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Research paper

Cost-effectiveness of an indicated preventive intervention for depression in adolescents: a model to support decision making

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ABSTRACT

Background: Adolescent depression has negative health and economic outcomes in the short- and long-term. Indicated preventive interventions, in particular group based cognitive behavioural therapy (GB-CBT), are effective in preventing depression in adolescents with subsyndromal depression. However, little is known about the cost-effectiveness of these interventions.

Methods: A Markov cohort model was used to conduct cost-effectiveness analyses comparing a GB-CBT indicated preventive intervention for depression, to a no-intervention option in a Swedish setting. Taking a time horizon of 5- and 10 years, incremental differences in societal costs and health benefits expressed as differences in the proportion of cases of depression prevented, and as quality adjusted life years (QALYs) gained were estimated. Through univariate and probabilistic sensitivity analyses, the robustness of the results was explored. Costs, presented in 2018 USD, and effects were discounted at a yearly rate of 3%.

Results: The base-case analysis showed that GB-CBT indicated preventive intervention incurred lower costs, prevented a larger proportion of cases of depression and generated higher QALYs compared to the no-intervention option for both time horizons. Offering the intervention was even a cost saving strategy and demonstrated a probability of being cost-effective of over 95%. In the sensitivity analyses, these results were robust to the modelling assumptions.

Limitations: The study considered a homogeneous cohort and assumed a constant annual decay rate of the relative treatment effect.

Conclusions: GB-CBT indicated preventive interventions for depression in adolescence can generate good value for money compared to leaving adolescents with subsyndromal depression untreated.

1. Introduction

Unipolar depressive disorder is relatively common in both adolescents and adults with an estimated point prevalence of about 5-6 % (Costello et al., 2006; Erskine et al., 2017; Kessler and Bromet, 2013). Thus, a public health problem imposing an economic strain on the healthcare- and welfare systems, and society at large.

A narrower focus on adolescence, when a substantial proportion of people experience their first depressive episode (Kessler et al., 2005; Thapar et al., 2012) paints a worrying picture. Recent research notes depression in adolescents to be one of the diseases contributing the most to the overall disease burden (Collaborators et al., 2019; Global Burden of Disease Pediatrics et al., 2016). It also suggests that the risk of depression in this age group tends to increase from 5% in early teens to 20% (Lewinsohn et al., 1999; Merikangas et al., 2010) during late adolescence with a high female to male ratio (Bromet et al.,

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2011). Adolescent depression seems to have a bad prognosis compared to adult onset disease. The bad prognosis is reflected in the longer durations of depressive episodes, and higher risk of relapses, recurrences (Kovacs, 1996), suicides (van Noorden et al., 2011) as well as a tendency to turn into bipolar affective disorder (Kovacs, 1996). Longitudinal studies have demonstrated the dire consequences of adolescent depression both in the short- and long-term (Alaie et al., 2019; Clayborne et al., 2019; Johnson et al., 2018; Linder et al., 2019). The consequences pertain mainly to the increased risk of future mental health illnesses, poor psychosocial functioning, increased mortality risk, and the high costs to society. Costs due to adolescent depression span from direct medical costs related to the use of medication, inpatient and outpatient care, to indirect costs related to work absence, early retirement and premature death of the adolescents but also their primary caretakers especially inform of work absence. Other indirect societal costs accrue from criminality, increased education needs and increased social welfare dependence (Bardone et al., 1996; McLeod et al., 2016) due to under performance at the labour market as many of these individuals with adolescent onset depression tend not to achieve the best of their education aspirations (Fletcher, 2008, 2010; Jonsson et al., 2010) to compete favourably. Concerning healthcare consumption costs, direct medical costs due to adolescent depressive disorders are substantial and differ between the clinical subtypes of depression (Bodden et al., 2018; Ssegonja et al., 2019). Further, indirect costs of adolescent depression are noted to contribute an even larger part of all depression related costs compared to the direct costs (Bodden et al., 2018; Evans-Lacko and Knapp, 2016; Lee et al., 2017a).

Several preventive interventions for adolescent depression have been developed and evaluated for their effectiveness (Cox et al., 2012; Hetrick et al., 2015; Merry et al., 2011; Ssegonja et al., 2018). These interventions are of different theoretical underpinnings, such as cognitive behavioural therapy, interpersonal therapy, and coaching. The interventions are usually delivered in healthcare centres, schools and other community settings by clinicians, teachers, and other trained non-healthcare personnel. In particular, interventions based on cognitive behavioural therapy (CBT) have been widely studied, well accepted and have demonstrated effects in both clinical and non-clinical settings (Hetrick et al., 2015). These interventions aim to equip adolescents with skills to be able to recognize certain life stressors (triggers or thoughts), develop alternative thinking patterns and ultimately employ appropriate behavioural responses to them. Group-based cognitive behavioural therapy (GB-CBT) may be delivered as indicated preventive interventions targeted towards individuals with clinical symptoms of depression below the threshold for a diagnosis, in other words subsyndromal depression (Rodríguez et al., 2012), to prevent depression. GB-CBT indicated preventive interventions for depression have shown promising results, e.g. they have demonstrated a substantial reduction in the risk of developing depression, with a relative risk (RR) ranging from 0.38 to 0.66 at 12 months follow-up, in addition to symptom improvement relative to the comparators (Merry et al., 2011; Ssegonja et al., 2018). These interventions have not been widely adopted despite the demonstrated benefits of increasing provision and access of such preventive interventions or early treatment of depression and the return on investment (Chisholm et al., 2016).

For broader implementation of GB-CBT indicated preventive interventions for depression, decision makers need evidence on the cost-effectiveness of these interventions. However, the evidence on the cost-effectiveness of GB-CBT indicated preventive interventions for depression is limited and the few studies (Lee et al., 2017b; Mihalopoulos et al., 2012) reporting these interventions to be cost-effective used population based models which do not present the breakdown of depressed individuals and those in remission. This is partly because of the difficulty to simulate the natural history of depression (Haji Ali Afzali et al., 2012; Kolovos et al., 2017a; Pirraglia et al., 2004). However, such a breakdown has implications on the costs and health benefits' estimates. Therefore, more modelling studies to address this knowledge gap are necessary.

