Online Supplementary Appendix to *The return on investment from adolescent mental health disorder prevention and treatment: a modelling study*

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Contents

Supplementary methodology 3
Model overview 3
Cohort 3
Base case, incidence, and remission of conditions of interest 5
Death 6
Bipolar disorder 7
Depression alone 7
Anxiety alone 8
Comorbid anxiety and depression 8
Accounting for age 9
Intrinsic value of health 10
Background morbidity 11
Interventions 11
Identification 11
Costing Approach 13
Costs of Interventions 15
Prevention of anxiety and depressive disorders 15
Treatment of anxiety disorders 16
Treatment of depressive disorders 18
Treatment of bipolar disorder 21
Suicide prevention 22
Intervention coverage and effectiveness 24
Universal prevention of anxiety and depressive disorders 25
Indicated prevention of depression 26
Treatment of anxiety disorders 26
Treatment of depressive disorders 27
Treatment of bipolar disorder 27
Suicide prevention 27
Education and employment outcomes 28

Education outcomes by age 28
Change in probability of graduation due to mental illness 29
Wage returns to education 30
Expected wages by adolescent experiences of mental illness 31
Acute effects of mental illness on employment 31
Model outputs 31
Sensitivity analysis 32
References 33

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Supplementary methodology

Model overview

In this model, we examine the health and economic effects of treating and preventing anxiety disorder, major depressive disorder, bipolar disorder, and death by suicide during adolescence (10-19 years of age). These conditions were selected because they represent the largest proportion of the burden of mental disorders among adolescents. In 2019, the top four conditions in terms of the burden of mental disorders among adolescents are anxiety disorders, major depression, conduct disorder, and bipolar disorder. Given the significant impact of premature mortality in this age group, we also considered suicide. Conduct disorder was eventually excluded given the lack of data on its diagnosis in low- and middle-income countries, and the fact that the majority of interventions identified focused on prevention through parenting interventions in early childhood, rather than during adolescence.

The model is a bespoke Markov model developed in R (version 4.1.1) with the package heemod.[1] It follows cohorts of adolescents for 80 years with a monthly model cycle length. We estimate the effects on lifelong health and economic outcomes, including education and employment, of intervening during adolescence for each cohort. None of the intervention effects endure more than 18 months after the intervention (see the Interventions section for more details on the sources of effect duration estimates). We therefore only track in detail the mental health of those who develop a condition of interest—except for death by suicide—before age 20. We include separate states for those who develop either anxiety or depression before age 20 and then develop the other in adulthood, as this allows us to account for both the long-term effects on education and employment of experiencing a mental disorder during adolescence and the short-term effects on employment of acute symptoms of mental illness during adulthood.

Following World Health Organization (WHO) guidance, all outputs are discounted at an annual rate of 3% (minimum 0%, maximum 5%), converted to a monthly discount rate of 0.25% (minimum 0%, maximum 0.42%).[2] Health values are converted to dollars, and both costs and benefits are discounted at the same rate.[3]

Cohort

Following the precedent set in the anxiety and depression investment case by Chisholm et al.,[4] the cohort includes all current 10-to-19-year-olds in the 36 countries that together accounted for 80% of the burden in DALYs of anxiety disorders, major depression, self-harm, and bipolar disorder in 2017, the most recent year of data from the Global Burden of Disease when we began modelling in early 2020.[5] The data have since been updated to 2019. The list of countries that account for 80% of the burden remains similar, though Thailand no longer appears on this list, and Angola, Myanmar, Spain, and Uzbekistan have been added. The countries included cover a wide range of income and geographic categories. *Table A1* presents the countries that account for 80% of the burden for both 2017 and 2019. In this analysis, we include the countries from the 2017 list.

Table A1: Countries that account for 80% of the burden of disease due to anxiety disorders, major depression, self-harm, and bipolar disorder for 2017 and 2019

Country	2017			2019		
	Global rank	DALYs lost	Percent of global DALYs lost	Global rank	DALYs lost	Percent of global DALYs lost
India	1	3,340,507	23.40%	1	2,907,868	20.96%
China	2	1,150,655	8.06%	2	1,166,300	8.41%
United States	3	799,324	5.60%	3	788,413	5.68%
Pakistan	4	505,338	3.54%	5	495,682	3.57%
Brazil	5	497,082	3.48%	4	535,809	3.86%
Nigeria	6	479,106	3.36%	6	420,804	3.03%
Bangladesh	7	417,377	2.92%	7	327,373	2.36%
Indonesia	8	361,434	2.53%	8	276,848	2.00%
Ethiopia	9	273,566	1.92%	11	239,655	1.73%
Mexico	10	243,551	1.71%	10	259,597	1.87%
Egypt	11	217,383	1.52%	9	260,446	1.88%
Democratic Republic of the Congo	12	208,700	1.46%	12	235,542	1.70%
Iran	13	191,736	1.34%	13	208,201	1.50%
Russian Federation	14	189,012	1.32%	15	181,447	1.31%
Philippines	15	183,859	1.29%	14	188,014	1.36%
Turkey	16	150,103	1.05%	16	177,724	1.28%
Japan	17	138,137	0.97%	25	112,977	0.81%
Tanzania	18	136,249	0.95%	20	131,822	0.95%
Argentina	19	136,002	0.95%	24	120,105	0.87%
France	20	126,174	0.88%	19	133,742	0.96%
Uganda	21	125,806	0.88%	23	125,026	0.90%
Germany	22	122,823	0.86%	22	126,498	0.91%
Kenya	23	120,355	0.84%	27	107,240	0.77%
Sudan	24	116,892	0.82%	17	143,390	1.03%
Afghanistan	25	106,105	0.74%	18	134,382	0.97%
Vietnam	26	105,407	0.74%	30	95,791	0.69%
Iraq	27	103,234	0.72%	21	127,198	0.92%
United Kingdom	28	102,832	0.72%	28	106,430	0.77%
South Africa	29	100,840	0.71%	33	91,146	0.66%
Morocco	30	98,174	0.69%	29	99,939	0.72%
Mozambique	31	93,806	0.66%	36	77,375	0.56%
Thailand	32	90,515	0.63%	40	74,471	0.54%
Yemen	33	88,373	0.62%	26	110,367	0.80%
Colombia	34	85,843	0.60%	32	91,546	0.66%

