APPENDIX 2. DESIGN, METHODS AND CONCLUSIONS OF THE INCLUDED REVIEWS[a,b]

[a]Presented in reverse chronological order, sorted by outcome or study design
[b]Limitations and conclusions as reported by the authors of each review

Q1. Which treatment therapy or method for depression is more successful for long-term remission or recovery?

Study and design	Participants	Methods	Limitations	Conclusions
Inducing remission in patients with depression				
Agency for Healthcare Research and Quality (AHRQ) comparative effectiveness review				
Gartlehner 2015 SR and meta-analysis	n = 606 adults with depression undergoing first-step therapy, from 5 RCTs (follow up: 4 to 52 weeks).	Meta-analysis of RCTs comparing the effects of SGAs and CBT or combination therapy (SGAs and CBT); included studies published up to January 2015.	Potential for publication bias and selective outcome reporting; few RCTs and small sample sizes; available evidence is mainly at high risk of bias; low strength of evidence.	No significant difference in rates of remission between patients treated with SGAs or CBT (RR 0.98, 95% CI 0.73 to 1.32); adding CBT to SGA did not show any beneficial effect (RR 1.06, 95% CI 0.82 to 1.38).
Gartlehner 2015 SR and meta-analysis	n = 174 adults with depression undergoing first-step therapy, from 2 RCTs (follow up: 8 to 24 weeks).	Meta-analysis of RCTs comparing the effects of SGAs and IPT or combination therapy (SGAs and IPT); included studies published up to January 2015.	Potential for publication bias and selective outcome reporting; few RCTs and small sample sizes; available evidence is mainly at high risk of bias; low strength of evidence.	No significant difference in rates of remission between patients treated with SGAs or IPT (RR 0.92, 95% CI 0.78 to 1.08). The combination of SGAs and IPT had 25% higher remission rates than SGAs alone (no pooled data).
Gartlehner 2015 SR and meta-analysis	n = 51 adults with depression undergoing first-step therapy, from 1 RCT (follow up: 8 weeks).	Meta-analysis of RCTs comparing the effects of SGAs and PSYD; included studies published up to January 2015.	Potential for publication bias and selective outcome reporting; only one available RCT; low strength of evidence.	No significant difference in rates of remission between patients treated with SGAs or short-term (2 to 4 months) PSYD (RR 1.04, 95% CI 0.58 to 1.86).
Gartlehner 2015 SR and meta-analysis	n = 243 adults with depression undergoing first-step therapy, from 2 RCTs (follow up: 16 to 49 weeks).	Meta-analysis of RCTs comparing the effects of SGAs and third-wave CBT; included studies published up to January 2015.	Potential for publication bias and selective outcome reporting; few RCTs and small sample sizes; available evidence is mainly at high risk of bias; inadequate evidence to draw conclusions.	There was insufficient evidence to draw conclusions about rates of remission for patients treated with SGAs compared to third-wave CBT (RR 0.57, 95% CI 0.44 to 0.74).
Gartlehner 2015 SR	n = 122 adults with depression undergoing second-step therapy, from 1 RCT (follow up: 14 weeks).	Systematic review of RCTs comparing the effects of switching from a SGA to a new SGA or to CT; included studies published up to January 2015.	Potential for publication bias and selective outcome reporting; only one available RCT; low strength of evidence.	No significant difference in rates of remission between patients who switched to a new SGA compared to CT (27.9 vs. 25.0%, P = 0.69).

Study and design	Participants	Methods	Limitations	Conclusions
Gartlehner 2015 SR	n = 182 adults with depression undergoing second-step therapy, from 1 RCT (follow up: 14 weeks).	Systematic review of RCTs comparing the effects of augmenting SGA therapy with another SGA or with CT; included studies published up to January 2015.	Potential for publication bias and selective outcome reporting; only one available RCT; low strength of evidence.	No significant difference in rates of remission between patients whose SGA treatment was augmented with another SGA compared to with CT (33.3 vs. 23.1%, P = 0.20).
Cochrane systematic review				
Cox 2014 SR and meta-analysis	n = 48 adolescents (12 to 18 years) with depression without co-morbid conditions, from 1 RCT (follow up: 6 months).	Meta-analysis of RCTs comparing the effects of CBT and SSRIs; included RCTs published up to June 2014.	Only one included RCT with a small sample size; included study was at high risk of bias.	It was not possible to draw robust conclusions, nor to establish whether SSRIs or CBT was most effective (OR 0.83, 95% CI 0.27 to 2.60).
Cox 2014 SR and meta-analysis	n = 203 adolescents (12 to 18 years) with depression without co-morbid conditions, from 2 RCTs (follow up: 6 to 9 months).	Meta-analysis of RCTs comparing the effects of SSRIs and combination therapy (CBT and SSRIs); included RCTs published up to June 2014.	Only two included RCTs with small sample sizes; included studies were at high risk of bias.	It was not possible to draw robust conclusions, nor to establish whether SSRIs or combination therapy was most effective (OR 1.93, 95% CI 0.93 to 4.00).
Cox 2014 SR and meta-analysis	n = 152 adolescents (12 to 18 years) with depression without co-morbid conditions, from 1 RCT (follow up: 12 months).	Meta-analysis of RCTs comparing the effects of SSRIs and combination therapy (CBT and SSRIs); included RCTs published up to June 2014.	Only one included RCT with a small sample size; included study was at high risk of bias.	It was not possible to draw robust conclusions, nor to establish whether SSRIs or combination therapy was most effective (OR 0.49, 95% CI 0.14 to 1.69).
Cox 2014 SR and meta-analysis	n = 47 adolescents (12 to 18 years) with depression without co-morbid conditions, from 1 RCT (follow up: 6 months).	Meta-analysis of RCTs comparing the effects of CBT and combination therapy (CBT and SSRIs); included RCTs published up to June 2014.	Only one included RCT with a small sample size; included study was at high risk of bias.	It was not possible to draw robust conclusions, nor to establish whether CBT or combination therapy was most effective (OR 2.55, 95% CI 0.78 to 8.36).
Cox 2014 SR and meta-analysis	n = 56 adolescents (13 to 19 years) with depression without co-morbid conditions, from 1 RCT (follow up: 12 months).	Meta-analysis of RCTs comparing the effects of combination therapy (CBT and SSRIs) and CBT plus placebo; included RCTs published up to June 2014.	Only one included RCT with a small sample size; included study was at high risk of bias.	It was not possible to draw robust conclusions, nor to establish whether combination therapy or CBT plus placebo was most effective (OR 1.20, 95% CI 0.29 to 5.02).
Other reviews				

Study and design	Participants	Methods	Limitations	Conclusions
Farah 2016 Umbrella SR	n = 7,455 adults with depression, from 69 RCTs located in 7 SRs (follow up: not reported).	Umbrella review of RCTs comparing the effects of ADM and alternative therapies; included RCTs were identified from SRs published up to February 2016.	Results are restricted to the reporting quality and rigour of existing SRs; risk of bias in included studies; between-study heterogeneity in interventions, patients, measurement scales, and follow up length; publication bias.	No significant difference in remission rate between CBT and ADM (RR 0.94, 95% CI 0.81 to 1.09), interpersonal therapy (RR 1.03, 95% CI 0.78 to 1.37), or psychotherapy (RR 0.99 95% CI 0.30 to 10.12).
Weitz 2015 Independent patient data meta-analysis	n = 1,700 adults with depression (all outpatients), from 16 RCTs (follow up: 8 to 20 weeks).	Independent patient data meta-analysis comparing the effects of ADM and CBT; patient data were retrieved from RCTs published up to January 2014.	Outcome measurement scales are prone to bias and have psychometric flaws; included studies may not be representative; quality of some included studies was sub-optimal; inpatients were excluded.	No significant difference in remission between patients treated with ADM or CBT (OR 1.18, P = 0.22); no significant difference in remission between treatments as a function of depression severity (OR 1.00, P = 0.93).
Trivedi 2009 SR	n = 467 adults with treatment-resistant depression, from 12 publications of 5 RCTs (follow up: 8 to 104 weeks).	Systematic review of RCTs comparing the effects of psychotherapy (DBT or CT) and ADM continuation, augmentation, or switch; included studies published up to 2009.	Most studies were underpowered to detect moderately large treatment effects; between-study heterogeneity in study designs and patient populations; limited number of good trials.	Evidence examining the effect of psychotherapy as augmentation or substitute therapy in resistant depression is sparse and reveals mixed results. Psychotherapy appears to be an equally effective treatment compared to ADM.
de Maat 2007 SR and meta-analysis	n = 903 adults with depression (all outpatients), from 7 RCTs (follow up: 8 to 20 weeks).	Meta-analysis of RCTs comparing the effects of psychotherapy and combination therapy (psychotherapy and ADM); included studies published up to 2005.	Analysis included few studies of mixed methodological quality; some studies had small sample sizes, limiting statistical power; evidence for chronic depression is limited to 1 RCT; between-study heterogeneity in treatments; study-level biases in patient selection.	Remissions rates were significantly higher for patients treated with combined therapy compared to psychotherapy alone (OR 1.59, 95% CI 1.22 to 2.09). The superiority of combined therapy was not demonstrated for non-chronic or mild depression.
Preventing relapse for patients in remission from depression				
Cochrane systematic review				
Cox 2012 SR and meta-analysis	n = 46 children or adolescents (11 to 18 years) in remission from depression, from 1 RCT (follow up: 24 weeks).	Meta-analysis of RCTs comparing the effects of SSRIs and combination therapy (SSRIs and CBT); included RCTs published up to June 2011.	Only one included RCT with a small sample size; included study was at high risk of bias.	There was a greater rate of relapse in patients who received ADM alone compared to combination therapy, but the difference was not statistically significant (OR 0.26, 95% CI 0.05 to 1.15).
Other reviews				

Study and design	Participants	Methods	Limitations	Conclusions
Biesheuvel-Leliefeld 2015 SR and meta-analysis	n = 914 adults aged 18 to 64 years in remission from depression, from 13 RCTs (average follow up: 90 weeks).	Meta-analysis of RCTs comparing the effects of ADM and psychological interventions (CBT, MBCT, or IPT); included RCTs published up to May 2014.	Low quality of evidence from the included studies; between-study heterogeneity in definitions (relapse, recovery, remission, and recurrence), type and duration of interventions.	The risk for relapse was significantly less for patients treated with ADM compared to those treated with psychological interventions (RR 0.83, 95% CI 0.70 to 0.97).
Guidi 2011 SR and meta-analysis	n = 875 adult patients in remission from depression, from 8 RCTs (follow up: 28 weeks to 6 years).	Meta-analysis of RCTs comparing the effects of psychotherapy and continuation of ADM following remission from depression; included RCTs published up to December 2008.	Sample sizes and number of studies were too small for definitive conclusions to be drawn; between-study heterogeneity in length of follow up and duration of treatments, and in control conditions.	The sequential administration of psychotherapy after response to acute-phase pharmacotherapy, either alone or in combination with ADM, may play a role in reducing relapse and recurrence (sequential psychotherapy with or without ADM, RR 0.80, 95% CI 0.66 to 0.96; psychotherapy + ADM discontinuation, RR 0.65, 95% CI 0.46 to 0.91)
Piet 2011 SR and meta-analysis	n = 177 adults in remission from recurrent depression, from 2 RCTs (follow up: 15 to 18 months).	Meta-analysis of RCTs comparing the effects of MBCT and ADM; included RCTs published up to November 2010.	Only two included RCTs with small sample sizes.	Although more studies are needed for firm conclusions, results from two studies suggest that MBCT is at least comparable to maintenance ADM for effective relapse prevention of recurrent depression (RR 0.80, 95% CI 0.60 to 1.08).
Chiesa 2010 SR and meta-analysis	n = 326 adults with depression, from 4 RCTs (follow up: up to 1 year).	Meta-analysis of RCTs comparing the effects of MBCT, TAU (including ADM), and combination therapy (MBCT and TAU); included RCTs published up to July 2010.	Low quality of some of the included studies; risk of bias in the included studies due to inability to blind the participants to treatment allocation and inadequate randomisation details; small samples sizes of included studies.	Augmentation of MBCT to TAU could result in significantly lower relapse or recurrence rates compared to TAU alone (including ADM) (OR 0.30, 95% CI 0.17 to 0.56); MBCT with gradual discontinuation of ADM was not significantly different from continuation ADM (OR 0.61, 95% CI 0.30 to 1.25; 1 RCT).

The reviews by Gartlehner (2015) and Cox (2014) reported on multiple comparisons, and we presented these in separate rows.
ADM: antidepressant medication; CBT: cognitive behavioural therapy; CT: cognitive therapy; DBT: dialectical behaviour therapy; IPT: interpersonal psychotherapy; MBCT: mindfulness-based cognitive therapy; PSYD: psychodynamic therapy; RCT: randomised controlled trial; SGA: second-generation antidepressant; SR: systematic review; SSRI: selective serotonin reuptake inhibitor; TAU: treatment as usual

Q2. What are the long-term physical implications of pharmacotherapy for treating depression?

