PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Prevalence of Depression and Depressive Symptoms among Outpatients: A Systematic Review and Meta-analysis
AUTHORS	Wang, Jinghui; Wu, Xiaohang; Lai, Weiyi; Long, Erping; Zhang, Xiayin; Li, Wangting; Zhu, Yi; Chen, Chuan; Zhong, Xiaojian; Liu, Zhenzhen; Wang, Dongni; Lin, Haotian

VERSION 1 - REVIEW

REVIEWER	Jenny Montgomery NHS Department of Otolaryngology Queen Elizabeth University Hospital Glasgow Scotland
REVIEW RETURNED	22-Apr-2017

GENERAL COMMENTS	This has been a large amount of work and is an important topic. I would like to see a more homogenous group of papers analysed for example there are several papers that use the same outcome measure - you could do a more robust analysis on a smaller group of papers. Also it would be good to see a tightening of diagnoses what you are including as depression or "depressive symptoms" should be clear to the reader. You have stated that there is a paucity of research identifying cognitive impairment and go into this in some detail, yet your analysis does not include cognitive impairment. This distracts from your message. What recommendations can you make regarding identification of depression at outpatient clinic? Finally some of the language at numbers need checking for accuracy.

REVIEWER	Roger Ho Associate Professor National University of Singapore Singapore
REVIEW RETURNED	23-Apr-2017

GENERAL COMMENTS	Thank you for inviting me to review the paper on Prevalence of Depressive Symptoms among Outpatients: A systematic review and meta-analysis written by Wang et al. This is a well-written paper and deserves publication in BMJ Open. I have the following recommendations: 1. Under abstract (Pg 3, line 21), the authors should indicate which specialities have the highest prevalence of depression (i.e. otolaryngology clinics (53%), dermatology clinics (39%) and

	neurology clinics (35%). This is the most important finding of this meta-analysis. 2. Under introduction (Pg 6, line 28), the authors only stated the prevalence of depression in oncology and hematology patients. Then the authors mentioned about prevalence of depression in mild cognitive impairment. I advise the authors to include prevalence of depression in the following chronic medical disorders to indicate the clinical significance. The following statement and references should be inserted: Depression is a significant comorbidity of chronic medical disorders. The prevalence of depression in chronic medical conditions are as follows: asthma (27%) (Lu Y et al 2012), atopic dermatitis (5%) (Lim VZ et al 2016), chronic obstructive pulmonary disease (24.6%) (Zhang MW et al 2011), gouty arthritis (20%) (Mak et al 2011), rheumatoid arthritis (15%) (Ho RC et al 2011), systemic lupus erythematosus (22%) (Mak A et al 2011) and stroke (30%) (Mak KK et al 2013). Please include these important references: Lu Y et al (2012) Prevalence of anxiety and depressive symptoms in adolescents with asthma: a meta-analysis and meta-regression. Pediatr Allergy Immunol. 2012 Dec;23(8):707-15. PMID: 22957535 Lim VZ et al (2016) Anxiety and Depression in Patients with Atopic Dermatitis in a Southeast Asian Tertiary Dermatological Centre. Ann Acad Med Singapore. 2016 Oct;45(10):451-455. PMID:27832219 Zhang MW et al (2011) Prevalence of depressive symptoms in patients with chronic obstructive pulmonary disease: a systematic review, meta-analysis and meta-regression. Gen Hosp Psychiatry. 2011 May-Jun;33(3):217-23. PMID:21601717 Mak A, et al (2011) Damage accrual, cumulative glucocorticoid dose and depression predict anxiety in patients with systemic lupus erythematosus. Clin Rheumatol. 2011 Jun;30(6):795-803. PMID:21221690 Ho RC et al (2011) Clinical and psychosocial factors associated with depression and anxiety in Singaporean patients with rheumatoid arthritis. Int J Rheum Dis. 2011 Feb;14(1):37-47. PMID: 21303480 Mak KK et al (2013) Polymorphisms of the serotonin transporter gene and post-stroke depression: a meta-analysis. J Neurol Neurosurg Psychiatry. 84(3):322-8. PMID:23236014 3. Under introduction (Pg 6, line 51), the authors stated that many previous studies have focused on depression in inpatient settings but mental disorders in outpatients are largely underestimated. The authors should discuss the economic burden of outpatients suffering from depression. Please add the following statement and reference: Depression in outpatients is associated with high indirect costs due to loss of productivity and unemployment (Ho RC et al 2013). The combination of chronic medical illnesses and depression will lead to significant economic burden. Please include this reference:

	Ho RC et al (2013) The effect of severity of depressive disorder on economic burden in a university hospital in Singapore. Expert Rev Pharmacoecon Outcomes Res. 2013 Aug;13(4):549-59. PMID:23977979 4. Under statistical analysis (Pg 10, line 9), the authors stated random-effects model was used to estimate the pooled prevalence of depressive symptoms. The authors should provide more explanation about the reasons for using random-effects model. I advise the authors to add the following statement and reference: Random-effect model attempted to generalize findings beyond the included studies by assuming that the selected studies are random samples from a larger population (Cheung MW 2012). Please include this important reference: Cheung MW et al. Conducting a meta-analysis: basics and good practices. Int J Rheum Dis. 2012 Apr;15(2):129-35. PMID:22462415 5. Under statistical analysis (Pg 10, line 39), the authors mentioned subgroup analysis and meta-regression. It is important to provide further explanation of meta-regression. I recommend the authors to add the following statement and reference. For models with considerable heterogeneity, a meta-regression was performed to identify the moderators which might contribute to the heterogeneity of the effect sizes (Ho RC et al 2011). Please include this reference: Ho RC et al (2011) Is high homocysteine level a risk factor for cognitive decline in elderly? A systematic review, meta-analysis, and meta-regression. Am J Geriatr Psychiatry. 2011 Jul;19(7):607-17. PMID:21705865 6. Under discussion (Pg 15), the authors should discuss the most important finding of this study – the highest prevalence of depression was found in outpatient otolaryngology, dermatology and neurology clinics. I advise the authors to add the following statement and references after stating the prevalence of depression (Pg 15, line 13). This study found outpatients from otolaryngology clinics had the highest prevalence of depression (53%). Depression was found to be an important mediator for otolaryngologic conditions such as chronic tinnitus (Trevis et al 2016). It was not surprised that dermatology ranked the second highest and 39.0% of outpatients from dermatology clinics suffered from depression. Atopic dermatitis was found to be associated with depression (Lim VZ et al) because the skin stigmata often causes embarrassment, low confidence and sadness (Chernyshov PV et al 2016). Atopic dermatitis is one of the most common dermatological disorders and was found to be associated with negative impact on the quality of life

	of patients, families and caregivers (Ho RC et al 2010a, Chernyshov PV et al 2013). There is psychoneuroimmunology connection between depression and medical illness (Ho RC et al 2010). The production of pro-inflammatory cytokine (e.g. IL-6) was found to be higher in patients with atopic dermatitis (Gharagozlou M et al 2013) and IL-6 was found to be raised in patients with depression (Liu et al 2012). Raised IL-6 may cause depression in patient with atopic dermatitis. This study found 35% of outpatients from neurology clinic suffered from depression. Genetic factors (Ho RC et al 2016a) and autoantibodies (Ho RC et al 2016b) play an important role in causing neuropsychiatric complications including depression. Stroke is a common neurological disorder and causes significant health burden (Zhang et al 2017). The burden of stroke causes depression in both stroke patients and their caregivers (Loh et al 2017). Novel rehabilitation intervention targeting at motor deficit was designed to improve functional status and quality of life of patients with stroke (Zhang et al 2015). This intervention might offer hope and reduce prevalence of depression in patients with stroke. Please include the following important references: Trevis KJ et al (2016) Psychological mediators of chronic tinnitus: The critical role of depression. J Affect Disord. 2016 Nov 1;204:234-40.. PMID:27391257 Lim VZ et al (2016) Anxiety and Depression in Patients with Atopic Dermatitis in a Southeast Asian Tertiary Dermatological Centre. Ann Acad Med Singapore. 2016 Oct;45(10):451-455. PMID:27832219 Chernyshov PV et al (2016) Gender Differences in Self-assessed Health-related Quality of Life in Children with Atopic Dermatitis.J Clin Aesthet Dermatol. 2016 Aug;9(8):19-24. PMID:27672414 Ho RC et al (2010a) The influence of childhood atopic dermatitis on health of mothers, and its impact on Asian families. Pediatr Allergy Immunol. 2010 May;21(3):501-7. PMID:20546527 Chernyshov PV et al (2013) An international multicenter study on quality of life and family quality of life in children with atopic dermatitis. Indian J Dermatol Venereol Leprol. 2013 Jan-Feb;79(1):52-8. PMID:23254729 Ho RC et al. (2010b) Research on psychoneuroimmunology: does stress influence immunity and cause coronary artery disease? Ann Acad Med Singapore. 2010 Mar;39(3):191-6. Review. PMID:20372754 Gharagozlou M et al (2013) Association between the interleukin 6 genotype at position -174 and atopic dermatitis. J Investig Allergol Clin Immunol. 2013;23(2):89-93. PMID:23654074 Liu Y et al (2012) Interleukin (IL)-6, tumour necrosis factor alpha (TNF-α) and soluble interleukin-2 receptors (sIL-2R) are elevated in patients with major depressive disorder: a meta-analysis and meta-regression. J Affect Disord. 2012 Aug;139(3):230-9. PMID: 21872339 Mak KK et al (2013) Polymorphisms of the serotonin transporter gene and post-stroke depression: a meta-analysis. J Neurol Neurosurg Psychiatry. 84(3):322-8. PMID:23236014