Italy	35	78,784	0.55%	35	79,783	0.58%
Algeria	36	77,637	0.54%	31	93,311	0.67%
Angola*	39	71,648	0.50%	34	81,064	0.58%
Myanmar*	37	76,472	0.55%	37	76,472	0.55%
Uzbekistan*	40	70,073	0.49%	38	75,454	0.54%
Spain*	50	59,061	0.41%	39	75,018	0.54%
*not in study sample						

The included countries appear in *Table A2* below, divided by WHO region and World Bank income classification.[6,7]

Table A2: 2017 countries by WHO region and World Bank income classification

	High	**Upper middle**	**Lower middle**	**Low**
AFRO	—	Algeria, South Africa	Kenya, Nigeria	Democratic Republic of the Congo, Ethiopia, Mozambique, Tanzania, Uganda
EMRO	—	Iran, Iraq	Egypt, Morocco, Pakistan, Sudan	Afghanistan, Yemen
EURO	France, Germany, Italy, United Kingdom	Russian Federation, Turkey	—	—
PAHO	Argentina, United States	Brazil, Colombia, Mexico	—	—
SEARO	—	Thailand	Bangladesh, India, Indonesia	—
WPRO	Japan	China	Philippines, Vietnam	—

Base case, incidence, and remission of conditions of interest

Each cohort begins with the number of people at the relevant age within each country, divided into male or female, from the United Nations Population Division.[8] These two groups are then divided into starting states according to the prevalence of acute major depressive disorder, anxiety disorders, and bipolar disorder according to the 2019 Global Burden of Disease (GBD) study. Following the GBD 2019 estimates, 23% of adolescents with bipolar disorder (range: 10%-39%) begin the model in a state of acute depression, 21% (range: 12%-33%) in a state of acute mania, and the balance begin in a state of

euthymia.[5] In addition, we used the global proportion of people with depression in the previous 12 months who also reported anxiety within the previous 12 months from the WHO World Mental Health surveys, 41.6%, to calculate the number of people to move from the single anxiety and depression states to the comorbid anxiety and depression starting state (see the section "comorbid anxiety and depression" for more details on this parameter).[9]

Wherever possible, the source for incidence, episode duration, and severity of symptoms was the 2019 GBD dataset and supporting documents. In all cases, probabilities are adjusted to account for the monthly cycle of the model instead of the annual probabilities in the source materials using the standard equation:

$$p_m = 1 - (1 - p_y)^{1/12} \quad (1)$$

Where p_m is the probability of an event in a given month and p_y is the annual probability of that event.

In the subsections below, we describe the additional sources of our estimates and our calculations in further detail for each condition. See *Supplementary File 2* for a summary of model parameters.

Death

From all non-death states in the model, it is possible to transition to two absorbing death states: death by suicide, and death not by suicide. The overall probability of death, adjusted for age, sex, and country, is taken from the United Nations Population Division (UNPD) World Population Prospects[8].

To calculate the probability of death not by suicide, we then subtract the GBD 2019 probability of death due to self-harm from this overall probability of death.[5] Then, to account for the increased probability of suicide among people with acute cases of our mental disorders of interest, we used the proportion of death by suicide attributable to each depression, anxiety, and bipolar disorder as calculated by Ferrari et al. in a meta-analysis of studies from 20 countries: Australia, Belgium, Canada, China, Colombia, Denmark, Finland, Germany, Hong Kong, Hungary, India, Italy, Ireland, Indonesia, Norway, Pakistan, Sweden, Taiwan, the United Kingdom, and the United States.[10]

To account for comorbidities, we then calculated the proportion of deaths by suicide due to depression, anxiety, or bipolar disorder with the following equation:

$$\Pr(D_s|mh) = 1 - \{[1 - \Pr(D_s|dep)] * [1 - \Pr(D_s|anx)] * ([1 - \Pr(D_s|bip)]\} \quad (2)$$

Where Pr(D_s|…) is the probability of death by suicide, given a condition: *mh* (any of our mental health disorders), *dep* (depression), *anx* (anxiety), or *bip* (bipolar). This calculation assumes that the probability of death by suicide is independent across the three disorders.[11] We subtracted this probability from the GBD 2019 probability of death by suicide to calculate the probability of death by suicide, given no acute mental health condition. For those with an acute case of anxiety, depression, comorbid anxiety and depression, or bipolar disorder, this baseline probability of death by suicide with no underlying mental health condition was then multiplied by the increased risk of suicide due to the relevant mental health conditions from Ferrari et al.[10] Ferrari et al. found no substantive differences by country income level or by sex in either the proportion of deaths by suicide attributable to our conditions of interest or the relative risk of death by suicide among those with our conditions of interest.

We assume that people who are not experiencing acute symptoms of a mental disorder face the same probability of death by suicide as people who have never experienced symptoms of a mental disorder.

Bipolar disorder

The baseline probability of developing symptoms of bipolar disorder from a healthy state comes from the incidence of bipolar disorder by country, sex, and age in the GBD 2019. Following the GBD assumptions, we account for only three states of bipolar—mania, depression, and euthymia—and do not differentiate between different types of bipolar disorder.[12] We assume that symptoms of bipolar disorder manifest first as a manic or depressive episode; that is, people cannot move directly from the healthy state to a state of euthymia. We divide the incidence of bipolar disorder between the manic and depressive states by dividing the average annual number of manic and depressive episodes, respectively, by the total average number of acute bipolar episodes per year. These estimates come from an Italian study including patients with bipolar I or bipolar II of different presentations.[13] See *Table A3* for the values of these parameters.