Study and design	Participants	Methods	Limitations	Conclusions
Reviews: bone mineral density and fracture				
Gebara 2014 Systematic review	n = 92,056 older adults (>60 y) from 18 studies (19 articles), follow-up NR.	Narrative synthesis of primary studies of older adults with a sample size ≥100 that assessed the association between SSRI or SNRI use and bone mineral density.	Inconsistency in the available data from primary studies; lack of controlling for confounders; no experimental studies found.	There is little evidence to support causation between SSRI or SNRI use and a decrease in bone mineral density.
Wu 2013 Systematic review	n = 313,748 adults from 13 studies with mean follow-up of 4.1 to 8.4 y (cohort studies).	Meta-analysis of case-control and cohort studies that assessed the association between SSRI use and bone mineral density and fracture risk published up to March 2011.	Some sources of heterogeneity could not be assessed; lack of controlling for confounders.	Current use of SSRIs is associated with an increased risk of fractures which may be independent of depression and bone mineral density (RR: 1.45, 95% CI: 1.31-1.60). Subgroup analysis showed increased risk for current but not former users.
Eom 2012 Systematic review	n = >906,446 adults from 12 studies with a follow-up of 1 to 13 y.	Meta-analysis of case-control and cohort studies that assessed the association between SSRI use and incident bone fractures published up to October 2010.	Lack of information regarding potential confounding variables in the primary studies; all studies were from Western countries.	Use of SSRIs to treat depression in the elderly may increase the odds of incident fracture (OR: 1.69, 95% CI: 1.51, 1.90). Subgroup analysis showed decreased strength of association with a longer window of administration before the index date.
Wu 2012 Systematic review	n = 269,381 adults from 12 studies with mean follow-up of 4.1 to 10 y (cohort studies).	Meta-analysis of case-control and cohort studies that assessed the association between TCA use and bone mineral density and fracture risk published up to August 2010.	Lack of information on falls; lack of controlling for confounders in the primary studies.	The use of TCAs is associated with a moderate increased risk of incident fractures, which may be independent of depression and bone mineral density (RR: 1.72, 95% CI: 1.51-1.95).
Wu 2010 Systematic review	n = 148,776 adults from 14 studies with mean follow-up of 1 to 22 y.	Meta-analysis of prospective cohort studies that assessed the effects of depression on risk of fracture or bone loss published up to July 2009.	Small number of studies with heterogeneity in outcomes and tools to measure depression; poor reporting; lack of controlling for confounders in the primary studies.	Depression is associated with an increased risk of incident fracture and bone loss, which may be mediated by antidepressant use; the HR for fracture was higher in studies that did not adjust for antidepressant use (HR: 1.30, 95% CI: 1.11-1.52, n = 14,777) vs. those that did (HR: 1.05; 95% CI: 0.86-1.29, n = 93,380).
Reviews: diabetes				
Rotella 2013 Systematic review	n = 424,557 adults from 23 studies with a mean follow-up of 2.8 to 34 y.	Meta-analysis of case-control and cohort studies that assessed the difference in risk of incident diabetes between those with and without symptoms of depression.	Heterogeneity in methods to diagnose depression and diabetes; heterogeneity in confounders included across primary studies.	Both depression (OR: 1.56, 95% CI: 1.37-1.77) and use of ADMs (OR: 1.68, 95% CI: 1.17-2.40) among those with depression are associated with an increased odds of incident diabetes.
Reviews: physical diseases (general)				

Correll 2015 Review (non-systematic)	NR	Narrative synthesis of studies that assessed the relationship between the use of antipsychotics, mood stabilizers, or ADMS and physical illness (both short- and long-term).	Review allows for little differentiation between studies of both short- and long-term adverse events; few details on included study characteristics provided.	There is some evidence to associate certain AMDs with mild to modest weight gain, incident diabetes, hypothyroidism (lithium), cardiovascular adverse events, sudden cardiac death, hepatotoxicity, nephrotoxicity, seizure disorders and fractures. There was no evidence of association with breast cancer.
Observational studies: cardiovascular risk factors				
Perez-Pinar 2016 Retrospective cohort	n = 524,952 adults aged ≥30 years from 140 primary care practices in east London, UK.	Medical and prescription records were reviewed for a 10 year period (2005-2015) and Cox regression models were used to estimate associations between use ADMs before 2005 and cardiovascular risk factors over the next 10 years.	Results might be affected by confounding variables; lack of information on ADM compliance or dosage; dichotomisation of continuous outcomes led to loss of data.	An independent association was observed between ADM prescriptions and risk of incident type 2 diabetes (HRs from 1.28, 95% CI: 1.23-1.33 to 1.35, 95% CI: 1.04-1.15), hypertension (HRs from 1.09, 95% CI: 1.05–1.12 to 1.11, 95% CI: 1.07–1.14), and hyperlipidemia (HRs 1.05, 95% CI: 1.03–1.07 to 1.12, 95% CI: 1.10–1.14).
Rubin 2013 Prospective cohort embedded within a RCT	n = 5,145 adults in the Look AHEAD weight loss RCT followed at 16 clinical centres in the US.	Patients in the Look AHEAD trial assessed yearly over 4 y for ADM exposure and cardiovascular risk factors; the relationship between ADM use in the past year and cardiovascular risk factors was assessed.	Observational design (cannot draw causal inferences); did not study a comprehensive array of cardiovascular risk factors; no information on dose or duration of treatment.	Both depression symptoms and use of ADMs during the prior year were associated with current elevated cardiovascular risk factors including adverse blood cholesterol changes, serum triglycerides, diastolic blood pressure, and obesity (variable by treatment arm, but reasons were not assessed).
Observational studies: hepatocellular carcinoma				
Pocha 2014 Retrospective cohort	n = 109,736 adults with HCV who entered the US Veterans Affairs HCV Clinical Case Registry in 2000-2009.	Medical and prescription records were extracted from the US Veterans Affairs HCV Case Registry and Cox regression models were used to estimate associations between ADM use and incident hepatocellular carcinoma.	All participants were veterans and most were male; cannot exclude association at larger doses; data on development of cirrhosis during the study period was not available (confounding).	The data from this large cohort of HCV patients does not support the hypothesis that SSRI exposure increases the risk of developing hepatocellular carcinoma for the highest observed average daily dose and for exposures between 6 and >30 months.

HCV: hepatitis C virus; HR: hazard ratio; NR: not reported; ns: not statistically significant; OR: odds ratio; RCT: randomised controlled trial; RR: risk ratio; SNRI: serotonin norepinephrine reuptake inhibitor; SSRI: selective serotonin reuptake inhibitor; TCA: tricyclic antidepressant; UK: United Kingdom; US: United States; y: years

Q3a. For various non-pharmacological treatment options, what are the advantages in terms of cost?

Study and design	Participants	Intervention (I) & comparator (C)	Methods	Limitations	Conclusions
Any psychotherapy					
Systematic Reviews					
Karyotaki 2016 Systematic review	n=477 individuals (age NR) from 3 RCTs with moderate or severe major depressive disorder.	I: any treatment C: any other treatment or control	Review of RCTs on cost-effectiveness of any treatment vs. any other type of treatment (e.g., psychological, pharmacological, treatment as usual) for common mental disorders published up to December 2014 .	Heterogeneity across studies limited the development of robust conclusions; individual study results may not be generalizable to other countries.	There was no difference in QALY gains for CBT- or psychologist enhanced-PEP vs. PEP alone over 36 months; at a willingness-to-pay >USD 405/depression-free day, CBT-enhanced PEP was the most cost-effective. There was no difference in costs for SPD vs. SSFT over 12 months.
Bower 2011 Cochrane systematic review	n=197 adults from one RCT diagnosed with depression or mixed depression and anxiety in the UK.	I: counselling C: CBT	Review of RCTs of counselling vs. other psychological or pharmacological therapies for mental health in primary care, published up to May 2011.	Study was at high risk of bias due to lack of blinding of participants, personnel and outcome assessors.	Cost effectiveness and minimization evaluation showed that at 4 and 12 months there was no difference in total costs across treatments.
RCTs					
Goodyer 2017 Multicentre superiority RCT	n=465 adolescents with major depressive disorder from 15 CAMHS clinics in England.	I_1: CBT I_2: SPA C: brief psychosocial therapy	Comparison of cost-effectiveness based on the Child and Adolescent Service Use Schedule and EuroQol 5D questionnaire, with follow-up to 86 weeks (21 months).	Reasons for type of pharmacotherapy, compliance and prescribing were not controlled; improvements could be a function of time; lack of no treatment control limits ability to infer that treatment was causally effective; missing data.	Intervention costs were lowest for CBT (mean (SD) £904.57 (607.25)) and highest for SPA (£1396.72 (1133.41)). The cost of health, social care and education services differed little between groups. There was no evidence for any difference in cost-effectiveness nor QALYs across treatments.
Egede 2017 Non-inferiority RCT	n=241 elderly (>58 years) veterans with major depressive disorder from clinics in South Carolina and Virginia, USA.	Behavioural activation I: BA via telemedicine C: traditional BA (same-room)	Comparison of overall, in- and outpatient, and pharmacy cost data collected from VA Health Economics Center datasets for the 1998-2014 fiscal years (6 years).	Limited generalisability to women and younger patients, or to other countries.	Overall, outpatient and pharmacy costs showed an increasing trend over time with minimal difference between groups. Telemedicine BA had a higher inpatient cost than same-room BA (~USD 2,750 vs. 1,500).
Richards 2016 Open-label non-inferiority RCT	n=221 adults with major depressive disorder from primary care services in Devon,	I: BA via junior health worker C: CBT via psychologists	Economic analysis using the Adult Service Use Schedule, the Health and Work Performance Questionnaire, and EuroQol-5D-3L, taking UK	Attrition rates may have affected the results; 35% of participants did not attend even a minimal number of sessions; did not control for	Intervention costs were higher for CBT than BA ((mean (SD) £1235.23 (610.03) vs. £974.81 (475.02), p<0.0001), but there were no differences in other or

Study and design	Participants	Intervention (I) & comparator (C)	Methods	Limitations	Conclusions
	Durham, and Leeds, UK.		National Health Services and personal social services perspectives with follow-up to 18 months.	use of medications; trial was not blinded.	total costs. Mean health state utility scores and QALYs did not differ between groups. The incremental cost-effectiveness ratio was -£6865 for BA vs. CBT; BA was less costly and more effective.
Maljanen 2016 Non-inferiority RCT	n=326 adult patients with a mood or anxiety disorder who were part of the Helsinki Psychotherapy Study from 1994-2000.	I_1: Solution-focused therapy I_2: SPD C: LPD	Comparison of direct and indirect costs due to treatment of mental disorders and non-mental (somatic) disorders across treatment conditions using data from patient level registers or self-report questionnaires, with follow-up to 5 years.	Patient preferences and suitability for treatment were not considered; results might be confounded by the fact that patients in the short-term therapy groups spent more time in auxiliary therapies; may not be generalizable to older populations, other countries.	Mean direct costs were about three times higher for the LPD (€22,132) compared to the SPD (€7,387) and solution-focused groups (€8,434), mainly due to the higher cost of the sessions. Indirect costs due to mental health problems were also higher in the LPD vs. other groups. LPD was somewhat more effective than the shorter therapies.
Warmerdam 2010 Three-armed RCT	n=236 adults with depressive symptoms.	I_1: Internet CBT I_2: Internet PST C: usual care	Comparison of costs from a societal perspective for direct medical costs and indirect or direct nonmedical costs using data from the Trimbos/iMTA as well as self-report, with follow-up to 12 weeks.	High attrition; short follow-up; underpowered to detect significant differences between CBT and PST.	Total costs between CBT and PST were not different. There was an incremental cost-effectiveness ratio of -36 for PST vs. CBT. There was no difference in cost-utility between groups. Sensitivity analyses showed a 72% probability that PST results in modestly better QALY gains at lower cost than CBT.
Morrell 2009 RCT (cluster randomised)	n= 2,659 women (418 at-risk women) with postnatal depression who were part of registered general practitioners' practices in the former Trent Regional Health Authority, UK.	I_1: CBT I_2: person-centered therapy approach C: usual care	Economic evaluation following NICE guidelines, taking a social service perspective and using resource use data from the literature and general practitioner records, and prescription cost data from the British National Formulary, with follow-up to 6 months.	High attrition; potential cluster effects; statistical tests used may be prone to bias.	For at-risk women the mean costs appeared lower for CBT than the person-centred approach. The number of QALYs gained did not differ. CBT had a higher probability of being cost-effective (>70%) than the person-centered approach in the range of QALY values between £20,000 and £30,000. For the full sample, there was very little difference in terms of cost or QALYs gained.