	Ho RC et al (2016a) Genetic Variants That Are Associated with Neuropsychiatric Systemic Lupus Erythematosus. J Rheumatol. 2016 Mar;43(3):541-51. PMID:26773105 Ho RC et al (2016b) A meta-analysis of serum and cerebrospinal fluid autoantibodies in neuropsychiatric systemic lupus erythematosus. Autoimmun Rev. 2016 PMID:26497108 Zhang MW et al (2017) Smartphone Applications Providing Information about Stroke: Are We Missing Stroke Risk Computation Preventive Applications? J Stroke. 2017 Jan;19(1):115-116. PMID:28178409 Loh AZ et al (2017) The Global Prevalence of Anxiety and Depressive Symptoms Among Caregivers of Stroke Survivors. J Am Med Dir Assoc. 2017 Feb 1;18(2):111-116. doi: 10.1016/j.jamda.2016.08.014. PMID:27742585 Zhang MW et al (2015) Harnessing smartphone technologies for stroke care, rehabilitation and beyond. BMJ Innov. 2015 Oct;1(4):145-150. PMID:26692351 7. Under discussion (Pg 16 line 6), the authors stated that Yang et al showed that depression declines with age. This statement may not be accurate and not supported by the finding of this meta-analysis (peak of depression in age 80-90 years). The authors need to strengthen the discussion that depression is common in elderly with chronic medical illnesses and associated with suicide risk. Please add the following statements after discussion of person and status losses (Pg 16, line 24). Risk factors of geriatric depression include poor health, brain injury, low folate and vitamin B12 and raised plasma homocysteine levels (Heok et al 2008). The association between depression and chronic medical illnesses in elderly are due to accompanying poor self-reported health and functional status (Niti M et al 2007). Further, history of depression and antidepressant treatment are important risk factors for elderly suicide (Ho et al 2014). Please include these important references: Heok KE et al (2008) The many faces of geriatric depression. Curr Opin Psychiatry. 2008 Nov;21(6):540-5. PMID:18852559 Niti M et al (2007) Depression and chronic medical illnesses in Asian older adults: the role of subjective health and functional status. Int J Geriatr Psychiatry. 2007 Nov;22(11):1087-94. PMID:17407107 Ho RC et al (2014) Elderly suicide with and without a history of suicidal behavior: implications for suicide prevention and management. Arch Suicide Res. 2014;18(4):363-75. PMID:24828390 8. There is not enough discussion on depression, chronic medical illness and suicide in adults. The second peak is 30-40 years and these are not young adults. I advise the authors to add the following statement and reference on Pg 16, line 4: Outpatients aged 30-40 years suffering from chronic medical

	illnesses are at higher risk for developing depression. Depressed outpatients might develop maladaptive rumination and illness perception towards their chronic medical illness (Lu et al 2014). Chronic medical illness may increase the risk of suicide in adult outpatients because psychosomatic complaint such as headache was found to be an important risk factor for suicide in adults (Choo C et al 2014). Please include these important references: Lu Y et al (2014) A regressional analysis of maladaptive rumination, illness perception and negative emotional outcomes in Asian patients suffering from depressive disorder. Asian J Psychiatr. 2014 Dec;12:69-76. PMID: 25440564 Choo C et al (2014) Cluster analysis reveals risk factors for repeated suicide attempts in a multi-ethnic Asian population. Asian J Psychiatr. 2014 Apr;8:38-42. PMID: 24655624 9. Under discussion, (Pg 16, line 22), the authors stated that depression reaches its highest level in “adults” 80 years or older. This is not correct in terms of grammar and content. It should be: highest levels in elderly aged 80 years or older.