Table A3: Bipolar disorder parameters

Parameter	Baseline (minimum, maximum)		Notes
	Depressive episode	Manic episode	
Number of episodes per year	0.96 (0.83, 1.10)	0.94 (0.78, 1.10)	Point estimates and 95% confidence interval for all participants in [13]
Duration of episodes in months	5.18 (1.65, 5.63)	3.46 (1.00, 7.08)	Point estimates from cohort in [12]; ranges from literature review in [12]

We calculated the probability of remission of a manic or depressive episode of bipolar disorder—that is, the probability of moving from a manic episode or a depressive episode into euthymia—with the following equation:

$$\Pr\left(Rem_{bip,i}\right) = \left(\frac{1}{t_{bip,i}}\right) - \left[\Pr(D_{ns}) + \Pr(D_s|no\_mh) * RR_{D_s|bip}\right] \quad (3)$$

Where *Rem* is remission of an episode, *bip,i* denotes a manic or depressive episode of bipolar, *t* is the duration in months of an episode, Pr(D_{ns}) is the probability of death not by suicide, $\Pr(D_s|no\_mh)$ is the probability of death by suicide given none of our mental health disorders of interests, and $RR_{D_s|bip}$ is the relative risk of death by suicide, given bipolar disorder.

Although bipolar disorder can co-occur with anxiety and lead to worse outcomes[14], for the sake of maintain a semblance of model clarity, we chose to assume that a person with bipolar disorder cannot develop anxiety or depression in addition to bipolar disorder.

Depression alone

The incidence of major depressive disorder by age, sex, and country was taken from the GBD 2019 dataset. We adjust for the incidence of combined anxiety and depression as described in the below subsection “Comorbid anxiety and depression”. The probability of remission of a depressive episode,

calculated as in equation (3), likewise uses the expected duration in months of a depressive episode from GBD 2019: 7.8 (minimum 7.08, maximum 8.4).

A person who has experienced depression once is generally more likely to experience depression again than a person who has never experienced depression.[15] The remission data for depression in the GBD 2019 analyses were drawn from a 1991 United States National Comorbidity study, when the average US life expectancy was 75.37 years.[16] We used this expected life to calculate the probability of relapse for all people with depression in the study. According to a systematic review conducted with no geographic constraints—though most of the sources found came from high-income countries, particularly the United States—a person who experiences at least one episode of depression is likely to experience 7 episodes of depression (minimum 5, maximum 9) over their lifetime.[15] We calculated the probability of a relapse of depression—that is, a return from a healthy state to a depressed state—with this equation:

$$\Pr(Rel_{dep}) = \frac{N_{dep}-1}{\frac{T}{12}} \quad (3)$$

Where $\Pr(Rel_{dep})$ is the monthly probability of a relapse, N_{dep} is the expected number of depressive episodes in a lifetime for a person with depression, and *T* is the expected lifespan in years.

Anxiety alone

The incidence of major depressive disorder by age, sex, and country was taken from the GBD 2019 dataset. We adjust this incidence for the incidence of combined anxiety and depression as described in the below subsection "Comorbid anxiety and depression". Unlike depression, which naturally occurs in cycles of remission and recurrence, anxiety without treatment tends to linger over the course of a person's lifetime.[17] The GBD 2019 documentation gives a maximum annual remission probability of anxiety 0.2, which we likewise take as our maximum. Following the findings of a review of the global literature on the epidemiology of anxiety, we set our annual probability of remission of anxiety to 0.05 (minimum 0.00, maximum 0.20).[17] To convert these annual probabilities to monthly probabilities, we use the standard formula:

$$\Pr(Rem_{month}) = 1 - [1 - \Pr(Rem_{year})]^{1/12} \quad (4)$$

Where $\Pr(Rem_{month})$ is the probability of remission in a month, given an overall annual probability of remission in a year of $\Pr(Rem_{year})$.

For the probability of relapse after recovery, we drew on the findings of a recent *Lancet* review on anxiety, which reported a relatively high relapse rate after ending successful cognitive behavioral therapy. For the base value, we adjusted the 12-month probability of relapse to be monthly, for a monthly probability of relapse of 4.17% (minimum 0.21%, maximum 4.17%). The minimum value reflects the monthly probability of the 24-month relapse value among adults from the same review; the maximum is the stated value.[18]

Comorbid anxiety and depression

Anxiety and depression frequently occur together, and people with symptoms of both conditions often face longer courses of illness and require more intensive treatment.[19–21] Our model includes states for people with both conditions. The probability of moving into a comorbid state from a healthy state is calculated as the product of the age-, sex-, and country-specific incidence of depression from the GBD

2019 and two parameters from the WHO World Mental Health surveys, which includes data from countries in all World Bank income groups:[9]

- The proportion of people who reported depression in the previous 12 months and also reported anxiety in the previous 12 months (41.6%, minimum 29.9%, maximum 90%), and
- The proportion of people who reported ever experiencing both depression and anxiety who reported that the two conditions manifested at the same time (18.5%, minimum 10.6%, maximum 23.7%).

The probability that a person will develop anxiety given that they have depression is calculated using the following equation:

$$\Pr(inc_{anx}|dep) = 1 - [1 - \Pr(anx|dep)]^{1/T_{dep}} \quad (4)$$

Where $\Pr(anx|dep)$ is the proportion of people who reported depression in the previous 12 months and also reported anxiety in the previous 12 months, and T_{dep} is the expected duration of a depressive episode.

As anxiety has a very low probability of resolving over a lifetime without treatment, we calculated the probability that a person will develop depression given that they have anxiety as follows:

$$\Pr\left(inc_{dep}\middle|anx\right) = \frac{Pr(dep|anx)}{(life-age_{init})*12} \quad (5)$$

Where *life* is the average 2017 global life expectancy in years according to the World Bank population (68.327 years),[16] age_{init} is the cohort's starting age, and $Pr(dep|anx)$ is the proportion of people with anxiety who develop depression. This latter parameter comes from a literature review, with the base value, 62.4%, reflecting the estimate for generalized anxiety disorder, the minimum of 20% reflecting the minimum value from the review, and the maximum of 85% reflecting the general estimate for all people with anxiety from that review.[20]

We used the same probability of remission of anxiety and depression as described above to calculate the probability of recovering from one of the comorbid conditions. We assumed that when a person recovers from one condition, they continue to experience the other condition, with a constant probability of remission from that condition. They cannot move directly from having both conditions to a healthy state. People with comorbid anxiety and depression therefore experience a longer expected course of illness than people with only one condition.

