Abramson, 2017; Stordal, Mykletun, & Dahl, 2003). Sensitivity analyses were conducted to examine if potential outliers, research designs, and low-quality studies, affected the pooled effect sizes. The minimum number of studies was set at 3 studies for the main and subgroup analyses, and 10 for meta-regression.

Patient and Public Involvement

No patient involved.

Results

Out of 69,667 identified records (see Figure 1), 42,133 records were inspected on title/abstract after removal of duplicates, of which 52 articles met initial inclusion criteria

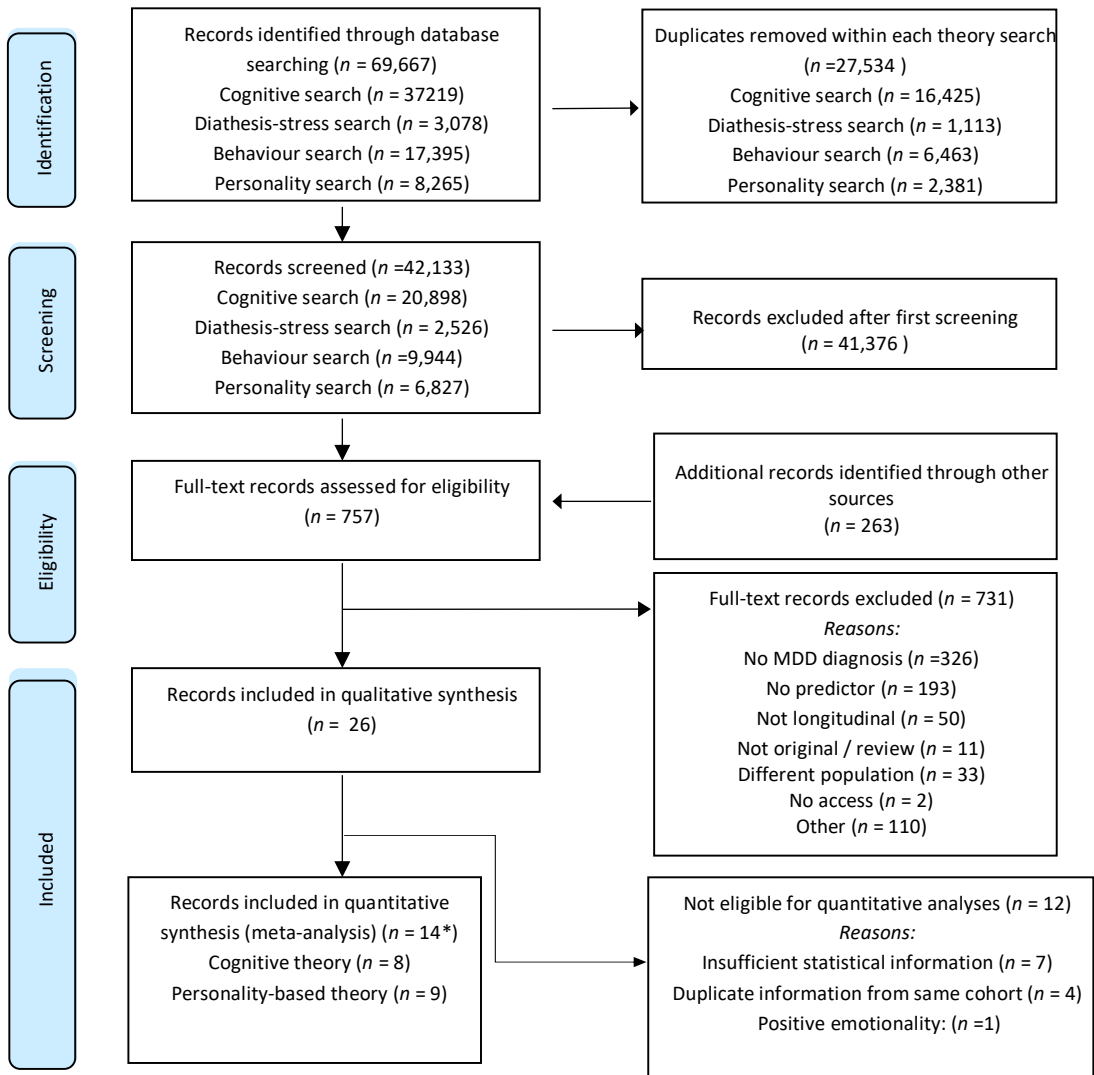


Figure 1 PRISMA flow diagram for the systematic review

*studies can be included in both theories at same time

with prior MDD episodes were included and therefore those articles were excluded. In total, 26 articles were included in the final review. There were no eligible articles detected for the psychodynamic theories. A quantitative meta-analysis was only possible for the cognitive and personality-based theories. See Table 1 for the characteristics of the included studies.

Behavioral theories Two studies were eligible for the behavioral theories (Ostergaard et al., 2012; Stavrakakis et al., 2013) and could not be meta-analyzed. Both studies investigated the association between physical activities and onset of MDD, involving 14,011 adolescents and adults. Low levels of physical activities were not associated with an increased risk of developing MDD.

Cognitive theories Eleven studies were included (8,320 participants), of which eight studies were eligible for the quantitative synthesis (6,585 participants; Mage range = 13-41; see Figure 1). Follow-up time ranged from one to 12 years. The result of the overall analysis is shown in Figure 2. The pooled OR for the cognitive theory was 2.12 (95% CI: 1.12 to 4.00), which indicates that the combination of cognitive theory-derived factors predicted the first onset of MDD. Heterogeneity was considerable ($I^2 = 97%$, 95% CI: 95% to 98%). Inspection of the funnel plot and the Egger's test ($p = 0.12$) did not indicate asymmetry; while Duval and Tweedie's trim and fill procedure (3 studies trimmed) suggest potential publication bias. After statistically adjusting for publication bias, the overall OR decreased to 1.11 with 95% CI as 0.60 to 2.06. The level of confidence was moderate.

Given the low number of studies (<10), no meta-regression analysis or subgroup analyses were conducted. Therefore, we were unable to examine potential moderators. The results remained comparable after removing one study with a moderate risk of bias (Otto et al., 2007) (OR = 1.90, 95% CI: 1.02 to 3.55), however, were non-significant after conducting sensitivity analyses where one study with a different research design was removed (behavior risk design; Alloy et al., 2006; OR = 1.88, 95% CI: 0.97 to 3.94). Two studies reported predictive value with one study controlling for baseline depressive symptom exclusively, and the other study controlling for other covariates concurrently (Nusslock et al., 2011; Otto et al., 2007). We could therefore not investigate the impact of depressive symptoms on the meta-analysis.

Table 1. Selected characteristics of included studies

Source (Author, year)	Vulnerability measure	N	Mean age/Range	SD of Age	Sex (%female)	Length of follow-up (months)	Diagnostic Tool	Baseline depression severity	Risk of bias										Country
									1	2	3	4	5	6	7	8	9		
Cognitive theories																			
Alloy 2006 ^{a,*}	CSQ, DAS	347	18.89	Nr	67.1	30	K-SADS	Nr	+	+	+	+	+	+	+	+	+	+	US
Goodyer 2000 ^b	RSQ	172	13.75	Nr	60.4	12	K-SADS	Low	+	+	+	?	+	+	+	+	?	?	UK
Giollabui 2018*	HSC, ACSQ-M	173	12-13	Nr	56	18	K-SADS-E	Low	+	+	+	+	+	+	+	+	+	+	US
Kruijt 2013 ^{c,*}	LEIDS	834	41.5	11.5	63.8	24	CIDI	Low	-	+	+	+	+	+	?	+	?	?	NL
Mathew 2011	DAS	1222	16.6	1.2	49.2	144	K-SAD/SCID;	Nr	+	+	-	+	?	+	?	+	?	-	US
Nusslock 2011*	CSQ, DAS, RSQ	40	20.32	1.25	42.5	36	SADS-C; SADS-L	Low	+	+	+	+	+	+	?	?	?	-	US
Ormel 2004 ^{d,*}	UCS	3998	40	11.4	49.7	36	CIDI	Nr	+	+	+	-	+	?	?	?	?	-	NL
Otto 2007*	DAS	500	40.9	2.5	100	36	SCID	Low	+	+	+	?	+	+	+	+	?	-	US
Stange 2016	CRSQ	341	12.41	0.63	53.2	34.13	K-SADS	Low	+	+	+	+	+	+	?	-	?	?	US
Stone 2011*	CRSQ	95	11-15	Nr	62	24	K-SADS	Nr	+	+	+	+	+	+	+	+	?	-	US
Wilkinson 2013 ^{b,*}	RDQ	598	13.7	1.2	43	12	K-SADS-L	Low	+	+	+	+	+	+	+	+	?	?	UK
Personality-based theories																			
Eldesouky 2018*	NEO-PI-R, MAPP, SIDP-IV	758	59.60	2.7	55	60	C-DIS-IV	Nr	+	+	+	+	+	+	?	+	+	+	US
DeGraaf 2002 ^d	GNQ	4455	18-64	Nr	50.3	12	CIDI	Nr	+	+	+	+	+	+	+	+	?	?	NL
Fanous 2007 ^{e,*}	EPQ	1862	36.8	9.1	0	12	SCID	Nr	+	+	+	+	+	+	+	+	?	-	US
Goldstein 2017*	BFI	463	14.4	0.63	100	18	K-SADS-PL	Nr	+	+	+	+	+	+	+	+	+	-	US
Kendler 1993 ^e	EPQ-FormB	1477	30.1	7.6	100	12	DSM-III	Nr	+	+	?	+	+	?	?	?	?	-	US
Kendler 2006	EPQ-FormB	20,081	29.2	8.9	Nr	17.4	CIDI	Nr	+	+	+	+	+	+	?	?	?	-	SE
Kessler 2008*	GPS, ABI	4470	18-54	Nr	Nr	120	CIDI	Nr	+	+	+	+	+	+	+	+	?	+	US
Kopala-Sibley 2017*	BFI	504	14.4	0.6	100	12	K-SADS-PL	Nr	+	+	+	+	+	+	+	+	?	-	US
Kruijt 2013 ^{c,*}	NEO-FFI	834	41.5	11.5	63.8	24	CIDI	Low	-	+	+	+	+	+	?	?	?	?	NL
Mathew 2011	MMPI	1222	16.6	1.2	49.2	144	K-SADS/SCID	Nr	+	+	+	-	+	?	?	?	?	+	US
Noteboom 2016 ^{c,*}	NEO-FFI	648	41.4	14.7	61.1	24	CIDI	Nr	+	+	+	+	+	?	?	?	?	+	NL
Nusslock 2011*	BAS/BIS	40	20.32	1.25	42.5	36	SADS-C; SADS-L	Low	+	+	+	+	+	+	?	?	?	-	US
Ormel 2004 ^{d,*}	ABI	3998	40	11.4	49.7	36	CIDI	Nr	+	+	+	-	+	?	?	?	?	-	NL
Roberts and Kendler 1999 ^e	EPQ	1128	30.1	7.6	100	17	SCID	Nr	+	+	+	-	+	+	+	+	?	-	US
Tokuyama 2003*	FFI	1365	34.2	10.3	52.6	12	DSM-IV	Nr	+	?	-	-	-	?	?	?	?	-	JP
Behavioral theories																			
Stavrakakis 2013	Physical activity	2149	13.02	0.61	52.9	30	CIDI	Nr	+	+	?	?	?	?	?	?	?	?	NL
Østergaard 2012	Time of sitting	11,862	43	Nr	60.6	144	ICD	Nr	+	+	+	+	+	+	+	+	?	-	DK

Source (Author, year)	Vulnerability measure	N	Mean age/Range	SD of Age	Sex (%female)	Length of follow-up (months)	Diagnostic Tool	Baseline depression severity	Risk of bias	Country
Coventry 2009	KPSS x SLE	6755	Nr	Nr	62.7	12	SSAGA	Nr	+ + + ? + + ? + ? +	+ AU
Carter and Garber 2011	CASQ x LED5-A	207	11.86	0.57	54.2	72	K-SADS-PL	Low	+ + + + + + + + + +	+ ? + ? + ? + ? + ? +

*Studies included in the meta-analysis;

^aData derived from the Cognitive Vulnerability of Depression project;

^bCambridge Secondary students;

^cData derived from the Netherlands Study of Depression and Anxiety project; both studies were included in the meta-analysis since they measured different personality factors;

^dData derived from the Netherlands Mental Health Survey and Incidence Study (NEMESIS); data with the longest follow-up were retained in the meta-analysis;

^eData derived from the Virginia Twin Study; data with longest follow-up were retained in the meta-analysis;

Nr = not reported. Risk of bias: 1 = selection of participants; 2 = diagnosis of MDD; 3 = without prior history of depression; 4 = covariates controlled; 5 = assessment of vulnerabilities; 6 = quality of assessment; 7 = adequate follow-up; 8 = similar treatment between onset and non-onset group; 9 = other sources of bias; '+' = low risk of bias; '-' = high risk of bias; '?' = unclear risk of bias. CSQ = Cognitive style questionnaire, DAS = Dysfunctional attitudes scale, K-SADS = Schedule for Affective Disorders and Schizophrenia for School-Age Children, LED5-r = Leiden Index of Depression Sensitivity-revised, RSQ = Response Style Questionnaire, HSC = Hopelessness Scale for Children, ACSQ-M = Adolescent Cognitive Style Questionnaire—Modified, CRSQ = Children's Response Styles Questionnaire, SCID = Structured Clinical Interview for DSM, SADS-C = Schedule for Affective Disorders and Schizophrenia- Change version, SADS-L = Schedule for Affective Disorders and Schizophrenia for School-Age Children—Epidemiological version—Present and Lifetime, UCS = Utrecht Coping Scale, K-SADS-L = Kiddie Schedule for the Affective Disorders Lifetime version, CAS = Child assessment scale (for structured interview), LED5 = Life events and difficulties (LED5) interview, PSE = Present state examination, ACSQ = Adolescent cognitive style questionnaire, RRS = Ruminative response scale, KASQ-C = Kasten Attributional Style Questionnaire for Children, SCID-NP = Structured Clinical Interview for DSM: Non-patient Lifetime, RDQ = Responses to Depression Questionnaire, NEO-PI-R=Neuroticism-Extraversion-Openness Personality Inventory-Revised, MAPP=Multisource Assessment of Personality Pathology, SIDP-IV=Semi-Structured Interview for DSM-IV Personality, GNQ = Groninge Neuroticisme Questionnaire, CIDI = composite international diagnostic interview, EPQ = Eysenck Personality Questionnaire, DSM-III = Diagnostic and Statistical Manual of Mental Disorders-III, ABI = Amsterdam Biographic Inventory, BFI = Big five inventory, NEO-FFI = Neuroticism-Extraversion-Openness Five Factor Inventory, KSADS-PL = Kiddie Schedule for the Affective Disorders Past and Lifetime version, MMPI = Minnesota Multiphasic Personality Inventory, NEO-FFI = Neuroticism-Extraversion-Openness Five Factor Inventory, DIA-X/M-CIDI = Munich-Composite International Diagnostic Interview, FPI = Freiburg Personality Inventory, SPIKE = Structured psychopathological interview and rating of the social consequences of psychological disturbances for epidemiology, MPQ = Multidimensional Personality Questionnaire, DIS = Diagnostic interview schedule, ICD = International Classification of Diseases, KPSS = Kessler Perceived Social Support, CASQ = Children's Attributional Style Questionnaire, LED5-A = Life events and difficulties (LED5) interview for adolescents, ALEQ = Adolescent Life Events Questionnaire, NRI = Network of Relationships Inventory, MLES = Major Life Events Scale, IPPA= Inventory of Parent and Peer Attachment, ASI = Attachment Style interview, PSE = Present state examination, SSAGA = Semi-Structured assessment for the Genetics of Alcoholism, SLE =Stressful life event

Personality-based theories

Negative emotionality. In total, 15 studies that investigated NE could be included in the qualitative synthesis (43,305 participants), of which nine studies were included in the quantitative analysis (14,394 participants, Mage range = 14-64). Follow-up length varied from one to 12 years. Eight of these nine studies investigated the role of neuroticism as a vulnerability factor; other factors were borderline personality and behavior inhibition system. The pooled OR for the negative emotionality was 2.43 (95% CI: 1.41 to 4.19), indicating that NE was related to the first onset of MDD. See Figure 2 for the overall results. Heterogeneity between studies was considerable ($I^2 = 96\%$; 95% CI: 94% to 97%), with a wide confidence interval. The confidence of evidence was of high certainty. Inspection of the funnel plot and the Egger's test ($p = 0.52$) did not indicate asymmetry, while trim and fill procedure indicated risk for publication bias with four trimmed studies resulted in an adjusted OR as 1.39 (95% CI: 0.74 to 2.59). Sensitivity analysis revealed similar decline after removal of 2 studies (Ormel et al, 2004; Tokuyama, Nakao, Seto, Watanabe, & Takeda, 2003) with moderate risk of bias (OR = 1.86; 95% CI: 1.25 to 2.78). The limited number of studies prohibited subgroup analyses and meta-regression to investigate the effects of baseline depressive symptoms on the results.

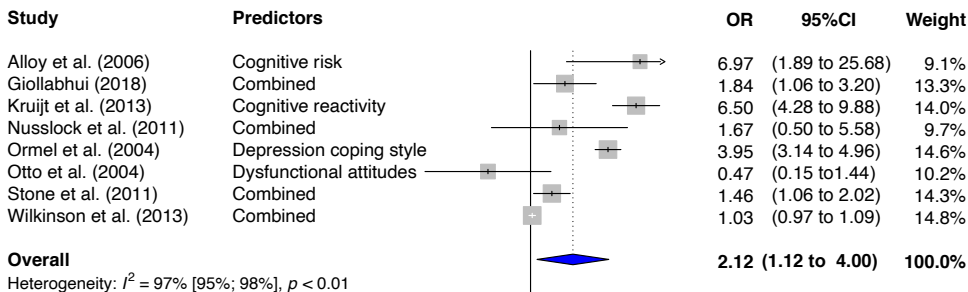
Positive emotionality. Six studies (8,848 participants) focused on PE. The pooled OR was 0.93 (95% CI: 0.84 to 1.03), which indicates that positive personality traits did not decrease the odds of MDD onset. After removing one study with a high risk of bias, the effect remained non-significant (OR = 0.94; 95% CI: 0.85 to 1.05). Heterogeneity between studies was low ($I^2 = 37\%$; 95% CI: 0% to 75%). A publication bias was not indicated (Egger's test $p = 0.63$; number of trimmed studies = 0).

Diathesis-stress theories

Two studies were identified that prospectively examined the interaction between theory-derived factors with stress on first onset of MDD, i.e. diathesis-stress theories (Carter & Garber, 2011; Coventry et al., 2009). Therefore, quantitative analyses were prohibited. The studies indicated non-significant results of social support (Ormel et al., 2004) and negative attributional style (Nusslock et al., 2011) separately in interaction with stress, as

predictors of MDD. No other studies included in the other theories combined the factors with measures of stress.

Cognitive theories



Personality-based theories

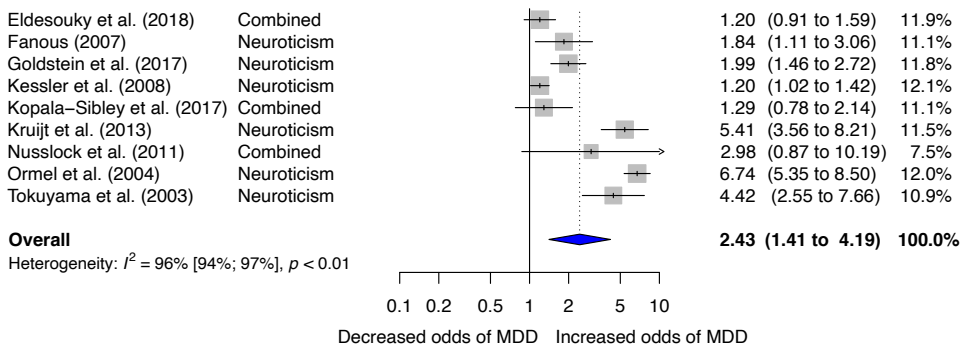


Figure 2 Forest plot of Cognitive and Personality-based theories to predict first onset of MDD.

Discussion

The aim was to systematically examine the evidence for psychological factors derived from five leading psychological theories that explain onset of MDD: Behavioral, cognitive, personality-based, psychodynamic theories, including the diathesis-stress theory. Out of 42,133 identified records, 26 studies examined theory-derived factors prospectively in participants without a history of MDD, of which 14 studies could be meta-analyzed for the cognitive and personality-based theories. We identified no prospective studies on psychological factors such as attachment, object relations, and identification, as mentioned in psychodynamic theories, and there were not enough studies for quantitative analyses of

factors derived from the behavioral theory or diathesis-stress theory. Consistent with previous reviews (Klein et al., 2011; Lakdawalla et al., 2007), individuals with higher levels of dysfunctional attitudes, rumination, and greater cognitive reactivity, as well as higher levels of the personality trait 'negative emotionality', had an increased odd to develop MDD. Therefore, there was some prospective evidence for the cognitive and personality-based theories of MDD.

This extensive systematic search enabled us to investigate prospectively assessed factors derived from five theories in clinically established MDD, while the lack of evidence overall remains noteworthy. Despite the strengths of this meta-analysis, i.e. the inclusion of prospective, longitudinal studies that assessed the psychological factors before the first onset of MDD, and where MDD was established through clinical interviews, some limitations should be noted. The influence of concurrent levels of baseline depressive symptoms on the prediction of MDD cannot be ruled out due to the low number of studies reporting baseline symptomatology (4/14). The marked heterogeneity that was observed may be attributed to low levels of consensus on operationalization of the theories, after consultation of lead experts in clinical psychology and psychiatry (see acknowledgements for details) to determine which factors belonged to which theories. Together with the potential publication bias, this can diminish the reliance of our result.

Despite these limitations, the present review takes an important first step to demonstrate the overall empirical status of five leading psychological theories that underpin widely used psychological interventions for MDD. The prospective evidence for the cognitive and personality-based theories in relation to onset of MDD could assist researchers and clinicians to identify potential treatment targets and/or defined high-risk groups. As mentioned, cognitive theories (Beck & Bredemeier, 2016) and personality theories (Klein et al., 2011) as well as psychodynamic theories have an overlap with the diathesis-stress theory, yet there were not enough studies prospectively measuring stress or life events to investigate diathesis-stress theories. This precluded further examination of the influence of theory-derived factors under certain stressful situation. Overall, the limited

number of eligible prospective studies on onset of MDD prevented us from drawing strong inferences.

The results highlight the lack of evidence of the factors derived from each theory in the onset of MDD. A research agenda should be formulated to systematically address these identified issues, including improved operationalization of leading theories, improved assessment of their factors, and the use of prospective designs. All to ensure that interventions for depression are grounded in a solid foundation of clinical research. A framework that incorporates psychological, biological, environmental, and social risk factors would provide a more integrative, holistic approach to unravel the underlying mechanisms of MDD.

Conclusion

There is some evidence that factors derived from cognitive and personality-based theories indeed predict the onset of MDD (i.e. dysfunctional attitudes, cognitive styles, cognitive reactivity, negative emotionality). However, there were no studies that prospectively studied factors derived from psychodynamic theories and not enough studies to be able to examine the robust evidence for behavioral and diathesis-stress theories. More prospective and unified research is required to enable future systematic reviews. Overall, the prospective evidence for theory-derived psychological factors of MDD is limited.

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Reference

- Abramson, L. Y., Metalsky, G. I., & Alloy, L. B. (1989). Hopelessness Depression: A Theory-Based Subtype of Depression. *Psychological Review*, 96(2), 358–372. <https://doi.org/10.1037/0033-295X.96.2.358>
- Abramson, L. Y., Seligman, M. E., & Teasdale, J. D. (1978). Learned helplessness in humans: critique and reformulation. *Journal of Abnormal Psychology*, 87(1), 49–74.
- Alloy, L. B., Abramson, L. Y., Whitehouse, W. G., Hogan, M. E., Panzarella, C., & Rose, D. T. (2006). Prospective incidence of first onsets and recurrences of depression in individuals at high and low cognitive risk for depression. *Journal of Abnormal Psychology*, 115(1), 145–156. <https://doi.org/10.1037/0021-843X.115.1.145>
- Bagby, R. M., Quilty, L. C., & Ryder, A. C. (2008). Personality and depression. *Canadian Journal of Psychiatry*, 53(1), 14–25. <https://doi.org/10.1177/070674370805300104>
- Beatson, J., & Taryan, S. (2003). Predisposition to depression: the role of attachment. *The Australian and New Zealand Journal of Psychiatry*, 37(2), 219–225.
- Beck, A. T., & Bredemeier, K. (2016). A Unified Model of Depression: Integrating Clinical, Cognitive, Biological, and Evolutionary Perspectives. *Clinical Psychological Science*, 4(4), 596–619. <https://doi.org/10.1177/2167702616628523>
- Beck, A. T., Rush, A. J., Shaw, B. F., & Emery, G. (1979). *Cognitive therapy of depression* (p. 425). New York City: The Guilford Press.
- Bibring, E. (1953). The mechanism of depression. In *Affective disorders: Psychoanalytic contributions to their study* (pp. 13–48). Oxford: International Universities Press.
- Blatt, S. J., & Homann, E. (1992). *Parent-child interaction in the etiology of dependent and self-critical depression*. Netherlands: Elsevier Science.
- Bockting, C. L. H., Hollon, S. D., Siegle, G., Cramer, A., Spinhoven, P., & Ormel, J. (2017). My Optimism Wears Heavy Boots: So Much Research, so Few Implications, towards ‘Patient-Proof’ Empirical Models and More Effective Interventions in Mental Health.
- Borenstein, M., Hedges, L. V., Higgins, J. P. T., & Rothstein, H. R. (2014). *Comprehensive meta-analysis (CMA) software*. Version 3.0.
- Bowlby, J. (1988). *A secure base: Clinical applications of attachment theory*. Routledge.
- Breedvelt, J. J. F., Kandola, A., Kousoulis, A. A., Brouwer, M. E., Karyotaki, E., Bockting, C. L. H., & Cuijpers, P. (2018). What are the effects of preventative interventions on major depressive disorder (MDD) in young adults? A systematic review and meta-analysis of randomized controlled trials. *Journal of Affective Disorders*, 239, 18–29. <https://doi.org/10.1016/j.jad.2018.05.010>
- Brouwer, M. E., Williams, A. D., Kennis, M., Fu, Z., Klein, N. S., Cuijpers, P., & Bockting, C. L. H. (2019). Psychological theories of depressive relapse and recurrence: A systematic review and meta-analysis of prospective studies. *Clinical Psychology Review*, 74, 101773. <https://doi.org/10.1016/j.cpr.2019.101773>
- Carter, J. S., & Garber, J. (2011). Predictors of the first onset of a major depressive episode and changes in depressive symptoms across adolescence: Stress and negative cognitions. *Journal of Abnormal Psychology*, 120(4), 779–796. <https://doi.org/10.1037/a0025441>

- Chandler, J., Cumpston, M., Li, T., Page, M. J., & Welch, V. A. (2019). *Cochrane Handbook for Systematic Reviews of Interventions*. John Wiley & Sons.
<https://doi.org/10.1002/9781119536604>
- Clark, L. A., & Watson, D. (1999). Temperament: A New Paradigm for Trait Psychology. *Handbook of Personality: Theory and Research*, 2, 399–423.
- Costello, C. G. (1972). Depression: Loss of Reinforcers or Loss of Reinforcer Effectiveness? *Behavior Therapy*, 3(2), 240–247. <https://doi.org/10.1016/j.beth.2016.08.007>
- Coventry, W. L., Medland, S. E., Wray, N. R., Thorsteinsson, E. B., Heath, A. C., & Byrne, B. (2009). Phenotypic and discordant-monozygotic analyses of stress and perceived social support as antecedents to or sequelae of risk for depression. *Twin Research and Human Genetics*, 12(5), 469–488. <https://doi.org/10.1375/twin.12.5.469>
- Coyne, J. C. (1976). Depression and the response of others. *Journal of Abnormal Psychology*, 85(2), 186.
- Cuijpers, P. (2017). Preventing the onset of depressive disorders an overview. *Public Health Perspectives on Depressive Disorders*, 411–430.
- Cuijpers, P., Geraedts, A. S., Van Oppen, P., Andersson, G., Markowitz, J. C., & Van Straten, A. (2011). Interpersonal psychotherapy for depression: A meta-analysis. *American Journal of Psychiatry*, 168(6), 581–592. <https://doi.org/10.1176/appi.ajp.2010.10101411>
- Cuijpers, P., Karyotaki, E., Reijnders, M., & Ebert, D. D. (2018). Was Eysenck right after all? A reassessment of the effects of psychotherapy for adult depression. *Epidemiology and Psychiatric Sciences*, 1–10. <https://doi.org/10.1017/S2045796018000057>
- Cuijpers, P., & Smit, F. (2004). Subthreshold depression as a risk indicator for major depressive disorder: a systematic review of prospective studies. *Acta Psychiatrica Scandinavica*, 109(5), 325–331. <https://doi.org/10.1111/j.1600-0447.2004.00301.x>
- Dimidjian, S., Barrera, M., Martell, C., Muñoz, R. F., & Lewinsohn, P. M. (2011). The Origins and Current Status of Behavioral Activation Treatments for Depression. *Annual Review of Clinical Psychology*, 7(1), 1–38. <https://doi.org/10.1146/annurev-clinpsy-032210-104535>
- Dozois, D. J. A., & Rnic, K. (2015). Core beliefs and self-schematic structure in depression. *Current Opinion in Psychology*, 4, 98–103. <https://doi.org/10.1016/j.copsyc.2014.12.008>
- Driessen, E., Hollon, S. D., Bockting, C. L., Cuijpers, P., & Turner, E. H. (2015). Does Publication Bias Inflate the Apparent Efficacy of Psychological Treatment for Major Depressive Disorder? A Systematic Review and Meta-Analysis of US National Institutes of Health-Funded Trials 1. *PLoS One*, 10(9), e0137864. <https://doi.org/10.1371/journal.pone.0137864>
- Enns, M. W., & Cox, B. J. (1997). Personality dimensions and depression: Review and commentary. *Canadian Journal of Psychiatry*, 42(3), 274–284.
<https://doi.org/10.1177/070674379704200305>
- Eldesouky, L., Thompson, R. J., Oltmanns, T. F., & English, T. (2018). Affective instability predicts the course of depression in late middle-age and older adulthood. *Journal of Affective Disorders*, 239, 72–78. <https://doi.org/10.1016/j.jad.2018.06.038>
- Fanou, A. H., Neale, M. C., Aggen, S. H., & Kendler, K. S. (2007). A longitudinal study of personality and major depression in a population-based sample of male twins. *Psychological Medicine*, 37(8), 1163–1172. <https://doi.org/10.1017/S0033291707000244>
- Fernald, D. (2008). *Psychology: Six Perspectives*. California: SAGE Publications, Inc.
<https://doi.org/10.4135/9781452224862>
- Ferrari, A. J., Charlson, F. J., Norman, R. E., Patten, S. B., Freedman, G., Murray, C. J. L., ... Whiteford, H. A. (2013). Burden of Depressive Disorders by Country, Sex, Age, and Year: Findings from the Global Burden of Disease Study 2010. *PLoS Medicine*, 10(11).
<https://doi.org/10.1371/journal.pmed.1001547>
- Ferster, C. B. (1974). Behavioral approaches to depression. In *The psychology of depression: Contemporary theory and research*. (pp. xvii, 318–xvii, 318). Oxford: John Wiley & Sons.

- Freud, S. (1994). *Mourning and melancholia*. New York: New York University Press.
- Giollabhui, N. M., Hamilton, J. L., Nielsen, J., Connolly, S. L., Stange, J. P., Varga, S., ... Alloy, L. B. (2018). Negative cognitive style interacts with negative life events to predict first onset of a major depressive episode in adolescence via hopelessness. *Journal of Abnormal Psychology, 127*(1), 1–11. <https://doi.org/10.1037/abn0000301>
- Goldberg, L. R. (2013). An alternative "Description of personality": The big-five factor structure. *The Science of Mental Health: Volume 7: Personality and Personality Disorder, 59*(6), 34–48. <https://doi.org/10.1037//0022-3514.59.6.1216>
- Goldstein, B. L., Kotov, R., Perlman, G., Watson, D., & Klein, D. N. (2018). Trait and facet-level predictors of first-onset depressive and anxiety disorders in a community sample of adolescent girls. *Psychological Medicine, 48*(8), 1282–1290. <https://doi.org/10.1017/S0033291717002719>
- Goodyer, I. M., Herbert, J., Tamplin, A., & Altham, P. M. (2000). First-episode major depression in adolescents: Affective, cognitive and endocrine characteristics of risk status and predictors of onset. *British Journal of Psychiatry, 176*(FEB.), 142–149. <https://doi.org/10.1192/bjp.176.2.142>
- Gotlib, I. H., & Joormann, J. (2010). Cognition and Depression: Current Status and Future Directions. *Annual Review of Clinical Psychology, 6*(1), 285–312. <https://doi.org/10.1146/annurev.clinpsy.121208.131305>
- Graaf, R. de, Bijl, R. V., Ravelli, A., Smit, F., & Vollebergh, W. A. (2002). Gender and age-specific first incidence of DSM-III-R psychiatric disorders in the general population. Results from the Netherlands mental health survey and incidence study (NEMESIS). *Social Psychiatry and Psychiatric Epidemiology, 37*(8), 372–379. <https://doi.org/10.1007/s00127-002-0566-3>
- Haaga, D. A., Dyck, M. J., & Ernst, D. (1991). Empirical status of cognitive theory of depression. *Psychological Bulletin, 110*(2), 215–236. <https://doi.org/10.1037/0033-2909.110.2.215>
- Hankin, B. L., & Abela, J. R. Z. (2005). *Development of Psychopathology: A Vulnerability-Stress Perspective*. 2455 Teller Road: SAGE Publications, Inc. <https://doi.org/10.4135/9781452231655>
- Hawke, L. D., & Provencher, M. D. (2011). Schema Theory and Schema Therapy in Mood and Anxiety Disorders: A review. *Journal of Cognitive Psychotherapy, 25*(4), 257–276. <https://doi.org/10.1891/0889-8391.25.4.257>
- Holmes, E. A., Craske, M. G., & Graybiel, A. M. (2014). Psychological treatments: A call for mental-health science. *Nature, 511*, 287–289. <https://doi.org/10.1038/511287a>
- Hong, R. Y., & Cheung, M. W. L. L. (2015). The structure of cognitive vulnerabilities to depression and anxiety: Evidence for a common core etiologic process based on a meta-analytic review. *Clinical Psychological Science, 3*(6), 892–912. <https://doi.org/10.1177/2167702614553789>
- Jacobson, E. (1975). *The psychoanalytic treatment of depressive patients*. *Depression and Human Existence*. Boston: Little, Brown, 431–443.
- Kendler, K. S., Neale, M. C., Kessler, R. C., Heath, A. C., & Eaves, L. J. (1993). A Longitudinal Twin Study of 1-Year Prevalence of Major Depression in Women. *Archives of General Psychiatry, 50*(11), 843–852. <https://doi.org/10.1001/archpsyc.1993.01820230009001>
- Kennis, M., Gerritsen, L., Dalen, M. van, Williams, A., Cuijpers, P., & Bockting, C. (2019). Prospective biomarkers of major depressive disorder: A systematic review and meta-analysis. *Molecular Psychiatry, 1*–18. <https://doi.org/10.1038/s41380-019-0585-z>
- Kessler, R. C., Gruber, M., Hettema, J. M., Hwang, I., Sampson, N., & Yonkers, K. A. (2008). Co-morbid major depression and generalized anxiety disorders in the National Comorbidity Survey follow-up. *Psychological Medicine, 38*(3), 365–374. <https://doi.org/10.1017/S0033291707002012>
- Kircanski, K., Joormann, J., & Gotlib, I. H. (2012). Cognitive aspects of depression (Vol. 3, pp. 301–313). Guilford Press. <https://doi.org/10.1002/wcs.1177>

- Klein, D. N., Kotov, R., & Bufferd, S. J. (2011). Personality and Depression: Explanatory Models and Review of the Evidence. *Annual Review of Clinical Psychology*, 7(1), 269–295. <https://doi.org/10.1146/annurev-clinpsy-032210-104540>
- Kohut, H. (1971). *The Analysis of the Self*. New York: Int. <https://doi.org/10.7208/chicago/9780226450148.001.0001>
- Kopala-Sibley, D. C., Klein, D. N., Perlman, G., & Kotov, R. (2017). Self-criticism and dependency in female adolescents: Prediction of first onsets and disentangling the relationships between personality, stressful life events, and internalizing psychopathology. *Journal of Abnormal Psychology*, 126(8), 1029–1043. <https://doi.org/10.1037/abn0000297>
- Kruijft, A. W., Antypa, N., Booij, L., Jong, P. J. de, Glashouwer, K., Penninx, B. W. J. H., & Van der Does, W. (2013). Cognitive reactivity, implicit associations, and the incidence of depression: a two-year prospective study. *PLoS One*, 8(7), e70245.
- Lakdawalla, Z., Hankin, B. L., & Mermelstein, R. (2007). Cognitive theories of depression in children and adolescents: A conceptual and quantitative review. *Clinical Child and Family Psychology Review*, 10(1), 1–24. <https://doi.org/10.1007/s10567-006-0013-1>
- Langer, G., Meerpohl, J. J., Perleth, M., Gartlehner, G., Kaminski-Hartenthaler, A., & Schönemann, H. (2012). GRADE Guidelines: 1. Introduction - GRADE evidence profiles and summary of findings tables. *Zeitschrift Fur Evidenz, Fortbildung Und Qualitat Im Gesundheitswesen*, 106(5), 357–368. <https://doi.org/10.1016/j.zefq.2012.05.017>
- Lazarus, A. A. (1972). Some reactions to Costello's paper on depression. *Behavior Therapy*, 3(2), 248–250. [https://doi.org/10.1016/S0005-7894\(72\)80085-6](https://doi.org/10.1016/S0005-7894(72)80085-6)
- Lejuez, C. W., Hopko, D. R., LePage, J. P., Hopko, S. D., & McNeil, D. W. (2001). A brief behavioral activation treatment for depression. *Cognitive and Behavioral Practice*, 8(2), 164–175. [https://doi.org/10.1016/S1077-7229\(01\)80022-5](https://doi.org/10.1016/S1077-7229(01)80022-5)
- Lewinsohn, P. (1975). The Behavioral Study and Treatment of Depression. In *Progress in behavior modification* (Vol. 1, pp. 19–64). Elsevier. <https://doi.org/10.1016/b978-0-12-535601-5.50009-3>
- Lewinsohn, P. M., Allen, N. B., Seeley, J. R., & Gotlib, I. H. (1999). First onset versus recurrence of depression: differential processes of psychosocial risk. *Journal of Abnormal Psychology*, 108(3), 483–489.
- Lewinsohn, P., Youngren, M., & Grosscup, S. (1979). Reinforcement and depression. *The Psychobiology of Depressive Disorders: Implications for the Effects of Stress*, 291–316.
- Luyten, P., & Blatt, S. J. (2012). Psychodynamic Treatment of Depression. *Psychiatric Clinics of North America*, 35(1), 111–129. <https://doi.org/10.1016/j.psc.2012.01.001>
- MaCkinnon, A., & Andrews, G. (1993). Parental 'affectionless control' as an antecedent to adult depression: A risk factor refined. *Psychological Medicine*, 23(1), 135–141. <https://doi.org/10.1017/S0033291700038927>
- Markon, K. E., Krueger, R. F., & Watson, D. (2005). Delineating the structure of normal and abnormal personality: An integrative hierarchical approach. *Journal of Personality and Social Psychology*, 88(1), 139–157. <https://doi.org/10.1037/0022-3514.88.1.139>
- Mathew, A. R., Pettit, J. W., Lewinsohn, P. M., Seeley, J. R., & Roberts, R. E. (2011). Co-morbidity between major depressive disorder and anxiety disorders: Shared etiology or direct causation? *Psychological Medicine*, 41(10), 2023–2034. <https://doi.org/10.1017/S0033291711000407>
- Mathews, A., & MacLeod, C. (2005). Cognitive Vulnerability to Emotional Disorders. *Annual Review of Clinical Psychology*, 1(1), 167–195. <https://doi.org/10.1146/annurev.clinpsy.1.102803.143916>
- Miranda, J. (1992). Dysfunctional thinking is activated by stressful life events. *Cognitive Therapy and Research*, 16(4), 473–483. <https://doi.org/10.1007/BF01183169>

- Nezu, A. M. (1987). A problem-solving formulation of depression: A literature review and proposal of a pluralistic model. *Clinical Psychology Review*, 7(2), 121–144.
[https://doi.org/10.1016/0272-7358\(87\)90030-4](https://doi.org/10.1016/0272-7358(87)90030-4)
- Nolen-Hoeksema, S. (1991). Responses to depression and their effects on the duration of depressive episodes. *Journal of Abnormal Psychology*, 100(4), 569–582. <https://doi.org/10.1037/0021-843X.100.4.569>
- Noteboom, A., Beekman, A. T., Vogelzangs, N., & Penninx, B. W. (2016). Personality and social support as predictors of first and recurrent episodes of depression. *Journal of Affective Disorders*, 190, 156–161. <https://doi.org/10.1016/j.jad.2015.09.020>
- Nusslock, R., Shackman, A. J., Harmon-Jones, E., Alloy, L. B., Coan, J. A., & Abramson, L. Y. (2011). Cognitive Vulnerability and Frontal Brain Asymmetry: Common Predictors of First Prospective Depressive Episode. *Journal of Abnormal Psychology*, 120(2), 497–503. <https://doi.org/10.1037/a0022940>
- Ormel, J., Oldehinkel, A. J., & Vollebergh, W. (2004). Vulnerability before, during, and after a major depressive episode: A 3-wave population-based study. *Archives of General Psychiatry*, 61(10), 990–996. <https://doi.org/10.1001/archpsyc.61.10.990>
- Ormel, J., Jeronimus, B. F., Kotov, R., Riese, H., Bos, E. H., Hankin, B., ... Oldehinkel, A. J. (2013). Neuroticism and common mental disorders: Meaning and utility of a complex relationship. *Clinical Psychology Review*, 33(5), 686–697. <https://doi.org/10.1016/j.cpr.2013.04.003>
- Ormel, J., Oldehinkel, A. J., & Vollebergh, W. (2004). Vulnerability before, during, and after a major depressive episode: a 3-wave population-based study. *Archives of General Psychiatry*, 61(10), 990–996. <https://doi.org/10.1001/archpsyc.61.10.990>
- Orsini, N., Bottai, M., Higgins, J., & Buchan, I. (2006). Heterogi: Stata module to quantify heterogeneity in a meta-analysis. *Statistical Software Components*.
- Ostergaard, D., Dalton, S. O., Bidstrup, P. E., Poulsen, A. H., Frederiksen, K., Eplöv, L. F., ... Mortensen, E. L. (2012). Mental vulnerability as a risk factor for depression: A prospective cohort study in Denmark. *International Journal of Social Psychiatry*, 58(3), 306–314. <https://doi.org/10.1177/0020764010396409>
- Otto, M. W., Teachman, B. A., Cohen, L. S., Soares, C. N., Vitonis, A. F., & Harlow, B. L. (2007). Dysfunctional Attitudes and Episodes of Major Depression: Predictive Validity and Temporal Stability in Never-Depressed, Depressed, and Recovered Women. *Journal of Abnormal Psychology*, 116(3), 475–483. <https://doi.org/10.1037/0021-843X.116.3.475>
- Roberts, S. B., & Kendler, K. S. (1999). Neuroticism and self-esteem as indices of the vulnerability to major depression in women. *Psychological Medicine*, 29(5), 1101–1109. <https://doi.org/10.1017/S0033291799008739>
- Salk, R. H., Hyde, J. S., & Abramson, L. Y. (2017). Gender differences in depression in representative national samples: Meta-analyses of diagnoses and symptoms. *Psychological Bulletin*, 143(8), 783–822. <https://doi.org/10.1037/bul0000102>
- Sandler, J., & Joffe, G. W. (1965). Notes on childhood depression. *International Journal of Psycho-Analysis*, 46, 88–96.
- Skinner, B. F. (1957). *Verbal behaviour*. New York: Copley Publishing Group.
- Stange, J. P., Connolly, S. L., Burke, T. A., Hamilton, J. L., Hamlat, E. J., Abramson, L. Y., & Alloy, L. B. (2016). Inflexible Cognition Predicts First Onset of Major Depressive Episodes in Adolescence. *Depression and Anxiety*, 33(11), 1005–1012. <https://doi.org/10.1002/da.22513>
- Stavrakakis, N., Roest, A. M., Verhulst, F., Ormel, J., Jonge, P. de, & Oldehinkel, A. J. (2013). Physical activity and onset of depression in adolescents: A prospective study in the general population cohort TRAILS. *Journal of Psychiatric Research*, 47(10), 1304–1308. <https://doi.org/10.1016/j.jpsychires.2013.06.005>

- Stone, L. B., Hankin, B. L., Gibb, B. E., & Abela, J. R. (2011). Co-Rumination Predicts the Onset of Depressive Disorders During Adolescence. *Journal of Abnormal Psychology, 120*(3), 752–757. <https://doi.org/10.1037/a0023384>
- Stone, L. (1986). Psychoanalytic observations on the pathology of depressive illness: Selected spheres of ambiguity or disagreement. *Journal of the American Psychoanalytic Association, 34*(2), 329–362.
- Stordal, E., Mykletun, A., & Dahl, A. A. (2003). The association between age and depression in the general population: a multivariate examination. *Acta Psychiatrica Scandinavica, 107*(2), 132–141. <https://doi.org/10.1034/j.1600-0447.2003.02056.x>
- Tokuyama, M., Nakao, K., Seto, M., Watanabe, A., & Takeda, M. (2003). Predictors of first-onset major depressive episodes among white-collar workers. *Psychiatry and Clinical Neurosciences, 57*(5), 523–531. <https://doi.org/10.1046/j.1440-1819.2003.01158.x>
- Weisz, J. R., Kuppens, S., Ng, M. Y., Vaughn-Coaxum, R. A., Ugueto, A. M., Eckshtain, D., & Corteselli, K. A. (2019). Are Psychotherapies for Young People Growing Stronger? Tracking Trends Over Time for Youth Anxiety, Depression, Attention-Deficit/Hyperactivity Disorder, and Conduct Problems. *Perspectives on Psychological Science, 14*(2), 216–237. <https://doi.org/10.1177/1745691618805436>
- Wilkinson, P. O., Croudace, T. J., & Goodyer, I. M. (2013). Rumination, anxiety, depressive symptoms and subsequent depression in adolescents at risk for psychopathology: A longitudinal cohort study. *BMC Psychiatry, 13*(1), 250–258. <https://doi.org/10.1186/1471-244X-13-250>

Chapter 3

Effectiveness of digital psychological interventions for mental health problems in low and middle income countries: A systematic review and meta-analysis

Fu, Z., Burger, H., Arjadi, R. & Bockting, C. L.(2020). Effectiveness of digital psychological interventions for mental health problems in low and middle income countries: A systematic review and meta-analysis. *Lancet Psychiatry*, 7(10), 851-864

Abstract

Background

The effectiveness of digital psychological interventions in low-income and middle-income countries (LMICs) remains unclear. We aimed to systematically investigate the available evidence for digital psychological interventions in reducing mental health problems in LMICs.

Methods

In this systematic review and meta-analysis, we searched PubMed, PsycINFO, Embase, and Cochrane databases for articles published in English from database inception to March 9, 2020. We included randomised controlled trials investigating digital psychological interventions in individuals with mental health problems in LMICs. We extracted data on demographics, inclusion and exclusion criteria, details of the intervention, including the setting, digital delivery method, control group conditions, number of sessions, therapeutic orientation (eg, cognitive therapy or behaviour therapy), presence or absence of guidance, and length of follow-up, and statistical information to calculate effect sizes. If a study reported insufficient data to calculate effect sizes, the corresponding authors were contacted to provide data that could be aggregated. We did random-effects meta-analyses, and calculated the standardised mean difference in scores of digital psychological interventions versus control conditions (Hedges' *g*). Quality of evidence was assessed by use of the Grading of Recommendations Assessment, Development, and Evaluation approach. The primary outcome was post-intervention mental health problems, as measured by self-reporting instruments or clinical interviews. This study is registered with PROSPERO, CRD42019137755.

Findings

We identified 22 eligible studies that were included in the meta-analysis. The included studies involved a total of 4104 participants (2351 who received a digital psychological intervention and 1753 who were in the control group), and mainly focused on young adults (mean age of the study population was 20–35 years) with depression or substance misuse. The results showed that digital psychological interventions are moderately effective when compared with control interventions (Hedges' *g* 0.60 [95% CI 0.45–0.75]; Hedges' *g* with treatment as usual subgroup for comparison 0.54 [0.35–0.73]). Heterogeneity between studies was substantial ($I^2=74%$ [95% CI 60–83]). There was no evidence of publication bias, and the quality of evidence according to the GRADE criteria was generally high.

Interpretation

Digital psychological interventions, which have been mostly studied in individuals with depression and substance misuse, are superior to control conditions, including usual care, and are moderately effective in LMICs. However, the considerable heterogeneity observed in our analysis highlights the need for more studies to be done, with standardised implementation of digital psychological intervention programmes to improve their reproducibility and efficiency. Digital psychological interventions should be considered for regions where usual care for mental health problems is minimal or absent.

Introduction

Together with substance use disorders, mental disorders are among the leading global contributors to the total burden of disease, as measured by the number of years lived with a disability (GBD Collaborators, 2018). Compared with high-income countries (HICs; defined by the World Bank, 2020.), low-income and middle-income countries (LMICs) are disproportionately affected by mental health disorders because of the substantial mental health gap (i.e., the gap between available treatment and the number of people with mental disorders in need of care; Patel et al., 2007). Indeed, the ratio of available mental health therapists per 100000 population in LMICs is approximately 0.5% of that in HICs (Saxena, Thornicroft, Knapp, & Whiteford, 2007). An analysis published in 2016 estimated that 79–93% of people with depression and 85–95% of people with anxiety are not covered by treatment in LMICs (Chisholm et al., 2016). Inadequate access to mental health care can lead to considerable distress, chronicity, and increased cost of care at the individual level, as well as low productivity and low participation in the workforce at the country level (Prince et al., 2007). The scale of this problem is illustrated by the fact that more than 80% of the world population lives in LMICs (World Bank, 2016).

Digital psychological interventions for mental health could contribute to improving access to mental health care in these countries through the advantages of the enormous reach of the internet, remote access, anonymity, and the diversity of formats (Amaroso, Flores Arango, & Bailey, 2011). A psychological intervention is considered as digital when technology is used in its delivery, such as the internet, computers, mobile phones or tablets, and text messaging services. The use of digital technology in LMICs has increased rapidly over the past several years. A previous report highlighted that 80% of the population in LMICs possess mobile phones, and nearly half of the population can get access to the internet (World Bank, 2016).

Given that there is evidence for short-term effectiveness of digital psychological interventions in HICs (Pasarelu, Andersson, Bergman Nordgren, & Dobrea, 2017; Sander, Rausch, & Baumeister, 2016), it is possible that these interventions would help to reduce the mental health gap in LMICs (Holmes et al., 2018). Of particular relevance, people around the world, including those living in LMICs, face increasing mental health problems during the COVID-19 pandemic (Brooks et al., 2020), which has forced millions of people to physically isolate themselves and has presented considerable challenges for mental health-care systems (Xiang, Jin, & Cheung, 2020). As recommended by some experts and the UN, digital psychological interventions for mental health problems

could have the potential to provide necessary mental support (Holmes et al., 2020; UN, 2020).

Nevertheless, the effectiveness of digital psychological interventions in LMICs remains unclear. Previous reviews have been unable to do a meta-analysis of the effects of digital psychological interventions because of the insufficient number of available randomised controlled trials (RCTs) (Arjadi, Nauta, Chowdhary, & Bockting, 2015; Naslund et al., 2017). Another two relevant reviews involved either a specific group of individuals (two RCTs involving patients with depression in LMICs; Martinez, Rojas, Martinez, Lara, & Perez, 2018), or were restricted to one specific region (three RCTs done in Latin America; Jimenez-Molina et al., 2019). A comprehensive umbrella review published in 2020, established robust evidence for the efficacy of psychosocial interventions for common mental health conditions in LMICs (Barbui et al., 2020). However, because no previous meta-analysis on digital psychological interventions in LMIC populations has been done, this umbrella review could not draw specific conclusions about the effectiveness of digital psychological interventions in LMICs (Barbui et al., 2020).

Long-standing concerns have been raised about the applicability of digital psychological interventions in LMICs. In addition to the potential concern of privacy imposed by technology (Huckvale, Prieto, Tilney, Benghozi, & Car, 2015), the WHO highlights that, “rigorous evaluation of digital health is necessary to generate evidence and promote the appropriate integration and use of technologies” (*WHO guideline: recommendations on digital interventions for health system strengthening*, 2019). Therefore, a systematic quantitative assessment of the effectiveness of digital psychological interventions in LMICs is needed.

