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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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Abstract

Background. Studies have consistently shown that subthreshold depression is associated with an increased risk of developing major depression. However, no study has yet calculated a pooled estimate that quantifies the magnitude of this risk across multiple studies.

Methods. We conducted a systematic review to identify longitudinal cohort studies containing data on the association between subthreshold depression and future major depression. A baseline meta-analysis was conducted using the inverse variance heterogeneity method to calculate the incidence rate ratio (IRR) of major depression among people with subthreshold depression relative to non-depressed controls. Subgroup analyses were conducted to investigate whether IRR estimates differed between studies categorised by age group or sample type. Sensitivity analyses were also conducted to test the robustness of baseline results to several sources of study heterogeneity, such as the case definition for subthreshold depression.

Results. Data from 16 studies ($n = 67\,318$) revealed that people with subthreshold depression had an increased risk of developing major depression (IRR = 1.95, 95% confidence interval 1.28–2.97). Subgroup analyses estimated similar IRRs for different age groups (youth, adults and the elderly) and sample types (community-based and primary care). Sensitivity analyses demonstrated that baseline results were robust to different sources of study heterogeneity.

Conclusion. The results of this study support the scaling up of effective indicated prevention interventions for people with subthreshold depression, regardless of age group or setting.

Introduction

Subthreshold depression occurs when an individual experiences depressive symptoms that fall short of the diagnostic threshold for a major depressive disorder – usually with respect to the frequency, duration and/or severity of symptoms (National Collaborating Centre for Mental Health, 2010; Rodriguez *et al.* 2012). Subthreshold depression is common with the estimates of adult prevalence ranging from 2.9% to 9.9% in primary care and from 1.4% to 17.2% in community settings (Rodriguez *et al.* 2012). Previous studies have shown that people with subthreshold depression experience greater functional impairment, have poorer quality of life and use health services more than those without depressive symptoms (Cuijpers *et al.* 2004; Rodriguez *et al.* 2012; Bertha & Balazs, 2013). In addition, subthreshold depression is an important risk indicator for developing major depression in the future (Shankman *et al.* 2009; Pietrzak *et al.* 2013). Recent studies and treatment guidelines have called for better identification and management of subthreshold depressive symptoms in community and primary care settings (Cuijpers *et al.* 2007; National Collaborating Centre for Mental Health, 2010; Davidson *et al.* 2015). This is complemented by evidence that interventions targeting individuals with subthreshold depressive symptoms (i.e. indicated prevention) can reduce the future incidence of major depression (van Zoonen *et al.* 2014; Stockings *et al.* 2016).

Previous systematic reviews have consistently found that subthreshold depression increases the risk of major depression in youth (Bertha & Balazs, 2013; Wesselhoeft *et al.* 2013), adult (Cuijpers & Smit, 2004; Hermens *et al.* 2004) and elderly populations (Meeks *et al.* 2011). However, estimates from individual studies vary widely. For instance, Cuijpers & Smit (2004) reviewed 20 studies and found that the relative risk of major depression among those with subthreshold depression ranged between 1.8 and 340.2 in community-based studies and 0.5 and 5.1 in clinic-based studies. A narrative systematic review by Bertha & Balazs

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(2013) identified eight community-based longitudinal studies – the largest study found the risk of first-onset major depression to be as high as 35.5% in people with subthreshold depression (Shankman *et al.* 2009), while another study found no statistically significant increase in risk among people with subthreshold depression (Jonsson *et al.* 2011).

A common finding across previous systematic reviews was that the study heterogeneity hindered direct comparisons between included studies. Cuijpers & Smit (2004) identified several study design factors as sources of heterogeneity, including the case definition for subthreshold depression, exclusion of participants with a history of major depression and the period of recency for subthreshold depression. These sources of heterogeneity can potentially bias the findings of affected studies. For instance, Bertha & Balazs (2013) found that the case definitions involving diagnostic interviews, based on the Diagnostic and Statistical Manual of Mental Disorders, Fourth edition (DSM-IV) criteria which assess the number and duration of depressive symptoms, to be more reliable than those involving self-reported depression rating scales. Similarly, failing to exclude participants with a history of major depression confounds the distinction between treated cases of major depression who have residual depressive symptoms and are at risk of relapse *v.* '*de novo*' cases of subthreshold depression at risk of first incidence major depression. Lastly, studies that use longer periods of recency when establishing a case of subthreshold depression (e.g. lifetime *v.* current) will be more susceptible to recall bias.

The aforementioned systematic reviews restricted themselves to a narrative synthesis of findings. Only one, conducted over 10 years ago, attempted to conduct a meta-analysis to quantify the increased risk of major depression among people with subthreshold depression (Cuijpers & Smit, 2004). Despite their initial intentions, however, the authors were unable to perform a meta-analysis due to considerable heterogeneity across the 20 included studies. Knowing the magnitude of this risk can help clinicians and policy makers determine the scope for intervention in this population subgroup – i.e. a small, positive risk of major depression may not be sufficiently large to warrant an intervention. A precise risk estimate can also act as a data input for epidemiologic and/or health economic models evaluating the effectiveness and/or cost-effectiveness of interventions targeting people with subthreshold depression. This study aims to: conduct a systematic review and meta-analysis of longitudinal cohort studies to estimate the incidence rate ratio (IRR) of major depression among people with subthreshold depression relative to non-depressed controls; and to explore the impact of potential sources of heterogeneity on pooled estimates.