REVIEWER	Faith Matcham King's College London, UK
REVIEW RETURNED	02-May-2017

GENERAL COMMENTS	This is a useful and timely review, addressing the prevalence of depression in outpatients. Overall, I think it is interesting and well-written. My major concern is the limited number of databases used to conduct the search; the general recommendation from the Cochrane Collaboration is to include at least three databases in your search strategy. There is also some fairly recent systematic review evidence to suggest that a small number of databases can result in database bias. I would recommend rerunning the search strategy using an additional database, to ensure no other relevant research is missed. I also have some fairly minor comments to improve the manuscript. 1. For future replication of your searh strategy, it would be helpful to include your exact search terms in an appendix. 2. Did you pre-select the specialties you included in your search strategy? Is there a fully inclusive list of international specialties available? If not, there's possibility of introducing bias by having forgotten some specialties, or systematically omitted culturally specific specialties which might be referred to using different phrases or terminology. 3. What is the justification (and implication) of only including studies where patients have clinically relevant depression. Might this lead to an overestimation of prevalence? 4. In the first paragraph of the results section, it's unclear what you mean by "uncorrected outcome measures". 5. At the top of page 13 in the results, I'm not sure how meaningful it is to combine prevalence estimates into one overall pooled estimate,

	given the heterogeneity particularly in how depression is measured. Perhaps it's more helpful to only report them separately by depression measurement. 6. Also at the top of page 13, it seems from you eligibility criteria that having a control group was one of your inclusion criteria, yet here you mention only 8 studies with a control group. Can this be clarified. 7. No mention is made of how the variation in thresholds in the different depression measurements impacted prevalence estimates. 8. In the limitations section, it would be helpful to have a wider discussion on the implications of your finding that there may be publication bias. 9. The conclusion section mentions several implications for clinical practice, but the first implication is just a reiteration of your methods. This could be rephrased.

VERSION 1 – AUTHOR RESPONSE

Reviewer #1:
Comment: This has been a large amount of work and is an important topic. I would like to see a more homogenous group of papers analyzed for example there are several papers that use the same outcome measure - you could do a more robust analysis on a smaller group of papers.
Response: Thanks so much for your appreciation on our manuscript. In fact, we have performed sub-group analysis based on a smaller group of papers as you suggested to explore the source of heterogeneity. Five particular subgroups were selected considering both the outpatients' characteristics and inspection of the included studies' baseline information as follows.
[Specialties/diagnostic method]: These are the two key factors that may affect the analysis of depression prevalence.
[Study Design/area]: These factors are influenced by regional and temporal distinction and may impact the representativeness and accuracy of the epidemiological statistics.
[Age] this subgroup analysis results could also enhance or challenge the former studies. (See in Discussion Section)

Also it would be good to see a tightening of diagnoses what you are including as depression or "depressive symptoms" should be clear to the reader.
I agree with you that the diagnosis of depression/depressive syptomes in the inclusions criteria is the key factor to affect the pooled estimation. As was claimed in the Methods Sections (Page 8-9, Line 133-142), Studies in which depression was confirmed by validated self-report instruments or diagnostic structured interviews was included. However, the diagnostic method varied between studies and no golden diagnostic stardard was recognized yet. We accordingly conducted subgroup calculation based on different diagnostic methods to provide a more robust analysis.

You have stated that there is a paucity of research identifying cognitive impairment and go into this in some detail, yet your analysis does not include cognitive impairment. This distracts from your message.
Thank you for the suggestion. We have rephrased the statement in the Introduction Section, accordingly. (Page 6-7, Line 96-101)

What recommendations can you make regarding identification of depression at outpatient clinic?
Thank you for this question. We would recommend that doctors should become more aware of patients' mental disorders in daily clinical practice and have more communication with patients. We have included these remcommendations in the Discusstion Section. (Page 16, Line 272-275).

Finally some of the language at numbers need checking for accuracy.
Thank youfor this suggestion. We have carefully checked the whole manuscript and corrected the inaccurate expressions

Reviewer #2:
Comment (1): Under abstract (Pg 3, line 21), the authors should indicate which specialties have the highest prevalence of depression (i.e. otolaryngology clinics (53%), dermatology clinics (39%) and neurology clinics (35%). This is the most important finding of this meta-analysis.
Response: Thanks for your helpful suggestion. We have reworded our result section accordingly. (Page 3, Line 48-50)

Comment (2): Under introduction (Pg 6, line 28), the authors only stated the prevalence of depression in oncology and hematology patients. Then the authors mentioned about prevalence of depression in mild cognitive impairment. I advise the authors to include prevalence of depression in the following chronic medical disorders to indicate the clinical significance. The following statement and references should be inserted:

Depression is a significant comorbidity of chronic medical disorders. The prevalence of depression in chronic medical conditions are as follows: asthma (27%) (Lu Y et al 2012), atopic dermatitis (5%) (Lim VZ et al 2016), chronic obstructive pulmonary disease (24.6%) (Zhang MW et al 2011), gouty arthritis (20%) (Mak et al 2011), rheumatoid arthritis (15%) (Ho RC et al 2011), systemic lupus erythematosus (22%) (Mak A et al 2011) and stroke (30%) (Mak KK et al 2013).