Methods

Search strategy and selection criteria

For this systematic review and meta-analysis, we searched PubMed, PsycINFO, Cochrane, and Embase from inception to March 9, 2020. We built on the search strategy used by Arjadi and colleagues (2015), which was expanded to include terms referring to some newly adopted digital methods (e. g., “personal digital assistant”, “video game”, and “reminder”). Search terms included a combination of Medical Subject Headings and text words (wild cards were used if necessary) indicative of: (1) digital psychological interventions, (2) LMICs, and (3) RCTs. The full search strings can be found in the appendix 2A. The reference lists of relevant reviews and the articles citing the included articles were examined to identify additional publications. We included studies in which the following

criteria were met: (1) the primary focus was the use of digital psychological interventions in individuals with mental health problems, as defined by specific diagnostic criteria (e.g., DSM-5 or ICD-10); (2) the digital psychological intervention was a type of standardised psychological intervention delivered to individuals via digital communication devices through smartphone apps, websites, emails, SMS text messages, videos, audio files, and computer programmes; (3) mental health symptoms were recorded by use of a self-report instrument measuring severity or a clinical interview; (4) participants from LMICs were included; and (5) studies were published in English and in peer-reviewed journals. If more than one study with data from the same patient cohort was identified, the study with the longest patient follow-up period was included. If these studies had the same follow-up periods, the study with the largest sample size was included.

A standardised online platform (Covidence) was used to screen studies. Title and abstract screening and full text screening were done by two reviewers (RA and ZF) independently. Data were extracted primarily by ZF and checked by RA. Disagreements about inclusion were resolved with the help of senior reviewers (HB and CLHB). The same inclusion criteria were applied for the systematic review as for the meta-analysis, except that available data for aggregation were required for the meta-analysis.

Data analysis

We extracted data on demographics, inclusion and exclusion criteria, details of the intervention, including the setting, digital method, control group condition, number of sessions, therapeutic orientation (e.g., cognitive therapy or behavioural therapy), the presence or absence of guidance, and length of follow-up, and statistical information to calculate effect sizes. If a study reported insufficient data to calculate effect sizes, the corresponding authors were contacted to request that they provide the aggregate data. Studies were excluded if these data were not provided.

We used the Cochrane Risk of Bias Tool to assess methodological quality of the included studies (Higgins et al., 2011). The following four domains were assessed: random sequence generation, allocation concealment, incomplete outcome data, and selective reporting. Two independent researchers (ZF and RA) assessed these domains independently, and disagreements were resolved by discussion. Each domain was assigned a “+” (low risk of bias, with a score of 0), a “?” (unclear risk of bias, with a score of 1), or a “-” (high risk of bias, with a score of 2). A total score of 0–2 indicated a low risk of bias (high quality), 3–5 a moderate risk of bias, and 6–8 a high risk of bias (i.e., low quality). The

Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach was used to evaluate the overall quality of the evidence (Balslem et al., 2011).

Comprehensive Meta-Analysis software (version 3) and the R software programme (version 3.6.2) were used to calculate pooled effect sizes and their 95% CIs. Given the various assessments used to assess different mental health problems, Hedges' g as an index of the standardised mean difference was used as a measure of the effect size, thus enabling us to include different outcome measures (e.g., Beck Depression Inventory and Patient Health Questionnaire-9 for depression assessment) in the same synthesis. The effect size was conventionally considered as small (Hedges' g 0.2), moderate (0.5), or large (0.8). The 95% prediction intervals were also calculated to illustrate which range of true effects can be expected in future research. The between-study component of variance τ^2 was estimated by use of the DerSimonian and Laird method. The number needed to treat was also calculated (Preti, 2017).

If applicable, two meta-analyses were done according to the type of comparison group. We subcategorised comparison groups into two primary types: (1) control groups, including treatment as usual (mixed treatments), assessment only, wait-list control, and active control; and (2) other specified groups, including those in which participants were given single psychological or pharmaceutical interventions.

Since considerable heterogeneity was expected, we chose a random effects pooling model for all analyses a priori. Post-intervention outcome data were used to compute Hedges' g . Continuous outcome data with means and standard deviations were used to directly calculate Hedges' g . If the outcomes were expressed as an event proportion, they were converted to odds ratios and then subsequently converted to Hedges' g . We excluded follow-up results, since not all studies had done a follow-up assessment after the intervention period, and follow-up periods differed extensively between studies. The I^2 was calculated to assess heterogeneity. In general, heterogeneity was categorised as low (0–40%), moderate (30–60%), substantial (50–90%), or considerable (75–100%) (Deeks, Higgins, Altman, & Group, 2019). Subgroup analyses based on type of mental health problem, risk of bias, format of intervention, type of control group, therapeutic orientation, type of guidance, missing values analysis, recruitment setting, region, and diagnosis at baseline were done only if at least three studies were present for each subgroup. All subgroup analyses were done by use of a mixed-effects analysis, in which the random-effects model was used to summarise the studies within the respective subgroups, and the fixed-effects model was used to test for significant differences between these subgroups.

Four preplanned sensitivity analyses were done to examine the effect of: (1) outliers, defined as those displaying a 95% CI that did not overlap with the 95% CI of the pooled effect size; (2) blended intervention studies; (3) studies including patients with coexisting physical disease; and (4) studies in which participants from HICs were present. To examine small study effects (e.g., those caused by publication bias), funnel plots and the Egger's test were used. Duval and Tweedie's trim-and-fill method was used to estimate the overall effect size, accounting for bias by small study effects. Statistical significance (α level) was set to a p value of less than 0.05 (type 1 error).

The study protocol was registered on PROSPERO, CRD42019137755, and followed the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA).

Role of the funding source

There was no funding source for this study. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Overall, 5441 reports were identified through a database search, with a further five reports identified through other sources. 1887 reports were deemed to be duplicates, and a further 3471 reports (titles and abstracts) were excluded. Of the remaining 88 full-text reports assessed for eligibility, 24 studies met the inclusion criteria and were included in the systematic review (Figure 1) (Arjadi et al., 2018; Baldin, Sanudo, & Sanchez, 2018; Burton et al., 2016; Christoff Ade & Boerngen-Lacerda, 2015; Darvish, Khodadadi-Hassankiadeh, Abdoosti, & Ghapandar Kashani, 2019; D'Souza et al., 2013; Durmaz et al., 2019; Guo et al., 2020; Knaevelsrud, Brand, Lange, Ruwaard, & Wagner, 2015; Liang, Han, Du, Zhao, & Hser, 2018; Liao et al., 2016; Marasinghe, Edirippulige, Kavanagh, Smith, & Jiffry, 2012; Moeini, Bashirian, Soltanian, Ghaleiha, & Taheri, 2019; Mogoşşe, Brăilean, & David, 2013; Salamanca-Sanabria et al., 2020; Sanchez & Sanudo, 2018; Su, Fang, Miller, & Wang, 2011; Thitipitchayanant, Somrongthong, Kumar, & Kanchanakharn, 2018; Tiburcio, Lara, Martinez, Fernandez, & Aguilar, 2018; Tulbure, Andersson, Salagean, Pearce, & Koenig, 2018; Wang, Wang, & Maercker, 2013; Yang et al., 2019; Zhu et al., 2018). One study (Zhu et al., 2018) did not include information on mental health outcomes, therefore the data from this study were not included in the meta-analysis. Two studies (Baldin et al., 2018; Sanchez & Sanudo, 2018) included the same cohort of individuals, therefore, the study with the largest sample size (Sanchez & Sanudo, 2018) was included in the meta-analysis. A total of 22 studies were included in the meta-analyses, with 31 comparisons: 28 between digital

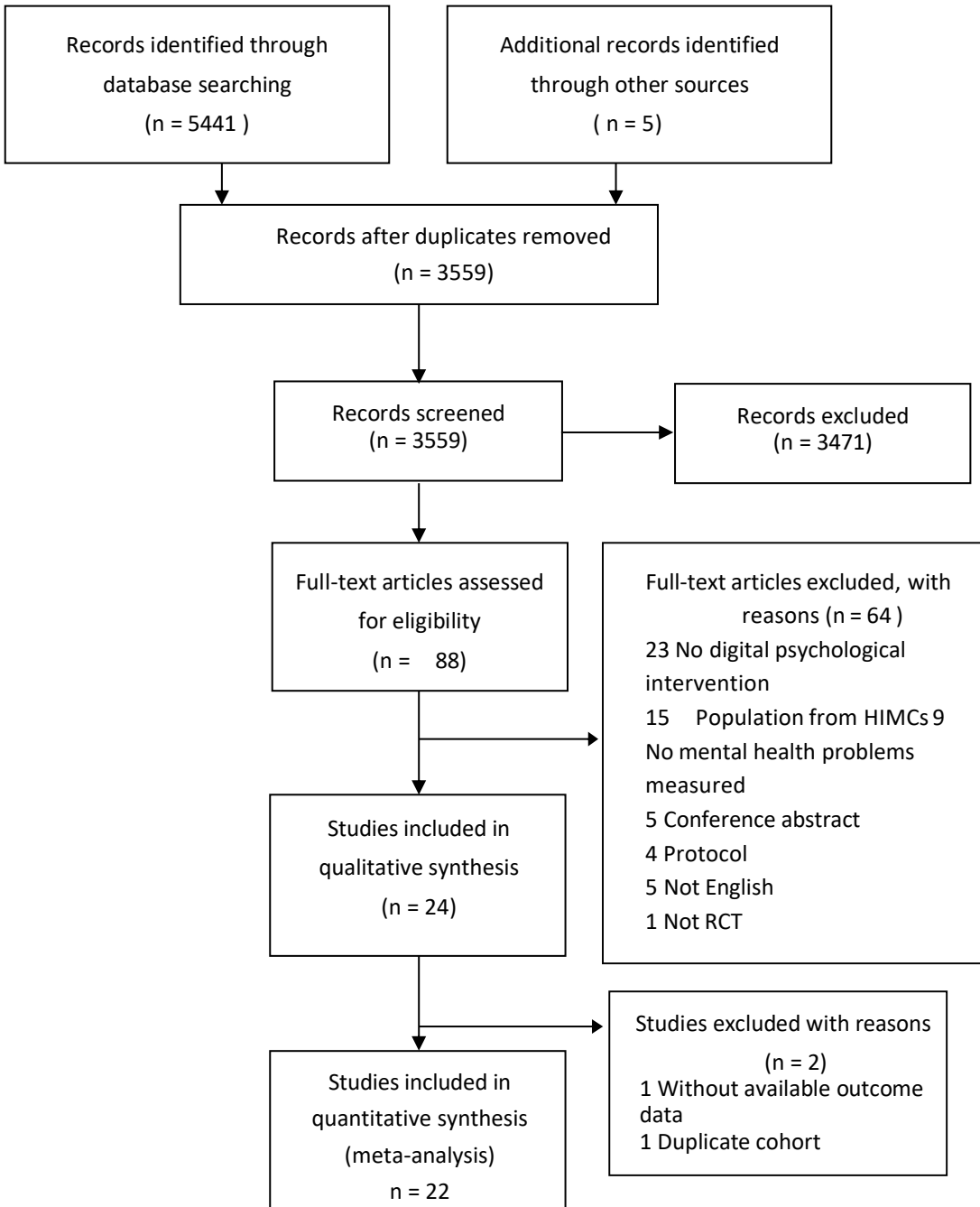


Figure 1 Study selection

psychological intervention groups and control groups, and three between digital psychological intervention groups and other specified single intervention groups (including face-to-face therapy, pharmacotherapy, and non-digital self-help interventions). We subsequently did two meta-analyses. Since the number of studies comparing digital psychological interventions with other specified single interventions was low, this meta-analysis was considered as exploratory (Appendix 2B).

Selected characteristics of studies included in the systematic review are shown in table 1 (additional details are in Appendix 2B Table s1). A total of 4104 participants (1505 of whom were female) were involved in the meta-analysis (2351 participants in digital psychological intervention groups and 1753 participants in control groups). Within these studies, the average number of participants per mental health problem was 80. The age of participants ranged from 16 years to 45 years. Studies were done between 2012 and 2020 in LMICs including China ($n=6$), Thailand ($n=1$), Brazil ($n=2$), Romania ($n=3$), Turkey ($n=1$), Iran ($n=3$), Indonesia ($n=1$), Sri Lanka ($n=1$), Mexico ($n=1$), and Colombia ($n=1$), or they were done in multiple sites across different countries ($n=2$). Participants were recruited from community ($n=8$), hospital ($n=8$), nightclub ($n=1$), and university or school ($n=5$) settings. Studies targeted mental health problems including depression ($n=14$), substance misuse ($n=7$), schizophrenia ($n=1$), post-traumatic stress disorder ($n=3$), internet addiction ($n=1$), and anxiety (social or public speaking; $n=4$). The severity of mental health problems was mostly measured by self-report questionnaires. Nine studies provided follow-up data, and the length of follow-up varied from 2 weeks to 6 months.

Digital psychological interventions were delivered in several formats, including via websites, smartphone apps, computer, audio-devices, and SMS (text) messages. The shared commonality of these interventions was that their content was adapted from relevant standardised psychological treatments. The therapeutic orientation of digital psychological interventions for substance misuse was mainly motivational interviewing, and for other mental health problems the therapeutic orientation of these interventions was mainly cognitive behavioural therapy (including mindfulness-based cognitive behavioural therapy). The number of digital psychological intervention sessions differed greatly between studies, from one to 24 sessions (with an average number of nine sessions across all studies). The intervention group in four studies combined digital psychological interventions with other types of intervention, such as face-to-face therapy (Marasinghe et al., 2012), pharmacotherapy (D'Souza et al., 2013), and usual care (Burton et al., 2016; Durmaz et al., 2019).

Assessments of adverse events were explicitly mentioned in four (Arjadi et al., 2018; D'Souza et al., 2013; Guo et al., 2020; Zhu et al., 2018) of 22 studies, indicating that there were no adverse events in patients who received the digital psychological intervention. In one study (D'Souza et al., 2013), three patients in the Indian sample population reported abdominal discomfort, which was judged to be possibly related to the study medication, and one patient experienced an exacerbation of psychosis after having missed one dose of depot neuroleptics. The remaining 18 studies did not report on adverse events (Baldin et al., 2018; Burton et al., 2016; Christoff Ade & Boerngen-Lacerda, 2015; Darvish et al., 2019; Knaevelsrud et al., 2015; Liang et al., 2018; Liao et al., 2016; Marasinghe et al., 2012; Moeini et al., 2019; Mogoşe et al., 2013; Salamanca-Sanabria et al., 2020; Sanchez & Sanudo, 2018; Su et al., 2011; Thitipitchayanant et al., 2018; Tiburcio et al., 2018; Tulbure et al., 2018; Wang et al., 2013; Yang et al., 2019; Zhu et al., 2018).

A total of 12 studies were considered to have a low risk of bias (Arjadi et al., 2018; Burton et al., 2016; Darvish et al., 2019; D'Souza et al., 2013; Durmaz et al., 2019; Knaevelsrud et al., 2015; Liao et al., 2016; Tiburcio et al., 2018; Tulbure et al., 2018; Wang et al., 2013; Zhu et al., 2018), and 12 studies were considered to have a moderate risk of bias (Baldin et al., 2018; Christoff Ade & Boerngen-Lacerda, 2015; Guo et al., 2020; Liang et al., 2018; Marasinghe et al., 2012; Moeini et al., 2019; Mogoşe et al., 2013; Salamanca-Sanabria et al., 2020; Sanchez & Sanudo, 2018; Su et al., 2011; Thitipitchayanant et al., 2018; Yang et al., 2019). Specifically, 15 studies reported a random component in the sequence generation process (Arjadi et al., 2018; Burton et al., 2016; Darvish et al., 2019; D'Souza et al., 2013; Durmaz et al., 2019; Guo et al., 2020; Knaevelsrud et al., 2015; Liao et al., 2016; Salamanca-Sanabria et al., 2020; Sanchez & Sanudo, 2018; Su et al., 2011; Tiburcio et al., 2018; Tulbure et al., 2018; Wang et al., 2013). Only seven studies described which procedures of allocation concealment were used (Arjadi et al., 2018; Burton et al., 2016; Darvish et al., 2019; Durmaz et al., 2019; Liao et al., 2016; Thitipitchayanant et al., 2018; Tulbure et al., 2018). With regards to reporting bias from selective outcome reporting, 13 studies provided trial registration information (Arjadi et al., 2018; Burton et al., 2016; Darvish et al., 2019; Durmaz et al., 2019; Knaevelsrud et al., 2015; Liao et al., 2016; Moeini et al., 2019; Salamanca-Sanabria et al., 2020; Tiburcio et al., 2018; Tulbure et al., 2018; Wang et al., 2013; Zhu et al., 2018). Regarding attrition bias, 13 studies reported a reasonable method to eliminate potential bias caused by missing data (Arjadi et al., 2018; Baldin et al., 2018; Christoff Ade & Boerngen-Lacerda, 2015; D'Souza et al., 2013; Knaevelsrud et al., 2015; Liao et al., 2016; Marasinghe et al., 2012; Tiburcio et al., 2018; Tulbure et al., 2018; Wang et al., 2013;

Yang et al., 2019; Zhu et al., 2018). The overall estimation of the quality of the evidence, according to the GRADE criteria, was generally high (see Appendix 2C).

Using data from the 22 studies (Figure 2), we compared the effects of digital psychological interventions with a control group (including assessment only, wait-list control, treatment as usual, and active control groups). The pooled effect size was 0.60 (95% CI 0.45–0.75; prediction interval –0.01 to 1.21), indicating that the number needed to treat was three patients (i.e., an average of three patients need to be given the digital psychological intervention for one of these patients to have a favourable outcome when compared with the control). Heterogeneity between studies was substantial ($I^2=74%$ [95% CI 60–83]). Two studies were identified as outliers (Christoff Ade & Boerngen-Lacerda, 2015; Sanchez & Sanudo, 2018). Both of these studies investigated interventions in individuals with substance use problems in Brazil. The digital psychological interventions were delivered via a website and consisted of psychoeducation on substance use. By contrast with the other studies, which delivered more than four sessions of the intervention to participants, only one session of the intervention was delivered to participants in these two studies (Christoff Ade & Boerngen-Lacerda, 2015; Sanchez & Sanudo, 2018). After removing these two studies from the analysis, we obtained a similar Hedges' g to that observed when all studies were included (0.61 [95% CI 0.48–0.74]; prediction interval 0.15–1.07; $I^2=59%$ [95% CI 33–75]).

Inspection of the funnel plot did not indicate publication bias (Appendix 2B). Egger's test of the intercept was not significant (intercept 0.60, SE = 1.12; $p = 0.60$). Using the Duval and Tweedie's trim-and-fill method, one study might be imputed to adjust the publication bias. After imputation, the overall Hedges' g decreased to 0.58 (95% CI 0.44–0.73; prediction interval –0.03 to 1.20)

The intervention groups in four studies used another type of treatment alongside the digital psychological intervention (Burton et al., 2016; D'Souza et al., 2013; Durmaz et al., 2019; Marasinghe et al., 2012). To avoid the consequent potential for inflation of the treatment effect, we did a post-hoc sensitivity analysis by removing these studies from the meta-analysis. The overall effect size was similar to that observed when all studies were included (0.63 [95% CI 0.47–0.80]; prediction interval: –0.02 to 1.29; $I^2=77%$ [95% CI 64–85]).

We also did a preplanned sensitivity analysis by removing two studies that included participants from HICs (Burton et al., 2016; D'Souza et al., 2013), and this analysis resulted in a similar effect size to that observed when all studies were included (Hedges' g 0.63 [95%

CI 0.48–0.78]; prediction interval 0.02–1.24; $I^2=74%$ [95% CI 60–84]). One study (Guo et al., 2020) involving participants with HIV was removed in another sensitivity analysis, resulting in an overall similar effect size to that observed when all studies were included (Hedges' g 0.60 [0.45–0.76]; prediction interval –0.04 to 1.25; $I^2=75%$ [62–84]). Subgrouping of studies by different characteristics had no significant effect on the overall effect size (Table 2).

Subgrouping of studies by different characteristics (e.g., by type of psychological symptoms, format of intervention, and type of control group) had no significant effect on the overall effect size.

Discussion

A considerable increase in the number of trials investigating digital psychological interventions since the previous systematic review (Arjadi et al., 2015) published in 2014 has enabled us to quantitatively assess the effectiveness of such interventions for mental health outcomes in LMICs. To our knowledge, this is the first study to do such a meta-analysis. Using the results of 22 studies, we found that digital psychological interventions in LMICs showed a moderate aggregated effect size, with a number needed to treat of around three. Most of the included studies focused on depression and substance misuse.

The studies included in our analysis used a diverse range of digital formats for delivering psychological interventions, with content similar to that of traditional face-to-face interventions. The results of our study indicate that psychological interventions perform well when delivered via digital formats. We observed a similar overall effect size of digital psychological interventions in LMICs as has been reported in HICs (e.g., in the study by Barak and colleagues (2008), reporting a Hedges' g of 0.53). In practice, a predominant question is how digital psychological interventions perform when compared with treatment as usual in local routine care. Eight studies (Burton et al., 2016; Darvish et al., 2019; Durmaz et al., 2019; Guo et al., 2020; Moeini et al., 2019; Thitipitchayanant et al., 2018; Tiburcio et al., 2018; Yang et al., 2019) in our meta-analysis compared the effectiveness of digital psychological interventions with treatment as usual (reflecting local routine care). Combining the results of these studies yielded a moderate effect size. Nevertheless, this result needs to be interpreted with caution, as treatment as usual in these eight studies differed considerably (ranging from health education to medication). Meanwhile, the large effect size we observed when digital psychological intervention groups were compared with assessment only or wait-list control groups could be relevant for regions where usual care for mental health problems consists of no care.

Only one study (Christoff Ade & Boerngen-Lacerda, 2015) of substance misuse directly compared a computerised intervention programme with a face-to-face intervention, with results showing that the effectiveness of the digital intervention was superior to the face-to-face intervention (Hedges' g 0.70 [95% CI 0.47–0.93]), even though both interventions were based on the same treatment manual. Some indirect comparisons of digital interventions with face-to-face interventions can be made by using findings from previous studies. Effect sizes observed in our study were generally smaller than those of talking therapy in LMICs (Barbui et al., 2020), and were larger than those pooled from trials of low-intensity psychological interventions delivered by non-specialists in LMICs (with Cohen's d as effect size ranging from 0.34 to 0.49) (Clarke, King, & Prost, 2013; Singla et al., 2017).

We examined the treatment effect of digital psychological interventions for different mental health problems, with moderate (depression and substance misuse) to large (anxiety and post-traumatic stress disorder) effect sizes. Depression was most commonly investigated (14 of the 22 included studies): studies included patients with major depressive disorder or depressive symptoms, and specific groups of individuals with depression, including those with HIV (Guo et al., 2020) and women with perinatal depression (Thitipitchayanant et al., 2018). Seven studies (Christoff Ade & Boerngen-Lacerda, 2015; Durmaz et al., 2019; Liang et al., 2018; Liao et al., 2016; Marasinghe et al., 2012; Sanchez & Sanudo, 2018; Tiburcio et al., 2018) investigated digital psychological interventions in individuals with substance use problems, and our analysis showed that the digital psychological intervention was moderately effective when compared with controls. The interventions in these studies were delivered over a low number of sessions, but attrition in general was considerable. The number of trials on anxiety ($n=4$) and post-traumatic stress disorder ($n=3$) included in our study was rather small.

In terms of type of mental health problem, none of the other subgroup indicators were found to be significant moderators of the overall treatment effect. Two subgroups, presumed a priori to be important, failed to explain the heterogeneity between studies. Guidance provided during the digital psychological intervention, which is considered to be important for assisting participants and maintaining adherence, had no significant effect on the overall effect size. This observation is partly consistent with that of previous studies (Baumeister, Reichler, Munzinger, & Lin, 2014), in which guided internet interventions were not superior to non-guided interventions in patients with depression and social phobia. The absence of effect of guidance on overall effect size could be attributed to mixed definitions of guidance and differences in how guidance is implemented across different studies, which

could dilute its influence. The type of control group had no significant effect on the overall effect size, by contrast with previous studies (Andersson, 2016). Treatment intensity was low in the treatment as usual group, which could explain the large effect size of digital psychological interventions, and few studies had an active control group. Both of these factors could have contributed to the insignificant result. Overall, because we were unable to do a meta-regression analysis, we could not exclude the confounding effects of other subgroup factors, such as recruitment setting or type of mental health problem.

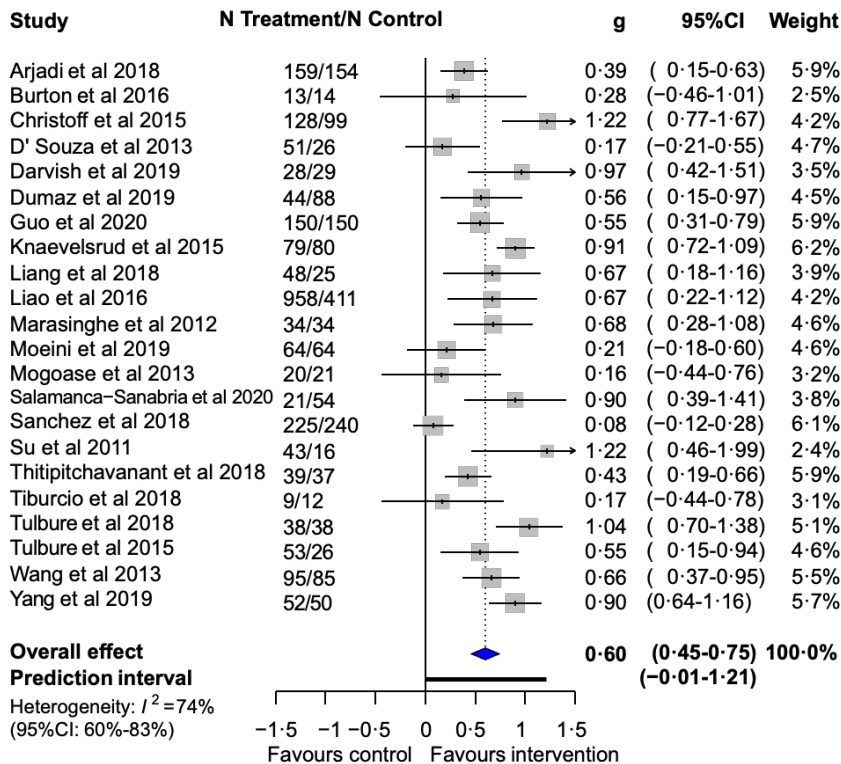


Figure 2: Effect of digital psychological interventions on mental health outcomes

It is encouraging that the trials included in our study had a low risk of bias. Most of the studies randomized participants and handled missing values appropriately. Nearly half of the studies included had pre-registered the trial by submitting the protocol to an independent registry, showing the efforts to avoid reporting bias. However, we also found that 70% of studies probably did not follow rigid rules to conceal the allocation sequence,

which could have introduced bias in the overall result. However, together with other strengths, in terms of research design and sample size, the low risk of bias implies a promising acceleration of the research quality in these resource-poor countries.

Some limitations should be mentioned. First, the overall moderate effect size in our meta-analysis could especially reflect the effect of digital psychological interventions when compared with no treatment or minimal treatment. However, this could be relevant for LMICs where usual care is minimal. Additionally, given that most studies have small sample sizes, bias cannot be ruled out. Second, except for depression, effect sizes for other conditions were either pooled from a limited number of studies or accompanied by wide confidence intervals, indicating low precision of the effect. Unfortunately, most of the subgroup analyses were not able to detect sources of this heterogeneity. This observation is consistent with previous meta-analyses on psychosocial interventions in LMICs (Barbui et al., 2020), suggesting the uncertain credibility of the evidence. Third, because of language barriers, local literature in LMICs was excluded, which could have biased our results. Fourth, most participants included in our analysis had a mean age of 20–35 years. Finally, we were not able to draw conclusions about the long-term treatment effect of digital psychological interventions, given that the follow-up periods were restricted to 6 months.

Several strengths of our analysis should be emphasised. First, the total number of participants involved in our meta-analysis ($n = 4104$) strengthened the reliability of our aggregated results. Second, the high quality of included studies and the low publication bias provide confidence in our overall result. Finally, our analysis provides data on the effect of digital psychological interventions in LMICs that can help researchers to compare results with those from studies done in HICs and can facilitate communication between various regions. Our study, as a timely quantitative synthesis, could help with the future planning of research in LMIC populations, in terms of mental health outcomes and digital psychological interventions.

The results of our analysis have clinical and policy implications. Our results suggest that digital psychological interventions can be incorporated in clinical practice to manage patients with depression. Second, psychological interventions delivered via a range of digital technologies could be useful clinically for patients aged 20–35 years with various mental health disorders. At the policy level, while more initiatives and investment are required from governmental as well as non-governmental organizations to ensure a sustainable health-care system, innovative and remotely delivered digital psychological interventions could make a valuable difference in treating mental health problems,

particularly during the COVID-19 pandemic. However, we need to remain aware of the potential risks of digital technology, and the unintended consequence of widening inequalities in mental health care between people who can and cannot get access to the internet and mobile devices, for example, children and older individuals, and extremely impoverished groups.

Suggested future directions for the research community include the rigorous evaluation of the effects of digital psychological interventions for specific mental health problems, particularly those that have been investigated in fewer than ten studies (i.e., anxiety, post-traumatic stress disorder, and substance misuse). Examining the long-term treatment effects of digital psychological interventions is also important, given the chronic nature of most mental health problems. Research is needed to identify specific moderators of treatment effects so that more precise and tailored interventions can be delivered. In addition, the inherent heterogeneity of the interventions, research contexts, and implementation approaches analyzed in our study suggest that comprehensive international guidance and standardized implementation programmes are needed to improve reproducibility and comparability.

In conclusion, the results of our systematic review and meta-analysis suggest that digital psychological interventions in mental health care hold promise in bridging the mental health-care gap in low-resource countries. This is particularly relevant during and after the COVID-19 pandemic, when physical distancing, the socioeconomic consequences of quarantine measures, and the loss of social support threaten public mental health.

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Table 1 Characteristics of studies included in the systematic review

Study	Outcome (measure)	Location	Population	Inclusion criteria	Follow-up	Study groups	Intervention details
Arjadi et al 2018	Depression (PHQ-9)	Indonesia	Community sample	Aged 16 years or older, a PHQ-9 score of ≥ 10 , and met the criteria for major depressive disorder or persistent depressive disorder according to the SCID-5	6 months	(1) Online intervention group: 159 participants (128 [81%] female) with a mean age of 24.5 years (SD 4.9). (2) Active control group: 154 participants (125 [81%] female) with a mean age of 24.5 years (SD 5.2).	(1) Online intervention group: participants used the ACT and FEEL online intervention programme based on Lewinsohn's behaviour activation theory; the programme consisted of eight weekly structured modules, involving psychoeducation on depression and basic skills of behaviour activation; the programme was guided by lay counsellors with supervision from clinical psychologists. (2) Active control group: participants had online psychoeducation, in which they obtained information about psychoeducation on depression and simple tips on how to handle the condition in general.
Burton et al 2016	Depression (BDI-II)	Multiple sites in Romania, Spain, and the UK	Clinic-based sample	Patients with major depressive disorder	2 weeks	(1) Online intervention group: 13 participants (10 [77%] female) with a mean age of 35.3 years (SD 12.1). (2) Treatment as usual group: 14 participants (8 [57%] female) with a mean age of 42.0 years (SD 10.3).	(1) Online intervention group: participants used Help4Mood, which consists of a personal monitoring system, a decision support system, and a virtual agent interface; the computer application can provide daily or weekly mood checks, identify negative or positive thoughts, and provide behavioural activation and relaxation exercises. (2) Treatment as usual group: participants attended an appointment with a local clinician once every 2 weeks.

Study	Outcome (measure)	Location	Population	Inclusion criteria	Follow-up	Study groups	Intervention details
Christoff et al 2015	Substance use (ASSIST)	Brazil	University sample	Scored as moderate-to-high risk of substance use on ASSIST	None	(1) Online intervention group: 128 participants (77 [60%] female) with a mean age of 24.0 years (SD 5.4). (2) Interview intervention questionnaire group: 106 participants (57 [54%] female) with a mean age of 23.0 years (SD 5.0). (3) Assessment-only group: 99 participants (58 [59%] female) with a mean age of 24 years (SD 5.7).	(1) Online intervention group: participants used a simple and rapid interactive website (ASSIST-MBic) that was constructed to mirror the content of the interview intervention; the website consisted of an initial screening questionnaire based on the self-report format of ASSIST, explanations of screening scores, and the inclusion of fictitious drug names. (2) Interview intervention: participants had a face-to-face motivational interview based on the WHO ASSIST manual, delivered by trained interviewers. (3) Assessment-only group: individuals were screened by use of the WHO ASSIST manual and received feedback about their scores.
D'Souza et al 2013	Schizophrenia symptoms (PANSS) and depression (CDS)	Multiple sites in India and the USA	Clinic-based sample	Patients aged 18–65 years, diagnosed with schizophrenia or schizoaffective disorder (by use of DSM-IV), and with at least 8 years of education	None	(1) Online intervention group: 27 participants. (2) Online intervention plus D-serine group: 24 participants. (3) D-serine group: 27 participants. (4) Active control group: 26 participants.	(1) Online intervention group: participants received cognitive retraining therapy for 5 h/week, 2–3 days per week, consisting of 20 computer-assisted tasks targeting attention, memory, verbal and visuospatial working memory, and executive function. (2) Online intervention group plus D-serine group: participants received cognitive retraining therapy combined with D-serine. (3) D-serine group: participants received D-serine alone. (4) Active

Study	Outcome (measure)	Location	Population	Inclusion criteria	Follow-up	Study groups	Intervention details
Darvish et al 2019	Post-traumatic stress disorder (SRS-PTSD)	Iran	Community sample	War veterans diagnosed with PTSD, who were aged <65 years	None	(1) Online intervention group: 28 participants with a mean age of 47.3 years (SD 3.57). (2) Treatment as usual group: 29 participants with a mean age of 48.4 years (SD 3.6).	control group: participants received a D-serine placebo and watched non-interactive, neutral videos of popular local television programmes. (1) Online intervention group: participants received daily SMS (text) messages for 6 months; the messages were written in Persian and focused on mental health improvement and the self-care needs of the patients; message content was decided on the basis of the opinions of both experts and patients. (2) Treatment as usual group: participants received routine psychiatric care in the clinic; all participants received multiple drugs (eg, SSRIs) and psychological consultation.
Durmaz et al 2019	Substance use (proportion of participants who abstained)	Turkey	Outpatient clinic	Patients who were older than 18 years, smoked at least one cigarette per day, wanted help to stop smoking, and used WhatsApp at least 4 days per week	1, 3, and 6 months	(1) Online intervention plus treatment as usual group: 44 participants (16 [36%] female) aged older than 18 years. (2) Treatment as usual group: 88 participants (36 [41%] female) aged older than 18 years.	(1) Online intervention plus treatment as usual group: aside from receiving usual care, participants were also sent daily WhatsApp messages according to their treatment plan, which involved having a plan of action and preventing relapse. (2) Treatment as usual group: participants received usual care by physicians in the clinic, involving a motivational interview or a 45-min face-to-face counselling session for quitting substance use.

Study	Outcome (measure)	Location	Population	Inclusion criteria	Follow-up	Study groups	Intervention details
Guo et al 2020	Depression (CES-D)	China	Hospital sample	Patients with HIV and depression, and a CES-D score ≥ 16	None	(1) Online intervention group: 150 participants (8 [5%] female) with a mean age of 28.0 years (SD 5.8). (2) Treatment as usual group: 150 participants (15 [10%] female) with a mean age of 28.6 years (SD 5.9).	(1) Online intervention group: participants received a 3-month intervention programme consisting of two major components; the first component included weekly SMS messages, greetings, and reminders about medication adherence and regular exercise; the second component consisted of short articles on disease management, which were sent via WeChat three times per week. (2) Treatment as usual group: participants received articles on nutrition via WeChat three times per week, and usual care for HIV treatment.
Knaevelsrud et al 2015	PTSD (PDS), anxiety (HSCL-25), and depression (HSCL-25)	Iran	Community sample	Participants with a PDS score of >11	None	(1) Online intervention group: 79 participants (60 [76%] female) with a mean age of 29.1 years (SD 8.2). (2) Wait-list control group: 80 participants (55 [69%] female) with a mean age of 27.2 years (SD 6.5).	(1) Online intervention group: participants received an internet-based intervention, in which they were assigned two structured writing activities each week over a 5-week period; there were three treatment phases; self-confrontation with the traumatic event, cognitive restructuring, and social sharing. (2) Wait-list control group: participants received no treatment for 6 weeks before they were given the same internet-based intervention as the online intervention group.
Liang et al 2018	Substance use (number of days of using primary	China	Community sample	Adults who had used heroin or	None	(1) Online intervention group: 49 participants (13	(1) Online intervention group: participants received surveys and text messages from S-Health, a self-

Study	Outcome (measure)	Location	Population	Inclusion criteria	Follow-up	Study groups	Intervention details
Liao et al 2016	drug of addiction each week	China	Community sample	other substances in the past 30 days		[27%] female) with a mean age of 41.7 years (SD 8.7). (2) Active control group: 25 participants (8 [32%] female) with a mean age of 41.3 years (SD 6.8).	management smartphone app; participants were asked to complete daily surveys at a time of their choosing, and they could also initiate a survey at any time or frequency by themselves; surveys in S-Health are designed to help patients to better identify triggers, recognise strategies for dealing with these situations, monitor substance use, and deal with cravings. (2) Active control group: participants received only text messages from S-Health (eg, about HIV prevention and other educational materials).
	Substance use (verified abstinence)			Daily smokers who were aged 18 years and older	None	(1) Online intervention group 1: 674 participants (33 [5%] female) with a mean age of 38.1 years (SD 9.7). (2) Online intervention group 2: 284 participants (17 [6%] female) with a mean age of 37.2 years (SD 9.8). (3) Active control group: 358 participants (24 [7%] female) with a mean age of 38.7 years (SD 9.8).	(1) Online intervention group 1: participants received high frequency text messaging (between three and five text messages per day until 12 weeks after the designated quit day) to motivate and increase behaviour change; after 12 weeks between three and five texts per week were sent. (2) Online intervention group 2: participants received low frequency text messaging (between three and five texts per week until 12 weeks after the designated quit day); after 12 weeks between one and two texts per week were sent. (3) Active control group: participants received one text per week thanking them for being in the study, providing study centre

Study	Outcome (measure)	Location	Population	Inclusion criteria	Follow-up	Study groups	Intervention details
Marasinghe et al 2012	Depression (BDI) and substance use (AUDIT)	Sri Lanka	Clinic-based sample	Being admitted to the hospital after attempting self-harm, aged 15–74 years, displaying significant suicidal intent at the interview or showing suicidal ideation (as assessed by the Beck scale)	6 months	(1) Face-to-face and remote intervention group: 34 participants (17 [50%] female) with a mean age of 30.0 years (SD 1.4). (2) Wait-list control group: 34 participants (17 [50%] female) with a mean age of 29.0 years (SD 1.4).	contact details, and reminding them of the time until the end of follow-up; after completion of the trial, the Happy Quit programme booklet was offered to each participant. (1) Face-to-face and remote intervention group: participants received a short two-phase mobile intervention involving a face-to-face component and distance follow-up component; the face-to-face component included assessment, meditation, and problem solving; distance follow-up included ten telephone calls post-discharge, continuous access to 5-min audio telephone messages, and weekly SMS reminders for up to 26 weeks. (2) Wait-list control group: participants received the same treatment as the intervention group 6 months after baseline (ie, when they had been discharged from hospital).
Moeini et al 2019	Depression (CES-D)	Iran	University sample	A CES-D score of 10–45	6 months	(1) Online intervention group: 64 female participants with a mean age of 16.2 years (SD 0.7). (2) Treatment as usual group: 64 female participants with a	(1) Online intervention group: participants received a web-based intervention involving CBT; the programme, named Dorehye Amozeshie Dokhtaran, contained seven core modules, including introduction and assessment, awareness-raising, positive psychology, problem-solving, thoughts and feelings, relaxation, physical exercise,

Study	Outcome (measure)	Location	Population	Inclusion criteria	Follow-up	Study groups	Intervention details
Mogoșe et al 2013	Depression (BDI-II)	Romania	University samples	Individuals with a BDI-II score of >12 at two consecutive assessments within a 2-week period	None	(1) Online intervention group: 20 participants. (2) Wait-list control group: 21 participants. Mean age of all participants was 22.9 years (SD 4.3).	and lifestyle modifications; text message reminders were sent to participants before each session. (2) Treatment as usual group: participants received the routine school curriculum (1) Online intervention group: participants received an email intervention involving seven scheduled daily sessions, each designed to last about 15 min; five positive and five negative written scenarios were used to train concrete processing; participants in the concreteness training group received two standard forms daily via email describing hypothetical events, one positive and one negative in valence. (2) Wait-list control group: participants received the seven scheduled daily sessions after the post-treatment assessment.
Salamanca-Sanabria et al 2020	Depression (PHQ-9)	Colombia	University samples	Individuals with a PHQ-9 score of 10–19 and who were aged older than 18 years	3 months	(1) Online intervention group: 21 participants with a mean age of 22.2 years (SD 5.4). (2) Wait-list control group: 54 participants with a mean age of 22.1 years (SD 3.9).	(1) Online intervention group: after cultural adaptation, participants received a web-based intervention comprising seven modules of CBT, including self-monitoring, behavioural activation, cognitive restructuring, and challenging core beliefs. (2) Wait-list control group: participants received no treatment until 7 weeks after enrollment.
Sanchez and Sanudo 2020 and	Substance use (AUDIT)	Brazil	Community sample	Nightclub patrons who reportes drinking in the past	None	(1) Online intervention group: 225 participants	(1) Online intervention group: participants received a web-based intervention of personalised normative

Study	Outcome (measure)	Location	Population	Inclusion criteria	Follow-up	Study groups	Intervention details
Baldin et al 2018				12 months and were considered to be in a high-risk group (AUDIT score of ≥ 8) or a low-risk group (AUDIT score of < 8)		(89 [40%] female) with a mean age of 25.8 years (SD 6.8). (2) Assessment-only group: 240 participants (76 [32%] female) with a mean age of 26.5 years (SD 5.7).	feedback consisting of four parts; the first was feedback on the AUDIT score at the investigated moment (with standardised information for each risk level); second was bar graphs comparing their episodic and weekly alcohol consumption with that of other people of the same age and sex in Brazil; third, a personalised estimate of expenditure on alcohol per month and per year; and fourth, general information with data to minimise the adverse consequences of alcohol consumption. (2) Assessment-only group: participants received no feedback after completing the data collection.
Su et al 2011	Internet addiction (YDQ and number of hours spent online per week)	China	University sample	Individuals with a YDQ score of 5 or higher, or high-risk internet-dependence (a YDQ score of 3–4), and being online for more than 14 h per week	None	(1) Online intervention in laboratory environment group: 17 participants (10 [59%] female). (2) Online intervention in natural environment group: 12 participants (8 [75%] female). (3) Non-interactive group: 14 participants (12	(1) Online intervention in laboratory environment group: participants received the online Expert System for internet addiction (HOSC), which was based on motivational interviewing procedures and a client-centered conversation style. It consisted of four models, including ready to start, understanding myself, goal of change, and methods of change. (2) Online intervention in natural environment group: participants received HOSC in their home or dormitory. (3) Non-interactive group: participants used an online non-interactive system (modified from HOSC) under

Study	Outcome (measure)	Location	Population	Inclusion criteria	Follow-up	Study groups	Intervention details
Thitipitchayana et al 2018	Post-partum depression (Stein's postpartum blues questionnaire)	Thailand	Hospital sample	Nulliparous mothers, aged 20–35 years, with a Stein's postpartum blues questionnaire score of 3 or higher and an Edinburgh perinatal depression scale score of less than 13	1, 2, and 3 months	(1) Audio group: 39 female participants with a mean age of 23.7 years (SD 3.8). (2) Treatment as usual group: 37 female participants with a mean age of 23.8 years (SD 4.3).	laboratory conditions with untailored feedback. (4) Wait-list group: 1 month after the baseline assessment, participants completed the post-treatment assessment and then received the HOSC intervention in the natural environment. (1) Audio group: participants received the Self-EAR programme, which includes self-empowerment, self-affirmation, and relaxation techniques; the programme was converted into audio files that were uploaded onto an MP3 digital device before it was provided to participants; participants completed the programme at home three times per day for 4 weeks. (2) Treatment as usual group: participants received regular and routine standard post-partum care.
Tiburcio et al 2018	Depression (PHQ-9) and substance use (ASSIST and ADAPT)	Mexico	Hospital sample	Patients with low-to-moderate risk of substance use	None	(1) Online intervention group: 9 participants (2 [22%] female). (2) ASSIST self-help and treatment as usual group: 12 participants (3 [25%] female). (3) Treatment as usual group: 10 participants (4 [40%] female).	(1) Online intervention group: participants received an 8-week web-based programme to be done for 1 h per week; the programme incorporated elements of the CBT approach, such as self-control techniques, functional analysis of substance use, exercises to identify high-risk situations, and action plans to cope with these situations; these CBT strategies were used to identify and transform the negative thoughts associated with depressive

Study	Outcome (measure)	Location	Population	Inclusion criteria	Follow-up	Study groups	Intervention details
Tulbure et al 2018	Social anxiety (LSAS-SR and SPIN) and depression (BDI-II)	Romania	Community sample	Individuals with a SPIN score of ≥ 19 , an LSAS-SR score of ≥ 30 , and who fulfilled the DSM-IV criteria for SAD on SPSQ	6 months	(1) Online intervention group: 38 participants (22 [58%] female) with a mean age of 30.6 years (SD 8.0). (2) Wait-list control group: 38 participants (23 [61%] female) with a mean age of 27.9 years (SD 7.8).	<p>symptomatology; in addition to the online intervention, a health professional also participated as a counsellor to accompany and motivate the participants. (2) ASSIST self-help and treatment as usual group: participants received two sessions of ASSIST learning guided by a counsellor and face-to-face CBT for six sessions. (3) Treatment as usual group: participants received face-to-face CBT for eight weekly sessions.</p> <p>(1) Online intervention group: participants received internet-based therapy with nine modules; participants were asked to answer essay questions, provide thoughts records, build anxiety hierarchies, describe their exposure exercise, and complete a weekly social anxiety measure; the programme included a psychoeducated introduction on social anxiety, negative automatic thoughts, challenging negative automatic thoughts, behaviour experiments, exposure and self-focus attention, exposure and getting closer to your fears, social skills, and the maintenance plan. (2) Wait-list control group: participants received no active treatment during the 9-week interval and were only asked to complete a</p>

Study	Outcome (measure)	Location	Population	Inclusion criteria	Follow-up	Study groups	Intervention details
Tulbure et al 2018	Depression (BDI-II) and anxiety (BAI)	Romania	Community sample	Individuals with a BDI-II score of 14–50 and a current diagnosis of major depressive disorder or dysthymia by SCID-I	None	(1) Conventional internet-based CBT group: 34 participants (30 [88%] female) with a mean age of 29.2 years. (2) Religious internet-based CBT group: 19 participants (16 [84%] female) with a mean age of 32.2 years. (3) Wait-list control group: 26 participants (19 [73%] female).	weekly social anxiety measure (LSAS-SR). (1) Conventional internet-based CBT group: participants were given weekly CBT sessions for 9 weeks; the standard component consisted of the core CBT approach for depression with behavioural activation, cognitive restructuring, and sleep improvement techniques; the non-standard component consisted of stress-related growth, forgiveness, altruism, and gratitude techniques; weekly feedback was provided by graduate students under the supervision of a clinical psychologist. (2) Religious internet-based CBT: participants received the same protocol as the conventional group, except that the framework used to augment the CBT intervention was tailored to accommodate the participant's philosophical or religious beliefs. (3) Wait-list control group: participants were asked to complete a weekly measure of depression symptoms (BDI-II) for 9 weeks.
Wang et al 2013	Post-traumatic stress disorder (PDS)	China	Community sample (urban setting)	Individuals with at least two PTSD symptoms in the trauma screening questionnaire	3 months	(1) Online intervention group: 46 participants. (2) Wait-list control group: 44 participants. Overall,	(1) Online intervention group: participants used the web-based intervention My Trauma Recovery, which is a self-help trauma intervention programme consisting of six modules of social support, self-talk, relaxation, identifying trauma triggers,

Study	Outcome (measure)	Location	Population	Inclusion criteria	Follow-up	Study groups	Intervention details
Wang et al 2013	Post-traumatic stress disorder (PDS)	China	Community sample (rural setting)	Individuals with at least two PTSD symptoms in the trauma screening questionnaire	3 months	(1) Online intervention group: 49 participants. (2) Wait-list control group: 44 participants. Overall, participants (76 [82%] female) were aged 25–70 years.	unhelpful coping mechanisms, and professional help. (2) Wait-list control group: participants did not receive any treatment for 1 month before receiving (1) Online intervention group: participants used the web-based intervention My Trauma Recovery, which is a self-help trauma intervention programme consisting of six modules of social support, self-talk, relaxation, identifying trauma triggers, unhelpful coping mechanisms, and professional help. (2) Wait-list control group: participants did not receive any treatment for 1 month before receiving the same intervention as the online intervention group.
Yang et al 2019	Depression (PHQ-9) and anxiety (GAD-7)	China	Hospital sample	Patients with a PHQ-9 score of >4 or GAD-7 score of >4	None	(1) Online intervention group: 52 female participants with a mean age of 31.3 years (SD 5.0). (2) Treatment as usual group: 50 female participants with a mean age of 30.4 years (SD 3.9).	(1) Online intervention group: participants underwent an 8-week mindfulness intervention programme done on the WeChat platform; the programme included theoretical guidance and meditation practice as primary parts. (2) Treatment as usual group: participants received antepartum health education related to childbirth, breastfeeding, nutrition, and parenting, emotion management skills through lectures, and psychoeducation on depression and anxiety.

Study	Outcome (measure)	Location	Population	Inclusion criteria	Follow-up	Study groups	Intervention details
Zhu et al 2018	Substance use (DSM-5 clinical interview)	China	Community sample	Met DSM-5 diagnosis criteria for moderate or severe methamphetamine use disorder, and no current use of methamphetamine or any other substances (except nicotine) for at least 7 days	None	(1) Online intervention plus treatment as usual group: 20 male participants with a mean age of 32.7 years (SD 5.3). (2) Treatment as usual group: 20 male participants with a mean age of 35.1 (SD 8.0).	(1) Online intervention plus treatment as usual group: the CCAT app consisted of four cognitive training tasks, including two working memory training tasks, and two methamphetamine-related attention bias control training tasks; the training programme lasted for 4 weeks (20 sessions); participants also received detoxification treatment. (2) Treatment as usual group: participants received regular detoxification treatment in drug rehabilitation centres.