Methods

Case definition

There is currently no accepted definition for subthreshold depression covered by existing diagnostic criteria for depressive disorders (National Collaborating Centre for Mental Health, 2010). Furthermore, there is a substantial variation in the terminology used to label subthreshold depression (e.g. minor depression, subthreshold depression, subclinical depression and subsyndromal depression), and considerable heterogeneity around case definitions used to classify subthreshold depression (Rodriguez *et al.* 2012). Generally speaking, most case definitions of subthreshold depression involve an individual experiencing less than five depressive symptoms (out of a total nine) for a duration of at least 2 weeks (Rodriguez *et al.* 2012; Bertha & Balazs, 2013). The strictest of these is the criteria for 'minor depression' included in the DSM-IV (American Psychiatric Association, 1994). Minor depression occurs when a person experiences 2–4 depressive symptoms (one of which is a core symptom of either depressed mood or anhedonia) with duration $\geqslant$2 weeks and does not meet criteria for major depression or dysthymia.

In this review, case definitions for subthreshold depression were categorised using a nomenclature adapted from a previous review by Bertha & Balazs (2013). These case definitions, in order from most to least stringent, are: (1) meeting DSM-IV diagnostic criteria for minor depression; (2) experiencing 2–4 (out of nine) depressive symptoms; (3) experiencing 1–4 (out of nine) depressive symptoms; (4) elevated scores on a self-reported measure without a diagnosis of major depression – i.e. scoring above a cut-off on a depression rating scale, as determined by the study; and (5) some 'other' definition of subthreshold depression. Recurrent brief depression (which involves major depressive episodes occurring on a monthly basis with a duration under 2 weeks) was not included in the nomenclature as it is characterised by a distinct clinical pattern to minor depression and is not considered to be either a prodromal or residual state of major depression (Bartova & Pezawas, 2015). Dysthymia (or dysthymic disorder) was also excluded as it is a separate diagnostic entity to minor depression (American Psychiatric Association, 1994; Fava, 1999).

Search strategy

The search strategy was developed in consultation with a research librarian and adhered to guidelines described in the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement (Moher *et al.* 2009). In October 2017, we conducted a systematic search for longitudinal cohort studies using the following electronic databases: PubMed, Embase and PsychINFO. Databases were searched using a combination of MeSH/Emtree terms and text words relating to subthreshold depression and longitudinal risk studies (see online Supplementary appendix for a complete list of search terms). In addition, we used a 'snowball' search method to identify additional relevant studies based on a manual search of the reference lists of all longitudinal cohort studies included in our analysis (Erasmus University Rotterdam, 2017).

Inclusion and exclusion criteria

A longitudinal cohort study was included if: (1) it was published between January 1980, around the publication date of DSM-III, and September 2017; (2) it prospectively examined the risk of developing major depression among people with subthreshold depression – based on assessments between two or more time points with at least 1-year follow-up; (3) it used a case definition for subthreshold depression that corresponded with one from the adapted nomenclature described earlier; (4) it included a control group without subthreshold depressive symptoms at commencement; (5) it involved study participants comprising people from either the general community or primary care settings (e.g. general practice clinics or general medical outpatient clinics). Statistical non-independence was controlled for by excluding overlapping studies that reported on the same cohort. In these instances, we applied hierarchy rules to first exclude overlapping

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studies that employed a less rigorous case definition of subthreshold depression (e.g. studies using minor depression as a case definition were preferred to those using elevated scores on a depression rating scale). If overlapping studies employed similar case definitions, then we only included the study which reported greater coverage of the overall cohort sample and/or a longer follow-up period.

Data extraction

Data were extracted from longitudinal cohort studies by two authors (Y.L. and I.S.P.) and double checked against data contained in the original paper by another author (E.A.S.). A standardised data extraction template, adapted from a previous systematic review by Cuijpers & Smit (2004), was developed prior to the commencement of the review. We recorded identifying features for each study, such as author name, publication year, country, setting (i.e. community or primary care) and title/name of cohort, when available. We extracted data required to calculate the IRR of a major depressive episode among people with subthreshold depression relative to those without – i.e. the number of incident cases of major depression, sample size and the average follow-up period in both the exposed and non-exposed cohorts. We also extracted data on study design factors that were identified '*a priori*' as having a potential impact on IRR outcomes, including the (1) case definition of subthreshold depression used by the study; (2) recency of subthreshold depression (i.e. current, past year or lifetime experience of subthreshold depressive symptoms); (3) diagnostic criteria used to identify the episodes of major depression; (4) whether people with a history of major depression were excluded from the study; (5) percentage of females included in the overall sample; (6) mean age of the cohort at study commencement; (7) year in which the study commenced; (8) average length of follow-up in years; and (9) total per cent lost to follow-up. Study cohorts were further categorised into one of three age groups based on their mean age at commencement. These included 'youth' aged 0–17 years, 'adults' aged 18–64 years and the 'elderly' aged 65 years and over.

Quality assessment

We assessed the methodological quality of longitudinal cohort studies using the Newcastle–Ottawa Quality Assessment Scale for Cohort Studies (Wells *et al.* 2008), which is recommended by the Cochrane Handbook as an appropriate tool for assessing methodological quality in non-randomised studies (Higgins & Green, 2011). The Newcastle–Ottawa Scale assesses risk of bias across three domains using nine separate items: (1) the selection of respondents in the exposed and non-exposed cohorts – four items, (2) the comparability of cohorts on the basis of the design or analysis – two items and (3) the measurement of outcomes – three items. A complete description of these domains and items is provided in online Supplementary appendix.