Study and design	Participants	Intervention (I) & comparator (C)	Methods	Limitations	Conclusions
Dunn 2007	n=101 male veterans with chronic combat-related PTSD and depressive disorder from two outreach centres in Virginia, USA.	I: self-management therapy C: PEP	Comparison of outpatient, hospitalisation, pharmacy, and other costs using data from the Virginia Health Economics Resource Centre and Pharmacy Benefits Management System, with follow up to 12 months.	Not generalizable to other groups (all male veterans); many eligible individuals refused to participate (potentially biased sample).	Self-management therapy was only marginally more effective than PEP during treatment (effect disappeared during follow-up). Self-management participants had lower outpatient psychiatric (mean (SD) USD 3,534 (2,956) vs. 5,246 (4,094)) and medical/surgical costs (USD 3,597 (3,235) vs. 5,453 (4,611)) than the PEP group. The groups did not differ in health care utilization.
Observational studies					
Berghout 2010 Quasi-experimental	n=182 adult patients from four mental healthcare organisations in the Netherlands.	I: psychoanalysis via mental health workers C: psychoanalytic psychotherapy (lower intensity)	Cost-utility analysis including costs of resource use obtained from administrative records, and societal costs measured with the Trimbos/iMTA and Health and Labor questionnaire over the course of therapy.	Large amounts of missed data imputed; unassessed covariates (confounding); patients may not have been equivalent at baseline.	Psychoanalysis was more costly than psychoanalytic psychotherapy (€103,507 vs. 22,576) but also more effective from a health-related quality of life perspective. The incremental cost-effectiveness ratio for psychoanalysis was €52,384 per QALY gained as compared to psychoanalytic psychotherapy.
Cognitive behavioural therapy					
Reviews					
Andersen 2016 Systematic review	n=133 adults from 2 RCTs with an anxiety or depressive disorder.	I: transdiagnostic CBT C: diagnosis-specific CBT or relaxation	Review of RCTs comparing CBT to any comparison condition in transdiagnostic studies published up to June 2013.	Lack of any available evidence to draw conclusions.	The review intended to compare costs however no cost-effectiveness data was reported by any of the included studies.
Boudreau 2010 CADTH rapid review	NR; one study of individuals with depression in Australia.	I: self-directed CBT (bibliotherapy) C: traditional CBT	Review of RCTs and economic studies comparing self-directed CBT to traditional CBT for treatment of depression published up to January 2010.	Generalisability limited to Australia or populations with similar funding structure; unclear how the economic model was constructed or patients recruited.	Bibliotherapy was the cheapest option for CBT, being cost-effective at A$10,000 per DALY. Group and individual CBT provided by a psychologist on public salary were also considered cost-effective.
RCTs					
Romero-Sanchiz 2017	n=194 adults with depression from	Internet-based CBT I_1: psychotherapist support	Economic analysis from a societal and healthcare perspective with follow-up at	Patient attrition may have limited the results; insufficient sample size for	Internet-based CBT was more cost-effective than supported CBT (mean (SD) €1402.81 (429.64) vs.

Study and design	Participants	Intervention (I) & comparator (C)	Methods	Limitations	Conclusions
Multi-centre three-armed parallel RCT	primary care centres in Spain.	I_2: no psychotherapist support C: usual care	12 months (based on publicly financed health care with universal coverage).	subgroup analyses (e.g., by age or sex).	€1717.15 (509.49)). Supported CBT showed more efficacy and utility, but clinical results for unsupported CBT were almost as good while saving costs.
Meuldijk 2015 RCT	n=182 adult patients with mild to moderate anxiety or depressive disorder at 5 Dutch outpatient Mental Healthcare Centres .	I: concise CBT (7 sessions/7 weeks) C: standard CBT (unlimited sessions/1 year)	Economic evaluation undertaken from a societal perspective using case records and the Trimbos/iMTA questionnaire for costs associated with psychiatric illness, with follow-up to 3, 6, and 12 months.	Small sample size and high attrition; study underpowered to detect cost differences; protocol deviations.	There was no difference in total direct healthcare and non-healthcare costs for concise vs. standard treatment. There was also no significant difference in QALYs by treatment type. The probability that concise care is more cost-effective than standard care remains below the turning point threshold of 0.5 for all acceptable values of willingness to pay.
Kafali 2014 Three-armed RCT	n=171 adult Latino patients with depression from multiple clinics in Boston, Massachusetts and San Juan, Puerto Rico, USA.	I_1: telephone CBT I_2: face-to-face CBT C: usual care	Comparison of the cost-effectiveness in terms of mental health care costs (intervention and non-intervention) using prices from the 2010 Medical Expenditure Panel Survey, with follow up to 4 months.	Short follow-up period; insufficient information to compute QALYs; service use due to comorbidities not quantified.	Telephone CBT was less costly in terms of mental health care costs by USD 501 compared to face-to-face CBT. For a one score reduction on the Patient Health Questionnaire, the cost of telephone CBT was USD 634 less than face-to-face CBT.
Observational studies					
Solomon 2015 Mathematical modelling study	Used data from a RCT of n=720 community-based volunteers with mild-to-moderate depression in Australia.	I: Internet-based CBT C_1: face-to-face CBT C_2: treatment as usual	Examination of a stepped-care treatment model including Internet CBT as a first step, with cost analysis based on time spent in each health state (depression, remission, maintenance) and resource utilization from literature and administrative data, with a time horizon of 28 weeks and a public insurance scheme.	Model has several assumptions (e.g., delivery costs, discontinuation rate); several cost sources not included in the model (indirect costs, cost of adverse effects); short-term time frame.	Internet CBT had a higher net monetary benefit than face-to-face CBT (mean (SD) A$12,474 (6,522-16,600) vs. A$11,952 (5,159-16,255). The incremental cost relative to Internet CBT was A$1,995 per individual for face-to-face CBT. At a willingness to pay threshold of A$50,000, there is a 75.5% probability that Internet CBT is cost effective.
Hammond 2012 Quasi-experimental	n=39,227 adults referred to psychological therapies in NE Herts,	Low-intensity CBT I: over telephone C: face-to-face	Comparison of cost-per-session for each type of therapy for the financial year 2009/2010 using a cost-	Potential that findings are the result of natural resolution of symptoms; unassessed covariates (confounding);	The per-session cost of telephone CBT was 36.2% lower than face-to-face CBT (mean (95% CI) £79.19 (55.0-103.3) vs. 118.76

Study and design	Participants	Intervention (I) & comparator (C)	Methods	Limitations	Conclusions
	NE Essex, Suffolk, W Herts, Mid Essex, Bedfordshire, and Cambridgeshire, UK.		minimization approach based on treatment equivalence for each therapy.	some patients excluded since they received a mix of treatments.	(82.5-155.0)). The telephone treatment also appeared to be more effective in reducing depression scores.
Brown 2011 Quasi-experimental	n=85 adults with a primary diagnosis of depression from five psychology services provided by a large mental health Trust in southeast London, UK.	I: group CBT C: individual CBT.	Comparison of costs of providing each type of treatment, including staff time, non-staff costs, organisational overheads, and capital at 2006-2007 rates over the course of treatment.	Unassessed covariates (confounding); patients may have differed in terms of other diagnoses or depression severity.	Individual CBT was 1.5 times more costly to provide than group CBT (mean (SD) £375.32 (216) vs. 246.33 (108)), with no difference in effectiveness in terms of reduced depressive and distress symptoms.

BA: behavioural activation; CADTH: Canadian Agency for Drugs and Technologies in Health; CAMHS: Child and Adolescent Mental Health Service (UK); CBT: cognitive behavioural therapy; DALY: disability-adjusted life-year; iMTA: Institute of Medical Technology Assessment; LPD: long-term psychodynamic therapy; NICE: National Institute for Health and Care Excellence; NR: not reported; PEP: psychoeducation program; PST: problem-solving therapy; PTSD: post-traumatic stress disorder; QALY: quality-adjusted life-years; RCT: randomised controlled trial; REBT: rational emotive behavioural therapy; SPA: short-term phychoanalytic therapy; SPD: short-term psychodynamic therapy; SSFT: short-term solution-focused therapy; SSRI: selective serotonin reuptake inhibitor; UK: United Kingdom; USA: United States of America

Q3b. For various non-pharmacological treatment options, what are the advantages in terms of safety?

Study	Participants	Methods	Limitations[b]	Conclusions[b]
Reviews				
Gertler 2015	n = 77 adults who had sustained a TBI undergoing psychotherapy for depression, from 1 RCT (follow up: 3 months).	Cochrane systematic review of RCTs comparing CBT and supportive psychotherapy for depression post-TBI. Included studies published up to February 2015.	Only one included study. Study was at high risk of bias.	No adverse events were reported.
Shinohara 2013	n = 955 adults undergoing psychotherapy for depression, from 25 RCTs and cross-over trials (follow up: up to 6 months).	Cochrane systematic review of RCTs and cross-over trials comparing: BT and all other psychotherapies; BT and CBT; BT and psychodynamic therapies; BT and integrative therapies. Included studies published up to July 2013.	Most studies had a small sample size and were at unclear or high risk of bias.	No study provided reports of adverse effects.
Randomised controlled trials				
Goodyer 2017	n = 470 adolescents (11 to 17 years) with depression recruited from NHS child and adolescent mental health service clinics, UK (follow up: 86 weeks).	Randomised trial comparing brief psychosocial intervention (12 sessions over 20 weeks), CBT (20 sessions over 30 weeks), and short-term psychoanalytical therapy (28 sessions over 30 weeks).	16% loss to follow up; some patients in all three groups received antidepressant medication (not controlled for); absence of a no-treatment control group.	Physical adverse events (self-reported breathing problems, sleep disturbances, drowsiness or tiredness, nausea, sweating, and being restless or overactive) did not differ between groups.
Richards 2016	n = 221 adults with depression recruited from primary care and psychological therapy services in Devon, Durham, and Leeds, UK (follow up: 6, 12, and 18 months).	Randomised trial comparing BA and CBT (maximum of 20 60-minute sessions over 16 weeks, with the option of four additional booster sessions).	High level of attrition (35%); did not control for the contribution of antidepressant medications; could not mask participants to treatment allocation.	No adverse events related to the treatments were reported.
Egede 2015	n = 780 veterans (≥58 years) with depression recruited from the Ralph H Johnson Veterans Affairs Medical Centre and four associated outpatient clinics in the USA (follow up: 12 months).	Randomised trial comparing BA provided for 60 minutes, once per week via telemedicine (in-home videoconferencing) and via same-room treatment.	Excluded patients with acute safety concerns, substance dependence, and active psychosis or dementia; information technology used is now obsolete; included few women; some patients were taking antidepressant medication.	We did not note any adverse events.

Study	Participants	Methods	Limitations[b]	Conclusions[b]
Berking 2013	n = 432 adult inpatients with depression from a routine mental health care hospital in Germany (mean follow up: 46 days).	Randomised trial comparing CBT (1.5 hours per week, plus four 45-minute sessions of transdiagnostic group therapy) and CBT-ERT (four 1.5-hour and two 45-minute ERT sessions replaced 10 of the CBT sessions).	Follow up only post-treatment; participants also received sports therapy and occupational therapy; no data on treatment integrity.	No adverse events were reported.
Himelhoch 2013	n = 34 low-income, urban dwelling, HIV infected adults with depression recruited from two HIV clinics in the USA (follow up: 14 weeks).	Randomised trial comparing telephone-based CBT (11 45-minute sessions over 14 weeks) and face-to-face CBT (11 60-minute sessions over 14 weeks).	Short length of treatment and follow up; small sample size.	None of the participants discontinued treatment due to adverse events.
Merry 2012	n = 187 adolescents (12 to 19 years) who sought help for depression, recruited from youth clinics, general practices, and school-based counseling services in New Zealand (follow up: 3 months).	Randomised trial comparing computerised CBT via interactive fantasy game (7 modules over 4 to 7 weeks) and face-to-face counseling.	Small sample sizes for some subgroup analyses.	One participant in the computerised CBT group and two in the face-to-face group experience mild adverse events, and eight in each group experienced moderately severe adverse events (e.g., worsening of mood, suicidal thinking); two participants in the computerised CBT group and one in the face-to-face group experienced suicide attempts (serious adverse event).

BA = behavioural activation; CBT = cognitive behavioural therapy; ERT = emotion regulation skills training; HIV: human immunodeficiency virus; NHS = National Health Service; RCT = randomised controlled trial; TBI = traumatic brain injury; UK = United Kingdom; USA = United States of America

Q3c. For various non-pharmacological treatment options, what are the advantages in terms of effectiveness and relapse prevention?

