**Supplementary appendix**

This document presents additional methods and results for the manuscript titled, ‘The risk of developing major depression among individuals with subthreshold depression: a systematic review and meta-analysis of longitudinal cohort studies’

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## Search terms used in the systematic review

### Pubmed

("Depression"[Mesh] OR "Depressive Disorder"[Mesh] OR depressi\*[tw])

AND

(minor[tw] OR subclinical[tw] OR sub-clinical[tw] OR subthreshold[tw] OR sub-threshold[tw] OR subsyndromal[tw] OR sub-syndromal[tw])

AND

("Risk"[Mesh] OR "Risk Factors"[Mesh] OR "Incidence"[Mesh] OR longitudinal[tw] OR prospective[tw] OR risk[tw] OR incidence[tw] OR onset[tw])

### Embase

('depression'/exp OR depressi\*:ct)

AND

(minor:ct OR subclinical:ct OR sub-clinical:ct OR subthreshold:ct OR sub-threshold:ct OR subsyndromal:ct OR sub-syndromal:ct)

AND

('risk factor'/exp OR 'longitudinal study'/exp OR 'prospective study'/exp OR 'incidence'/exp OR longitudinal:ct OR prospective:ct OR risk:ct OR incidence:ct OR onset:ct)

### PsycINFO

((Depression (Emotion)) OR (Dysthymic Disorder) OR (Major Depression) OR depressi\*.tw)

AND

(minor OR subclinical OR sub-clinical OR subthreshold OR sub-threshold OR subsyndromal OR sub-syndromal)

AND

((Risk Factors) OR (Follow up Studies) OR (Longitudinal Studies) OR (Prospective Studies) OR longitudinal.tw OR prospective.tw OR risk.tw OR incidence.tw OR onset.tw)

## Newcastle-Ottawa quality assessment scale for cohort studies

Here we provide a summary list of the domains/items that were used to assess the quality of longitudinal cohort studies included in the meta-analysis. There are 3 domains encompassing: (S) the selection of the study groups; (C) the comparability of the groups; and (O) the ascertainment of the outcome of interest. A star is awarded for each quality item if it satisfies the requirements for any of the assessments below in green font. A study can be awarded a maximum of one star for each numbered item within the Selection (S) and Outcome (O) categories. A maximum of two stars can be given for Comparability (C). Overall, a study can be awarded up to nine stars in total.

|  |  |
| --- | --- |
| Domains / Items | Assessment for each quality item |
| Selection (S) |  |
| S1 – Representativeness of the exposed cohort | a) truly representative of the average case of subthreshold depression in the community  b) somewhat representative of the average case of subthreshold depression in the community  c) selected group of users (e.g., nurses, volunteers)  d) no description of the derivation of the cohort |
| S2 – Selection of the non-exposed cohort | a) drawn from the same community as the exposed cohort  b) drawn from a different source  c) no description of the derivation of the non-exposed cohort |
| S3 – Ascertainment of exposure | a) structured interview or secure records  b) written self-report  c) no description |
| S4 – Demonstration that outcome of interest was not present at start of study | a) yes  b) no |
| Comparability (C) |  |
| C1a – Comparability of cohorts on the basis of the design or analysis (treatment) | a) study controls for previous treatment  b) study does not control for previous treatment |
| C1b – Comparability of cohorts on the basis of the design or analysis (other mental disorder) | a) study controls for other mental disorders  b) study does not control for other mental disorders |
| Outcome (O) |  |
| O1 – Assessment of outcome | a) independent blind assessment  b) structured interview  c) self-report  d) no description |
| O2 – Was follow-up long enough for outcomes to occur | a) yes, at least 1 year  b) no |
| O3 – Adequacy of follow up of cohorts | a) follow-up rate > 75%  b) follow-up rate < 75% and no description of those lost  c) no statement |

## PRISMA checklist

|  |  |  |  |
| --- | --- | --- | --- |
| **Section/topic** | **#** | **Checklist item** | **Section reported** |
| **TITLE** | | |  |
| Title | 1 | Identify the report as a systematic review, meta-analysis, or both. | See Title |
| **ABSTRACT** | | |  |
| Structured summary | 2 | Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number. | See Abstract |
| **INTRODUCTION** | | |  |
| Rationale | 3 | Describe the rationale for the review in the context of what is already known. | Rationale outlined in the Introduction |
| Objectives | 4 | Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS). | See the study aim provided at the end of the Introduction |
| **METHODS** | | |  |
| Protocol and registration | 5 | Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number. | Not applicable |
| Eligibility criteria | 6 | Specify study characteristics (e.g., PICOS, length of follow‐up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. | See *Search strategy* subsection in the Methods |
| Information sources | 7 | Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched. | See *Search strategy* subsection in the Methods |
| Search | 8 | Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated. | See *Search strategy* subsection in the Methods |
| Study selection | 9 | State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta‐analysis). | See *Search strategy* subsection in the Methods |
| Data collection process | 10 | Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators. | See *Data extraction* subsection in the Methods |
| Data items | 11 | List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made. | See *Data extraction* and *Statistical analysis* subsections in the Methods |
| Risk of bias in individual studies | 12 | Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis. | See *Quality assessment* subsection in the Methods |
| Summary measures | 13 | State the principal summary measures (e.g., risk ratio, difference in means). | See *Statistical analysis* subsection in the Methods |
| Synthesis of results | 14 | Describe the methods of handling data and combining results of studies, if done, including measures of consistency  (e.g., I2 for each meta‐analysis) | See *Statistical analysis* subsection in the Methods |