The present study aimed to assess whether a GB-CBT indicated preventive intervention for depression offered to adolescents with subsyndromal depression provides good value for money in the long-term. The study used input data from existing literature to conduct model-based cost-effectiveness analyses comparing a GB-CBT indicated preventive intervention for depression in adolescents to a no-intervention option.

2. Methods

2.1. Economic evaluation framework

This study used a decision analytic modelling approach to assess the cost-effectiveness of a GB-CBT indicated intervention for the prevention of depression in adolescents in a Swedish setting. A hypothetical homogeneous cohort, with uniform clinical and background characteristics, of adolescents at a start-age of 15 years with subsyndromal depression (sD) was modelled, as GB-CBT indicated preventive interventions have demonstrated effectiveness in reducing depressive symptoms and preventing full-blown depression in this particular group (Ssegonja et al., 2018). Using the model, the long-term costs and health benefits expressed as differences in the proportion of cases of depression prevented as well as quality adjusted life years (QALYs) gained for a population of adolescents with sD were modelled over a period of 5- and 10 years. The analyses were done taking into account healthcare costs alone, healthcare perspective and then also including productivity losses due to morbidity and premature death (limited societal perspective). The necessary data inputs were sourced from published literature and assumptions were made when data was not available. An annual discount rate of 3% was applied to both costs and benefits occurring after the first year of follow-up as recommended by current Washington panel recommendations (Sanders et al., 2016) and the Swedish Dental and Pharmaceutical Benefits Agency's (Edling A and Stenberg A M, 2003). Thereafter, the incremental differences in costs and effects were estimated for the alternatives (GB-CBT indicated preventive intervention vs no-intervention) and the cost-effectiveness judged over a range of willingness to pay (WTP) threshold values.

2.2. Study population

The study population was a homogeneous group of adolescents with subsyndromal depression defined as having depressive symptoms above a given cut-off on a validated screening instrument, such as the Beck's depression inventory II (Beck et al., 1996) and Children's depression inventory (Kovacs, 1985), or diagnostic scales, for example the Schedule for Affective disorder and Schizophrenia for School Age Children tool (K-SADS) (Kaufman et al., 1997), but not fulfilling the criteria for a major depressive disorder (Rodríguez et al., 2012). The group was assumed to be homogeneous with respect to age, school year, socioeconomic status, type of school, participation, adherence and symptom severity, to name a few. Therefore, the modelling process started with a population of 15-year-old males and females already screened for depression and found to have subsyndromal disease, that then get offered the intervention and accepted to participate.

3. Intervention and comparators

3.1. A GB-CBT indicated preventive intervention

GB-CBT indicated preventive interventions include similar components and conform to the same general format. Thus, the example of a GB-CBT indicated preventive intervention studied was constructed using characteristics from a recent systematic review and meta-analysis (Ssegonja et al., 2018). The intervention was assigned the following characteristics: an indicated preventive programme built on GB-CBT

Table 1
GB-CBT indicated preventive intervention's characteristics.

Intervention feature	Mean (SD)
Number of participants per group	8 (1.69) adolescents
Average number of sessions	9 (3.21) sessions
Average attendance	6.5 (2.14) sessions
Average follow-up	13 (10.82) months
Average duration per session	70 (20.44) minutes
Supervision	Once weekly
Number of facilitators	1 to 2
Intervention duration	9 (3.18) weeks

principles, delivered mainly by school nurses and psychologists (2 facilitators) through teaching, seminars or workshops in a school setting, and requiring weekly supervision of the intervention facilitators over a period of 9 weeks. The intervention was assumed to be delivered in both public and private schools in municipalities in Sweden to first year high school students. The characteristics are summarized in Table 1.

3.2. Comparator

In this work, the no-intervention option was considered as the comparator.

3.3. Model description

Due to the chronic and recurrent nature of depression, a Markov cohort model was chosen to simulate how the cohort of adolescents with sD transitioned between different states of disease progression over time. The model consisted of six health states:

Healthy (H), individuals with no depressive symptoms and without a functional impairment related to depression;
Subsyndromal depression (sD), individuals with depressive symptoms below the threshold for a depressive disorder and related functional impairment;
Depressed (D), individuals with a depressive disorder and related functional impairment;
Remission (R), previously depressed individuals with minimal or absence of depressive symptoms and with regained premorbid functionality (Kennedy, 2002);
Recovered (Re), individuals in remission who have been symptom free and regained premorbid functionality for the last four to six months or more, and possibly still on or not on medication (Furukawa et al., 2008);
Dead (De), was the absorbing state in the model, as shown in Figure 1.

Based on the study population, the model assumes that all participants start in the sD state before going through the rest of the natural history of the disease. The model used one-year cycles, as a year was considered long enough to capture important changes in the clinical progression and costs for majority of the individuals with depression throughout the disease course (Furukawa et al., 2008; Furukawa et al., 2000). The study population was modelled from a start-age of 15 years with everyone in the intervention group receiving the intervention. We used two time-horizons: I) 5 years (until adolescents reached adulthood) because of the differences in disease epidemiology, participation on the employment market and healthcare consumption patterns between adolescents and adults. II) Ten years: because we expected the treatment effect to have decayed to the minimum, and thus offering no advantage to have a longer time horizon.

4. Model Inputs

4.1. Effectiveness estimates

Intervention effectiveness inputs were derived from a recent systematic review and meta-analysis (Ssegonja et al., 2018). The meta-analysis pooled effectiveness estimates, expressed as relative risks (RR) and standardized mean differences (SMD), from randomized control trials comparing GB-CBT indicated preventive interventions for depression in adolescents with control conditions with a follow-up of over a year, using random effects models (Ssegonja et al., 2018). In this work, the SMDs were transformed into ORs/RRs for use in the model using the Cochrane conversion method (Higgins and Green, 2011; Lee et al., 2018).