Study	Participants	Methods	Limitations	Conclusions
Children and adolescents				
Zhou 2015	n = 2,361 children and adolescents with a diagnosis of major or minor depression, intermittent depression, or dysthymia; short- (1-6 months) and long-term (6-12 months) follow-up.	Network meta-analysis of 52 RCTs including 9 psychotherapy conditions to test their comparative efficacy (CBT, IPT, supportive, cognitive, family, play, behavioural, problem-solving, and psychodynamic therapies), published from 1980 to 2013.	Heterogeneity in treatments included in some nodes of the analysis; exclusion of treatment-resistant and psychotic depression.	For efficacy at post-treatment, IPT (SMD = -0.93, 95% CI = -1.66 to -0.20) and CBT (SMD = -0.80, 95% CI = -1.55 to -0.06) were more beneficial than play therapy. At short-term follow-up, IPT was more effective than problem-solving therapy (SMD = -0.99); CBT was more effective than cognitive therapy and problem-solving therapy (data NR). At long-term follow-up, IPT was more beneficial than CBT and cognitive therapy (data NR). Overall, at follow-up IPT (SMD = -1.10, 95% CI = -1.90 to -0.27) and CBT (SMD = -0.90, 95% CI = -1.56 to -0.3) were more beneficial than problem-solving therapy. Thus, IPT and CBT should be the initial choice of treatment.
Hazell 2009	n = NR children and adolescents with depression; follow-up variable across comparisons; follow-up to 24 months.	'Clinical evidence review' of SRs, RCTs and observational studies comparative effects of various psychotherapies (CBT, IPT), published up to April 2008.	Low quality evidence.	One SR found no difference between IPT and CBT in remission rates or depressive symptoms at the end of treatment. Compared with family therapy, individual CBT may be more effective at increasing remission rates but not at improving self-rated depressive symptoms (1 SR). Compared to supportive therapy, CBT may be more effective at increasing remission rates at the end of treatment but not at maintaining remission at 9 or 24 months or at improving self-rated symptoms (1 SR). In 1 RCT there was no difference in effectiveness between group therapeutic support and social skills training. There was no evidence for difference in effectiveness of family therapy vs. supportive therapy or psychodynamic therapy. There was no difference between CBT and non-directive supportive therapy in maintenance of remission at 9 or 24 months.
Spielmans 2007	n = NR children and adolescents (≤18 years) suffering from symptoms of anxiety or depression; follow-up NR.	Meta-analysis of RCTs to compare the effectiveness of CBT to other *bona fide* and non-*bona fide* treatments, published up to May 2005.	Lack of data for a number of treatments.	Cognitive behavioural therapy was more efficacious than non-*bona fide* treatments when assessed with directly relevant measures (d = 0.570, P < 0.0001). There was no evidence to suggest any difference in efficacy between CBT and other *bona fide* treatments. *Bone fide* treatments overall were significantly superior to non-*bone fide* treatments (d = 0.525, p < 0.0001). Full CBT treatments (e.g., adolescent CBT + parent training) were similarly efficacious as component treatment (e.g., adolescent CBT alone).
Adults				

Study	Participants	Methods	Limitations	Conclusions
Steinert 2017	n = 2,751 adult patients with depressive disorders or other mental disorders; follow-up of 0 to 55.5 months.	Meta-analysis of 23 RCTs testing the equivalence of psychodynamic therapy versus other treatments with established efficacy published up to December 2016.	No trials comparing psychodynamic therapy to therapies other than CBT were identified.	All comparisons were to CBT. The pooled between-group difference for target symptoms at post-treatment was g = -0.158, 90% CI = -0.236 to -0.080, P = 0.026, indicating equivalence. Treatments were equivalent for general psychiatric symptoms post-treatment and at follow-up, and psychosocial functioning post-treatment. Moderator analysis showed that results were valid across disorders.
Gertler 2015	n = 77 adults with post-TBI depression; follow-up NR.	Planned meta-analysis that included only 1 RCT comparing the effectiveness of CBT and supportive psychotherapy, published up to February 2015.	Lack of data for children; high dropout rate; very limited evidence.	No studies in children were identified. There was no difference between treatment groups in terms of reduction in depression symptoms or quality of life at post-treatment. High drop-out rate may suggest these treatments are not practical for those with TBI. No compelling evidence in support of either treatment.
Linde 2015	n = 7,024 adult primary care patients with unipolar depressive disorders; follow-up NR.	Network meta-analysis of 37 RCTs including 9 psychotherapy conditions to test their comparative efficacy (CBT, IPT, problem-solving, psychodynamic, other, combination therapies), published up to June 2013.	Possible systematic differences in study groups across nodes; low confidence in outcomes; lack of head-to-head trials.	There was no difference in efficacy in terms of response to treatment across the 9 conditions, except that remote therapist-led CBT was superior to face-to-face IPT (OR = 0.60, 95% CrI = 0.37 to 0.95). There was no difference between remote-therapist led, guided self-help, non/minimal contact, and therapist-led CBT. Findings were similar when remission or post-treatment scores were used as the outcome. Credible intervals were often too large to rule out clinically relevant differences.
Andersson 2014	n = 1,053 adults with psychiatric and somatic conditions; follow-up NR.	Meta-analysis of 13 (2 for depression) studies to compare the effectiveness of guided I-CBT and face-to-face CBT (individual or group format), published up to July 2013.	Few studies for each condition (limited power); no analysis of long-term effects.	Pooled between-group treatment effect size was non-significant, indicating equivalence between the two treatments. Analysis specific to the two studies on depression also showed equivalence.
Kriston 2014	n = 2,657 adults with persistent depressive disorder; follow-up NR.	Network meta-analysis of 15 RCTs of acute psychotherapeutic (CBASP, IPT) or combined interventions (with medication) to test their comparative effectiveness, published up to January 2013.	Possible confounding by diagnosis; lack of RCTs on some treatments (e.g., psychodynamic psychotherapy).	CBASP was more efficacious in terms of response rate than IPT (OR = 0.45, CrI = 0.18 to 0.93). A moderate recommendation can be given to CBASP as acute monotherapy but IPT without medication cannot be recommended.
Barth 2013	n = 15,118 adults with a depressive disorder or an elevated level of depressive	Network meta-analysis of 198 RCTs to compare the efficacy of various psychological treatments (CBT, BA, IPT, problem-solving, supportive, social skills, psychodynamic	Variation in robustness of evidence across therapeutic approaches; lack of generalisability	Most relative effects of psychotherapeutic interventions were absent to small, and all but one failed to reach statistical significance. Interpersonal therapy was significantly superior to supportive therapy (d = -0.30, 95% CI = -0.54 to -0.05), but this was based on only 2 studies. Subgroup analysis showed

Study	Participants	Methods	Limitations	Conclusions
	symptoms; no follow-up.	therapy) and modes of delivery, published up to November 2012.	outside Western countries; no long-term outcome data.	that patient characteristics and intervention format had no influence on treatment effects.
Braun 2013	n = 3,965 adults with a depressive disorder or an elevated level of depressive symptomology; follow-up from 1 to 24 months.	Meta-analysis of 53 RCTs directly comparing two or more *bona fide* psychological therapies (CBT, BA, IPT, ACT, psychodynamic, supportive, problem-solving, interpersonal, social skills, mindfulness-based CBT therapies, others), published up to June 2012.	Small sample sizes for some studies; inadequate studies to investigate all treatment pairs; potential confounding by unmeasured variables.	CBT, BA, IPT and psychodynamic therapies were equally efficacious at post-treatment, except for supportive therapy which was less efficacious according to patient (Rogers, g = 0.26, 95% CI = 0.02 to 0.49, P < 0.05) and clinician (non-Rogers, g = 0.36, 95% CI = 0.15 to 0.58, P < 0.01) ratings. All treatments were equally efficacious for remission, except for supportive therapies which were less efficacious (OR = 0.61, 95% CI = 0.42 to 0.89, P = 0.010). No difference between treatments was found at follow-up. Subgroup analyses showed a higher efficacy of BA vs. other treatments with increasing age, and CBT appeared to be more efficacious for females than males. CBT appeared to be more efficacious than other treatments when it lasted >90 minutes, while BA was more efficacious when it lasted <90 minutes.
Dedert 2013	n = 7,270 adults with depressive disorder, PTSD, panic disorder, or generalized anxiety disorder; no follow-up analyses.	Meta-analysis of 47 RCTs (15 for depression) comparing the effectiveness of I-CBT with face-to-face CBT and varying levels of therapist support, published from 1990 to 2013.	Limited available data; insufficient evidence to draw conclusions.	Exploratory analysis using indirect comparisons showed an association between higher levels of support and greater treatment effects. Two small studies compared different levels of therapist support directly and found no differences in treatment effect. There were inadequate data (2 studies, 254 participants) to evaluate the differential effect between I-CBT and face-to-face CBT for depression specifically.
Hunot 2013	n = 144 adults with acute depression; follow-up to 2 months.	Meta-analysis of 3 RCTs comparing the effectiveness of 3rd wave CBT approaches with any other psychological therapy approach (CBT, psychodynamic, behavioural, humanistic, integrative therapies), published up to 2013.	Limited evidence in terms of quantity, quality and breadth; low quality of evidence; lack of statistical power.	Post-treatment results showed no difference between 3rd wave CBT (ACT and BA) and other psychological therapies for efficacy of clinical response or remission rate. At 2-month follow-up there was no evidence of any difference between 3rd wave CBT and other psychological therapies for clinical response. Quality of evidence was very low as assessed using GRADE.
Shinohara 2013	n = 955 adults with acute depression; follow-up from 5 weeks to 6 months.	Meta-analysis of 25 RCTs comparing the effectiveness of various behavioural therapies with any other psychological therapy approach (CBT, 3rd wave CBT, psychodynamic, humanistic, integrative	Weak evidence base; small sample sizes and large amounts of imputed data.	Compared to all other psychological therapies together, behavioural therapy showed no difference in response rate. In subgroup analyses comparing BT to the five other classes of psychotherapies, low-quality evidence showed no difference in treatment response. There was also no difference in remission rates between BT and CBT or humanistic therapies (no data for other therapies). At up to 6 month follow-up, behavioural therapy was inferior to CBT for response (RR =

Study	Participants	Methods	Limitations	Conclusions
		therapies), published up to 2010.		0.76, 95% CI = 0.59 to 0.99) and remission (RR = 0.77, 95% CI = 0.61 to 0.98).
Jakobsen 2012	n = 741 adults with major depressive disorder; follow-up to 1 year in 1 study.	Meta-analysis of 7 RCTs to compare the effectiveness of CBT and IPT, published up to August 2010.	Few included trials; all trials at risk of bias; limited evidence for long-term effects.	At treatment completion, the effect of CBT and IPT on depressive symptoms did not differ. There was no difference in risk of 'no remission' across therapies. Only one trial included follow-up data showing no difference between the effect of CBT and IPT on depressive symptoms at 1-year post-treatment.
Cuijpers 2011	n = NR adults with depression, no follow-up.	Meta-analysis of 173 RCTs to compare the effectiveness of 7 psychological therapy approaches (CBT, BA, IPT, non-directive supportive, problem-solving, interpersonal, social skills therapies) and formats, published up to January 2010.	Though the number of RCTs was large, the number of studies for specific subgroups was small; potential lack of statistical power; no long-term outcomes.	There was no indication that CBT, BA, psychodynamic therapy, problem-solving therapy, and social skills training differ from each other in terms of effectiveness in reducing symptoms of depression. However, IPT was slightly more efficacious than all other therapies combined (d = 0.21, 95% CI = 0.01 to 0.42), and non-directive supportive therapy was slightly less efficacious than all other therapies combined (d = -0.17, 95% CI = -0.32 to -0.03). Treatments in varying formats (face-to-face vs. guided self-help and individual vs. group) appeared to be equally efficacious.
Cape 2010	n = 3,962 adults with anxiety, depression, unspecified common mental health problems, or 'emotional distress'; follow-up NR.	Meta-analysis of 34 RCTs (14 for depression) comparing the effectiveness of various brief psychological therapies (CBT, IPT, counselling, problem-solving therapy, psychodynamic psychotherapy).	Possible publication bias; high heterogeneity.	For studies of depression and mixed anxiety and depression, there was no difference in effectiveness between counselling and CBT, problem-solving therapy and CBT, or counselling and problem-solving therapy.
Tolin 2010	n = 1,981 adults with mental disorders including depression, anxiety, eating disorders, psychosis, and substance use disorders; follow-up to 6 and 12 months.	Meta-analysis of 26 RCTs to test whether the effectiveness of CBT is superior to other *bona fide* forms of psychotherapy (psychodynamic, supportive, interpersonal therapies), published up to September 2007.	Small number of studies for some sub-analyses; findings not robust.	Cognitive behavioural therapy was superior to psychodynamic therapy but not to interpersonal or supportive therapies at post-treatment (d = 0.28, 95% CI – 0.12 to 0.44, P < 0.05) and at 6-month follow-up (d = 0.50, 95% CI = 0.29 to 0.71) and at 12- month follow-up (d = 0.55, 95% CI = 0.30 to 0.81) in terms of scores on measures of primary symptoms. At follow-up there was only one study to compare CBT to IPT or supportive therapy. For anxiety and depressive disorder specifically, the findings were similar. Effect sizes were not significantly associated with the number of sessions or group vs. individual therapies.

Study	Participants	Methods	Limitations	Conclusions
Cuijpers 2010	n = 810 adults with anxiety or depressive disorders; follow-up to 12 months.	Meta-analysis of 21 RCTs (6 for depression) to compare the effectiveness of guided self-help compared to face-to-face psychotherapies, published up to January 2009.	Need to investigate applicability to clinical practice; small sample size in some studies; low quality of many studies.	At post-treatment and at 1-3 months, 4-6 months, and 12-months follow-up, there was no difference in effectiveness between guided self-help and face-to-face psychotherapy.
Cuijpers 2008	n = 2,757 adults with mild to moderate depression; follow-up to maximum of 24 months.	Meta-analysis of 53 RCTs comparing the effectiveness of 7 major types of psychological treatment (CBT, BA, IPT, nondirective supportive, problem-solving, psychodynamic, interpersonal, social skills therapies), published up to May 2007.	Inadequate number of studies for all analyses; suboptimal study quality; may not be generalizable to non-Caucasian populations.	There was no strong indication that any of the treatments were more or less efficacious than the others, with the exception of IPT which was somewhat more efficacious (d = 0.20, 95% CI = 0.02, 0.38, P < 0.05) and supportive treatment which was somewhat less efficacious than the other treatments (d = -0.12, 95% CI = -0.30 to -0.01, P < 0.05). There was no evidence that the differences between treatments increased or decreased over time for follow-up of up to 24 months.
Nieuwenhuijsen 2008	n = 247 adult workers (employees or self-employed) with depressive disorders; follow-up to one year.	Planned meta-analysis which included only 1 RCT comparing the effectiveness of worker-directed psychological interventions (problem-solving therapy vs. generic community mental health care), published up to August 2006.	Few studies; low quality evidence.	No difference in effectiveness was found for days of sickness absence or depressive symptoms between the two treatments.
Postpartum women				
Dennis 2007	n = 788 postpartum women with depressive symptomology; no follow-up analyses.	Meta-analysis of 2 RCTs to compare the effectiveness of psychosocial and psychological interventions, as well as intervention modes, published up to August 2007.	Poor methodological quality of studies.	There was no difference in the beneficial effect of reducing depressive symptoms between psychological and psychosocial interventions. There was inadequate evidence to ascertain if group vs. individual approaches were equally efficacious.
Older adults				
Samad 2011	n = 154 older adults (≥55 years) with depression; follow-up to 3 months.	Meta-analysis of 5 RCTs to compare the effectiveness of various psychological therapies (CBT, IPT, psychodynamic and supportive therapies), published up to July 2009.	Studies were underpowered to detect differences; short follow-up.	There was no difference in the self-rated effectiveness of behavioural therapy and cognitive therapy at treatment completion or at 1-3 months follow-up (data combined). The type of health professional did not appear to impact this comparison. Behavioural therapy seemed slightly more effective than brief psychodynamic therapy but this was not significant.