## Complete list of excluded studies – with reasons

### Did not examine link between subthreshold depression and major depression (N=47)

1. Adams KB, Moon H. Subthreshold depression: Characteristics and risk factors among vulnerable elders. Aging Ment Health 2009;13(5):682-92.

2. Ahern MM, Hendryx M. Community participation and the emergence of late-life depressive symptoms: differences between women and men. J Womens Health 2008;17(9):1463-70.

3. Alexandrino-Silva C, Alves TF, Tofoli LF, Wang YP, Andrade LH. Psychiatry: life events and social support in late life depression. Clinics (Sao Paulo) 2011;66(2):233-8.

4. Angst J, Merikangas KR, Preisig M. Subthreshold syndromes of depression and anxiety in the community. J Clin Psychiatry 1997;58 Suppl 8:6-10.

5. Beekman AT, Penninx BW, Deeg DJ, Ormel J, Braam AW, van Tilburg W. Depression and physical health in later life: results from the Longitudinal Aging Study Amsterdam (LASA). J Affect Disord 1997;46(3):219-31.

6. Canals J, Domenech-Llaberia E, Fernandez-Ballart J, Marti-Henneberg C. Predictors of depression at eighteen. A 7-year follow-up study in a Spanish nonclinical population. Eur Child Adolesc Psychiatry 2002;11(5):226-33.

7. Chopra MP, Zubritsky C, Knott K, Have TT, Hadley T, Coyne JC, et al. Importance of subsyndromal symptoms of depression in elderly patients. Am J Geriatr Psychiatry 2005;13(7):597-606.

8. Cui X, Lyness JM, Tang W, Tu X, Conwell Y. Outcomes and predictors of late-life depression trajectories in older primary care patients. Am J Geriatr Psychiatry 2008;16(5):406-15.

9. Fava GA, Grandi S, Canestrari R, Molnar G. Prodromal symptoms in primary major depressive disorder. J Affect Disord 1990;19(2):149-52.

10. Ferro MA, Gorter JW, Boyle MH. Trajectories of Depressive Symptoms in Canadian Emerging Adults. Am J Public Health 2015;105(11):2322-7.

11. Fichter MM, Kohlboeck G, Quadflieg N, Wyschkon A, Esser G. From childhood to adult age: 18-year longitudinal results and prediction of the course of mental disorders in the community. Soc Psychiatry Psychiatr Epidemiol 2009;44(9):792-803.

12. Fils JM, Penick EC, Nickel EJ, Othmer E, Desouza C, Gabrielli WF, et al. Minor versus major depression: a comparative clinical study. Prim Care Companion J Clin Psychiatry 2010;12(1):PCC.08m00752.

13. Fredman L, Schoenbach VJ, Kaplan BH, Blazer DG, James SA, Kleinbaum DG, et al. The association between depressive symptoms and mortality among older participants in the Epidemiologic Catchment Area-Piedmont Health Survey. J Gerontol 1989;44(4):S149-56.

14. Gallo JJ, Rabins PV, Lyketsos CG, Tien AY, Anthony JC. Depression without sadness: functional outcomes of nondysphoric depression in later life. J Am Geriatr Soc 1997;45(5):570-8.

15. Georgiades K, Lewinsohn PM, Monroe SM, Seeley JR. Major depressive disorder in adolescence: the role of subthreshold symptoms. J Am Acad Child Adolesc Psychiatry 2006;45(8):936-44.

16. Hegel MT, Oxman TE, Hull JG, Swain K, Swick H. Watchful waiting for minor depression in primary care: remission rates and predictors of improvement. Gen Hosp Psychiatry 2006;28(3):205-12.

17. Hybels CF, Pieper CF, Blazer DG. The complex relationship between depressive symptoms and functional limitations in community-dwelling older adults: the impact of subthreshold depression. Psychol Med 2009;39(10):1677-88.