4.2. Health benefits

Health benefits were expressed as differences in the proportion of cases of depression prevented and QALYs gained. The difference in the proportion of cases of depression prevented were estimated by taking the difference in the proportions of the study cohort in the depressed state per cycle between the intervention and comparator groups. The health-related quality of life (HRQoL) utility weights were derived from existing literature. The HRQoL utility weight for the health state sD was considered to be 0.62 (0.58 – 0.65), as reported in a recent patient level data meta-analytic study (Kolovos et al., 2017b). In view of absence of symptoms and regaining premorbid functioning, the utility weight for the health state “Re” was assumed to be equal to that of a health individual, “H” in the general Swedish population, that is, 0.89 (0.78 – 0.95) (Burstrom et al., 2001, 2006). The utility weights for the states “R” and “D” were assumed as 0.70 (0.67 – 0.73) and 0.39 (0.35 – 0.43) respectively (Kolovos et al., 2017b). In the model, total QALYs attributed to a given health state were calculated by multiplying the proportion of the cohort in the health state at a given cycle by the corresponding utility weight.

4.3. Costs

All costs were converted to USD and uprated to 2018 prices, using purchasing power parities and inflation indices (Shemilt et al., 2010).

4.4. Intervention cost

The intervention cost was estimated from the characteristics of the indicated preventive intervention described above (Table 1). The unit costs, estimated intervention cost and their related information sources are summarized in Table 2. All costs were based on a group size of eight participants and two facilitators. The cost of materials was sourced from an intervention study with a similar group size (Sarkadi et al., 2018) while the facilitators’ training allowance was estimated using the cost for leisure time lost (Johannesson et al., 1991).

4.5. Direct healthcare costs

The study used an average yearly total direct cost due to depression (including inpatient care, general practice and specialized outpatient care, and medication) of $16,170 ($14,885 - $17,455) (Bodden et al., 2018) per person for a depressed adolescent patient, “D” and $5,920 ($5,372 - $6,699) (Sobocki et al., 2007) for a depressed adult, and an average yearly cost of $1,075 ($727 - $1,423) (Buntrock et al., 2017) per person for an individual with “sD”. The average yearly direct healthcare cost related to depression for an individual in “R” was estimated at $1,154 ($908 - $1,400) (Woo et al., 2014). The average yearly direct healthcare cost for an individual in the “H” and “Re” state was considered to be zero, as these groups were assumed to consume healthcare resources for other concerns other than depression.

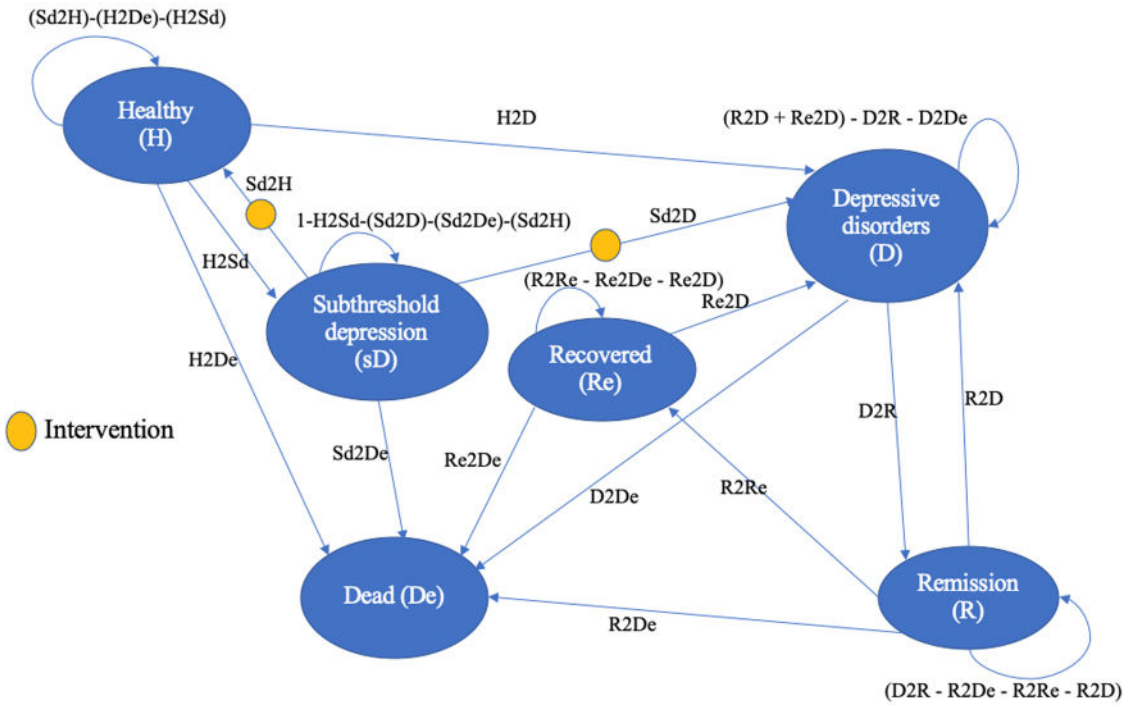

Figure 1. Model structure
Note: transition probabilities; H2Sd: healthy to subthreshold depression, H2De: healthy to dead, H2D: healthy to depressed, Sd2H: subthreshold depression to healthy, Sd2D: subthreshold depression to depressed, Sd2De: subthreshold depression to dead, D2R: depressed to remission, D2De: depressed to dead, R2Re: remission to recovery, R2D: remission to depressed, R2De: remission to death, Re2D: recovered to depressed and Re2De: recovered to dead.

4.6. Indirect costs

Indirect costs related to depression comprised of average estimates of total productivity losses related to both morbidity and early mortality, including sick leave/work absence (absenteeism), reduced productivity while at work (presenteeism), and premature death. The costs related to absenteeism and presenteeism were sourced from the literature. The productivity losses due to premature death were estimated using the human capital approach multiplying the proportion of the working population, 16 years and above, that dies during the follow-up time and the average annual wage in Sweden for the 15-17 year olds, and then those 18 years and above retrieved from Statistics Sweden (SCB, 2019a). All the indirect costs and assumptions for their distributions are presented in Table 3. Productivity losses for the states "H" and "Re" were considered to be negligible as the individual is considered to have regained premorbid functionality. While modelling, the total costs due to depression for each cost component were calculated by multiplying the cost attributed to a given health state by the proportion of the cohort remaining in that health state at a particular time.