Similarly, we use the same probabilities of relapse for anxiety and depression independent of whether a person has experienced just anxiety, just depression, or both. A person who has experienced both, however, has a higher overall probability of experiencing a relapse because they can relapse into either anxiety or depression.

Accounting for age

We track only the lifetime mental health of those adolescents who experience one of our conditions of interest before the age of 19. We assume the rest of people in the adolescent age groups stay healthy until their death, either by suicide or not.

In the model diagram (*Supplementary Figure A1*), any arrows that appear in green dashes are only available when the people in the model are less than 20 years of age. When the people in the model reach the age of 20, the purple dotted arrows become available. Black solid arrows are always available, though not all of them can be reached during all years of the model.

Intrinsic value of health

To value health states, we used the disability weights from the GBD 2019, which values the utility lost due to disability or death from 0 (full health) to 1 (death) (*Table A4*). Following Lee et al., we use weighted averages by severity for the disability weights for anxiety and depression.[22] We did not include asymptomatic cases in our model. To allow the proportions of severity to vary in the sensitivity analysis, we calculated the overall proportion of symptomatic cases with moderate and severe depression, respectively, and used the complement of the sum of these as the proportion of cases with mild depression.

Table A4: Disability weights from GBD 2019

Condition	State	Weight			Raw proportion		
		Baseline	Minimum	Maximum	Baseline	Minimum	Maximum
Bipolar	*Euthymia*	0.032	0.018	0.051	—	—	—
	Depressive state	0.396	0.267	0.531	—	—	—
	Manic state	0.492	0.341	0.646	—	—	—
Depression	*Asymptomatic*	—	—	—	0.130	0.10	0.170
	Mild	0.145	0.099	0.209	0.590	0.490	0.690
	Moderate	0.396	0.267	0.531	0.170	0.130	0.220
	Severe	0.658	0.477	0.807	0.100	0.030	0.200
Anxiety	*Asymptomatic*	—	—	—	0.288	0.275	0.300
	Mild	0.030	0.018	0.046	0.393	0.342	0.442
	Moderate	0.133	0.091	0.186	0.191	0.158	0.227
	Severe	0.523	0.362	0.677	0.127	0.092	0.167
Health	—	0.000	0.000	0.000	—	—	—
Death	*Suicide*	1.000	1.000	1.000	—	—	—
	Not suicide	1.000	1.000	1.000	—	—	—

For inclusion in the calculation of ROI, these disability weights are then converted to utility weights by subtracting them from 1, which puts them on a scale where 1 is perfect health and 0 is death. To convert these health values into 2019 USD dollars, we use the 2019 PPP-adjusted GDP per capita by country [23] times a multiplier of 1 (minimum 0.5, maximum 1).[4,24] This is within the range of multipliers used by recent economic studies and conforms with WHO-authored publications that measured the economic benefits of a year of life at 1.0 times GDP per capita.[4,25] It is conservative as it incorporates an instrumental value of health but not an intrinsic value which, as argued by the Commission on Investing in Health, would substantially increase the multiplier.[26] However, other methods suggest a multiplier of 0.2 to 2.1 for LMICs.[24]

Background morbidity

In order to account for the other health conditions that affect populations beyond our mental health conditions of interest, our model includes a background morbidity disability weight in all non-death states equal to the 2019 GBD years lost due to disability (YLDs) rate *less* YLDs from our conditions of interest, by country, age, and sex. This background morbidity weight is added as an independent comorbid variable to the disability weights listed in Table A4.

$$DW_{combined} = 1 - [(1 - DW_{mental\_health}) * (1 - DW_{background\_morbidity})] \quad (6)$$

This measure is imperfect, as it assumes no interaction between our conditions of interest and other health conditions, despite the documented association between mental and physical health conditions, such as depression and diabetes.[27] Treating background morbidity as independent of our mental health conditions is, therefore, a conservative assumption that is likely to understate the value of treating or preventing mental illness.

Interventions

Identification

Interventions were identified from the peer-reviewed literature, international best practice guidelines such as WHO Mental Health Gap Action Programme (mhGAP) Intervention Guide, and consultation with mental health experts. We first conducted a systematic literature search for studies of adolescent mental health interventions that included an economic evaluation. We searched for articles listed in PubMed, Embase, Web of Science, CAB Abstracts, IndMED, Directory of Open Access Journals, Google Scholar, and the New York Academy of Medicine Grey Literature Database. The search was conducted between January 1, 2010 and April 6, 2020. Only articles published in English or French were included. The search terms are included in *Table A5*.

Table A5: Intervention search strategy

Category	Search Terms
Adolescent Age Group	Adolescent/Adolescence/young adult/youth/teenage
Interventions	Intervention/program/policy/outcome/impact OR Prevention
Mental Health Disorders	mental health/ mental disorder/mental illness/education/employment OR anxiety/suicide/depression/bipolar disorder/conduct disorder
Economic Evaluation	cost*/economic*
Country and Region Names	Africa/Asia/Caribbean/West Indies/South America/Latin America/Central America/Abkhazia/Afghanistan/Albania/Algeria/Angola/Antigua/Andorra/Australia/Austria Barbuda/Argentina/Armenia/Armenian/Artsakh/Aruba/Azerbaijan/Bahrain/Bahamas/Bangladesh/Barbados/Benin/Byelarus/Byelorussian/Belarus/Belorussian/Belorussia/Belize/Bermuda/Bhutan/Bolivia/Borneo/Bosnia/ Herzegovina/Hercegovina/Botswana/Brasil/Brazil/Bulgaria/Burkina Faso/Burkina Fasso/Upper Volta/Burundi/ Urundi/Belgium/British Virgin Islands/Brunei Darussalam/Cambodia/Khmer Republic/Kampuchea/Cameroon/Cameroons/Cameron/Camerons/Cape