18. Ialongo NS, Edelsohn G, Kellam SG. A further look at the prognostic power of young children's reports of depressed mood and feelings. Child Dev 2001;72(3):736-47.

19. Judd LL, Paulus MP, Wells KB, Rapaport MH. Socioeconomic burden of subsyndromal depressive symptoms and major depression in a sample of the general population. Am J Psychiatry 1996;153(11):1411-7.

20. Katon W, Von Korff M, Lin E, Lipscomb P, Russo J, Wagner E, et al. Distressed high utilizers of medical care. DSM-III-R diagnoses and treatment needs. Gen Hosp Psychiatry 1990;12(6):355-62.

21. Kaufman J, Birmaher B, Brent D, Rao U, Flynn C, Moreci P, et al. Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL): initial reliability and validity data. J Am Acad Child Adolesc Psychiatry 1997;36(7):980-8.

22. Keenan K, Hipwell A, Chung T, Stepp S, Stouthamer-Loeber M, Loeber R, et al. The Pittsburgh Girls Study: overview and initial findings. J Clin Child Adolesc Psychol 2010;39(4):506-21.

23. Kennedy N, Abbott R, Paykel ES. Longitudinal syndromal and sub-syndromal symptoms after severe depression: 10-Year follow-up study. Br J Psychiatry 2004;184(APR.):330-6.

24. Klaassen RM, Heins M, Luteijn LB, van der Gaag M, van Beveren NJ, Genetic R, et al. Depressive symptoms are associated with (sub)clinical psychotic symptoms in patients with non-affective psychotic disorder, siblings and healthy controls. Psychol Med 2013;43(4):747-56.

25. Kuchibhatla MN, Fillenbaum GG, Hybels CF, Blazer DG. Trajectory classes of depressive symptoms in a community sample of older adults. Acta Psychiatr Scand 2012;125(6):492-501.

26. Kuhn KU, Quednow BB, Barkow K, Heun R, Linden M, Maier W. [Chronic course and psychosocial disability caused by depressive illnesses in general practice patients during a one year period. Results of a study by the World Health Organization]. Nervenarzt 2002;73(7):644-50.

27. Lewinsohn PM, Rohde P, Klein DN, Seeley JR. Natural course of adolescent major depressive disorder: I. Continuity into young adulthood. J Am Acad Child Adolesc Psychiatry 1999;38(1):56-63.

28. Lyness JM, King DA, Cox C, Yoediono Z, Caine ED. The importance of subsyndromal depression in older primary care patients: prevalence and associated functional disability. J Am Geriatr Soc 1999;47(6):647-52.

29. Mattisson C, Bogren M, Nettelbladt P, Munk-Jorgensen P, Bhugra D. First incidence depression in the Lundby Study: a comparison of the two time periods 1947-1972 and 1972-1997. J Affect Disord 2005;87(2-3):151-60.

30. Meller I, Fichter MM, Schroppel H. Incidence of depression in octo- and nonagenerians: results of an epidemiological follow-up community study. Eur Arch Psychiatry Clin Neurosci 1996;246(2):93-9.

31. Mossaheb N, Weissgram S, Zehetmayer S, Jungwirth S, Rainer M, Tragl KH, et al. Late-onset depression in elderly subjects from the Vienna Transdanube Aging (VITA) study. J Clin Psychiatry 2009;70(4):500-8.

32. Olfson M, Broadhead WE, Weissman MM, Leon AC, Farber L, Hoven C, et al. Subthreshold psychiatric symptoms in a primary care group practice. Arch Gen Psychiatry 1996;53(10):880-6.

33. Palsson SP, Ostling S, Skoog I. The incidence of first-onset depression in a population followed from the age of 70 to 85. Psychol Med 2001;31(7):1159-68.

34. Penninx BW, Geerlings SW, Deeg DJ, van Eijk JT, van Tilburg W, Beekman AT. Minor and major depression and the risk of death in older persons. Arch Gen Psychiatry 1999;56(10):889-95.

35. Preisig M, Merikangas KR, Angst J. Clinical significance and comorbidity of subthreshold depression and anxiety in the community. Acta Psychiatr Scand 2001;104(2):96-103.

36. Prince MJ, Harwood RH, Thomas A, Mann AH. A prospective population-based cohort study of the effects of disablement and social milieu on the onset and maintenance of late-life depression. The Gospel Oak Project VII. Psychol Med 1998;28(2):337-50.

37. Rihmer Z, Nemcsik J, Ho C, Jin A, Nyunt MS, Feng L, et al. Mortality rates in major and subthreshold depression: 10-year follow-up of a Singaporean population cohort of older adults. BMC Cardiovasc Disord 2016;128(7):642-7.