Notes: PHQ-9=Patient Health Questionnaire-9. SCID-5=Structured Clinical Interview for DSM-5. BDI-II=Beck Depression Inventory-II. ASSIST=Alcohol, Smoking, and Substance Involvement Screening Test. ASSIST/MBIC=Alcohol, Smoking and Substance Involvement Screening Test-Motivational Brief Intervention by computer. PANSS=Positive and Negative Syndrome Scale. CDS=Calgary Depression Scale. SRS-PTSD=Self-Rating Scale for post-traumatic stress disorder. CES-D=Centre of Epidemiology Scale-Depression. HSCL=Hopkins Symptom Checklist. PDS=Post-traumatic Stress Diagnostic Scale. CBT=Cognitive Behavioural Therapy. AUDIT=Alcohol Use Disorders Identification Test. YDQ=Young's Diagnostic Questionnaire. HOSC=Healthy Online Self-helping Centre. Self-EAR=Self-Empowerment-Affirmation-Relaxation. LSAS-SR=Liebowitz Social Anxiety Scale-Self Report version. SPIN=Social Phobia Inventory. SAD=social anxiety disorder. SPSQ=Social Phobia Screening Questionnaire. BAJ=Beck Anxiety Inventory. GAD=Generalised Anxiety Disorder Scale. CCAT=Computerised Cognitive Addiction Therapy

Table 2: Subgroup analysis of digital psychological interventions compared with control groups

Subgroup	n	<i>g</i> [95%CI]	<i>R</i> (%) [95%CI]	<i>p</i>
Psychological symptoms				0.221
Anxiety	4	0.81[0.48, 1.14]	59% [0, 86]	
Depression	14	0.57[0.41, 0.73]	53% [15, 75]	
PTSD	3	0.8[0.6, 1]	0% [0, 88]	
Substance use	7	0.53[0.18, 0.88]	77% [52, 89]	
Intervention format				0.722
APP	6	0.67[0.46, 0.88]	37% [0, 75]	
Web	10	0.59[0.35, 0.83]	84% [73, 91]	
Others	6	0.56[0.32, 0.8]	78% [60, 87]	
Control group				0.137
Active control	4	0.43[0.23, 0.64]	22% [0, 88]	
TAU	8	0.54[0.35, 0.73]	54% [0, 79]	
WLC/Assessment only	10	0.72[0.45, 0.97]	84% [72, 91]	
Theoretical orientation of intervention				0.891
Behavior theory	6	0.59[0.28, 0.9]	83% [64, 92]	
Cognitive theory	15	0.61[0.45, 0.77]	64% [37, 79]	
Problem-solving	1	NA	NA	
Missing values analysis				0.74
Complete case	6	0.52[0.2, 0.84]	53% [0, 81]	
ITT	11	0.65[0.5, 0.81]	63% [30, 81]	
Nr	5	0.57[0.16, 0.98]	85% [66, 93]	
Presence of guidance				0.998
No	8	0.6[0.35, 0.86]	77% [55, 89]	
Yes	14	0.61[0.43, 0.78]	67% [43, 81]	
Recruitment setting				0.54
Community	8	0.69[0.51, 0.86]	57% [6, 80]	
Hospital	8	0.55[0.35, 0.74]	57% [7, 81]	
University	5	0.72[0.25, 1.2]	76% [41, 90]	
Nightclubs	1	NA	NA	
Region				0.983
Asian	13	0.64[0.5, 0.78]	57% [21, 77]	
Latin America	4	0.58[-0.02, 1.19]	88% [73, 95]	
Multisite	2	NA	NA	
Others	3	0.63[0.14, 1.11]	73% [11, 92]	
Quality of study				0.484
High	10	0.66[0.48, 0.84]	58% [15, 79]	
Other	12	0.56[0.33, 0.79]	78% [61, 87]	
Diagnosis at baseline				0.812
Yes	6	0.57[0.28, 0.86]	7% [29, 87]	
No	16	0.61[0.44, 0.79]	76% [61, 85]	

Note: NA = not available;

Reference

- Amoroso, C., Flores Arango, J., & Bailey, C. (2011). Call to action on global eHealth evaluation. In Consensus statement of the who global eHealth evaluation meeting bellagio. The bellagio eHealth evaluation group.
- Andersson, G. (2016). Internet-Delivered Psychological Treatments. *Annu Rev Clin Psychol*, 12, 157–179. <https://doi.org/10.1146/annurev-clinpsy-021815-093006>
- Arjadi, R., Nauta, M. H., Chowdhary, N., & Bockting, C. L. H. (2015). A systematic review of online interventions for mental health in low and middle income countries: a neglected field. *Glob Ment Health (Camb)*, 2, e12. <https://doi.org/10.1017/gmh.2015.10>
- Arjadi, R., Nauta, M. H., Scholte, W. F., Hollon, S. D., Chowdhary, N., Suryani, A. O., ... Bockting, C. L. H. (2018). Internet-based behavioural activation with lay counsellor support versus online minimal psychoeducation without support for treatment of depression: a randomised controlled trial in Indonesia. *Lancet Psychiatry*, 5(9), 707–716. [https://doi.org/10.1016/S2215-0366\(18\)30223-2](https://doi.org/10.1016/S2215-0366(18)30223-2)
- Baldin, Y. C., Sanudo, A., & Sanchez, Z. M. (2018). Effectiveness of a web-based intervention in reducing binge drinking among nightclub patrons. *Rev Saude Publica*, 52, 2. <https://doi.org/10.11606/s1518-8787.2018052000281>
- Balshem, H., Helfand, M., Schünemann, H. J., Oxman, A. D., Kunz, R., Brozek, J., ... others. (2011). GRADE guidelines: 3. Rating the quality of evidence. *Journal of Clinical Epidemiology*, 64(4), 401–406.
- Bank, T. W. (n.d.). (T. W. Bank, Ed.). The World Bank: The World Bank. Retrieved from <https://data.worldbank.org/income-level/low-and-middle-income>
- Barak, A., Hen, L., Boniel-Nissim, M., & Shapira, N. (2008). A Comprehensive Review and a Meta-Analysis of the Effectiveness of Internet-Based Psychotherapeutic Interventions. *Journal of Technology in Human Services*, 26(2-4), 109–160. <https://doi.org/10.1080/15228830802094429>
- Barbui, C., Purgato, M., Abdulmalik, J., Acarturk, C., Eaton, J., Gastaldon, C., ... Thornicroft, G. (2020). Efficacy of psychosocial interventions for mental health outcomes in low-income and middle-income countries: an umbrella review. *Lancet Psychiatry*, 7(2), 162–172. [https://doi.org/10.1016/S2215-0366\(19\)30511-5](https://doi.org/10.1016/S2215-0366(19)30511-5)
- Baumeister, H., Reichler, L., Munzinger, M., & Lin, J. (2014). The impact of guidance on Internet-based mental health interventions — A systematic review. *Internet Interventions*, 1(4), 205–215. <https://doi.org/10.1016/j.invent.2014.08.003>
- Brooks, S. K., Webster, R. K., Smith, L. E., Woodland, L., Wessely, S., Greenberg, N., & Rubin, G. J. (2020). The psychological impact of quarantine and how to reduce it: rapid review of the evidence. *Lancet*, 395(10227), 912–920. [https://doi.org/10.1016/S0140-6736\(20\)30460-8](https://doi.org/10.1016/S0140-6736(20)30460-8)
- Burton, C., Szentagotai Tatar, A., McKinstry, B., Matheson, C., Matu, S., Moldovan, R., ... Help4Mood, C. (2016). Pilot randomised controlled trial of Help4Mood, an embodied virtual agent-based system to support treatment of depression. *J Telemed Telecare*, 22(6), 348–355. <https://doi.org/10.1177/1357633X15609793>
- Chisholm, D., Sweeny, K., Sheehan, P., Rasmussen, B., Smit, F., Cuijpers, P., & Saxena, S. (2016). Scaling-up treatment of depression and anxiety: a global return on investment analysis. *Lancet Psychiatry*, 3(5), 415–424. [https://doi.org/10.1016/S2215-0366\(16\)30024-4](https://doi.org/10.1016/S2215-0366(16)30024-4)
- Christoff Ade, O., & Boerngen-Lacerda, R. (2015). Reducing substance involvement in college students: a three-arm parallel-group randomized controlled trial of a computer-based intervention. *Addict Behav*, 45, 164–171. <https://doi.org/10.1016/j.addbeh.2015.01.019>
- Clarke, K., King, M., & Prost, A. (2013). Psychosocial interventions for perinatal common mental disorders delivered by providers who are not mental health specialists in low- and middle-

- income countries: a systematic review and meta-analysis. *PLoS Med*, 10(10), e1001541. <https://doi.org/10.1371/journal.pmed.1001541>
- Darvish, A., Khodadadi-Hassankiadeh, N., Abdoosti, S., & Ghapandar Kashani, M. (2019). Effect of Text Messaging-based Psychiatric Nursing Program on Quality of Life in Veterans with Post-Traumatic Stress Disorder: A Randomized Controlled Trial. *Int J Community Based Nurs Midwifery*, 7(1), 52–62. Retrieved from <https://www.ncbi.nlm.nih.gov/pubmed/30643833>
- Deeks, J. J., Higgins, J. P., Altman, D. G., & Group, C. S. M. (2019). Analysing data and undertaking meta-analyses. *Cochrane Handbook for Systematic Reviews of Interventions*, 241–284.
- D’Souza, D. C., Radhakrishnan, R., Perry, E., Bhakta, S., Singh, N. M., Yadav, R., ... Andrade, C. (2013). Feasibility, safety, and efficacy of the combination of D-serine and computerized cognitive retraining in schizophrenia: an international collaborative pilot study. *Neuropsychopharmacology*, 38(3), 492–503. <https://doi.org/10.1038/npp.2012.208>
- Durmaz, S., Ergin, I., Durusoy, R., Hassoy, H., Caliskan, A., & Okyay, P. (2019). WhatsApp embedded in routine service delivery for smoking cessation: effects on abstinence rates in a randomized controlled study. *BMC Public Health*, 19(1), 387. <https://doi.org/10.1186/s12889-019-6727-z>
- GBD Collaborators (2018). Global, regional, and national comparative risk assessment of 84 behavioural, environmental and occupational, and metabolic risks or clusters of risks for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017.
- Guo, Y., Hong, Y. A., Cai, W., Li, L., Hao, Y., Qiao, J., ... Penedo, F. J. (2020). Effect of a WeChat-Based Intervention (Run4Love) on Depressive Symptoms Among People Living With HIV in China: A Randomized Controlled Trial. *J Med Internet Res*, 22(2), e16715. <https://doi.org/10.2196/16715>
- Higgins, J. P. T., Altman, D. G., Gøtzsche, P. C., Jüni, P., Moher, D., Oxman, A. D., ... Sterne, J. A. C. (2011). The Cochrane Collaboration’s tool for assessing risk of bias in randomised trials. *Bmj*, 343, d5928.
- Holmes, E. A., Ghaderi, A., Harmer, C. J., Ramchandani, P. G., Cuijpers, P., Morrison, A. P., ... Craske, M. G. (2018). The Lancet Psychiatry Commission on psychological treatments research in tomorrow’s science. *Lancet Psychiatry*, 5(3), 237–286. [https://doi.org/10.1016/S2215-0366\(17\)30513-8](https://doi.org/10.1016/S2215-0366(17)30513-8)
- Holmes, E. A., O’Connor, R. C., Perry, V. H., Tracey, I., Wessely, S., Arseneault, L., ... Everall, I. (2020). Multidisciplinary research priorities for the COVID-19 pandemic: a call for action for mental health science. *The Lancet Psychiatry*.
- Huckvale, K., Prieto, J. T., Tilney, M., Benghozi, P. J., & Car, J. (2015). Unaddressed privacy risks in accredited health and wellness apps: a cross-sectional systematic assessment. *BMC Med*, 13(1), 214. <https://doi.org/10.1186/s12916-015-0444-y>
- Jimenez-Molina, A., Franco, P., Martinez, V., Martinez, P., Rojas, G., & Araya, R. (2019). Internet-Based Interventions for the Prevention and Treatment of Mental Disorders in Latin America: A Scoping Review. *Frontiers in Psychiatry*, 10(664). <https://doi.org/ARTN 664 10.3389/fpsy.2019.00664>
- Knaevelsrud, C., Brand, J., Lange, A., Ruwaard, J., & Wagner, B. (2015). Web-Based Psychotherapy for Posttraumatic Stress Disorder in War-Traumatized Arab Patients: Randomized Controlled Trial. *J Med Internet Res*, 17(3), e71. <https://doi.org/ARTN e71 10.2196/jmir.3582>
- Liang, D., Han, H., Du, J., Zhao, M., & Hser, Y. I. (2018). A pilot study of a smartphone application supporting recovery from drug addiction. *J Subst Abuse Treat*, 88, 51–58. <https://doi.org/10.1016/j.jsat.2018.02.006>
- Liao, Y., Wu, Q., Tang, J., Zhang, F., Wang, X., Qi, C., ... Cohen, J. (2016). The efficacy of mobile phone-based text message interventions (‘Happy Quit’) for smoking cessation in China. *BMC Public Health*, 16(1), 833. <https://doi.org/10.1186/s12889-016-3528-5>

- Marasinghe, R. B., Edirippulige, S., Kavanagh, D., Smith, A., & Jiffry, M. T. (2012). Effect of mobile phone-based psychotherapy in suicide prevention: a randomized controlled trial in Sri Lanka. *Journal of Telemedicine and Telecare*, 18(3), 151–155. <https://doi.org/10.1258/jtt.2012.SFT107>
- Martinez, P., Rojas, G., Martinez, V., Lara, M. A., & Perez, J. C. (2018). Internet-based interventions for the prevention and treatment of depression in people living in developing countries: A systematic review. *J Affect Disord*, 234, 193–200. <https://doi.org/10.1016/j.jad.2018.02.079>
- Moeini, B., Bashirian, S., Soltanian, A. R., Ghaleiha, A., & Taheri, M. (2019). Examining the Effectiveness of a Web-Based Intervention for Depressive Symptoms in Female Adolescents: Applying Social Cognitive Theory. *J Res Health Sci*, 19(3), e00454. Retrieved from <https://www.ncbi.nlm.nih.gov/pubmed/31586376>
- Mogoșe, C., Brăilean, A., & David, D. (2013). Can concreteness training alone reduce depressive symptoms? A randomized pilot study using an internet-delivered protocol. *Cognitive Therapy and Research*, 37(4), 704–712.
- Naslund, J. A., Aschbrenner, K. A., Kim, S. J., McHugo, G. J., Unutzer, J., Bartels, S. J., & Marsch, L. A. (2017). Health behavior models for informing digital technology interventions for individuals with mental illness. *Psychiatr Rehabil J*, 40(3), 325–335. <https://doi.org/10.1037/prj0000246>
- Pasarelu, C. R., Andersson, G., Bergman Nordgren, L., & Dobrean, A. (2017). Internet-delivered transdiagnostic and tailored cognitive behavioral therapy for anxiety and depression: a systematic review and meta-analysis of randomized controlled trials. *Cogn Behav Ther*, 46(1), 1–28. <https://doi.org/10.1080/16506073.2016.1231219>
- Patel, V., Araya, R., Chatterjee, S., Chisholm, D., Cohen, A., De Silva, M., ... Ommeren, M. van. (2007). Treatment and prevention of mental disorders in low-income and middle-income countries. *Lancet*, 370(9591), 991–1005. [https://doi.org/10.1016/S0140-6736\(07\)61240-9](https://doi.org/10.1016/S0140-6736(07)61240-9)
- Preti, A. (2017). How to calculate the number needed to treat (NNT) from Cohen's d or Hedges' g.
- Prince, M., Patel, V., Saxena, S., Maj, M., Maselko, J., Phillips, M. R., & Rahman, A. (2007). Global mental health 1 - No health without mental health. *Lancet*, 370(9590), 859–877. [https://doi.org/10.1016/S0140-6736\(07\)61238-0](https://doi.org/10.1016/S0140-6736(07)61238-0)
- Salamanca-Sanabria, A., Richards, D., Timulak, L., Connell, S., Mojica Perilla, M., Parra-Villa, Y., & Castro-Camacho, L. (2020). A Culturally Adapted Cognitive Behavioral Internet-Delivered Intervention for Depressive Symptoms: Randomized Controlled Trial. *JMIR Ment Health*, 7(1), e13392. <https://doi.org/10.2196/13392>
- Sanchez, Z. M., & Sanudo, A. (2018). Web-based alcohol intervention for nightclub patrons: Opposite effects according to baseline alcohol use disorder classification. *Substance Abuse*, 39(3), 361–370. <https://doi.org/10.1080/08897077.2018.1437586>
- Sander, L., Rausch, L., & Baumeister, H. (2016). Effectiveness of Internet-Based Interventions for the Prevention of Mental Disorders: A Systematic Review and Meta-Analysis. *JMIR Ment Health*, 3(3), e38. <https://doi.org/10.2196/mental.6061>
- Saxena, S., Thornicroft, G., Knapp, M., & Whiteford, H. (2007). Resources for mental health: scarcity, inequity, and inefficiency. *Lancet*, 370(9590), 878–889. [https://doi.org/10.1016/S0140-6736\(07\)61239-2](https://doi.org/10.1016/S0140-6736(07)61239-2)
- Singla, D. R., Kohrt, B. A., Murray, L. K., Anand, A., Chorpita, B. F., & Patel, V. (2017). Psychological Treatments for the World: Lessons from Low- and Middle-Income Countries. *Annu Rev Clin Psychol*, 13, 149–181. <https://doi.org/10.1146/annurev-clinpsy-032816-045217>
- Su, W., Fang, X., Miller, J. K., & Wang, Y. (2011). Internet-based intervention for the treatment of online addiction for college students in China: a pilot study of the Healthy Online Self-helping Center. *Cyberpsychol Behav Soc Netw*, 14(9), 497–503. <https://doi.org/10.1089/cyber.2010.0167>
- Thitipitchayanant, K., Somrongsong, R., Kumar, R., & Kanchanakharn, N. (2018). Effectiveness of self-empowerment-affirmation-relaxation (Self-EAR) program for postpartum blues mothers: A

- randomize controlled trial. *Pak J Med Sci*, 34(6), 1488–1493.
<https://doi.org/10.12669/pjms.346.15986>
- Tiburcio, M., Lara, M. A., Martinez, N., Fernandez, M., & Aguilar, A. (2018). Web-Based Intervention to Reduce Substance Abuse and Depression: A Three Arm Randomized Trial in Mexico. *Subst Use Misuse*, 53(13), 2220–2231. <https://doi.org/10.1080/10826084.2018.1467452>
- Tulbure, B. T., Andersson, G., Salagean, N., Pearce, M., & Koenig, H. G. (2018). Religious versus Conventional Internet-based Cognitive Behavioral Therapy for Depression. *J Relig Health*, 57(5), 1634–1648. <https://doi.org/10.1007/s10943-017-0503-0>
- UN. (2020). Policy brief: COVID-19 and the need for action on mental health. <https://unsdg.un.org/Resources/Policy-Brief-Covid-19-and-Need-Action-Mental-Health>.
- Wang, Z., Wang, J., & Maercker, A. (2013). Chinese My Trauma Recovery, a Web-based intervention for traumatized persons in two parallel samples: randomized controlled trial. *J Med Internet Res*, 15(9), e213. <https://doi.org/10.2196/jmir.2690>
- World Bank Group. (2016). World development report 2016: Digital dividends. World Bank Publications.
- World Health Organization. WHO guideline: recommendations on digital interventions for health system strengthening. (2019).
- Xiang, Y. T., Jin, Y., & Cheung, T. (2020). Joint International Collaboration to Combat Mental Health Challenges During the Coronavirus Disease 2019 Pandemic. *JAMA Psychiatry*.
<https://doi.org/10.1001/jamapsychiatry.2020.1057>
- Yang, M., Jia, G., Sun, S., Ye, C., Zhang, R., & Yu, X. (2019). Effects of an Online Mindfulness Intervention Focusing on Attention Monitoring and Acceptance in Pregnant Women: A Randomized Controlled Trial. *J Midwifery Womens Health*, 64(1), 68–77.
<https://doi.org/10.1111/jmwh.12944>
- Zhu, Y. W., Jiang, H. F., Su, H., Zhong, N., Li, R. J., Li, X. T., ... Zhao, M. (2018). A Newly Designed Mobile-Based Computerized Cognitive Addiction Therapy App for the Improvement of Cognition Impairments and Risk Decision Making in Methamphetamine Use Disorder: Randomized Controlled Trial. *JMIR mHealth and uHealth*, 6(6), e10292. <https://doi.org/ARTN10292> 10.2196/10292

Chapter 4

Psychological interventions for depression in Chinese university students: A systematic review and meta-analysis

Fu, Z., Zhou, S., Burger, H., Bockting, C. L., & Williams, A. D. (2020). Psychological interventions for depression in Chinese university students: A systematic review and meta-analysis. *Journal of affective disorders*, 262, 440-450.

Abstract

Background:

University students in China are vulnerable to depression with a high estimated prevalence. However, it is currently unknown which types of psychological interventions are being delivered to treat depression in this population and whether they are effective. Therefore, a systematic review was conducted to examine the types and effects of psychological interventions on depression amongst Chinese university students.

Methods:

We searched records in English databases (PubMed, PsychINFO, Cochrane, and Embase) and Chinese databases (Weipu, Wanfang, CNKI) published up to January 2019.

Results:

From 2,739 records, we identified 39 randomized controlled trials (RCT) and 54 non-RCT articles. A range of psychological interventions were identified including cognitive behaviour therapy (CBT), interpersonal therapy (IPT), as well as some local interventions. Hedge's g pooled effect size of 23 comparisons from 21 RCTs ($N=858$) compared to a control group (e.g., waitlist, assessment only, treatment as usual, placebo; $N = 802$) was 1.08 (95% CI: 0.72 to 1.45). Heterogeneity was moderate with $I^2 = 47$ (95%CI: 14 to 68). Three RCTs had low risk of bias. Publication bias was present. The effect sizes pooled from 10 RCTs comparing different interventions were not significant.

Limitations:

In addition to potential publication bias, high risk of bias of inclusions limited interpretation of the results.

Conclusions:

Collectively, there is evidence that psychological interventions for depression in Chinese university students are effective as compared to control groups, although the effects merit further examination by research of higher quality. Innovations in treatment delivery could facilitate wider dissemination of evidence-based interventions.

Introduction

Depression is a prevalent mental health condition predicted to be the leading cause of disease burden by 2020 (Ferrari et al., 2013). It is characterised by loss of interest or pleasure in daily activities and depressed mood. Along with other cognitive and somatic symptoms, depression can cause significant distress and have impact on multiple aspects of individuals' life (Marcus et al., 2012).

One population that might be particularly vulnerable is university students (Auerbach et al., 2018). University students are in a period of life in which they grow from adolescents to adults denoted as “emerging adulthood” (Arnett, 2000), during which adolescents explore their identities and possible directions in life, and slowly come into contact with their future responsibilities. During this crucial stage, university students can experience substantial stress due to academic pressures, interpersonal relationships, and preoccupation with post-graduation life (Bayram and Bilgel, 2008). On top of their regular academic demands, university students have to cope with challenges connected to the development of an autonomous personal life both in psychological and psychosocial domains. These accumulated stresses could jeopardize the mental health status of this group and increase the likelihood of depression.

Depression can be detrimental to the college students' life in many aspects including their physical and emotional health (Bardone et al., 1998; Hare et al., 2014), relationship dysfunction (Kerr and Capaldi, 2011), academic achievement (Hysenbegasi et al., 2005), and can be a contributing factor that leads to suicide (Wang et al., 2014). Furthermore, depression in the early adulthood is associated with far-reaching adverse outcomes in later adulthood like labour market marginalization, and persistent physical health problems (Li et al., 2014; Scott et al., 2016).

Evidence supports the high prevalence of depression in this population. From a large-scaled survey among the university students worldwide, 18.5% had major depression episodes in the last 12 months, which was higher than the 12-month prevalence in general young adults aged 18-25 years old (9.6%) (Auerbach et al., 2016; Mojtabai et al., 2016). A recent meta-analysis concluded that around 30% of college students worldwide report depressive symptoms (Ibrahim et al., 2013). In China, with the large increases of college enrolment, around 28 million students are on campus now (*China Health and Family Planning Statistics Yearbook*, 2018). Recent epidemiology data from a meta-analysis of prevalence in China revealed that the occurrence of depressive symptoms in university

students was also in a parallel level with point prevalence around 24% (Lei et al., 2016).

Depression among Chinese university students has become a salient problem, emphasizing the necessity to examine factors that are uniquely related to depression in this population, and to provide suitable interventions to mitigate depression symptoms among university students (Evans-Lacko and Thornicroft, 2019; Parker et al., 2001). With the increasing awareness of the depression prevalence in Chinese students, professional counselling centers situated inside the campus have become a standard configuration in Chinese universities and more studies on psychological interventions have been done in this group. However, these centres offer psychological interventions that vary in theoretical orientation and format and are not necessarily aligned with evidence-based interventions recommended in Western clinical guidelines, such as the National Institute for Health and Care Excellence (NICE; Middleton et al., 2005). For example, Zhongyong psychoeducation (which has roots in traditional Chinese philosophy) is concurrently delivered alongside evidence-based psychotherapies such as cognitive behavior therapy (CBT) in some Chinese universities (Cui et al., 2016; Yang et al., 2016). The effectiveness of the combination of these interventions still remains unclear.

Previous reviews focused on interventions delivered in low and middle-income countries have identified several randomized controlled trials conducted in China. However, they did not specifically assess effectiveness amongst university students and only included articles in English language (Arjadi et al., 2015; Cuijpers et al., 2018, 2016). Therefore, it is currently unknown to what extent different psychological interventions are being implemented to treat depression amongst the Chinese university students, and more importantly, whether or not they are effective. Thus, in an effort to fill this gap, we conducted a systematic review and meta-analysis of RCTs to examine the effectiveness of psychological interventions when delivered to university students in China. To provide an overview of the different types of psychological interventions being delivered, we also conducted a qualitative synthesis of psychological interventions investigated in other types of study designs (e.g., pre-post, non-randomized controlled trial, case study).

Methods

The current systematic review and meta-analysis was registered on PROSPERO (<https://www.crd.york.ac.uk/PROSPERO/>) with registration number CRD42018088221. The Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) were

followed (Moher et al., 2009).

Identification and selection of studies

A comprehensive search in four international databases (PubMed, PsycINFO, Cochrane, and Embase) and three Chinese local academic databases (Weipu, Chinese Academic Journals (CNKI), Wanfang) was performed up to December, 2017 and updated in January, 2019. The search terms combined Mesh terms and text words (wildcards were used if necessary) indicative of (1) depression, (2) intervention, (3) China, and (4) university students. The full search string can be found in Appendix 3A of the supplementary material. Reference lists of relevant reviews and included articles in the current review were examined. The articles citing the included articles were also examined in case of missing studies beyond the period in which the initial search was carried out.

Studies were included eligible if the following criteria were fulfilled:

- a) The primary focus of the psychological intervention should be depression;
- b) 'psychological intervention' herein was broadly interpreted as any intervention in which a psychological element was involved according to the description of the articles;
- c) a measure of depressive symptom severity was used as an outcome;
- d) only studies with participants from universities situated in the mainland of China, HongKong, Macau, and Taiwan were included; publications in Chinese or English were all included.

Unpublished data of any form including dissertations, conference proceedings were excluded. When multiple publications with available data from the same study cohort were available, the publications with longest period of follow-up length were included. If equal, the studies with largest number of total participants were included.

Covidence (<https://www.covidence.org>) was used for importing the initially identified records from the databases and for removing duplicates. Title/Abstract screening, full text screening, and data extraction of records were conducted by two researchers (SZ and ZF) independently. Disagreements were resolved with the help of a senior reviewer (AW).

Data extraction and risk of bias assessment

The following information was extracted:

- (1) Identification: name of first author, publication year;
- (2) Study population: sample size, gender distribution, age, geographical.
- (3) Research design: type of research design ((pair-matched, cluster, individual) random controlled trials, control before-and-after with/without control studies,

- case control study, case series), inclusion/exclusion criteria, intervention details (setting, manual/theoretical foundation, guidance and delivery, follow-up length);
- (4) Methodological and Statistical: measure of depression, effect size definition (including post-test and follow-up data after intervention), incomplete data handling (per protocol, intent to treat analysis)

If a study met the inclusion criteria but reported insufficient data to calculate effect sizes, the corresponding authors were requested to provide the aggregate data. Studies were excluded in the available meta-analysis if the data were not provided.

The Cochrane risk of bias tool was used to assess the quality of the included RCT studies (Higgins et al., 2011). The following domains were addressed: random sequence generation, allocation concealment, blinding of participants and personnel (participants were not aware of what condition they were allocated), blinding of outcome assessment, incomplete outcome data, and selective reporting. Two independent researchers (ZF and SZ) assessed these domains independently and disagreements were solved with discussion. Each domain was rated as '+' (low risk of bias with score 1), '?' (unclear with score 0), '-' (high risk of bias with score 0). An article was defined as "high quality" when it scored 60% or more of the maximal possible score (max score = 6). In this case, 4 or more indicated low risk of bias (i.e. high quality) and lower than 4 indicated high risk of bias (low quality). Grading of Recommendations Assessment, Development and Evaluation (GRADE) systems was adopted to evaluate the overall confidence of the included studies in the available meta-analysis.

Analyses

Comprehensive Meta-Analysis software (CMA, Version 3; Borenstein et al., 2013) was used to calculate the pooled effect sizes on post-intervention comparisons between intervention and control groups if enough randomized controlled trials could be retrieved. We calculated effect sizes (Hedges' g) for each comparison between a psychological intervention and a comparison group. In case of more than one depression measure, the outcomes of different measures were combined within the study via the calculation in CMA, so that each study contributed one effect size to the overall analysis. Number-needed-to-treat (NNT) was calculated to facilitate clinical interpretation of the effect size (Preti, 2015). The NNT indicates how many patients should receive the treatment to have one more positive outcome than the comparison group.

If applicable, two meta-analyses were conducted according to the type of comparison group. We categorized the comparison group into two primary types: control group

(including treatment as usual, assessment only, waitlist, other non-psychological treatment, and active control) and other psychological/medication intervention group.

Because we expected considerable heterogeneity (variation in study outcomes between studies), we a priori chose a random effects pooling model in all analyses (Borenstein et al., 2009). We analysed the effect sizes at post-intervention and excluded the follow-up results since not all studies had a follow-up assessment, and the follow-up periods differed extensively between studies. To assess heterogeneity, Q -statistics were calculated to indicate distribution of effect sizes and systematic differences between studies (Higgins and Thompson, 2002). The I^2 was calculated to describe the proportion of total variation across studies caused by heterogeneity in effect size. In general, heterogeneity is categorized at 25% (low), 50% (moderate), and 75% (high) (Higgins et al., 2003). We calculated 95% confidence intervals around I^2 in accordance with the formula of (Borenstein et al., 2011). If the I^2 is larger than 50%, subgroup analysis or meta-regression is recommended to investigate possible explanations of the variance. Subgroup analyses based on the risk of bias, type of intervention, type of control group, theoretical framework, type of guidance, intensity of intervention were performed if at least three studies could be included in each subgroup as a prerequisite.

In the cases with multiple comparison (in which one psychological intervention was compared with two or more control groups), to avoid the inflation of the possibility of an artificial reduction of heterogeneity and the further impact on the pooled effect size (ES), sensitivity analyse were conducted by including only 1 ES from this study.

Sensitivity analyses were also performed to examine the effect of outliers (95% CI of the effect size did not overlap with the 95% CI of the pooled effect size) and to investigate whether risk of bias affected the pooled effect sizes. To examine potential publication bias, we inspected the funnel plot and tested its asymmetry with Egger's test (Egger et al., 1997). Duval and Tweedie's trim and fill procedure was implemented to estimate the overall effect size accounted for publication bias (Duval and Tweedie, 2000).

Qualitative synthesis

For each intervention implemented in the Chinese universities, we determined the following features: the psychotherapeutic orientation (CBT, psychodynamic intervention, interpersonal therapy (IPT), Zhongyong psychoeducation, etc.), the format to deliver the intervention (individual, group, self-help, blended, etc), the quality of the intervention (manual based, delivered by professionals), and cultural ingredients' involvements. A qualitative synthesis based on these features was also conducted.

Results

Selection and inclusion of studies

A total of 5,029 records were identified in the search. After removal of duplicates, the Titles and Abstracts of 2,739 articles were screened for eligibility. Full texts of 762 articles were retrieved. A total of 93 articles were included in this systematic review (see Figure 1 for flow diagram). The major reasons for exclusion were that the identified articles were not original research studies ($k = 196$), did not include a psychological intervention ($k = 160$), or focused on a different study population (e.g., children, adolescents, elderly group, unselected population etc.; $k = 199$). Of the retrieved 93 articles with 92 studies (Li et al., 2006 a,b included same cohort), 39 were randomized controlled trials (RCT), 10 were non-randomized controlled trials with parallel groups, 14 were pre-post treatment design without a control group, and 30 were case series. RCTs with available data (28 studies) were included in the meta-analysis. All 92 studies were included in the qualitative synthesis. Selected characteristic of each of the included studies is reported in the Appendix 3B. An overview of the characteristics of the included RCTs is reported in Table 1.

Characteristics of included RCTs

The 39 studies included a total of 2,887 participants ($N = 1,462$ in the intervention group and $N = 1,421$ in the control group) who completed the baseline measurement of depression and 2,798 ($N = 1,405$ in the intervention group and $N = 1,393$ in the control group) participants who completed post-intervention measures. The follow-up time period varied (8 studies ≤ 3 months, 6 studies ≥ 6 months) and 26 studies did not include any follow-up.

Twenty-nine studies (21 with data available to calculate effect sizes) compared a psychological intervention to a control group (e.g., treatment as usual, assessment only, waitlist, placebo) and ten studies (seven with available data) compared a psychological intervention to another active psychological/medical treatment (e.g., CBA vs. ACT, psychological intervention vs. medicine for depression). Most studies recruited from a university setting ($k = 34$) whereas four studies recruited from a hospital setting and one from a mental health centre. CBT was referred to as the most commonly adopted intervention in the included studies ($k = 13$). The number of intervention sessions ranged from 5 to 20. Most interventions used a group format ($k = 28$). The quality of the included studies was far from optimal. Only four studies met at least 4 quality criteria (scored as low risk of bias) and characteristics of risk of bias for all RCT studies can be found in Appendix 3C.

Psychological intervention, compared with control groups

The overall effect (Hedges' g) of psychological interventions compared with a control

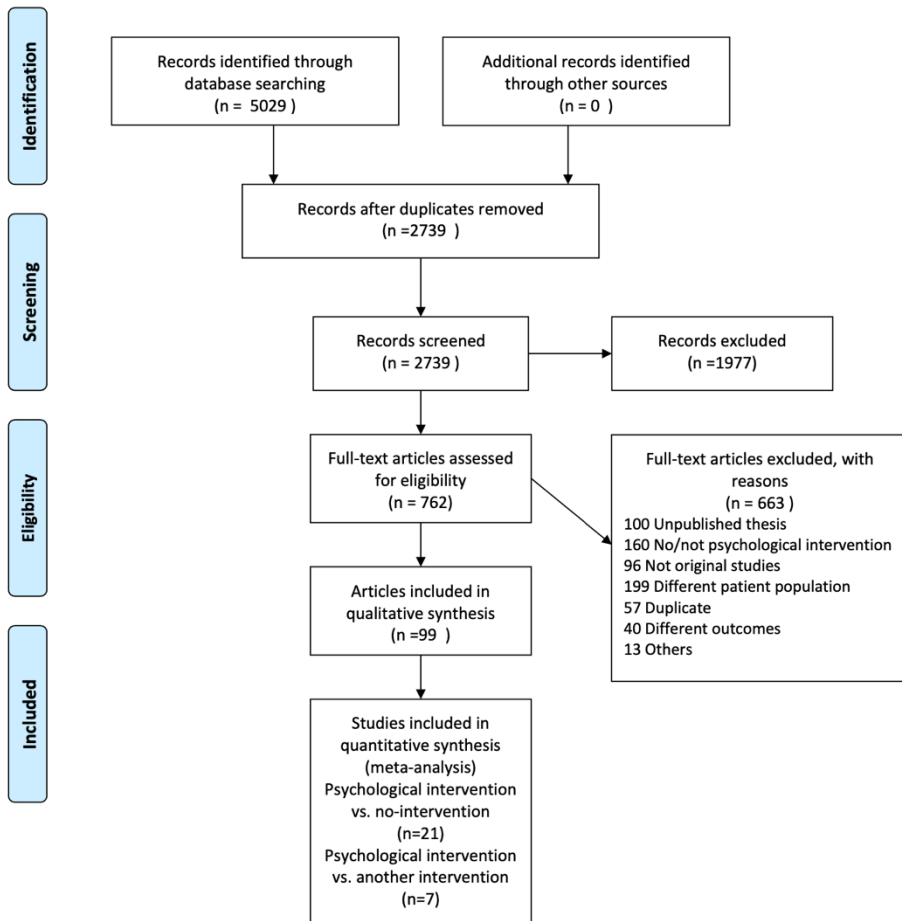


Figure 1 Flow diagram of systematic review

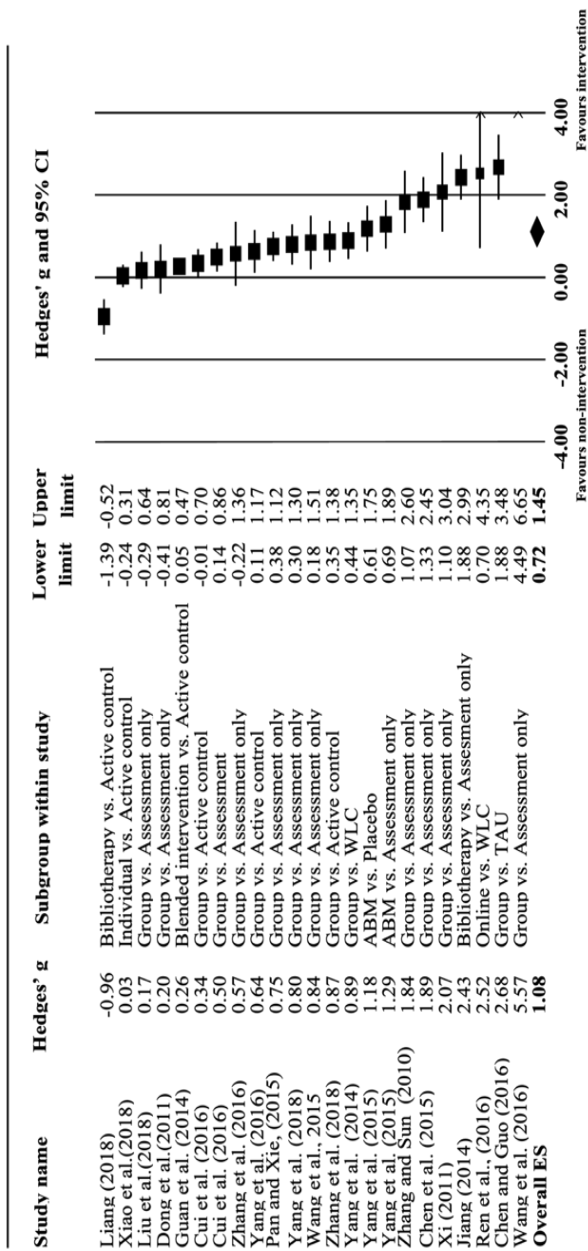


Figure 2 Forest plot of effect sizes from randomized controlled trials of psychological interventions for depression in university students in China (compared with no-intervention group).

Table 1 Characteristic of RCTs included in the systematic review

Author, Year	Setting	Condition	Inclusion criteria	N(pre)	N(post)	Mean age (SD)	Female (%)	Follow-up length	Depression measure
Bao, 2015	Hospital	Intervention A vs. Intervention B (vs. Intervention C)	depression diagnosis of WHO, HAMD >20; no physical disease;	110	110	24.84 (3.15)	0.45	0	HAMD
Chen and Gu 2016	University	Intervention vs. Usual care	SCL-90 depression subscale >3;	45	45	20.6 (1.01)	0.59	3 months	HAMD
Chen et al 2015	Nursing school	Intervention vs. Assessment only	DMSRIA >8; no severe hearing impairments, acute disease or pain; not taking any psychotropic medication	80	80	18.5 (NA)	0.97	0	DMRIA
Cui et al., 201	University	Intervention vs. Assessment only	SDS >56; not currently receiving psychotherapy or medication for psychological problems; without MDE;	180	158	19.42 (1.66)	0.61	6 months	SDS
Dong et al 2011	University	Intervention vs. Assessment only	SDS standard >=50; not bipolar disorder	20	20	22.33 (2.27)	NA	6 months	SDS
Guan et al 2014	University	Intervention vs. Placebo	BDI>=14;	355	355	21.43(2.04)	0.39	0	BDI
Han, 2017	University	Intervention vs. Assessment only	depressive symptoms; no comorbidity with physical disease, psychotic disorder, communication disorder	50	50	22.36 (1.12)	0.56	3 months	BDI
Jiang, 2014	University	Intervention vs. Assessment only	SDS 53-72	86	86	NA	0.54		SDS
Li and Jian 2018	Hospital	Intervention A vs. Intervention B (vs. Intervention C)	Met diagnosis criteria of depression	50	50	18.02 (2.65)	0.51	0	HAMD
Li et al., 2016	Hospital	Intervention A vs. Intervention B (vs. Intervention C)	fulfil diagnosis criteria of CCMD-3 depressive episode;	100	100	26.3 (4.9)	NA	0	HAMD-3
Li et al., 2016 a	University	Intervention vs. Assessment only	53<SDS<72; no physical disease; psychoactive substance abuse;	70	68	NA	NA	0	SDS
Li, 2014	University	Intervention A vs. Intervention B (vs. Intervention C)	CCMD-3 minor depression	49	49	22.13 (1.44)	0.71	4-6 months	SDS
Liang, 2018	University	Intervention vs. Placebo	Mild to moderate depression based on BDI (>10)	90	90	NA	NA	0	BDI
Lin et al., 201	University	Intervention A vs. Intervention B (vs. Intervention C)	Ko's depression inventory >21; Chinese version of borderline personality disorder features scale >5 and confirmed by clinical diagnosis; no psychotic disorders; no psychotropic medications;	82	81	20.38(0.68) 20.46(0.76)	0.71	8 months	KDI

Author, Year	Setting	Condition	Inclusion criteria	N(pre)	N(post)	Mean age (SD)	Female (%)	Follow-up length	Depression measure
Liu et al., 2018	University	Intervention vs. Assessment only	SDS>53; Pittsburgh Sleep Quality Index >7; without mindfulness training within one year, no medical treatment; no other severe physical and mental disorder;	70	70	NA	NA	3m	SDS
Pan and Xie, 2015	University	Intervention vs. Assessment only	SDS, SAS, SCL-90 positive	56	56	20.5 (0.6)	0.59	0	SDS
Ren et al., 2016	University	Intervention vs. Waitlist	SCL-90 depression subscale >3 in the first screening; second-screening, CES-D >15 and PHQ-9 >5; third screening step: ICD-10 diagnosis as first depression episode was confirmed by a psychiatrist; no suicidal intention;	62	45	20.82 (1.62)	0.62	0	CES-D
Song and Zhang, 2009	University	Intervention vs. Assessment only	SDS>50; limited annual income;	24	24	NA	NA	0	SDS
Tai et al., 2010	Medical college	Intervention A vs. Intervention B (vs. Intervention C)	met CCMD II-R depression diagnosis, HAM-D >17; no physical disease; BDI>15	76	76	18-29	0.54	2,4,6 weeks	HAMD
Wang and Wu, 2014	University	Intervention vs. Usual care		26	26	19.75(1.37)	0.3	0	BDI
Wang et al., 2015	University	Intervention vs. Assessment only	SDS	36	36	19.15 (1.46)	0.56	0	SDS
Wang et al., 2016	University	Intervention vs. Assessment only	BDI>=10	64		17.86 (1.25)	0.25	0	BDI
Wu and Lv, 2019	University	Intervention A vs. Intervention B (vs. Intervention C)	HAMD -24 scored mild to moderate (>8); without physical disease and other mental disorders;	70	70	19.52(1.91)	0.59	0	HAMD-24
Xi, 2011	University	Intervention vs. Assessment only	SDS>42	24	24	NA	NAA	3, 6 months	SDS
Xiang, 2007	University	Intervention vs. Assessment only	SDS>50; limited annual income;	22	22	NA	NA	0	SDS
Xiao et al., 2018	University	Intervention vs. Placebo	CES-D>25 in the first screening, HAM-D17 17-24 in the second screening.	196	196	22.57 (4.21)	0.43	10 weeks	HAMD-17
Xiong et al., 2017	Hospital	Intervention A vs. Intervention B (vs. Intervention C)	BDI>=8; exclude those with communication disorder, psychotic disorder, severe physical disease	120	120	19.7(1.2)	0.53	3 months	BDI

Author, Year	Setting	Condition	Inclusion criteria	N(pre)	N(post)	Mean age (SD)	Female (%)	Follow-up length	Depression measure
Xu et al., 2017	University	Intervention vs. Assessment only	SCL>=3	300	291	18.53 (16-24)	0.76	0	
Yang et al., 2014	University	Intervention vs. Waitlist control	5<=BDI-II<21;	81	80	19.2 (1.4)	0.68	3 months	BDI-II
Yang et al., 2015	University	Intervention vs. Placebo	BDI-II >14; exclude participants: 1.current episode of MDD, bipolar disorder, schizophrenia, or organic mental disorder; 2. any concurrent psychotherapy; 3. any concurrent psychotropic medication;	77	77	19.44 (1.58)	0.74		BDI-II
Yang et al., 2016	Medical School	Intervention vs. Placebo	50<SDS<60; exclude those with previous psychological disorders diagnosis, without serious suicidal ideation, and not attending any other intervention programs	30	27	18.8 (0.99)	0.8	0	SDS
Yang et al., 2017	University	Intervention vs. Assessment only	53<SDS<72; exclude physical disease; psychoactive substance abuse;	70	68			0	SDS
Yang et al., 2018	University	Intervention vs. Assessment only	SDS>50, MINI diagnosed depressive disorders;	74	67	18.5 (1.0)	0.6	6 months	BDI-II
Ye et al., 2012	University	Intervention A vs. Intervention B (vs. Intervention C)	ICD-10 major depression diagnosis; course >=2 months; HAMD>=25;	100	94	20.2 (2.10)	NA	0	HAMD
Haiyin Sun, 2010	University	Intervention vs. Assessment only	SDS >=40, has interpersonal problems;	36	36	NA	0.67	0	SDS
Zhang et al., 2016	University	Intervention vs. Assessment only	UPI item positive; UPI >=25;SDS>=53;	24	24	NA	0.75	0	SDS
Zhang et al., 2018	University	Intervention vs. Placebo	PHQ-9 had 2-4 symptoms of depression experienced more than half of the days or nearly every day for 2 or more weeks	62	60	18.41(2.01)	NA	0	PHQ-9
Zhao et al., 2013	University	Intervention A vs. Intervention B (vs. Intervention C)	Depression and rumination scores higher than mean score	40	27	19.43/19.15	0.56	9 weeks	SDS
Zhong et al., 2017	Mental health center	Intervention A vs. Intervention B (vs. Intervention C)	Met ICD-10 criteria for depression; first onset;	60	60	23.45 (2.29)	NA	0	SDS

Note: NA, not available; TAU, treatment as usual; WLC, waitlist control; BDI, Beck Depression Inventory-I, II; CES-D, Centre Epidemiological Screening – Depression; DMSRIA, Depression Mood Self Report Inventory for Adolescence; HAMD-17, 17-item Hamilton Depression rating scale; PHQ-9, Patient Health Questionnaire-9; SCL-90, Symptom Checklist-90; SDS, Self-Rating Depression Scale; Cognitive Behaviour Therapy; ACT, Acceptance and Commitment therapy; RET, Rational Emotion Therapy; KDI=Ko's depression inventory; MINI, MINI, University personality inventory; ICD-10, International Categories of Disease; SAS, Self-reported Anxiety Scale; HAMD, Hamilton Rating Scale of Depression.

group in 21 studies with 23 comparisons was 1.08 (95% CI: 0.72 to 1.45), which corresponds to a NNT of 1.8. Heterogeneity was moderate with I^2 as 47% (95%CI: 14-68). Effect sizes and 95% confidence intervals of each comparison were presented in the forest plot in Figure 2.

In this meta-analysis, we included two studies (Yang et al., 2015; Cui et al., 2016) with multiple comparisons. We first included only the comparison with the largest ES and then we conducted another analysis by only including the smallest ES. The resulting ESs were comparable with the ones found in the overall analyses (see Table 2). Heterogeneity remained moderate (both I^2 were 47%).

Eight comparisons were potential outliers (Cui et al., 2016; Guan et al., 2014; Xiao et al., 2017; Liang, 2018; Liu et al., 2018; Jiang, 2014; Wang et al., 2016; Chen and Guo, 2016). After exclusion of these outliers, the pooled Hedges' g was 0.99 (95% CI: 0.74-1.26; NNT=1.94) with low heterogeneity as $I^2=17$ (95% CI: 0-54).

Visual inspection of the funnel plot, as well as Egger's regression intercept ($p < 0.001$) indicated possible publication bias, although Duval and Tweedie's trim and fill procedure suggested otherwise (studies needed to be trimmed = 0; overall ES required no adjustment). With the evaluation of GRADE system, the overall effect size can be interpreted with high levels of confidence. Several subgroup analyses were conducted based on key characteristics of the study (e.g., theory of intervention, guidance of treatment, format of intervention, outcome measures, geographic region, language of publication, baseline depression). The results are shown in Table 2. We found that the type of control group was significantly associated with the effect size ($p=0.039$). Comparisons between the psychological intervention condition and the 'no intervention' condition (including assessment only and waitlist) yielded a higher effect size (Hedges' $g = 1.38$, 95% CI: 0.89 to 1.87) than comparisons between the psychological intervention condition and the 'usual care/active control' condition (Hedges' $g = 0.56$, 95%CI: 0.08 to 1.05). No other significant differences based on the study characteristics were observed.

Psychological intervention, compared with other interventions

There were ten studies with 12 comparisons of one type of psychological intervention against another psychological/medical intervention for depression. Specifically, three compared a psychological intervention plus physical exercise to another psychological intervention, five compared a psychological intervention plus medicine to medical treatment, one compared a psychological intervention plus acupuncture to another psychological intervention, and three compared two different psychological interventions (i.e., ACT vs. CBT, Psychodynamic group therapy vs. Problem solving group therapy, and DBT

vs. CBT).

Table 2 Subgroup analysis based on study characteristics (among studies compared with control groups)

	N	Hedge's <i>g</i>	95% CI	<i>p</i> value
Control group				<i>p</i> = 0.019
Assessment only/WLC	15	1.38	0.89 1.87	
Placebo/TAU	8	0.56	0.08 1.05	
Outcome measures				<i>p</i> = 0.798
BDI	7	1.18	0.33 2.04	
SDS	12	1.06	0.59 1.52	
Region				<i>p</i> = 0.36
South	10	1.13	0.73 1.54	
North	7	1.52	0.79 2.27	
Theory based intervention				
Yes	20	1.07	0.64 1.50	<i>p</i> = 0.168
CBT (including third wave)	11	0.94	0.47 1.40	<i>p</i> < 0.001
Others	9	1.74	0.69 2.78	
No	1	0.57	-0.22 1.36	<i>p</i> = 0.155
Guidance of intervention				<i>p</i> = 0.859
Professional	12	1.21	0.59 1.81	
Non-professional/NA	9	1.29	0.57 2.01	
Format of intervention				<i>p</i> = 0.882
Group	15	1.25	0.81 1.69	
Others (individual, combined, self-help)	6	1.17	0.14 2.19	
Language of article				<i>p</i> = 0.272
Chinese	15	1.38	0.75 2.01	
English	6	0.95	0.53 1.38	
Quality				<i>p</i> = 0.578
High	3	1.00	0.72 1.28	
Low	18	1.15	0.71 1.60	

Note: ES, effect size; CBT, cognitive behaviour therapy; BDI, Beck Depression Inventory-I, II; SDS, Self-Rating Depression Scale; NA, not available; WLC, waiting list control; TAU, treatment as usual.

Given the number of each type of comparisons were limited and data were available from only seven studies, explorative analysis based on these seven studies with two types

of comparisons (psychological intervention combined with medicine compared to medicine, psychological intervention combined with physical exercise compared with psychological intervention) were conducted (see Figure 3). Results revealed that the overall effect sizes pooled from both comparisons (Hedges' $g = 0.52$ with 95% CI: -0.58 to 1.63; Hedges' $g = -0.11$ with 95% CI: -2.42 to 2.40) were not significant with zero in their confidence intervals, which indicated combination of interventions were no better than singular intervention in the current review.

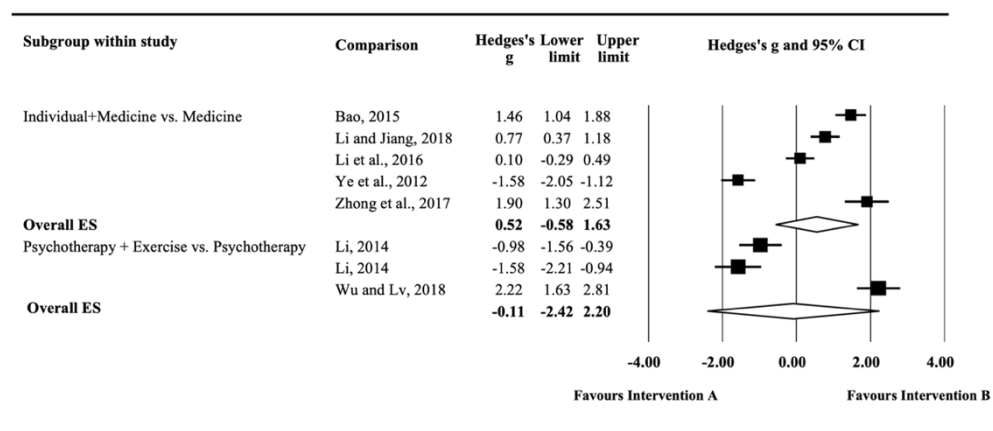


Figure 3 Forest plot of effect sizes from randomized controlled trials of psychological interventions for depression in university students in China (compared with medicine or other psychological intervention)

Qualitative Synthesis

Several types of studies (e.g., non-randomized controlled trials, pre-post studies, case study) were also identified. This section provides a qualitative summary of the theoretical orientations of the psychological interventions delivered, irrespective of study design. The other characteristics of the intervention (e.g., format, guidance) are presented in Appendix 3B.