Please include these important references:
Lu Y et al (2012) Prevalence of anxiety and depressive symptoms in adolescents with asthma: a meta-analysis and meta-regression. Pediatr Allergy Immunol. 2012 Dec;23(8):707-15. PMID: 22957535

Lim VZ et al (2016) Anxiety and Depression in Patients with Atopic Dermatitis in a Southeast Asian Tertiary Dermatological Centre. Ann Acad Med Singapore. 2016 Oct;45(10):451-455. PMID:27832219

Zhang MW et al (2011) Prevalence of depressive symptoms in patients with chronic obstructive pulmonary disease: a systematic review, meta-analysis and meta-regression. Gen Hosp Psychiatry. 2011 May-Jun;33(3):217-23. PMID:21601717

Mak A, et al (2011) Damage accrual, cumulative glucocorticoid dose and depression predict anxiety in patients with systemic lupus erythematosus. Clin Rheumatol. 2011 Jun;30(6):795-803. PMID:21221690

Ho RC et al (2011) Clinical and psychosocial factors associated with depression and anxiety in Singaporean patients with rheumatoid arthritis. Int J Rheum Dis. 2011 Feb;14(1):37-47. PMID: 21303480

Mak KK et al (2013) Polymorphisms of the serotonin transporter gene and post-stroke depression: a meta-analysis. J Neurol Neurosurg Psychiatry. 84(3):322-8. PMID:23236014
Response: Thank you for your constructive suggestion. We added this statement to indicate the clinical significance and cited the references.（Page 6, Line 91-95）

Comment (3): Under introduction (Pg 6, line 51), the authors stated that many previous studies have focused on depression in inpatient settings but mental disorders in outpatients are largely underestimated. The authors should discuss the economic burden of outpatients suffering from depression. Please add the following statement and reference:

Depression in outpatients is associated with high indirect costs due to loss of productivity and unemployment (Ho RC et al 2013). The combination of chronic medical illnesses and depression will lead to significant economic burden.

Please include this reference:
Ho RC et al (2013) The effect of severity of depressive disorder on economic burden in a university hospital in Singapore. Expert Rev Pharmacoecon Outcomes Res. 2013 Aug;13(4):549-59. PMID:23977979
Response: Thank you for your suggestion. We added this statement to discuss the significance of outpatients suffering from depression and cited this reference. (Page 7, Line 103-106)

Comment (4): Under statistical analysis (Pg 10, line 9), the authors stated random-effects model was used to estimate the pooled prevalence of depressive symptoms. The authors should provide more explanation about the reasons for using random-effects model. I advise the authors to add the following statement and reference:

Random-effect model attempted to generalize findings beyond the included studies by assuming that the selected studies are random samples from a larger population (Cheung MW 2012).

Please include this important reference:
Cheung MW et al. Conducting a meta-analysis: basics and good practices. Int J Rheum Dis. 2012 Apr;15(2):129-35. PMID:22462415
Response: Thanks for your suggestion. We have clarified this detail and cited the reference. (Page 10, Line159-161)

Comment (5): Under statistical analysis (Pg 10, line 39), the authors mentioned subgroup analysis and meta-regression. It is important to provide further explanation of meta-regression.

I recommend the authors to add the following statement and reference.

For models with considerable heterogeneity, a meta-regression was performed to identify the moderators which might contribute to the heterogeneity of the effect sizes (Ho RC et al 2011).

Please include this reference:
Ho RC et al (2011) Is high homocysteine level a risk factor for cognitive decline in elderly? A systematic review, meta-analysis, and meta-regression. Am J Geriatr Psychiatry. 2011 Jul;19(7):607-17. PMID:21705865
Response: Thanks for your recommendation. We have added this statement and cited the reference (Page 10, Line 174-176.)