38. Rorsman B, Grasbeck A, Hagnell O, Lanke J, Ohman R, Ojesjo L, et al. A prospective study of first-incidence depression. The Lundby study, 1957-72. Br J Psychiatry 1990;156:336-42.

39. Schaub RT, Linden M, Copeland JR. A comparison of GMS-A/AGECAT, DSM-III-R for dementia and depression, including subthreshold depression (SD)--results from the Berlin Aging Study (BASE). Int J Geriatr Psychiatry 2003;18(2):109-17.

40. Sherbourne CD, Wells KB, Hays RD, Rogers W, Burnam MA, Judd LL. Subthreshold depression and depressive disorder: clinical characteristics of general medical and mental health specialty outpatients. Am J Psychiatry 1994;151(12):1777-84.

41. Smit F, Beekman A, Cuijpers P, de Graaf R, Vollebergh W. Selecting key variables for depression prevention: results from a population-based prospective epidemiological study. J Affect Disord 2004;81(3):241-9.

42. Tamburrino MB, Lynch DJ, Nagel RW, Smith MK. Primary care evaluation of mental disorders (PRIME-MD) screening for minor depressive disorder in primary care. Prim Care Companion J Clin Psychiatry 2009;11(6):339-43.

43. Wells KB, Stewart A, Hays RD, Burnam MA, Rogers W, Daniels M, et al. The functioning and well-being of depressed patients. Results from the Medical Outcomes Study. JAMA 1989;262(7):914-9.

44. Wesselhoeft R, Heiervang ER, Kragh-Sørensen P, Juul Sørensen M, Bilenberg N. Major depressive disorder and subthreshold depression in prepubertal children from the Danish National Birth Cohort. Compr Psychiatry 2016;70:65-76.

45. Wesselhoft RT. Childhood depressive disorders. Dan Med J 2016;63(10).

46. Xiao S, Lewis M, Mellor D, McCabe M, Byrne L, Wang T, et al. The China longitudinal ageing study: overview of the demographic, psychosocial and cognitive data of the Shanghai sample. J Ment Health 2016;25(2):131-6.

47. Yang J, Yao S, Zhu X, Zhang C, Ling Y, Abela JR, et al. The impact of stress on depressive symptoms is moderated by social support in Chinese adolescents with subthreshold depression: a multi-wave longitudinal study. J Affect Disord 2010;127(1-3):113-21.

### Review/commentary (N=18)

1. Bertha EA, Balazs J. Subthreshold depression in adolescence: a systematic review. Eur Child Adolesc Psychiatry 2013;22(10):589-603.

2. Buchtemann D, Luppa M, Bramesfeld A, Riedel-Heller S. Incidence of late-life depression: a systematic review. J Affect Disord 2012;142(1-3):172-9.

3. Cuijpers P, Smit F. Subthreshold depression as a risk indicator for major depressive disorder: a systematic review of prospective studies. Acta Psychiatr Scand 2004;109(5):325-31.

4. Cuijpers P, Smit F. Subklinische depressie: een klinisch relevante conditie? Tijdschrift voor Psychiatrie, 2008;50(8):519-28.

5. Fava GA. Subclinical symptoms in mood disorders: pathophysiological and therapeutic implications. Psychol Med 1999;29(1):47-61.

6. Fava GA, Mangelli L. Assessment of subclinical symptoms and psychological well-being in depression. Eur Arch Psychiatry Clin Neurosci 2001;251 Suppl 2:Ii47-52.

7. Fava GA, Tossani E. Prodromal stage of major depression. Early Interv Psychiatry 2007;1(1):9-18.

8. Hermens ML, van Hout HP, Terluin B, van der Windt DA, Beekman AT, van Dyck R, et al. The prognosis of minor depression in the general population: a systematic review. Gen Hosp Psychiatry 2004;26(6):453-62.

9. Judd LL. The clinical course of unipolar major depressive disorders. Arch Gen Psychiatry 1997;54(11):989-91.

10. Magnusson H. Mental health of octogenarians in Iceland. An epidemiological study. Acta Psychiatr Scand Suppl 1989;349:1-112.

11. Meeks TW, Vahia IV, Lavretsky H, Kulkarni G, Jeste DV. A tune in "a minor" can "b major": a review of epidemiology, illness course, and public health implications of subthreshold depression in older adults. J Affect Disord 2011;129(1-3):126-42.

12. Ormel J, De Jonge P. Subclinical depression poses interesting questions. Tijdschrift voor Psychiatrie 2008;50(8):529-31.

13. Penninx BW, Beekman AT, Smit JH, Zitman FG, Nolen WA, Spinhoven P, et al. The Netherlands Study of Depression and Anxiety (NESDA): rationale, objectives and methods. Int J Methods Psychiatr Res 2008;17(3):121-40.