Statistical analysis

We calculated IRRs for each study by dividing the incidence rate of major depression in the exposed cohort (i.e. people with subthreshold depression) by the incidence rate of major depression in the control cohort (i.e. non-depressed people). When data were available, we calculated the incidence rate for each respective cohort by dividing the total number of people diagnosed with major depression at follow-up by the total person-years of the cohort. If a study reported incidence proportions (i.e. the proportion of people developing major depression in each respective cohort over a given time period), then incidence rates for the exposed and control cohorts were approximated using the following formula:

$$\text{Incidence rate} = \frac{-ln\,(1-(d/N))}{t} \quad (1)$$

where: 'd' is the number of diagnosed cases of major depression, 'N' is the sample size of the cohort and 't' is the average follow-up period in years (Briggs *et al.* 2006). Resulting incidence rate estimates for the exposed and control cohorts were then used to calculate the IRR and 95% confidence intervals (CIs) (Higgins & Green, 2011).

We conducted a baseline meta-analysis to calculate an overall IRR based on the inclusion of all in-scope studies. Meta-analyses were conducted using the 'inverse variance heterogeneity' model – which calculates an estimator under the fixed-effect model assumption with a quasi-likelihood-based variance structure (Doi *et al.* 2015). The I^2 statistic was used to measure the presence of statistical heterogeneity in pooled estimates, with heterogeneity being classified as low, moderate or high based on I^2 values of 25, 50 and 75%, respectively; and the Q statistic was used to evaluate whether heterogeneity was statistically significant (Higgins & Green, 2011).

It was hypothesised '*a priori*' that pooled IRR estimates would differ on the basis of age group (youth *v.* adults *v.* the elderly) and sample type (community *v.* primary care). A subgroup analysis was subsequently conducted to investigate whether pooled IRR estimates differed between studies categorised by age group or sample type. In addition, the Q-test for heterogeneity was performed to test for differences between pooled IRR estimates calculated across subgroups.

A sensitivity analysis was conducted to determine if the baseline IRR estimate was robust to changes involving several study design factors: case definitions for subthreshold depression (minor depression *v.* other case definitions); whether people with a history of major depression were excluded from the study (yes *v.* no); the recency of subthreshold depression (current *v.* past year *v.* lifetime); the average length of follow-up (more than 5 years *v.* 5 years or less); and the total per cent lost to follow-up (⩽25% *v.* >25%). Studies that did not report on the inclusion or exclusion of people with a history of major depression were assumed not to have done so.

Funnel plots, Doi plots and the Luis Furuya–Kanamori (LFK) index were used to investigate the presence of publication bias (Higgins & Green, 2011; Onitilo *et al.* 2013). Briefly, the Doi plot is an alternative approach to the funnel plot for graphically representing publication bias – where a symmetrical triangle implies the absence of publication bias, while an asymmetrical triangle indicates possible publication bias. Likewise, the LFK index is a quantitative measure of Doi plot asymmetry, whereby a score that is within ±1 indicates 'no asymmetry', exceeds ±1 but is within ±2 indicates 'minor asymmetry' and exceeds ±2 indicates 'major asymmetry'. A guide on the application of these methods is available from the MetaXL User Guide (EpiGear, 2016). A 'trim and fill' analysis was conducted if major funnel plot asymmetry was detected in the baseline meta-analysis. This method attempts to identify and correct for publication bias by imputing a set of missing studies that would occur if funnel plot asymmetry was not present (Duval & Tweedie, 2000; Higgins & Green, 2011). These imputed study estimates are, in turn, used to calculate a

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revised set of IRR estimates that can be employed to investigate the impact of publication bias.

Meta-analyses were conducted using MetaXL 5.3, an Excel add-in developed by EpiGear International Pty Ltd (available at: http://www.epigear.com/index_files/metaxl.html). The trim and fill analysis was conducted using the 'metatrim' command in Stata 11 (StataCorp, 2009).

Results

Summary of search results

The results of the systematic review are presented in Fig. 1 (a PRISMA checklist is provided in online Supplementary appendix). Of the 126 full-text articles that were assessed for eligibility, 16 were deemed in-scope and 110 were excluded with reasons (see online Supplementary appendix for a complete list of excluded studies). A total of 67 318 participants were recruited among the 16 longitudinal studies included in the meta-analysis. There were between 133 and 34 923 participants per study, with follow-up periods ranging between 1.0 and 17.5 years.

Study design factors

Table 1 presents a summary of study design factors for the 16 cohort studies included in the meta-analysis. Of the 16 studies, six involved community-based adult samples ($n = 57\,813$) (Horwath *et al.* 1992; Bruce & Hoff, 1994; Cuijpers *et al.* 2004;