Comment (6): Under discussion (Pg 15), the authors should discuss the most important finding of this study – the highest prevalence of depression was found in outpatient otolaryngology, dermatology and neurology clinics. I advise the authors to add the following statement and references after stating the prevalence of depression (Pg 15, line 13).

This study found outpatients from otolaryngology clinics had the highest prevalence of depression (53%). Depression was found to be an important mediator for otolaryngologic conditions such as chronic tinnitus (Trevis et al 2016). It was not surprised that dermatology ranked the second highest and 39.0% of outpatients from dermatology clinics suffered from depression. Atopic dermatitis was found to be associated with depression (Lim VZ et al) because the skin stigmata often causes embarrassment, low confidence and sadness (Chernyshov PV et al 2016). Atopic dermatitis is one of

the most common dermatological disorders and was found to be associated with negative impact on the quality of life of patients, families and caregivers (Ho RC et al 2010a, Chernyshov PV et al 2013). There is psychoneuroimmunology connection between depression and medical illness (Ho RC et al 2010). The production of pro-inflammatory cytokine (e.g. IL-6) was found to be higher in patients with atopic dermatitis (Gharagozlou M et al 2013) and IL-6 was found to be raised in patients with depression (Liu et al 2012). Raised IL-6 may cause depression in patient with atopic dermatitis. This study found 35% of outpatients from neurology clinic suffered from depression. Genetic factors (Ho RC et al 2016a) and autoantibodies (Ho RC et al 2016b) play an important role in causing neuropsychiatric complications including depression. Stroke is a common neurological disorder and causes significant health burden (Zhang et al 2017). The burden of stroke causes depression in both stroke patients and their caregivers (Loh et al 2017). Novel rehabilitation intervention targeting at motor deficit was designed to improve functional status and quality of life of patients with stroke (Zhang et al 2015). This intervention might offer hope and reduce prevalence of depression in patients with stroke.

Please include the following important references:

Trevis KJ et al (2016) Psychological mediators of chronic tinnitus: The critical role of depression. J Affect Disord. 2016 Nov 1;204:234-40.. PMID:27391257

Lim VZ et al (2016) Anxiety and Depression in Patients with Atopic Dermatitis in a Southeast Asian Tertiary Dermatological Centre. Ann Acad Med Singapore. 2016 Oct;45(10):451-455. PMID:27832219

Chernyshov PV et al (2016) Gender Differences in Self-assessed Health-related Quality of Life in Children with Atopic Dermatitis.J Clin Aesthet Dermatol. 2016 Aug;9(8):19-24. PMID:27672414

Ho RC et al (2010a) The influence of childhood atopic dermatitis on health of mothers, and its impact on Asian families. Pediatr Allergy Immunol. 2010 May;21(3):501-7. PMID:20546527

Chernyshov PV et al (2013) An international multicenter study on quality of life and family quality of life in children with atopic dermatitis. Indian J Dermatol Venereol Leprol. 2013 Jan-Feb;79(1):52-8. PMID:23254729

Ho RC et al. (2010b) Research on psychoneuroimmunology: does stress influence immunity and cause coronary artery disease? Ann Acad Med Singapore. 2010 Mar;39(3):191-6. Review. PMID:20372754

Gharagozlou M et al (2013) Association between the interleukin 6 genotype at position -174 and atopic dermatitis. J Investig Allergol Clin Immunol. 2013;23(2):89-93. PMID:23654074

Liu Y et al (2012) Interleukin (IL)-6, tumour necrosis factor alpha (TNF-α) and soluble interleukin-2 receptors (sIL-2R) are elevated in patients with major depressive disorder: a meta-analysis and meta-regression. J Affect Disord. 2012 Aug;139(3):230-9. PMID: 21872339

Mak KK et al (2013) Polymorphisms of the serotonin transporter gene and post-stroke depression: a meta-analysis. J Neurol Neurosurg Psychiatry. 84(3):322-8. PMID:23236014

Ho RC et al (2016a) Genetic Variants That Are Associated with Neuropsychiatric Systemic Lupus Erythematosus. J Rheumatol. 2016 Mar;43(3):541-51. PMID:26773105

Ho RC et al (2016b) A meta-analysis of serum and cerebrospinal fluid autoantibodies in neuropsychiatric systemic lupus erythematosus. Autoimmun Rev. 2016 PMID:26497108

Zhang MW et al (2017) Smartphone Applications Providing Information about Stroke: Are We Missing Stroke Risk Computation Preventive Applications? J Stroke. 2017 Jan;19(1):115-116. PMID:28178409