14. Pincus HA, Davis WW, McQueen LE. 'Subthreshold' mental disorders. A review and synthesis of studies on minor depression and other 'brand names'. Br J Psychiatry 1999;174:288-96.

15. Robinson RG, Jorge RE. Prevention of first-episode depression: progress and potential. Br J Psychiatry 2009;194(4):296-7.

16. Rodriguez MR, Nuevo R, Chatterji S, Ayuso-Mateos JL. Definitions and factors associated with subthreshold depressive conditions: a systematic review. BMC Psychiatry 2012;12:181.

17. Sadek N, Bona J. Subsyndromal symptomatic depression: a new concept. Depress Anxiety 2000;12(1):30-9.

18. Wesselhoeft R, Sorensen MJ, Heiervang ER, Bilenberg N. Subthreshold depression in children and adolescents - a systematic review. J Affect Disord 2013;151(1):7-22.

### Used incompatible case definitions (N=12)

1. Angst J, Merikangas K. The depressive spectrum: diagnostic classification and course. J Affect Disord 1997;45(1-2):31-9; discussion 9-40.

2. de la Camara C, Saz P, Lopez A, Ventura T, Dia J, Lobo A. Depression in the elderly community: II, Outcome in a 4.5 years follow-up. Eur J Psychiatry 2008;22:141-50.

3. Kandel DB, Davies M. Adult sequelae of adolescent depressive symptoms. Arch Gen Psychiatry 1986;43(3):255-62.

4. Lyness JM, Chapman BP, McGriff J, Drayer R, Duberstein PR. One-year outcomes of minor and subsyndromal depression in older primary care patients. International Psychogeriatrics 2009;21(1):60-8.

5. Lyness JM, Heo M, Datto CJ, Ten Have TR, Katz IR, Drayer R, et al. Outcomes of minor and subsyndromal depression among elderly patients in primary care settings. Ann Intern Med 2006;144(7):496-504.

6. Maier W, Gansicke M, Weiffenbach O. The relationship between major and subthreshold variants of unipolar depression. J Affect Disord 1997;45(1-2):41-51.

7. Merikangas KR, Wicki W, Angst J. Heterogeneity of depression. Classification of depressive subtypes by longitudinal course. Br J Psychiatry 1994;164(3):342-8.

8. Merikangas KR, Zhang H, Avenevoli S, Acharyya S, Neuenschwander M, Angst J. Longitudinal trajectories of depression and anxiety in a prospective community study: the Zurich Cohort Study. Arch Gen Psychiatry 2003;60(10):993-1000.

9. Murphy JM, Nierenberg AA, Laird NM, Monson RR, Sobol AM, Leighton AH. Incidence of major depression: prediction from subthreshold categories in the Stirling County Study. J Affect Disord 2002;68(2-3):251-9.

10. Norton MC, Skoog I, Toone L, Corcoran C, Tschanz JT, Lisota RD, et al. Three-year incidence of first-onset depressive syndrome in a population sample of older adults: the Cache County study. Am J Geriatr Psychiatry 2006;14(3):237-45.

11. Rohde P, Beevers CG, Stice E, O'Neil K. Major and minor depression in female adolescents: onset, course, symptom presentation, and demographic associations. J Clin Psychol 2009;65(12):1339-49.

12. W M. Onset and course of affective disorders in subjects at risk: a prospective family study. Psychiatr Ann 1996;26:315–9.

### Did not include a healthy control group (N=12)

1. Azar A. Late -life subthreshold depressive symptoms: Predicting the course and examining the relationship with major depression. Mast B. ProQuest Dissertations Publishing; 2007.

2. Bjerkeset O, Nordahl HM, Larsson S, Dahl AA, Linaker O. A 4-year follow-up study of syndromal and sub-syndromal anxiety and depression symptoms in the general population: the HUNT study. Soc Psychiatry Psychiatr Epidemiol 2008;43(3):192-9.

3. Broadhead WE, Blazer DG, George LK, Tse CK. Depression, disability days, and days lost from work in a prospective epidemiologic survey. JAMA 1990;264(19):2524-8.

4. Cuijpers P, Beekman A, Smit F, Deeg D. Predicting the onset of major depressive disorder and dysthymia in older adults with subthreshold depression: A community based study. Int J Geriatr Psychiatry 2006;21(9):811-8.

5. Eaton WW, Badawi M, Melton B. Prodromes and precursors: epidemiologic data for primary prevention of disorders with slow onset. Am J Psychiatry 1995;152(7):967-72.

6. Hill RM, Pettit JW, Lewinsohn PM, Seeley JR, Klein DN. Escalation to Major Depressive Disorder among adolescents with subthreshold depressive symptoms: Evidence of distinct subgroups at risk. J Affect Disord 2014;158:133-8.