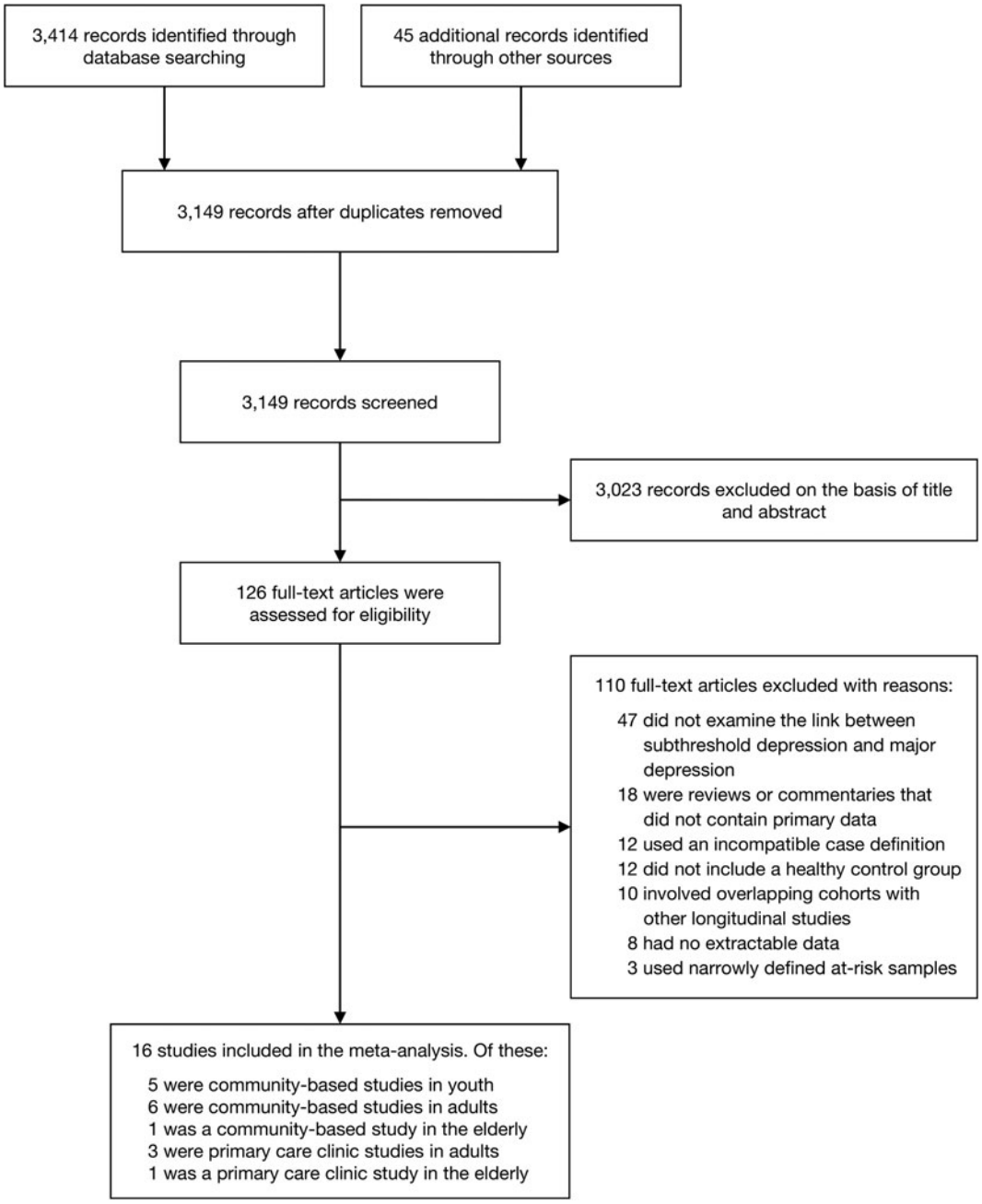

Fig. 1. PRISMA flow chart. PRISMA, Preferred Reporting Items for Systematic reviews and Meta-analyses.

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Table 1. Summary of longitudinal cohort studies included in this review

Study	Country	Description of study cohort	Sample size (n)	Per cent who are female	Mean age of the cohort at study commencement	Average length of follow-up	Loss to follow-up (%)	Case definition of subthreshold depression	Recency of subthreshold depression	Diagnostic tool used to identify MD cases	History of MD excluded?
Studies conducted in community-based youth samples											
Johnson *et al.* (2009)	USA	Children in the Community Study (CICS)	755	NR	15 years (s.d. 2.8)	12.3 years (since 1983)	2.7%	I. Meeting diagnostic criteria for minor depression	Past year	DISC-I/SCID (DSM-III/IV)	NR
Jonsson *et al.* (2011)	Sweden	Unspecified Uppsala cohort	195	77.0%	16.5 years (range 16–17)	15.1 years (since 1992)	38.5%	IV. Elevated scores on a self-reported scale (*BDI* $\geqslant$ *16*)	Current	DICA-R-A (DSM-III-R)	Yes
McLeod *et al.* (2016)	New Zealand	Christchurch Health and Development Study (CHDP)	860	50.2%	15 years (range 14–16)	17.5 years (since 1992)	21.3%	I. Meeting diagnostic criteria for minor depression	Current	CIDI (DSM-IV)	NR
Oldehinkel *et al.* (1999)	Germany	Early Development Stages of Psychopathology (EDSP) study	1128	49.6%	15.5 years (range 14–17)	1.6 years (since 1995)	12.0%	II. Having 2–4 depressive symptoms without a diagnosis of major depression	Lifetime	M-CIDI (DSM-IV)	Yes
Shankman *et al.* (2009)	USA	Oregon Adolescent Depression Project (OADP)	1198	49.3%	16.6 years (s.d. 1.2)	6.3 years (since 1988)	12.0%	I. Meeting diagnostic criteria for minor depression	Current	K-SADS/SCID (DSM-III-R/IV)	Yes
Studies conducted in community-based adult samples											
Bruce & Hoff (1994)	USA	ECA study – New Haven	3170	57.3%	58.9 years (s.d. 20.3)	1 year (since 1980)	26.5%	I. Meeting diagnostic criteria for minor depression	Lifetime	DIS (DSM-III)	Yes
Cuijpers *et al.* (2004)	The Netherlands	The Netherlands Mental Health Survey and Incidence Study (NEMESIS)	3465	49.3%	39.5 years (s.d. 12.5)	2 years (since 1996)	32.2%	I. Meeting diagnostic criteria for minor depression	Past year	CIDI (DSM-III-R)	Yes