4.7. Transition probabilities and mortality

Estimates of transition probabilities between the different health states were retrieved from published literature (Table 3). The probability of getting full depression was retrieved from the Global burden of disease data 2017 (IHME, 2017) while the probability of getting subsyndromal depression when healthy from the literature (Oldehinkel et al., 1999). The probability of remission or recovery for individuals with "sD" was assumed to be similar to the natural remission of depression (Furukawa et al., 2000; Whiteford et al., 2013). Age dependent mortality data was derived from Swedish life tables for both males and females for year 2018, accessed from Statistics Sweden (SCB, 2019b). Rates were converted to probabilities and adjusted for time (Fleurence and Hollenbeak, 2007). The mortality rates/probabilities for the different health states were adjusted with relative risks derived from the literature (Table 3). Individuals in "R" were considered to have the same elevated mortality risk as in the state "sD". The individuals in the "Re" state were assumed to have the same mortality risk as the general population.

Table 2
Unit costs, cost items and intervention cost (2018 prices, 1 SEK = 0.11 USD).

Cost item	Unit cost (USD)	Frequency	Total cost/USD	Source
Training costs				
Facilitator training	68.05	7	3 810.80	Sweden's municipalities and counties
Rent of the venue	11.88	7	665.28	Uppsala municipality
Participants' allowances	10.69	7	598.64	35% of hourly wage (50)
Delivery costs				
Facilitator payment	68.05	9	1 429.05	Sweden's municipalities and counties
Supervision costs	68.05	9	714.53	Sweden's municipalities and counties
Rent of the venue	11.88	9	124.74	Uppsala municipality
Costs of materials	-	-	405.00	A proxy from another study (49)
Total cost			7 748.04	
Average cost per child			968.50	

Table 3
Uncertainty parameters of the model inputs and distributions.

Parameter description	Estimate (95% CI)	Distribution	Source
Transition probabilities			
Healthy to depressed	0.0093 (0.0065 - 0.0128)	Beta	(GBD, 2017)
sD to depression	0.041 (0.029 - 0.055)	Beta	(GBD, 2017)
sD to healthy	0.53 (0.45 - 0.60)	Beta	(Whiteford et al., 2013)
Healthy to sD	0.0249 (0.0132 - 0.0288)	Beta	(Oldehinkel et al., 1999)
Remission to recovered	0.40 (0.31 - 0.68)	Beta	(Hollon et al., 2014)
Depression to remission	0.72 (0.46 - 0.81)	Beta	(Hollon et al., 2014)
Remission to depression	0.50 (0.32 - 0.83)	Beta	(Sobocki et al., 2006)
Recovered to depression	0.20 (0.13 - 0.64)	Beta	(Sobocki et al., 2006)
Relapse/recurrence combined	0.14 (0.07 - 0.27)	Beta	(Machmutow et al., 2019)
RR of death with sD	1.33 (1.11 - 1.61)	LogNormal	(Cuijpers et al., 2013)
RR of death when depressed	1.58 (1.31 - 1.89)	LogNormal	(Cuijpers et al., 2013)
RR of depression given sD	4.47 (2.82; 7.08)	LogNormal	(Cuijpers and Smit, 2004)
HRQoL utilities			
Healthy	0.89 (0.78–0.95)	Beta	(Burstrom et al., 2006)
Subthreshold depression	0.62 (0.58 -0.62)	Beta	(Kolovos et al., 2017b)
Depressed	0.39 (0.35 - 0.43)	Beta	(Kolovos et al., 2017b)
Remission	0.70 (0.67 - 0.73)	Beta	(Kolovos et al., 2017b)
Recovered	0.89 (0.78–0.95)	Beta	(Burstrom et al., 2006)
Dead	0.00 (0.00 - 0.00)	Beta	_
Total cost for each state			
Healthy			
Direct cost	0 (0.00 - 0.00)	Gamma	_
Productivity losses	0 (0.00 - 0.00)	Gamma	_
Subsyndromal depression (sD)			
Direct cost	1,075 (727 - 1,423)	Gamma	(Buntrock et al., 2017)
Direct non-medical	981 (629 - 1,333)	Gamma	(Buntrock et al., 2017)
Productivity losses (absenteeism)	1,641 (1,208 - 2,074)	Gamma	(Buntrock et al., 2017)
Productivity losses (presenteeism)	2,829 (2,284 - 3,374)	Gamma	(Buntrock et al., 2017)
Depressed			
Direct cost	16,170 (14,885 - 17,455)	Gamma	(Bodden et al., 2018)
Direct non-medical	387 (328 - 446)	Gamma	(Bodden et al., 2018)
Productivity losses*	4,782 (4,513 - 5,051)	Gamma	(Bodden et al., 2018)
Direct cost#	5,920 (5,372 - 6,699)	Gamma	(Sobocki et al., 2007)
Direct non-medical#	387 (328 - 446)	Gamma	(Bodden et al., 2018)
Productivity losses* #	11,033 (9,517 - 12,665)	Gamma	(Sobocki et al., 2007)
Remission			
Direct	1,154 (908 - 1,400)	Gamma	(Woo et al., 2014)
Direct non-medical	386 (226 - 546)	Gamma	(Woo et al., 2014)
Productivity losses (absenteeism)	3,330 (1,906 - 4,754)	Gamma	(Woo et al., 2014)
Productivity losses (presenteeism)	7,828 (6,365 - 9,291)	Gamma	(Woo et al., 2014)
Recovered			
Direct cost	0 (0.00 - 0.00)	Gamma	_
Productivity losses	0 (0.00 - 0.00)	Gamma	_
Intervention effect			
Intervention effect on cases	0.49 (0.35 - 0.69)	LogNormal	(Ssegonja et al., 2018)
Intervention effect on symptoms	0.52 (0.33 - 0.85)	LogNormal	(Ssegonja et al., 2018)

sD: subsyndromal depression, RR: relative risk,
* Both absenteeism and presenteeism,
# Depression costs in adulthood, HRQoL: Health related quality of life

4.8. Base case analysis and uncertainty analysis

The base case analysis involved comparing the GB-CBT indicated preventive intervention to the no-intervention option, where the whole cohort in the intervention group was assumed to be homogeneous and have a complete uptake of the intervention. A rate of decay of the relative intervention effect of 40% each year was calculated from the estimates reported in a recent review (Ssegonja et al., 2018) and applied in the model. The decay rate was calculated as the difference in the relative effectiveness between two follow-up time points and expressed as a percentage. The intervention was assumed to be delivered once only, with no booster sessions; thus, the intervention cost was applied only in the first year of follow-up. The total costs, difference in proportion of cases of depression, and QALYs gained during each cycle were summed up for the different time horizons, that is, 5- and 10 years for both the intervention and no-intervention groups from both the healthcare and societal perspectives. This process was repeated in a Markov chain Monte Carlo simulation with 1000 iterations, from which mean estimates of the costs and effects were computed.