Study	Participants	Methods	Limitations	Conclusions
Wilson 2008	n = 197 older adults (≥55 years) with depression; follow-up from 12 to 16 weeks.	Meta-analysis of 3 RCTs comparing the effectiveness of various psychological therapies (CBT, cognitive, behavioural, psychodynamic therapies), published up to September 2006.	Few trials and small sample sizes; high dropout rates; cannot be generalized to clinical populations (all trials were in the community).	There was no difference in treatment effect between CBT and psychodynamic therapy in terms of reduction in symptoms or clinical response. There was no difference in treatment effect between cognitive and behavioural therapies in terms of reduction in symptoms.
Mixed populations				
Burlingame 2016	n = 6,293 children and adults with a mental disorder amenable to psychological treatment; maximum follow-up of 30 months.	Meta-analysis of 70 studies testing the equivalence of individual and group formats of any *bona fide* psychological treatments (CBT, behavioural, cognitive, psychodynamic, interpersonal, supportive, mixed, integrative and dialectal behavioural therapies).	Unexplained heterogeneity in some analyses; low power; uncorrected intragroup dependency.	The average effect sizes for primary outcomes for the 46 studies comparing identical treatments and the 21 studies comparing non-identical treatments were non-significant, indicating equivalence. Effects for short, moderate, and long-term follow-up, post-treatment remission and improvement also supported equivalence. Heterogeneity in some analyses not explained by diagnosis.
Montgomery 2010	n = 289 adults and older adults with anxiety or depressive disorders; follow-up NR.	Narrative review of 4 studies to compare the effectiveness of cognitive and/or behavioural therapies delivered via paraprofessional compared to a professionally trained therapist, published up to September 2005.	Small number of included studies; lack of recent studies.	It appears than paraprofessional therapists can be effective in delivering CBT. Data from two studies show slight outcome advantages for professionals, but overall paraprofessionals seem to be able to achieve similar outcomes. When CBT was applied more rigorously, patients showed greater improvements in outcome measures.
Jorm 2008	n = 286 children and adults with depression or with a high level of depressive symptoms; follow-up from 1 to 6 months.	Meta-analysis of 9 RCTs to compare the effectiveness of relaxation compared to other psychological therapies	Unexplained heterogeneity; lack of functional outcomes; risk of bias in older trials.	Relaxation produced less effect than psychological (mainly CBT) treatments on self-reported depression at post-treatment (SMD = 0.38, 95% CI = 0.14 to 0.62) and at short-term follow-up (SMD = 0.36, 95% CI = 0.07 to 0.65); there was no difference at long-term follow-up. Three trials showed no difference between relaxation and other psychological treatments on clinician-rated depression at post-intervention or at follow-up. Risk of non-response was higher for relaxation at post-treatment based on self-report (RR = 1.71, 95% CI = 1.25 to 2.34) and clinician measures (RR = 1.96, 95% CI – 1.20 to 3.22), as well as at follow up based on self-report (RR = 1.88, 95% CI = 1.05 to 3.34) and clinician measures (RR = 1.42, 95% CI = 0.91 to 2.21).
Henken 2007	n = 519 individuals (children and	Narrative synthesis of 6 RCTs comparing the effectiveness of	Limited available evidence.	There is limited evidence that family therapy is less effective than individual CBT for depressive symptoms, limited evidence that cognitive behavioural family therapy is equally

Study	Participants	Methods	Limitations	Conclusions
	adults) with depression.	family therapy compared to CBT or behavioural therapy.		effective as behaviour family therapy for depressive symptoms.

ACT: acceptance and commitment therapy; BA: behavioural activation therapy; CBASP: cognitive behavioural analysis system of psychotherapy; CBT: cognitive behavioural therapy; CI: confidence interval; CrI: credible interval; GRADE: Grading of Recommendations, Assessment, Development and Evaluation; I-CBT: Internet cognitive behavioural therapy; IPT: Interpersonal psychotherapy; NR: not reported; OR: odds ratio; PTSD: post-traumatic stress disorder; RCT: randomised controlled trial; RR: risk ratio; SMD: standardised mean difference; TBI: traumatic brain injury

Q4. What are the prevention strategies/tactics for reducing self-harm and suicide in children, youth and adults with depression?

Study and design	Participants	Methods	Limitations	Conclusions
Children, Adolescents and Young Adults				
Pu 2017 Systematic review	n = 538 young depressive patients from 7 trials.	Multiple databases were searched until May 2016 for publications examining IPT compared to a control condition in children and adolescents with depression, with meta-analysis performed.	Small number of included studies, leading to small sample size and low statistical power. Did not find studies in children, and there is potential publication bias. Modified IPT was not examined.	No evidence that IPT reduces the risk of suicide, based on this data. IPT appears to be superior to control in treating adolescent depression.
Das 2016 Overview of reviews	n = NR adolescents and youth (11-24y) from 38 publications, with a variety of mental health concerns.	Multiple databases were searched until December 2015 for systematic reviews looking at mental health interventions in an adolescent population. Quality assessment was performed on included studies.	Findings from school-based studies are limited due to low quality.	School-based suicide prevention programs indicate that didactic and experiential programs can increase short-term suicide and suicide prevention knowledge, but do not appear to impact suicide-related attitudes or behaviours.
Devenish 2016 Systematic review	n = NR adolescents (11-19y) from 35 publications, where adolescents received a psychological intervention to reduce symptoms of depression.	Systematic review of multiple databases up to April 2015 to identify publications examining psychological interventions to prevent or treat depression, where suicidality outcomes were reported.	High risk of bias in included studies, and limited research to date. High rates of attrition in some types of intervention studies created small sample sizes for analysis, and lack of reporting on comparisons all require the results to be interpreted with caution.	The studies examined in this review suggest that psychological interventions are at least as efficacious as other treatments for depressive symptoms, and shows promise for the treatment suicidality. However, further research is needed.
Perry 2016 Systematic review	n = 22 adolescents (14-18y) from one trial, reporting previous suicidal ideation.	Systematic review of multiple databases for online and mobile psychosocial interventions for suicide prevention in young people, with results up to May 2015.	Lack of relevant literature on this topic.	The single included study shows promising results, however, more evidence is needed to determine the effectiveness of online and mobile interventions on suicide prevention in youth.
Bennett 2015 Overview of reviews	n = NR youth (0-24y) from 28 included reviews, focusing on both school-based and non-school-based interventions.	Systematic review methodology was applied to locate existing systematic reviews, up to May 2012, of youth suicide prevention intervention, both in and outside of schools.	Few RCTs of prevention programs for suicidal youth, with little data on the impact of these programs. Little to no evidence is available for gender differences and other subgroups such as Indigenous youth.	School-based prevention reviews did not report reduced suicide death, but did report less suicide attempts, ideation, and other measures of suicide risk. Interventions aiming to reduce repeat suicide attempts show promise, but more research is needed to determine the successful elements of these programs.

Study and design	Participants	Methods	Limitations	Conclusions
Hawton 2015 Systematic review	n = 1126 participants from 11 trials (up to 18y) with recent (≤6mo) self-harm episode.	Systematic review of multiple databases to 30 January 2015, examining psychosocial and pharmacological interventions for self-harm in children and adolescents.	Conclusions are limited to small range of potential interventions and outcomes. Included trials were of high risk of bias.	There is minimal support for group-based psychotherapy for adolescents who have self-harmed, and therapeutic assessment, mentalization, and dialectical behaviour therapy require further evaluation. More large-scale trials are required.
Katz 2013 Systematic review	n = NR participants from 16 studies (0-18y) enrolled in school-based suicide prevention programs.	Systematic review of literature up to 2012 examining school-based suicide prevention programs for youth.	Few programs evaluated reduction of suicide attempts, and few RCTs exist on this topic.	Few evidence-based, school-based suicide prevention programs were identified. A combination of programs may be effective.
Townsend 2010 Systematic review	n = NR participants from 10 studies (mean age 19y).	Systematic review of multiple databases up to August 2007 to identify interventions for young offenders with mood disorders, anxiety, or self-harm.	Included trials are methodologically weak, with short follow-up periods and a wide variety of comparison interventions.	Group-based CBT may be helpful among young offenders for treatment of depressive symptoms.
Adults				
Hawton 2016a Systematic review	n = 8480 participants (adults) from 29 studies, where participants had a prior episode of self-harm.	Systematic review of multiple databases until 29 April 2015, examining effectiveness of aftercare interventions for self-harm in adults at reducing future self-harm.	Few trials exist for interventions other than CBT, limiting the ability to draw conclusions.	CBT appears to be effective in patients with a history of self-harm. Dialectical therapy reduced frequency of self-harm but not proportion of patients repeating self-harm.
Hawton 2016b Systematic review	N = 17,699 participants (adults) from 55 included trials of self-harm interventions.	Systematic review of multiple databases until 29 April 2015 of psychosocial treatments for adults who have a history of self-harm.	Data on adverse effects were not reported, and information on subgroups, such as male vs female, was limited.	CBT reduces the number of patients repeating self-harm, however quality of evidence is low. Dialectical behaviour therapy may reduce the frequency of self-harm in people with multiple episodes. Data on other interventions is inconclusive.
Cuijpers 2013 Systematic review	n = 616 patients (adults) from 13 studies.	Systematic review, until January 2012, of psychotherapy for depression that included studies reporting suicidality outcomes.	There are few included studies, resulting in insufficient statistical power to make strong conclusions. Quality of included studies was low, heterogeneity was high, and the studies do not provide long-term outcomes.	Evidence available is insufficient to determine if psychotherapy can reduce the risk of suicidality in depressed patients.

Study and design	Participants	Methods	Limitations	Conclusions
Jakobsen 2011 Systematic review	n = 669 participants with major depressive disorder from 12 studies (>17y).	Systematic review with meta-analysis, up to February 2010, of depressive patients receiving either cognitive therapy or no intervention.	All included studies had high risk of bias. Patient characteristics, including depression severity, differed by trial.	Cognitive therapy appears to be effective for depression, but the effect on suicidality is unclear.
Elderly				
Okolie 2017 Systematic review	n = NR elderly participants (≥60y) in 21 included studies.	A systematic review including publications up to 1 April 2016. Interventions to prevent suicide and suicide ideation in the elderly were examined.	Results are limited to only English publications. Some included studies had overlapping populations.	Primary care and population-based multifaceted interventions, as well as those focused on at-risk elderly individuals in the community may be effective at preventing suicidal behaviour and suicidal ideation in older adults.
Lapierre 2011 Systematic review	n = NR elderly participants (≥60y) in 19 included studies which described 11 unique interventions.	Systematic review of interventions of elderly suicidal people, to 2009.	NR	Interventions for suicidal elderly people should improve resilience, promote positive aging, engage family and community, and use telecommunication to reach them. Studies evaluating means restriction and physician education are needed. Interventions seemed more successful in women.
All ages or age not indicated				
Berrouiguet 2016 Systematic review	n = NR participants from 36 studies, receiving text messaging interventions for a variety of mental health concerns.	Systematic review of applications of text messaging in mental health care, up to May 2015.	Baseline use of technology varied greatly between groups, which might impact the success of a program.	A positive attitude to text messaging interventions was found across conditions. Text messaging was found to be effective in studies looking at suicidal behaviour.
Meerwijk 2016 Systematic review	n = 13,369 participants from 53 articles reporting on 44 unique trials.	Systematic review of literature to 25 December 2015, for publications comparing interventions that directly target suicidal thoughts and behaviour with those that approach suicide in an indirect way (ex. Hopelessness, depression, anxiety).	Suicide outcomes may not have captured benefits to other areas of mental health. Diagnostic groups were varied, with different medication regimes (which could influence suicide risk). There was heterogeneity between control groups.	Psychosocial and behavioural interventions that directly address suicide are effective in both long and short term, while indirect interventions are only effective in the long term.
Zalsman 2016 Systematic review	n = NR participants from 164 studies.	Systematic review of suicide prevention studies, between 1 January 2005 and 31 December 2014.	Study heterogeneity did not allow meta-analysis.	No strategy appeared to be more effective than others. Combined evidence-based strategies for

Study and design	Participants	Methods	Limitations	Conclusions
				suicide prevention should be tested to determine the best individual and population level options.
O'Connor 2013 Systematic review	n = NR participants of all ages in 56 included studies.	Systematic review of literature until 17 July 2012 on screening instruments and treatments for suicide risk in primary care populations.	Populations were high-risk rather than screening-confirmed. Evidence for groups other than adults, and for racial/ethnic minorities was limited.	Psychotherapy may reduce the risk of suicide attempts in high-risk adults, but no effective therapy for high-risk adolescents was identified.
Van Der Feltz-Cornelis 2011 Overview of reviews	n = NR participants from 6 included systematic reviews.	This overview searched for systematic reviews examining intervention to prevent suicidal behaviour.	Unable to generate effect sizes due to provided data. Due to inclusion of systematic reviews only, newer research may have been missed. Most studies were conducted in Europe, which may limit global generalizability.	Evidence-based best practice activities for suicide prevention were identified, however more research is needed to identify synergistic multi-level interventions.
Fountoulakis 2009 Systematic review	n = NR participants from 17 included studies.	Systematic review of a single database up to January 2008 of suicide prevention in patients with bipolar disorder.	NR	Three psychosocial strategies appeared successful in this review of the literature: Applying interventions to elicit emergency care at times of distress; Training in problem-solving strategies; and combining comprehensive interventions for suicide prevention.