Of the total 92 studies, 11 did not report the theoretical orientation of the intervention, therefore only the psychological interventions in the remaining 81 studies were synthesized. As presented in the supplementary material, psychological interventions based on different theories were identified including Cognitive Behavior Therapy (CBT), Psychodynamic therapy, Art therapy, Interpersonal therapy, Sand-play, and supportive care. A number of psychological interventions were roughly categorized into CBT including traditional CBT

based on Beck's theory ($k=17$), Solution focused behaviour therapy (SFBT, $k=2$), Mindfulness-based cognitive therapy (MBCT, $k=3$), Comprehensive self-control training (CSCT, $k=1$), Meta-cognitive therapy ($k=1$), and Rational emotive behaviour therapy (REBT, $k=5$). In the 81 studies implementing intervention with theoretical basis, CBT was reported in 29 studies.

The second category of intervention frequently delivered was a blended intervention (15/81 studies), which combined different types of interventions (e.g. cognitive therapy combined with medication, cognitive therapy combined with interpersonal therapy). Specifically, cognitive therapy was identified as the primary intervention within these integrations ($k=7$). Art therapy including music therapy and painting therapy (8 studies), and supportive care (6 studies) were identified as the third and fourth frequently implemented interventions. Supportive care included basic therapeutic skills (e.g. sympathy, listening, etc.). Other psychological interventions of minority were identified as positive psychology ($k=5$), bibliotherapy ($k=5$), interpersonal therapy ($k=3$), Morita therapy ($k=1$), psychodynamic therapy ($k=2$), sand-play ($k=3$), narrative therapy ($k=1$), attention bias modification ($k=1$) and some innovative working frameworks (one with "The Work" by Byron Katie, one with Zhongyong psychoeducation).

Seven studies integrating local Chinese elements in their interventions were identified. Among these studies, three integrated Chinese traditional philosophy in the intervention. One combined the traditional Chinese physical exercise Taichi with the education of philosophy underlying Taichi (i.e. submissive to the nature, to approach to the world in a dialectic way). The other one investigated the Zhongyong Thinking (Doctrine of the Mean) rooted in Confucian Culture in the intervention on mild depression. Two studies combined acupuncture with psychological interventions in their treatment on depression. In the other two studies, music therapy based on Chinese Five-element music (water, fire, wood, metal, and earth, which represent the transformation of everything in the universe) were implemented to diminish depression.

Discussion

In the current systematic review, we aimed to examine the effect of psychological interventions for depression delivered to local Chinese university students. When comparing all psychological interventions to the control groups (assessment only, waitlist, care-as-usual/placebo; 21 studies), the overall effect size and corresponding NNT (Hedges' $g = 1.08$; 95% CI: 0.72 to 1.45; NNT=1.8) collectively indicated the potential clinical relevance of such psychological interventions. This overall effect size is comparable to that reported

in the psychological intervention studies in low-and-middle income countries (Hedges' $g=1.10$, 95% CI: 0.91 to 1.30) (Cuijpers et al., 2018), but is higher than that based on Western samples ($g=0.60$, 95%CI: 0.55 to 0.64) (Cuijpers et al., 2018). Researchers suggest that this discrepancy could be related to differences in the use of control groups across countries (Cuijpers et al., 2018). For example, in Western societies the term 'usual-care' often implies some standard level of care, whereas, in the case of the current review and other studies conducted in low-and-middle income countries, the term more often means 'no care' (Cuijpers et al., 2011). In the current meta-analysis, the control group comprised of 'assessment only' represented a large portion of the control group, therefore the observed effect may have been inflated by this contrast. Additionally, some of the included studies were rated as being of low quality, which could also have inflated the observed effect size. Therefore, caution is warranted when interpreting the overall effect size.

In terms of the specific psychological interventions studied in university students in China, cognitive behaviour therapy was identified as the most common type of intervention (36%). This could be due to pragmatic issues relating to the requirement of psychological service delivery as structured and time limited under the university setting, which in alignment with the nature of CBT. It is of note that in the current review the delivery of CBT was generally of lower intensity (normally 6-8 group sessions) compared to the delivery of the other types of interventions (normally more than 8 sessions). Nevertheless, CBT did not produce differential results when compared to the other psychological interventions (e.g. IPT, psychodynamic therapy etc.) relative to control groups which is in line with the findings of previous meta-analysis (Cuijpers et al., 2011). As such, it implicated a potentially important step forward in further dissemination of CBT in Chinese universities. However, the limited data precluded a full analysis of potential moderators (e.g., treatment length/intensity, specific theoretical orientation), therefore these limitations need to be taken into account when considering the lack of difference in outcomes amongst the interventions based on varied theories.

A range of psychological interventions based on well-known theoretical classes such as CBT, psychodynamic therapy, and IPT were identified, as well as others like sand-play, bibliotherapy and art therapy. Whereas many of the psychological interventions delivered were drawn from Western culture, several interventions adopted local cultural elements, particularly the perspective of body-mind unification of Chinese tradition. This demonstrated an attempt to integrate empirically supported techniques in Western countries with local Chinese culture.

The current systematic review aimed to address this issue by taking an inclusive approach to the search process. By including studies published in both English and Chinese databases, we were able to examine efficacy data based on 21 available RCTs. However, the limited number of total inclusions prevented us from conducting a more fine-grained analysis based on cultural factors (e.g., comparing interventions based exclusively on Chinese culture compared with Western interventions). Interpretation of the results requires cautions due to the exclusive reliance on self-report measures, and high risk of bias (which indicated low quality) of the included studies.

Taken together, our meta-analysis provides evidence for the efficacy of psychological interventions for treating depressive symptomatology in Chinese students, even when some of these interventions deviate from the prototypical ‘Western’ approach to psychological wellbeing. The findings call for efforts for more studies of high quality to confirm the current findings in order to facilitate the dissemination of evidence-based psychological interventions. Innovative methods like Internet and mobile application could also be considered to provide efficient ways to address the large demand for psychological services in such a densely populated country. In addition, investigation of therapeutic components of traditional Chinese approaches could benefit the intervention in a culturally sensitive manner.

Reference

- Arjadi, R., Nauta, M.H., Chowdhary, N., Bockting, C.L.H., 2015. A systematic review of online interventions for mental health in low and middle income countries: a neglected field. *Glob. Ment. Heal.* <https://doi.org/10.1017/gmh.2015.10>
- Arnett, J.J., 2000. Emerging adulthood: A theory of development from the late teens through the twenties. *Am. Psychol.* 55, 469.
- Auerbach, R.P., Alonso, J., Axinn, W.G., Cuijpers, P., Ebert, D.D., Green, J.G., Hwang, I., Kessler, R.C., Liu, H., Mortier, P., Nock, M.K., Pinder-Amaker, S., Sampson, N.A., Aguilar-Gaxiola, S., Al-Hamzawi, A., Andrade, L.H., Benjet, C., Caldas-de-Almeida, J.M., Demyttenaere, K., Florescu, S., de Girolamo, G., Gureje, O., Haro, J.M., Karam, E.G., Kiejna, A., Kovess-Masfety, V., Lee, S., McGrath, J.J., O’Neill, S., Pennell, B.E., Scott, K., ten Have, M., Torres, Y., Zaslavsky, A.M., Zarkov, Z., Bruffaerts, R., 2016. Mental disorders among college students in the World Health Organization World Mental Health Surveys. *Psychol. Med.* 46, 2955–2970. <https://doi.org/10.1017/S0033291716001665>
- Auerbach, R.P., Mortier, P., Bruffaerts, R., Alonso, J., Benjet, C., Cuijpers, P., Demyttenaere, K., Ebert, D.D., Green, J.G., Hasking, P., Murray, E., Nock, M.K., Pinder-Amaker, S., Sampson, N.A., Stein, D.J., Vilagut, G., Zaslavsky, A.M., Kessler, R.C., Collaborators, W.W.-I., 2018. WHO World Mental Health Surveys International College Student Project: Prevalence and distribution of mental disorders. *J Abnorm Psychol* 127, 623–638. <https://doi.org/10.1037/abn0000362>

- Bao, L., 2015. Qingnian yiyuzheng huanzhe yingyong xinli zhiliao de jiazhi fenxi [Value Analysis of Psychotherapy in Young Patients with Depression]. *Shijie Zuixin Yixue Xinxi Wenzhai* 7–8. <https://doi.org/10.3969/j.issn.1671-3141.2015.78.004>
- Bardone, A.M., Moffitt, T.E., Caspi, A., Dickson, N., Stanton, W.R., Silva, P.A., 1998. Adult Physical Health Outcomes of Adolescent Girls With Conduct Disorder, Depression, and Anxiety. *J. Am. Acad. Child Adolesc. Psychiatry* 37, 594–601.
- Bayram, N., Bilgel, N., 2008. The prevalence and socio-demographic correlations of depression, anxiety and stress among a group of university students. *Soc. Psychiatry Psychiatr. Epidemiol.* 43, 667–672.
- Borenstein, M., Hedges, L., Higgins, J., Rothstein, H., 2013. *Comprehensive Metaanalysis* (Vers. 3). Englewood Cliffs, NJ: Biostat.
- Borenstein, M., Hedges, L. V., Higgins, J.P.T., Rothstein, H.R., 2009. Fixed-effect versus random-effects models, in: *Introduction to Meta-Analysis*. <https://doi.org/10.1002/9780470743386>
- Borenstein, M., Hedges, L. V., Higgins, J.P.T., Rothstein, H.R., 2011. *Introduction to meta-analysis*. John Wiley & Sons.
- Chen, C., Takahashi, T., Nakagawa, S., Inoue, T., Kusumi, I., 2015. Neuroscience and Biobehavioral Reviews Reinforcement learning in depression : A review of computational research. *Neurosci. Biobehav. Rev.* 55, 247–267. <https://doi.org/10.1016/j.neubiorev.2015.05.005>
- Chen, X., Guo, S., 2016. Jiji xinli tuanti fudao dui daxuesheng yiyu zhengzhuang de ganyu xiaoguo pingjia [Evaluation of Intervention Effect of Positive Psychological Group Counseling on Depressive Symptoms of College Students]. *Zhongguo Xuexiao Weisheng* 37, 874–877.
- China Health and Family Planning Statistics Yearbook, 2018. . Peking Union Medical College Press.
- Cui, L., He, F., Han, Z., Yang, R., Xiao, J., Oei, T.P.S., 2016. A brief group cognitive-behavioral program for the prevention of depressive symptoms in Chinese college students. *Int. J. Group Psychother.* 66, 291–307. <https://doi.org/http://dx.doi.org/10.1080/00207284.2015.1111098>
- Cuijpers, P., Andersson, G., Donker, T., van Straten, A., 2011. Psychological treatment of depression: Results of a series of meta-analyses. *Nord. J. Psychiatry* 65, 354–364.
- Cuijpers, P., Cristea, I.A., Ebert, D.D., Koot, H.M., Auerbach, R.P., Bruffaerts, R., Kessler, R.C., 2016. Psychological treatment of depression in college students: A meta-analysis. *Depress Anxiety* 33, 400–414. <https://doi.org/10.1002/da.22461>
- Cuijpers, P., Karyotaki, E., Reijnders, M., Purgato, M., Barbui, C., 2018. Psychotherapies for depression in low-and-middle-income countries: a meta-analysis. *World Psychiatry* 17, 90–101.
- Dong, S., Dong, X., Dai, J., Wang, C., Wu, J., Zeng, H., Wang, S., 2011. Tuanti xunlian dui daxuesheng yiyu qingxu de ganyu xiaoguo pingjia [Evaluation of intervention effect of group training on college students' depression]. *Zhonghua Jibing Kongzhi Zazhi* 758–761.
- Duval, S., Tweedie, R., 2000. Trim and fill: A simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. *Biometrics* 56, 455–463. <https://doi.org/10.1111/j.0006-341X.2000.00455.x>
- Egger, M., Davey Smith, G., Schneider, M., Minder, C., 1997. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 315, 629–634.
- Evans-Lacko, S., Thornicroft, G., 2019. Viewpoint: WHO World Mental Health Surveys International College Student initiative: Implementation issues in low- and middle-income countries. *Int. J. Methods Psychiatr. Res.* <https://doi.org/10.1002/mpr.1756>
- Ferrari, A.J., Charlson, F.J., Norman, R.E., Patten, S.B., Freedman, G., Murray, C.J.L., Vos, T., Whiteford, H.A., 2013. Burden of Depressive Disorders by Country, Sex, Age, and Year: Findings from the Global Burden of Disease Study 2010. *PLoS Med.* 10.
- Guan, X., Qiao, Z., Qiu, X., Yang, X., Wang, L., Yang, Y., 2014. Daxuesheng yiyu xinli ganyu xiaoguo fenxi [Analysis of the effect of psychological intervention on college students' depression]. *Zhongguo Xuexiao Weisheng* 35, 240–242.

- Haiyin, Z., Sun, Z., 2010. Renji tuanti fudao dui gaishan daxuesheng yiyuzhuangkuang de shizhengyanjiu [An Empirical Study of Interpersonal Group Counseling on Improving College Students' Depression Status]. *Wenzhou Daxue Xuebao* 31, 36–39.
- Han, Y., 2017. Dongli daoxiang tuanti xinlizhiliao dui daxuesheng yiyuqingxu ganyuxiaoguo pingjia [Evaluation of the effect of dynamic-oriented group psychotherapy on college students' depression]. *Zhongguo Baojian Yingyang* 27, 36.
- Hare, D.L., Toukhsati, S.R., Johansson, P., Jaarsma, T., 2014. Depression and cardiovascular disease: a clinical review. *Eur. Heart J.* 35, 1365–1372. <https://doi.org/10.1093/eurheartj/eht462>
- Higgins, J.P.T., Altman, D.G., Gøtzsche, P.C., Jüni, P., Moher, D., Oxman, A.D., Savović, J., Schulz, K.F., Weeks, L., Sterne, J.A.C., 2011. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *Br. Med. J.* 343, d5928.
- Higgins, J.P.T., Thompson, S.G., 2002. Quantifying heterogeneity in a meta-analysis. *Stat. Med.* 21, 1539–1558. <https://doi.org/10.1002/sim.1186>
- Higgins, J.P.T., Thompson, S.G., Deeks, J.J., Altman, D.G., 2003. Measuring inconsistency in meta-analyses Testing for heterogeneity. *BMJ* 327, 557–60.
- Hysenbegasi, A., Hass, S.L., Rowland, C.R., 2005. The impact of depression on the academic productivity of university students. *J. Ment. Health Policy Econ.* 8, 145.
- Ibrahim, A.K., Kelly, S.J., Adams, C.E., Glazebrook, C., 2013. A systematic review of studies of depression prevalence in university students. *J. Psychiatr. Res.* 47, 391–400.
- Jiang, Q., 2014. Yuedu liaofa zai yufang he ganyu daxuesheng yiyuzheng zhong de yingyong [Application of reading therapy in prevention and intervention of college students' depression]. *Taishan Yixueyuan Xuebao* 370–371.
- Kerr, D.C.R., Capaldi, D.M., 2011. Young men's intimate partner violence and relationship functioning: long-term outcomes associated with suicide attempt and aggression in adolescence. *Psychol. Med.* 41, 759–769. <https://doi.org/10.1017/S0033291710001182>
- Lei, X.Y., Xiao, L.M., Liu, Y.N., Li, Y.M., 2016. Prevalence of depression among chinese university students: a meta-analysis. *PLoS One* 11, e0153454.
- Li, H., 2014. Youyang yundong yu xinli jiankang jiaoyu lianhe ganyu dui daxuesheng zaoqi yiyuzheng de liaoxiao guanचा [Therapeutic effect of combined intervention of aerobic exercise and mental health education on early depression in college students]. *Tiyu Yanjiu yu Jiaoyu* 114–117.
- Li, Y., Han, W., Fu, Y., Xie, J., 2016. Jiankang xinliganyu shudao dui qingnian xinyinxing yiyuzheng de yingxiang [Effect of Health Psychological Intervention on Young People's "Psychogenic" Depression]. *Yixue Dongwu Fangzhi* 0, 87–88.
- Li, Y., Jiang, W., 2018. Xinli zhiliao lianhe yaowu zhiliao dui qingshaonian xuesheng jiaolv yiyu de liaoxiao fenxi [Therapeutic effect of psychotherapy combined with drug therapy on anxiety and depression of adolescent students]. *Zhijie jiankang* 4, 142–143.
- Li, Z.Z., Li, Y.M., Lei, X.Y., Zhang, D., Liu, L., Tang, S.Y., Chen, L.Z., 2014. Prevalence of suicidal ideation in Chinese college students: a meta-analysis. *PLoS One* 9, e104368.
- Liang, J., 2018. Yuedu liaofa dui daxuesheng yiyu qingxu de yingxiang [The effect of reading therapy on college students' depression]. *Qingbao Tansuo* 1, 72–75.
- Lin, T.J., Ko, H.C., Wu, J.Y., Oei, T.P., Lane, H.Y., Chen, C.H., 2019. The Effectiveness of Dialectical Behavior Therapy Skills Training Group vs. Cognitive Therapy Group on Reducing Depression and Suicide Attempts for Borderline Personality Disorder in Taiwan. *Arch Suicide Res* 23, 82–99. <https://doi.org/10.1080/13811118.2018.1436104>
- Liu, W., Xue, Z., Wang, L., Sun, F., 2018. Zhengnian renzhi xunlian dui yiyu qingxiang daxuesheng shuimian ganyu xiaoguo pingjia [Evaluation of the effect of mindfulness cognitive training on sleep intervention of college students with depression]. *Zhongguo xuexiao weisheng* 39, 138–140.
- Marcus, M., Taghi Yasamy, M., van Ommeren, M., Chisholm, D., Saxena, S., 2012. DEPRESSION A Global Public Health Concern, in: *World Mental Health Day*.

- Middleton, H., Shaw, I., Hull, S., Feder, G., 2005. NICE guidelines for the management of depression: Are clear for severe depression, but uncertain for mild or moderate depression. *Br. Med. J.* 330, 267.
- Moher, D., Liberati, A., Tetzlaff, J., Altman, D.G., 2009. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Ann. Intern. Med.* 151, 264–269.
- Mojtabai, R., Olfson, M., Han, B., 2016. National Trends in the Prevalence and Treatment of Depression in Adolescents and Young Adults. *Pediatrics* 138.
- Pan, C., Xie, Y., 2015. Yuanrenzhi ganyufa jiehe tuanti xinlifudao dui daxuesheng yiyu de ganyu xiaoguo yanjiu [Interventional effect of metacognitive intervention combined with group psychological counseling on college students' depression]. *Kaili Xueyuan Xuebao* 33, 135–137. <https://doi.org/10.3969/j.issn.1673-9329.2015.04.35>
- Parker, G., Gladstone, G., Chee, K.T., 2001. Depression in the planet's largest ethnic group: the Chinese. *Am. J. Psychiatry* 158, 857–864.
- Preti, A., 2015. How to calculate the Number Needed to Treat (NNT) from Cohen's d or Hedges'g. [WWW Document]. URL <https://rpubs.com/RatherBit>
- Ren, Z., Li, X., Zhao, L., Yu, X., Li, Z., Lai, L., Ruan, Y., Jiang, G., 2016. Yiyuzheng wangluohua zizhu ganyu de xiaoguo ji zuoyong jizhi -- yi hanhua MoodGYM weili [The effect and mechanism of networked self-intervention in depression: A case study of Chinese MoodGYM]. *Xinli xuebao* 48, 818–832.
- Scott, K.M., Lim, C., Al-Hamzawi, A., 2016. Association of mental disorders with subsequent chronic physical conditions: World mental health surveys from 17 countries. *JAMA Psychiatry* 73, 150–158. <https://doi.org/10.1001/jamapsychiatry.2015.2688>
- Song, Y., Zhang, H., 2009. Tuanti xinlifudao dui pinkun daxuesheng yiyuxinli de ganyu yanjiu [Intervention Study of Group Counseling on Depressive Psychology of Poor College Students]. *Shandong Qingnian Zhengzhi Xueyuan Xuebao* 56–58.
- Tai, X., Han, T., Teng, L., Li, B., 2010. Zhenci jiehe xinliliaofa zhiliao daxuesheng yiyuzheng 37 li linchuang guan cha [Clinical Observation on 37 Cases of College Students with Depression Treated by Acupuncture Combined with Psychotherapy]. *Zhongyiyao Xinxi* 27, 92–93. <https://doi.org/10.3969/j.issn.1002-2406.2010.04.043>
- Wang, J., Liu, S., Zhang, P., Wu, H., Chi, X., 2016. Jiji xinli ganyu dui yiyuzhengzhuang daxuesheng qingxu ji zhuguanxingfugan de yingxiang [The effect of positive psychological intervention on the emotion and subjective well-being of college students with depressive symptoms]. *Zhongguo Teshu Jiaoyu* 11, 44–50.
- Wang, J., Wu, H., 2014. Jiyu jijixinlijiankang jiaoyu sixiang de yiyu ganyu yanjiu [Depression Intervention Based on Positive Mental Health Education Thought]. *Zhongguo Teshu Jiaoyu* 3, 80–84.
- Wang, J., Wu, H., Li, Q., Zhang, D., 2015. Jiyu jijixinli ganyu jishu de yiyu gean fenxi [Analysis of depression cases based on positive psychological intervention techniques]. *Chongqing Yixue* 44, 3577–3579.
- Wang, L., He, C.Z., Yu, Y.M., Qiu, X.H., Yang, X.X., Qiao, Z.X., Sui, H., Zhu, X.Z., Yang, Y.J., 2014. Associations between impulsivity, aggression, and suicide in Chinese college students. *BMC Public Health* 14, 551. <https://doi.org/10.1186/1471-2458-14-551>
- Wu, X., Lv, B., 2019. Xinli jiankang jiaoyu lianhe youyang yundong dui daxuesheng xinli yiyu chengdu zaoqi ganyu xiaoguo de yanjiu [Effect of mental health education combined with aerobic exercise on early intervention of college students' psychological depression]. *Zhonghua Baojian Yingyang* 1, 185–186.
- Xi, M., 2011. Jiaodian jie jue quxiang tuanti fudao zhiliao daxuesheng yiyu [Focus-solving orientation group counseling to treat college students' depression]. *Zhongguo Jiankang Xinlixue Zazhi* 2, 223–225.
- Xiang, Q., 2007. Pinkun daxuesheng yiyuxinli tuanti fudao xiaoguo pingjia [Evaluation on counseling effect of depression psychological group in poor college students]. *Zhongguo Xuexiao Weisheng* 28, 924–925. <https://doi.org/10.3969/j.issn.1000-9817.2007.10.025>

- Xiao, C., Zhu, X., Wang, Y., Zhou, H., Gao, Y., Yan, J., Wang, C., 2018. Shehui juese yindao ganyufa kongzhi yalinchuang yiyuzhangai bingqingfazhan de youxiaoxing tanjiu [The effectiveness of social role-guided intervention in controlling the development of subclinical depressive disorder]. *Huanan Yufang Yixue* 2, 187–190.
- Xiong, L., Li, Y., Gao, R., Yan, Q., 2017. Dongli daoxiang tuanti xinlizhiliao dui daxuesheng yiyuqingxu ganyu xiaoguo de yanjiu [Study on the effect of dynamic-oriented group psychotherapy on college students' depression]. *Zhongguo Yixue Chuangxin* 14, 137–141. <https://doi.org/10.3969/j.issn.1674-4985.2017.20.035>
- Xu, C., Jiao, Y., Zhang, F., Zhang, J., Li, P., Zhao, X., 2017. Wuwei tongyi zhenghe liaofa dui daxuesheng yiyuqingxu zhangai de ganyu yanjiu [Intervention study of Wuwei unified integration therapy on college students with depression and emotional disorder]. *Jiazhi Gongcheng* 4, 143–146.
- Yang, M., Li, T., Ge, L., 2017. Zixinxin tuanti xunlian dui daxuesheng yiyuqingxu he yigndui fagnshi de ganyuyanjia [Intervention Study on Self-confidence Group Training on College Students' Depression and Coping Style]. *Zhongguo Yixue Chuangxin* 14, 121–124.
- Yang, W., Ding, Z., Dai, T., Peng, F., Zhang, J., 2015. Attention Bias Modification training in individuals with depressive symptoms: a randomized controlled trial. *J. Behav. Ther. Exp. Psychiatry* 49, 101–111. <https://doi.org/10.1016/j.jbtep.2014.08.005>
- Yang, X., Zhang, P., Zhao, J., Zhao, J., Wang, J., Chen, Y., Ding, S., Zhang, X., 2016. Confucian culture still matters: The benefits of Zhongyong thinking (Doctrine of the mean) for mental health. *J. Cross. Cult. Psychol.* 47, 1097–1113.
- Yang, X., Zhao, J., Chen, Y., Zu, S., 2018. Comprehensive self-control training benefits depressed college students: a six-month randomized controlled intervention trial. *J. Affect. Disord.* 226, 251–260. <https://doi.org/10.1016/j.jad.2017.10.014>
- Yang, Y., Yang, R., Lin, X., Xiao, J., Oei, T.P.S., Cui, L., 2014. Renzhi xingwei tuanti zixun dui daxuesheng yiyuzhengzhuagn de ganyu xiaoguo [Intervention effect of cognitive behavioral group counseling on college students' depressive symptoms]. *Zhongguo Xinli Weisheng Zazhi* 12, 913–919.
- Ye, Q., Tang, K., Chen, Z., Tao, L., Yang, C., Jiang, D., Qi, W., Li, C., 2012. Guilin gaoxiao daxuesheng yiyuzhengzhuang diaocha ji ganyu yanjiu [Investigation and Intervention Study on Depressive Symptoms of College Students in Guilin]. *Zhongguo Jiankang Xinlixue Zazhi* 20, 1185–1187.
- Zhang, J., Qin, S., Zhou, Y., Meng, L., Su, H., Zhao, S., 2018. a randomized controlled trial of mindfulness-based Tai chi chuan for subthreshold depression adolescents. *Neuropsychiatr. Dis. Treat.* 14, 2313.
- Zhang, J., Zhang, H., Yu, R., 2016. Tuanti xinlifudao dui daxuesheng yiyuzhengzhuang de ganyu yanjiu - jiyu jijixinlixue de lilun shijiao [Intervention Study of Group Counseling on College Students' Depressive Symptoms-Based on the Theoretical Perspective of Positive Psychology]. *Jiaoyu Xiandaihua* 16, 118.
- Zhao, W., Zhou, Y., Liu, X., Ran, L., 2013. Jieshou yu chengnuo liaofa ganyu yiyu de xiaoguo zhuzhong [Follow-up of the effects of acceptance and commitment therapy intervention depression]. *Zhongguo Linchuang Xinlixue Zazhi* 1, 153–157.
- Zhong, Y., Gong, L., Wen, Y., 2017. Zhengxing yinyue ciji lianhe shequlin zhiliao dui shoufa yiyuzheng daxuesheng jiaolv yiyuqingxu ji shenghuozhiliang de yingxiang [Effect of positive music stimulation combined with sertraline on anxiety, depression and quality of life in first-episode]. *Nanchang Daxue Xuebao* 45–49.

Chapter 5

Explaining the efficacy of an internet-based behavioral activation Intervention for major depression: a mechanistic study of a randomized-controlled trial in Indonesia

Fu, Z., Burger, H., Arjadi, R., Nauta, M. H., & Bockting, C. L. (2021). Explaining the Efficacy of an Internet-Based Behavioral Activation Intervention for Major Depression: A Mechanistic Study of a Randomized-Controlled Trial. *Clinical Psychology in Europe*, 3(3), 1-24.

Abstract

Background: Behavioral activation is an effective treatment for depression that is theorized to facilitate structured increases in enjoyable activities that increase opportunities for contact with positive reinforcement; to date, however, only few mechanistic studies focused on a standalone intervention.

Method: Interventions using internet-based behavioral activation or psychoeducation were compared based on data from a randomized-controlled trial of 313 patients with major depressive disorder. Activation level and depression were measured fortnightly (baseline, weeks 2, 4, 6, 8, 10), using the Patient Health Questionnaire-9 and the Behavioral Activation for Depression Scale-Short Form, respectively. Analysis was performed to determine if a change in activation level mediated treatment effectiveness.

Results: Latent growth modeling showed that internet-based behavioral activation treatment significantly reduced depressive symptoms from baseline to the end of treatment (standardized coefficient = -0.13 , $p = 0.017$) by increasing the rate of growth in the activation level (mediated effect estimate = -0.17 , 95% CI: -0.27 to -0.07). Results from mixed effects and simplex models showed that it took 4 weeks before mediation occurred (i.e., a significant change in activation that led to a reduction in depressive symptoms).

Conclusion: Activation level likely mediated the therapeutic effect of behavioral activation on depression in our intervention. This finding may be of significant value to clinicians and depressed individuals who should anticipate a 4-week window before seeing a prominent change in activation level and a 6-week window before depressive symptomatology reduces. Future research must consolidate our findings on how behavioral activation works and when mediation occurs.

Introduction

Depression is a prevalent and disabling mental health condition characterized by sadness and lack of interest (American Psychiatry Association, 2015). Behavioral activation is well-established as an effective treatment (Cuijpers, Straten, & Warmerdam, 2007; Stein, Carl, Cuijpers, Karyotaki, & Smits, 2020) and as a standalone therapy in relevant clinical guidelines (National Collaborating Centre for Mental Health (UK), 2010). It is also considered a cost-effective therapy that can be delivered easily and disseminated in a range of formats (Arjadi et al., 2018; Carlbring et al., 2013). However, more research is needed to clarify uncertainties about how behavioral activation exerts its clinical effects (Janssen et al., 2020).

Rooted in behavioral frameworks, the theory underpinning behavioral activation conceptualizes depression as the result of low levels of (response-contingent) positive reinforcement: the consequences of environmental interaction that increase the likelihood of a given behavior (Ferster, 1973, 1981; Lazarus, 1972; Lewinsohn, 1974). The theory posits that a lack of this positive reinforcement can result in decreased behavioral activation or withdrawal from the environment, which precipitates depression (Manos, Kanter, & Busch, 2010). Therefore, actively engaging in behavioral activation can help to break the negative cycle of depression by promoting meaningful and adaptive engagement in life (Martell, Dimidjian, & Herman-Dunn, 2013). This strong theoretical basis allows for changes in levels of activation and avoidance (i.e., the activation level) to be evaluated as the hypothesized mediator of change in depressive symptoms during treatment (Curry & Meyer, 2016). However, two research gaps remain. First, contrasting starkly with research into cognitive processes, there is limited empirical evidence of activation level as a potential mediator (Lemmens, Müller, Arntz, & Huibers, 2016; Moreno-Peral et al., 2020). Second, mediators have rarely been examined in randomized-controlled trials (RCTs) of behavioral activation as a standalone treatment (Janssen et al., 2020). Further study is needed to correct this lack of mechanistic research into mediation processes.

Most research into behavioral activation has investigated it as a component of cognitive behavior therapy (e.g., Luenen, Kraaij, Spinhoven, Wilderjans, & Garnefski, 2019), for which the underlying theoretical assumption differs, suggesting instead that behavioral change helps to improve symptoms through cognitive restructuring. To date, ten studies have examined activation level for the treatment of depression (Dimidjian et al., 2017; Forand et al., 2018; Gaynor & Harris, 2008; Luenen et al., 2019; Nasrin, Rimes, Reinecke,

Rinck, & Barnhofer, 2017; Richards et al., 2017; Rovner et al., 2014; Santos et al., 2019; Silverstein et al., 2018; Weidberg, González-Roz, Garcí'a-Fernández, & Secades-Villa, 2020). Among these, four investigated a standalone behavioral activation intervention, producing inconsistent results, and none assessed both depression and activation during treatment, precluding mediation analyses. The inconsistent findings likely result from clinical heterogeneity and a failure to meet specific methodological requirements, such as using an RCT design, examining variables of interest longitudinally to assess temporal ordering, and being sufficiently large to ensure robust statistical analyses (Curran et al., 2011; Kazdin, 2007; Lemmens et al., 2016). Studies assessing the activation level as a mediator of depression treatment have not complied with all these requirements (Janssen et al., 2020), with some adopting small samples (e.g., <40 per trial arm) (Gaynor & Harris, 2008) and others using too few repeat observations (e.g., <3) (Richards et al., 2017; Weidberg et al., 2020) or no control group (e.g., Santos et al., 2019). Thus, adequately powered trials of standalone behavioral activation interventions for depression are needed to clarify the extent to which the activation level mediates treatment outcomes.

Our group has previously conducted an RCT for an internet-based intervention involving a large sample of patients with major depressive disorder treated by behavioral activation under the guidance of lay counselors (intervention) compared with psychoeducation (controls) (Arjadi et al., 2018). In that study, we examined activation level as the mechanism underlying the treatment effect and concluded that, after 10 weeks, patients in the intervention group reported significantly fewer depressive symptoms (effect size, 0.24) and had a 50% higher chance of remission than those in the control group. Crucially, this study complied fully with the methodological requirements of mechanistic research into mediation processes. In the present study, we therefore aimed to use data from that study to demonstrate that the activation level mediates the relationship between treatment with behavioral activation and improved depression. This was considered achievable if we could demonstrate two criteria (Kazdin, 2007; MacKinnon, 2008). First, that the treatment condition correlated with changes in the activation level, which in turn, correlated with changes in depressive symptoms and was conditional on treatment allocation (criterion 1). Second, that the change in activation level produced the change in depressive symptoms, and not vice versa (i.e., temporal ordering; criterion 2).

Methods

Design

This study reports on a post-hoc analysis of an earlier two-group RCT of an internet-based behavioral activation program for patients with major depressive disorders ($N = 313$). Details of the original RCT are reported elsewhere (Arjadi et al., 2018). All assessments were completed on the Qualtrics survey platform and administered at baseline and every 2 weeks thereafter up to the main post-treatment evaluation at week 10 (endpoint), with follow-up at 12 and 24 weeks after baseline. For the purposes of the current study, depression and activation level were examined fortnightly at baseline and at weeks 2, 4, 6, 8, and 10.

Participants and Randomization

In total, 313 participants were included and randomized into the treatment ($n = 159$) and control ($n = 154$) groups (see Arjadi et al., 2018, for a detailed flowchart). The baseline characteristics were comparable in each group, as presented in Table 1, indicating successful randomization. Participants were recruited via online self-referral. Eligible participants were aged ≥ 16 years, scored ≥ 10 on the Patient Health Questionnaire-9 (PHQ-9), and had a principal diagnosis of major depressive disorder or persistent depressive disorder defined according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition. Diagnosis was by semi-structured diagnostic interview (SCID-5) (First et al., 2015). Participants with current substance use disorder, current or previous manic or hypomanic episodes, psychotic disorder, or acute suicidality were excluded, as were those receiving psychological interventions.

Eligible participants were allocated (1:1) by a research assistant in a random permuted block design stratified by sex and depression severity (score 10–14 or ≥ 15 on the PHQ-9) via a web-based program. Current depressive episodes and post-traumatic stress disorder were assessed by clinical diagnostic interview conducted by trained clinical interviewers who were required to hold at least a bachelor's degree in psychology.

Treatments

Intervention group: Guided Act-and-Feel-Indonesia (GAF-ID). Participants in the intervention group received an internet-based behavioral activation intervention (the GAF-ID) supported by lay counselors. The intervention program was adapted from an online intervention for behavioral activation based on Lewinsohn's (1974) theory of depression. The original program was published in Dutch (Doe en Voel; Bockting, van Valen, 2015) and

was translated to Bahasa Indonesian. The GAF-ID program was delivered using an online platform in eight structured modules delivered weekly. Each module was expected to be completed online in 30–45 minutes. The intervention group was guided and supported by lay counselors who were supervised by a licensed clinical psychologist. A detailed description of the guidance and support is available elsewhere (Arjadi et al., 2018).

Control group: online psychoeducation. Participants in the control group were given access to another online platform from which they could find basic psychoeducation on depression and brief tips on coping with depression in general. This information was distilled from the psychoeducation module of the GAF-ID program, but no guidance or support was provided.

Demographic information was collected at baseline, including age, gender, ethnicity, education (above bachelor/other), living area (urban/other), and socioeconomic class. The latter was determined by monthly expenditure in Indonesian rupiah (IDR): low, <1 million; middle, 1–5 million; and high, >5 million. In addition, the PHQ-9 and Behavioral Activation for Depression Scale-Short Form (BADDS-SF) were completed fortnightly.

Table 1 Descriptive statistics of baseline demographic characteristics

		GAF (<i>n</i> = 159)*	PE (<i>n</i> =154)*
Age (Mean, SD)		24.5 (4.9)	24.5 (5.2)
Sex		128	125
	Male	31	29
Current PTSD	Yes	22	30
	No	137	124
Education	Above bachelor	89	81
	Others	70	73
Living area	Urban	93	96
	Others	67	58
Socioeconomic class	Low	32	27
	Middle	98	100
	High	29	27
Ethnicity	Java	69	64
	Tionghoa	30	18
	Sunda	21	22
	Others	39	40

* Note that all patients were in a depressive episode.

Abbreviations: GAF = Guided Act-and-Feel-Indonesia; PE = Psychoeducation; PTSD = post-traumatic stress disorder; SD = standard deviation.

Measures

Patient Health Questionnaire-9 item version. The PHQ-9 is a 9-item self-report questionnaire in which participants rate how they felt during the previous two weeks (e.g., “Feeling tired or having little energy”). Each question is scored 0 to 3 (0 = not at all, 1 = several days, 2 = more than half the days, and 3 = nearly every day). Sum scores range from 0 to 27, with higher scores representing higher levels of depression. The PHQ-9 has acceptable validity and reliability (Carroll et al., 2020), and the Cronbach’s alphas in the current study ranged from 0.78 to 0.87 at the different assessments.

Behavioral Activation for Depression Scale-Short Form. The BADS-SF is a 9-item self-report questionnaire that measures changes in activation and avoidance in the previous week (e.g., “There were certain things I needed to do that I didn’t do”). Each question is scored 0 to 6 (0 = Not at all, 6 = Completely). Items 1, 6, 7, and 8 are reverse-coded. Sum scores can range from 0 to 54, with higher scores representing higher activation. The validity and reliability of BADS-SF have been established (Manos, Kanter, & Luo, 2011), and the Cronbach’s alphas in the current study ranged from 0.78 to 0.88 at different assessments.

Data Analysis

Mixed effects model to compare mean depression and activation levels. Mixed effects models were used to inspect how treatment influenced activation level and depression at each time point. Baseline and follow-up measures were treated as response variables. Missing values were imputed by multiple imputation, including treatment allocation and all PHQ-9 and BADS-SF assessments in the predictor matrix. Given that the functional form of the mean responses during treatment can be difficult to anticipate, time was specified as a class effect in an unstructured manner. The contrasts between treatment groups at each time point were obtained by comparing the least squares means of the variables of interest. Mixed effect analyses were conducted using the nlme R package (Pinheiro, Bates, DebRoy, Sarkar, & R Core Team, 2020), and for multiple imputations, we used the mice R package (van Buuren & Groothuis-Oudshoorn, 2011).

Mediation analyses using latent growth and simplex mediation models. Mediation analyses were based on latent growth models to address criterion 1 (MacKinnon, Cheong, & Pirlott, 2012) and simplex mediation models to address criterion 2 (Goldsmith et al., 2018) in a structural equation model framework.

We refer to the path estimating the relationship between treatment allocation (T) and activation level (M) as the α path and refer to the path between activation level and

depression (Y) as the b path. The direct effect from treatment allocation to depression is noted as the c path, after accounting for M as c' . The product of $a \times b$ coefficients method was used to indicate the indirect effect (Goldsmith et al., 2018). Coefficients were provided based on a completely standardized solution, and the confidence intervals of $a \times b$ were estimated by bootstrapping (1,000 times). A mediated effect was deemed statistically significant if the 95% confidence interval (95% CI) did not cross zero.

Latent growth model analyses were performed in three steps to model the relationship between treatment and the growth trajectories of activation and depression (Cheong, MacKinnon, & Khoo, 2003). First, to investigate the shape of the growth trajectories for depression and activation, unconditional growth models were built. Second, to examine if the growth rates of depression and activation differed by treatment condition, two conditional models were constructed with the treatment conditions. Third, to assess the indirect effect of treatment allocation on the outcome, via the mediator (activation level), we combined the two conditional growth models into a parallel process growth model. In this, the path coefficients (a , b , c , and c') of the mediation model were estimated and the contributions of baseline characteristics as covariates were examined (e.g., sex, ethnicity, urban/rural, socioeconomic status, post-traumatic stress disorder, and education level).

A simplex mediation model was then adopted to determine if there was temporal ordering. This was achieved by evaluating whether a prior activation level was associated with the level of depression at a subsequent measurement. We specified models as either a lagged b path (activation affects depression at adjacent time points) or a contemporaneous b path (activation affects depression at the same time point). We added treatment allocation as a time-invariant antecedent variable to predict depression and activation level at each time point. Autoregressive and cross-lagged effects were constrained to be equal over time (Goldsmith et al., 2018). To assess the timing of the potential mediation process, a paths were freely estimated. In addition, to evaluate the extent to which prior depression influenced the subsequent activation level, we reversed the position of depression and activation level in a supplementary analysis.

The time-specific indirect effect was estimated using a series of product terms to indicate the possible timing of the putative mediator taking effect. Figure 3 shows an example simplex model with lagged b paths: for the third time point, depression Y_3 (i.e., week 4 depression), one indirect effect of treatment could be $T \rightarrow M_2 \rightarrow Y_3$. Calculation was performed as $a_2 \times b_{23}$, where the subscripts indicated direction (e.g., the coefficient a_2

was the effect to activation at point 2, and b_{23} was the effect from activation at point 2 to depression at point 3, and all b paths were considered equal). A significant result could suggest a lagged mediation effect from week 2 activation (M_2) to week 4 depression (Y_3). The overall indirect effect in the model for Y_3 was the sum of all time-specific indirect effects estimated by the products of the parameters that estimated the paths between T and Y_3 and passed through the mediator. Coefficient a at baseline (i.e., a_1) was fixed at zero because treatment had not been implemented at this time.

Data were assumed to be missing at random or completely at random (Graham, 2009), so we used a full-information maximum likelihood estimation in the structural equation modeling analysis. Participants who had at least one measurement for depression were retained in the model and analysis performed on an intention-to-treat basis. Model fit was assessed by the comparative fit index (CFI), Tucker–Lewis index (TLI), root mean squared error of approximation (RMSEA), and standardized root mean square residual (SRMR). We used established guidelines of acceptable fit, requiring that the CFI and TLI should exceed 0.90–0.95, that the RMSEA should not exceed 0.06–0.10, and that the SRMR should not exceed 0.08. All structural equation modeling analyses were performed in Mplus 8.3 (Muthén & Muthén, 2019).

Results

A full overview of the levels of activation and depression at each measurement is presented in Table 2. Each fortnightly assessment was completed by at least 83% of the sample, but 17.5% of all data points were missing in the GAF-ID group versus 4.3% in the control group. Participants in both groups had at least 4 data points (83.6% for the GAF-ID group and 95.4% for the control group). The main reasons for dropout at week 10 were “no time” (18 in the GAF-ID group) and “no improvement” (12 in GAF-ID group and 6 in the control group).

Mixed Effects Model: Differences of Depression and Activation level

Treatment allocation had significant effects on depression ($p < .001$) and activation ($p < .001$) across all included time points. As shown in Table 3, the mean differences in activation and depression increased over time between the treatment and control groups, reaching statistical significance from week 4 (assessment 3) for activation and week 6 (assessment 4) for depression.

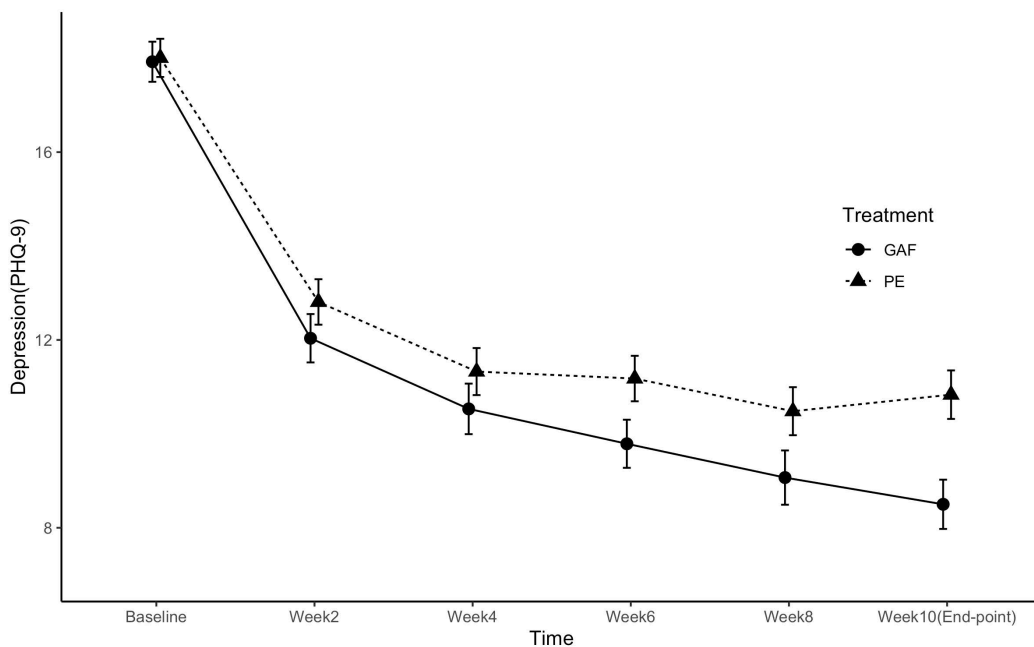


Figure 1a Trajectories of depression (PHQ-9) across measurements in treatment (GAF) and control (PE) groups. GAF = Guided Act and Feel treatment; PE = Psychoeducation.

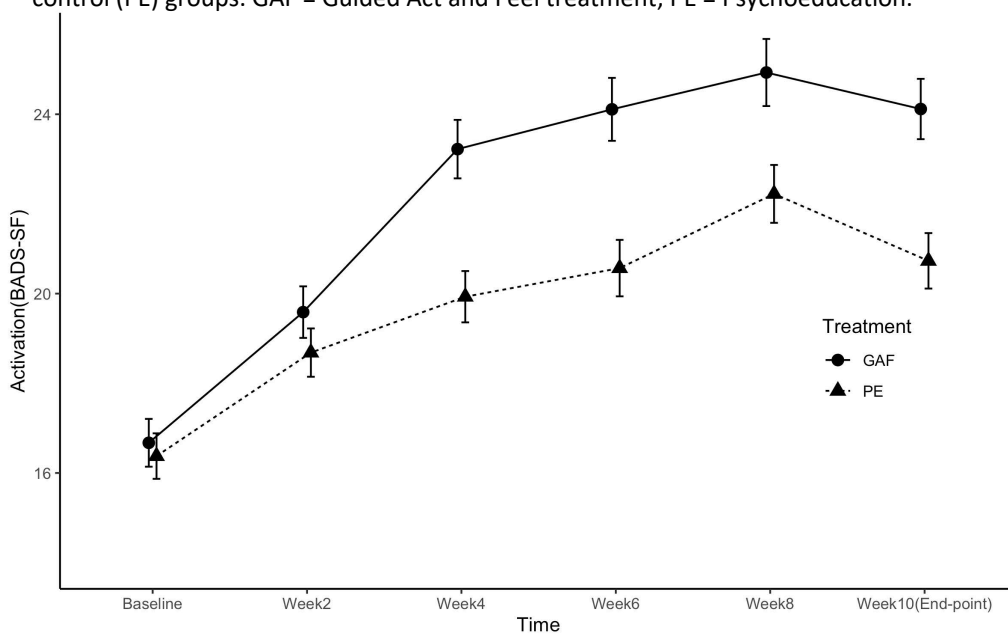


Figure 1b Trajectories of activation (BADS-SF) across measurements in treatment (GAF) and control (PE) groups. GAF = Guided Act and Feel treatment; PE = Psychoeducation

Table 2 Means and standard deviations of PHQ-9 and BAD-SF for each group at each assessment

	GAF-ID			PE		
	Missing	Means	SD	Missing	Means	SD
Depression (PHQ-9)						
Week 0 (Baseline)	0	17.92	5.39	0	18.01	5.05
Week2	21	12.04	6.05	2	12.81	5.97
Week4	33	10.53	6.04	10	11.33	6.01
Week6	31	9.79	5.80	8	11.18	5.85
Week8	43	9.07	6.22	11	10.48	6.12
Week 10 (Endpoint)	39	8.50	5.75	9	10.83	6.21
Behavioral activation (BAD-SF)						
Week 0 (Baseline)	0	16.67	6.72	0	16.38	6.29
Week2	21	19.59	6.75	2	18.68	6.64
Week4	33	23.22	7.32	10	19.93	6.87
Week6	31	24.11	7.94	8	20.57	7.61
Week8	43	24.93	8.06	11	22.22	7.72
Week 10 (Endpoint)	39	24.12	7.37	9	20.73	7.45

Abbreviations: BADS-SF = Behavioral Activation for Depression Scale – Short Form; GAF = Guided Act-and-Feel-Indonesia; PE = Psychoeducation; PHQ-9 = Patient Health Questionnaire-9; SD = standard deviation.

Latent Growth Model for Mediation

Unconditional growth model. Model fit indices, as shown in Table 4, were acceptable. The RMSEA for the model of depression was higher than that of activation level, suggesting that the variance in depression could be explained by a potential covariate (e.g., treatment).

Conditional growth models: the effect of treatment. The fitness of both conditional models appeared acceptable (Table 4). The GAF-ID group showed a larger increase in activation (standardized coefficient = 0.27, $p < .001$) and a larger reduction in depression compared with the control group (standardized coefficient = -0.13 , $p = .017$). This confirmed that treatment was effective in producing a difference in trajectories between the treatment and control groups.

Parallel process growth models: the mediation effect. Model fit of the parallel process growth model was acceptable (Figure 2). Factor loadings of the slope growth factor indicating the predicted trajectory of depression and activation are presented in Table 5. Consistent with the plotted growth trajectory for depression based on data for the whole sample (see Figure 1a), there was a sharp decrease (0.65 unit) in depressive symptoms from the second week. The reduction in depression continued, reaching a trough at week 8 that persisted to week 10 (endpoint). A slightly different pattern was observed for the trajectory

of the activation level. As shown in Figure 1b and Table 5, activation increased by 0.42 units after the second week of treatment, peaking at week 8 before decreasing slightly at week 10 (endpoint).

Table 3 Means difference of depression and activation between treatment and control groups over time (Unstructured Time Model)

Time point	LSMD	SE	95% CI	<i>p</i> value
Behavioral Activation (BADs-SF)				
Week 0 (Baseline)	0.30	0.74	(-0.77, 1.36)	.688
Week 2	0.70	0.77	(-0.46, 1.87)	.360
Week 4	3.47	0.94	(1.72, 5.21)	< .001
Week 6	3.41	1.01	(1.39, 5.42)	.002
Week 8	2.86	0.96	(1.05, 4.63)	.004
Week 10 (Endpoint)	3.36	0.89	(1.82, 4.91)	< .001
Depression (PHQ-9)				
Week 0 (Baseline)	-0.08	0.59	(-0.77, 0.60)	.89
Week 2	-0.61	0.69	(-1.55, 0.33)	.379
Week 4	-0.97	0.72	(-1.97, 0.04)	.178
Week 6	-1.41	0.68	(-2.31, -0.50)	.039
Week 8	-1.76	0.74	(-0.68, -2.84)	.019
Week 10 (Endpoint)	-2.59	0.71	(-3.56, -1.61)	< .001

Abbreviations: BADs-SF = Behavioral activation for depression scale-short form; CI = confidence interval; LSMD = least squares mean difference; PE = Psychoeducation; PHQ-9 = Patient Health Questionnaire-9; SE = standard error.

Table 4 Fit indices of latent growth models

	CFI	TLI	RMSEA (90%CI)	SRMR
Depression (unconditional model)	0.96	0.94	0.11(0.08, 0.14)	0.07
Treatment–Depression	0.96	0.94	0.09(0.07, 0.12)	0.06
BA (unconditional model)	0.99	0.99	0.04 (0, 0.08)	0.04
Treatment–BA	0.99	0.99	0.04 (0, 0.07)	0.04
Treatment–BA–Depression	0.97	0.96	0.05(0.04, 0.07)	0.05

Abbreviations: BA = Behavioral activation; CFI = comparative fit index; CI = confidence interval; RMSEA = root mean squared error of approximation; SRMR = standardized root mean square residual; TLI = Tucker–Lewis index.

Treatment condition (GAF-ID or control) was significantly associated with the slope factor of activation level (path a , standardized coefficient = 0.28, $p < .001$), which in turn was associated with the slope factor of depression (path b , standardized coefficient = -0.60 , $p < .001$). After accounting for the growth trajectory of the activation level, the prediction that treatment affected depression was no longer significant (path c' , standardized coefficient = 0.03, $p = .483$). Table 6 shows that the estimated mediated effect ($a \times b$ product) was standardized as -0.17 (95% CI: -0.27 to -0.07 , $p = .001$). After adding the baseline characteristics as covariates, model fit was similar (CFI = 0.97, TLI = 0.96, RMSEA = 0.04 [90% CI, 0.03–0.05], and SRMR = 0.05). The estimated mediated effect in this model was similar to that in the model without baseline characteristics as covariates (standardized estimate = -0.15 , 95% CI: -0.25 to -0.08 , $p < .001$).