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Forsell (2007)	Sweden	Unspecified Stockholm County cohort	7925	42.1%	39 years (s.d. 12.5)	3 years (since 1999)	21.0%	I. Meeting diagnostic criteria for minor depression	Current	MDI (DSM-IV)	NR
Horwath *et al.* (1992)	USA	ECA study – Baltimore, Durham, Los Angeles and St Louis	9900	NR	57 years (range 18–96)	1 year (since 1980)	26.8%	II. Having 2–4 depressive symptoms	Lifetime	DIS (DSM-III)	Yes
Jinnin *et al.* (2017)	Japan	Unspecified cohort of first year undergraduate students attending Hiroshima University	173	40.0%	18.3 years (s.d. 0.5)	1 year (since NR)	2.3%	IV. Elevated scores on a self-reported scale. (*BDI* ⩾ *18*)	Current	CIDI (DSM-IV)	No
Peters *et al.* (2015)	USA	National Epidemiologic Survey on Alcohol and Related Conditions (NESARC)	34 923	57.9%	47.7 years (s.d. 0.1)	3 years (since 2001)	19.0%	I. Meeting diagnostic criteria for minor depression	Lifetime	AUDADIS-IV (DSM-IV)	Yes
Studies conducted in community-based elderly samples											
Beekman *et al.* (2002)	The Netherlands	Longitudinal Aging Study Amsterdam	604	65.0%	71.8 years (s.d. 8.8)	6 years (since 1992)	38.2%	IV. Elevated scores on a self-reported scale (*CES-D* ⩾ *16*)	Current	DIS	NR
Studies conducted in primary care adult samples											
Crum *et al.* (1994)	USA	ECA study – Baltimore, Durham and Los Angeles	4012	53.5%	42.6 years (range 18–65+)	1 year (since 1982)	32.9%	II. Having 2–4 depressive symptoms	Past year	DIS (DSM-III)	No
Jackson *et al.* (2007)	USA	Primary Care Evaluation of Mental Disorders (PRIME-MD)	394	51.8%	54.7 years (range NR)	5 years (since 1995)	22.6%	I. Meeting diagnostic criteria for minor depression	Current	PRIME-MD (DSM-IV)	Yes
Wagner *et al.* (2000)	USA	Unspecified cohort attending Duke University Health Service	133	72.2%	36.8 years (s.d. 1.44)	1 year (since 1991)	13.6%	I. Meeting diagnostic criteria for minor depression	Past year	DIS	No

(*Continued*)

Table 1. (*Continued.*)

Study	Country	Description of study cohort	Sample size (n)	Per cent who are female	Mean age of the cohort at study commencement	Average length of follow-up	Loss to follow-up (%)	Case definition of subthreshold depression	Recency of subthreshold depression	Diagnostic tool used to identify MD cases	History of MD excluded?
Studies conducted in primary care elderly samples											
Lyness *et al.* (2002)	USA	Unspecified cohort from three private internal medicine offices and a university family medicine clinic	225	58.0%	71.1 years (S.D. 7.5)	1 year (since 1995)	19.0%	I. Meeting diagnostic criteria for minor depression	Current	SCID	No

AUDADIS-IV, Alcohol Use Disorder and Associated Disabilities Interview Schedule; BDI, Beck Depression Inventory, DSM-IV version; CES-D, Center for Epidemiologic Studies Depression Scale; CIDI, Composite International Diagnostic Interview; DICA, Diagnostic Interview for Children and Adolescents; DIS, Diagnostic Interview Schedule; DISC, Diagnostic Interview Schedule for Children; DSM-III, Diagnostic and Statistical Manual of Mental Disorders, Third edition; DSM-III-R, Diagnostic and Statistical Manual of Mental Disorders, Third edition, Revised; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, Fourth edition; ECA, Epidemiologic Catchment Area study; K-SADS, Kiddie Schedule for Affective Disorders and Schizophrenia; MD, major depression; MDI, Major Depression Inventory; NR, not reported; PRIME-MD, Primary Care Evaluation of Mental Disorders; SCID, Structured Clinical Interview for DSM-IV Disorders; S.D., standard deviation

Forsell, 2007; Peters *et al.* 2015; Jinnin *et al.* 2017), five involved community-based youth samples ($n = 4136$) (Oldehinkel *et al.* 1999; Johnson *et al.* 2009; Shankman *et al.* 2009; Jonsson *et al.* 2011; McLeod *et al.* 2016), three involved primary care adult samples ($n = 4540$) (Crum *et al.* 1994; Wagner *et al.* 2000; Jackson *et al.* 2007), one involved a community-based elderly sample ($n = 604$) (Beekman *et al.* 2002) and one involved a primary care elderly sample ($n = 225$) (Lyness *et al.* 2002). The average starting age of study participants ranged between 15.0 and 16.6 years in youth samples, 18.3 and 58.9 years in adult samples and 71.1 and 71.8 in elderly samples. In addition, studies reported a range between 40.0% and 77.0% of participants being female. Most studies commenced follow-up in the 1980s or early 1990s and the follow-up period ranged between 1.0 and 17.5 years with a mean of 4.9 years (S.D. 5.4). All studies were conducted in high-income countries (USA, $n = 9$; the Netherlands, $n = 2$; Sweden, $n = 2$; Germany, $n = 1$; Japan, $n = 1$; and New Zealand, $n = 1$).