An incremental cost-effectiveness ratio (ICER) was then estimated by dividing incremental differences in mean costs by incremental differences in mean health benefits between the alternatives for each perspective, which was expressed as cost per additional case of depression prevented and cost per additional QALY gained. Using QALYs as the outcome, cost-effectiveness was judged at an implied willingness to pay (WTP) threshold value of $0 - $100000 per QALY from a societal perspective as reflected in international literature (Shiroiwa et al., 2010). In all analyses, 95% uncertainty intervals around the net costs, difference in proportion of cases of depression prevented, QALYs gained and ICERs estimates were produced from the probabilistic uncertainty analysis. All parameters thought to affect the results were attributed relevant distributions, and their combined impact on the model results were considered in the uncertainty analysis. To visualize the uncertainty in the output, simulated data points of cost differences and effects differences were plotted on a cost-effectiveness plane. Further, a cost-effectiveness acceptability curve was used to illustrate the

uncertainty around the estimates and inform decision uncertainty, that is the probability that the GB-CBT interventions are cost-effective given a range of willingness to pay ceiling values.

4.9. Sensitivity analyses

Through a series of univariate (one-way) sensitivity analyses, the effect of changes in key parameters of interest on the cost-effectiveness results was examined. The following scenarios were modelled: 1) the intervention effectiveness was applied to the first cycle only; 2) increasing the intervention cost by 50% to accommodate screening costs; 3) using an annual discount rate of 0% for health benefits and 6% for costs; 4) collapsing the health states "R" and "Re" into one state (also acted as a form of structural validation), that is, a combined estimate of the probability of relapse and recurrence (Machmutow et al., 2019); 5) treating the utility weights deterministically; 6) varying the proportion of intervention uptake; and 7) using a cycle length of 3 and then 6 months as reflected in some literature where patients may transit from one health state to another in less than a year (Angst et al., 2003; Furukawa et al., 2008; Judd et al., 1998). All the analyses and modelling were conducted in Microsoft EXCEL version 2016. For further details on the methods, see the technical report in the appendix, online supplement 1.

5. Results

5.1. Base case and uncertainty analyses

The base-case and uncertainty analyses demonstrated that a GB-CBT indicated preventive intervention for depression resulted into 0.07 (0; 0.14) proportion of depression cases prevented, and 0.12 (-0.36; 0.57) increased QALYs gained for the 5-year time horizon, and 0.10 (-0.05; 0.25) proportion of depression cases prevented and 0.15 (-0.79; 1.05) QALYs gained for the 10-year time horizon, compared to" no-intervention". At the same time, the intervention generated costs-savings when taking the societal and healthcare perspectives, compared to "no-intervention" during the 5 years, $-1,884 ($-3,581; $-324) and the 10 years, $-2,752 ($-6,317; $713) time horizons as illustrated in Table 4 and 5. The cost savings were significant over the 5-years follow-up from both the healthcare and societal perspectives. The intervention resulted into lower costs and increased health benefits for both, proportion of cases of depression prevented and QALYs, as shown on the cost-effectiveness plane in the online supplement 2, Figure S1- S4. Here, the majority of the observations fall on the lower-right quadrant of the plane, demonstrating that the intervention dominates the "no-intervention" comparator, entailing lower costs (plotted on the y-axis) and higher benefits (plotted on the x-axis). The probability of the intervention being cost-effective compared to the control was over 95% at a WTP threshold value of $0/depression case prevented and $0/QALY. Taking QALYs as the outcome, the probability of cost-effectiveness plateaus at 70% at a WTP threshold value of about $ 20000/QALY as most observations were in the right- and left lower quadrants of the cost effectiveness plane. This is illustrated in the cost-effectiveness acceptability curve in the online supplement 2, Figure S5-S8, which denotes the probability of the intervention being cost-effective over different WTP-values.

5.2. Sensitivity and uncertainty analyses

Changing different parameter values in the univariate (one-way) sensitivity analysis impacted the magnitude of the results, but overall, the direction of the findings remained unchanged. Applying the treatment effect to the first cycle resulted in decreased cost savings and a reduction in the probability of cost-effectiveness. Collapsing the health states, "R" and "Re", resulted in significant cost savings in the long-term. Increasing the intervention cost by 50%, reducing the cycle length to 3 and 6 months (not presented in the tables), varying the proportion of intervention uptake (not presented in the tables) and discounting costs at 6% while leaving the health benefits undiscounted, did not change the direction of the findings. A scenario analysis treating the utility weights as deterministic resulted into the intervention being largely cost saving and increasing the probability of cost-effectiveness over the WTP threshold values, $0 - $100000/QALY. However, it did not change the overall direction or meaning of the findings. In all scenarios, the GB-CBT indicated preventive intervention dominated the "no-intervention" option entailing lower costs and higher benefits (see Table 4 and 5).

6. Discussion

6.1. Main results

This study used a Markov cohort model to investigate whether adopting a GB-CBT indicated preventive intervention for depression in adolescents compared to a "no-intervention" option is good value for money in the long-term. The results demonstrated that GB-CBT indicated preventive interventions for depression have the potential to be cost saving while taking a societal and a healthcare perspective over both a 5- and 10-year time horizon.

The uncertainty and sensitivity analyses did not change the overall direction of results but highlighted some subtle features. The incremental differences in health benefits were relatively similar over the 5- and 10-year time horizons. This could be explained by the relationship between decay of the intervention effect over time and the natural remission of depressive disorders given that the intervention is a one-time endeavour, and thus may not be sufficient to protect an individual for a long time. During the first five years, the relative intervention effect decayed reflecting a decrease in the absolute effect difference to such a level that any improvements noted thereafter may be due to natural remission rather than the intervention effect, as per the assumptions considered.