Table 5 Growth factor loadings for intercept and slope factors in the parallel latent growth models for depression and activation level

	Depression (PHQ-9)		Behavioral Activation (BADSF)	
	Intercept	Slope	Intercept	Slope
Week 0 (Baseline)	1	0	1	0
Week 2	1	0.65	1	0.42
Week 4	1	0.85	1	0.84
Week 6	1	0.93	1	1.00
Week 8	1	1.01	1	1.17
Week 10 (Endpoint)	1	1.00	1	1.00

Abbreviations: BADSF = Behavioral activation for depression scale-short form; PHQ-9 = Patient Health Questionnaire-9.

Time-specific Mediation Effect in the Simplex Models

For the simplex models with activation level as a mediator, fit indices with a contemporaneous b path were adequate (CFI = 0.96, TLI = 0.95, RMSEA = 0.06 [90% CI, 0.05–0.08], and SRMR = 0.07). Table 7a shows that the contemporaneous indirect effect reached significance from week 6. Table 7b summarizes the results with only significant lagged indirect paths, showing that the paths all passed through M_3 (i.e., activation level at week 4) to influence either contemporary depression or subsequent mediators (M_n), and ultimately, later depression. Fit indices of the simplex mediation model with the lagged b path were adequate (CFI = 0.95, TLI = 0.94, RMSEA = 0.07 [90% CI, 0.06–0.08], and SRMR =

0.08). As shown in Table 8, the indirect effect reached significance from week 6 onwards. As with the contemporaneous b paths, M_3 was the only mediator to be passed through during the treatment.

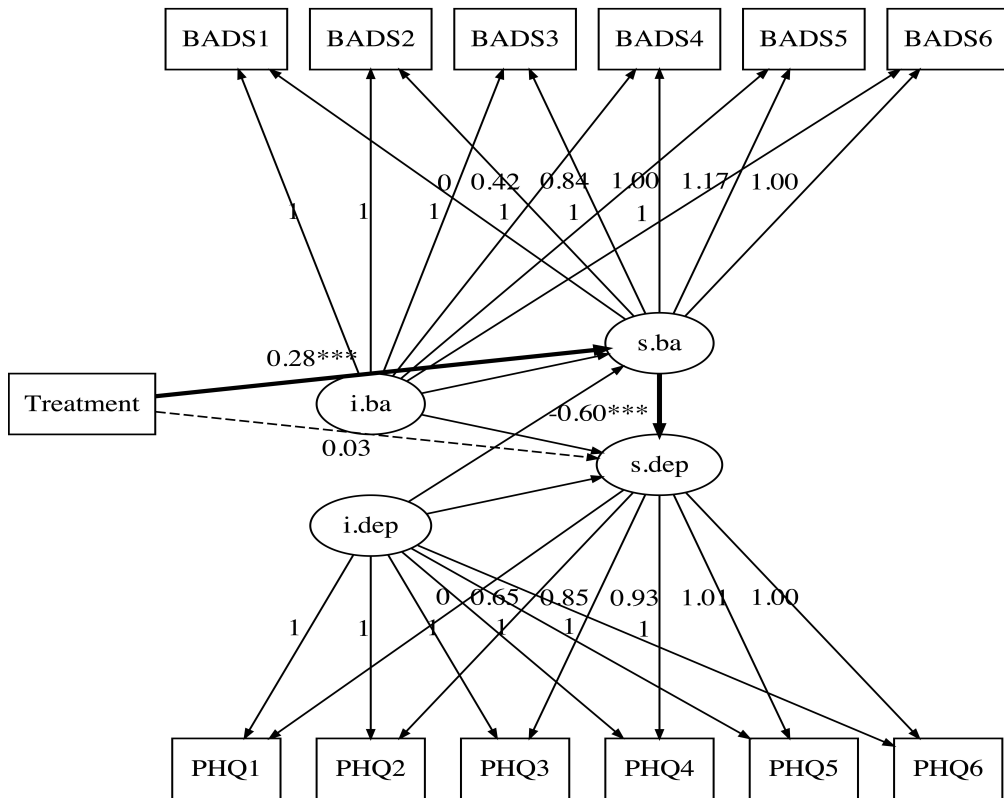


Figure 2 Parallel process latent growth model of depression and activation level conditioned on treatment groups.

Note: Rectangles denote observed variables, and ellipses denote latent variables. Bolded arrows indicated the significant prediction from treatment to growth of activation, growth of activation to growth of depression. Dashed arrow indicated the insignificant prediction from treatment to growth of depression.

Abbreviations: BADS (1, 2, 3, 4, 5, 6) = Behavioral activation of depression scale-Short form (baseline and 2, 4, 6, 8, 10 weeks, respectively); i.dep = intercept growth factor of depression; i.ba = intercept growth factor of behavioral activation; PHQ (1, 2, 3, 4, 5, 6) = Patient Health Questionnaire-9 items (baseline and 2, 4, 6, 8, 10 weeks, respectively); s.ba = slope growth factor of behavioral activation; s.dep = slope growth factor of depression.

For the simplex models with depression as a mediator, the fit indices were acceptable for both contemporary *b* paths (CFI = 0.97, TLI = 0.95, RMSEA = 0.06 [90% CI, 0.05–0.08], SRMR = 0.06) and lagged *b* paths (CFI = 0.95, TLI = 0.93, RMSEA = 0.07 [90% CI, 0.06–0.09], SRMR = 0.08). None of the significant indirect effect from treatment allocation to activation level at each time point passed through depression, indicating that our intervention works though the impact of activation on depression rather than the other way around. More detailed results are provided in the supplementary materials (Appendix 4).

Table 6 Regression coefficients of mediational parallel process growth models

	Standard coefficient	SE	<i>p</i> value
Conditional Models			
Treatment–Depression	–0.13	0.06	.017
Treatment–BA	0.27	0.06	< .001
Parallel process model			
Treatment–BA (<i>a</i> path)	0.28	0.06	< .001
BA–Depression (<i>b</i> path)	–0.60	0.08	< .001
Treatment–Depression (<i>c'</i> path)	0.03	0.05	.483
<i>a</i> × <i>b</i> product	–0.17	0.05	.001

Abbreviations: BA = Behavioral activation; SE = standard error.

Discussion

In this study of data from a large RCT, we provide evidence that activation level underpinned the clinical response to a guided internet-based intervention for depression. During the 8-week treatment period, we showed that (1) our treatment improved activation levels from week 4 and reduced depressive symptoms from week 6, and (2) the activation level acted as a mediator for the change in depressive symptoms.

These findings support the theory that a change in depression is contingent on a change in activation level (e.g., Lewinsohn, 1974). We first confirmed that statistically significant associations existed between treatment allocation, activation, and depression level that were not affected by controlling for baseline characteristics. We further supported this by demonstrating temporal order, evidencing that the significant increase in activation level at week 4 preceded the significant decrease in depressive symptoms at week 6. This was strengthened by the lack of a “reverse” effect of depression on the

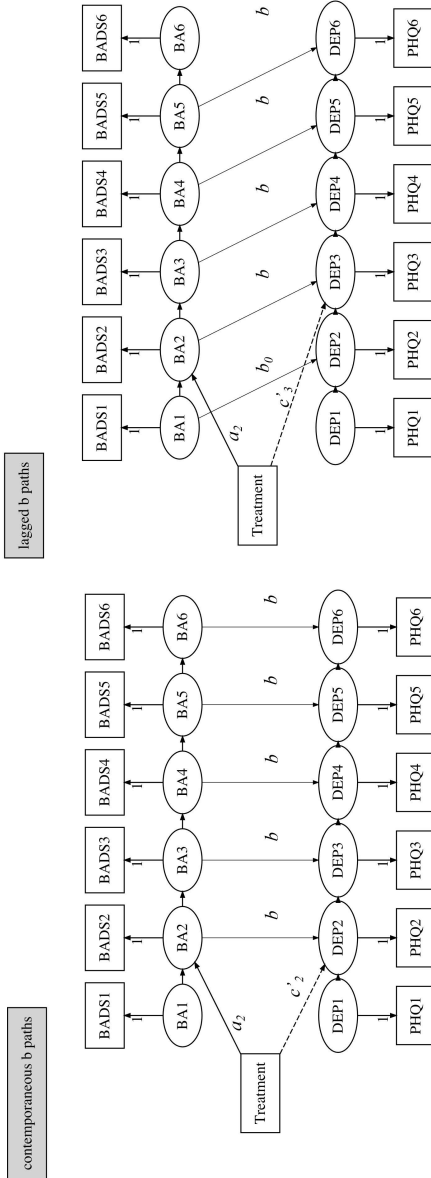


Figure 3 Example diagram of simplex models for mediation with contemporaneous b paths (right side) and lagged b paths (left side) with depression at third timepoint (week 6) as outcome.

Abbreviations: a_2 = parameter estimated coefficient from treatment to week 4 behavioral activation; b = parameter estimated coefficient from mediator to outcome; b_0 = parameter estimated coefficient from baseline mediator to week 2 depression; BA, behavioral activation; BADS(1, 2, 3, 4, 5, 6) = Behavioral activation of depression scale-Short form (baseline and 2, 4, 6, 8, 10 weeks, respectively); c'_2 , c'_3 = parameter estimated coefficient from treatment to week 4, 6 depression after controlled for intermediate behavioral activation; PHQ(1, 2, 3, 4, 5, 6) = Patient Health Questionnaire-9 items (baseline and 2, 4, 6, 8, 10 weeks, respectively).

activation level when conditioned on treatment. Together, these findings strongly suggest that the hypothesized mediation process occurred around week 4.

Our findings are consistent with those of similar randomized studies (e.g., Dimidjian et al., 2017; Nasrin et al., 2017; Santos et al., 2017), but conflict with those presented elsewhere. For example, Richards et al. (2017) observed no mediation effect of activation level in a large RCT comparing behavioral activation and cognitive behavioral therapy, nor did Rovner et al. (2014), when they compared behavioral activation and supportive therapy to prevent depression in older adults. There are a couple of plausible explanations for these incongruencies. First, different control conditions were used, with inactive control groups in the first two (waitlist control or usual obstetric care; similar to ours) (Dimidjian et al., 2017; Nasrin et al., 2017) and active control groups in the latter two (Richards et al., 2017; Rovner et al., 2014). Second, measurements were taken at different times, with previous studies assessing mediation either immediately (Dimidjian et al., 2017; Nasrin et al., 2017) or 4 to 6 months (Richards et al., 2017; Rovner et al., 2014) after completing the intervention. Delaying measurements in this way is less likely to capture significant changes caused by the mediator during treatment.

Two studies have used interventions for depression in which the activation level was examined as a putative mediator, and among these, our findings agree with one and disagree with another. In the research by Luenen et al. (2019) who adopted a similar intervention timeframe (eight sessions completed in 8–10 weeks), it was concluded that the investigated mediation occurred between weeks 3 and 5. However, this was not apparent in the research by Forand et al. (2018) in another 10-week internet-based trial of cognitive behavioral therapy for depression, who found that the change in activation from baseline to week 3 did not predict the subsequent change in depression. This inconsistency could be attributed to the fact that Forand et al. (2018) included another potential mediator (cognitive skills) in their mediation model. If activation level were a proximal process that led to another mediation process, controlling for this specific factor may fail to reveal the activation level as a mediator. It could also be that mediation occurred after week 3 of the intervention; therefore, a test based on earlier change will not have captured the required period. Nevertheless, although the weight of evidence may be shifting, these inconsistencies point to a requirement for more evidence to confirm the mediational role of activation level.

Regarding missing data, more was missing in the intervention group (17.5%) than in the control group (4.3%). This was presumably because the GAF-ID intervention demanded

greater effort to accomplish and because some participants could not afford the time. Alternatively, sending the fortnightly measurements via email separately to monitoring within the intervention may have led to some participants erroneously believing that they had already completed the questionnaires.

Our results help to clarify how internet-based and lay-counselor-guided behavioral activation treatments work. Clinicians can use this new knowledge to prepare patients with depression for a 4- to 6-week lag before a major change occurs in their activation level, and subsequently, their symptoms of depression improve. This may encourage depressed individuals to persevere with treatment when they encounter difficulties increasing activity levels in the first phase of treatment. Clinicians and patients alike can be reassured that persistence with therapy will reduce depressive symptoms and lead to recovery.

The present study has several strengths. First, we used data from a well-powered RCT to ensure that the effect estimates from treatment allocation to activation level and depression could be readily and precisely interpreted as causal. The sample size calculated for the RCT was ample for the current mediation analysis, for which a sample size of at least 100 with at least three repeated observations per individual was considered appropriate (Curran et al., 2011). Second, the fortnightly measures added precision and the low dropout rate (0.20%) contributed to both precision and low risk of bias. Third, we adopted latent growth and simplex mediation modeling to estimate, as precisely as possible, the association between the mediator and depression while controlling for the within-participant change. According to criteria set by Lemmens (2016), our work constitutes a high-quality mediation study.

Some limitations also warrant discussion. Notably, the mediator–outcome relationship could still have been confounded by a third unmeasured variable (e.g., cognition). In addition, we only included a single mediator in our model, limiting us to identifying activation as the mediator. Other working mechanisms correlated with activation level may have mediated part its effect, such as a change in cognition that may have preceded the reduction in depressive symptomatology. Aside from using the SCID-5 to assess unipolar depressive disorder before and after treatment, measurements in the RCT relied on self-reporting every 2 weeks. Thus, the assessments of activation level may not have been objective and may have missed a more nuanced dynamic (Folke et al., 2015). Moreover, lay counselors had no role in assessment of the participants and the effect of change in activation level on depression outcomes was also not assessed by lay counselors and fully independently conducted from these counselors. Therefore, although some bias

can never be fully excluded, it is unlikely bias explained the outcomes.

Future research must seek to replicate our findings with different control groups. It should have a more temporally sensitive design (e.g., experience sampling method), more objective measures of activation, and include other variables (e.g., cognitive variables). Such research may also benefit from experimental manipulation of mediator levels (e.g., component analysis) (Emmelkamp et al., 2014) and micro-trials using experimental designs, such as RCTs with temporally sensitive designs (Brouwer et al., 2020; Slofstra et al., 2018), to reach firm (causal) conclusions (Lorenzo-Luaces, Lemmens, Keefe, Cuijpers, & Bockting, 2021).

Conclusions

This study provides evidence that a change in activation level underpinned the effects of a guided internet-based intervention using behavioral activation to treat depression. In a large-scale RCT, it took 4 and 6 weeks to change activation levels and depressive symptoms, respectively. More studies are still required to support these findings and optimize treatment strategies.

Table 7a Simplex model with contemporaneous b paths for activation level as a mediator

Simplex for mediation with contemporaneous b path		95%CI				
Time-specific outcome	Significant Paths and Effect of treatment	Standardized estimate	SE	p value	Lower limit	Upper limit
Week 2 Depression (Y ₂)	Total effect	-0.05	0.05	.320	-0.17	0.06
	Indirect effect	-0.01	0.01	.379	-0.03	0.01
Week 4 Depression (Y ₃)	Total effect	-0.08	0.06	.189	-0.20	0.05
	Indirect effect T → M ₃ → Y ₃	-0.09 -0.04	0.04 0.02	.035 .006	-0.19 -0.08	-0.001 -0.01
Week 6 Depression (Y ₄)	Total effect	-0.13	0.06	.028	-0.25	-0.004
	Indirect effect T → M ₃ → Y ₃ → Y ₄ T → M ₃ → M ₄ → Y ₄	-0.12 -0.03 -0.04	0.05 0.01 0.02	.016 .005 .006	-0.22 -0.06 -0.08	-0.01 -0.01 -0.02
Week 8 Depression (Y ₅)	Total effect	-0.15	0.06	.012	-0.27	-0.02
	Indirect effect T → M ₃ → Y ₃ → Y ₄ → Y ₅ T → M ₃ → M ₄ → Y ₄ → Y ₅ T → M ₃ → M ₄ → M ₅ → Y ₅	-0.14 -0.02 -0.03 -0.04	0.05 0.01 0.01 0.01	.003 .004 .004 .005	-0.25 -0.04 -0.05 -0.07	-0.04 -0.01 -0.01 -0.01
Week 10 Depression (Endpoint, Y ₆)	Total effect	-0.22	0.06	< .001	-0.34	-0.09
	Indirect effect T → M ₃ → Y ₃ → Y ₄ → Y ₅ → Y ₆ T → M ₃ → M ₄ → Y ₄ → Y ₅ → Y ₆ T → M ₃ → M ₄ → M ₅ → Y ₅ → Y ₆ T → M ₃ → M ₄ → M ₅ → M ₆ → Y ₆	-0.16 -0.02 -0.02 -0.04	0.05 0.01 0.01 0.01	.001 .004 .004 .005	-0.26 -0.03 -0.03 -0.06	-0.06 -0.01 -0.01 -0.01

Note: Only significant paths are shown to save space. Abbreviations: M₃, M₄, M₅ = mediator measurements (taken at weeks 4, 6, and 8, respectively); SE = standard error; T = Treatment allocation (treatment group = 1, control group = 0); Y₂, Y₃, Y₄, Y₅, Y₆ = outcome measurements (taken at weeks 2, 4, 6, 8, and 10, respectively).

Table 7b Simplex model with lagged b paths for activation level as a mediator

Simplex model for mediation with lagged b path					95% CI	
Time-specific outcome	Significant Paths and Effect of treatment	Standardized estimate	SE	p value	Lower limit	Upper limit
Week 4 Depression (Y ₃)	Total effect	-0.08	0.06	.187	-0.21	0.05
	Indirect effect	-0.05	0.05	.269	-0.15	0.03
Week 6 Depression (Y ₄)	Total effect	-0.13	0.06	.025	-0.25	-0.01
	Indirect effect T→M ₃ →Y ₄	-0.11 -0.04	0.05 0.02	.033 .01	-0.22 -0.07	0.001 -0.01
Week 8 Depression (Y ₅)	Total effect	-0.16	0.06	.01	-0.28	-0.02
	Indirect effect T→M ₃ →Y ₄ →Y ₅ T→M ₃ →M ₄ →Y ₅	-0.15 -0.03 -0.04	0.05 0.01 0.02	.003 .008 .01	-0.26 -0.05 -0.07	-0.04 -0.01 -0.01
Week 10 Depression (Endpoint, Y ₆)	Total effect	-0.22	0.06	< .001	-0.35	-0.09
	Indirect effect T→M ₃ →Y ₄ →Y ₅ →Y ₆ T→M ₃ →M ₄ →Y ₅ →Y ₆ T→M ₃ →M ₄ →M ₅ →Y ₆	-0.15 -0.02 -0.03 -0.04	0.05 0.01 0.01 0.01	.002 .007 .008 .009	-0.26 -0.04 -0.05 -0.07	-0.04 -0.01 -0.01 -0.01

Note: Only significant paths are shown to save space.

Abbreviations: M₃, M₄, M₅ = mediator measurements (taken at weeks 4, 6, and 8, respectively); SE = standard error; T = Treatment allocation (treatment group = 1, control group = 0); Y₂, Y₃, Y₄, Y₅, Y₆ = outcome measurements (taken at weeks 2, 4, 6, 8, and 10, respectively).

References

- American Psychiatry Association (2015). *Depressive disorders: DSM-5 selections*. American Psychiatric Pub.
- Arjadi, R., Nauta, M. H., Scholte, W. F., Hollon, S. D., Chowdhary, N., Suryani, A. O., & Bockting, C. L. (2016). Guided Act and Feel Indonesia (GAF-ID) - Internet-based behavioral activation intervention for depression in Indonesia: Study protocol for a randomized controlled trial. *Trials*, 17(1), 1–10. <https://doi.org/10.1186/s13063-016-1577-9>
- Arjadi, R., Nauta, M. H., Scholte, W. F., Hollon, S. D., Chowdhary, N., Suryani, A. O., ... Bockting, C. L. (2018). Internet-based behavioural activation with lay counsellor support versus online minimal psychoeducation without support for treatment of depression: a randomised controlled trial in Indonesia. *The Lancet Psychiatry*, 5(9), 707–716. [https://doi.org/10.1016/S2215-0366\(18\)30223-2](https://doi.org/10.1016/S2215-0366(18)30223-2)
- Bockting, C.L., & Van Valen. (2015) *Doe en Voel*. The Netherlands.
- Brouwer, M. E., Molenaar, N. M., Burger, H., Williams, A. D., Albers, C. J., Lambregtse-van den Berg, M. P., & Bockting, C. L. (2020). Tapering antidepressants while receiving digital preventive cognitive therapy during pregnancy: An experience sampling methodology trial. *Frontiers in Psychiatry*, 11, 1116.
- Carlbring, P., Hägglund, M., Luthström, A., Dahlin, M., Kadowaki, Å., Vernmark, K., & Andersson, G. (2013). Internet-based behavioral activation and acceptance-based treatment for depression: A randomized controlled trial. *Journal of Affective Disorders*, 148(2-3), 331–337.
- Carroll, H. A., Hook, K., Perez, O. F. R., Denckla, C., Vince, C. C., Ghebrehiwet, S., ... others. (2020). Establishing reliability and validity for mental health screening instruments in resource-constrained settings: Systematic review of the phq-9 and key recommendations. *Psychiatry Research*, 113236.
- Cheong, J., MacKinnon, D. P., & Khoo, S. T. (2003). Investigation of mediational processes using parallel process latent growth curve modeling. *Structural Equation Modelling*, 10(2), 238–262. <https://doi.org/10.1207/S15328007SEM1002>
- Cuijpers, P., Straten, A. van, & Warmerdam, L. (2007). Behavioral activation treatments of depression: A meta-analysis. *Clinical Psychology Review*, 27(3), 318–326. <https://doi.org/http://dx.doi.org/10.1016/j.cpr.2006.11.001>
- Cuijpers, P., Van Straten, A., Andersson, G., & Van Oppen, P. (2008). Psychotherapy for depression in adults: A meta-analysis of comparative outcome studies. *Journal of Consulting and Clinical Psychology*, 76(6), 909.
- Curran, P. J., Obeidat, K., & Losardo, D. (2010). Twelve Frequently Asked Questions About Growth Curve Modeling. *Journal of cognition and development*, 11(2), 121–136. <https://doi.org/10.1080/15248371003699969>
- Curry, J. F., & Meyer, A. E. (2016). Can less yield more? Behavioral activation for adolescent depression. *Clinical Psychology: Science and Practice*, 23(1), 62–65. <https://doi.org/http://dx.doi.org/10.1111/cpsp.12141>
- Dimidjian, S., Goodman, S. H., Sherwood, N. E., Simon, G. E., Ludman, E., Gallop, R., ... others. (2017). A pragmatic randomized clinical trial of behavioral activation for depressed pregnant women. *Journal of Consulting and Clinical Psychology*, 85(1), 26.
- Dimidjian, S., Martell, C. R., Herman-Dunn, R., & Hubley, S. (2014). Behavioral activation for depression.
- Emmelkamp, P. M., David, D., Beckers, T., Muris, P., Cuijpers, P., Lutz, W., ... others. (2014). Advancing psychotherapy and evidence-based psychological interventions. *International Journal of Methods in Psychiatric Research*, 23(S1), 58–91.
- Ferster, C. B. (1973). A functional analysis of depression. *American Psychologist*, 28(10), 857.
- Ferster, C. B. (1981). A functional analysis of behavior therapy. *Behavior Therapy for Depression:*

- Present Status and Future Directions, 181–196.
- Finning, K., Richards, D. A., Moore, L., Ekers, D., McMillan, D., Farrand, P. A., ... Fletcher, E. (2017). Cost and outcome of behavioural activation versus cognitive behavioural therapy for depression (COBRA): a qualitative process evaluation. *BMJ Open*, 7(4).
- First, M. B., Williams, J. B. W., Karg, R. S., & Spitzer, R. L. (2015). Structured clinical interview for DSM-5—Research version (SCID-5 for DSM-5, research version; SCID-5-RV). Arlington, VA: American Psychiatric Association, 1-94.
- Folke, F., Hursti, T., Tungström, S., Söderberg, P., Kanter, J. W., Kuutmann, K., ... Ekselius, L. (2015). Behavioral activation in acute inpatient psychiatry: A multiple baseline evaluation. *Journal of Behavior Therapy and Experimental Psychiatry*, 46, 170–181.
- Forand, N. R., Barnett, J. G., Strunk, D. R., Hindiyeh, M. U., Feinberg, J. E., & Keefe, J. R. (2018). Efficacy of guided iCBT for depression and mediation of change by cognitive skill acquisition. *Behavior Therapy*, 49(2), 295–307.
- Gaynor, S. T., & Harris, A. (2008). Single-participant assessment of treatment mediators: Strategy description and examples from a behavioral activation intervention for depressed adolescents. *Behavior Modification*, 32(3), 372–402.
- Goldsmith, K. A., MacKinnon, D. P., Chalder, T., White, P. D., Sharpe, M., & Pickles, A. (2018). Tutorial: The practical application of longitudinal structural equation mediation models in clinical trials. *Psychological Methods*, 23(2), 191.
- Graham, J. W. (2009). Missing Data Analysis: Making It Work in the Real World. *Annual Review of Psychology*, 60(1), 549–576. <https://doi.org/10.1146/annurev.psych.58.110405.085530>
- Herrman, H., Kieling, C., McGorry, P., Horton, R., Sargent, J., & Patel, V. (2019). Reducing the global burden of depression: A lancet–world psychiatric association commission. *The Lancet*, 393(10189), e42–e43.
- Janssen, N. P., Hendriks, G.-J., Baranelli, C. T., Lucassen, P., Voshaar, R. O., Spijker, J., & Huibers, M. J. (2020). How does behavioural activation work? A systematic review of the evidence on potential mediators. *Psychotherapy and Psychosomatics*, 1–9.
- Kazdin, A. E. (2007). Mediators and mechanisms of change in psychotherapy research. *Annu. Rev. Clin. Psychol.*, 3, 1–27.
- Lazarus, A. A. (1972). Some reactions to Costello’s paper on depression. *Behavior Therapy*, 3(2), 248–250.
- Lemmens, L. H., Müller, V. N., Arntz, A., & Huibers, M. J. (2016). Mechanisms of change in psychotherapy for depression: An empirical update and evaluation of research aimed at identifying psychological mediators. *Clinical Psychology Review*, 50, 95–107. <https://doi.org/10.1016/j.cpr.2016.09.004>
- Lewinsohn, P. M. (1974). A behavioral approach to depression. *Essential Papers on Depression*, 150–172.
- Lorenzo-Luaces, L., Lemmens, L. H. J. M., Keefe, J. R., Cuijpers, P., & Bockting, C. L. (2021). The efficacy of cognitive behavioral therapy for emotional disorders. In A. Wenzel (Ed.), *Handbook of cognitive behavioral therapy* (Vol. 1, pp. 51–89). American Psychological Association.
- Luenen, S. van, Kraaij, V., Spinhoven, P., Wilderjans, T. F., & Garnefski, N. (2019). Exploring Mediators of a Guided Web-Based Self-Help Intervention for People With HIV and Depressive Symptoms: Randomized Controlled Trial. *JMIR Mental Health*, 6(8), e12711. <https://doi.org/10.2196/12711>
- Ly, K. H., Trüschel, A., Jarl, L., Magnusson, S., Windahl, T., Johansson, R., ... & Andersson, G. (2014). Behavioural activation versus mindfulness-based guided self-help treatment administered through a smartphone application: a randomised controlled trial. *BMJ open*, 4(1).
- MacKinnon, D. P. (2008). Introduction to statistical mediation analysis. Routledge.
- MacKinnon, D. P., Cheong, J., & Pirlott, A. G. (2012). Statistical mediation analysis.

- Manos, R. C., Kanter, J. W., & Busch, A. M. (2010). A critical review of assessment strategies to measure the behavioral activation model of depression. *Clinical Psychology Review, 30*(5), 547–561.
- Manos, R. C., Kanter, J. W., & Luo, W. (2011). The behavioral activation for depression scale—short form: Development and validation. *Behavior Therapy, 42*(4), 726–739.
- Martell, C. R., Dimidjian, S., & Herman-Dunn, R. (2013). *Behavioral activation for depression: A clinician's guide*. Guilford Press.
- National Collaborating Centre for Mental Health (UK, 2010). *Depression: The treatment and management of depression in adults (updated edition)*. In. British Psychological Society.
- Nyström, M. B., Stenling, A., Sjöström, E., Neely, G., Lindner, P., Hassmén, P.,... & Carlbring, P. (2017). Behavioral activation versus physical activity via the internet: A randomized controlled trial. *Journal of affective disorders, 215*, 85-93.
- Moreno-Peral, P., Bellón, J. Á., Huibers, M. J., Mestre, J. M., Garcí'a-López, L. J., Taubner, S., ... Conejo-Cerón, S. (2020). Mediators in psychological and psychoeducational interventions for the prevention of depression and anxiety. A systematic review. *Clinical Psychology Review, 76*, 101813.
- Muthén, B. O., & Muthén, L. K. (2019). *Mplus (Version 8.3)*. Los Angeles, CA.
- Nasrin, F., Rimes, K., Reinecke, A., Rinck, M., & Barnhofer, T. (2017). Effects of brief behavioural activation on approach and avoidance tendencies in acute depression: Preliminary findings. *Behavioural and Cognitive Psychotherapy, 45*(1), 58–72.
- Pinheiro, J., Bates, D., DebRoy, S., Sarkar, D., & R Core Team. (2020). nlme: Linear and nonlinear mixed effects models. Retrieved from <https://CRAN.R-project.org/package=nlme>
- Richards, D. A., Ekers, D., McMillan, D., Taylor, R. S., Byford, S., Warren, F. C., ... Kuyken, W. (2016). Cost and Outcome of Behavioural Activation versus Cognitive Behavioural Therapy for Depression (COBRA): a randomised, controlled, non-inferiority trial. *The Lancet, 388*(10047), 871–880.
- Richards, D. A., Rhodes, S., Ekers, D., McMillan, D., Taylor, R. S., Byford, S., ... others. (2017). Cost and outcome of behavioural activation (cobra): A randomised controlled trial of behavioural activation versus cognitive-behavioural therapy for depression. *Health Technology Assessment (Winchester, England), 21*(46), 1–366.
- Rovner, B. W., Casten, R. J., Hegel, M. T., Massof, R. W., Leiby, B. E., Ho, A. C., & Tasman, W. S. (2014). Low vision depression prevention trial in age-related macular degeneration: A randomized clinical trial. *Ophthalmology, 121*(11), 2204–2211.
- Santos, M. M., Rae, J. R., Nagy, G. A., Manbeck, K. E., Hurtado, G. D., West, P., ... Kanter, J. W. (2017). A client-level session-by-session evaluation of behavioral activation's mechanism of action. *Journal of Behavior Therapy and Experimental Psychiatry, 54*, 93–100.
- Santos, M. M., Ullman, J., Leonard, R. C., Puspitasari, A. J., Cook, J., & Riemann, B. C. (2019). Behavioral Activation as a Mechanism of Change in Residential Treatment for Mood Problems: A Growth Curve Model Analysis. *Behavior Therapy, 50*(6), 1087–1097. <https://doi.org/10.1016/j.beth.2019.05.004>
- Silverstein, M., Cabral, H., Hegel, M., Diaz-Linhart, Y., Beardslee, W., Kistin, C. J., & Feinberg, E. (2018). Problem-solving education to prevent depression among low-income mothers: A path mediation analysis in a randomized clinical trial. *JAMA Network Open, 1*(2), e180334–e180334.
- Slofstra, C., Nauta, M. H., Bringmann, L. F., Klein, N. S., Albers, C. J., Batalas, N., ... Bockting, C. L. (2018). Individual negative affective trajectories can be detected during different depressive relapse prevention strategies. *Psychotherapy and Psychosomatics, 87*(4), 243–245.
- Stein, A. T., Carl, E., Cuijpers, P., Karyotaki, E., & Smits, J. A. J. (2020). Looking beyond depression: A meta-analysis of the effect of behavioral activation on depression, anxiety, and activation. *Psychological Medicine, Not Specified*.

- <https://doi.org/http://dx.doi.org/10.1017/S0033291720000239>
- van Buuren, S., & Groothuis-Oudshoorn, K. (2011). mice: Multivariate imputation by chained equations in r. *Journal of Statistical Software*, 45(3), 1–67. Retrieved from <https://www.jstatsoft.org/v45/i03/>
- Weidberg, S., González-Roz, A., Garcí'a-Fernández, G., & Secades-Villa, R. (2020). Activation level as a mediator between behavioral activation, sex, and depression among treatment-seeking smokers. *Addictive Behaviors*, 106715.
- Weisz, J. R., McCarty, C. A., & Valeri, S. M. (2006). Effects of psychotherapy for depression in children and adolescents: A meta-analysis. *Psychological Bulletin*, 132(1), 132.

Chapter 6

General discussion

This dissertation was set out to explore potential accessible routes to facilitate bridging the mental health gap in LMICs. In the previous four *chapters* we described (meta-analytic) studies that may provide evidence to underpin this process of narrowing or even closing this gap. The effectiveness of digital interventions for all types of mental health problems and conditions have been studied and described. For depression specifically, the leading psychological theories of depression onset, and the effectiveness, and working mechanism of a digital intervention have been studied. In the current *chapter*, the main findings of this dissertation are presented and put into scientific and clinical perspectives. In addition, clinical and research implications are addressed to inform the relative stakeholders. Limitations of the studies and potential future directions for research are also provided.

Main findings of the current dissertation

Evidence of vulnerability factors predictive of major depressive disorder (MDD) onset derived from five leading psychological theories, i.e., cognitive, diathesis-stress, behavioral, personality-based and psychodynamic theories, were systematically reviewed in *Chapter 2*. Only 26 studies could be included within a search that included 42,133 articles and out of these, 14 studies with available data were meta-analyzed providing some evidence of predictors of MDD onset rooted in cognitive- (6,585 participants), and personality-based (14,394 participants) theories (i.e., dysfunctional attitudes, (negative) cognitive styles, and cognitive reactivity, or negative emotionality). There was no prospective empirical evidence for psychological factors derived from psychodynamic theories and there were not enough studies (< three studies) available to examine the robust evidence for behavioral-, and diathesis-stress theories. Overall, the prospective evidence for psychological factors derived from these leading psychological theories of MDD onset is limited.

Effectiveness of minimal interventions, specifically effectiveness of digital and psychosocial interventions, were examined in *Chapter 3* and *4*. In *Chapter 3*, we presented the results from a meta-analysis of 22 studies ($N = 4,104$; 2,351 in the intervention group, 1,753 in the control group) on the treatment effects of digital psychological interventions for all types of mental health problems and conditions in LMICs. Digital interventions were overall moderately effective when compared with control groups, especially versus usual care. These interventions were mainly studied amongst young adults with depression or substance misuse. In three to four studies, interventions on anxiety ($n=4$) and Post Traumatic Stress Disorders ($n=3$) were investigated. In *Chapter 4*, the treatment effect of psychosocial interventions on depression amongst university students in China was meta-

analyzed. An overall large effect size was found compared to the control groups (most were waitlist control/assessment only), although the effects merit further examination by research of high quality due to the overall high risk of bias of the included studies.

Further, in *Chapter 5*, the working mechanism of one specific type of minimal treatment, i.e., internet-based behavioral activation (BA) treatment, was examined in a randomized controlled trial. This RCT evaluated an eight-week internet-based BA treatment guided by lay counselors for MDD in Indonesia. Results showed that it took around four weeks before significant change in activation level occurred, which led to subsequent reduction of depressive symptoms after (in 6 weeks). It confirmed the mediational role of activation as a working mechanism in BA treatment.

Psychological theories of depression

To enrich the understanding of how MDD develops and furthermore to provide essential insights that could guide potential innovation in interventions, in *Chapter 2*, we investigated and summarized the evidence for the five leading theories of MDD that underpin current treatment options. However, the available evidence is of surprising scarcity. A very small proportion (0.06%) from the records ($n = 42,133$) we searched answered our research question: what is the predictive evidence for MDD onset of the factors derived from the leading psychological theories based on prospective longitudinal studies.

Among them, there is evidence for factors from cognitive (6,585 participants) and personality-based theories (14,394 participants). Consistent with previous reviews (Klein et al. 2011; Lakdawalla et al. 2007), individuals with higher levels of dysfunctional attitudes, rumination, and greater cognitive reactivity, as well as higher levels of the personality trait 'negative emotionality', had an increased odd to develop MDD. But overall, this evidence is far less than sufficient to reach a firm conclusion due to the wide confidence intervals of pooled odds ratios and high heterogeneity.

Findings in *Chapter 2* should inform us about the robustness of evidence for factors derived from leading psychological theories to predict MDD onset. The results however rather point at limited evidence. Other CMDs may face the similar situation. For example, Spence and Rapee (2016) reviewed the evidence of etiology of social anxiety disorder (SAD). With acknowledging the considerable progress in empirical literature, the researchers, at the same time, highlighted the significant gap in knowledge of longitudinal research to clarify causal pathways from vulnerable factors to the development of SAD.

Working mechanism

On the other hand, we certainly have robust and replicable evidence on the efficacy of some psychotherapies rooted in the theories/models described in *Chapter 2*, e.g., cognitive behavioral therapy (CBT), BA for depression. Identification of a valid mediator, as an important part of treatment working mechanism, forms essential input for refinement and potentially also for simplification of interventions, and provide important feedback loops in theories of depression.

Therefore, in *Chapter 5*, we used data from an RCT of an 8-week internet-based BA intervention on depression involving a large sample of MDD patients to examine change of activation level as a working mechanism of treatment. Evidence from our trial supported the putative working mechanism, that is, BA treatment exhilarated activation level from week 4 and reduced depressive symptoms from week 6; activation level acted as a mediator for change of depressive symptoms during treatment.

This result indicates the probable timing of mediation occurred in our BA program. It further contributed to clarify the inconsistency observed in previous similar randomized studies. This inconsistency might be explained by several factors: type of control group; intervention scale and measurement scheme; and controlling for other variables. Our findings were consistent with those RCTs which 1) used an inactive control group (e.g., Dimidjian et al., 2017; Nasrin et al., 2017; Santos et al., 2017); 2) with a similar measurement scheme (Luenen et al., 2019). Neither of these studies controlled for other variables than behavioral activation level. On the other hand, for the studies with an active control group (Richards et al. 2017; Rovner et al. 2014), or a different measurement scheme (Dimidjian et al., 2017; Nasrin et al., 2017), or with other factor such as cognitive skills controlled (Forand et al., 2018), null findings of targeted mediation process were reported. Overall, the mediational role of activation was not replicated consistently across studies due to the fact that they were mostly heterogeneous and unsatisfactory in methodological respect. More studies on working mechanisms are still needed.

Effectiveness of minimal psychological intervention in LMICs

Results in *Chapter 3* and *4* shared the commonality of evaluating minimal psychological interventions in LMICs, which has the potential to reduce the mental health gap, if effective. Two meta-analyses were conducted focusing on digital interventions and psychosocial interventions, respectively.

Firstly, in *Chapter 3*, we systematically investigated the available evidence for digital psychological interventions in reducing mental health problems and conditions in LMICs.

With 22 studies meta-analyzed, results showed that the identified interventions are moderately effective when compared with control groups including usual care, waitlist, and active control. This overall effect size is similar to that reported in HICs (e.g., $g = 0.53$; Barak et al., 2018). Specifically, an overall moderate effect size was yielded from eight studies using treatment as usual as control group, whereas this effect size should be interpreted with caution as treatment as usual in these studies differed considerably (ranging from health education to medication).

It is encouraging to witness the considerable increase in the number of trials investigating digital psychological interventions in LMICs since the previous systematic review (in 2014, with only three studies included). This increase has enabled us to quantitatively assess their effectiveness for the first time. These studies were primarily conducted in regions of Asian and Latin America, which are home to the majority of the population in the LMICs. Relevant research in Africa was not identified during the literature search conducted in *Chapter 3*.

Secondly, in *Chapter 4*, the treatment effect of psychological interventions for depression studied in local Chinese university students was examined. Compared to the control groups, a large overall effect size ($g = 1.08$) was obtained. This effect size is comparable to that previously reported in a meta-analysis of psychological intervention on depression in LMICs ($g = 1.10$; Cuijpers et al., 2018), but is higher than that based on Western samples ($g=0.60$; Cuijpers et al., 2018). Researchers suggest that this discrepancy could be related to the differences in the use of control groups across countries (Cuijpers et al., 2018). For example, in Western studies, control group normally consisted of ‘usual-care’ which often implies some standard level of care, whereas, in the case of the current review and other studies conducted in low-and-middle income countries, the control group more often means ‘no care’ (Cuijpers et al., 2011). When the effect size was calculated exclusively based on studies that compared to usual care/placebo, the overall effect size was similar to that reported in Western samples ($g=0.56$), suggesting that the effectiveness of psychological intervention in both Western and Eastern samples may be comparable.

Taken together, both meta-analyses showed moderate to large effect sizes of minimal psychological interventions compared to control groups. Specifically, they both found a remarkably similar moderate effect size when compared to usual care ($g = 0.54$ in *Chapter 3*; 0.56 in *Chapter 4*). The studies included in *Chapter 3* and *4* have been conducted mostly in adults with depression, and the majority of interventions studied was CBT either in individual or group format. Both of these studies indicated the effectiveness of minimal

psychological interventions, and the promise of them to be incorporated in the future management of depression in clinical/university counselling practice.

However, these results are still challenged by the considerable heterogeneity (I^2 ranged from 47% to 74%) observed in our analysis. The heterogeneity likely included clinical heterogeneity (different interventions/mental health problems) and methodological heterogeneity (various measurements of same mental health problem). Unfortunately, we were not able to provide key subgroups to explain this divergence, which calling for further efforts on the investigation of a broader range of the moderators to pinpoint those predominant ones.

Minimal psychological interventions amongst young generations

This dissertation particularly related to young people (mean age of the study population was 20 to 35 years in *Chapter 3, 4*), a group that represents critical societal capitals. The young people studied in this dissertation can be roughly categorized into two groups: university students, and young participants recruited from community. These two groups could differ in their available access to mental health service. Take China as an example, in total there are around **84 million individuals** aged 20 to 25 years old in 2019, out of these, 37 million are university students at campus (Chinese Ministry of Education). The corresponding therapist-population ratio in university campus is 1:2.363, whereas the ratio in community is 1:100.000 (*Simple Psychology Report*, according to the data at 2015).

Given the evidence for minimal interventions, especially guided digital psychological interventions as reported in *Chapter 3* and *4*, these interventions might be the most feasible way to target mental health problems for those young adults without access to the mental health care resource. Their sufficient internet literacy also prepares them for the innovative method to deliver mental health care service (e.g., Simons et al., 2016; Arjadi et al., 2018). Hopefully further application of guided digital intervention may ultimately help reduce the negative consequences (e.g. unable to get timely treatment, poor prognosis) related to disproportional access to mental health care in the young generation in LMICs.

Digital Technology

In the field of mental health care, technology contained great potential to revolutionize the way to deliver mental health care. Through Internet and smartphones, mental health care can be offered in combination with guidance.

Despite of this, the adoption of evidence-based digital intervention programs in real clinical practice is of concern. For example, the evidence for apps targeting depression included in *Chapter 3* has been rapidly growing but most available digital interventions and

APPs in, for example, app stores are not evaluated on their effectiveness (Chang et al., 2020). A recent summary of apps or programs available in China for postpartum depression found 26 programs whereas these apps were barely evidence based (Li et al., 2020). On the other hand, for those effective programs we meta-analyzed in *Chapter 3*, it still remains uncertain how many of them are still active in clinical uptake and utilization. Therefore, regulation and guidance are needed to responsibly help users navigate towards a better choice in the jungle of digital intervention programs.

Alongside the benefits brought by digital technology, we meanwhile still need to remain aware of its potential risks, and the unintended consequence of widening inequalities in mental health care between people who can and cannot get access to the internet and mobile devices, for example, children and older individuals, and extremely impoverished groups. An investigation on the internet intervention trial in *Chapter 5* found that the online program is promising for all social economic status groups in a (sub)urban LMIC setting (van der Wal et al., 2020). This result is promising, but further studies are warranted to examine the effectiveness of online treatment in lower social economic status groups, rural participants and elderly, to delineate and reduce any possible barriers for them to get access to the available online treatment.

Embrace the similarities and leverage resources to adjust the differences (HICs vs. LMICs)

Nevertheless, the mental health gap is not exclusively a problem of LMICs, but also one in HICs (Chisholm, 2016). The evidence aggregated in this dissertation certainly warrant continuous in-depth debate and research regarding the possible and innovative ways to close the mental health gap globally. Only if a collective global commitment has been made to increase investments in mental health and expand efforts at the country level, the target of closing the mental health gap can be approached in a substantive way.

Two aspects shared globally could help carry this field forward. First, the way of delivering mental health care via digital devices/channels work globally as long as basic infrastructure is secured (*Chapter 3*). Second, interventions that can be applied universally could help break the nation's borders. For example, BA intervention, with parsimonious underlying mechanism and insensitivity to culture, can serve as a good candidate in this regard (*Chapter 5*). Local adaptations of delivery methods including guidance are encouraged to strategically build upon these two aspects to address the variations in terms of societal norms and capacities of mental health care across the countries.

Besides, building on research capacity in LMICs should be put on the agenda, particularly involving both LMICs and HICs in this communication. Many initiatives have been taken with this goal and been integrated in clinical practice in LMICs (e.g. Emerald Project) leaving legacy of educational value. For example, systematic reviews can be regarded as an efficient way to collect and summarize studies in a particular area of health science. Researchers of diverse disciplines can use this methodology to aggregate the local evidence. In *Chapter 4*, we included articles published in Chinese language and thereby we contributed to the local voice as well as diminished potential publication bias in this field. Training courses on systematic review and collaborative scientific writing have been applied in some cases to increase the research capacity of LMICs (e.g. Jack et al., 2020; DaSilva et al., 2019). In this way, LMICs can participate more in the campaign of global mental health from research perspective.

Methodological considerations in evaluation of minimal psychological intervention

During the investigation of effectiveness and mechanism of digital intervention, two considerations regarding methodology were observed in this thesis. The first reflection concerns the validity of the results we summarized. Conclusions on effectiveness made in the current thesis were all from randomized efficacy trials which secured the internal validity of the interventions we were interested in. However, mental health apps/online programmes suffer from the low engagement issues that patients do not have sufficient motivation to adhere to the programs in reality. This phenomenon might threaten the external validity of digital intervention which are normally developed and tested in a research setting. As mentioned above, it has been witnessed that many websites/app intervention programs stopped after the research output delivered. Since it is relying on other factors other than research efforts (e.g. fundamental infrastructure, financial budgets, policy making), the translations into real application appears painfully difficult.

The second aspect should be noted is the need of rigid methodology during the examination of effectiveness and the working mechanism of minimal intervention. Methodology guidance on an RCT are well-documented (Higgins et al., 2011), nonetheless, it has been noticed, from *Chapter 3* and *4*, that these well-documented methodology instruction have not yet been translated well in research practice in LMICs. The included RCTs were rated as high risk of bias regarding multiple aspects. On top of this, when it comes to the examination of mechanism of change, inherent heterogeneity from measurement to data analytic methods are observed across studies. This phenomenon calls for a consensus

on the standard of an appropriate design to investigate treatment effectiveness, mechanisms and a consensus on the value of a good clinical trial design, in the LMICs.

Limitation of the current thesis

Several limitations should be acknowledged. The majority of the evidence we summarized in this thesis relied heavily on self-report or retrospective measures. In *Chapter 2*, we did not limit the way that theoretical concepts measured though we ended up with publications using mostly self-reports to measure factors derived from the leading theories. In *Chapter 5*, behavioral activation was measured using questionnaires without other more objective measures, although depressive episodes were assessed with clinical interviews (SCID-5, First et al., 2015). Taken together this can impose the risk of information bias on the results of this dissertation.

As a common concern in systematic reviews, potential publication bias should be taken into account during the interpretation of the results. Firstly, in *Chapters 2* and *3*, only publication in English were searched. This conduct could have introduced bias in our results, especially within the context of global mental health where research output is expected to present in various languages. Though there was no substantial publication bias detected by analytic methods, this omission of publications in other languages has to be notified.

Due to the selection of participants, the generalizability of our results may be limited. The studies summarized in *Chapter 2* were mainly from Western sample that makes one hesitant to generalize the primary findings into population in other countries (which accounted for more than 80% total population in the world). In *Chapter 3, 4*, the 'assessment only' group represented a large portion of the control condition; therefore the observed effect may have been inflated by this contrast. *Chapter 3, 4*, and *5* largely focused on young adults which was partly due to our intentional choice and partly due to the intrinsic feature of digital technology (i.e., more accessible in younger generation). This limited us to have conclusions regarding the application of these interventions in older adults and children/adolescents. Besides, the results from *Chapter 3* and *4* may not be generalized in a long-term effect since few studies provided proper follow-up data.

Lastly, although we aimed to clarify the direction of relationship among predictive factors and depression onset (*Chapter 2*), and to identify pathway of working mechanisms during treatment of depression (*Chapter 5*), causal inference should bear more caution. The observational studies included in *Chapter 2* may not able to exclude potential confounding factors (e.g. environmental factors, biological factors) in the explanations of MDD etiology. For the same reason, the working mechanisms identified in *Chapter 5* cannot be interpreted

in a completely causal manner because the mediator-outcome relation can still be confounded by a third unmeasured variable (such as a change in cognitions). Besides, given that we only had repeated data of activation level and depressive symptoms over time we could not control for change in cognitions or other potential alternative mediators.

Implications

To understand to what extent the leading theories explain the development of MDD, researchers firstly should be aware of the scarcity of predictive evidence of those factors derived from these theories. There was some prospective evidence for the cognitive and personality-based theories in relation to onset of MDD, which supports current treatments that targets these factors (such as cognitive therapy). However, the overall limited number of eligible prospective studies on onset of MDD prevented us from drawing strong inferences on the evidence for the five leading psychological theories, in line with findings of a previous extensive meta-analysis indicating limited evidence for neurobiological theories of depression (Kennis et al., 2019).

In the evaluation of effectiveness of minimal psychological intervention in LMICs, the results from *Chapter 3* and *4* can have clinical and policy implications. Our results suggest that guided digital psychological interventions can be incorporated in clinical practice to manage patients with depression and substance misuse. They also have potential for anxiety and PTSD. Second, psychological interventions delivered via a range of digital technologies with guidance could be useful clinically for patients aged 20–35 years with various mental health problems and conditions. In terms of the specific psychological interventions studied in university students in China, cognitive behaviour therapy (CBT) was identified as the most common type of intervention (36% of the included studies), and was generally of low intensity (normally 6-8 group sessions) with a large effect size in *Chapter 4*. As such, it implicated a potentially important step forward in further dissemination of CBT in Chinese universities. At the policy level, while more initiatives and investment are required from governmental as well as non-governmental organisations to ensure a sustainable health-care system, innovative and remotely delivered digital psychological interventions could make a valuable difference in treating mental health problems, particularly during the COVID-19 pandemic.

The current dissertation can also have implications on clinical practice related to BA intervention on depression. Results in *Chapter 5* can help clinicians understand the process during BA treatment (particularly via internet) more precisely, and also to help depressed individuals to get prepared for a four to six-week time window before prominent change

occurs in activation level and subsequently a reduction of depressive symptomatology. Our findings may help to encourage depressed individuals as well as clinicians that have difficulty to increase the activity level in the first phase of treatment by ensuring that persistence in continuing BA will result in reduction of depressive symptomatology and recovery.

Future direction of research

Future research may address the three topics we examined. To start, leading psychological theories of depression and other CMDs require more synthesis, ideally based on a patient-level individual analysis and using a holistic framework with evidence to enlighten the dynamic of CMDs, therefore provide a solid scientific base to understand CMDs.

Meanwhile, despite of the promising preliminary results in *Chapter 3* and *4*, rigorous evaluation of the effects of minimal psychological interventions for specific mental health problems using well-designed RCTs are still needed (i.e., additional trials for anxiety, post-traumatic stress disorder). For digitalized intervention, investigation of optimal type of guidance is also encouraged as well as other possible factors to improve engagement of patients. For those who might not be familiar with digital applications, e.g., older adults and very young children, adaptations should be investigated to suit their situation. The long-term treatment effect of these psychological interventions is also necessary to examine, given the chronic nature of most mental health problems.

Future research should also continue with the exploration of working mechanisms of psychological treatment, especially those that can be delivered in a parsimonious and effective way, with more careful and innovative designs. A reasonable time frame of assessment using reliable measurements installed in a well-powered RCT is the first firm step. Awareness to integrate the examination of potential mechanisms of action into a clinical trial design should be introduced at the beginning of design, thus making optimal use of the resources needed to implement a trial. Design of temporally sensitivity with ideally more (objective) measurement, and possible experimental manipulation of levels of mediators (e.g., component analysis, micro trial) should also be considered in research practice, to reach more firm (causal) statements.