CBT: Cognitive behaviour therapy; ex.: example; IPT: interpersonal psychotherapy; mo: months; NR: not reported; RCT: randomized controlled trial; y: years.

Q7. Can diet or exercise affect the development of depression?

Study and design	Participants	Methods	Limitations	Conclusions
Reviews: Diet and depression				
Lang 2015 Review	NR	NR – narrative review, methods of identifying studies is not specified.	Most studies are retrospective, meaning mechanisms of dietary interaction or causation cannot be fully explained.	Unhealthy Western diet is associated with higher prevalence of depression, while the Japanese and Mediterranean diets are associated with a lower risk of depression. Specific nutrients have been studied, and have been found to have a relationship with depression prevalence.
Williamson 2009 Review	NR	NR – narrative review, methods of identifying studies is not specified.	NR	The importance of healthy lifestyle habits and good nutrition is emphasized in the literature, especially for older people where poor nutrition status may be common. Health professionals should prioritize supporting the elderly in making healthy lifestyle and dietary choices.
Observational studies: Diet and depression				
Chang 2016 Prospective cohort study	n = 82,643 women from the Nurses' Health Study, without depression at study entry.	Dietary intake of flavonoids (and subclasses) was assessed from a FFQ. Incident cases of depression (n = 10,752) at 10 year follow-up were assessed for flavonoid intake, compared to those who did not develop depression, to assess any associations between dietary flavonoid intake and depression.	FFQ may miss certain foods, or foods could be misclassified due to variations in flavonoid content. There is also the potential for misclassification of depression, likely under ascertainment. Residual confounding, above that controlled for in the analysis, may be present.	Higher intake of flavonoids may be associated with a lower risk of depression, especially among older women. Further research is needed to confirm this association.
Goinpath 2016 Prospective cohort study	n = 2,334 participants ≥55 y and 1,952 participants ≥60y, from the Blue Mountains Eye Study.	Participants provided dietary data through a FFQ, and an assessment of depressive symptoms. Information on potential covariates, such a medical history and lifestyle and health risk behaviours was also collected. Dietary behaviour was assessed for carbohydrate consumption, including GI, GL, total	Potential misclassification due to self-reported dietary intake. Tools for assessing depression are screening tools and not diagnostic. There may be additional confounding factors beyond those controlled for in the analysis.	There is a modest association between dietary fibre intake and depressive symptoms. Due to the prevalence of depression, it is important to study the relationship between carbohydrate intake and depression further, with RCTs, to determine potential preventative effects in older adults.

Study and design	Participants	Methods	Limitations	Conclusions
		carbohydrate consumption, and total sugar intake.		
Perez-Cornago 2016 Prospective cohort study	n = 14,051 university graduates and professionals. Participants with energy intakes outside of pre-set limits, with chronic disease, or with pre-existing depression were excluded from this analysis. Part of the SUN Project.	Participants were administered a semi-quantitative FFQ at baseline and follow-up (at 4, 6 and 8 years). Dietary intake was assessed for compliance with the DASH diet, and assessed for major depressive disorder. Participants were divided into quintiles based on their diet's comparison to the different aspects of the DASH diet, and rates of depression were assessed for each quintile.	Self-reported clinical diagnosis of depression was accepted, and subtypes/levels of depression were not considered. The compliance with DASH diet indices were self-reported based on the FFQ, and changes to dietary intake in follow-up periods were not updated.	Moderate adherence to some indices for the DASH diet may be associated with a lower risk for depression. Associations are non-linear, requiring further prospective studies to confirm findings before clinical recommendations and generalization can be applied.
Gougeon 2015 Prospective cohort study	n = 1,358 community-dwelling older adults, 67-84y. From a larger cohort. Participants with depression at baseline were excluded.	Dietary assessment was performed at baseline through three 24h dietary recalls, and dietary patterns were analyzed. The Geriatric Depression Scale or new use of antidepressant medication at any year up to the three years of follow-up measured depression incidence. Multiple logistic regression was applied, with adjustments for covariates.	There may have been insufficient variation in diet within this population to observe any differences in depression incidence.	Dietary patterns did not appear related to depression in older adults, however overall intake, possibly reflecting general health decline, is associated with a higher risk of becoming depressed.
Sanchez-Villegas 2015 Prospective cohort study	n = 15,093 university graduates and professionals. Participants with energy intakes outside of pre-set limits, with chronic disease, or with pre-existing depression were excluded from this analysis. Part of the SUN Project.	Participants were administered a semi-quantitative FFQ at baseline and at 10 y follow-up. Dietary patterns were scored for adherence to three diet types: Mediterranean diet, Pro-Vegetarian dietary pattern, and Alternative Health Eating index. Incident cases of depression were the main outcome, and the dietary behaviours of people presenting with depression were compared to those who did not, adjusted for demographic covariates.	Self-reported dietary intake and depression diagnosis. Participants were not representative of the general Spanish population.	Higher adherence scores for all three diet types was associated with a lower risk of depression among Spanish adults. If the potential influence of the Mediterranean diet is removed, the Alternative Health Eating diet demonstrates a much weaker inverse association. There does not appear to be a dose-response relationship, rather a threshold pattern was observed, with the biggest risk reduction occurring between the low and moderate adherence score groups.
Chocano-Bedoya 2013	n = 50,605 participants from the Nurses'	Participants completed a condensed FFQ at baseline, followed by an expanded FFQ every four years	The development of the dietary patterns involves some arbitrary decisions. Self-report of both	This study does not demonstrate a clear association between risk of depression and dietary patterns.

Study and design	Participants	Methods	Limitations	Conclusions
Prospective cohort study	Health Study, without depression at baseline.	thereafter, between 1980 and 2000. Dietary patterns were evaluated to assess adherence to a prudent or Western dietary pattern. In 2000, participants were asked about antidepressant use and physician-diagnosed depression. Dietary patterns were then assessed for association with depression, with relevant covariates considered.	diet and depression status may allow for some mis-classification.	
Lehto 2013 Prospective cohort study	n = 2,317 Finnish men, aged 42-61y, from the Kuopio Ischemic Heart Disease Risk Factor study. Individuals did not have depressive symptoms at baseline.	Participants completed a four-day food record to assess zinc intake. Over 20 years of follow-up, participants who were hospitalized and received a discharge diagnosis of depression were noted, and zinc intake was compared for those who did and did not require a hospitalization.	The results may not be generalizable to women or patients with depression that does not warrant hospitalization.	Zinc intake was not found to be associated with depression risk in middle-aged men. Low dietary zinc may not be a precursor to depression in this population.
Li 2011 Prospective cohort study	n = 2,039 men and 3,029 women followed over 10.6 years. Participants were from the National Health and Nutrition Examination Survey.	Participants completed a FFQ based on the previous three months, and completed an assessment for severely depressed mood at baseline and at follow-up. Fish consumption was taken from the FFQ. First consumption was compared for those who did and did not develop severely depressed mood, with analysis accounting for potential covariates.	Limitations include potential bias related to loss-to-follow-up and participants who were excluded due to incomplete records. Assessing fish intake by a single FFQ may introduce errors in dietary assessment, and eating patterns may have changed during the follow-up period prior to the development of depression.	Fish consumption was inversely associated with severely depressed mood in men, but not in women. Further studies are needed to explore this connection, and differences between men and women.
Lucas 2011 Prospective cohort study	n = 54,632 women, 50-77y old with no depressive symptoms at baseline. Participants were from the Nurses' Health Study.	Participants provided a FFQ for dietary information at four periods during the study. Over 10y of follow-up, incident cases of depression were reported. Diets were examined for consumption of n-3 and n-6 PUFA, linoleic acid and α-linoleic acid.	Due to similar food sources, there may be misclassification of linoleic and α-linoleic consumption. There could also be reverse causation occurring (depression altering diet) and other confounding factors, as well as misclassification of depression diagnosis.	Data collected does not support a link between n-3 PUFA and depression. Higher α-linoleic acid and lower linoleic acid consumption may be associated with a lower depression risk, but further research is needed.
Oddy 2011	n = 1,407 participants from the Western	Adolescents completed a FFQ and the BDI for youth (BDI-Y) at 14y and	FFQ data was self-reported, which may limit accuracy of food	Intake of saturated fat and n-3 PUFA was inversely related to depression

Study and design	Participants	Methods	Limitations	Conclusions
Prospective cohort study	Australian Pregnancy Cohort, participants were adolescents aged 14y at first measurement and 17y at final measurement.	again at 17 years. Intake of saturated fat, n-3 PUFA, and other dietary and lifestyle factors, were compared to depression scores.	intake data. Taking depression data only from patient self-report, without parental report, may have underestimated rates of depression in the sample. Participants in study are more likely to be socioeconomically advantaged than the general population, limiting generalizability of results.	symptoms. However, these relationships did not remain when total energy intake and other lifestyle factors were accounted for. Previous associations between depression and n-3 PUFA could be due to confounding factors among other dietary and lifestyle factors.
Sanchez-Villegas 2011 Prospective cohort study	n = 12,059 participants free of depression at baseline. Part of the SUN Project.	At baseline, participants completed a FFQ to assess dietary SFA, TFA, MUFA, PUFA and culinary fats. Incident cases of depression were reported at follow-up, and participants were assessed based on quintiles of fat intake.	Single assessment of dietary intake limits the level of analysis possible. Depression cases were self-reported.	Higher TFA intake was associated with increased depression risk, and an inverse association was found between MUFA, PUFA, and olive oil intake and depression risk. Authors suggest that depression and cardiovascular disease may share nutritional determinants with relation to fat subtypes.
Colangelo 2009 Prospective cohort study	n = 3,317 men and women in the Coronary Artery Risk Development in Young Adults study. Participants with bipolar disorder at entry were excluded.	Data on diet were collected at baseline, at 7y and 20y by FFQ. Depressive symptoms were assessed at 10y, 15y, and 20y. Other covariates were collected at 10y and 20y. Dietary data were assessed to determine consumption of fish, EPA, and DHA in comparison to depressive symptom development.	Dietary data was collected at 7y but not 10y, when depressive data was collected. This may weaken associations between diet and depressive symptoms. The tool used to assess depression may be weaker than clinical interviews, and participants who were excluded from the analysis had less favourable characteristics at baseline, such as smoking, alcohol consumption, and education, which may influence depression rates.	Intake of fish and sources of n-3 fatty acids may be associated inversely with development of chronic depressive symptoms in women. The same relationship was not demonstrated for men in this cohort.
Sanchez-Villagas 2009 Prospective cohort study	n = 10,094 participants without depressive symptoms at baseline. Part of the SUN Study.	Participants answered a FFQ to assess adherence to a Mediterranean diet pattern. At follow-up, incident depression was measured, and compared to Mediterranean diet adherence.	Lack of control for potential confounding factors may limit the interpretation of these results. The possibility for reverse causality exists, and the method used to determine	The Mediterranean dietary pattern may have a protective effect against depressive symptoms. Additional longitudinal studies are required to confirm these findings.