7. Kessler RC, Zhao S, Blazer DG, Swartz M. Prevalence, correlates, and course of minor depression and major depression in the national comorbidity survey. J Affect Disord 1997;45(1-2):19-30.

8. Kovacs M, Feinberg TL, Crouse-Novak M, Paulauskas SL, Pollock M, Finkelstein R. Depressive disorders in childhood. II. A longitudinal study of the risk for a subsequent major depression. Arch Gen Psychiatry 1984;41(7):643-9.

9. Magnil M, Janmarker L, Gunnarsson R, Bjorkelund C. Course, risk factors, and prognostic factors in elderly primary care patients with mild depression: a two-year observational study. Scand J Prim Health Care 2013;31(1):20-5.

10. Schoevers RA, Smit F, Deeg DJ, Cuijpers P, Dekker J, van Tilburg W, et al. Prevention of late-life depression in primary care: do we know where to begin? Am J Psychiatry 2006;163(9):1611-21.

11. Vuorilehto MS, Melartin TK, Isometsa ET. Course and outcome of depressive disorders in primary care: a prospective 18-month study. Psychol Med 2009;39(10):1697-707.

12. Wells KB, Burnam MA, Rogers W, Hays R, Camp P. The course of depression in adult outpatients. Results from the Medical Outcomes Study. Arch Gen Psychiatry 1992;49(10):788-94.

### Involved an overlapping cohort with another study (N=10)

1. Chen LS, Eaton WW, Gallo JJ, Nestadt G, Crum RM. Empirical examination of current depression categories in a population-based study: symptoms, course, and risk factors. Am J Psychiatry 2000;157(4):573-80.

2. Fergusson DM, Horwood LJ, Ridder EM, Beautrais AL. Subthreshold depression in adolescence and mental health outcomes in adulthood. Arch Gen Psychiatry 2005;62(1):66-72.

3. Fogel J, Eaton WW, Ford DE. Minor depression as a predictor of the first onset of major depressive disorder over a 15-year follow-up. Acta Psychiatr Scand 2006;113(1):36-43.

4. Gotlib IH, Lewinsohn PM, Seeley JR. Symptoms versus a diagnosis of depression: differences in psychosocial functioning. J Consult Clin Psychol 1995;63(1):90-100.

5. Horwath E, Johnson J, Klerman GL, Weissman MM. What are the public health implications of subclinical depressive symptoms? Psychiatr Q 1994;65(4):323-37.

6. Judd LL, Akiskal HS, Paulus MP. The role and clinical significance of subsyndromal depressive symptoms (SSD) in unipolar major depressive disorder. J Affect Disord 1997;45(1-2):5-17; discussion -8.

7. Laborde-Lahoz P, El-Gabalawy R, Kinley J, Kirwin PD, Sareen J, Pietrzak RH. Subsyndromal depression among older adults in the USA: Prevalence, comorbidity, and risk for new-onset psychiatric disorders in late life. Int J Geriatr Psychiatry 2015;30(7):677-85.

8. Lewinsohn PM, Solomon A, Seeley JR, Zeiss A. Clinical implications of "subthreshold" depressive symptoms. J Abnorm Psychol 2000;109(2):345-51.

9. Pietrzak RH, Kinley J, Afifi TO, Enns MW, Fawcett J, Sareen J. Subsyndromal depression in the United States: prevalence, course, and risk for incident psychiatric outcomes. Psychol Med 2013;43(7):1401-14.

10. Regeer EJ, Krabbendam L, de Graaf R, ten Have M, Nolen WA, van Os J. A prospective study of the transition rates of subthreshold (hypo)mania and depression in the general population. Psychol Med 2006;36(5):619-27.

### No extractable data (N=8)

1. Allan CL, Sexton CE, Filippini N, Topiwala A, Mahmood A, Zsoldos E, et al. Sub-threshold depressive symptoms and brain structure: A magnetic resonance imaging study within the Whitehall II cohort. J Affect Disord 2016;204:219-25.

2. Gledhill J, Garralda M. Sub-syndromal depression in adolescents attending primary care: frequency, clinical features and 6 months outcome. Soc Psychiatry Psychiatr Epidemiol 2013;48(5):735-44.

3. Grabovich A, Lu N, Tang W, Tu X, Lyness JM. Outcomes of subsyndromal depression in older primary care patients. Am J Geriatr Psychiatry 2010;18(3):227-35.

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## Quality assessment of longitudinal cohort studies included in the baseline meta-analysis

### Newcastle-Ottawa quality assessment graph

The figure below presents the relative proportion of studies that have been awarded a star (i.e., low risk of bias) versus those that have not (i.e., high risk of bias) for each quality item across the 3 domains – i.e., selection (S), comparability (C) and outcome (O).