General conclusion

The current dissertation aimed to explore potential accessible routes to bridge the mental health gap globally, especially in LMICs. It demonstrated the scarcity of the prospective predictive evidence of leading psychological theories of MDD onset and the

pressing need to study the evidence for these theories as well as to develop new theories. The dissertation also depicted the growing number of (digitalized) psychological interventions on CMDs in LMICs with moderate to large treatment effect sizes, which are still challenged by substantial heterogeneity. With a further inspection of an RCT intervention study of BA, the mediation effect of behavioral activation as one possible working mechanism was confirmed in a RCT in Indonesia.

Collectively, this dissertation will conclude with an optimistic tone that the mental health gap might be reduced with help of minimal interventions, including guided digital interventions, in the light of cumulative research evidence in LMICs. The studies in this thesis illustrated a circular and iterative process from etiology to the effectiveness and working mechanism of minimal interventions. These studies provided evidence that hopefully will contribute to make mental health care in LMICs more effective and accessible. Much has been done, but far more needs to be done in the future.

References

- Arjadi, R., Nauta, M. H., & Bockting, C. L. H. (2018). Acceptability of internet-based interventions for depression in Indonesia. *Internet Interventions*, 13(May), 8–15.
- Barak, A., Hen, L., Boniel-Nissim, M., & Shapira, N. (2008). A comprehensive review and a meta-analysis of the effectiveness of internet-based psychotherapeutic interventions. *Journal of Technology in Human Services*, 26(2-4), 109–160.
- Chang, B. P., Kessler, R. C., Pincus, H. A., & Nock, M. K. (2020). Digital approaches for mental health in the age of covid-19. *Bmj*, 369.
- Chinese Ministry of Education (2020). National Report of High Education in China.
- Chisholm, D., Sweeny, K., Sheehan, P., Rasmussen, B., Smit, F., Cuijpers, P., & Saxena, S. (2016). Scaling-up treatment of depression and anxiety: A global return on investment analysis. *The Lancet Psychiatry*, 3(5), 415–424.
- Cuijpers, P., Andersson, G., Donker, T., & Straten, A. van. (2011). Psychological treatment of depression: Results of a series of meta-analyses. *Nordic Journal of Psychiatry*, 65(6), 354–364.
- Cuijpers, P., Karyotaki, E., Reijnders, M., Purgato, M., & Barbui, C. (2018). Psychotherapies for depression in low-and middle-income countries: A meta-analysis. *World Psychiatry*, 17(1), 90–101.
- Da Silva, A. T. C., Hanlon, C., Susser, E., Rojas, G., Claro, H. G., Quayle, J., ... others. (2019). Enhancing mental health research capacity: Emerging voices from the national institute of mental health (nimh) global hubs. *International Journal of Mental Health Systems*, 13(1), 1–9.
- Dimidjian, S., Goodman, S. H., Sherwood, N. E., Simon, G. E., Ludman, E., Gallop, R., ... others. (2017). A pragmatic randomized clinical trial of behavioral activation for depressed pregnant women. *Journal of Consulting and Clinical Psychology*, 85(1), 26.
- First, M. B., Williams, J. B., Karg, R. S., Spitzer, R. L., & others. (2015). Structured clinical interview for DSM-5—research version (SCID-5 for DSM-5, research version; SCID-5-RV). Arlington, VA: American Psychiatric Association, 1–94.

- Forand, N. R., Barnett, J. G., Strunk, D. R., Hindiyeh, M. U., Feinberg, J. E., & Keefe, J. R. (2018). Efficacy of guided iCBT for depression and mediation of change by cognitive skill acquisition. *Behavior Therapy*, 49(2), 295–307.
- Higgins, J. P., Altman, D. G., Gøtzsche, P. C., Jüni, P., Moher, D., Oxman, A. D., ... Sterne, J. A. (2011). The cochrane collaboration's tool for assessing risk of bias in randomised trials. *Bmj*, 343.
- Jack, H. E., Merritt, C., Medhin, G., Musesengwa, R., Mafuta, C., Gibson, L. J., ... Abas, M. (2020). Developing sustainable capacity-building in mental health research: implementation outcomes of training of trainers in systematic reviewing. *Global Health Action*, 13(1). <https://doi.org/10.1080/16549716.2020.1715325>
- Kennis, M., Gerritsen, L., Dalen, M. van, Williams, A., Cuijpers, P., & Bockting, C. (2020). Prospective biomarkers of major depressive disorder: A systematic review and meta-analysis. *Molecular Psychiatry*, 25(2), 321–338.
- Klein, D. N., Kotov, R., & Bufferd, S. J. (2011). Personality and depression: Explanatory models and review of the evidence. *Annual Review of Clinical Psychology*, 7, 269–295.
- Lakdawalla, Z., Hankin, B. L., & Mermelstein, R. (2007). Cognitive theories of depression in children and adolescents: A conceptual and quantitative review. *Clinical Child and Family Psychology Review*, 10(1), 1–24.
- Li, Y., Zhao, Q., Cross, W. M., Chen, J., Qin, C., & Sun, M. (2020). Assessing the quality of mobile applications targeting postpartum depression in China. *International Journal of Mental Health Nursing*, 29(5), 772–785. <https://doi.org/10.1111/inm.12713>
- Luenen, S. van, Kraaij, V., Spinhoven, P., Wilderjans, T. F., & Garnefski, N. (2019). Exploring mediators of a guided web-based self-help intervention for people with hiv and depressive symptoms: Randomized controlled trial. *JMIR Mental Health*, 6(8), e12711.
- Nasrin, F., Rimes, K., Reinecke, A., Rinck, M., & Barnhofer, T. (2017). Effects of brief behavioural activation on approach and avoidance tendencies in acute depression: Preliminary findings. *Behavioural and Cognitive Psychotherapy*, 45(1), 58–72.
- Richards, D. A., Rhodes, S., Ekers, D., McMillan, D., Taylor, R. S., Byford, S., ... others. (2017). Cost and outcome of behavioural activation (cobra): A randomised controlled trial of behavioural activation versus cognitive-behavioural therapy for depression. *Health Technology Assessment (Winchester, England)*, 21(46), 1–366.
- Rovner, B. W., Casten, R. J., Hegel, M. T., Massof, R. W., Leiby, B. E., Ho, A. C., & Tasman, W. S. (2014). Low vision depression prevention trial in age-related macular degeneration: A randomized clinical trial. *Ophthalmology*, 121(11), 2204–2211.
- Santos, M. M., Rae, J. R., Nagy, G. A., Manbeck, K. E., Hurtado, G. D., West, P., ... Kanter, J. W. (2017). A client-level session-by-session evaluation of behavioral activation's mechanism of action. *Journal of Behavior Therapy and Experimental Psychiatry*, 54, 93–100.
- Simons, D., De Bourdeaudhuij, I., Clarys, P., De Cocker, K., Vandelanotte, C., & Deforche, B. (2018). A smartphone app to promote an active lifestyle in lower-educated working young adults: Development, usability, acceptability, and feasibility study. *JMIR mHealth and uHealth*, 6(2), 1–18. <https://doi.org/10.2196/mhealth.8287>
- Simple Psychology. Simple Psychology Report of Mental Health Service in China. 2016. <https://www.jiandanxinli.com/pages/701>
- Spence, S. H., & Rapee, R. M. (2016). The etiology of social anxiety disorder: An evidence-based model. *Behaviour Research and Therapy*, 86, 50–67.
- Wal, J. M. van der, Arjadi, R., Nauta, M. H., Burger, H., & Bockting, C. L. (2020). Guided internet interventions for depression: Impact of sociodemographic factors on treatment outcome in indonesia. *Behaviour Research and Therapy*, 130, 103589

Summary
Nederlandse samenvatting

Summary

Common mental disorders, including depressive disorders, anxiety disorders, and substance use disorders, can substantially impair the quality of life of affected persons. Unfortunately, not every patient can get access to care. The mental health gap, defined as the gap between available treatment and the number of people with mental disorders in need of treatment, has become a global issue. Due to the limited mental health resource, low- and middle-income countries (LMICs) are disproportionately affected by the mental health gap.

The implementation of minimal psychological interventions is deemed as a potential strategy to increase access to evidence-based mental health care, thereby narrowing the mental health gap. Strategies that include the deployment of digital technology and the inclusion of layperson to deliver the minimal treatment are expected to handle the shortage of mental health professionals. In Chapters 3 and 4, we presented two systematic reviews and meta-analyses on the effectiveness of certain types of minimal psychological intervention on common mental disorders in LMICs. In Chapter 3, digital psychological interventions which have been mostly studied in individuals with depression and substance misuse, were found overall effective with a medium effect size in the aggregate of 22 studies comparing with control groups, especially versus usual care. In chapter 4 psychological interventions for depression were investigated amongst Chinese university students. By aggregating 21 studies, an overall large effect size was found compared to the control groups, which consisted of waitlist control/assessment only in most cases. Studies identified and included in both meta-analyses were mainly studied in young adults (18-35 years old). Our results exhibited the promise of minimal psychological interventions, including digital interventions, in the mitigation of common mental disorders especially amongst young adults in LMICs, and possible integration into their patient management system to supplement the usual care; however, more evidence-based on high quality randomized controlled trials focused on all mental health conditions to disentangle the substantial heterogeneity appeared in these meta-analyses.

Mechanistic and etiological research provided other angles to address the mental health gap by providing essential insights to guide innovation in interventions and to pinpoint relevant therapeutic paths during the treatment. In Chapter 2, we went one step



backward to scrutinize the prospective longitudinal evidence underlying the leading theories for treatment on depression etiology in which various theoretical risk factors were hypothesized to precipitate the first onset of major depressive disorder. However, the available evidence is surprisingly scarce. Out of 42,133 records of studies aiming to answer the question: What is the predictive evidence for MDD onset of the factors derived from the leading theories, only 0.06% of the studies fulfilled the necessary eligibility criteria. The result provided evidence to support cognitive (6,585 participants) and personality-based theories (14,394 participants); nevertheless, we could not make a conclusion on the other three main theories (psychodynamic, diathesis-stress, and behavioral) due to the limited number of prospective studies. Our results shed some light on innovation of preventive interventions by targeting risk factors like high levels of dysfunctional attitudes, rumination, and cognitive reactivity, as well as high levels of the ‘negative emotionality’ as a personality trait. But overall, far more well-controlled longitudinal observational studies are required to reach a firm conclusion on the validity of these leading theories.

To illustrate the working mechanisms of minimal psychological intervention, in Chapter 5, we used data of a randomized controlled trial of an internet-based behavioral activation (BA) program on major depressive disorder guided by lay counselors as compared to psychoeducation alone, in Indonesia as an example. To investigate the working mechanism of BA intervention, depressive patients ($n = 313$) were asked to report their levels of activation and depression level every two weeks from baseline to the end of the intervention (Week 10). Results from mediation analyses supported the putative working mechanism, that is, BA intervention exhilarated activation level from week 4 and subsequently reduced depressive symptoms from week 6. In this process, activation level acted as a mediator within the treatment. This finding provided a clear time window for our treatment program to take effect and empirical evidence for proper psychoeducation on the expected timing of an effect on symptomatology for patients using the intervention program.

Finally, in Chapter 6, we provided a general discussion to summarize our main findings. We concluded that minimal psychological interventions like digital psychological intervention and minimal psychological interventions could make a difference to narrow the mental health gap, especially in LMICs. However, sufficient evidence rooted in high-quality research is still necessary. On the other hand, more knowledge is still needed from the etiological and mechanistic research to enrich our understanding of the common

mental disorders. In sum, this dissertation illustrated several routes to address the mental health gap, especially in LMICs, by focusing on common mental disorders, all to ensure the increase of opportunity that people in need of treatment could get timely access to effective interventions.



Nederlandse Samenvatting (Summary in Dutch)

Veelvoorkomende psychische stoornissen, waaronder depressieve stoornissen, angststoornissen en stoornissen in middelengebruik, bedreigen de kwaliteit van leven van degenen die hieraan lijden aanzienlijk. Helaas is toegang tot geestelijke gezondheidszorg (GGZ) niet vanzelfsprekend. De kloof tussen de beschikbare GGZ en het aantal mensen met psychische stoornissen dat behandeling nodig heeft, de geestelijk gezondheidszorgkloof, is een wereldwijd probleem. Vanwege beperkte financiële middelen voor GGZ worden lage- en middeninkomenslanden hierdoor onevenredig hard getroffen.

Minimale psychologische interventies kunnen de toegang tot 'evidence-based' GGZ verbeteren waardoor de geestelijke gezondheidszorgkloof kleiner kan worden. Strategieën die digitale technologie en niet gespecialiseerd professionals en zelfs 'leken' als behandelaren inzetten voor deze interventies zouden het tekort aan professionals in de GGZ kunnen opvangen. In hoofdstuk 3 en 4 presenteerden we twee systematische reviews en meta-analyses over de effectiviteit van minimale psychologische interventies (d.w.z. digitale psychologische interventies) op veelvoorkomende psychische stoornissen in lage- en middeninkomenslanden. In hoofdstuk 3 lieten wij op basis van de 'gepoolde' resultaten van 22 studies zien dat digitale psychologische interventies, die voornamelijk onderzocht werden bij depressieve stoornis en stoornissen in middelengebruik, over het algemeen effectief zijn (d.w.z. een medium effect size) in vergelijking met diverse controlegroepen, vooral versus gebruikelijke zorg. De effectiviteit van psychologische interventies voor depressie onder Chinese studenten werd met een systematische review en meta-analyse onderzocht in hoofdstuk 4. De resultaten lieten zien dat over het geheel genomen het effect van psychologische interventies groot is ten opzichte van een controle conditie, meestal betrof dit een wachtlijstcontrole groep of een vergelijkingsgroep waarin alleen depressieve symptomen gemeten werden. Beide meta-analyses bevatten voornamelijk studies onder jongvolwassenen (18-35 jaar oud). Onze resultaten ondersteunen de belofte van minimale waaronder digitale psychologische interventies voor veelvoorkomende psychische stoornissen, vooral bij jonge volwassenen in lage- en middeninkomenslanden. Deze interventies kunnen mogelijk geïntegreerd worden in de bestaande patiëntenzorg indien deze aanwezig is in het betreffende land. Desalniettemin zijn er meer gerandomiseerde studies nodig met voldoende kwaliteit naar de effectiviteit van deze interventies bij alle

psychische aandoening. Dit is belangrijk gezien de substantiële heterogeniteit van de studies die in de meta-analyses naar voren kwam.

Mechanistisch en etiologische onderzoek kunnen vanuit een ander perspectief bijdragen aan de mogelijkheden om de geestelijke gezondheidszorgkloof te verkleinen. Dit type onderzoek kan inzichten verschaffen om innovatieve behandelingen te ontwikkelen en om therapeutische aangrijpingspunten te identificeren. In Hoofdstuk 2 werd het prospectieve longitudinale bewijs onderzocht voor de leidende etiologische theorieën van depressie die van invloed waren op de huidige behandeling van depressie. Hierbij werd verondersteld dat verschillende risicofactoren voortvloeiend uit deze theorieën, het ontstaan van een eerste depressieve stoornis zouden kunnen bespoedigen. Het beschikbare bewijs was voor deze theorieën echter verrassend schaars. Van de 42.133 onderzoeken die gericht waren op het beantwoorden van de vraag: wat is het bewijs voor de voorspellende waarde voor het ontstaan van depressieve stoornis van de risicofactoren die volgen uit de toonaangevende theorieën, was slechts 0,06% geschikt. Het resultaat leverde bewijs ter ondersteuning van cognitieve-, (6.585 deelnemers) en persoonlijkheidsgebaseerde theorieën (N=14.394 deelnemers). Over de drie andere grote theorieën (psychodynamisch, diathese-stress, en gedrag) konden wij geen conclusies trekken als gevolg van het beperkte aantal studies. Onze resultaten kunnen van belang zijn voor de ontwikkeling van nieuwe preventieve interventies door interventies te richten op hoge niveaus van disfunctionele attitudes, rumineren en cognitieve reactiviteit, evenals hoge niveaus van 'negatieve emotionaliteit' als persoonlijkheidskenmerk. Desalniettemin zijn er meer longitudinale observationele studies van hoge kwaliteit nodig om definitieve conclusies te trekken wat betreft het bewijs voor deze toonaangevende etiologische theorieën.

Om het werkingsmechanisme van een minimale psychologische interventie te bestuderen gebruikten we in hoofdstuk 5 de data van een gerandomiseerde gecontroleerde studie naar de effectiviteit van een online gedragsactivatieprogramma (GA) begeleid door getrainde 'leken' vergeleken met een controle groep die enkel psychoeducatie kreeg voor de behandeling van depressieve stoornis in Indonesië. In deze studie werden patiënten (n = 313) met depressieve stoornis gevraagd om hun mate van gedragsactivatie en depressie elke twee weken te rapporteren vanaf baseline tot het einde van de interventie (week 10). Resultaten van een mediatieanalyse van de data uit deze studie ondersteunden het vermeende werkingsmechanisme, dat wil zeggen, GA-interventie verhoogde het activatie niveau vanaf week 4 en verminderde vervolgens



depressieve symptomen vanaf week 6. Wij lieten zien dat in dit proces het activatieniveau als een mediator fungeerde van het effect van de behandeling. Het resultaat van dit onderzoek laat zien dat er een bepaalde tijd nodig is voordat bepaalde behandelingseffecten verwacht kunnen worden van gedragstherapie. Dit is tevens belangrijke informatie voor therapeuten en patiënten.

Tenslotte, hebben we in hoofdstuk 6 onze belangrijkste bevindingen samengevat en de beperkingen van de studies beschreven. We concludeerden dat minimale psychologische interventies zoals digitale psychologische interventies en overige minimale psychologische interventies een verschil kunnen maken om de kloof in de GGZ te verkleinen, vooral in lage-en-middeninkomenslanden. Echter, voordat we deze innovatieve minimale interventies aan patiënten gaan aanbieden, is er meer bewijs nodig uit hoogwaardig onderzoek. Aan de andere kant is er ook meer kennis nodig ten aanzien van de etiologie en instandhoudende factoren bij veel voorkomende aandoeningen als ook de werkingsmechanismen van minimale psychologische interventies. Samenvattend, illustreerde dit proefschrift verschillende manieren om de geestelijke gezondheidskloof aan te pakken, vooral in lage- en middeninkomenslanden. Hierbij werd gefocust op veelvoorkomende psychische stoornissen. Uiteindelijk moet dit ervoor zorgen dat mensen die een behandeling nodig hebben voor deze stoornissen, tijdig toegang krijgen tot effectieve interventies.

Appendices

Supplementary materials to Chapter 2/3/4/5

Appendix 1 Supplement to Chapter 2

Appendix 1A: Search terms for all the theories

Note: The searches for psychodynamic, personality and part of cognitive theories were combined for onset and relapse/recurrence; the search for diathesis-stress theory combined psychological and biological risk factors for MDD. We then re-ran each search using only the specific terms for depression onset to calculate the number of hits, exclusions, and inclusions for the current overview. Snowballing procedures including checking inclusions of previous relative reviews and articles cited each inclusion were also conducted to identify any studies undetected in the original search.

Search terms Behavioral theories

Database	Search strategy
Pubmed	1. ("depressive disorder"[MeSH Terms] OR "depression"[MeSH Terms] OR depression[Title/Abstract] OR depressive[Title/Abstract] OR depressed [Title/Abstract] OR affective[Title/Abstract])
	2. ("behavior* theory"[Title/Abstract] OR "behaviour* theory" [Title/Abstract] OR "behavioral model" [Title/Abstract] OR "behavioural model" [Title/Abstract] OR "behavioral intervention" [Title/Abstract] OR "behavioural intervention" [Title/Abstract] OR "behaviour* therapy"[Title/Abstract] OR "behaviour* therapy"[Title/Abstract] OR "social learning"[Title/Abstract] OR "self-efficacy" [Title/Abstract] OR "observational learning" [Title/Abstract] OR "self-regulation" [Title/Abstract] OR conditioning [Title/Abstract] OR conditioned [Title/Abstract] OR "classical condition*" [Title/Abstract] OR "operant condition*" [Title/Abstract] OR reinforcement [Title/Abstract] OR "learning theory" [Title/Abstract] OR "behavior* activation" [Title/Abstract] OR "behaviour* activation" [Title/Abstract] OR "functional analysis" [Title/Abstract] OR "problem solving" [Title/Abstract] OR "social skills" [Title/Abstract])
	3. (onset [Title/Abstract] OR first-ever [Title/Abstract] OR predictor [Title/Abstract] OR preventi* [Title/Abstract] OR prospective [Title/Abstract] OR risk [Title/Abstract] OR vulnerability [Title/Abstract] OR longitud* [Title/Abstract] OR precipitating [Title/Abstract] OR protective [Title/Abstract] OR resilience [Title/Abstract] OR susceptibility [Title/Abstract] OR epidemiology [Title/Abstract])
	4. 1 AND 2 AND 3 [Filter: human, English, not review]
PsychInfo	1. (depression/ or depressive/ or depressed/ or affective).ab,ti.
	2. (onset/ or first-ever /or predictor/ or prevention/or preventive/or prospective/or risk/or vulnerability/or longitud*/or precipitating/or protective/or resilience/or susceptibility/or epidemiology)).ab,ti.
	3. (*behavioral theory/ or *behavioural theory/ or *behavioral model/ or *behavioural model/ or *behavioral intervention/ or *behavioural intervention/ or *behavioral therapy/ or *behavioural therapy/ or *social learning/ or *self-efficacy/ or *observational learning/ or *self-regulation/ or conditioning/ or conditioned/ or *classical conditioning/ or *classical conditioned/or *operant conditioning/or *operant conditioned/ or reinforcement/ or *learning theory/ or *behavioral



	activation/ or *behavioural activation/ or *functional analysis/ or *problem solving/ or *social skills).ab,ti. 4. 1 and 2 and 3
Cochrane library	1. (Depress* or affective) 2. (onset or first-ever or predictor or prevent* or perspective or risk or vulnerability or longitud* or precipitating or protective or resilience or susceptibility or epidemiology) 3. (behavioral theory or behavioural theory or behavioral model or behavioural model or behavioral intervention or behavioural intervention or behavioral therapy or behavioural therapy or social learning or self-efficacy or observational learning or self-regulation or conditioning or conditioned or classical condition* or operant condition* or reinforcement or learning theory or behavioral activation or behavioural activation or functional analysis or problem solving or social skills) 4. 1 and 2 and 3
Embase	1. ('depress*/exp or 'affective'/exp OR depress*:ab,ti) 2. (onset:ab,ti or first-ever:ab,ti or predictor:ab,ti or prevent*:ab,ti or perspective:ab,ti or risk:ab,ti or vulnerability:ab,ti or 'longitud*':ab,ti or precipitating:ab,ti or protective:ab,ti or resilience:ab,ti or susceptibility:ab,ti or epidemiology:ab,ti) 3. ('behavior* theory':ab,ti or 'behaviour* theory':ab,ti or 'behavioral model':ab,ti or 'behavioral intervention':ab,ti or 'behaviour* therapy':ab,ti or 'behavioural model':ab,ti or 'behavioural intervention':ab,ti or 'behaviour* therapy':ab,ti or 'social learning':ab,ti or 'self-efficacy':ab,ti or 'observational learning':ab,ti or 'self-regulation':ab,ti or 'conditioning':ab,ti or 'conditioned':ab,ti or 'classical condition*':ab,ti or 'operant condition*':ab,ti or 'reinforcement':ab,ti or 'learning theory':ab,ti or 'behavior* activation':ab,ti or 'behaviour* activation':ab,ti or 'functional analysis':ab,ti or 'problem solving':ab,ti or 'social skills':ab,ti) 4. 1 and 2 and 3

Search terms Cognitive theories

Database	Search strategy
Pubmed	1. ("depressive disorder"[MeSH Terms] OR "depression"[MeSH Terms] OR depression[Title/Abstract] OR depressive[Title/Abstract] OR depressed [Title/Abstract] OR affective[Title/Abstract]) 2. ("cognitive theory" [Title/Abstract] OR "cognitive model"[Title/Abstract] OR "cognitive therapy"[MeSH Terms] OR "cognitive therapy"[Title/Abstract] OR "cognitive intervention" [Title/Abstract] OR cognitive [Title/Abstract] OR hopelessness[Title/Abstract] OR helplessness[Title/Abstract] OR "dual processing"[Title/Abstract] OR "information processing"[Title/Abstract] OR "information processing bias"[Title/Abstract] OR "cognitive bias"[Title/Abstract] OR "cognitive biased"[Title/Abstract] OR "cognitive biases"[Title/Abstract] OR "scar model"[Title/Abstract] OR "scarring"[Title/Abstract] OR "diathesis-stress"[Title/Abstract] OR "attitude"[MeSH Terms] OR "attitude"[Title/Abstract] OR "attitudes"[Title/Abstract] OR "dysfunctional attitude*"[Title/Abstract] OR "dysfunctional belief"[Title/Abstract] OR "self-control"[Title/Abstract] OR schema[Title/Abstract] OR "automatic negative thought"[Title/Abstract] ruminat*[Title/Abstract] OR "repetitive thought"[Title/Abstract] OR "repetitive thinking"[Title/Abstract] OR worry[Title/Abstract] OR persev*[Title/Abstract] OR "intrusive thought"[Title/Abstract] OR "intrusive thinking"[Title/Abstract] OR "negative thought"[Title/Abstract] OR "negative thinking"[Title/Abstract] OR "stress

	<p>thought"[Title/Abstract] OR "stress thinking"[Title/Abstract] OR "obsessive thought"[Title/Abstract] OR "obsessive thinking"[Title/Abstract] OR "unconscious stress"[Title/Abstract] OR "implicit stress"[Title/Abstract] OR "anticipatory stress"[Title/Abstract] OR "anticipation stress"[Title/Abstract] OR "cognitive intrusion*"[Title/Abstract] OR reflection[Title/Abstract] OR brooding[Title/Abstract] OR "reflect*"[Title/Abstract] OR "self referential thought"[Title/Abstract] OR "counterfactual thinking"[Title/Abstract] OR "mind wandering"[Title/Abstract] OR "post-event processing"[Title/Abstract] OR "habitual negative self-thinking"[Title/Abstract] OR "catastrophizing"[Title/Abstract] OR "automatic thoughts questionnaire"[Title/Abstract] OR "Crandell cognitions inventory"[Title/Abstract] OR "cognitions checklist"[Title/Abstract] OR "cognitive style test"[Title/Abstract] OR "sociotropy-autonomy scale"[Title/Abstract] OR attribution[Title/Abstract] OR schema[Title/Abstract] OR "automatic thoughts"[Title/Abstract] OR "depressive realism"[Title/Abstract] OR "illusion of control"[Title/Abstract] OR "cognitive distortion"[Title/Abstract] OR "judgment of contingency"[Title/Abstract] OR "attentional bias"[Title/Abstract] OR "response styles theory"[Title/Abstract] OR preoccupation[Title/Abstract] OR "self-focus"[Title/Abstract] OR "self-focused attention"[Title/Abstract] OR "emotion regulation" OR "coping strategy"[Title/Abstract] OR "coping style"[Title/Abstract] OR metacognit*[Title/Abstract])</p> <p>3. (onset [Title/Abstract] OR first-ever [Title/Abstract] OR predictor [Title/Abstract] OR preventi* [Title/Abstract] OR prospective [Title/Abstract] OR risk [Title/Abstract] OR vulnerability[Title/Abstract] OR longitud*[Title/Abstract] OR precipitating [Title/Abstract] OR protective [Title/Abstract] OR resilience[Title/Abstract] OR susceptibility[Title/Abstract] OR epidemiology[Title/Abstract])</p> <p>4. 1 AND 2 AND 3 [Filter: human, English, not review]</p>
PsychInfo	<p>1. (depression/ or depressive/ or depressed/ or affective).ab,ti.</p> <p>2. (onset/ or first-ever /or predictor/ or prevention/or preventive/or prospective/or risk/or vulnerability/or longitud*/or precipitating/or protective/or resilience/or susceptibility/or epidemiology)).ab,ti.</p> <p>(*cognitive theory or *cognitive model or cognitive or *cognitive therapy or *cognitive intervention/ or hopelessness or helplessness or *dual processing or *information processing or *cognitive bias or *cognitive biased or *cognitive biases or *scar model or scarring or *diathesis-stress or attitude* or *dysfunctional belief or *dysfunctional attitude or *dysfunctional attitudes or rumination or ruminative or ruminating or *repetitive thought or *repetitive thinking or worry or persev* or *intrusive thought or *intrusive thinking or *negative thought or *negative thinking or *stress thought or *stress thinking or *obsessive thought or *obsessive thinking or *unconscious stress or *implicit stress or *anticipatory stress or *anticipation stress or *cognitive intrusion or reflection or brooding or *reflect or *referential thought or *counterfactual thinking or *mind wandering or *post-event processing or *habitual negative self-thinking or *catastrophizing or *automatic thoughts questionnaire or *Crandell cognitions inventory or *cognitions checklist or *cognitive style test or *sociotropy-autonomy scale or attribution or schema or *automatic thoughts or *depressive realism or *illusion of control or *cognitive distortion or *judgment of contingency or *attentional bias or *response styles theory or preoccupation OR *self-focus OR *self-focused attention OR *emotion regulation OR *coping strategy OR *coping style).ab,ti.</p> <p>4. 1 and 2 and 3</p>
Cochrane library	<p>1. (Depress* or affective)</p>



	<p>2. (onset or first-ever or predictor or preventi* or perspective or risk or vulnerability or longitud* or precipitating or protective or resilience or susceptibility or epidemiology)</p> <p>3. (cognitive theory or cognitive model or cognitive or cognitive therapy or cognitive intervention or hopelessness or helplessness or dual processing or information processing or cognitive bias or cognitive biased or cognitive biases or scar model or scarring or diathesis-stress or attitude* or dysfunctional belief or dysfunctional attitude or dysfunctional attitudes ruminat* OR 'repetitive thought' OR 'repetitive thinking' OR worry OR persev* OR 'intrusive thought' OR 'intrusive thinking' OR 'negative thought' OR 'negative thinking' OR 'stress thought' OR 'stress thinking' OR 'obsessive thought' OR 'obsessive thinking' OR 'unconscious stress' OR 'implicit stress' OR 'anticipatory stress' OR 'anticipation stress' OR 'cognitive intrusion*' OR reflection OR brooding OR 'reflect*' OR 'self referential thought' OR 'counterfactual thinking' OR 'mind wandering' OR 'post-event processing' OR 'habitual negative self-thinking' OR 'catastrophizing' OR 'automatic thoughts questionnaire' OR 'Crandell cognitions inventory' OR 'cognitions checklist' OR 'cognitive style test' OR 'sociotropy-autonomy scale' OR attribution OR schema OR 'automatic thoughts' OR 'depressive realism' OR 'illusion of control' OR 'cognitive distortion' OR 'judgment of contingency' OR 'attentional bias' OR 'response styles theory' OR preoccupation OR 'self-focus' OR 'self-focused attention' OR 'emotion regulation' OR 'coping strategy' OR 'coping style')</p> <p>4. 1 and 2 and 3</p>
Embase	<p>1. ('depress*/exp or 'affective'/exp OR depress*:ab,ti)</p> <p>2. (onset:ab,ti or first-ever:ab,ti or predictor:ab,ti or preventi*:ab,ti or perspective:ab,ti or risk:ab,ti or vulnerability:ab,ti or 'longitud*':ab,ti or precipitating:ab,ti or protective:ab,ti or resilience:ab,ti or susceptibility:ab,ti or epidemiology:ab,ti)</p> <p>3. ('cognitive theory':ab,ti or 'cognitive model':ab,ti or cognitive:ab,ti or 'cognitive therapy':ab,ti or 'cognitive intervention':ab,ti or hopelessness:ab,ti or helplessness:ab,ti or 'dual processing':ab,ti or 'information process*':ab,ti or 'cognitive bias':ab,ti or 'cognitive bias*':ab,ti or 'scar model':ab,ti or scarring:ab,ti or 'diathesis-stress':ab,ti or attitude*:ab,ti or 'dysfunctional belief':ab,ti or 'dysfunctional attitude*':ab,ti or ruminat*:ab,ti OR 'repetitive thought':ab,ti OR 'repetitive thinking':ab,ti OR worry:ab,ti OR persev*:ab,ti OR 'intrusive thought':ab,ti OR 'intrusive thinking':ab,ti OR 'negative thought':ab,ti OR 'negative thinking':ab,ti OR 'stress thought':ab,ti OR 'stress thinking':ab,ti OR 'obsessive thought':ab,ti OR 'obsessive thinking':ab,ti OR 'unconscious stress':ab,ti OR 'implicit stress':ab,ti OR 'anticipatory stress':ab,ti OR 'anticipation stress':ab,ti OR 'cognitive intrusion*':ab,ti OR reflection:ab,ti OR brooding:ab,ti OR 'reflect*':ab,ti OR 'self referential thought':ab,ti OR 'counterfactual thinking':ab,ti OR 'mind wandering':ab,ti OR 'post-event processing':ab,ti OR 'habitual negative self-thinking':ab,ti OR 'catastrophizing':ab,ti OR 'automatic thoughts questionnaire':ab,ti OR 'Crandell cognitions inventory':ab,ti OR 'cognitions checklist':ab,ti OR 'cognitive style test':ab,ti OR 'sociotropy-autonomy scale':ab,ti OR attribution:ab,ti OR schema:ab,ti OR 'automatic thoughts':ab,ti OR 'depressive realism':ab,ti OR 'illusion of control':ab,ti OR 'cognitive distortion':ab,ti OR 'judgment of contingency':ab,ti OR 'attentional bias':ab,ti OR 'response styles theory':ab,ti OR preoccupation:ab,ti OR 'self-focus':ab,ti OR 'self-focused attention':ab,ti OR 'emotion regulation' OR 'coping strategy':ab,ti OR 'coping style':ab,ti)</p> <p>4. 1 and 2 and 3</p>

Search terms Psychodynamic theories

Database	Search strategy
Pubmed	1. ("depressive disorder"[MeSH Terms] OR "depression"[MeSH Terms] OR depression[Title/Abstract] OR depressive[Title/Abstract] OR depressed [Title/Abstract] OR affective[Title/Abstract])
	2. ("attachment anxiety"[Title/Abstract] OR "secure attachment"[Title/Abstract] OR "insecure attachment"[Title/Abstract] OR "avoidant attachment"[Title/Abstract] OR "withdrawn attachment"[Title/Abstract] OR "attachment style"[Title/Abstract] OR "dismissive attachment"[Title/Abstract] OR "object relations"[Title/Abstract] OR "object relational functioning"[Title/Abstract] OR "self object"[Title/Abstract] OR "loved object"[Title/Abstract] OR "self object representations"[Title/Abstract] OR "depressive position"[Title/Abstract] OR "mirroring"[Title/Abstract] OR "twinship"[Title/Abstract] OR "poignant sadness"[Title/Abstract] OR "remorseful guilt"[Title/Abstract] OR "guilt"[Title/Abstract] OR "shame"[Title/Abstract] OR "compromise formation"[Title/Abstract] OR "narcissistic identification"[Title/Abstract] OR psychodynam*[Title/Abstract] OR psychoanal*[Title/Abstract])
	3. (onset [Title/Abstract] OR first-ever [Title/Abstract] OR predictor [Title/Abstract] OR preventi* [Title/Abstract] OR prospective [Title/Abstract] OR risk [Title/Abstract] OR vulnerability[Title/Abstract] OR longitud*[Title/Abstract] OR precipitating [Title/Abstract] OR protective [Title/Abstract] OR resilience[Title/Abstract] OR susceptibility[Title/Abstract] OR epidemiology[Title/Abstract])
	4. 1 AND 2 AND 3 [Filter: human, English, not review]
PsychInfo	1. (depression/ or depressive/ or depressed/ or affective).ab,ti.
	2. (onset/ or first-ever /or predictor/ or prevention/or preventive/or prospective/or risk/or vulnerability/or longitud*/or precipitating/or protective/or resilience/or susceptibility/or epidemiology).ab,ti.
	3. (psychoanal*/ or psychodynam*/ or *object relation*/ or *attachment anxiety*/ or *insecure attachment*/ or *enmeshed attachment*/ or *secure attachment*/ or *avoidant attachment*/ or *withdrawn attachment*/ or *dismissive attachment*/ or *self object*/ or twinship/ or mirroring/ or *idealizing transference*/ or *reassurance seeking*/ or *narcissistic identification*).mp.
	4. 1 and 2 and 3
Cochrane library	1. (Depress* or affective)
	2. (onset or first-ever or predictor or preventi* or perspective or risk or vulnerability or longitud* or precipitating or protective or resilience or susceptibility or epidemiology)
	3. (behavioral theory or behavioural theory or behavioral model or behavioural model or behavioral intervention or behavioural intervention or behavioral therapy or behavioural therapy or social learning or self-efficacy or observational learning or self-regulation or conditioning or conditioned or classical condition* or operant condition* or reinforcement or learning theory or behavioral activation or behavioural activation or functional analysis or problem solving or social skills)
	4. 1 and 2 and 3
Embase	1. ('depress*/exp or 'affective'/exp OR depress*:ab,ti)
	2. (onset:ab,ti or first-ever:ab,ti or predictor:ab,ti or preventi*:ab,ti or perspective:ab,ti or risk:ab,ti or vulnerability:ab,ti or 'longitud*':ab,ti or precipitating:ab,ti or protective:ab,ti or resilience:ab,ti or susceptibility:ab,ti or epidemiology:ab,ti)



	3. (object relations or attachment anxiety or insecure attachment or enmeshed attachment or secure attachment or avoidant attachment or withdrawn attachment or dismissive attachment or self object or object relation function or twinship or mirroring or idealizing transference or guilt or shame or reassurance seeking or narcissistic identification or compromise formation or poignant sadness or remorseful guilt or psychodynam* or psychoanal*)
	4. 1 and 2 and 3

Search terms Personality-based theories

Database	Search strategy
Pubmed	1. ("depressive disorder"[MeSH Terms] OR "depression"[MeSH Terms] OR depression[Title/Abstract] OR depressive[Title/Abstract] OR depressed [Title/Abstract] OR affective[Title/Abstract])
	2. (personality[Title/Abstract] OR Eysenck[Title/Abstract] OR Neuroticism[Title/Abstract] OR Psychoticism[Title/Abstract] OR BAS[Title/Abstract] OR FFFS[Title/Abstract] OR BIS[Title/Abstract] OR Big Five[Title/Abstract] OR volatility[Title/Abstract] OR Agreeableness[Title/Abstract] OR "Openness to experience"[Title/Abstract] OR Conscientiousness[Title/Abstract] OR Cloninger[Title/Abstract] OR "Novelty seeking"[Title/Abstract] OR "Harm avoidance"[Title/Abstract] OR Persistence[Title/Abstract] OR "Reward dependence"[Title/Abstract] OR "Self-directedness"[Title/Abstract] OR "Watson & Tellegen"[Title/Abstract] OR Constraint[Title/Abstract])
	3. (onset [Title/Abstract] OR first-ever [Title/Abstract] OR predictor [Title/Abstract] OR preventi* [Title/Abstract] OR prospective [Title/Abstract] OR risk [Title/Abstract] OR vulnerability[Title/Abstract] OR longitud* [Title/Abstract] OR precipitating [Title/Abstract] OR protective [Title/Abstract] OR resilience[Title/Abstract] OR susceptibility[Title/Abstract] OR epidemiology[Title/Abstract])
	4. 1 AND 2 AND 3 [Filter: human, English, not review]
PsychInfo	1. (depression/ or depressive/ or depressed/ or affective).ab,ti.
	2. (onset/ or first-ever /or predictor/ or prevention/or preventive/or prospective/or risk/or vulnerability/or longitud*/or precipitating/or protective/or resilience/or susceptibility/or epidemiology)).ab,ti.
	3. (personality or Eysenck or Neuroticism or Psychoticism or BAS or FFFS or BIS or *Big Five or volatility or Agreeableness or *Openness to experience or Conscientiousness or Cloninger or *Novelty seeking or *Harm avoidance or *Reward dependence or *Self-directedness or *Watson & Tellegen).ab,ti.
	4. 1 and 2 and 3
Cochrane library	1. (Depress* or affective)
	2. (onset or first-ever or predictor or preventi* or perspective or risk or vulnerability or longitud* or precipitating or protective or resilience or susceptibility or epidemiology)
	3. (personality or Eysenck or Neuroticism or Psychoticism or BAS or FFFS or BIS or "Big Five" or volatility or Agreeableness or "Openness to experience" or Conscientiousness or Cloninger or "Novelty seeking" or "Harm avoidance" or "Reward dependence" or "Self-directedness" or "Watson & Tellegen")
	4. 1 and 2 and 3
Embase	1. ('depress*/exp or 'affective'/exp OR depress*:ab,ti)
	2. (onset:ab,ti or first-ever:ab,ti or predictor:ab,ti or preventi*:ab,ti or perspective:ab,ti or risk:ab,ti or vulnerability:ab,ti or 'longitud*':ab,ti or

	precipitating:ab,ti or protective:ab,ti or resilience:ab,ti or susceptibility:ab,ti or epidemiology:ab,ti)
	3. (personality:ab,ti OR eysenck:ab,ti OR neuroticism:ab,ti OR psychoticism:ab,ti OR bas:ab,ti OR fffs:ab,ti OR bis:ab,ti OR 'big five':ab,ti OR volatility:ab,ti OR agreeableness:ab,ti OR 'openness to experience':ab,ti OR conscientiousness:ab,ti OR cloning:ab,ti OR 'novelty seeking':ab,ti OR 'harm avoidance':ab,ti OR 'reward dependence':ab,ti OR 'self-directedness':ab,ti OR 'watson & tellegen':ab,ti)
	4. 1 and 2 and 3

Search terms of diathesis theories

Database	Search strategy
Pubmed	1. ("depressive disorder"[MeSH Terms] OR "depression"[MeSH Terms] OR depression[Title/Abstract] OR depressive[Title/Abstract] OR depressed [Title/Abstract] OR affective[Title/Abstract])
	2. ("predisposition nature" [Title/Abstract] OR "predisposition nurture" [Title/Abstract] OR "diathesis stress"[Title/Abstract] OR "diathesis-stress"[Title/Abstract] OR "diathesis stressor"[Title/Abstract] OR diathesis[Title/Abstract] OR diatheses [Title/Abstract] OR interaction [Title/Abstract] OR "nurture nature" [Title/Abstract] OR "nature/nurture model"[Title/Abstract] OR "social support" [Title/Abstract] OR coping [Title/Abstract] OR OR vulnerab* [Title/Abstract])
	3. ("stress/stressor" [Title/Abstract] "stress/trauma" [Title/Abstract] OR "stress/vulnerability" [Title/Abstract] OR "stress/vulnerability stress" [Title/Abstract] OR "stress/death" [Title/Abstract] OR "stress/stressful" [Title/Abstract] OR "stress/stressors" [Title/Abstract] OR "stress/adversity" [Title/Abstract] OR "stress/affect" [Title/Abstract] OR "stress/anxiety/depression" [Title/Abstract] OR "adverse event*" [Title/Abstract] OR trauma[Title/Abstract] OR "life event*" [Title/Abstract] OR "traumatic" [Title/Abstract] OR "bereavement" [Title/Abstract] OR "grief" [Title/Abstract] OR "humiliation" [Title/Abstract] OR "social rejection" [Title/Abstract] or maltreatment [Title/Abstract] OR "childhood trauma" [Title/Abstract] OR "early trauma" [Title/Abstract])
	4. (onset [Title/Abstract] OR first-ever [Title/Abstract] OR predictor [Title/Abstract] OR preventi* [Title/Abstract] OR prospective [Title/Abstract] OR risk [Title/Abstract] OR vulnerability[Title/Abstract] OR longitud*[Title/Abstract] OR precipitating [Title/Abstract] OR protective [Title/Abstract] OR resilience[Title/Abstract] OR susceptibility[Title/Abstract] OR epidemiology[Title/Abstract])
	5. 1 AND 2 AND 3 AND 4 [Filter: human, English, not review]
PsychInfo	1. (depression/ or depressive/ or depressed/ or affective).ab,ti.
	2. (onset/ or first-ever /or predictor/ or prevention/or preventive/or prospective/or risk/ or vulnerability/or longitud*/or precipitating/or protective/or resilience/or susceptibility/or epidemiology)).ab,ti.
	3. (*predisposition or diathesis or diatheses or interaction or * nature nurture or *social support or coping or vulnerability or vulnerable or vulnerabilities).ab,ti
	4. (Stress or *adverse event or trauma or *life event or traumatic or bereavement or grief or humiliation or *social rejection or maltreatment or *childhood trauma or *early trauma).ab,ti
	5. 1 and 2 and 3 and 4
Cochrane library	1. (Depress* or affective)

	2. (onset or first-ever or predictor or preventi* or perspective or risk or vulnerability or longitud* or precipitating or protective or resilience or susceptibility or epidemiology)
	3. (predisposition OR *nature*nurture* OR 'diathesis stress' OR diathesis-stress OR 'diathesis stressor' OR diathesis OR diatheses OR 'social support' OR coping or vulnerability or vulnerable or vulnerabilities)
	4. (stress OR 'adverse event*' OR trauma or maltreatment' OR 'childhood trauma' OR 'early trauma' OR 'life event*' OR 'life-event*' or traumatic or bereavement or grief or humiliation or 'social rejection')
	5. 1 and 2 and 3 and 4
Embase	1. ('depress*/exp or 'affective'/exp OR depress*:ab,ti)
	2. (onset:ab,ti or first-ever:ab,ti or predictor:ab,ti or preventi*:ab,ti or perspective:ab,ti or risk:ab,ti or vulnerability:ab,ti or 'longitud*':ab,ti or precipitating:ab,ti or protective:ab,ti or resilience:ab,ti or susceptibility:ab,ti or epidemiology:ab,ti)
	3. (predisposition:ab,ti OR "nature-nurture":ab,ti OR "diathesis stress":ab,ti OR diathesis-stress:ab,ti OR "diathesis stressor":ab,ti OR diathesis:ab,ti OR diatheses:ab,ti OR "social support":ab,ti or coping:ab,ti or vulnerability:ab,ti or vulnerable:ab,ti or vulnerabilities:ab,ti)
	4. (stress:ab,ti OR "adverse event":ab,ti or "adverse events":ab,ti OR trauma:ab,ti or "life event":ab,ti or traumatic:ab,ti or bereavement:ab,ti or grief:ab,ti or humiliation:ab,ti OR "life events":ab,ti or "social rejection":ab,ti or maltreatment:ab,ti)
	5. 1 and 2 and 3 and 4

Appendix 1B: Articles included in the systematic review (reference with asterisk were included in the meta-analysis)

*Alloy, L. B., Abramson, L. Y., Whitehouse, W. G., Hogan, M. E., Panzarella, C., & Rose, D. T. (2006). Prospective incidence of first onsets and recurrences of depression in individuals at high and low cognitive risk for depression. *Journal of Abnormal Psychology, 115*(1), 145–156. <https://doi.org/10.1037/0021-843X.115.1.145>

Bijl, R. V., Graaf, R. de, Ravelli, A., Smit, F., & Vollebergh, W. A. (2002). Gender and age-specific first incidence of DSM-III-R psychiatric disorders in the general population. Results from the Netherlands mental health survey and incidence study (NEMESIS). *Social Psychiatry and Psychiatric Epidemiology, 37*(8), 372–379. <https://doi.org/10.1007/s00127-002-0566-3>

Carter, J. S., & Garber, J. (2011). Predictors of the first onset of a major depressive episode and changes in depressive symptoms across adolescence: Stress and negative cognitions. *Journal of Abnormal Psychology, 120*(4), 779–796. <https://doi.org/10.1037/a0025441>

Coventry, W. L., Medland, S. E., Wray, N. R., Thorsteinsson, E. B., Heath, A. C., & Byrne, B. (2009). Phenotypic and discordant-monozygotic analyses of stress and perceived social support as antecedents to or sequelae of risk for depression. *Twin Research and Human Genetics, 12*(5), 469–488. <https://doi.org/10.1375/twin.12.5.469>

*Eldesouky, L., Thompson, R. J., Oltmanns, T. F., & English, T. (2018). Affective instability predicts the course of depression in late middle-age and older adulthood. *Journal of Affective Disorders, 239*, 72–78. <https://doi.org/10.1016/j.jad.2018.06.038>

- *Fanous, A. H., Neale, M. C., Aggen, S. H., & Kendler, K. S. (2007). A longitudinal study of personality and major depression in a population-based sample of male twins. *Psychological Medicine*, 37(8), 1163–1172. <https://doi.org/10.1017/S0033291707000244>
- *Giollabhui, N. M., Hamilton, J. L., Nielsen, J., Connolly, S. L., Stange, J. P., Varga, S., ... Alloy, L. B. (2018). Negative cognitive style interacts with negative life events to predict first onset of a major depressive episode in adolescence via hopelessness. *Journal of Abnormal Psychology*, 127(1), 1–11. <https://doi.org/10.1037/abn0000301>
- *Goldstein, B. L., Kotov, R., Perlman, G., Watson, D., & Klein, D. N. (2018). Trait and facet-level predictors of first-onset depressive and anxiety disorders in a community sample of adolescent girls. *Psychological Medicine*, 48(8), 1282–1290. <https://doi.org/10.1017/S0033291717002719>
- Goodyer, I. M., Herbert, J., Tamplin, A., & Altham, P. M. (2000). First-episode major depression in adolescents: Affective, cognitive and endocrine characteristics of risk status and predictors of onset. *British Journal of Psychiatry*, 176(FEB.), 142–149. <https://doi.org/10.1192/bjp.176.2.142>
- Kendler, K. S., Gatz, M., Gardner, C. O., & Pedersen, N. L. (2006). Personality and major depression: A Swedish longitudinal, population-based twin study. *Archives of General Psychiatry*, 63(10), 1113–1120. <https://doi.org/10.1001/archpsyc.63.10.1113>
- Kendler, K. S., Neale, M. C., Kessler, R. C., Heath, A. C., & Eaves, L. J. (1993). A Longitudinal Twin Study of 1-Year Prevalence of Major Depression in Women. *Archives of General Psychiatry*, 50(11), 843–852. <https://doi.org/10.1001/archpsyc.1993.01820230009001>
- *Kessler, R. C., Gruber, M., Hettema, J. M., Hwang, I., Sampson, N., & Yonkers, K. A. (2008). Co-morbid major depression and generalized anxiety disorders in the National Comorbidity Survey follow-up. *Psychological Medicine*, 38(3), 365–374. <https://doi.org/10.1017/S0033291707002012>
- *Kopala-Sibley, D. C., Klein, D. N., Perlman, G., & Kotov, R. (2017). Self-criticism and dependency in female adolescents: Prediction of first onsets and disentangling the relationships between personality, stressful life events, and internalizing psychopathology. *Journal of Abnormal Psychology*, 126(8), 1029–1043. <https://doi.org/10.1037/abn0000297>
- *Kruijt, A. W., Antypa, N., Booiij, L., Jong, P. J. de, Glashouwer, K., Penninx, B. W. J. H., & Van der Does, W. (2013). Cognitive reactivity, implicit associations, and the incidence of depression: a two-year prospective study. *PLoS One*, 8(7), e70245.
- Mathew, A. R., Pettit, J. W., Lewinsohn, P. M., Seeley, J. R., & Roberts, R. E. (2011). Co-morbidity between major depressive disorder and anxiety disorders: Shared etiology or direct causation? *Psychological Medicine*, 41(10), 2023–2034. <https://doi.org/10.1017/S0033291711000407>
- Noteboom, A., Beekman, A. T., Vogelzangs, N., & Penninx, B. W. (2016). Personality and social support as predictors of first and recurrent episodes of depression. *Journal of Affective Disorders*, 190, 156–161. <https://doi.org/10.1016/j.jad.2015.09.020>
- *Nusslock, R., Shackman, A. J., Harmon-Jones, E., Alloy, L. B., Coan, J. A., & Abramson, L. Y. (2011). Cognitive Vulnerability and Frontal Brain Asymmetry: Common Predictors of First Prospective Depressive Episode. *Journal of Abnormal Psychology*, 120(2), 497–503. <https://doi.org/10.1037/a0022940>
- *Ormel, J., Oldehinkel, A. J., & Vollebergh, W. (2004). Vulnerability before, during, and after a major depressive episode: A 3-wave population-based study. *Archives of General Psychiatry*, 61(10), 990–996. <https://doi.org/10.1001/archpsyc.61.10.990>
- Ostergaard, D., Dalton, S. O., Bidstrup, P. E., Poulsen, A. H., Frederiksen, K., Elov, L. F., ... Mortensen, E. L. (2012). Mental vulnerability as a risk factor for depression: A prospective cohort study