Of the 16 studies, 10 used a case definition corresponding with the diagnostic criteria for minor depression (Bruce & Hoff, 1994; Wagner *et al.* 2000; Lyness *et al.* 2002; Cuijpers *et al.* 2004; Forsell, 2007; Jackson *et al.* 2007; Johnson *et al.* 2009; Shankman *et al.* 2009; Peters *et al.* 2015; McLeod *et al.* 2016), three involved experiencing 2–4 depressive symptoms (Horwath *et al.* 1992; Crum *et al.* 1994; Oldehinkel *et al.* 1999) and three involved having elevated scores on a depression rating scale (Beekman *et al.* 2002; Jonsson *et al.* 2011; Jinnin *et al.* 2017). Most studies ($N = 15$) used structured clinical interviews that identified cases of major depression based on DSM-III or DSM-IV criteria (Horwath *et al.* 1992; Bruce & Hoff, 1994; Crum *et al.* 1994; Oldehinkel *et al.* 1999; Wagner *et al.* 2000; Beekman *et al.* 2002; Lyness *et al.* 2002; Cuijpers *et al.* 2004; Jackson *et al.* 2007; Johnson *et al.* 2009; Shankman *et al.* 2009; Jonsson *et al.* 2011; Peters *et al.* 2015; McLeod *et al.* 2016; Jinnin *et al.* 2017), with one study by Forsell (2007) using a self-report questionnaire to identify cases of major depression that meet DSM-IV diagnostic criteria.

Quality assessment

We found that the risk of selection bias among exposed and non-exposed cohorts was low-to-moderate. The majority of studies ($N = 12$) had exposed cohorts that were highly representative of people with subthreshold depression in the community. All studies ($N = 15$) had non-exposed cohorts that were drawn from the same community as the exposed cohort. Similarly, the majority of studies ($N = 14$) used structured interviews to ascertain the exposure (i.e. subthreshold depression) rather than relying on written self-report. Half of the studies ($N = 8$) did not explicitly exclude participants with a history of major depression.

When assessing the comparability of cohorts on the basis of the design or analysis, we found that most studies ($N = 12$) did not control for previous treatments, while, conversely, most studies ($N = 11$) did control for the presence of other mental disorders.

When assessing risk of bias in the measurement of outcomes, we found that most studies ($N = 14$) used structured interviews rather than self-report to assess depression outcomes, and as per the inclusion criteria, all studies ($N = 15$) had a follow-up period of >1 year. Conversely, there was a moderate risk of bias when measuring outcomes due to seven studies having a follow-up rate that was <75% of the starting sample. Detailed risk of bias assessments are presented in online Supplementary appendix.

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Baseline meta-analysis

Baseline meta-analysis results are shown in Fig. 2, with a summary of underlying input data provided in online Supplementary appendix. Overall, the pooled IRR of major depression among those with subthreshold depression (16 studies, $n = 67\,318$) was 1.95 (95% CI 1.28–2.97). Considerable statistical heterogeneity ($I^2 > 75\%$) was detected in the baseline meta-analysis (see Fig. 2). Two of the studies comprised IRR estimates with very wide confidence intervals due to the occurrence of zero cases of major depression in the control cohorts (Wagner *et al.* 2000; Jinnin *et al.* 2017).

Subgroup and sensitivity analyses

The subgroup analysis resulted in pooled IRR estimates that were not statistically different across age group or sample type (see Table 2). Point estimates were observed to be lower for studies comprising community-based samples (12 studies, $n = 62\,553$) with an IRR of 1.90 (95% CI 1.22–2.94), when compared with studies comprising primary care samples (four studies, $n = 4765$) with an IRR of 3.27 (95% CI 1.71–6.28). However, the *Q*-test for heterogeneity did not suggest a statistically significant difference between these two IRR estimates because the uncertainty around these estimates was large. Sensitivity analysis results are also presented in Table 2. These results demonstrated that IRR estimates were robust to changes in selection criteria, although there was some attenuation of point estimates when minor depression was used as the case definition, when study participants with a history of major depression were excluded or when studies analysed lifetime recency of subthreshold depression.

Analysis of publication bias

Funnel and Doi plots depicting publication bias in the baseline meta-analysis are presented in Fig. 3. We detected major asymmetry (LFK index: 5.02) in the baseline meta-analysis with plots indicating a potential under-representation of negative studies and the presence of bias towards the selective publication of positive studies. A trim and fill analysis was conducted on all 16 studies included in the baseline meta-analysis, which produced an adjusted IRR of 1.74 (95% CI 1.12–2.69). These results suggest that the IRR may be somewhat overstated in this study, but that IRR estimates remain significantly positive even after correcting for funnel plot asymmetry due to potential publication bias. Additional results for the trim and fill analysis are presented in online Supplementary appendix.