Loh AZ et al (2017) The Global Prevalence of Anxiety and Depressive Symptoms Among Caregivers of Stroke Survivors. J Am Med Dir Assoc. 2017 Feb 1;18(2):111-116. doi: 10.1016/j.jamda.2016.08.014. PMID:27742585

Zhang MW et al (2015) Harnessing smartphone technologies for stroke care, rehabilitation and beyond. BMJ Innov. 2015 Oct;1(4):145-150. PMID:26692351
Response: Thank you for your insightful suggestion. We have added these statements in the revised manuscript and cited the references accordingly. (Page 15, Line 245-265)

Comment (7): Under discussion (Pg 16 line 6), the authors stated that Yang et al showed that depression declines with age. This statement may not be accurate and not supported by the finding of this meta-analysis (peak of depression in age 80-90 years). The authors need to strengthen the discussion that depression is common in elderly with chronic medical illnesses and associated with suicide risk. Please add the following statements after discussion of person and status losses (Pg 16, line 24).

Risk factors of geriatric depression include poor health, brain injury, low folate and vitamin B12 and raised plasma homocysteine levels (Heok et al 2008). The association between depression and chronic medical illnesses in elderly are due to accompanying poor self-reported health and functional status (Niti M et al 2007). Further, history of depression and antidepressant treatment are important risk factors for elderly suicide (Ho et al 2014).

Please include these important references:

Heok KE et al (2008) The many faces of geriatric depression. Curr Opin Psychiatry. 2008 Nov;21(6):540-5. PMID:18852559

Niti M et al (2007) Depression and chronic medical illnesses in Asian older adults: the role of subjective health and functional status. Int J Geriatr Psychiatry. 2007 Nov;22(11):1087-94. PMID:17407107

Ho RC et al (2014) Elderly suicide with and without a history of suicidal behavior: implications for suicide prevention and management. Arch Suicide Res. 2014;18(4):363-75. PMID:24828390
Response: Thank you for these constructive suggestions. We have added these statements and cited the reference to strengthen the discussion. (Page 17, Line 296-300)

Comment (8): There is not enough discussion on depression, chronic medical illness and suicide in adults. The second peak is 30-40 years and these are not young adults. I advise the authors to add the following statement and reference on Pg 16, line 4:

Outpatients aged 30-40 years suffering from chronic medical illnesses are at higher risk for developing depression. Depressed outpatients might develop maladaptive rumination and illness perception towards their chronic medical illness (Lu et al 2014). Chronic medical illness may increase the risk of suicide in adult outpatients because psychosomatic complaint such as headache was found to be an important risk factor for suicide in adults (Choo C et al 2014).

Please include these important references:

Lu Y et al (2014) A regressional analysis of maladaptive rumination, illness perception and negative emotional outcomes in Asian patients suffering from depressive disorder. Asian J Psychiatr. 2014 Dec;12:69-76. PMID: 25440564

Choo C et al (2014) Cluster analysis reveals risk factors for repeated suicide attempts in a multi-ethnic Asian population. Asian J Psychiatr. 2014 Apr;8:38-42. PMID: 24655624
Response: Thank you for your kind reminding. We have rephrased our statement as you suggested, and cited the references accordingly. (Page 17, Line 283-288)

Comment (9): Under discussion, (Pg 16, line 22), the authors stated that depression reaches its highest level in “adults” 80 years or older. This is not correct in terms of grammar and content. It should be: highest levels in elderly aged 80 years or older.
Response: Thank you for your kind reminding. We have corrected the grammar accordingly in the revised manuscript. (Page 17, Line 294-295)

Reviewer #3:
Comment (1): This is a useful and timely review, addressing the prevalence of depression in outpatients. Overall, I think it is interesting and well-written. My major concern is the limited number of databases used to conduct the search; the general recommendation from the Cochrane Collaboration is to include at least three databases in your search strategy. There is also some fairly recent systematic review evidence to suggest that a small number of databases can result in database bias. I would recommend rerunning the search strategy using an additional database, to ensure no other relevant research is missed.
Response: Many thanks for your comments. We have conducted the search using four databases including PubMed, PsycINFO, EMBASE and Cochrane Library. All databases were manually searched by our search strategies. However, the EMBASE and Cochrane Library databases didn’t contribute more articles that meet the inclusion criteria after PubMed and PsycINFO were searched. In the revised manuscript, we have added EMBASE and Cochrane Library to the search strategy. (Page 8, Line 121)

Comment (2): For future replication of your search strategy, it would be helpful to include your exact search terms in an appendix.
Response: Thank you for this suggestion. We have added detailed search terms and strategies for PubMed in the appendix accordingly. (Supplementary Method 1)