	Verde/Cabo Verde/Cayman/Central African Republic/Chad/Chile/China/Colombia/Comoros/Comoro Islands/Comores/Cook Islands/Mayotte/Congo/DRC/Congo-Brazzaville/Congo-Kinshasa/Zaire/Costa Rica/Cote d'Ivoire/Ivory Coast/ Croatia/Cuba/Cyprus/Czechoslovakia/Czech Republic/Canada/Channel Islands/Curaçao/Slovakia/Slovak Republic/Djibouti/French Somaliland/Dominica/Dominican Republic/ Denmark/East Timor/East Timor/Timor Leste/Ecuador/Egypt/United Arab Republic/El Salvador/Eritrea/Estonia/Ethiopia/Fiji/Faroe Islands/Finland/France/French Polynesia/Gabon/Gabonese Republic/Gambia /Gaza/Georgia/Georgian/Ghana/Gold Coast/Greece/Grenada/Guatemala/Guinea/Guam/Germany/Gibraltar/ Greenland/Guiana/Guyana/Haiti/Honduras/Hungary/Hong Kong/India/Ireland/Israel/Iceland/Italy/Maldives/Indonesia/Iran/Iraq/Isle of Man/Jamaica/Jordan/Japan/Kazakhstan/Kazakh/Kenya/Kiribati/Korea/DPRK/Kosovo/ Kyrgyzstan/Kirghizia/Kyrgyz Republic/Kirghiz/Kirgizstan/Kuwait/ Lao PDR/Laos/Latvia/Lebanon/Lesotho/Basutoland/ Liechtenstein/Luxembourg/ Liberia/Libya/Lithuania/Macedonia/FYROM/Macao/Madagascar/Malagasy Republic/Malaysia/Malaya/Malay or Sabah/Sarawak/Malawi/Nyasaland/Mali/Malta/Marshall Islands/Mauritania/Mauritius/Agalega Islands/Mexico Micronesia/Middle East/Moldova/Moldovia/Moldovian/Mongolia/Montenegro/Montserrat/Morocco /Ifni/ Monaco/ Mozambique/Myanmar/Myanma/Burma/Namibia/Nauru/Nepal/Netherlands Antilles/New Caledonia/New Zealand/Nicaragua/Niger/Nigeria/Niue/Northern Mariana Islands/Norway Virgin islands/Oman/Muscat/Pakistan/Palau/Palestine/Panama/Paraguay/Peru/Philippines/ Philipines/Phillipines/Phillippines/Poland/Polynesia/Portugal/Puerto Rico/Qatar/Romania/ Rumania/Roumania/Russia/Russian/Rwanda/Ruanda/Saint Kitts/Saint Helena/St Kitts/Nevis/Saint Martin/Saint Pierre/Miquelon/Saint Lucia/St Lucia/Saint Vincent/St Vincent/Grenadines/Samoa/Samoan Islands/Navigator Island/Navigator Islands/Sao Tome/Principe/Saudi Arabia/Senegal/Serbia/Montenegro/Seychelles/Sierra Leone/ Slovenia/Sri Lanka/Ceylon/Solomon Islands/Somalia/Somaliland/South Africa/South Ossetia/Sudan/Suriname/ Surinam/Swaziland/Syria/San Marino/Sint Maarten/Sweden/Spain/Singapore/Switzerland/ Tajikistan/Tadzhikistan/Tadjikistan/Tadzhik/Tanzania/Thailand/Tibet/Togo/Togolese Republic/Tokelau/Tonga/Transnistria/Trinidad/Tobago/Tunisia/Turkey/Turkmenistan/Turkmen/Turks and Caicos/Tuvalu/Taiwan/Uganda/Ukraine/Uruguay/USSR/Soviet Union/Union of Soviet Socialist Republics/Uzbekistan/Uzbek/United Kingdom/United States/Vanuatu/New Hebrides/Venezuela/Vietnam/Viet Nam/Mekong valley/Mekong delta/Virgin Islands/ Wallis and Futuna/Western Sahara/Sahrawi/West Bank/Yemen/Yugoslavia/Zambia/Zimbabwe/Zanzibar/Rhodesia

This search resulted in 156 articles. We screened the titles and abstracts and later full text articles using the following criteria: 1) published between January 1, 2010 and April 6, 2020, 2) intervention to prevent or treat anxiety, bipolar disorder, depression, or suicide, 3) outcomes include impact on incidence of developing the disorder or recovering (as applicable), and 4) assessment of the cost and/or cost-effectiveness of the intervention. Using these criteria, we narrowed down to two modeling studies that assessed the cost-effectiveness of depression prevention in Australia. Because these studies used the same meta-analysis as the source of the effectiveness estimates, we maintained Lee et al.[28]

However, the results of the systematic search did not include any adolescent-specific intervention studies with cost information for the prevention of anxiety or suicide, or the treatment of anxiety, bipolar disorder, or major depression. As a result, we conducted additional non-systematic searches in PubMed to identify interventions published prior to 2010 for which there was cost-effectiveness evidence. Through this search we identified articles that estimated the cost and cost-effectiveness of prevention of suicide, prevention of anxiety, and treatment of anxiety and depression. No studies were identified that evaluated the cost of treatment for bipolar disorder. We conducted an additional non-systematic and non-time limited search to identify interventions that have been determined to be effective.

The identified studies were used as the basis for each of the model interventions, in terms of identifying the unit counts for each resource (including provider time, supplies, and medicines) required for implementation. Guidance for the use of medications among adolescents with bipolar disorder and major depression came from the mhGAP Intervention Guide and the British National Formulary for Children.[29,30] Additional information and literature about internet-based interventions was obtained through expert consultations. All the identified intervention evidence comes from high income settings.

Costing Approach

The literature review identified the costs of the selected interventions from studies conducted in high income countries. To adjust those intervention costs to LMIC settings, we conducted an ingredients-based costing using cost inputs tailored to the countries included in the model. For each intervention the total costs of the necessary materials and human resources in current local currency, adjusted for local cost levels, was established based on the published studies, international guidelines, and consultation with experts.

The unit costs for these ingredients were generated for each of the included countries from primary data or country income level approximation when country specific data were not available. See *Supplementary File 3* for the values of these parameters for each country.