Discussion

Summary of main findings

This study found that people with subthreshold depression were approximately two times more likely than non-depressed people to develop major depression. This result was mostly robust to sensitivity analyses. For example, similar IRR estimates were observed when comparing studies comprising different case definitions, follow-up periods and rates of attrition. Furthermore, subgroup

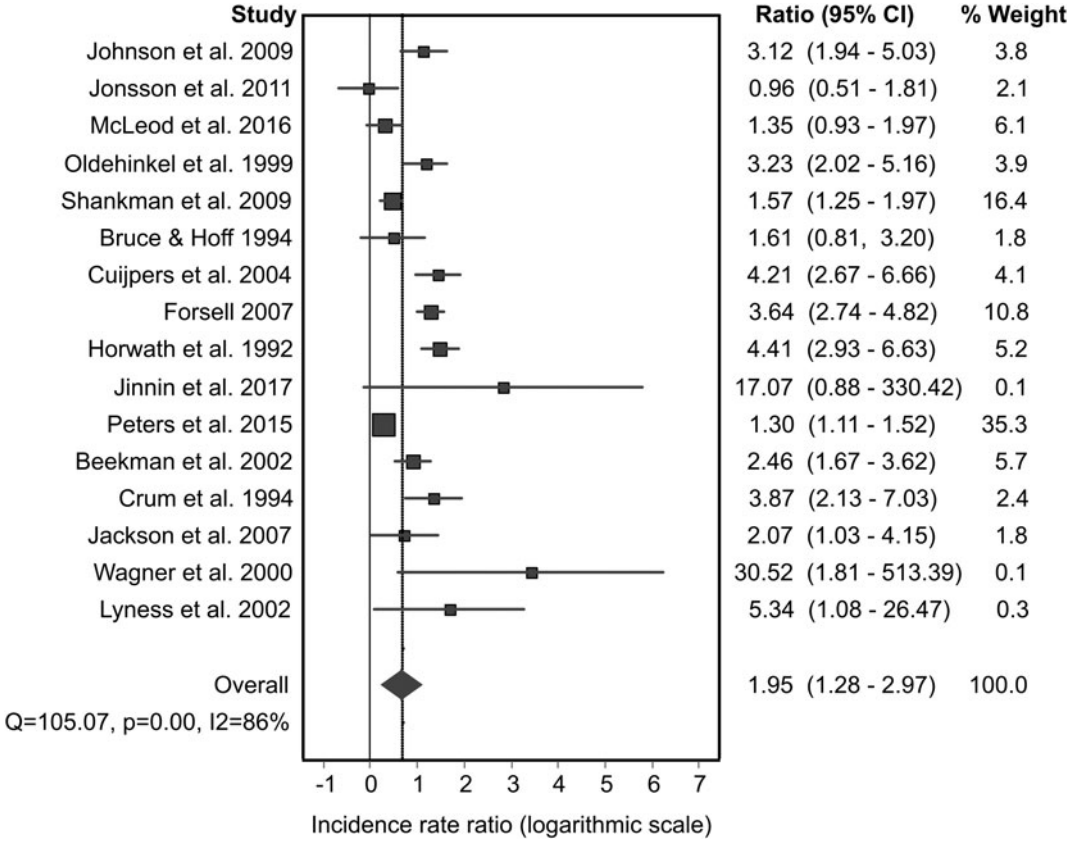

Fig. 2. Forest plot for the baseline meta-analysis calculating the pooled incidence rate ratio of developing major depression among people with subthreshold depression.

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Table 2. Results of the subgroup and sensitivity analyses

Analysis and variable	Studies (*n*)	Participants (*N*)	Incidence rate ratio (95% CI)	Cochran's *Q* (*p* value)	I^2 statistic (95% CI)
***Subgroup analysis* (*by predefined subgroup*)**					
Age group					
Youth samples	5	4136	1.75 (1.10–2.76)	18.4 (<0.01)	78%
Adult samples	9	62 353	2.01 (0.91–4.43)	81.8 (<0.01)	90%
Elderly samples	2	829	1.95 (1.28–2.97)	105.1 (<0.01)	86%
Test for subgroup differences: $\chi^2 = 0.149$, df = 2, $p = 0.928$					
Sample type					
Community-based samples	12	62 553	1.90 (1.22–2.94)	94.5 (<0.01)	88%
Primary care samples	4	4765	3.27 (1.71–6.28)	4.7 (0.19)	37%
Test for subgroup differences: $\chi^2 = 1.837$, df = 1, $p = 0.175$					
***Sensitivity analysis* (*by study design factor*)**					
Case definition					
Minor depression	10	53 049	1.76 (1.08–2.87)	68.3 (<0.01)	87%
Other case definition	6	14 269	2.92 (1.82–4.68)	18.9 (<0.01)	74%
History of major depression excluded?					
Yes	8	52 630	1.69 (0.97–2.93)	58.5 (<0.01)	88%
No	8	14 688	2.75 (1.78–4.25)	24.3 (<0.01)	71%
Recency of subthreshold depression					
Current	7	10 714	2.15 (1.27–3.62)	30.5 (<0.01)	80%
Past year	5	9226	2.58 (1.39–4.81)	21.1 (<0.01)	81%
Lifetime	4	47 378	1.63 (0.58–4.52)	39.1 (<0.01)	92%
Average length of follow-up					
More than 5 years	5	3612	1.72 (1.18–2.52)	14.8 (0.01)	73%
5 years or less	11	63 706	2.07 (1.02–4.23)	86.9 (<0.01)	88%
Per cent lost to follow-up					
⩽25%	10	47 715	1.75 (1.08–2.84)	62.9 (<0.01)	86%
>25%	6	19 603	2.90 (1.83–4.61)	22.7 (<0.01)	78%

95% CI, 95% confidence interval; df, degrees of freedom; N/A, not applicable; *p*, *p* value.