Our results showed that the intervention is largely cost saving. However, taking QALYs gained as the outcome, there is a probability of 30% that the intervention may result into cost savings without a corresponding increase in health benefits or even more expensive about less than 1% of the time. That could be explained by several factors. Firstly, it could be due to a disruption in the ordinal nature of the utility weights for the different health states, that is, ensuring that an individual in the well state has a utility weight higher than an individual in remission, depressed and subsyndromal depression, as values are being drawn from the parameter assigned distributions during the Monte Carlo simulations. This observation is supported by the scenario modelled in the sensitivity analysis where the utility weights were treated deterministically (maintaining the ordinal nature) while allowing other parameters to vary. Here, we could see the no-intervention option being completely dominated. Secondly, it could also be due to the uncertainty in the utility weights for depression and the intervention effectiveness. Overall, in all the sensitivity analyses, the direction of results was robust to changes in the assumptions modelled. Applying the treatment effect to the first model cycle resulted in higher costs and lower benefits, as this affected the proportions of the cohort remaining in each health state on which the costs and effects depend. The intervention effect is central in determining the proportions of individuals in the different health states at any given timepoint, since it adjusts the transition probabilities of getting depressed or not for individuals in the subsyndromal depression state. However, changes in the assumptions on the decay rate of the treatment effect did not affect the direction of results either.

6.2. Comparison to other studies

The few studies examining the cost-effectiveness of preventive

Table 4
Costs effects, incremental differences and cost-effectiveness results - QALYs.

Perspective	5 years				10 years				
			Incremental differences				Incremental differences		
	QALYs	Costs (USD)	QALY difference	Cost difference	QALYs	Costs (USD)	QALY difference	Cost difference	Comment
Healthcare	Mean (95% UI)	Mean (95% UI)	Mean (95% UI)	Mean (95% UI)	Mean (95% UI)	Mean (95% UI)	Mean (95% UI)	Mean (95% UI)	
Base case									
Intervention	3.98 (3.59; 4.31)	607 (201; 974)	0.12 (-0.36; 0.57)	-313 (-2,141; -207)	7.45 (6.73; 8.00)	865 (442; 1,330)	0.15 (-0.79; 1.05)	-349 (-2,858; -31)	GB-CBT is Dominant
Control	3.87 (3.51; 4.13)	919 (638; 1,269)			7.30 (6.55; 7.83)	1,214 (885; 1,630)			
Sensitivity 1									
Intervention	3.98 (3.61; 4.30)	655 (238; 1,088)	0.10 (-0.36; 0.56)	-262 (-1,956; -25)	7.43 (6.67; 7.99)	902 (449; 1,377)	0.13 (-0.74; 1.03)	-297 (-2,874; 254)	GB-CBT is Dominant
Control	3.88 (3.53; 4.14)	918 (643; 1,252)			7.30 (6.65; 7.81)	1,199 (867; 1,626)			
Sensitivity 2									
Intervention	3.98 (3.59; 4.28)	619 (254; 994)	0.11 (-0.37; 0.60)	-299 (-2,044; -50)	7.43 (6.65; 7.98)	868 (487; 1,272)	0.14 (-0.75; 1.03)	-338 (-2,816; -10)	GB-CBT is Dominant
Control	3.87 (3.53; 4.13)	918 (660; 1,265)			7.29 (6.60; 7.81)	1,207 (863; 1,624)			
Sensitivity 3									
Intervention	4.21 (3.77; 4.55)	590 (240; 950)	0.11 (-0.44; 0.61)	-298 (-1,919; -184)	8.44 (7.50; 9.04)	815 (385; 1,212)	0.17 (-0.82; 1.21)	-300 (-2,569; -28)	GB-CBT is Dominant
Control	4.07 (3.73; 4.39)	888 (626; 1,191)			8.27 (7.44; 8.83)	1,114 (800; 1,509)			
Sensitivity 4									
Intervention	3.99 (3.59; 4.31)	620 (229; 985)	0.11 (-0.35; 0.55)	-316 (-2,078; -220)	7.44 (6.73; 8.00)	938 (467; 1,343)	0.17 (-0.67; 0.99)	-361 (-2,634; -122)	GB-CBT is Dominant
Control	3.86 (3.53; 4.14)	936 (661; 1,282)			7.26 (6.60; 7.77)	1299 (947; 1,712)			
Sensitivity 5									
Intervention	3.98 (3.90; 4.09)	612 (165; 970)	0.12 (0.03; 0.24)	-308 (-2,122; -152)	7.44 (7.34; 7.57)	871 (446; 1,302)	0.14 (0.01; 0.28)	-324 (-2,705; -12)	GB-CBT is Dominant
Control	3.86 (3.82; 3.90)	921 (660; 1,273)			7.30 (7.22; 7.38)	1,196 (860; 1,621)			
Societal									
Base case									
Intervention	3.98 (3.59; 4.31)	3,850 (2,507; 5,057)	0.12 (-0.36; 0.57)	-1,884 (-3,581; -324)	7.45 (6.73; 8.00)	9,880 (7,587; 12,409)	0.15 (-0.79; 1.05)	-2,752 (-6,317; 713)	GB-CBT is Dominant
Control	3.87 (3.51; 4.13)	5,733 (4,703; 6,879)			7.30 (6.55; 7.83)	12,632 (10,197; 15,382)			
Sensitivity 1									
Intervention	3.98 (3.61; 4.30)	4,038 (2,368; 5,523)	0.10 (-0.36; 0.56)	-1,682 (-3,672; -75)	7.43 (6.67; 7.99)	10,127(7,301; 12,892)	0.13 (-0.74; 1.03)	-2,597 (-6,498; 1,339)	GB-CBT is Dominant
Control	3.88 (3.53; 4.14)	5,720 (4,688; 6,836)			7.30 (6.65; 7.81)	12,724 (10,170; 15,647)			
Sensitivity 2									
Intervention	3.98 (3.59; 4.28)	3,889 (2,234; 4,686)	0.11 (-0.37; 0.60)	-1,868 (-3,527; -334)	7.43 (6.65; 7.98)	9,958 (7,684; 12,225)	0.14 (-0.75; 1.03)	-2,750 (-6,476; 859)	GB-CBT is Dominant
Control	3.87 (3.53; 4.13)	5,757 (4,754; 6,882)			7.29 (6.60; 7.81)	12,707 (10,252; 15,437)			
Sensitivity 3									
Intervention	4.21 (3.77; 4.55)	3,889 (2,234; 4,686)	0.11 (-0.44; 0.61)	-1,793 (-3,434; -314)	8.44 (7.50; 9.04)	8,626 (6,603; 10,866)	0.17 (-0.82; 1.21)	-2,447 (-5,700; 659)	GB-CBT is Dominant
Control	4.07 (3.73; 4.39)	5,757 (4,754; 6,882)			8.27 (7.44; 8.83)	11,073 (8,802; 13,520)			
Sensitivity 4									
Intervention	3.99 (3.59; 4.31)	4,193 (2,676; 5,474)	0.11 (-0.35; 0.55)	-2,129 (-3,899; -414)	7.44 (6.73; 8.00)	11,797 (9,220; 14,345)	0.17 (-0.67; 0.99)	-3,761 (-7,348; -236)	GB-CBT is Dominant
Control	3.86 (3.53; 4.14)	6,322 (5,206; 7,493)			7.26 (6.60; 7.77)	15,559 (13,172; 18,148)			
Sensitivity 5									
Intervention	3.98 (3.90; 4.09)	3,855 (2,491; 5,106)	0.12 (0.03; 0.24)	-1,904 (-3,600; -381)	7.44 (7.34; 7.57)	9,926 (7,626; 12,417)	0.14 (0.01; 0.28)	-2,764 (-6,378; 725)	GB-CBT is Dominant
Control	3.86 (3.82; 3.90)	5,759 (4,763; 6,886)			7.30 (7.22; 7.38)	12,690(10,112; 15,458)			