- in Denmark. *International Journal of Social Psychiatry*, 58(3), 306–314.
<https://doi.org/10.1177/0020764010396409>
- *Otto, M. W., Teachman, B. A., Cohen, L. S., Soares, C. N., Vitonis, A. F., & Harlow, B. L. (2007). Dysfunctional Attitudes and Episodes of Major Depression: Predictive Validity and Temporal Stability in Never-Depressed, Depressed, and Recovered Women. *Journal of Abnormal Psychology*, 116(3), 475–483. <https://doi.org/10.1037/0021-843X.116.3.475>
- Roberts, S. B., & Kendler, K. S. (1999). Neuroticism and self-esteem as indices of the vulnerability to major depression in women. *Psychological Medicine*, 29(5), 1101–1109.
<https://doi.org/10.1017/S0033291799008739>
- Stange, J. P., Connolly, S. L., Burke, T. A., Hamilton, J. L., Hamlat, E. J., Abramson, L. Y., & Alloy, L. B. (2016). Inflexible Cognition Predicts First Onset of Major Depressive Episodes in Adolescence. *Depression and Anxiety*, 33(11), 1005–1012.
<https://doi.org/10.1002/da.22513>
- Stavrakakis, N., Roest, A. M., Verhulst, F., Ormel, J., Jonge, P. de, & Oldehinkel, A. J. (2013). Physical activity and onset of depression in adolescents: A prospective study in the general population cohort TRAILS. *Journal of Psychiatric Research*, 47(10), 1304–1308.
<https://doi.org/10.1016/j.jpsychires.2013.06.005>
- *Stone, L. B., Hankin, B. L., Gibb, B. E., & Abela, J. R. (2011). Co-Rumination Predicts the Onset of Depressive Disorders During Adolescence. *Journal of Abnormal Psychology*, 120(3), 752–757. <https://doi.org/10.1037/a0023384>
- *Tokuyama, M., Nakao, K., Seto, M., Watanabe, A., & Takeda, M. (2003). Predictors of first-onset major depressive episodes among white-collar workers. *Psychiatry and Clinical Neurosciences*, 57(5), 523–531. <https://doi.org/10.1046/j.1440-1819.2003.01158.x>
- *Wilkinson, P. O., Croudace, T. J., & Goodyer, I. M. (2013). Rumination, anxiety, depressive symptoms and subsequent depression in adolescents at risk for psychopathology: A longitudinal cohort study. *BMC Psychiatry*, 13(1), 250–258. <https://doi.org/10.1186/1471-244X-13-250>

Appendix 2 Supplement to Chapter 3

Appendix 2A Search strategies in databases

Pubmed

"cell phone"[MeSh Terms] or
 "Text Messaging"[MeSh Terms] or
 "Reminder Systems"[MeSh Terms] or
 "internet"[MeSH Terms] or
 "Social Media"[MeSh Terms] or
 "Mobile Applications"[Mesh Terms] or
 "Computers, Handheld"[Mesh Terms] or
 "Software"[Mesh Terms] or
 "Electronic Mail"[Mesh Terms] or
 "Video Games"[Mesh Terms] or
 "Social Networking"[Mesh Terms] or
 (digital[tiab] or email[tiab] or e-mail[tiab] or telephone[tiab] or phone[tiab] or web[tiab] or
 web-based[tiab] or internet[tiab] or "internet-based"[tiab] or online[tiab] or electronic[tiab])
 Or ("text messag*" [tiab] or SMS[tiab] or "short messag* service*" [tiab] or texting[tiab] or
 messaging[tiab])
 Or ("mobile phone*" [tiab] or "cell phone*" [tiab] or cellphone* [tiab] or "smart phone*" [tiab] or
 smartphone* [tiab])
 Or ("mobile health" [tiab] or "mobile technolog*" [tiab] or mhealth[tiab] or "e-mental health" [tiab]
 or "e-therapy" [tiab] or "e-health" [tiab])
 Or (email[tiab] or e-mail[tiab] or "electronic mail" [tiab] or "electronic reminder*" [tiab])
 Or ("new media" [tiab] or "social media" [tiab] or "electronic media" [tiab])
 Or ((phone* [tiab] or smartphone* [tiab] or cellphone* [tiab] or mobile* [tiab] or web* [tiab] or
 internet[tiab]) and (app[tiab] or apps[tiab] or application* [tiab]))
 Or (facebook[tiab] or twitter[tiab] or instagram[tiab] or social networking[tiab])
 Or (internet[tiab] or website* [tiab] or "web site*" [tiab])
 Or (laptop* [tiab] or PDA* [tiab] or "personal digital assistant*" [tiab])
 or ("video game*" [tiab])

AND

"psychotherapy"[MeSH Terms] OR psychotherapy[Text Word] OR intervention[all field] OR
 treatment [all field]

AND

"Clinical Trials as Topic"[Mesh] or "clinical trials"[tiab] or "crossover procedure"[tiab] or "double blind
 procedure"[tiab] or placebo[tiab] or randomization[tiab] or "random sample"[tiab] or "single blind
 procedure"[tiab] "randomized controlled trial"[Publication Type] OR "randomized controlled
 trial"[tiab]

AND

LMIC filter

Not (review[ti] or meta-analysis[ti])

LMIC filter (search in Pubmed as example)

#10 search #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9

#9 search "developing country"[tiab] OR "developing countries"[tiab] OR "developing nation"[tiab]
 OR "developing nations"[tiab] OR "developing population"[tiab] OR "developing populations"[tiab] OR
 "developing world"[tiab] OR "less developed country"[tiab] OR "less developed countries"[tiab] OR

"underdeveloped nations"[ot] OR "underdeveloped population"[ot] OR "underdeveloped populations"[ot] OR "underdeveloped world"[ot] OR "middle income country"[ot] OR "middle income countries"[ot] OR "middle income nation"[ot] OR "middle income nations"[ot] OR "middle income population"[ot] OR "middle income populations"[ot] OR "low income country"[ot] OR "low income countries"[ot] OR "low income nation"[ot] OR "low income nations"[ot] OR "low income population"[ot] OR "low income populations"[ot] OR "lower income country"[ot] OR "lower income countries"[ot] OR "lower income nation"[ot] OR "lower income nations"[ot] OR "lower income population"[ot] OR "lower income populations"[ot] OR "underserved country"[ot] OR "underserved countries"[ot] OR "underserved nation"[ot] OR "underserved nations"[ot] OR "underserved population"[ot] OR "underserved populations"[ot] OR "underserved world"[ot] OR "under served country"[ot] OR "under served nations"[ot] OR "under served nation"[ot] OR "under served nations"[ot] OR "under served population"[ot] OR "under served populations"[ot] OR "under served world"[ot] OR "deprived country"[ot] OR "deprived countries"[ot] OR "deprived nation"[ot] OR "deprived nations"[ot] OR "deprived population"[ot] OR "deprived populations"[ot] OR "deprived world"[ot] OR "poor country"[ot] OR "poor countries"[ot] OR "poor nation"[ot] OR "poor nations"[ot] OR "poor population"[ot] OR "poor populations"[ot] OR "poor world"[ot] OR "poorer country"[ot] OR "poorer countries"[ot] OR "poorer nation"[ot] OR "poorer nations"[ot] OR "poorer population"[ot] OR "poorer populations"[ot] OR "poorer world"[ot] OR "developing economy"[ot] OR "developing economies"[ot] OR "less developed economy"[ot] OR "less developed economies"[ot] OR "lesser developed economy"[ot] OR "lesser developed economies"[ot] OR "under developed economy"[ot] OR "under developed economies"[ot] OR "underdeveloped economy"[ot] OR "underdeveloped economies"[ot] OR "middle income economy"[ot] OR "middle income economies"[ot] OR "low income economy"[ot] OR "low income economies"[ot] OR "lower income economy"[ot] OR "lower income economies"[ot] OR "low gdp"[ot] OR "low gnp"[ot] OR "low gross domestic"[ot] OR "low gross national"[ot] OR "lower gdp"[ot] OR "lower gnp"[ot] OR "lower gross domestic"[ot] OR "lower gross national"[ot] OR lmic[ot] OR lmic[ot] OR "third world"[ot] OR "lami country"[ot] OR "lami countries"[ot] OR "transitional country"[ot] OR "transitional countries"[ot]

#7 Search Africa[pl] OR Asia[pl] OR Caribbean[pl] OR West Indies[pl] OR South America[pl] OR Latin America[pl] OR Central America[pl] OR Afghanistan[pl] OR Albania[pl] OR Algeria[pl] OR Angola[pl] OR Antigua[pl] OR Barbuda[pl] OR Argentina[pl] OR Armenia[pl] OR Armenian[pl] OR Aruba[pl] OR Azerbaijan[pl] OR Bahrain[pl] OR Bangladesh[pl] OR Barbados[pl] OR Benin[pl] OR Byelarus[pl] OR Byelorussian[pl] OR Belarus[pl] OR Belorussian[pl] OR Belorussia[pl] OR Belize[pl] OR Bhutan[pl] OR Bolivia[pl] OR Bosnia[pl] OR Herzegovina[pl] OR Hercegovina[pl] OR Botswana[pl] OR Brasil[pl] OR Brazil[pl] OR Bulgaria[pl] OR Burkina Faso[pl] OR Burkina Fasso[pl] OR Upper Volta[pl] OR Burundi[pl] OR Urundi[pl] OR Cambodia[pl] OR Khmer Republic[pl] OR Kampuchea[pl] OR Cameroon[pl] OR Camerons[pl] OR Cameron[pl] OR Camerons[pl] OR Cape Verde[pl] OR Central African Republic[pl] OR Chad[pl] OR Chile[pl] OR China[pl] OR Colombia[pl] OR Comoros[pl] OR Comoro Islands[pl] OR Comores[pl] OR Mayotte[pl] OR Congo[pl] OR Zaire[pl] OR Costa Rica[pl] OR Cote d'Ivoire[pl] OR Ivory Coast[pl] OR Croatia[pl] OR Cuba[pl] OR Cyprus[pl] OR Czechoslovakia[pl] OR Czech Republic[pl] OR Slovakia[pl] OR Slovak Republic[pl] OR Djibouti[pl] OR French Somaliland[pl] OR Dominica[pl] OR Dominican Republic[pl] OR East Timor[pl] OR East Timur[pl] OR Timor Leste[pl] OR Ecuador[pl] OR Egypt[pl] OR United Arab Republic[pl] OR El Salvador[pl] OR Eritrea[pl] OR Estonia[pl] OR Ethiopia[pl] OR Fiji[pl] OR Gabon[pl] OR Gabonese Republic[pl] OR Gambia[pl] OR Gaza[pl] OR Georgia Republic[pl] OR Georgian Republic[pl] OR Ghana[pl] OR Gold Coast[pl] OR Greece[pl] OR Grenada[pl] OR Guatemala[pl] OR Guinea[pl] OR Guam[pl] OR Guiana[pl] OR Guyana[pl] OR Haiti[pl] OR Honduras[pl] OR Hungary[pl] OR India[pl] OR Maldives[pl] OR Indonesia[pl] OR Iran[pl] OR Iraq[pl] OR Isle of Man[pl] OR Jamaica[pl] OR Jordan[pl] OR Kazakhstan[pl] OR Kazakh[pl] OR Kenya[pl] OR Kiribati[pl] OR Korea[pl] OR Kosovo[pl] OR Kyrgyzstan[pl] OR Kirghizia[pl] OR Kyrgyz Republic[pl] OR



Kirghiz[pl] OR Kirgizstan[pl] OR "Lao PDR"[pl] OR Laos[pl] OR Latvia[pl] OR Lebanon[pl] OR Lesotho[pl] OR Basutoland[pl] OR Liberia[pl] OR Libya[pl] OR Lithuania[pl]

#6 Search Macedonia[pl] OR Madagascar[pl] OR Malagasy Republic[pl] OR Malaysia[pl] OR Malaya[pl] OR Malay[pl] OR Sabah[pl] OR Sarawak[pl] OR Malawi[pl] OR Nyasaland[pl] OR Mali[pl] OR Malta[pl] OR Marshall Islands[pl] OR Mauritania[pl] OR Mauritius[pl] OR Agalega Islands[pl] OR Mexico[pl] OR Micronesia[pl] OR Middle East[pl] OR Moldova[pl] OR Moldavia[pl] OR Moldovan[pl] OR Mongolia[pl] OR Montenegro[pl] OR Morocco[pl] OR Ifni[pl] OR Mozambique[pl] OR Myanmar[pl] OR Myanma[pl] OR Burma[pl] OR Namibia[pl] OR Nepal[pl] OR Netherlands Antilles[pl] OR New Caledonia[pl] OR Nicaragua[pl] OR Niger[pl] OR Nigeria[pl] OR Northern Mariana Islands[pl] OR Oman[pl] OR Muscat[pl] OR Pakistan[pl] OR Palau[pl] OR Palestine[pl] OR Panama[pl] OR Paraguay[pl] OR Peru[pl] OR Philippines[pl] OR Philipines[pl] OR Phillipines[pl] OR Phillippines[pl] OR Poland[pl] OR Portugal[pl] OR Puerto Rico[pl] OR Romania[pl] OR Rumania[pl] OR Roumania[pl] OR Russia[pl] OR Russian[pl] OR Rwanda[pl] OR Ruanda[pl] OR Saint Kitts[pl] OR St Kitts[pl] OR Nevis[pl] OR Saint Lucia[pl] OR St Lucia[pl] OR Saint Vincent[pl] OR St Vincent[pl] OR Grenadines[pl] OR Samoa[pl] OR Samoan Islands[pl] OR Navigator Island[pl] OR Navigator Islands[pl] OR Sao Tome[pl] OR Saudi Arabia[pl] OR Senegal[pl] OR Serbia[pl] OR Montenegro[pl] OR Seychelles[pl] OR Sierra Leone[pl] OR Slovenia[pl] OR Sri Lanka[pl] OR Ceylon[pl] OR Solomon Islands[pl] OR Somalia[pl] OR South Africa[pl] OR Sudan[pl] OR Suriname[pl] OR Surinam[pl] OR Swaziland[pl] OR Syria[pl] OR Tajikistan[pl] OR Tadjhikistan[pl] OR Tadjikistan[pl] OR Tadjhik[pl] OR Tanzania[pl] OR Thailand[pl] OR Togo[pl] OR Togolese Republic[pl] OR Tonga[pl] OR Trinidad[pl] OR Tobago[pl] OR Tunisia[pl] OR Turkey[pl] OR Turkmenistan[pl] OR Turkmen[pl] OR Uganda[pl] OR Ukraine[pl] OR Uruguay[pl] OR USSR[pl] OR Soviet Union[pl] OR Union of Soviet Socialist Republics[pl] OR Uzbekistan[pl] OR Uzbek OR Vanuatu[pl] OR New Hebrides[pl] OR Venezuela[pl] OR Vietnam[pl] OR Viet Nam[pl] OR West Bank[pl] OR Yemen[pl] OR Yugoslavia[pl] OR Zambia[pl] OR Zimbabwe[pl] OR Rhodesia[pl]

#5 Search Africa[tiab] OR Asia[tiab] OR Caribbean[tiab] OR West Indies[tiab] OR South America[tiab] OR Latin America[tiab] OR Central America[tiab] OR Afghanistan[tiab] OR Albania[tiab] OR Algeria[tiab] OR Angola[tiab] OR Antigua[tiab] OR Barbuda[tiab] OR Argentina[tiab] OR Armenia[tiab] OR Armenian[tiab] OR Aruba[tiab] OR Azerbaijan[tiab] OR Bahrain[tiab] OR Bangladesh[tiab] OR Barbados[tiab] OR Benin[tiab] OR Byelarus[tiab] OR Byelorussian[tiab] OR Belarus[tiab] OR Belorussian[tiab] OR Belorussia[tiab] OR Belize[tiab] OR Bhutan[tiab] OR Bolivia[tiab] OR Bosnia[tiab] OR Herzegovina[tiab] OR Hercegovina[tiab] OR Botswana[tiab] OR Brasil[tiab] OR Brazil[tiab] OR Bulgaria[tiab] OR Burkina Faso[tiab] OR Burkina Fasso[tiab] OR Upper Volta[tiab] OR Burundi[tiab] OR Urundi[tiab] OR Cambodia[tiab] OR Khmer Republic[tiab] OR Kampuchea[tiab] OR Cameroon[tiab] OR Cameroons[tiab] OR Cameron[tiab] OR Camerons[tiab] OR Cape Verde[tiab] OR Central African Republic[tiab] OR Chad[tiab] OR Chile[tiab] OR China[tiab] OR Colombia[tiab] OR Comoros[tiab] OR Comoro Islands[tiab] OR Comores[tiab] OR Mayotte[tiab] OR Congo[tiab] OR Zaire[tiab] OR Costa Rica[tiab] OR Cote d'Ivoire[tiab] OR Ivory Coast[tiab] OR Croatia[tiab] OR Cuba[tiab] OR Cyprus[tiab] OR Czechoslovakia[tiab] OR Czech Republic[tiab] OR Slovakia[tiab] OR Slovak Republic[tiab] OR Djibouti[tiab] OR French Somaliland[tiab] OR Dominica[tiab] OR Dominican Republic[tiab] OR East Timor[tiab] OR East Timur[tiab] OR Timor Leste[tiab] OR Ecuador[tiab] OR Egypt[tiab] OR United Arab Republic[tiab] OR El Salvador[tiab] OR Eritrea[tiab] OR Estonia[tiab] OR Ethiopia[tiab] OR Fiji[tiab] OR Gabon[tiab] OR Gabonese Republic[tiab] OR Gambia[tiab] OR Gaza[tiab] OR Georgia Republic[tiab] OR Georgian Republic[tiab] OR Ghana[tiab] OR Gold Coast[tiab] OR Greece[tiab] OR Grenada[tiab] OR Guatemala[tiab] OR Guinea[tiab] OR Guam[tiab] OR Guiana[tiab] OR Guyana[tiab] OR Haiti[tiab] OR Honduras[tiab] OR Hungary[tiab] OR India[tiab] OR Maldives[tiab] OR Indonesia[tiab] OR Iran[tiab] OR Iraq[tiab] OR Isle of Man[tiab] OR Jamaica[tiab] OR Jordan[tiab] OR Kazakhstan[tiab] OR Kazakh[tiab] OR Kenya[tiab] OR Kiribati[tiab] OR Korea[tiab] OR Kosovo[tiab] OR Kyrgyzstan[tiab] OR Kirghizia[tiab]

OR Kyrgyz Republic[tiab] OR Kirghiz[tiab] OR Kirgizstan[tiab] OR "Lao PDR"[tiab] OR Laos[tiab] OR Latvia[tiab] OR Lebanon[tiab] OR Lesotho[tiab] OR Basutoland[tiab] OR Liberia[tiab] OR Libya[tiab] OR Lithuania[tiab]

#4 Search Macedonia[tiab] OR Madagascar[tiab] OR Malagasy Republic[tiab] OR Malaysia[tiab] OR Malaya[tiab] OR Malay[tiab] OR Sabah[tiab] OR Sarawak[tiab] OR Malawi[tiab] OR Nyasaland[tiab] OR Mali[tiab] OR Malta[tiab] OR Marshall Islands[tiab] OR Mauritania[tiab] OR Mauritius[tiab] OR Agalega Islands[tiab] OR Mexico[tiab] OR Micronesia[tiab] OR Middle East[tiab] OR Moldova[tiab] OR Romania[tiab] OR Moldavia[tiab] OR Moldovan[tiab] OR Mongolia[tiab] OR Montenegro[tiab] OR Morocco[tiab] OR Ifni[tiab] OR Mozambique[tiab] OR Myanmar[tiab] OR Myanma[tiab] OR Burma[tiab] OR Namibia[tiab] OR Nepal[tiab] OR Netherlands Antilles[tiab] OR New Caledonia[tiab] OR Nicaragua[tiab] OR Niger[tiab] OR Nigeria[tiab] OR Northern Mariana Islands[tiab] OR Oman[tiab] OR Muscat[tiab] OR Pakistan[tiab] OR Palau[tiab] OR Palestine[tiab] OR Panama[tiab] OR Paraguay[tiab] OR Peru[tiab] OR Philippines[tiab] OR Philipines[tiab] OR Phillipines[tiab] OR Phillippines[tiab] OR Poland[tiab] OR Portugal[tiab] OR Puerto Rico[tiab] OR Romania[tiab] OR Rumania[tiab] OR Roumania[tiab] OR Russia[tiab] OR Russian[tiab] OR Rwanda[tiab] OR Ruanda[tiab] OR Saint Kitts[tiab] OR St Kitts[tiab] OR Nevis[tiab] OR Saint Lucia[tiab] OR St Lucia[tiab] OR Saint Vincent[tiab] OR St Vincent[tiab] OR Grenadines[tiab] OR Samoa[tiab] OR Samoan Islands[tiab] OR Navigator Island[tiab] OR Navigator Islands[tiab] OR Sao Tome[tiab] OR Saudi Arabia[tiab] OR Senegal[tiab] OR Serbia[tiab] OR Montenegro[tiab] OR Seychelles[tiab] OR Sierra Leone[tiab] OR Slovenia[tiab] OR Sri Lanka[tiab] OR Ceylon[tiab] OR Solomon Islands[tiab] OR Somalia[tiab] OR Sudan[tiab] OR Suriname[tiab] OR Surinam[tiab] OR Swaziland[tiab] OR Syria[tiab] OR Tajikistan[tiab] OR Tadjhikistan[tiab] OR Tadjikistan[tiab] OR Tadjhik[tiab] OR Tanzania[tiab] OR Thailand[tiab] OR Togo[tiab] OR Togolese Republic[tiab] OR Tonga[tiab] OR Trinidad[tiab] OR Tobago[tiab] OR Tunisia[tiab] OR Turkey[tiab] OR Turkmenistan[tiab] OR Turkmen[tiab] OR Uganda[tiab] OR Ukraine[tiab] OR Uruguay[tiab] OR USSR[tiab] OR Soviet Union[tiab] OR Union of Soviet Socialist Republics[tiab] OR Uzbekistan[tiab] OR Uzbek OR Vanuatu[tiab] OR New Hebrides[tiab] OR Venezuela[tiab] OR Vietnam[tiab] OR Viet Nam[tiab] OR West Bank[tiab] OR Yemen[tiab] OR Yugoslavia[tiab] OR Zambia[tiab] OR Zimbabwe[tiab] OR Rhodesia[tiab]

#3 Search Africa[ot] OR Asia[ot] OR Caribbean[ot] OR West Indies[ot] OR South America[ot] OR Latin America[ot] OR Central America[ot] OR Afghanistan[ot] OR Albania[ot] OR Algeria[ot] OR Angola[ot] OR Antigua[ot] OR Barbuda[ot] OR Argentina[ot] OR Armenia[ot] OR Armenian[ot] OR Aruba[ot] OR Azerbaijan[ot] OR Bahrain[ot] OR Bangladesh[ot] OR Barbados[ot] OR Benin[ot] OR Byelarus[ot] OR Byelorussian[ot] OR Belarus[ot] OR Belorussian[ot] OR Belorussia[ot] OR Belize[ot] OR Bhutan[ot] OR Bolivia[ot] OR Bosnia[ot] OR Herzegovina[ot] OR Hercegovina[ot] OR Botswana[ot] OR Brasil[ot] OR Brazil[ot] OR Bulgaria[ot] OR Burkina Faso[ot] OR Burkina Fasso[ot] OR Upper Volta[ot] OR Burundi[ot] OR Urundi[ot] OR Cambodia[ot] OR Khmer Republic[ot] OR Kampuchea[ot] OR Cameroon[ot] OR Cameroons[ot] OR Cameron[ot] OR Camerons[ot] OR Cape Verde[ot] OR Central African Republic[ot] OR Chad[ot] OR Chile[ot] OR China[ot] OR Colombia[ot] OR Comoros[ot] OR Comoro Islands[ot] OR Comores[ot] OR Mayotte[ot] OR Congo[ot] OR Zaire[ot] OR Costa Rica[ot] OR Cote d'Ivoire[ot] OR Ivory Coast[ot] OR Croatia[ot] OR Cuba[ot] OR Cyprus[ot] OR Czechoslovakia[ot] OR Czech Republic[ot] OR Slovakia[ot] OR Slovak Republic[ot] OR Djibouti[ot] OR French Somaliland[ot] OR Dominica[ot] OR Dominican Republic[ot] OR East Timor[ot] OR East Timur[ot] OR Timor Leste[ot] OR Ecuador[ot] OR Egypt[ot] OR United Arab Republic[ot] OR El Salvador[ot] OR Eritrea[ot] OR Estonia[ot] OR Ethiopia[ot] OR Fiji[ot] OR Gabon[ot] OR Gabonese Republic[ot] OR Gambia[ot] OR Gaza[ot] OR "Georgia Republic"[ot] OR "Georgian Republic"[ot] OR Ghana[ot] OR Gold Coast[ot] OR Greece[ot] OR Grenada[ot] OR Guatemala[ot] OR Guinea[ot] OR Guam[ot] OR Guiana[ot] OR Guyana[ot] OR Haiti[ot] OR Honduras[ot] OR Hungary[ot] OR India[ot] OR Maldives[ot]



OR Indonesia[ot] OR Iran[ot] OR Iraq[ot] OR Isle of Man[ot] OR Jamaica[ot] OR Jordan[ot] OR Kazakhstan[ot] OR Kazakh[ot] OR Kenya[ot] OR Kiribati[ot] OR Korea[ot] OR Kosovo[ot] OR Kyrgyzstan[ot] OR Kirghizia[ot] OR Kyrgyz Republic[ot] OR Kirghiz[ot] OR Kirgizstan[ot] OR "Lao PDR"[ot] OR Laos[ot] OR Latvia[ot] OR Lebanon[ot] OR Lesotho[ot] OR Basutoland[ot] OR Liberia[ot] OR Libya[ot] OR Lithuania[ot]

#2 Search Macedonia[ot] OR Madagascar[ot] OR Malagasy Republic[ot] OR Malaysia[ot] OR Malaya[ot] OR Malay[ot] OR Sabah[ot] OR Sarawak[ot] OR Malawi[ot] OR Nyasaland[ot] OR Mali[ot] OR Malta[ot] OR Marshall Islands[ot] OR Mauritania[ot] OR Mauritius[ot] OR Agalega Islands[ot] OR Mexico[ot] OR Micronesia[ot] OR Middle East[ot] OR Moldova[ot] OR Moldavia[ot] OR Moldovan[ot] OR Mongolia[ot] OR Montenegro[ot] OR Morocco[ot] OR Ifni[ot] OR Mozambique[ot] OR Myanmar[ot] OR Myanma[ot] OR Burma[ot] OR Namibia[ot] OR Nepal[ot] OR Netherlands Antilles[ot] OR New Caledonia[ot] OR Nicaragua[ot] OR Niger[ot] OR Nigeria[ot] OR Northern Mariana Islands[ot] OR Oman[ot] OR Muscat[ot] OR Pakistan[ot] OR Palau[ot] OR Palestine[ot] OR Panama[ot] OR Paraguay[ot] OR Peru[ot] OR Philippines[ot] OR Philipines[ot] OR Phillipines[ot] OR Phillippines[ot] OR Poland[ot] OR Portugal[ot] OR Puerto Rico[ot] OR Romania[ot] OR Rumania[ot] OR Roumania[ot] OR Russia[ot] OR Russian[ot] OR Rwanda[ot] OR Ruanda[ot] OR Saint Kitts[ot] OR St Kitts[ot] OR Nevis[ot] OR Saint Lucia[ot] OR St Lucia[ot] OR Saint Vincent[ot] OR St Vincent[ot] OR Grenadines[ot] OR Samoa[ot] OR Samoan Islands[ot] OR Navigator Island[ot] OR Navigator Islands[ot] OR Sao Tome[ot] OR Saudi Arabia[ot] OR Senegal[ot] OR Serbia[ot] OR Montenegro[ot] OR Seychelles[ot] OR Sierra Leone[ot] OR Slovenia[ot] OR Sri Lanka[ot] OR Ceylon[ot] OR Solomon Islands[ot] OR Somalia[ot] OR Sudan[ot] OR Suriname[ot] OR Surinam[ot] OR Swaziland[ot] OR Syria[ot] OR Tajikistan[ot] OR Tadjikistan[ot] OR Tadjikistan[ot] OR Tadjhik[ot] OR Tanzania[ot] OR Thailand[ot] OR Togo[ot] OR Togolese Republic[ot] OR Tonga[ot] OR Trinidad[ot] OR Tobago[ot] OR Tunisia[ot] OR Turkey[ot] OR Turkmenistan[ot] OR Turkmen[ot] OR Uganda[ot] OR Ukraine[ot] OR Uruguay[ot] OR USSR[ot] OR Soviet Union[ot] OR Union of Soviet Socialist Republics[ot] OR Uzbekistan[ot] OR Uzbek OR Vanuatu[ot] OR New Hebrides[ot] OR Venezuela[ot] OR Vietnam[ot] OR Viet Nam[ot] OR West Bank[ot] OR Yemen[ot] OR Yugoslavia[ot] OR Zambia[ot] OR Zimbabwe[ot] OR Rhodesia[ot]

#1 Search Developing Countries[Mesh:noexp] OR Africa[Mesh:noexp] OR Africa, Northern[Mesh:noexp] OR Africa South of the Sahara[Mesh:noexp] OR Africa, Central[Mesh:noexp] OR Africa, Eastern[Mesh:noexp] OR Africa, Southern[Mesh:noexp] OR Africa, Western[Mesh:noexp] OR Asia[Mesh:noexp] OR Asia, Central[Mesh:noexp] OR Asia, Southeastern[Mesh:noexp] OR Asia, Western[Mesh:noexp] OR Caribbean Region[Mesh:noexp] OR West Indies[Mesh:noexp] OR South America[Mesh:noexp] OR Latin America[Mesh:noexp] OR Central America[Mesh:noexp] OR Afghanistan[Mesh:noexp] OR Albania[Mesh:noexp] OR Algeria[Mesh:noexp] OR American Samoa[Mesh:noexp] OR Angola[Mesh:noexp] OR "Antigua and Barbuda"[Mesh:noexp] OR Argentina[Mesh:noexp] OR Armenia[Mesh:noexp] OR Azerbaijan[Mesh:noexp] OR Bahrain[Mesh:noexp] OR Bangladesh[Mesh:noexp] OR Barbados[Mesh:noexp] OR Benin[Mesh:noexp] OR Byelarus[Mesh:noexp] OR Belize[Mesh:noexp] OR Bhutan[Mesh:noexp] OR Bolivia[Mesh:noexp] OR Bosnia-Herzegovina[Mesh:noexp] OR Botswana[Mesh:noexp] OR Brazil[Mesh:noexp] OR Bulgaria[Mesh:noexp] OR Burkina Faso[Mesh:noexp] OR Burundi[Mesh:noexp] OR Cambodia[Mesh:noexp] OR Cameroon[Mesh:noexp] OR Cape Verde[Mesh:noexp] OR Central African Republic[Mesh:noexp] OR Chad[Mesh:noexp] OR Chile[Mesh:noexp] OR China[Mesh:noexp] OR Colombia[Mesh:noexp] OR Comoros[Mesh:noexp] OR Congo[Mesh:noexp] OR Costa Rica[Mesh:noexp] OR Cote d'Ivoire[Mesh:noexp] OR Croatia[Mesh:noexp] OR Cuba[Mesh:noexp] OR Cyprus[Mesh:noexp] OR Czechoslovakia[Mesh:noexp] OR Czech Republic[Mesh:noexp] OR Slovakia[Mesh:noexp] OR Djibouti[Mesh:noexp] OR "Democratic Republic of the Congo"[Mesh:noexp] OR

Dominica[Mesh:noexp] OR Dominican Republic[Mesh:noexp] OR East Timor[Mesh:noexp] OR Ecuador[Mesh:noexp] OR Egypt[Mesh:noexp] OR El Salvador[Mesh:noexp] OR Eritrea[Mesh:noexp] OR Estonia[Mesh:noexp] OR Ethiopia[Mesh:noexp] OR Fiji[Mesh:noexp] OR Gabon[Mesh:noexp] OR Gambia[Mesh:noexp] OR "Georgia (Republic)"[Mesh:noexp] OR Ghana[Mesh:noexp] OR Greece[Mesh:noexp] OR Grenada[Mesh:noexp] OR Guatemala[Mesh:noexp] OR Guinea[Mesh:noexp] OR Guinea-Bissau[Mesh:noexp] OR Guam[Mesh:noexp] OR Guyana[Mesh:noexp] OR Haiti[Mesh:noexp] OR Honduras[Mesh:noexp] OR Hungary[Mesh:noexp] OR India[Mesh:noexp] OR Indonesia[Mesh:noexp] OR Iran[Mesh:noexp] OR Iraq[Mesh:noexp] OR Jamaica[Mesh:noexp] OR Jordan[Mesh:noexp] OR Kazakhstan[Mesh:noexp] OR Kenya[Mesh:noexp] OR Korea[Mesh:noexp] OR Kosovo[Mesh:noexp] OR Kyrgyzstan[Mesh:noexp] OR Laos[Mesh:noexp] OR Latvia[Mesh:noexp] OR Lebanon[Mesh:noexp] OR Lesotho[Mesh:noexp] OR Liberia[Mesh:noexp] OR Libya[Mesh:noexp] OR Lithuania[Mesh:noexp] OR Macedonia[Mesh:noexp] OR Madagascar[Mesh:noexp] OR Malaysia[Mesh:noexp] OR Malawi[Mesh:noexp] OR Mali[Mesh:noexp] OR Malta[Mesh:noexp] OR Mauritania[Mesh:noexp] OR Mauritius[Mesh:noexp] OR Mexico[Mesh:noexp] OR Micronesia[Mesh:noexp] OR Middle East[Mesh:noexp] OR Moldova[Mesh:noexp] OR Mongolia[Mesh:noexp] OR Montenegro[Mesh:noexp] OR Morocco[Mesh:noexp] OR Mozambique[Mesh:noexp] OR Myanmar[Mesh:noexp] OR Namibia[Mesh:noexp] OR Nepal[Mesh:noexp] OR Netherlands Antilles[Mesh:noexp] OR New Caledonia[Mesh:noexp] OR Nicaragua[Mesh:noexp] OR Niger[Mesh:noexp] OR Nigeria[Mesh:noexp] OR Oman[Mesh:noexp] OR Pakistan[Mesh:noexp] OR Palau[Mesh:noexp] OR Panama[Mesh:noexp] OR Papua New Guinea[Mesh:noexp] OR Paraguay[Mesh:noexp] OR Peru[Mesh:noexp] OR Philippines[Mesh:noexp] OR Poland[Mesh:noexp] OR Portugal[Mesh:noexp] OR Puerto Rico[Mesh:noexp] OR Romania[Mesh:noexp] OR Russia[Mesh:noexp] OR "Russia (Pre-1917)"[Mesh:noexp] OR Rwanda[Mesh:noexp] OR "Saint Kitts and Nevis"[Mesh:noexp] OR Saint Lucia[Mesh:noexp] OR "Saint Vincent and the Grenadines"[Mesh:noexp] OR Samoa[Mesh:noexp] OR Saudi Arabia[Mesh:noexp] OR Senegal[Mesh:noexp] OR Serbia[Mesh:noexp] OR Montenegro[Mesh:noexp] OR Seychelles[Mesh:noexp] OR Sierra Leone[Mesh:noexp] OR Slovenia[Mesh:noexp] OR Sri Lanka[Mesh:noexp] OR Somalia[Mesh:noexp] OR South Africa[Mesh:noexp] OR Sudan[Mesh:noexp] OR Suriname[Mesh:noexp] OR Swaziland[Mesh:noexp] OR Syria[Mesh:noexp] OR Tajikistan[Mesh:noexp] OR Tanzania[Mesh:noexp] OR Thailand[Mesh:noexp] OR Togo[Mesh:noexp] OR Tonga[Mesh:noexp] OR "Trinidad and Tobago"[Mesh:noexp] OR Tunisia[Mesh:noexp] OR Turkey[Mesh:noexp] OR Turkmenistan[Mesh:noexp] OR Uganda[Mesh:noexp] OR Ukraine[Mesh:noexp] OR Uruguay[Mesh:noexp] OR USSR[Mesh:noexp] OR Uzbekistan[Mesh:noexp] OR Vanuatu[Mesh:noexp] OR Venezuela[Mesh:noexp] OR Vietnam[Mesh:noexp] OR Yemen[Mesh:noexp] OR Yugoslavia[Mesh:noexp] OR Zambia[Mesh:noexp] OR Zimbabwe[Mesh:noexp]

Randomized controlled trial filter-Pubmed

"Clinical Trials as Topic"[Mesh] or "clinical trials"[tiab] or "crossover procedure"[tiab] or "double blind procedure"[tiab] or placebo[tiab] or randomization[tiab] or "random sample"[tiab] or "single blind procedure"[tiab] "randomized controlled trial"[Publication Type] OR "randomized controlled trial"[tiab]

Appendix 2B Effects of digital psychological intervention on mental health problems versus other intervention

Three studies (Christoff et al., 2015; D’ Souza et al., 2013; Tiburcio et al., 2018) were identified comparing digital psychological interventions with other intervention. One study (Christoff et al., 2015) compared Web-based intervention with face-to-face intervention using the same treatment manual in participants with substance use and found a moderate effect size. One study (D’Souza et al., 2013) compared computer-based intervention with medication in patients of schizophrenia, and did not find difference in two groups. The other study (Tiburcio et al., 2018) compared web-based program with self-help intervention with the handbook within substance misuse participants and found no difference between the two groups. Since the number of studies was limited, we only presented their calculated Hedges’ g in the forest plot without pooling an overall effect size.

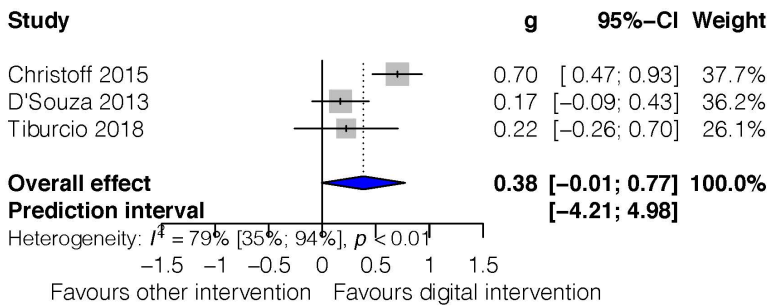


Figure S1: Forest plot of studies with digital interventions compared to other interventions

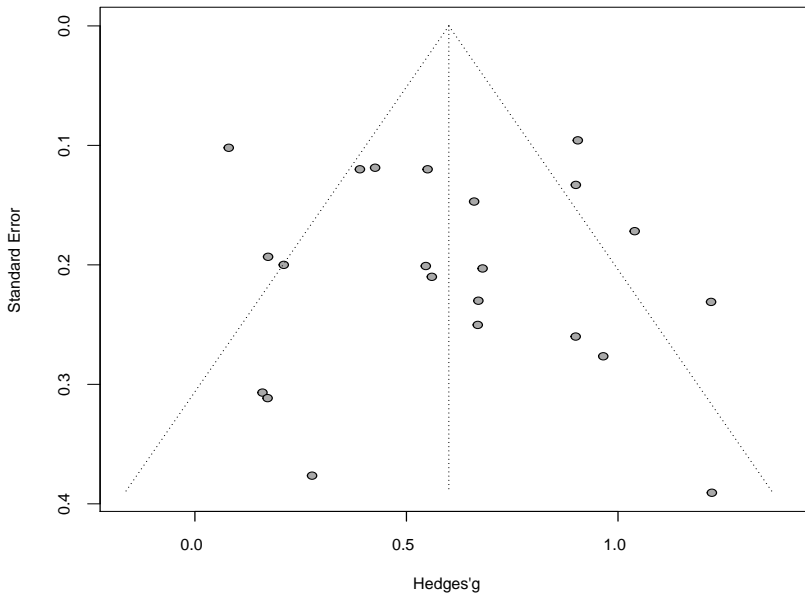


Figure S2: Funnel plot of studies included in the random-effects meta-analysis of digital psychological interventions for mental health problems compared with control group

Table S1 Supplemental characteristics of included studies.

Author	Format	Theory	Guidance	Missing value	Recruitment	Country
Arjadi 2018	Web	Behavior Activation	Lay counsellor	ITT	Community	Indonesia
Baldin 2016	Web	Personalized feedback	NA	ITT	Nightclubs	Brazil
Burton 2016	App	CBT	Professional	NA	Clinics	Multisite
Christoff 2015	App	Motivational intervention	NA	NA	University	Brazil
D'Souza 2013	Others	Cognitive functioning	Clinical Psychologist	ITT	Hospital	Multisite
Darvish 2018	Others	Social cognitive theory	Clinical psychiatry nurse	NA	Hospital	Iran
Dumaz 2019	APP	Behavior theory	NA	ITT	Community	Turkey
Guo 2020	App	Motivational intervention	NA	ITT	Hospital	China
Knaevelsrud 2015	Web	CBT	Therapist	ITT	Community	Iran
Liang 2018	App	CBT	NA	Complete case	Community	China
Liao 2018	Others	CBT	NA	ITT	Community	China
Marasinghe 2012	App	Problem-Solving	Therapist	ITT	Hospital	Sri Lanka
Mogoase 2013	Others	Construal levels theory	Researcher	Complete case	University	Romania
Moeini 2019	Web	Cognitive theory	NA	Complete case	University	Iran
Salamanca-Sanabria 2020	Web	Cognitive theory	NA	Complete case	University	Colombia
Sanchez 2018	Web	Personalized feedback	NA	NA	Nightclubs	Brazil
Su 2011	Others	Motivational intervention	NA	Complete case	University	China
Thitipitchavanant 2018	Others	Social cognitive theory	NA	NA	Hospital	Thailand
Tiburcio 2018	Web	CBT	Health professional	ITT	Hospital	Mexico
Tulbure 2015	Web	CBT	Online psychologist	ITT	Community	Romania
Tulbure 2018	Web	CBT	Online psychologist	ITT	Community	Romania
Wang 2013	Web	Social cognitive theory	Researcher	ITT	Community	China
Yang 2019	Web	Mindfulness	Nurse	ITT	Hospital	China
Zhu 2018	Web	Behavior theory	NA	NA	Hospital	China

Note: CBT=Cognitive behavior therapy; NA=Not applicable; ITT=Intention-to-Treat analysis

Appendix 2C GRADE evaluation of different mental health outcomes

Question: Digital intervention compared to control groups for mental health problems **Setting:** Low and middle income countries

Certainty assessment							No of patients		Effect		Certainty		Importance	
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Digital intervention	control groups	Absolute (95% CI)					
Mental health problems														
22	randomised trials	serious ^a	not serious	not serious	not serious	strong association all plausible residual confounding would suggest spurious effect, while no effect was observed ^b	2301	1739	SMD 0.6 SD higher (0.45 higher to 0.75 higher)	⊕⊕⊕⊕ HIGH			IMPORTANT	
Depression (assessed with: Multiple)														
14	randomised trials	serious ^c	not serious	not serious	not serious	all plausible residual confounding would suggest spurious effect, while no effect was observed	855	752	SMD 0.57 SD higher (0.41 higher to 0.73 higher)	⊕⊕⊕⊕ HIGH			IMPORTANT	
Anxiety (assessed with: Multiple)														
4	randomised trials	not serious	not serious	not serious	not serious	publication bias strongly suspected strong association all plausible residual confounding would suggest spurious effect, while no effect was observed ^d	230	194	SMD 0.81 SD higher (0.48 higher to 1.14 higher)	⊕⊕⊕⊕ HIGH			IMPORTANT	
PTSD (assessed with: Multiple)														

Certainty assessment											
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	No of patients		Effect	Certainty	Importance
							Digital intervention	control groups			
3	randomised trials	not serious	not serious	not serious	not serious	publication bias suspected strong association all plausible residual confounding would suggest spurious effect, while no effect was observed ^e	202	197	SMD 0.8 SD higher (0.6 higher to 1 higher)	⊕⊕⊕⊕ HIGH	IMPORTANT
Substance use (assessed with: Multiple)											
7	randomised trials	serious ^f	serious ^g	not serious	not serious	all plausible residual confounding would suggest spurious effect, while no effect was observed	1266	864	SMD 0.53 SD higher (0.18 higher to 0.88 higher)	⊕⊕⊕○ MODERATE	IMPORTANT

CI: Confidence interval, **SMD**: Standardised mean difference
 Explanations

- a. Around 70% of the studies did not report or violate the concealment rule; and around half of the studies did not pre-register therefore cannot rule out the selective outcome reporting.
- b. Publication was detected from the funnel plot, egger's test, and after trim-and-fill procedure, the effect size not has confidence interval with zero.
- c. 8/14 of the studies on depression were rated as high risk of bias
- d. Only four studies were identified for this outcome.
- e. Only three studies were identified for this outcome.
- f. 4/7 of the studies on substance use were rated as high risk of bias.
- g. Results of studies presented mixed direction of treatment effects



Appendix 3 Supplement to Chapter 4

Appendix 3A Search terms

Pubmed

("Depressive disorder"[MeSH Terms] OR "Depression"[MeSH Terms] OR "Mood Disorders"[Mesh] OR "Mood disorders" [Title/Abstract] OR depression [Title/Abstract] OR "Major Depressive Disorder" [Title/Abstract] OR Anhedonia [Title/Abstract] OR depressed [Title/Abstract] OR affective [Title/Abstract] OR "Beck depression inventory"[All Fields]OR "Patient Health Questionnaire"[All fields] OR "Center for Epidemiologic studies depression" [All fields] OR "SCL-90" OR Dysphoria [Title/Abstract] OR Dysphoric [Title/Abstract] OR Melancholia [Title/Abstract])

AND

(Psychotherapy [MeSH Terms] OR Psychotherapy[Title/Abstract] OR Intervention [Title/Abstract] OR Treatment [Title/Abstract] OR "Psychological intervention" [Title/Abstract] OR "Psychological treatment" [Title/Abstract] OR Therapy [Title/Abstract] OR Intervening [Title/Abstract] OR "Psychological adjustment" [Title/Abstract] OR Medication [Title/Abstract])

AND

(China[Title/Abstract] or Chinese[Title/Abstract] or Hongkong[Title/Abstract] OR Taiwan[Title/Abstract] or Macau[Title/Abstract])

AND

(student* [Title/Abstract] OR "University students" [Title/Abstract] OR College students [Title/Abstract] OR "University pupils" [Title/Abstract] OR "college pupils" [Title/Abstract] OR "Chinese-American students" [Title/Abstract] OR "oversea students" [Title/Abstract] OR youth[Title/Abstract] OR undergraduate*[Title/Abstract])

PsycInfo

(depression or depressive or depressed or affective or Anhedonia or *Major Depressive Disorder or *Beck Depression Inventory or *Patient Health Questionnaire or SCL-90 or *Center for Epidemiologic studies depression or Dysphoria or Dysphoric or Melancholia or *Mood disorder).ab,ti.

AND

(Psychotherapy or Intervention or Treatment or *Psychological intervention or *Psychological treatment or Therapy or Intervening or *Psychological adjustment or Medication).ab,ti.