Table A6: Types of costs and data sources

Type of Cost	Unit of Cost	Year	Source
Health worker salaries	Hourly salary	2008	mhGAP costing tool [31]
Teacher salaries	Hourly salary	2017	International Labor Organization [32]
Medicines	Per defined daily dose	2015	International Medical Products Price Guide [33]
Laboratory tests	Per test	2020	Personal communication, C. Masila, 2020
Computer equipment	Per computer	2008	mhGAP costing tool [24]
Internet access (fixed broadband)	Per month	2017	[34]
Online platform for guided self-help interventions	Per patient	2016	[35]
Printed materials	Per participant manual	2010	[36]
Transportation costs	Per visit	Varied (2013-2018)	Country household expenditure surveys[37–43]

Adaptation of Unit Costs

Non-traded unit costs were converted to the local currency unit using the study year exchange rate, inflated to 2019 using the country Consumer Purchasing Index, converted to US$ using the 2019 exchange rate, and finally adjusted for purchasing power parity using the country 2019 conversion factor. This adjusted unit cost was then increased by 50% to account for facility level system costs and a further 17% for above facility level system costs.[44]

Traded costs were similarly converted to the local currency unit using the study year exchange rate, inflated to reflect change to 2019 using the global inflation rate, and converted to US$ using the 2019 exchange rate. For physical goods, the cost of transportation and distribution were added to the unit cost using the WHO CHOICE price multipliers for the appropriate geographic region.[45]

Task Shifting of Intervention Delivery

Many of the identified interventions were conducted using specialist providers in high resource settings. Given the scarcity of specialist mental health providers (including psychologists and psychiatrists) in many LMICs, this approach is unlikely to be feasible or scalable. Task shifting of mental health care to non-specialist health workers has proven cost-effective in LMICs and is recommended under the mhGAP intervention guide.[46] As a result, we assume that the identified interventions will be delivered by the lowest level of provider deemed appropriate. Psychological interventions are delivered by lay health workers under supervision of primary care doctors. Interventions involving pharmacotherapy are delivered by primary care doctors under supervision by a psychiatrist. Initial and annual training

requirements for these providers are aligned with the mhGAP Training Guidelines.[47] We assume an estimated annual attrition of 8.8% for doctors and 4.7% for community health workers.[48,49] All health workers providing interventions receive monthly supervision in a group setting.

Calculating monthly costs per adolescent

The model is structured so that costs are expressed in terms of the cost per adolescent per month. For each intervention, we calculated the monthly intervention cost per adolescent, which we assumed to remain constant throughout a year. We also calculated the costs of initial and refresher trainings per adolescent. In the first 12 months of the model, we assume that all people delivering the interventions require an initial training. In subsequent years, we assume that all people receive a refresher training except for the attritors, whom we assume are replaced by people who require a round of initial training in their first year.

For any cost incurred over a period longer than a month, we divided that cost evenly across the time period by month. For example, with a training that occurs once a year, we calculate the monthly cost by dividing the annual training cost by 12. Please see *Supplementary File 3* for the unit costs and counts, as well as the overall monthly costs, by country.

Costs of Interventions

The costs for each of the selected interventions was calculated by building it from the human resources, supplies, and other elements needed to deliver the intervention. These elements are called ingredients and are measured in common units as indicated in the below tables. The costs of ingredients needed for each intervention on a per capita served basis are added up to provide the total intervention cost.

Prevention of anxiety and depressive disorders

School-based mental health education

A school-based universal prevention intervention involving teacher delivered mental health education can help prevent the development of anxiety and depression in adolescents. This intervention involves 10 group sessions (1.2 hours each) delivered by teachers to all students in their class each year.[22] Teachers are trained annually by a psychologist to conduct these sessions.[50]

Table A7: Unit counts for costing of school-based mental health education

Ingredient	Units	Description
Teacher salary	12	Hours to deliver group-based intervention per class (23 students)
Teacher salary for training	9.5	Initial training to conduct intervention (annual)
Psychologist salary	9.5	Hours to conduct teacher training per school (33 teachers per school, each teacher covers 1 class of 23 students)
Psychologist salary	40	Adaptation of educational materials to country, per country. Include initial adaptation then repeat every 5 years.
Psychologist salary	40	Training for trainers/supervisors (initial). Includes 16 trainees.
Psychologist salary	8	Training for trainers/supervisors (annual refresher training). Includes 16 trainees.
Psychiatrist salary	40	Master trainer – training supervisors (initial)
Psychiatrist salary	8	Master trainer – training supervisors (annual)

Screening and indicated prevention of major depression

Indicated prevention of major depression using group-based CBT for adolescents with sub-threshold depression first involves a school-based, universal screening questionnaire administered by teachers. Adolescents who have a high score for symptoms of depression receive further diagnostic testing with a psychologist to determine whether they have major depression or subthreshold depression. Those adolescents who have subthreshold depression then complete a 1-hour individual consultation with a psychologist and are enrolled in group CBT sessions, conducted by a non-specialist health worker. The intervention includes 10 1-hour sessions with a group of 10 adolescents. Effectiveness data for this intervention are drawn from a meta-analysis conducted in 2017.[22]

Table A8: Unit counts for costing of treatment of subthreshold depression with group-based cognitive behavioral therapy

Ingredient	Units	Description
Teacher salary	1	1 hour to disseminate screening tool in class (23 students)
Teacher salary	1	Initial training to conduct intervention (annual)
Psychologist salary	1	1 hour to conduct teacher training per school (33 teachers per school, each teacher covers 1 class of 23 students)
Psychologist salary	.5	0.5 hour for diagnostic testing with students who score high on screening tool
Psychologist salary	1	1-hour individual consultation for students at high risk
Health worker salary	10	10 1-hour group CBT sessions (10 students)
Health worker salary	16.1	Initial training to conduct intervention.
Health worker salary	8	Annual refresher training
Psychologist salary	16.1	Initial training of health workers, 24 health workers per training
Psychologist salary	8	Annual refresher training of health workers, 24 health workers per training
Health worker salary	24	2 hours per month for supervision
Psychologist salary	24	Supervision – 2 hours per month, group of 10 health workers
Psychologist salary	40	Adaptation of educational materials to country, per country. Include initial adaptation then repeat every 5 years.
Psychologist salary	40	Training for trainers/supervisors (initial). Includes 16 trainees.
Psychologist salary	8	Training for trainers/supervisors (annual refresher training). Includes 16 trainees.
Psychiatrist salary	40	Master trainer – training supervisors (initial)
Psychiatrist salary	8	Master trainer – training supervisors (annual)

Treatment of anxiety disorders

Adolescents diagnosed with anxiety will receive one of three possible treatments.