GB-CBT: group based cognitive behavioural therapy intervention

Table 5
Costs, effects, incremental differences and cost-effectiveness results - cases of depression prevented.

Perspective	5 years				10 years				
			Incremental differences				Incremental differences		
Health care	Proportion depressed Mean (95% UI)	Costs (USD) Mean (95% UI)	Cases prevented Mean (95% UI)	costs difference Mean (95% UI)	Proportion depressed Mean (95% UI)	Costs (USD) Mean (95% UI)	Cases prevented Mean (95% UI)	costs difference Mean (95% UI)	Comment
Base case									
Intervention	0.11 (0.08; 0.16)	607 (201; 974)	0.07 (0; 0.14)	-313 (-2,141; -207)	0.28 (0.19; 0.37)	865 (442; 1,330)	0.10 (-0.05; 0.25)	-349 (-2,858; -31)	GB-CBT is dominant
Control	0.18 (0.13; 0.25)	919 (638; 1,269)			0.38 (0.27; 0.51)	1,214 (885; 1,630)			
Sensitivity 1									
Intervention	0.12 (0.08; 0.17)	655 (238; 1,088)	0.06 (0; 0.13)	-262 (-1,956; -25)	0.29 (0.2; 0.39)	902 (449; 1,377)	0.09 (-0.06; 0.26)	-297 (-2,874; 254)	GB-CBT is dominant
Control	0.18 (0.13; 0.24)	918 (643; 1,252)			0.38 (0.26; 0.51)	1,199 (867; 1,626)			
Sensitivity 2									
Intervention	0.11 (0.08; 0.16)	619 (254; 994)	0.07 (0; 0.14)	-299 (-2,044; -50)	0.28 (0.2; 0.37)	868 (487; 1,272)	0.10 (-0.04; 0.27)	-338 (-2,816; -10)	GB-CBT is dominant
Control	0.18 (0.13; 0.24)	918 (660; 1,265)			0.38 (0.26; 0.52)	1,207 (863; 1,624)			
Sensitivity 3									
Intervention	0.12 (0.08; 0.17)	590 (240; 950)	0.07 (0; 0.15)	-298 (-1,919; -184)	0.32 (0.22; 0.44)	815 (385; 1,212)	0.11 (-0.06; 0.3)	-300 (-2,569; -28)	GB-CBT is dominant
Control	0.19 (0.14; 0.26)	888 (626; 1,191)			0.43 (0.31; 0.6)	1,114 (800; 1,509)			
Sensitivity 4									
Intervention	0.11 (0.07; 0.15)	620 (229; 985)	0.06 (0.01; 0.13)	-316 (-2,078; -220)	0.25 (0.18; 0.33)	938 (467; 1,343)	0.09 (-0.04; 0.21)	-361 (-2,634; -122)	GB-CBT is dominant
Control	0.17 (0.13; 0.23)	936 (661; 1,282)			0.33 (0.24; 0.45)	1299 (947; 1,712)			
Societal									
Base case									
Intervention	0.11 (0.08; 0.16)	3,850 (2,507; 5,057)	0.07 (0; 0.14)	-1,884 (-3,581; -324)	0.28 (0.19; 0.37)	9,880 (7,587; 12,409)	0.10 (-0.05; 0.25)	-2,752 (-6,317; 713)	GB-CBT is dominant
Control	0.18 (0.13; 0.25)	5,733 (4,703; 6,879)			0.38 (0.27; 0.51)	12,632 (10,197; 15,382)			
Sensitivity 1									
Intervention	0.12 (0.08; 0.17)	4,038 (2,368; 5,523)	0.06 (0; 0.13)	-1,682 (-3,672; -75)	0.29 (0.2; 0.39)	10,127(7,301; 12,892)	0.09 (-0.06; 0.26)	-2,597 (-6,498; 1,339)	GB-CBT is dominant
Control	0.18 (0.13; 0.24)	5,720 (4,688; 6,836)			0.38 (0.26; 0.51)	12,724 (10,170; 15,647)			
Sensitivity 2									
Intervention	0.11 (0.08; 0.16)	3,889 (2,234; 4,686)	0.07 (0; 0.14)	-1,868 (-3,527; -334)	0.28 (0.2; 0.37)	9,958 (7,684; 12,225)	0.10 (-0.04; 0.27)	-2,750 (-6,476; 859)	GB-CBT is dominant
Control	0.18 (0.13; 0.24)	5,757 (4,754; 6,882)			0.38 (0.26; 0.52)	12,707 (10,252; 15,437)			
Sensitivity 3									
Intervention	0.12 (0.08; 0.17)	3,889 (2,234; 4,686)	0.07 (0; 0.15)	-1,793 (-3,434; -314)	0.32 (0.22; 0.44)	8,626 (6,603; 10,866)	0.11 (-0.06; 0.3)	-2,447 (-5,700; 659)	GB-CBT is dominant
Control	0.19 (0.14; 0.26)	5,757 (4,754; 6,882)			0.43 (0.31; 0.6)	11,073 (8,802; 13,520)			
Sensitivity 4									
Intervention	0.11 (0.07; 0.15)	4,193 (2,676; 5,474)	0.06 (0.01; 0.13)	-2,129 (-3,899; -414)	0.25 (0.18; 0.33)	11,797 (9,220; 14,345)	0.09 (-0.04; 0.21)	-3,761 (-7,348; -236)	GB-CBT is dominant
Control	0.17 (0.13; 0.23)	6,322 (5,206; 7,493)			0.33 (0.24; 0.45)	15,559 (13,172; 18,148)			