Study and design	Participants	Methods	Limitations	Conclusions
			clinical depression may have resulted in misclassification.	
Reviews: Exercise and depression				
Netz 2017 Systematic review	n = NR participants from NR studies, adults with depression.	PubMed was searched up to 2016 for RCTs and meta-analyses and systematic reviews. Studies examined exercise as a treatment for depression, compared to or alongside conventional pharmacological treatments.	NR	Majority of studies examining exercise for depression support exercise as a treatment for depression, at least as an adjunct to other forms of treatment. Additional longitudinal studies are required to examine exercise in real life settings, and more research is needed on dose-response for exercise and depression.
Radovic 2017 Systematic review	n = 297 participants from 8 included studies, mean ages 12-18y, diagnosed with depressive disorders or depressive symptoms.	Meta-analysis using random effects model. Multiple databases were searched up to 30 January 2015, with duplicate quality assessment. Participants had to receive an intervention of any type of exercise, compared to a control, and depressive symptoms were measured before and after.	High level of between-study heterogeneity, meaning summary effect should be considered with caution. Included studies were generally of low quality, and with a range of control and comparison groups, and the total number of studies is small.	Exercise appears to be effective at improving depressive symptoms among adolescents with clinical depression. Exercise is a low risk treatment, which may have other positive health effects. Exercise will most likely contribute to existing treatments, such as psychotherapy or pharmacotherapy.
Carter 2016 Systematic review	n = 1,449 participants from 11 included studies. Participants were adolescents (13-17y) with depression.	Multiple databases and reference lists were searched up to April 2014. RCTs and Non-RCTs were included, and meta-analysis was performed on eight of the included studies. Included studies enrolled participants in a physical activity intervention.	Cannot present a firm recommendation on type and intensity of exercise as a treatment for adolescents due to a limited number of trials.	Exercise appears to improve symptoms of depression in adolescents. Suggestion for clinical guidance includes supervised light-to-moderate exercise three times per week for 6-12 weeks. Larger trials with sufficient sample size to reduce bias are needed to examine the dose-response relationship for exercise as a treatment for depression.
Gartlehner 2016 Systematic review	n = NR participants from 45 trials. Participants were adult outpatients with major depressive disorder.	Multiple databases were searched up to September 2015 for trials examining multiple types of complementary and alternative medicine techniques, as well as exercise, as first and second line intervention for major depressive	Confidence in the evidence is limited by high drop out rates in the included studies, inequalities in dosing, small sample sizes, and poor adverse event reporting.	Studies comparing exercise to antidepressants found no difference in remission rates. Studies examining exercise as an add-on treatment with antidepressants presented mixed results, with one finding no difference and the second showing significant

Study and design	Participants	Methods	Limitations	Conclusions
		disorder, compared to antidepressants.		improvement in patients with both exercise and antidepressants.
Kvam 2016 Systematic review	n = 977 participants from 23 RCTs, adults ≥18y with a depression diagnosis.	Meta-analysis, with random effects model, of RCTs. Articles were found through multiple database search and bibliography searches up to November 2014, and quality assessment was performed. Participants in included studies received an anaerobic intervention, alone or in combination with another depression treatment, or a control condition.	Effect estimate of exercise may have been over-estimated due to use of the largest clinical effect arm in the meta-analysis rather than largest dose. Included studies often had poor quality assessment, and there was high heterogeneity.	Exercise was an effective treatment for depression when compared to no intervention. Effects were small and insignificant when compared to psychological or pharmacological treatments. It can be considered a viable treatment or adjunct treatment for depression.
Qaseem 2016 Systematic review	n = NR patients in NR studies, patients were ≥18y with major depressive disorder.	This paper presents a guideline, supported by a systematic review. Multiple databases were searched up to September 2015, identifying studies that compared pharmacologic treatment to non-pharmacologic treatment for adults with major depressive disorder.	Limited data on population subgroups for treatments for depression, and insufficient evidence for many of the other treatments identified.	Overall recommendations of this guideline were to select cognitive behavioural therapy or antidepressants for treatment of major depressive disorder. For exercise specifically, low quality evidence found no difference in response to exercise compared to second generation antipsychotics, and no difference in remission.
Rhyner 2016 Systematic review	n = NR patients from 45 included studies. Patients were older adults (≥60y) with depression.	Meta-analysis of included studies, multiple databases searched up to January 2014, with manual search of identified article reference lists. Quality of primary studies was assessed. Included studies examined an exercise intervention compared to a non-exercise control treatment.	Immediate outcome data was used, without longer term follow-up data presented. Grouping variables were dichotomized, which results in a loss of information (ex. Age as continuous but presented as older or younger). Some data was not possible to capture, around exercise program details, due to lack of reported information in the primary studies. Data was only coded by a single reviewer.	Exercise was associated with a significantly reduced depression score, with no difference between participant age, control group type, or exercise intervention type. This systematic review suggests that older people with depression symptoms can be effectively treated with exercise.
Schuch 2016a Systematic review	n = 267 participants from 8 RCTs, older people (≥60y) with depression.	Random-effects meta analysis of studies comparing exercise with control for older people with depression. Included studies found	With only eight included studies, some subgroups were very small. All included studies had a small number of participants,	Exercise was associated with a large and significant antidepressant effect in the study population. Moderate intensity exercise, mixed aerobic and

Study and design	Participants	Methods	Limitations	Conclusions
		via a Cochrane review published in 2013 and a multiple database search from 2013 to 1 August 2015. Results were adjusted for publication bias. Participants received an exercise intervention or a control condition.	meaning that the subgroup analysis should only be considered a direction for future research and should be considered with caution.	strength programs, in participants without major comorbidities showed the greatest improvement in depressive symptoms.
Schuch 2016b Systematic review	n = 1,487 participants from 30 RCTs, participants were adults with primary diagnosis of major depressive disorder.	Included studies were found via a Cochrane review published in 2013 and a multiple database search to capture studies published after that review, up to 1 August 2015. Meta-analysis was performed, with adjustment for publication bias. Participants received an exercise intervention, or control, and had depressive symptoms measured pre and post.	NR	The antidepressant effect of exercise is large and significant, even in those people with major depressive disorder. Reviews showing a lesser effect may have underestimated the benefits due to publication bias, which this review has accounted for. Data strongly support exercise as an evidence-based treatment for depression.
de Souza Moura 2015 Systematic review	n = 1,570 patients from 13 included studies, containing adults aged 18-60y with depression.	Authors searched multiple databases up to 20 June 2014, examining aerobic exercise compared to other types of exercise and other depression treatments. Risk of bias was assessed for each included study.	Methodological and program heterogeneity limit the ability to make practical recommendations about aerobic exercise program details.	Aerobic exercise contributed to an improvement in depression symptoms in over half of the included studies (69.3%), with the remaining 30.7% showing physiological improvements without change to depressive symptoms.
Meekums 2015 Systematic review	n = 147 participants from 3 included studies, made up of adults and adolescents with depression.	Multiple databases were searched to 2 October 2014 for RCTs studying dance movement therapy for depression. Meta-analysis and risk of bias (Cochrane) assessment were completed.	Low quality evidence limits the ability to draw conclusions.	Three small trials with low quality evidence did not allow for firm conclusions about dance movement therapy as a treatment for depression. Larger, high quality studies are required.
Ranjbar 2015 Systematic review	n = NR participants from NR studies, with depression.	Multiple databases were searched to October 2014, looking at the effects of exercise on depression.	Methodological weakness and inconsistencies in included studies require caution when interpreting conclusions.	Evidence shows that exercise may benefit patients, specifically those ≤20y or ≥40y, with higher educational and physical status, females, untrained patients, and those with mild to moderate depression.
Josefsson 2014 Systematic review	n = 720 participants included in meta-analysis (from 13/15 included studies).	Multiple databases were searched for publications examining exercise interventions compared to no treatment, placebo, or usual care, up	NR	While it is difficult to determine how effective exercise is in depressive symptom reduction, this study recommends exercise for people with

Study and design	Participants	Methods	Limitations	Conclusions
	Participants had both clinical and nonclinical depression.	to April 2012, with additional hand searching of specific journals. Meta analysis was performed and methodological quality of included studies was assessed.		mild to moderate depression who are physically healthy and sufficiently willing and motivated to participate in an exercise program.
Mura 2014 Systematic review	n = 1,101 participants from 13 included studies, diagnosed with depression.	Multiple databases were searched until April 2013 for studies examining exercise as an adjunct treatment to antidepressant medications, compared to standard treatment, no treatment, or placebo. Quality assessment of included studies was performed.	Included studies have a variety of methodological weaknesses which could devalue the results.	Exercise appears to be an effective strategy to improve the effect of antidepressant medications in major depressive disorder, and appears to be appropriately and safely used in a real-life context.
Park 2014 Systematic review	n = NR patients with depression.	Multiple databases searched for data on multiple complementary therapies for depression, for development of guideline evidence. Exercise compared to placebo or antidepressants was one question explored.	Lack of evidence from studies conducted within Korea (for Korean guideline).	Exercise can be recommended for adults with mild to moderate depression (strong evidence). Exercise therapy that is structured may be used as a non-pharmacological treatment for mild or moderate depression (extrapolated evidence).
Cooney 2013 Systematic review	n = 2,326 participants from 39 included trials. Participants were adults with depression.	Multiple databases were searched up to 13 July 2012 for RCTs comparing exercise to standard, no, or placebo treatment. Meta-analysis and risk of bias (Cochrane) assessment were completed.	Quality of some included studies is low, which limits confidence in the findings.	Exercise was moderately more effective than control at reducing depressive symptoms when assessing all studies, with a smaller effect in methodologically rigourous studies. Exercise compared to psychological or pharmacological therapies is no more effective based on the small sample available.
Danielsson 2013 Systematic review	n = 1,139 participants from 14 included studies. Participants were adults with major depression.	Multiple databases were searched until August 2012 for studies containing depressive patients and an exercise intervention. Quality of the included evidence was assessed.	Small number of included studies limits the interpretation of the results, as well as the heterogeneity in program length and follow-up measurements demonstrated in the included studies.	Exercise seems beneficial for depression, when combined with medication, with aerobic exercise showing no greater benefit than other types of physical activity. Previous studies have not addressed the potential risks of exercise, such as injuries or cardiac events, and further research is needed to determine the successful components of a physical activity regimen for depression.

Study and design	Participants	Methods	Limitations	Conclusions
Mura 2013 Systematic review	n = 1,318 participants from 10 studies. Participants were >60y with depression.	A single database was searched until January 2013 for RCTs on exercise as an adjunctive treatment for depressive symptoms in older adults. Quality assessment was carried out on the included studies.	There is heterogeneity among intervention and control groups for exercise interventions, and general poor quality of studies in this group among older adults.	Due to a lack of high quality research, there have been few advances in the study of efficacy of exercise as a treatment for depression in older adults, over the past 20 years. The most promising results are found when exercise is combined with antidepressants in those with treatment-resistant late life depression.
Ravindran 2013 Systematic review	n = NR; participants with depression, anxiety, and bipolar disorder were examined.	A single database was searched for publications examining multiple complementary and alternative therapies, up to December 2012, including exercise and yoga, as an-add on for depression treatment.	Heterogeneity between studies in form of exercise limit the interpretation of these results. Methodological weakness limits generalizability of yoga studies.	There is Level 3 evidence (prospective uncontrolled studies/case series/high quality retrospective studies) supporting exercise and/or yoga as an adjunct treatment for depression, along with pharmacotherapy.
Herring 2012 Systematic review	n = 10,534 patients from 90 included studies. Patients were sedentary adults with chronic disease.	Meta-regression of RCTs, multiple databases searched up to June 1, 2011, with manual search of reference lists. Quality of primary studies assessed. Participants in included studies had depression outcomes measured before and after an exercise program.	Analysis did not permit testing of the minimal/optimal effective dose for exercise program.	Exercise was found to reduce depressive symptoms in patients with chronic disease. The largest antidepressant effects were found in those with mild-to-moderate depression.
Shivakumar 2011 Systematic review	n = NR patients from NR studies, examining pregnant women with depression.	Systematic review of multiple publication types examining exercise during pregnancy and the impact on pregnant women with depressive symptoms, including publications up to January 2010.	NR	There are no randomized trials of exercise for treatment of depression in pregnant women. Observational studies reported a reduction in anxiety and depression with regular exercise during pregnancy.
Randomized controlled trials: Diet, exercise and depression				
Serrano Ripoll 2015 RCT*	n = 273 primary care patients ≥ 18 y, with depressive symptoms, received intervention or control, with follow up at 6 and 12 m.	Participants randomized to six months of following an active group intervention, advising on sleep patterns, 1h of walking per day, 2h sunlight exposure per day, and a healthy, balanced diet (specific recommendations included), or a control condition where the same four topics were mentioned without	Unable to monitor whether patients carried out recommendations. Interventions may be too difficult for depressed patients to carry out independent of support and supervision.	Participants in both groups had improved depression scores, with no significant difference between the two. Providing written lifestyle recommendations to depressive patients without support and supervision is not sufficient to provide benefit to the patients.

Study and design	Participants	Methods	Limitations	Conclusions
		specific recommendations (ex. participants instructed to do what they think would make them feel better).		
Garcia-Toro 2012 RCT*	n = 80 nonseasonal depressive outpatients, ≥ 18 y.	Participants randomized to six months of following an active group intervention, advising on sleep patterns, 1h of walking per day, 2h sunlight exposure per day, and a healthy, balanced diet (specific recommendations included), or a control condition where the same four topics were mentioned without specific recommendations (i.e. participants instructed to do what they think would make them feel better).	Small sample size, poor homogeneity participants' of affective disorders	Lifestyle recommendations (sleep, exercise, sunlight exposure, diet) can effectively complement antidepressant therapy.

BDI: Beck Depression Inventory; DASH diet: Dietary Approaches to Stop Hypertension diet; DHA: docosahexaenoic acid; EPA: eicosapentaenoic acid; ex.: example; FFQ: food frequency questionnaire; GI: Glycemic index; GL: glycemic load; h: hour; m: months; MUFA: monounsaturated fatty acids; n-3: omega-3; n-6: omega-6; NR: not reported; PUFA: omega-3/omega-6 polyunsaturated fatty acids; RCT: randomized controlled trial; SFA: saturated fatty acids; TFA: trans unsaturated fatty acids; y: years

*Garcia-Toro 2012 is a pilot study of the same program being tested in Serrano Ripoll 2015

^Four narrative reviews are not included in the Appendix due to the quantity of SRs that provided a more in-depth analysis of the evidence on this topic.

Q8. What are the functional, social, intellectual, physical and psychological problems experienced by children and teens living with an immediate family member who has depression?