* + - * 1. Newcastle-Ottawa quality assessment graph for included studies

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### Newcastle-Ottawa checklist of quality assessment items

The figure below presents a checklist of the quality items for each longitudinal cohort study included in the meta-analysis. Each study has been awarded a green star (signifying low risk of bias) or a red cross (signifying high risk of bias) for each quality item, across the 3 domains – i.e., selection (S), comparability (C) and outcome (O).

* + - * 1. Newcastle-Ottawa checklist of quality assessment items for included studies

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## Baseline meta-analysis data

* + - 1. Data extracted from in-scope longitudinal studies

|  |  |  | **Exposed cohort (subthreshold depression)** | | | |  | **Control cohort (non-depressed)** | | | |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Study** | **Incidence rate ratio (95% CI)** |  | **Incidence density rate** | **No. of new cases** | **Person years** | **Sample size** |  | **Incidence density rate** | **No. of new cases** | **Person-years** | **Sample size** |  | **Follow-up period (years)** |
| *Studies conducted in community-based youth samples* | | | | | | | | | | | | | |
| Johnson *et al.* (2009) | 3.1 (1.9 – 5.0) |  | 0.034 | 21 | 622 | 62 |  | 0.011 | 86 | 7,956 | 693 |  | 12.3 |
| Jonsson *et al.* (2011) | 1.0 (0.5 - 1.8) |  | 0.024 | 12 | 508 | 40 |  | 0.025 | 48 | 1,956 | 155 |  | 15.1 |
| McLeod *et al.* (2016) | 1.4 (0.9 – 2.0) |  | 0.013 | 37 | 2,848 | 182 |  | 0.010 | 105 | 10,920 | 678 |  | 17.5 |
| Oldehinkel *et al.* (1999) | 3.2 (2.0 – 5.2) |  | 0.101 | 28 | 278 | 184 |  | 0.031 | 47 | 1,511 | 944 |  | 1.6 |
| Shankman *et al.* (2009) | 1.6 (1.2 - 2.0) |  | 0.058 | 139 | 2,401 | 394 |  | 0.037 | 155 | 4,193 | 804 |  | 6.3 |
| *Studies conducted in community-based adult samples* | | | | | | | | | | | | | |
| Bruce & Hoff (1994) | 1.6 (0.8 - 3.2) |  | 0.028 | 10 | 352 | 514 |  | 0.018 | 45 | 2,557 | 2,656 |  | 1.0 |
| Cuijpers *et al.* (2004) | 4.2 (2.7 - 6.7) |  | 0.035 | 29 | 829 | 429 |  | 0.008 | 50 | 6,022 | 3,036 |  | 2.0 |
| Forsell (2007) | 3.6 (2.7 - 4.8) |  | 0.048 | 58 | 1,216 | 435 |  | 0.013 | 289 | 22,034 | 7,490 |  | 3.0 |
| Horwath *et al.* (1992) | 4.4 (3.1 - 6.1) |  | 0.034 | 80 | 2,369 | 2,369 |  | 0.008 | 58 | 7,531 | 7,531 |  | 1.0 |
| Jinnin *et al.* (2017) | 17.1 (0.9 – 330.4) |  | 0.070 | 4.5 \* | 50 | 52.5 \* |  | 0.004 | 0.5 \* | 121 | 121.5 \* |  | 1.0 |
| Peters *et al.* (2015) | 1.3 (1.1 - 1.5) |  | 0.016 | 184 | 11,425 | 3,901 |  | 0.012 | 1,130 | 91,361 | 31,022 |  | 3.0 |
| *Studies conducted in community-based elderly samples* | | | | | | | | | | | | | |
| Beekman *et al.* (2002) | 2.5 (1.7 - 3.6) |  | 0.052 | 75 | 1,426 | 277 |  | 0.021 | 39 | 1,842 | 327 |  | 6.0 |
| *Studies conducted in primary care adult samples* | | | | | | | | | | | | | |
| Crum *et al.* (1994) | 3.9 (2.1 - 7.0) |  | 0.029 | 19 | 654 | 664 |  | 0.007 | 25 | 3,335 | 3,348 |  | 1.0 |
| Jackson *et al.* (2007) | 2.1 (1.0 - 4.2) |  | 0.032 | 12 | 379 | 82 |  | 0.015 | 23 | 1,502 | 312 |  | 5.0 |
| Wagner *et al.* (2000) | 30.5 (1.8 - 513.4) |  | 0.227 | 13.5 \* | 59 | 66.5 \* |  | 0.007 | 0.5 \* | 67 | 67.5 \* |  | 1.0 |
| *Studies conducted in primary care elderly samples* | | | | | | | | | | | | | |
| Lyness *et al.* (2002) | 5.3 (1.1 ­­- 26.5) |  | 0.154 | 2 | 13 | 14 |  | 0.029 | 6 | 208 | 211 |  | 1.0 |