Comment (3): Did you pre-select the specialties you included in your search strategy? Is there a fully inclusive list of international specialties available? If not, there's possibility of introducing bias by having forgotten some specialties, or systematically omitted culturally specific specialties which might be referred to using different phrases or terminology.
Response: Thank you for pointing this out. During the process of database searching, a thorough search strategy was designed to identify the entire observational studies that contained information on the prevalence of depression and depressive symptoms in outpatients. Different phrases or terminologies of the candidate specialties were collected and used for searching. After a robust study screening process, 83 studies covering 11 specialties fulfilled all the inclusion criteria and were finally included in the meta-analysis. The fully inclusive list of international specialties was provided in Supplementary Method 1.

Comment (4): What is the justification (and implication) of only including studies where patients have clinically relevant depression. Might this lead to an overestimation of prevalence?
Response: Thanks for raising this concern. There is no “golden standard” yet to diagnoise depression and depressive symptoms, and depression was usually diagnosed by validated self-report instruments or diagnostic structured interviews. Patients with clinically relevant depression will present

typical signs of depression, and can be evaluated more objectively by standard diagnostic scales. The similar method was also used by the previous study. (Anderson RJ, Diabetes Care. 2001)

Comment (5): In the first paragraph of the results section, it's unclear what you mean by "uncorrected outcome measures".
Response: Thanks for it pointing this out. The original words have been rephrased to ‘improper outcome measures’ to avoid potential controversy. (Page 12, Line 191)

Comment (6): At the top of page 13 in the results, I'm not sure how meaningful it is to combine prevalence estimates into one overall pooled estimate, given the heterogeneity particularly in how depression is measured. Perhaps it's more helpful to only report them separately by depression measurement.
Response: Thank you for bringing this concern. We agree that it is more meaningful to estimate the prevalence in separate subgroups, and we therefore performed subgroup analyes based on age, clinical department, study year, country, and diagnosis in this study. For models with considerable heterogeneity, we also conducted a meta-regression to identify the moderators potentially contribute to the heterogeneity of the effect sizes. However, we think it is also helpful for the readers to know the overall pooled estimate of depression and depressive symptoms among outpatients in daily clinical practice. Actually, in meta-analysis, it is common to report the results from the pooled data as well as the results from sub-group analyses, respectively. (Jones. Lancet. 2012; Tham. Ophthalmology. 2014).

Comment (7): Also at the top of page 13, it seems from you eligibility criteria that having a control group was one of your inclusion criteria, yet here you mention only 8 studies with a control group. Can this be clarified?
Response: Thanks for bringing this to our attention. In fact, having a control group was not one of the inclusion criteria in this meta-analysis. However, we chose the studies with a control group to perfrom subgroup analysis. We have revised the eligibility criteria accordingly. (Page 8-9, Line 132-139).

Comment (8): No mention is made of how the variation in thresholds in the different depression measurements impacted prevalence estimates.
Response: Thanks for pointing this out. We agree with you that the variation in the thresholds in different depression measurements may impact the heterogeneity and estimated results of depression prevalence. This variation was captured in part by the modified Newcastle-Ottawa score, which assessed the risk of bias in each study. We have added the statement accordingly in the revised manuscript. (Page 18, Line 323-324)

Comment (9): In the limitations section, it would be helpful to have a wider discussion on the implications of your finding that there may be publication bias.
Response: Thanks for your suggestion. We have added more discussion as a separate paragraph to assess the potential publication bias of this study. (Page 19, Line 327-343)

Comment (10): The conclusion section mentions several implications for clinical practice, but the first implication is just a reiteration of your methods. This could be rephrased.
Response: Thank you for your kind comment. We have rephrased the statement to avoid reiteration of the methods. (Page 22, Line 376-388)

At last, we again wish to thank you and all reviewers for your helpful comments, and hope you will now find the paper suitable for publication.
Sincerely yours,
Haotian Lin on behalf of all authors

VERSION 2 – REVIEW

REVIEWER	Roger Ho Department of Psychological Medicine National University of Singapore Singapore
REVIEW RETURNED	15-Jun-2017

GENERAL COMMENTS	I am satisfied with amendments and recommend acceptance.

REVIEWER	Faith Matcham King's College London, UK
REVIEW RETURNED	26-Jun-2017

GENERAL COMMENTS	Thank you for addressing the comments raised in my previous review. I am happy with the changes made and to recommend this paper for publication.