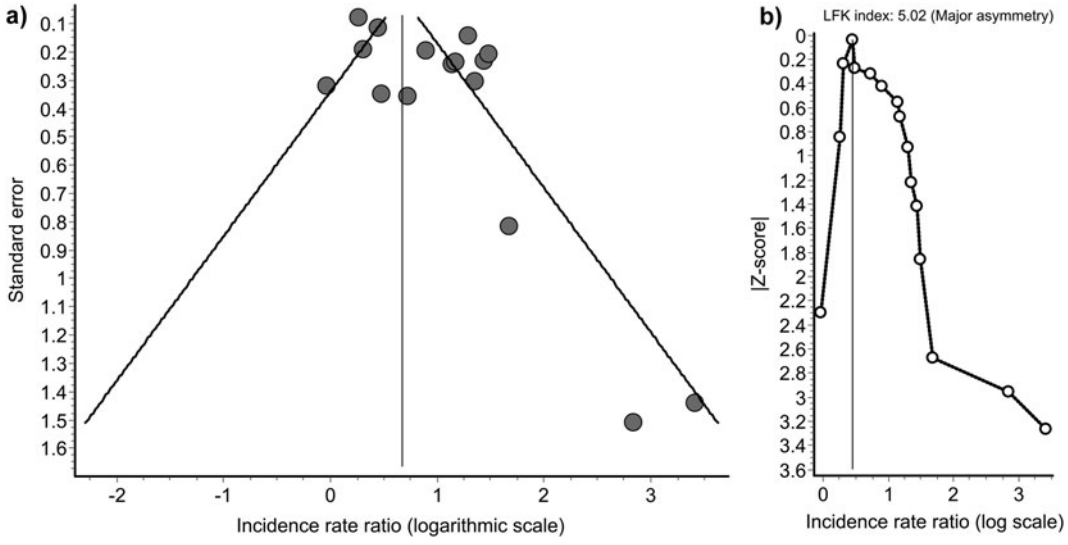

Fig. 3. Depiction of publication bias in the baseline meta-analysis using the: (*a*) funnel plot; and (*b*) Doi plot.

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analyses did not suggest a statistically significant difference of IRR estimates between studies comprising different age groups or sample types.

Comparison with previous systematic reviews

Previous systematic reviews have relied on narrative syntheses to demonstrate that subthreshold depression is a risk factor for developing major depression among adults (Cuijpers & Smit, 2004; Hermens *et al.* 2004), youth (Bertha & Balazs, 2013; Wesselhoeft *et al.* 2013) and the elderly (Meeks *et al.* 2011). Our study has built upon these findings by calculating a pooled outcome measure that quantifies, with uncertainty, the likely magnitude of this risk factor. Furthermore, our study demonstrates that the association between subthreshold depression and the future risk of major depression has a high probability of being positive even after accounting for different sources of study heterogeneity. Lastly, our systematic review identified one new study conducted in youth (McLeod *et al.* 2016) and five new adult studies (Crum *et al.* 1994; Forsell, 2007; Jackson *et al.* 2007; Peters *et al.* 2015; Jinnin *et al.* 2017) to supplement those compiled by previous systematic reviews examining the link between subthreshold depression and major depression (Cuijpers & Smit, 2004; Hermens *et al.* 2004; Bertha & Balazs, 2013; Wesselhoeft *et al.* 2013).

Implication of findings

The findings of this meta-analysis have several clinical and research implications. First, these findings provide evidence to support scaling up indicated prevention interventions for people with subthreshold depression. Indicated prevention interventions that conduct screening and subsequently provide brief psychological therapy to people with subthreshold depression have been shown to be effective in both schools (Merry *et al.* 2011; Stockings *et al.* 2016) and primary care clinics (Willemse *et al.* 2004; van Zoonen *et al.* 2014). It is, however, important to ensure that people who experience normal, self-remitting depressive symptoms are not subjected to unnecessary treatments that are burdensome and/or stigmatising (Dowrick & Frances, 2013; Davidson *et al.* 2015). Further studies are needed to investigate the impacts of scaling up the provision of indicated prevention interventions in the population, alongside the trade-off between benefits *v.* harms. Quantitative estimates produced by this study will be a useful data source for epidemiologic and health economic models conducted in the future (Lee *et al.* 2017). Second, positive IRRs among youth, adults and the elderly provide evidence for preventive interventions to be made available across the life course. Intervening early in the life course of an individual could have flow-on benefits in both preventing a first episode of depression and, in turn, reducing the risk of recurrence later in life (Allen *et al.* 2007). Statistically significant IRRs were also observed in studies comprising community-based samples and primary care samples, a finding that supports the merits of delivering preventive interventions across both settings. Third, the results of this study highlight the benefits of using a shorter period of recency when identifying people with subthreshold depression to reduce the risk of recall bias.

Limitations

There are several limitations in this study. First, we detected publication bias among included studies. This may bias results upwards, though the findings of the trim and fill analysis suggest that subthreshold depression remains a significant risk factor even after adjusting for funnel plot asymmetry. Second, fewer studies were included in this meta-analysis compared with previous systematic reviews due to the adoption of a strictly defined case definition and the exclusion of studies with either overlapping cohorts or at-risk samples (e.g. hospital patients with a chronic physical condition). These inclusion/exclusion criteria reflect a trade-off between increasing the robustness of pooled estimates by excluding heterogeneous studies *v.* decreasing the external validity of findings by restricting the analysis to a particular set of subjects.

Conclusions

Despite considerable heterogeneity across studies, we calculated a pooled IRR estimate denoting the increased risk of major depression among people with subthreshold depression relative to those without. The findings of this study provide evidence to support the scaling up of effective indicated prevention interventions for people experiencing subthreshold depression, regardless of age and setting.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S0033291718000557

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Conflict of interest. None.

Ethical standards. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

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