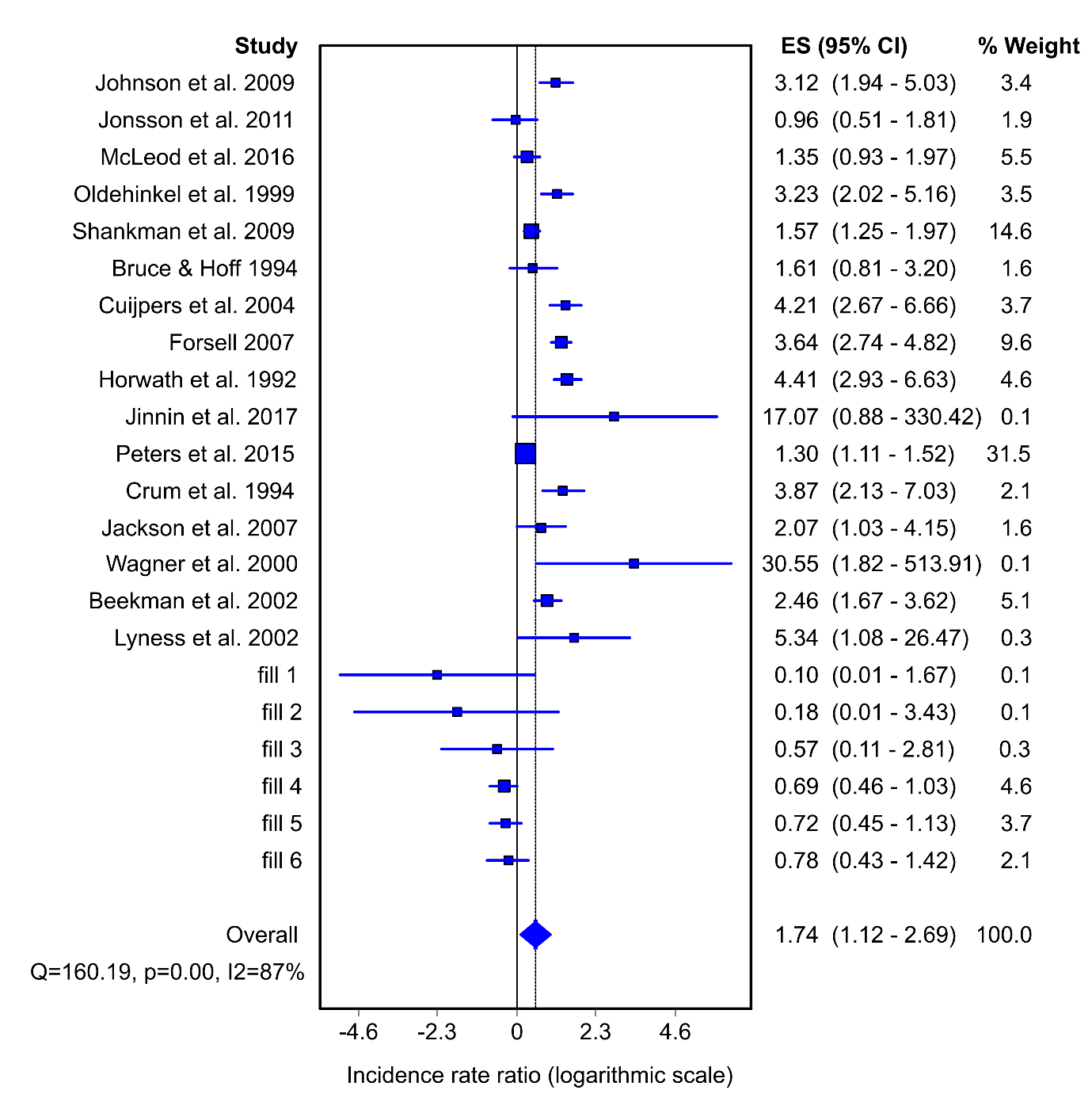
\* Continuity correction (+0.5) was applied to cells in this study due to the presence of zero events in the control cohort.

## Trim and fill analysis

### Overview

A trim and fill analysis was conducted as major asymmetry was detected in the results of the baseline meta-analysis. A forest plot showing unbiased pooled estimates after correcting for asymmetry using the trim and fill method is presented below. In addition, we present an accompanying: a) funnel plot, with imputed studies represented by hollow dots; and b) Doi plot.

* + - * 1. Forest plot presenting the results of the trim and fill analysis



* + - * 1. Depiction of publication bias in the trim and fill analysis using the: a) funnel plot; and b) Doi plot

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