interventions for depression in adolescents were essentially different compared to the current study (Lee et al., 2017b; Mihalopoulos et al., 2012). These differences span from the setting, population studied, the comparator condition, time horizons, age-groups, model type and health states, to the choice of outcome measure. For example, we chose to use QALYs rather than DALYs as done in other similar studies (Lee et al., 2017b; Mihalopoulos et al., 2012) because of the availability of utility weights and the acceptability of methods to determine them compared to disability weights.

However, in accordance with the findings, the two Australian studies presenting the cost-effectiveness of preventive interventions for depression (Lee et al., 2017b; Mihalopoulos et al., 2012), reported that indicated preventive interventions for adolescents are cost effective, thus, emphasizing that their implementation is good use of public money.

6.3. Strengths and limitations

This study is one of the few studies contributing evidence on the cost-effectiveness of such preventive measures for depression (Lee et al., 2017b; Mihalopoulos et al., 2012). It is also a unique study, that focuses on a high-risk population, that is, adolescents with subsyndromal depression and explores structural changes in the model to accommodate the natural history of the disease. The model was validated structurally by collapsing two health states ("Remission" and "Recovered") into one and the results were stable given those changes. Furthermore, the model in this study is generic with a relatively comprehensive presentation of the natural history of depression. Therefore, it offers a solid platform for modelling the cost-effectiveness of other clinical subtypes of depression, situations where the decision problem entails a different comparator, or a different setting other than Sweden.

However, this work has some shortcomings that should be noted. It considers a constant annual rate of decay of the treatment effect over time and homogeneity of the study population regarding treatment acceptance, adherence, and differential benefit. This choice was fuelled by data limitations. Another concern were inherent biases in the studies from which the model data inputs were retrieved, for example the quality of life weights as well as cost data are retrieved from different countries. There were no adolescent specific utility weights pertaining to the different health states in the model and thus adult values were used as model inputs. This was a conservative approach and could have resulted into lower quality of life estimates. The generalizability of the results may be limited by the contextual differences of the costing, healthcare system, and what qualifies as the treatment as usual or status quo. Our work assumes that treatment of depression translates into improvements in health-related quality of life. However, the literature on such an association is conflicting with recent advances supporting the observation that treatments of depression may result into clinical improvement without necessarily corresponding improvements in quality of life (IsHak et al., 2011; Zimmermann et al., 2018). Another aspect to pay attention to is the inclusion of screening costs and health care costs of the absorbing state in such analyses. This is especially important given the research reporting the difficulty with low response rates and implementation of CBT interventions in general (McMain et al., 2015). Finally, we also assumed that the interventions have no spill-over effects and have no substantial side-effects, but it is a risk that participants partaking in the intervention will be stigmatized, which in turn affects adherence (Linden, 2013; Scott and Young, 2016).

6.4. Policy implications and future research

Our results suggest that GB-CBT indicated preventive interventions for depression have the potential to be cost-effective. The results demonstrate that the interventions are not only effective in preventing depression, but that they also represent a good use of resources. Thus, we believe that both the clinical and economic evidence supports a policy of broader implementation of GB-CBT interventions after such results are replicated in other health economics studies using better data sources, e.g on the HRQoL utility weights and productivity losses. Of course, policy recommendations require consideration of additional attributes such as equity, acceptability, feasibility, and affordability. Furthermore, future health economics research should also focus on exploring the equity concerns or aspects that could impact the cost-effectiveness results. For example, it could be the case that the intervention completely dominates current practice or is cost-effective for a particular population sub-group, or the cost-effectiveness results are sensitive to a particular equity parameter. There should also be a focus on investigating the pattern or rate of decay of the treatment effect of these interventions over time.

7. Conclusion

GB-CBT indicated preventive interventions for depression in adolescents seem to have a potential to be good value for money. Further studies to replicate these findings are needed before a large-scale adoption and implementation is undertaken.

Authors' contributions

Concept and design: Ssegonja, Sampaio, Feldman, Jonsson, Alaie, Philipson, Murray, Langenskiöld, Hagberg, Sarkadi.

Drafting of the manuscript: Ssegonja, with contributions from Sampaio, Alaie, Murray, Philipson, Jonsson, Sarkadi, Langenskiöld.

Modelling plan: Ssegonja, Sampaio, Feldman, Jonsson, Alaie, Philipson, Hagberg, Langenskiöld.

Acquisition of data from the literature: Ssegonja, Sampaio, Feldman, Jonsson, Alaie, Philipson, Hagberg

Modelling and analysis: Ssegonja, Sampaio.

Interpretation of results: All authors.

Critical revision of the manuscript for important intellectual content: All authors.

Supervision: Murray, Jonsson and Feldman.

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Declaration of Competing Interest

The authors declare no conflict of interest.

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Supplementary materials

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