AND

(China or Chinese or Hongkong or Taiwan or Macau).ab,ti

AND

(student* or *University students or *College students or *University pupils or *college pupils or *Chinese-American students or youth or undergraduate* or *oversea students).ab,ti

Cochrane

#1 (depression or depressive or depressed or affective or 'Major Depressive Disorder' or 'Beck Depression Inventory' or 'Patient Health Questionnaire' or SCL-90 or 'Center for Epidemiologic studies depression' or Dysphoria or Dysphoric or Melancholia or 'mood disorder')

AND

#2 (Psychotherapy or Intervention or Treatment or 'Psychological intervention' or 'Psychological treatment' or Therapy or Intervening or 'Psychological adjustment' or Medication)

AND

#3

(China or Chinese or Hongkong or Taiwan or Macau)

AND

#4 (student* or *University students or *College students or *University pupils or *college pupils or *Chinese-American students or youth or undergraduate* or *oversea students)

(#1 AND #2 AND #3 AND #4)

Embase

('depression':ti,ab,kw OR 'depressive':ti,ab,kw OR 'depressed':ti,ab,kw OR 'affective':ti,ab,kw OR 'major depressive disorder':ti,ab,kw OR 'Beck Depression Inventory':ti,ab,kw OR 'Patient Health Questionnaire':ti,ab,kw OR SCL-90 OR 'Center for Epidemiologic studies depression' OR 'dysphoria':ti,ab,kw OR 'dysphoric':ti,ab,kw OR 'melancholia':ti,ab,kw OR 'mood disorder':ti,ab,kw)

AND

('Psychotherapy':ti,ab,kw OR 'intervention':ti,ab,kw OR 'treatment':ti,ab,kw OR 'psychological intervention':ti,ab,kw OR 'psychological treatment':ti,ab,kw OR 'therapy':ti,ab,kw OR 'intervening':ti,ab,kw OR 'psychological adjustment':ti,ab,kw OR 'medication':ti,ab,kw)

AND

(China:ti,ab,kw OR Chinese:ti,ab,kw OR Hongkong:ti,ab,kw or Taiwan:ti,ab,kw or Macau:ti,ab,kw)

AND

(student*:ti,ab,kw OR 'university students':ti,ab,kw OR 'college students':ti,ab,kw OR 'university pupils':ti,ab,kw OR 'college pupils':ti,ab,kw OR 'chinese-american students':ti,ab,kw OR 'oversea students':ti,ab,kw OR youth:ti,ab,kw OR undergraduate*:ti,ab,kw)

CNKI (Knowledge Discovery Network Platform) 中国知网

(TI= '抑郁'+ '情绪障碍'+ '心境障碍'+ '忧郁'+ '抑郁症状'+ '难过'+ '郁闷'+ '躁动'+ '病理性心境恶劣'+ '烦躁不安'+ '心理健康') And (TI = '治疗'+ '干预'+ '疗法'+ '医治'+ '心理干预'+ '心理治疗'+ '心理调整'+ '辅导'+ '心理疏导') And ((TI = '大学生'+ '青年'+ '学生'+ '海外留学生'+ '华裔学生'+ '高校学生') OR (AB = '大学生'))

万方数据知识服务平台 (Wanfang Database)

题名:(抑郁+情绪障碍+心境障碍+忧郁+抑郁症状+难过+郁闷+躁动+病理性心境恶劣+烦躁不安+心理健康)* 题名:(治疗+干预+疗法+医治+心理干预+心理治疗+心理调整+辅导+心理疏导)*(题名:(大学生+青年+学生+海外留学生+华裔学生+高校学生) +(摘要: (大学生))

维普期刊资源整合服务平台 (Weipu database)

(T=(抑郁+心境障碍+情绪障碍 +忧郁+抑郁症状+难过+郁闷 +躁动+病理性心境恶劣+烦躁不安+心理健康))*(T=(心理治疗+治疗+干预+疗法+医治+心理干预+心理调整+辅导+心理疏导))*((T=(大学生+青年+学生+海外留学生+华裔学生+高校学生)) + R=大学生)



Appendix 3B Characteristic of all studies identified in the systematic review

Table S2 Characteristics of included studies in qualitative synthesis

Format of intervention	Number of studies
Group	49
Individual	33
Individual+Group	1
Medicine+Individual	1
Self-help	6
NA	2
Guidance of intervention	
Professional	51
Professional + peer	1
Self-help	2
Tutor Support	10
NA	28
Setting	
Hospital	6
Mental health center	1
University	85

Table S3 Characteristics of psychological interventions in studies retrieved with different research designs

Author, Year	Setting	Intervention Details	Theory/Type of intervention	Guidance	Delivery	Location
Bao, 2015	Hospital	use basic counselling skills and cognitive therapy skills to assist the medicine treatment	CBT+Medicine	Professional	Individual	North
Cai et al.,	University	Correct negative automatic thoughts	CBT	Professional	Individual	
Chen & Guo, 2016	University	6 session, once a week; to explore the trait advantage of participants;	NA	NA	Group	South
Chen et al., 2015	Medical school	twice a week, 10 weeks, each session 40min	Art therapy	Professional	Group	South (Taiwan)
Chen et al., 2016	University	REBT group therapy, 8 sessions, each session 50min, once a week;	REBT	Professional	Group	
Cui et al., 2016	University	8 sessions, once a week, based on treatment manual, including psychoeducation, behavioral activation, relaxation, cognitive techniques, and so forth.	CBT	Professional	Group	North
Ding & Wen, 2015	University	six weekly group sessions, each session last 90-150 min. These sessions covered self-introduction, relaxation, painting on specific topic.	Art therapy	Professional	Group	
Dong et al., 2011	University	seven sessions, once a week, one session last 2h. Themes included psychoeducation on depression, alteration of attributing and coping style, construct social support system. Ten members in one group.	CBT	NA	Group	South
Fang & Chang, 2010	University	deliver psychoeducation on the association between emotion and beliefs, reconstruct negative cognition via typical cognitive therapeutic skills;	CBT	Professional	Individual	
Gong, 2017	University	Three months of reading	Bibliotherapy	NA	Self-help	
Gong, 2016	University	Crisis intervention with intensive care (client centred therapy and CBT) and refer to psychiatrist.	Client centred therapy, CBT	Tutor Support	Individual	
Gong, 2016	University	Two weeks of reading	Bibliotherapy	NA	Self-help	
Guan et al., 2014	University	A blended treatment program including 8 individual sessions and 4 group sessions. Each week had one session which last 1h. The program started with individual sessions and transferred into group sessions later. Topic	CBT	NA	Individual +Group	North

Author, Year	Setting	Intervention Details	Theory/Type of intervention	Guidance	Delivery	Location
		covered emotion management, interpersonal skills, and confidence building.				
Guo et al., 2016	Medical school	six weekly sessions each lasting 1.5-2h;	CBT	Professional	Group	
Guo, 2013	Vocational school	8 sessions, each session 150min	CBT	Professional	Group	
Han, 2017	University	ten sessions	Psychodynamic	NA	Group	North
Hu, 2014	University	evaluate the depression status and risk of crisis, stabilize the client, and refer to psychiatrist.	NA	Tutor Support	Individual	
Huang & Li, 2017	University	5 sessions of art therapy (painting) to establish good relationship, evaluate psychological condition via projection test, to cope with negative emotion, to improve communication skills, etc.	Art therapy	Professional	Individual	
Jiang, 2014	University	three months' reading according to the book list prescribed by professionals	Bibliotherapy	Professional	Self-help	North
Jing et al., 2013	University	Introduce the philosophy of TaiChi (24 sets) to the students which are to harmonize human and nature, to think in a dialectical way.	CT+Physical exercise	Professional	Group	
Li & Jiang, 2018	Hospital	supportive non-directive psychological intervention;	NA	Professional	Individual	
Li et al., 2008	University	Group intervention targeted specifically on interpersonal relationship, including four sections: cognition of interpersonal relationship, interpersonal communication, emotion, and relationship.	Interpersonal therapy	Professional	Group	
Li et al., 2016a,b	University	CBT group treatment, 8 sessions, twice each week, each session 2h;	CBT	NA	Group	North
Li et al., 2016	Hospital	Psychological education, group peer support	NA	Professional, peer	Group	
Li, 2014	University	NA	NA	Professional	NA	South
Li, 2015	University	6 sessions of sand-play therapy, each session 45 min, once a week	Sand-play	Professional	Individual	

Author, Year	Setting	Intervention Details	Theory/Type of intervention	Guidance	Delivery	Location
Li, Luan & Liu, 2018	Vocational school	the four inquiries to detect the underlying beliefs and work on the beliefs;	The work (Byron Katie)	Professional	Individual	
Liang, 2018	University	within three months, participants were asked to read at least three books on the prescribed booklet and the process were monitored via online network and reading notes;	Bibliotherapy	Professional	Self-help	
Liao & Sun, 2015	University	6 sessions, each session 2h, once a week	Positive psychology	Professional	Group	
Lin & Li,	Vocational school	6 sessions, each session 3h, once a week. Including cognitive coping regulation.	Interpersonal therapy	NA	Group	
Lin & Yao, 2010	University	10 sessions, once each week; identify emotion problems and correspondent behavior and beliefs, replace irrational beliefs with rational beliefs, consolidate with homework; Supportive care with listening; music therapy;	CBT+Supportive care+music therapy	Professional	Individual	
Lin et al., 2011	University	21 sessions of sand-play in a 10-month period; 4 stages divided: presence of depression emotion, regression and reversal, integration and application, progressing;	Sand-play	Professional	Individual	
Lin et al., 2018	University	Cognitive therapy Group program: based on manual adapted from M. Free (2007); 8 sessions, each 120min each week, structured by a series of topics including input in the relationship between thoughts and feelings, guided relaxation imagery, introduction of the cognitive theory of depression and suicide, working on dysfunctional thoughts, etc. Dialectical behavior therapy skills	CBT/DBT	Professional	Group	
Lin, 2017	University	supportive communication.	Supportive care	Tutor Support	Individual	
Liu et al., 2018	University	8 weeks of group mindfulness training;	Mindfulness	NA	Group	
Liu, 2010	University	Psychodynamic therapy+CBT	Psychodynamic+CBT	Professional	Individual	
Mao, 2011	University	solution focused therapy via minor changes and self-reinforcement to make difference	SFBT	Professional	Individual	
Murphy & Shao, 2012	University	CBT、 medication (SSRI), physical exercise	CBT+Medicine	Professional	Individual	

Author, Year	Setting	Intervention Details	Theory/Type of intervention	Guidance	Delivery	Location
Nie et al., 2012	University	three months' guided reading	Bibliotherapy	Professional	Self-help	
Niu & Cao, 2011	University	8 sessions, once a week, each session 2h.	Art therapy	NA	Group	
Ouyang, 2001	University	RET combined with physical exercise. 15-18 sessions, 25-30 hours in total.	REBT	NA	Group	
Pan & Xie, 2015	University	6 sessions of general group intervention. No details about meta-cognitive intervention.	Meta-cognitive intervention	Professional	Group	South
Pei, 2006	Vocational school	8 sessions, once a week, each session last two hours; including social skills training, alteration of dysfunctional attitudes;	CBT+IPT	NA	Group	
Ren et al., 2016	University	Moodgym, a self-help online intervention website. It includes five training programs targeting on feeling, thought/beliefs, cognitive distortion, stress reduction, and interpersonal relationship. Each program cost 20-40 min, participants were encouraged to finish within 3 weeks.	CBT+IPT	Self-help	Self-help	Blended
Ren, 2008	University	7 sessions of sandplay and 9 sessions of face to face therapy	Sandplay	Professional	Individual	
Shi, 2017	University	supportive communication, involve the parents in and educate them the knowledge of mental disorder	Supportive care	Tutor Support	Individual	
Song & Zhang, 2009	University	Group treatment with 8 sessions in two months, each session 120min	NA	NA	Group	North
Tai et al., 2010	Medical school	supportive care	Supportive care	Professional	Individual	North
Wang & Chen, 2015	University	in combination with medicine care, attain support from family members and peers of clients, guide students on time management, encourage physical exercise, and facilitate the student to explore his self-worth.	Supportive care	Tutor Support	Individual	
Wang & Wu, 2014	University	9 sessions, once a week, each session last 1.5h, including building positive personality trait, being grateful, being optimistic ect.	Blended	Professional	Group	South
Wang et al., 2014	Medical school	8 sessions, each session 2h, once a week; improve social skills, interpersonal relationships, emotion expression;	NA	NA	Group	

Author, Year	Setting	Intervention Details	Theory/Type of intervention	Guidance	Delivery	Location
Wang et al., 2014	Medical school	8 sessions, each session 2h, once a week; improve social skills, interpersonal relationships, emotion expression;	NA	NA	Group	
Wang et al., 2015	University	8 sessions, each session 1.5h, twice a week including psychoeducation of depression, being aware of the depressive emotion, learning to manage depression and knowing the cause of depression.	Positive psychology	Professional	Group	South
Wang et al., 2015	University	9 session, each session 60min, once a week; to build positive psychological personality by learning PERMA theory (positive psychology) with assistance of cognitive therapy	CBT+Positive psychology	Professional	Individual	
Wang et al., 2016	University	12 sessions, once a week, each session 2h. The program aimed to encourage students involved into the volunteering work within different communities to improve tendency of being altruism. Each session was conducted after volunteer work and discuss and share the thing students get from the volunteering work.	Positive psychology	Professional	Group	North
Wei & Zhang, 2010	University	8 sessions, once a week, one session last 2h. Target on altering irrational cognition.	CBT	NA	Group	
Wu & Lv, 2018	University	psychoeducation and supportive communication; 3-5 times of physical exercise each week for 6 weeks;	NA	Professional	Group	
Wu et al., 2013	University	1. 8-week-premium mindfulness training including body scanning, breathing training, meditation, breathing space, emotion-thoughts relationship; 2. 8-week-brief mindfulness training ruled out body scanning in the 8-week-premium training and encouraged participants connect everyday life with the training. 3. 4-week training with one-time practice of the skill in each session.	Mindfulness	Professional	Group	
Xi, 2011	University	A six-week Solution-focused group therapy program was conducted with one session each week last 2-3h.	SFBT	Professional	Group	North
Xiang, 2007	University	Group treatment with 8 sessions in two months, each session 120min	NA	NA	Group	South
Xiao et al., 2018	University	social role guidance intervention, similar with RET, 5 sessions, once two weeks.	REBT	Professional	Individual	North

Author, Year	Setting	Intervention Details	Theory/Type of intervention	Guidance	Delivery	Location
Xie, 2013	Hospital	three stages of intervention, each stage last for 3 months.	Morita therapy	Professional	Individual	
Xiong et al., 2017	Hospital	10 sessions, each session 120min, once a week; to facilitate group members being aware of the inner conflicts and the relationship with original family, to fix psychological trauma on the level of unconsciousness.	Psychodynamic	NA	Group	South
Xu et al., 2017	University	integrate dance therapy, physical exercise, biological system, sand play, music therapy	Art therapy + Sandplay	NA	Group	North
Xu, 2009	University	Cognitive reconstruction, behavior change, relaxation	CBT	Professional	Individual	
Xu, 2014	University	supportive communication, encouragement, etc.	Supportive care	Tutor Support	Individual	
Yan, 2012	University	music therapy including listening to selected music under guidance and involving in percussion music	Art therapy	NA	NA	
Yang et al., 2014	University	8 sessions of group CBT based on manual; once a week, each session 2h.	CBT	Professional	Group	North
Yang et al., 2015	University	8 sessions in the ABM during a 2-week period, each session 1-2h	Attention bias modification	Self-help	Individual	South
Yang et al., 2016	Medical school	eight weekly Zhongyong thinking group intervention sessions, each session 1.5h	Zhongyong thinking	Professional	Group	South
Yang et al., 2017	University	CBT group treatment, 8 sessions, twice each week, each session 2h;	CBT	NA	Group	North
Yang et al., 2018	University	eight-week CSCT training followed by a four-month follow-up consolidation intervention; each group session 1.5h; average 7.5 (1.0) sessions during the period; eight modules including psychological education, behavioral analyses, goals setting, mindfulness meditation, behavioral activation, self-monitoring and reward, cognitive correction, coping improving, consolidation. Supportive communication and listening	CSCT	Professional	Group	South
Yang, 2009	University	REBT	Supportive care	Professional	Individual	
Yang, 2013	University	REBT	REBT	Professional	Individual	

Author, Year	Setting	Intervention Details	Theory/Type of intervention	Guidance	Delivery	Location
Ye et al., 2012	University	Duloxetine (20-40mg/d, up to 120mg/d in two weeks) and psychotherapy (8 weeks, twice each week, each session 60-90mins)	Psychotherapy+Medicine	Professional	Individual	South
Zeng & Dong, 2009	University	8 sessions, each session 60 min;	CBT	Professional	Individual	
Zhang & Bai, 2006	Medical school	A CBT group therapy were conducted with eight-weekly-session with 100min each session. The intervention targeted on reconstructing negative cognition and improve interpersonal skills.	CBT	Professional	Group	
Zhang & Liu, 1997	University	Client centered therapy	Positive psychology	Professional	Individual	
Zhang & Sun, 2010	University	An eight-weekly group counselling focused on improving interpersonal relationship and develop more rational perception of self. It conducted with one session last 2.5h per week.	CBT	NA	Group	South
Zhang et al., 2005	Hospital	8 sessions, once a week, 3h per session;	REBT	Professional	Group	
Zhang et al., 2006	University	psychological intervention in combination with medicine	Psychotherapy+Medicine	Professional	Individual	
Zhang et al., 2014	University	Music therapy with traditional Chinese music. 12 sessions, each session last 30min, twice a week.	Art Therapy	NA	Group	
Zhang et al., 2016	University	six sessions, each session last 60min, once two weeks.	Narrative therapy	Professional	Individual	
Zhang et al., 2016	University	8 sessions, once a week, each session last 2.5h.	Positive psychology	NA	Group	South
Zhang et al., 2018	University	8 weeks of Taichi Chuan training combined with mindfulness; twice a week, 16 sessions in total;	Mindfulness+Taichi	Professional	Group	
Zhao et al., 2013	University	A six-weekly group session, each session last for 2.5h; CBT group focused on altering negative cognition, ACT group aimed to improve acceptability of problems and distress;	CBT	NA	Group	South
Zhong et al., 2017	Mental health center	12 sessions of music therapy, once a week. Plus anti-depressants;	Art therapy + Medicine	Professional	Medicine + Individual	

Author, Year	Setting	Intervention Details	Theory/Type of intervention	Guidance	Delivery	Location
Zhong, 2016	Vocational school	five weekly group session with five different musical theme, each session last 90min.	Art therapy	Professional	Group	
Zhou et al., 2010	University	music therapy	Art therapy	Professional	Individual	
Zhu & Feng, 2012	University	Psychotherapy + hospitalization	NA	Professional	Individual	
Zhu et al., 2012	University	11 sessions of interpersonal group therapy, once a week, each session 90-120min.	Interpersonal therapy	Professional	Group	
Zou & Yin, 2015	University	8 sessions, once a week, each session 2.5 hours. Interpersonal skills focused, alter dysfunctional attitudes using ABC theory.	CBT	NA	Group	

Appendix 3C Risk of bias assessment of included RCT studies (Cochrane Collaboration's tool for assessing risk of bias in randomised trials; Higgins et al., 2011).
Table S4 Risk of bias Assessment of included studies

Author, year	Sequence Generation	Allocation concealment	Blinding of participants and personnel for All outcomes	Blinding of outcome assessors for All outcomes	Incomplete outcome data for All outcomes	Selective outcome reporting	Other sources of bias
Bao, 2015	Unclear	Unclear	Unclear	SR	Unclear	Unclear	Unclear
Chen et al. 2015	Low	High	High	SR	Unclear	Unclear	High
Chen, 2016	Unclear	Unclear	Unclear	SR	Unclear	Unclear	Unclear
Cui et al. 2016	Unclear	High	High	SR	Low	Unclear	Unclear
Dong, 2011	Unclear	Unclear	Unclear	SR	Unclear	Unclear	Unclear
Guan, 2014	Unclear	Unclear	Unclear	SR	Unclear	Unclear	Unclear
Han, 2017	Unclear	Unclear	Unclear	SR	Low	Unclear	Unclear

Author, year	Sequence Generation	Allocation concealment	Blinding of participants and personnel for All outcomes	Blinding of outcome assessors for All outcomes	Incomplete outcome data for All outcomes	Selective outcome reporting	Other sources of bias
Jiang, 2014	Unclear	Unclear	Unclear	SR	Unclear	Unclear	Unclear
Li & Jiang, 2018	Unclear	Unclear	unclear	SR	Unclear	Unclear	Unclear
Li, 2014	Unclear	Unclear	Unclear	SR	Unclear	Unclear	Unclear
Li, 2016	Unclear	Unclear	Unclear	SR	Low	Unclear	Unclear
Li, 2016 a,b	Unclear	Unclear	Unclear	SR	Unclear	Unclear	Unclear
Liang, 2018	Unclear	Unclear	Unclear	SR	Unclear	Unclear	Unclear
Lin et al., 2018	Low	Unclear	Unclear	SR	Low	Unclear	High
Liu et al., 2018	Unclear	Unclear	Unclear	SR	Unclear	Unclear	Unclear
Pan, 2015	Low	Unclear	Unclear	SR	Unclear	Unclear	High
Ren, 2016	Unclear	Unclear	Unclear	SR	Low	Unclear	Unclear
Song, 2009	Unclear	Unclear	Unclear	SR	Unclear	Unclear	High
Tai, 2010	Unclear	Unclear	Unclear	SR	Low	Unclear	Low
Wang, 2014	Unclear	Unclear	Unclear	SR	Unclear	Unclear	Unclear
Wang, 2015	Unclear	Unclear	Unclear	SR	Unclear	Unclear	High
Wang, 2016	Unclear	Unclear	Unclear	SR	Low	Unclear	Unclear
Wu & Lv, 2018	Low	Unclear	Unclear	Unclear	Unclear	Unclear	High
Xi, 2011	Unclear	Unclear	Unclear	SR	Unclear	Unclear	Unclear
Xiang, 2007	Unclear	Unclear	Unclear	SR	Unclear	Unclear	Unclear

Author, year	Sequence Generation	Allocation concealment	Blinding of participants and personnel for All outcomes	Blinding of outcome assessors for All outcomes	Incomplete outcome data for All outcomes	Selective outcome reporting	Other sources of bias
Xiao, 2018	Unclear	Unclear	Unclear	SR	Unclear	Unclear	Unclear
Xiong, 2017	Low	Unclear	Unclear	SR	Unclear	Unclear	Unclear
Xu, 2017	Unclear	Unclear	Unclear	SR	Unclear	Unclear	Unclear
Yang et al. 2015	Low	Low	Low	SR	Low	Unclear	High
Yang et al. 2016	Unclear	Unclear	Unclear	SR	Unclear	Unclear	Low
Yang et al. 2018	Low	Low	Low	SR	Low	Unclear	Low
Yang, 2014	Low	Unclear	Unclear	SR	Low	Unclear	Unclear
Yang, 2017	Unclear	Unclear	Unclear	SR	Unclear	Unclear	Unclear
Ye, 2012	Unclear	Unclear	Unclear	SR	Low	Unclear	Unclear
Zhang et al., 2018	Low	Low	Low	SR	Low	Unclear	Unclear
Zhang, 2010	Unclear	Unclear	Unclear	SR	Unclear	Unclear	Unclear
Zhang, 2016	Unclear	Unclear	Unclear	SR	Unclear	Unclear	High
Zhao, 2013	Unclear	Unclear	Unclear	SR	High	Unclear	Unclear
Zhong, 2017	Low	Unclear	Unclear	SR	Low	Unclear	Unclear

Appendix 3D Reference list included articles in the systematic review

- Bao, L., 2015. Qingnian yiyuzheng huanzhe yingyong xinli zhiliao de jiazhi fenxi [Value Analysis of Psychotherapy in Young Patients with Depression]. *Shijie zuixin yixue xinxi wenzhai* 7–8. <https://doi.org/10.3969/j.issn.1671-3141.2015.78.004>
- Cai, J., Yang, W., Liu, Y., 2013. Baituo yinmai, chongshi kuaile yu zixin --yili daxuesheng gaokao shili dao zhi qindu yiyu de yuanrenzhi xinliganyu [Get rid of the haze, regain happiness and self-confidence--a metacognitive psychological intervention of a college student's college entranc. *Shehui xinli kexue* 118–120.
- Chen, C.J., Sung, H.C., Lee, M.S., Chang, C.Y., 2015. The effects of Chinese five-element music therapy on nursing students with depressed mood. *J. Int. Nurs. Pract.* 21, 192–199. <https://doi.org/10.1111/ijn.12236>
- Chen, J., Tu, Y., Yang, X., Ma, W., Guo, T., Zhang, W., Yang, X., Yang, X., Feng, C., Liang, Y., 2016. REBT dui gaowei yiyu daxuesheng renqun jinxing tuanti xinliganyu de sheji yu shijian [Design and practice of group psychological intervention in high-risk depression college students by REBT]. *Zhonghua zhongyiyao zazhi* 3178–3182.
- Chen, X., Guo, S., 2016. Jiji xinli tuanti fudao dui daxuesheng yiyu zhengzhuang de ganyu xiaoguo pingjia [Evaluation of Intervention Effect of Positive Psychological Group Counseling on Depressive Symptoms of College Students]. *Zhongguo xuexiao weisheng* 37, 874–877.
- Cu, C., Zhang, M., 2014. Xiaoyaowan peihe xinlihuli dui daxuesheng qindu yiyu zhiliao xiaoguo [Effect of Xiaoyao Pill Combined with Psychological Nursing on College Students' Mild Depression]. *Zhongguo xiandai yaowu yingyong* 8, 178–179.
- Cui, L., He, F., Han, Z., Yang, R., Xiao, J., Oei, T.P.S., 2016. A brief group cognitive-behavioral program for the prevention of depressive symptoms in Chinese college students. *Int. J. Group Psychother.* 66, 291–307. <https://doi.org/http://dx.doi.org/10.1080/00207284.2015.1111098>
- Ding, Z., Wen, W., 2015. Jiti huihua dui daxuesheng yiyu qingxiang de zaoqi ganyu [Early Intervention of Collective Painting on College Students' Depression Tendency]. *Nanfeng* 172–173.
- Dong, S., Dong, X., Dai, J., Wang, C., Wu, J., Zeng, H., Wang, S., 2011. Tuanti xunlian dui daxuesheng yiyu qingxu de ganyu xiaoguo pingjia [Evaluation of intervention effect of group training on college students' depression]. *Zhonghua jibing kongzhi zazhi* 758–761.
- Fang, J., Chang, B., 2010. Yunyong renzhi xingwei liaofa he ziwo fagnyu jizhi lilun gaibian daxuesheng yiyuqingxu de gean baogao [Case report of changing college students' depression using cognitive behavioral therapy and self-defense mechanism theory]. *Shehui xinli kexue* 111–115.
- Gong, M., 2016. Shilian yinfa de daxuesheng yiyuzhangai yuedu liaofa shufang fenxi ji peiwu [Analysis and compatibility of reading therapy for depression in college students caused by lovelorn]. *Daxue tushuguan xuebao* 0, 80–88.
- Gong, M., Xu, H., Lei, J., Zhang, H., Liu, W., Chu, C., 2017. Tongnianchuangshang yinfa de yiyuzhangai yuedu liaofa shufangfenxi ji peiwu [Analysis and compatibility of reading therapy for depression caused by childhood trauma]. *Daxue tushuguan xuebao* 35, 36–45.
- Gong, W., 2016. Youyu zaizao, yangguang zaiyou -- dui yili qingdu yiyuzheng xuesheng de changqi xinli fuzhu zhiliao [Melancholy is on the left and the sun is on the right - long-term psychotherapeutic treatment for a student with mild depression]. *Kuaile yuedu* 72.
- Guan, X., Qiao, Z., Qiu, X., Yang, X., Wang, L., Yang, Y., 2014. Daxuesheng yiyu xinli ganyu xiaoguo fenxi [Analysis of the effect of psychological intervention on college students' depression]. *Zhongguo xuexiao weisheng* 35, 240–242.
- Guo, N., 2013. Daxuesheng qingdu yiyu de tuanti renzhi xingwei zhiliao [Group cognitive behavioral therapy for college students with mild depression]. *Taiyuan zhiye jishuxueyuan xuebao* 1, 110–112. <https://doi.org/10.3969/j.issn.1673-0046.2013.01.056>



- Guo, T., Guo, Z., Zhang, W., Ma, W., Yang, X., Yang, X., Hwang, J., He, X., Chen, X., Ya, T., 2016. Electroacupuncture and cognitive behavioural therapy for sub-syndromal depression among undergraduates: a controlled clinical trial. *Acupunct. Med.* 34, 356–363.
- Han, Y., 2017. Dongli daoxiang tuanti xinlizhiliao dui daxuesheng yiyuqingxu ganyuxiaoguo pingjia [Evaluation of the effect of dynamic-oriented group psychotherapy on college students' depression]. *Zhongguo baojian yingyang* 27, 36.
- Hu, H., 2014. Yili yiyuzheng xuesheng de xinliweiji ganyu anli [A case of psychological crisis intervention for depression students]. *Wangyou shijie* 219–220.
- Huang, Y., Li, M., 2017. Huihua zhiliao dui zhican daxuesheng qingxuzhangai ganyu de gean yanjiu [Case Study on the Treatment of Mental Disorders of Disabled College Students with Painting Treatment]. *Shenghuo jiaoyu* 116–119.
- Jiang, Q., 2014. Yuedu liaofa zai yufang he ganyu daxuesheng yiyuzheng zhong de yingyong [Application of reading therapy in prevention and intervention of college students' depression]. *Taishan yixueyuan xuebao* 370–371.
- Jin, J., Xi, Y., Yan, W., 2013. Taijiquan de renzhifangshi dui zhiliao daxuesheng yiyuzheng de gongxiaoyanjiu [Study on the Effect of Taijiquan's Cognitive Style on the Treatment of College Students' Depression]. *Xiandai yangsheng* 62–67.
- Li, F., Zheng, X., 2008. Renji jiaowang tuanti fudao gaishan daxuesheng yiyu zhuangkuang xiaoguo pingjia [Evaluation of the effect of interpersonal group counseling on improving college students' depression]. *Zhongguo xuexiao weisheng* 29, 519–520.
- Li, H., 2014. Youyang yundong yu xinli jiankang jiaoyu lianhe ganyu dui daxuesheng zaoqi yiyuzheng de liaoxiao guanCha [Therapeutic effect of combined intervention of aerobic exercise and mental health education on early depression in college students]. *Tiyu yanjiu yu jiaoyu* 114–117.
- Li, J., 2015. Yige yiyuzheng nv daxuesheng de shapanyouxi zhiliao [A depression female college student sand table game treatment]. *Shenghuo jiaoyu* 0, 122–127.
- Li, T., Ge, L., Wang, Y., Xu, Y., 2016a. Zixinxin tuanti xunlian dui daxuesheng yiyu qingxu ji zidong siwei de ganyuyanjiu [Intervention Study on Self-confidence Group Training on College Students' Depression and Automated Thinking]. *Zhonghua xingwei yixue yu naokexue zazhi* 25, 171–174.
- Li, T., Ge, L., Wang, Y., Xu, Y., 2016b. Zixinxin tuanti xunlian dui daxuesheng yiyuqingxu ji xinren shuiping de ganyuyanjiu [Intervention Study on Self-confidence Group Training on College Students' Depression and Trust Level]. *Zhongguo gaodeng yixue jiaoyu* 0, 55–56.
- Li, Y., Han, W., Fu, Y., Xie, J., 2016. Jiankang xinliganyu shudao dui qingnian xinyinxing yiyuzheng de yingxiang [Effect of Health Psychological Intervention on Young People's "Psychogenic" Depression]. *Yixue dongwu fangzhi* 0, 87–88.
- Li, Y., Jiang, W., 2018. Xinli zhiliao lianhe yaowu zhiliao dui qingshaonian xuesheng jiaolv yiyu de liaoxiao fenxi [Therapeutic effect of psychotherapy combined with drug therapy on anxiety and depression of adolescent students]. *Zhihui jiankang* 4, 142–143.
- Liang, J., 2018. Yuedu liaofa dui daxuesheng yiyu qingxu de yingxiang [The effect of reading therapy on college students' depression]. *Qingbao tansuo* 1, 72–75.
- Liao, R., Sun, J., 2015. Jijixinli tuanti fudao zai yiyu daxuesheng zhong de yingyongyanjiu [Application Research of Positive Psychological Group Counseling in College Students with Depression]. *Beijing jiaoyu* 69–70.
- Lin, P., Yao, A., 2010. Xinli zhiliao gaozhi xuesheng yiyuzheng 40 li anli fenxi [Case Analysis of 40 Cases of Depression in Higher Vocational Students with Psychotherapy]. *Nanfeng yike daxue xuebao* 30, 1760–1761.
- Lin, T.J., Ko, H.C., Wu, J.Y., Oei, T.P., Lane, H.Y., Chen, C.H., 2019. The Effectiveness of Dialectical Behavior Therapy Skills Training Group vs. Cognitive Therapy Group on Reducing Depression

- and Suicide Attempts for Borderline Personality Disorder in Taiwan. *Arch Suicide Res* 23, 82–99. <https://doi.org/10.1080/13811118.2018.1436104>
- Lin, Y., 2017. Qianxi peibanshi fudao dui daxuesheng yiyuzheng ganyu de zuoyong -- Yiyuzheng bangfu anli fenxi [Analysis of the Effect of Accompanying Counseling on College Students' Depression Intervention—A Case Study of Depression Help]. *Jilingsheng jiaoyu xueyuan xuebao* 33, 126–128. <https://doi.org/10.16083/j.cnki.1671-1580.2017.06.039>
- Lin, Y., Zhang, R., Wang, X., Jin, W., 2011. Xiangting liaofa zhiliao zhongdu yiyu daxuesheng de guocheng he xiaoguo [The process and effect of box therapy in the treatment of moderately depressed college students]. *Zhongguo linchuang xinlixue zazhi* 19, 404–406.
- Liu, D., 2010. Yiming yiyuzheng daxuesheng de zhenduan, zixun he zhiliao [Diagnosis, counseling and treatment of a depressed college student]. *Xianda qiye jiaoyu* 164–165.
- Liu, W., Xue, Z., Wang, L., Sun, F., 2018. Zhengnian renzhi xunlian dui yiyu qingxiang daxuesheng shuimian ganyu xiaoguo pingjia [Evaluation of the effect of mindfulness cognitive training on sleep intervention of college students with depression]. *Zhongguo xuexiao weisheng* 39, 138–140.
- Lu, W., 2016. "Wo yao shangxue" -- Dui yiyuzheng huifuqi xuesheng ganyu de anli baogao ["I want to go to school" case report on student intervention in depression recovery period]. *Jiaoyu* 0, 265–266.
- Mao, S., 2011. Yiyu shenjingzhengxing nvdaxuesheng jiaodian jiejie liaofa de gean yanjiu [Case study of focal treatment for depressive neurosis female college students]. *Zhongguo xibu keji* 10, 92–93. <https://doi.org/10.3969/j.issn.1671-6396.2011.10.045>
- Murphy, E., Shao, J., 2012. Case History: A Student in China with Depression. *Zhongguo quanke yixue* 15, 3211–3212, 3217. <https://doi.org/10.3969/j.issn.1007-9572.2012.28.002>
- Nie, H., Pan, J., Li, X., 2012. Yuedu liaofa dui gaishan daxuesheng yiyuxinli de shizheng yanjiu [An Empirical Study of Reading Therapy on Improving College Students' Depression]. *Dangdai jiaoyu lilun yu shijian* 25–26.
- Niu, Z., Cao, Y., 2011. Huihua liaofa gaishan feipang nvdaxuesheng yiyu de shiyan yanjiu [Experimental Study on Improving the Depression of Obese Female College Students by Painting Therapy]. *Zhongguo xuexiao weisheng* 32, 558–559.
- Ouyang, W., 2001. Yundong youxi yu renzhi zhiliao yiyuqingxiang daxuesheng de liaoxiao guan cha [Therapeutic effect of sports games and cognitive therapy on college students with depression]. *Zhongguo linchuang xinlixue zazhi* 9, 113–114.
- Pan, C., Xie, Y., 2015. Yuanrenzhi ganyufa jiehe tuanti xinlifudao dui daxuesheng yiyu de ganyu xiaoguo yanjiu [Interventional effect of metacognitive intervention combined with group psychological counseling on college students' depression]. *Kaili xueyuan xuebao* 33, 135–137. <https://doi.org/10.3969/j.issn.1673-9329.2015.04.35>
- Pei, L., 2006. Renji guanxi tuanti zixun dui daxuesheng yiyuzhengzhuang de ganyu tantao [Intervention of interpersonal relationship group counseling on depression symptoms of college students]. *Zhongguo jiankang xinlixue zazhi* 371–373.
- Ren, Z., Li, X., Zhao, L., Yu, X., Li, Z., Lai, L., Ruan, Y., Jiang, G., 2016. Yiyuzheng wangluohua zizhu ganyu de xiaoguo ji zuoyong jizhi -- yi hanhua MoodGYM weili [The effect and mechanism of networked self-intervention in depression: A case study of Chinese MoodGYM]. *Xinli xuebao* 48, 818–832.
- Ren, Z., Zhao, H., Liu, F., 2008. Xiangting liaofa yingyongyu yiyuzheng zhiliao de gean yanjiu [Case Study of Boxing Therapy for Treatment of Depression]. *Zhongguo teshu jiaoyu* 46–51.
- Shi, M., 2017. Pengbei fudaoyuan, huhang jiankang xinling - 95 hou daxuesheng yanzhong xinlijiankang wenti anli fenxi [Peer Counselor, Escorting Healthy Mind—A Case Study of Serious Mental Health Problems of College Students after 95s]. *Haixia keji yu chanye* 218–219. <https://doi.org/10.3969/j.issn.1006-3013.2017.06.089> [doi]



- Song, Y., Zhang, H., 2009. Tuanti xinlifudao dui pinkun daxuesheng yiyuxinli de ganyu yanjiu [Intervention Study of Group Counseling on Depressive Psychology of Poor College Students]. Shandong qingnian zhengzhi xueyuan xuebao 56–58.
- Tai, X., Han, T., Teng, L., Li, B., 2010. Zhenci jiehe xinliliaofa zhiliao daxuesheng yiyuzheng 37 li lincuang guan cha [Clinical Observation on 37 Cases of College Students with Depression Treated by Acupuncture Combined with Psychotherapy]. Zhongyiyao xinxi 27, 92–93. <https://doi.org/10.3969/j.issn.1002-2406.2010.04.043>
- Wang, J., Liu, S., Zhang, P., Wu, H., Chi, X., 2016. Jiji xinli ganyu dui yiyuzhengzhuang daxuesheng qingxu ji zhuguanxingfugan de yingxiang [The effect of positive psychological intervention on the emotion and subjective well-being of college students with depressive symptoms]. Zhongguo teshu jiaoyu 11, 44–50.
- Wang, J., Wang, H., Zhang, B., Su, J., 2014a. Yundong chufang jiehe tuanti xinli fudao dui heilongjiangsheng mou yixueyuan xuesheng yiyuqingxu de yigxiang [Effects of exercise prescription combined with group psychological counseling on depression of students in a medical school in Heilongjiang Prov. Yixue yu shehui 27, 83–84.
- Wang, J., Wang, H., Zhang, B., Su, J., 2014b. Yundong chufang jiehe tuanti fudao dui yixuesheng yiyuqingxu de ganyu yanjiu [Intervention study of sports prescription combined with group counseling on depression of medical students]. Zhongguo gaodeng yixue jiaoyu 10, 52–53.
- Wang, J., Wu, H., 2014. Jiyu jijixinlijiankang jiaoyu sixiang de yiyu ganyu yanjiu [Depression Intervention Based on Positive Mental Health Education Thought]. Zhongguo teshu jiaoyu 3, 80–84.
- Wang, J., Wu, H., Li, Q., Zhang, D., 2015. Jiyu jijixinli ganyu jishu de yiyu gean fenxi [Analysis of depression cases based on positive psychological intervention techniques]. Chongqing yixue 44, 3577–3579.
- Wang, L., Chen, Z., 2015. Qiantan gaoxiaofudaoyuan ruhe yingdui yiyuzhen gxuesheng -- Jiyu yiming yiyuzhengxuesheng de anli fenxi [A Brief Talk on How College Counselors Cope with Depressive Students—A Case Study Based on a Depressed Student]. dangdai jiaoyu shijian yu jiaoxue yanjiu 12, 534. <https://doi.org/10.3969/j.issn.2095-6711.2015.12.466>
- Wang, L., Xu, W., Zhang, T., 2015. Jiji tuanti fudao dui daxuesheng yiyu de ganyu yanjiu [Intervention Study of Active Group Counseling on College Students' Depression]. Kejiao daokan 5, 165–166.
- Wei, Y., Zhang, M., 2010. Renzhi yingdui tuanti fudao gaishan daxuesheng yiyu de yanjiu [Cognitive Coping Group Counseling to Improve College Students' Depression]. Zhongguo lincuang xinlixue zazhi 1, 127–129.
- Wu, Q., Shi, L., Xia, Z., Lu, L., Du, X., 2013. Butong shichang he neirong de zhengnian xunlian dui yiyu de ganyu xiaoguo [Intervention effect of mindfulness training with different durations and content on depression]. Zhongguo lincuang xinlixue zazhi 21, 685–689.
- Wu, X., Lv, B., 2019. Xinli jiankang jiaoyu lianhe youyang yundong dui daxuesheng xinli yiyu chengdu zaoqi ganyu xiaoguo de yanjiu [Effect of mental health education combined with aerobic exercise on early intervention of college students' psychological depression]. Zhonghua baojian yingyang 1, 185–186.
- Xi, M., 2011. Jiaodian jie jue quxiang tuanti fudao zhiliao daxuesheng yiyu [Focus-solving orientation group counseling to treat college students' depression]. Zhongguo jiankang xinlixue zazhi 2, 223–225.
- Xiang, Q., 2007. Pinkun daxuesheng yiyuxinli tuanti fudao xiaoguo pingjia [Evaluation on counseling effect of depression psychological group in poor college students]. Zhongguo xuexiao weisheng 28, 924–925. <https://doi.org/10.3969/j.issn.1000-9817.2007.10.025>
- Xiao, C., Zhu, X., Wang, Y., Zhou, H., Gao, Y., Yan, J., Wang, C., 2018. Shehui jue se yindao ganyufa kongzhi yalincuang yiyuzhangai bingqingfazhan de youxiaoxing tanjiu [The effectiveness of

- social role-guided intervention in controlling the development of subclinical depressive disorder]. *Huanan yufang yixue* 2, 187–190.
- Xie, J., 2013. Menzhen sentianliaofa zhiliao zhongdu yiyu daxuesheng de guocheng he xiaoguo [The process and effect of Morita therapy in the treatment of moderately depressed college students]. *Chifeng xueyuan xuebao* 21, 84–86.
- Xiong, L., Li, Y., Gao, R., Yan, Q., 2017. Dongli daoxiang tuanti xinlizhiliao dui daxuesheng yiyuqingxu ganyu xiaoguo de yanjiu [Study on the effect of dynamic-oriented group psychotherapy on college students' depression]. *Zhongguo yixue chuanguan* 14, 137–141. <https://doi.org/10.3969/j.issn.1674-4985.2017.20.035>
- Xu, C., 2014. Dui qingdu yiyujiaolv xuesheng de shendu fudao [In-depth counseling for students with mild depression and anxiety]. *Beijing jiaoyu* 11, 69–70.
- Xu, C., Jiao, Y., Zhang, F., Zhang, J., Li, P., Zhao, X., 2017. Wuwei tongyi zhenghe liaofa dui daxuesheng yiyuqingxu zhangai de ganyu yanjiu [Intervention study of Wuwei unified integration therapy on college students with depression and emotional disorder]. *Jiazhi gongcheng* 4, 143–146.
- Xu, H., 2009. 1 li yiyuzheng de yuanrenzhi xinli ganyu [Metacognitive psychological intervention in 1 case of depression]. *Zhongguo jiankang xinlixue zazhi* 12, 1535–1536.
- Yan, W., 2012. Qiantan yinyue yishuxinshang dui daxuesheng yiyu, jiaolvzheng de xinli ganyu yingxiang [On the Influence of Appreciation of Music Art on Psychological Intervention of College Students' Depression and Anxiety]. *Huanghe zhisheng* 17, 82–83.
- Yang, M., Li, T., Ge, ling, 2017. Zixinxin tuanti xunlian dui daxuesheng yiyuqingxu he yingdui fagnshi de ganyuyanjiu [Intervention Study on Self-confidence Group Training on College Students' Depression and Coping Style]. *Zhongguo yixue chuanguan* 14, 121–124.
- Yang, S., 2009. Zouchu yiyu yinying de nv daxuesheng -- yunong zhichixing liaofa jiaozhi yiyuzheng de anli [Female college students who emerged from the shadow of depression: a case of using supportive psychotherapy to correct depression]. *Jiling huaqiao waiguoyu xueyuan xuebao* 2, 9–11.
- Yang, W., Ding, Z., Dai, T., Peng, F., Zhang, J., 2015. Attention Bias Modification training in individuals with depressive symptoms: a randomized controlled trial. *J. Behav. Ther. Exp. Psychiatry* 49, 101–111. <https://doi.org/10.1016/j.jbtep.2014.08.005>
- Yang, X., Zhang, P., Zhao, J., Zhao, J., Wang, J., Chen, Y., Ding, S., Zhang, X., 2016. Confucian culture still matters: The benefits of Zhongyong thinking (Doctrine of the mean) for mental health. *J. Cross. Cult. Psychol.* 47, 1097–1113. <https://doi.org/http://dx.doi.org/10.1177/0022022116658260>
- Yang, X., Zhao, J., Chen, Y., Zu, S., 2018. Comprehensive self-control training benefits depressed college students: a six-month randomized controlled intervention trial. *J. Affect. Disord.* 226, 251–260. <https://doi.org/10.1016/j.jad.2017.10.014>
- Yang, Y., 2013. Yili zhongdu yiyu de xuesheng de xinli yu yingyang ganyu de geanbaogao [Case report of a psychological and nutritional intervention for a moderately depressed student]. *Keji shijie* 12, 119.
- Yang, Y., Yang, R., Lin, X., Xiao, J., Oei, T.P.S., Cui, L., 2014. Renzhi xingwei tuanti zixun dui daxuesheng yiyuzhengzhuagn de ganyu xiaoguo [Intervention effect of cognitive behavioral group counseling on college students' depressive symptoms]. *Zhongguo xinli weisheng zazhi* 12, 913–919.
- Ye, Q., Tang, K., Chen, Z., Tao, L., Yang, C., Jiang, D., Qi, W., Li, C., 2012. Guilin gaoxiao daxuesheng yiyuzhengzhuang diaocha ji ganyu yanjiu [Investigation and Intervention Study on Depressive Symptoms of College Students in Guilin]. *Zhongguo jiankang xinlixue zazhi* 20, 1185–1187.
- Zeng, X., Dong, X., 2009. Xinli ganyu zhiliao 1 li you zisha qingxiang de yiyuxing shenjignzheng huanzhe [Psychological intervention for a patient with suicidal depression and neurosis]. *Baojian yixue yanjiu yu shijian* 2, 95–96.



- Zhang, B., Chen, Y., Qiu, Z., 2014. Zhongguo wuxing yinyue liaofa dui daxuesheng yiyuqingxu de yingxiang [Effect of Chinese Medicine Five Elements Music Therapy on College Students' Depressive Emotion]. *Nanjing zhongyiyao daxue xuebao* 15, 115–117.
- Zhang, D., Bai, Y., 2006. Dui yiyuqingxiang daxuesheng de renzhi - xingwei tuanti ganyu [Cognitive-behavioral group intervention for college students with depression]. *Zhongguo zuzhi gongcheng yanjiu* 10, 164–165.
- Zhang, H., Sun, Z., 2010. Renji tuanti fudao dui gaishan daxuesheng yiyuzhuangkuang de shizhengyanjiu [An Empirical Study of Interpersonal Group Counseling on Improving College Students' Depression Status]. *Wenzhou daxue xuebao* 31, 36–39.
- Zhang, J., Qin, S., Zhou, Y., Meng, L., Su, H., Zhao, S., 2018. a randomized controlled trial of mindfulness-based Tai chi chuan for subthreshold depression adolescents. *Neuropsychiatr. Dis. Treat.* 14, 2313.
- Zhang, J., Zhang, H., Yu, R., 2016. Tuanti xinlifudao dui daxuesheng yiyuzhengzhuang de ganyu yanjiu - jiyu jijixinlixue de lilun shijiao [Intervention Study of Group Counseling on College Students' Depressive Symptoms-Based on the Theoretical Perspective of Positive Psychology]. *Jiaoyu xiandehua* 16, 118.
- Zhang, L., Liu, M., 1997. Yong "yiren weizhongxin" lilun zhiliao daxuesheng yiyu shenjingzheng yili [Treating a case of depressive neurosis in college students with the "client-centered" theory]. *Zhongguo xiaoyi* 5, 366–367.
- Zhang, M., Song, J., Bai, X., Zhang, H., 2005. Xiaozu ganyu moshi zhiliao daxuesheng yiyu de xiaoguo [Effect of group intervention mode on depression of college students]. *Zhongguo linchuang kangfu* 9, 28–29.
- Zhang, S., Wang, D., Zou, X., Chen, Y., 2016. Xushi liaofa dui yiyuqingxiang daxuesheng ganyu xiaoying de chubutantaotao [Preliminary study on the intervention effect of narrative therapy on college students with depression tendency]. *Xiaoyuan xinli* 14, 123–124. <https://doi.org/10.3969/j.issn.1673-1662.2016.02.018>
- Zhang, Y., Zhang, Y., Zhang, Y., 2006. Zonghe liaofa zhiliao daxuesheng giyuzheng 26 li liaoxiao guan cha [Therapeutic effect of comprehensive therapy on 26 cases of college students with depression]. *Zhongguo xuexiao weisheng* 27, 176. <https://doi.org/10.3969/j.issn.1000-9817.2006.02.056>
- Zhao, W., Zhou, Y., Liu, X., Ran, L., 2013. Jieshou yu chengnuo liaofa ganyu yiyu de xiaoguo zhuizong [Follow-up of the effects of acceptance and commitment therapy intervention depression]. *Zhongguo linchuang xinlixue zazhi* 1, 153–157.
- Zhong, D., 2016. Tuanti yinyue zhiliao duiyu gaishan daxuesheng yiyuqingxu de shizheng yanjiu [An Empirical Study of Group Music Therapy for Improving College Students' Depression]. *Xiju zhijia* 7, 64–65. <https://doi.org/10.3969/j.issn.1007-0125.2016.07.049>
- Zhong, Y., Gong, L., Wen, Y., 2017. Zhengxing yinyu ciji lianhe shequlin zhiliao dui shoufa yiyuzheng daxuesheng jiaolv yiyuqingxu ji shenghuozhiliang de yingxiang [Effect of positive music stimulation combined with sertraline on anxiety, depression and quality of life in first-episode coll. *Nanchang daxue xuebao* 5, 45–49.
- Zhou, Q., Guo, C., Zhang, D., 2010. Zhongdu yiyuzhengzhuang daxuesheng yinyushenmei xinshang ganyu de gean yanjiu [A Case Study of Music Aesthetic Appreciation Intervention of College Students with Moderate Depression Symptoms]. *Zhongguo teshu jiaoyu* 6, 69–74.
- Zhu, J., Feng, Q., 2012. Quanyuan peihe, aixin ganyu, huanta ruhua qingchun -- Ji yihuan you xinjingzhangai xuesheng de chenggong ganyu anli [All staff cooperate, love to intervene, and she is as youthful as possible - remember a successful intervention case for students with mood. *Zhongguo xiaowai jiaoyu* 4, 57.
- Zhu, X., Zhou, Q., Wang, C., Cao, Y., Wang, Y., Sun, D., Zhao, C., 2012. Xiaozu renji xinli zhiliao dui er tongqi shouchuangshang daxuesheng yiyuzhangai de liaoxiao [Effect of group interpersonal

psychotherapy on depressive disorder in traumatic college students]. *Zhonghua xingwei yixue yu naokexue zazhi* 21, 712–715. <https://doi.org/10.3760/cma.j.issn.1674-6554.2012.08.013>

Zou, L., Yin, D., 2015. Tuanti fudao gaishan daxuesheng yiyuqingxu de xiaoguo guanCha [Observation on the effect of group counseling on improving college students' depression]. *Huli yanjiu* 29, 2597-259.

Appendix 4 Supplement to Chapter 5

Table 5: Simplex model with lagged *b* paths for depression as mediator

Simplex for mediation with lagged <i>b</i> path		95%CI			
Time-specific outcome	Significant Paths and Effect of treatment	Standardized estimate	<i>p</i> value	Lower limit	Upper limit
Week 2 Behavioral Activation (Y_2)	Total effect	0.07	0.336	-0.06	0.20
	Indirect effect	0	1.000	0	0
Week 4 Behavioral Activation (Y_3)	Total effect	0.27	<.001	0.13	0.40
	Indirect effect	0.06	0.296	-0.05	0.16
Week 6 Behavioral Activation (Y_4)	Total effect	0.29	<.001	0.15	0.42
	Indirect effect	0.23	<.001	0.11	0.35
	T→ Y_3 → Y_4	0.18	0.002	0.07	0.29
Week 8 Behavioral Activation (Y_5)	Total effect	0.24	0.001	0.09	0.38
	Indirect effect	0.26	<.001	0.13	0.49
	T→ Y_3 → Y_4 → Y_5	0.15	0.003	0.06	0.26
Week 10 Behavioral Activation (End-point, Y_6)	Total effect	0.30	<.001	0.16	0.44
	Indirect effect	0.24	0.001	0.09	0.38
	T→ Y_3 → Y_4 → Y_5 → Y_6	0.14	0.004	0.05	0.24

Note: Only significant paths were showed in the above table to save space. T = Treatment allocation (treatment group = 1, control group = 0); Y_2 , Y_3 , Y_4 , Y_5 , Y_6 = behavioral activation measurement taken at week 2, 4, 6, 8, 10.

Table s6: Simple model with contemporary *b* paths for depression as mediator

Simplex for mediation with contemporary <i>b</i> path		95%CI			
Time-specific outcome	Significant Paths and Effect of treatment	Standardized estimate	p value	Lower limit	Upper limit
Week 2 Behavioral Activation (Y ₂)	Total effect	0.07	0.332	-0.06	0.20
	Indirect effect	0.02	0.386	-0.02	0.06
Week 4 Behavioral Activation (Y ₃)	Total effect	0.27	<.001	0.13	0.40
	Indirect effect	0.06	0.255	-0.04	0.16
Week 6 Behavioral Activation (Y ₄)	Total effect	0.28	<.001	0.14	0.41
	Indirect effect	0.24	<.001	0.12	0.35
	T->Y ₃ ->Y ₄	0.17	0.002	0.07	0.27
Week 8 Behavioral Activation (Y ₅)	Total effect	0.24	0.001	0.09	0.38
	Indirect effect	0.26	<.001	0.13	0.38
	T->Y ₃ ->Y ₄ ->Y ₅	0.14	0.003	0.06	0.24
Week 10 Behavioral Activation (End-point, Y ₆)	Total effect	0.30	<0.001	0.16	0.43
	Indirect effect	0.25	0.001	0.11	0.38
	T->Y ₃ ->Y ₄ ->Y ₅ ->Y ₆	0.13	0.003	0.06	0.22

Note: Only significant paths were showed in the above table to save space. T = Treatment allocation (treatment group = 1, control group = 0); Y₂, Y₃, Y₄, Y₅, Y₆ = behavioral activation measurement taken at week 2, 4, 6, 8, 10.

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PhD Portfolio

Name: Zhongfang Fu

PhD period: October 2016 – October 2021

Supervisors: Prof. Dr. Claudi L.H. Bockting, Dr. Huibert Burger

Courses

General courses

EndNote

Systematic Review

Scientific Writing for Publication

Project Management

Peer to Peer Group Coaching

Research Data Management

Specific courses

Randomized Controlled Trials

Observational Epidemiology

Survey Research: Statistical Analysis and Estimation

Data Science: Multiple Imputation in Practice

Advanced Course on using Mplus

Modeling the Dynamics of Intensive Longitudinal Data

Introduction of Machine Learning

Workshop

Amsterdam Public Health Spring Session – Implementation Science

Conference Presentations

Oral Presentations

Fu, Z., Kennis, M., Brouwer, M., Williams, A., & Bockting, C.L.H. (July 2017). *Are we on the right track in research on etiological theories of depression?* 15th European Psychology Conference, Amsterdam, Netherlands. (Oral presentation in the symposium with Kennis, M., Brouwer, M., and Bockting, C.)

Fu, Z., Williams, A.D., Burger, H., & Bockting, C.L.H. (March 2019). *Effectiveness of Psychological intervention on depression in Chinese university students.* International Convention of Psychological Science, Paris, France. (Oral presentation).

Fu, Z., Burger, H., & Bockting, C.L.H. (November 2019). *Effectiveness of digital psychological intervention on mental health problems in low-income and middle-income countries.* 1st European Congress on Clinical Psychology and Psychological Treatment. Dresden, Germany. (Oral Presentation).



Poster presentations

Fu, Z., Williams, A.D., Burger, H., & Bockting, C.L.H. (November 2018). *Effectiveness of Psychological intervention on depression in Chinese university students*. Amsterdam Public Health Winter Conference.

Fu, Z., Burger, H., & Bockting, C.L.H. (August 2019). *Effectiveness of digital psychological intervention on mental health problems in low-income and middle-income countries*. World Cognitive Behavioral Therapy Conference, Berlin, Germany.

List of publications

Fu, Z., Burger, H., Arjadi, R., & Bockting, C.L. (2020). Effectiveness of digital psychological intervention on mental health problems in low and middle income countries: a systematic review and meta-analysis. *Lancet Psychiatry*, 7(10), 851-864.

Fu, Z., Zhou, S., Burger, H., Bockting, C. L., & Williams, A. D. (2020). Psychological interventions for depression in Chinese university students: A systematic review and meta-analysis. *Journal of affective disorders*, 262, 440-450.

Fu, Z., Brouwer, M. E., Kennis, M., Williams, A. D., Cuijpers, P., & Bockting, C. L. (2021) Psychological factors for the depression onset: A meta-analysis of prospective studies. *BMJ Open*. doi:10.1136/bmjopen-2021-050129

Fu, Z., Burger, H., Arjadi, R., Nauta M.H. & Bockting, C.L. (2021) Explaining the efficacy of an internet-based behavioral activation intervention for major depression: a mechanistic study of a randomized-controlled trial. *Clinical Psychology in Europe*, 3(3), 1-24.

Brouwer, M. E., Williams, A. D., Kennis, M., **Fu, Z.**, Klein, N. S., Cuijpers, P., & Bockting, C. L. (2019). Psychological theories of depressive relapse and recurrence: A systematic review and meta-analysis of prospective studies. *Clinical psychology review*, 74, 101773.

PROFESSIONAL AFFILIATIONS

2019 – present European Association of Clinical Psychology and Psychological Treatment

OTHER ACTIVITIES

Guest Lectures

2019/2020 Global health Course – Mental Health section,
Utrecht Medical Center, Utrecht University (Coordinator: Julius Org.)

2020 Digital Psychological Intervention in LMICs
University of Buenos Aires

Mentoring experience

2017/2018 Co-supervisor, Master thesis of Clinical Psychology (Sijia Zhou)
Department of Clinical Psychology, Utrecht University