Treatment of anxiety with group-based cognitive behavioral therapy

Treatment of anxiety with in-person, group-based cognitive behavioral therapy (CBT) has been shown to be effective in groups of 10 adolescents. The intervention includes 12 1-hour sessions, delivered over the course of 12 weeks. The intervention is delivered by non-specialist health workers who are supervised by psychologists. Effectiveness data for this intervention are drawn from a 2018 meta-analysis of group-based CBT interventions for adolescents with anxiety.[51]

Table A9: Unit counts for costing of treatment of anxiety with group-based cognitive behavioral therapy

Ingredient	Units	Description
Health worker salary	12	12 1-hour group sessions with 10 adolescents
Health worker salary	16.1	Initial training to conduct intervention
Health worker salary	8	Annual refresher training
Health worker salary	24	2 hours per month for supervision
Psychologist salary	16.1	Initial training of health workers, 24 health workers per training
Psychologist salary	8	Annual refresher training of health workers, 24 health workers per training
Psychologist salary	24	Supervision – 2 hours per month, group of 10 health workers
Psychologist salary	40	Training for trainers/supervisors (initial). Includes 16 trainees.
Psychologist salary	8	Training for trainers/supervisors (annual refresher training). Includes 16 trainees.
Psychiatrist salary	40	Master trainer – training supervisors (initial)
Psychiatrist salary	8	Master trainer – training supervisors (annual)
Travel to group session	12	1 unit per adolescent per session

Treatment of anxiety with individual telehealth CBT

Treatment of anxiety with individual cognitive behavioral therapy can be delivered through telehealth visits using Skype. The intervention includes 12 1-hour sessions that occur over the course of 12 weeks. The intervention will be delivered by non-specialist health workers who are supervised by psychologists. Effectiveness data for this intervention are drawn from a 2018 meta-analysis of individual CBT interventions for adolescents with anxiety.[46] Comparable effectiveness is assumed for CBT sessions delivered in person and via telehealth.[52]

Table A10: Unit counts for costing of treatment of anxiety with individual telehealth CBT

Ingredient	Units	Description
Computer	1	Assume useful life of 5.4 years, 1 per health worker
Internet platform	0	Use of Skype is free for internet calls
Internet access	12	Cost of 1-hour internet access for health worker for video calls
Health worker salary	12	12 1-hour telehealth sessions
Health worker salary	16.1	Initial training to conduct intervention
Health worker salary	8	Annual refresher training
Health worker salary	24	2 hours per month for supervision
Psychologist salary	16.1	Initial training of health workers, 24 health workers per training
Psychologist salary	8	Annual refresher training of health workers, 24 health workers per training
Psychologist salary	24	Supervision – 2 hours per month, group of 10 health workers
Psychologist salary	40	Training for trainers/supervisors (initial). Includes 16 trainees.
Psychologist salary	8	Training for trainers/supervisors (annual refresher training). Includes 16 trainees.
Psychiatrist salary	40	Master trainer – training supervisors (initial)
Psychiatrist salary	8	Master trainer – training supervisors (annual)

Treatment of anxiety with internet-based, guided self-help intervention

Treatment of anxiety with an internet-based, guided self-help intervention can be delivered using a specialized internet platform. The intervention includes 12 weekly sessions in which the adolescent completes online modules based on principles of CBT. Adolescents have access to limited asynchronous support from non-specialist health worker throughout the intervention period. The non-specialist health workers are supervised by psychologists. Effectiveness data for this intervention are drawn from a 2016 randomized controlled trial conducted in Sweden.[53]

Table A11: Unit counts for costing of treatment of anxiety with internet-based, guided self-help intervention

Ingredient	Units	Description
IT infrastructure	1	Cost of maintaining IT infrastructure per user
Computer	1	Assume useful life of 5.4 years, 1 per health worker
Internet access – web browsing	5.4	Cost of 1-hour internet access for health worker to provide asynchronous support
Health worker salary	5.4	Hours for asynchronous support
Health worker salary	16.1	Initial training to conduct intervention
Health worker salary	8	Annual refresher training
Health worker salary	24	2 hours per month for supervision
Psychologist salary	16.1	Initial training of health workers, 24 health workers per training
Psychologist salary	8	Annual refresher training of health workers, 24 health workers per training
Psychologist salary	24	Supervision – 2 hours per month, group of 10 health workers
Psychologist salary	40	Adaptation of educational materials to country, per country. Include initial adaptation then repeat every 5 years.
Psychologist salary	40	Training for trainers/supervisors (initial). Includes 16 trainees.
Psychologist salary	8	Training for trainers/supervisors (annual refresher training). Includes 16 trainees.
Psychiatrist salary	40	Master trainer – training supervisors (initial)
Psychiatrist salary	8	Master trainer – training supervisors (annual)

Treatment of depressive disorders

Adolescents diagnosed with mild depression will receive one of three possible treatments.

Treatment of mild and moderate depression with group-based cognitive behavioral therapy

The group-based CBT for adolescents with mild and moderate depression involves in person group CBT sessions, conducted by a non-specialist health worker. The intervention includes 10 1-hour sessions with a group of 10 adolescents. Effectiveness data for this intervention are drawn from a meta-analysis conducted in 2018.[54]

Table A8: Unit counts for costing of treatment of subthreshold depression with group-based cognitive behavioral therapy

Ingredient	Units	Description
Health worker salary	10	10 1-hour group CBT sessions (10 students)
Health worker salary	16.1	Initial training to conduct intervention.
Health worker salary	8	Annual refresher training
Psychologist salary	16.1	Initial training of health workers, 24 health workers per training
Psychologist salary	8	Annual refresher training of health workers, 24 health workers per training
Health worker salary	24	2 hours per month for supervision
Psychologist salary	24	Supervision – 2 hours per month, group of 10 health workers
Psychologist salary	40	Adaptation of educational materials to country, per country. Include initial adaptation then repeat every 5 years.
Psychologist salary	40	Training for trainers/supervisors (initial). Includes 16 trainees.
Psychologist salary	8	Training for trainers/supervisors (annual refresher training). Includes 16 trainees.
Psychiatrist salary	40	Master trainer – training supervisors (initial)
Psychiatrist salary	8	Master trainer – training supervisors (annual)

Treatment of mild and moderate depression with individual telehealth CBT

Adolescents with mild and moderate depression may also receive treatment through individual CBT telehealth visits using Skype. The intervention includes 12 1-hour sessions that occur over the course of 12 weeks. The intervention will be delivered by non-specialist health workers who are supervised by psychologists. Effectiveness data for this intervention are drawn from a meta-analysis conducted in 2018.[54] Comparable effectiveness is assumed for CBT sessions delivered in person and via telehealth.