Study / Included	Participants	Methods	Limitations	Conclusions
Systematic Review with Meta-analysis				
Sui 2016	n = 974 mothers with PND and n = 5596 mothers without PND from 9 prospective cohort studies.	Meta-analysis of prospective cohort studies reporting IQ among children of PND mothers and non-PND mothers for all years up to December 2013.	Among the included studies only one had a relatively large sample size and numbers in each of the subgroups was small; although the majority of the primary studies were high quality most did not adequately control for confounding factors; the method of diagnosing PND varied in primary studies.	Children of PND mothers had significantly lower full IQ scores than those of non-PND mothers (WMD = -4.384; 95%CI, -6.715 to -2.053; p = .001); heterogeneity across studies was marginally significant (I2 = 51.9%, p = .052); for verbal IQ the SMD between children of PND mothers and those of non-PND mothers was -0.361 (95% CI, -0.564 to -0.158; p< .001); no significant results were found for subgroup analysis of socioeconomic status, child's age at evaluation, study quality, or diagnostic method of postnatal depression.
Goodman 2011	n = 80,851 mother-child dyads from 193 prospective studies.	Meta-analysis of studies presenting quantitative data on the association between maternal depression and the child outcomes of interest published between 1982 and 2009.	Minimal information about included studies; most studies sampled largely homogeneous, middle- and upper-middle income, predominantly Caucasian families; this meta-analysis does not address any causal associations.	Maternal depression was more strongly associated with children internalizing problems than with negative emotion/behaviour (g = .21, p< .001) or positive emotion/behaviour (g = .30, p< .001). Maternal depression was more strongly associated with their children's general psychopathology than with their externalizing problems (g = -.05, p< .01) and than their negative (g = .22, p< .001) and positive emotion/ behaviour (g = .30, p< .001). Maternal depression was more strongly associated with externalizing problems than with negative (g = .17, p< .001) or positive affect/behaviour (g = .25, p< .001) and more strongly associated with negative affect/behaviour than with positive affect/behaviour (g = .08, p< .05).
Systematic Review with Narrative Synthesis				
Sanger 2015	n = 13,199 families across 8 cohorts (16 studies) with a mean follow-up of 14 years.	Narrative synthesis examining if maternal PND is associated with offspring psychological (cognitive, externalising, internalising, psychosocial, and psychiatric) outcomes up until September 2013.	Many of the primary studies reported relatively high drop-out rates at follow-up.	*Cognitive* (n=4 studies): overall studies found significant association between PND and cognitive outcomes (i.e., IQ scores, secondary school completion); *internalizing problems* (n=10), *externalizing problems* (n=7): studies found either weak or no significant results between PND and offspring internalizing and externalising problems; *psychopathology*

				(n=2): no significant associations were found between exposure to maternal PND and offspring DSM-IV psychiatric diagnoses (depression, anxiety, ODD, CD, ADHD, bipolar disorder, eating disorders, and psychosis) at follow-up (OR=1.25, 95 % CI=0.51–3.10); offspring of mothers with PND were four times more likely to meet a psychiatric diagnosis than offspring in the control group (OR=4.0, p<.01); *psychosocial development* (n=2): PND was associated with lower offspring Social Competence scores at 16 years; female offspring who were exposed to PND experienced elevated levels of emotional sensitivity at age 13 (F=10.73, p=0.01).
Waters 2014	n = 40,843 mothers from 26 prospective studies.	Narrative synthesis of primary studies assessing the impact of antenatal depression on children's cognitive, behavioural, emotional, psychiatric, neuroendocrine, nervous system, and brain-related outcomes; searched all years up to December 2013.	Common methodological problem of the included studies is the reliance on mothers' reports of variables, potentially giving rise to biased maternal reports of child outcomes; inconsistent findings in studies likely reflect methodological differences between studies as well as other limitations including sampling problems, measurement inconsistencies, and variability across studies regarding the presence of unmeasured residual confounding factors.	A consistent finding that antenatal depression effected children's conduct problems and antisocial behaviour, with adverse offspring outcomes demonstrated in infancy, childhood and adolescence; for cognitive outcomes the results are contradictory, reporting either no effect or small effects that attenuate following adjustment for other antenatal or postnatal risk factors; women who are depressed during pregnancy and their children are typically exposed to multiple risk factors.
Lampard 2014	n = 59,658 children across 7 cohorts (9 studies) with a follow-up range from 1 – 12 years.	Narrative synthesis examining prospective studies on the association between maternal episodic and chronic depression and child weight outcomes, for all years up to January 2013.	Heterogeneity in the results for BMI and indicators of adiposity; across included studies, the ascertainment of exposure to maternal depression was weak.	Episodic maternal depression and risk for child overweight or obesity failed to observe an effect; results suggest that chronic depression may play an important role in a child being overweight.
Hendricks 2012	n = 8,455 parent/child dyads from 13 cohort and cross-sectional studies with a mean	Narrative synthesis and qualitative thematic analysis, included articles with relevance to maternal depression and early childhood aggression (age 0-6)	Difficult to control for many confounders in primary studies; many of the studies included diverse populations.	Found that when maternal depression exists, early childhood aggression is more likely to occur; mothers with depression exhibited forms of negative parenting behaviours including emotional withdrawal, maternal

	follow-up of 23 months to 5 years.	and empirical studies with a sample size greater than 50; searched between 2000 and 2010.		intolerance and irritability; all of the articles agree that internal and external influencing factors mediate the relationship between child-bearing depression and early childhood aggression.
Corriea 2007	NR; 19 studies (cross-sectional and prospective longitudinal) primarily focused on maternal anxiety with 4 reporting on maternal depression.	Narrative synthesis, included all study designs between 1998 and 2003.	Full text reviewed only for articles that could be found in Brazil libraries; few details on included study characteristics provided.	In children at four years of age parental pre- and postnatal depression was responsible for increasing the mean rate of behavioural and emotional problems; findings from one study indicate that maternal anxiety/depression appear as risk factors for the development of psychopathologies during the child's adolescence.

CI: confidence interval; IQ: intelligence quotient; NR: not reported; ns: not statistically significant; OR: odds ratio; PND: post-natal depression; RCT: randomised controlled trial; RR: risk ratio; SMD: standard mean difference; UK: United Kingdom; US: United States; WMD: weighted mean difference; y: years

Q9. What interventions are effective in preventing and treating workplace depression and reducing stigma associated with depression in the workplace?

Study and design	Participants	Methods	Limitations	Conclusions
Main outcome measure: Depression				
Joyce 2016 Meta-review	N=NR, 20 reviews (481 primary studies).	Synthesis of SRs of effectiveness of workplace mental health interventions for anxiety and depression.	Exclusion of occupation specific reviews, studies had small sizes in the treatment groups and there was a lack of randomization.	Primary prevention strategies of increased employee control and promotion of physical activity appear to enhance well-being and reduce symptoms of depression and anxiety (moderate evidence). Impact of primary prevention strategies on work-related outcomes is unknown. CBT-stress management as a secondary intervention reduces the impact of work stress (strong evidence) while there is strong evidence *against* psychological debriefing. There is moderate evidence supporting tertiary interventions with a specific focus on the workplace, such as CBT and exposure therapy for improving individual outcomes, but mixed results for work-related outcomes such as absenteeism.
Tan 2014 Systematic review	N=2501 patients from 9 RCTs.	Pooled meta-analysis of RCTs of work place interventions aimed at preventing the development of depression.	There were not enough studies to make direct comparisons on which type of intervention is most effective. No studies had a non-depressed sample at baseline and are not true prevention studies.	There is good quality evidence that universally delivered workplace interventions targeting mental health can reduce depression symptoms among workers. There is more evidence for the effectiveness of CBT-based programs than other interventions.
Chu 2014 Systematic review	N=2025 patients from 17 studies (13 RCTs, 2 comparison trials, 2 controlled trials); 2 RCTs were on depression (N=71).	Narrative synthesis of studies examining the effectiveness of workplace physical activity interventions on depression, stress and anxiety.	Outcome measurements for depression were inconsistent across studies.	Workplace physical activity programs in combination with a behavior modification program can significantly reduce depression scores, while exercise training alone improves depression scores but not significantly.
Dietrich 2012 Systematic review	N=9743 employees in 1 quasi-experimental study, n=667 had depression.	Narrative summary of existing evidence-based prevention strategies for depression in the workplace.	No randomization, intervention was for staff on sick leave, only one study.	Providing psychoeducation along with the diagnosis of depression significantly decreases symptom severity and improves remission rates. Men over the age of 40 appear to benefit more from this intervention than persons under 40, especially women.

Martin 2009 Systematic review	N=2640 adults in 17 studies (14 RCTs and 3 quasi-experimental studies).	Meta-analysis on the impact of workplace health promotion interventions on depressive symptoms.	High heterogeneity between populations and interventions.	A variety of direct and indirect workplace health promotion interventions appear to have a small effect on decreasing depression symptoms.
Main outcome measure: absenteeism				
Nieuwenhuijsen 2014 Systematic review	N=5996 patients from 23 studies, 5 were work-directed interventions (N=544).	Pooled analysis of RCTs and cluster RCTs of interventions aimed at reducing work disability in employees with depression. Work-directed interventions included modified work duties or hours and/or supporting the worker in coping with depression.	Two of the five work-directed studies were rated as a high risk of bias.	Adding a work-directed intervention to a clinical depression intervention has a positive effect on sickness absences (moderate evidence) in the medium term. Similar effects on depressive symptoms could not be confirmed.
Furlan 2012 Systematic review	N=NR, adults in 14 articles from 10 RCTs and 2 NRS.	Narrative summary of existing workplace interventions to manage depression determined by work-related outcomes such as absenteeism.	All included studies had a high risk of bias and GRADED as very low quality evidence for all outcomes.	Insufficient evidence to determine effectiveness of workplace interventions to manage depression.

CBT: cognitive behavioural therapy, NR: not reported, NRS: non-randomized study, RCT: randomized control trial, SR: systematic review

Q10. Are there structural or functional changes in brains due to antidepressant therapy during brain development (in children)?

Study and design	Participants	Methods	Limitations	Conclusions
Cousins 2015 Review	NA	Narrative review of selected publications relating to neurodevelopment during adolescence and the effects of antidepressants on the adolescent brain.	Selected review, only addresses the serotonin reuptake inhibitor (SSRI) fluoxetine and not escitalopram due to licensing differences in this population between the UK (country of authorship) and the USA.	Studies on the effects of antidepressants on the brain of adolescents have been mainly based on animal models and suggest an age-dependent response. Only referenced one human study (Tao 2012 below).
Tao 2012 Prospective cohort study	n = 15 adolescents.	Measured brain activation in response to changing negative facial expressions in depressed adolescents being treated with fluoxetine compared to normal controls.	Patients with comorbid psychiatric disorders such as anxiety were included which may confound results. Responses to positive emotions were not evaluated.	Brain activity normalized in the depressed adolescents after 8 weeks of treatment with fluoxetine.

NA: not applicable, UK: United Kingdom, USA: United States of America

Q11. What is the role of the family in the treatment and trajectory of depression?

Study and design	Participants	Methods	Limitations	Conclusions
Main diagnosis: Depression				
Brady 2017 Systematic review	N= 928 patients with MDD ages 14-85 yrs from 9 studies (10 articles-7 RCTs, 3 within-subject studies).	Narrative synthesis of RCTs and within-subject studies of the evidence for family psychoeducation (FPE) for MDD.	Population restricted to 14 years and older and only articles and abstracts published in peer-reviewed journals.	Current evidence suggests that FPE interventions lead to improved outcomes for patients and improved well-being for their families (carers). Multi-family FPE is at least as effective and single family FPE for improving outcomes.
Stahl 2016 Systematic review	N= 1870 adults >60 yrs from 10 studies.	Narrative synthesis of RCTs of interventions that target both a patient with depression and their support person (dyadic interventions).	Majority of studies compared dyadic intervention with usual care rather than single vs. dyadic interventions. Not all patients met the CES-D criteria for clinically significant depressive symptoms.	Dyadic interventions can decrease symptoms with medium effect sizes in patients with MDD and small effect sizes in patients with depressive symptoms.
Meis 2013 Systematic review	Adults from 39 studies (51 RCTs), only 1 (n=35) was on depression.	Narrative synthesis of RCTs of family interventions for adult mental health conditions.	Only 1 RCT (n=35) addressed patients with depression.	The single RCT on depression found brief couple therapy significantly improved depression symptoms compared to patients on a waitlist with a low strength of evidence.
Henken 2007 Systematic review	N= 519 patients of all ages from 6 studies.	Narrative synthesis of RCTs of different types of family therapy and their association with depression symptom levels.	Available evidence was too heterogeneous and scarce to determine the effectiveness of family therapy on depressive symptoms.	Family therapy appears to be more effective than no treatment however the certainty of its effectiveness is unclear.
Main diagnosis: Cancer				
Wang 2017 Systematic Review	N= 697 adults diagnosed with cancer in 6 studies (6 additional studies did not address depression).	Meta-analysis of RCTs of the impact of couples therapy on Quality of Life scores of cancer patients and their spouses.	Small number of studies with significant heterogeneity between studies, results should be considered preliminary.	Couple-based intervention revealed significant improvements in depression scores with psychoeducational interventions yielding larger effects than skill training.
Main diagnosis: Stroke				
Vallury 2015[4] Systematic Review	N=3739 adult stroke survivors in 25 studies.	Narrative synthesis of RCTs and quasi-experimental designs of the available evidence regarding family-oriented interventions to prevent and manage depression after stroke.	All relevant studies were included regardless of bias or quality, over half had some risk of bias.	Family-oriented interventions aimed at reducing post-stroke depression can be effective for both patients and caregivers.

CES-D: Center for Epidemiologic Studies Depression Scale FPE: Family psychoeducation MDD: Major Depressive Disorder RCT: randomized control trial