Table A13: Unit counts for costing of treatment of subthreshold depression with individual telehealth CBT

Ingredient	Units	Description
Computer	1	Assume useful life of 5.4 years, 1 per health worker
Internet platform	0	Use of Skype is free for internet calls
Internet access	12	Cost of 1-hour internet access for health worker for video calls
Health worker salary	12	12 1-hour telehealth sessions
Health worker salary	16.1	Initial training to conduct intervention
Health worker salary	8	Annual refresher training
Health worker salary	24	2 hours per month for supervision
Psychologist salary	16.1	Initial training of health workers, 24 health workers per training
Psychologist salary	8	Annual refresher training of health workers, 24 health workers per training
Psychologist salary	24	Supervision – 2 hours per month, group of 10 health workers
Psychologist salary	40	Training for trainers/supervisors (initial). Includes 16 trainees.
Psychologist salary	8	Training for trainers/supervisors (annual refresher training). Includes 16 trainees.
Psychiatrist salary	40	Master trainer – training supervisors (initial)
Psychiatrist salary	8	Master trainer – training supervisors (annual)

Treatment of mild and moderate depression with internet-based, guided self-help intervention

Treatment of mild and moderate depression with an internet-based, guided self-help intervention can be delivered using a specialized internet platform. The intervention includes 12 online modules based on the principles of CBT that adolescents complete over the course of 12 weeks. Adolescents have access to limited asynchronous support from non-specialist health workers throughout the intervention period. The non-specialist health workers are supervised by psychologists. Comparable effectiveness can be assumed for psychological interventions delivered via in-person CBT and internet-based, guided self-help programs.[52] Effectiveness data for this intervention are drawn from a meta-analysis conducted in 2018.[54]

Table A14: Unit counts for costing of treatment of subthreshold depression with internet-based, guided self-help intervention

Ingredient	Units	Description
IT infrastructure, per user	1	Cost of maintaining IT infrastructure
Computer	1	Assume useful life of 5.4 years, 1 per health worker
Internet access	5.4	Cost of 1-hour internet access for health worker to provide asynchronous support
Health worker salary	5.4	Hours for asynchronous support
Health worker salary	16.1	Initial training to conduct intervention
Health worker salary	8	Annual refresher training
Health worker salary	24	2 hours per month for supervision
Psychologist salary	16.1	Initial training of health workers, 24 health workers per training
Psychologist salary	8	Annual refresher training of health workers, 24 health workers per training
Psychologist salary	24	Supervision – 2 hours per month, group of 10 health workers
Psychologist salary	40	Adaptation of educational materials to country, per country. Include initial adaptation then repeat every 5 years.
Psychologist salary	40	Training for trainers/supervisors (initial). Includes 16 trainees.
Psychologist salary	8	Training for trainers/supervisors (annual refresher training). Includes 16 trainees.
Psychiatrist salary	40	Master trainer – training supervisors (initial)
Psychiatrist salary	8	Master trainer – training supervisors (annual)

Treatment of severe depression with individual CBT and pharmacotherapy

Adolescents diagnosed with severe depression will receive more intensive treatment, including pharmacotherapy. The intervention includes 12 1-hour CBT sessions with a primary care doctor over a 12-week period. Adolescents also receive daily treatment with fluoxetine (20mg) and 6 30-minute medication management sessions, conducted by a primary care doctor under supervision of a psychiatrist. Effectiveness data for this intervention are drawn from the Treatment for Adolescents with Depression Study.[55–57]

Table A15: Unit counts for costing of treatment of major depression with individual CBT and pharmacotherapy

Ingredient	Units	Description
Medical officer salary	15	12 1-hour CBT sessions, 6 30-minute medication management sessions
Medical officer salary	24	2 hours per month for supervision
Psychiatrist salary	24	Supervision – 2 hours per month, group of 10 medical officers
Medical officer salary	16.1	Initial training to conduct intervention
Medical officer salary	8	Annual refresher training
Psychiatrist salary	16.1	Initial training of medical officers, 24 health workers per training
Psychiatrist salary	8	Annual refresher training of medical officers, 24 health workers per training
Fluoxetine	84	Daily for duration of 12-week treatment
Psychologist salary	40	Training for trainers/supervisors (initial). Includes 16 trainees.
Psychologist salary	8	Training for trainers/supervisors (annual refresher training). Includes 16 trainees.
Psychiatrist salary	40	Master trainer – training supervisors (initial)
Psychiatrist salary	8	Master trainer – training supervisors (annual)

Treatment of bipolar disorder

Treatment of bipolar disorder with family focused treatment for adolescents and pharmacotherapy

Adolescents diagnosed with bipolar disorder can benefit from family focused treatment for adolescents (FFT-A), a psychological intervention accompanied by pharmacotherapy.[58] The intervention involves 21 hour-long sessions delivered over the course of 9 months. These sessions are administered by a primary care doctor and attended by adolescents and their family members. Adolescents in all stages of bipolar disorder receive treatment with a mood stabilizer (lithium carbonate). When in a depressive episode, adolescents receive a mood stabilizer and anti-depressant medication (fluoxetine). When in a manic episode, adolescents receive a mood stabilizer and an antipsychotic (haloperidol). These medications are accompanied by routine monitoring with laboratory tests for lithium, prolactin, electrolytes, creatinine, and thyroid function. Effectiveness data for this intervention are from a randomized trial conducted in the United States.[58]

Table A16 Unit counts for costing of treatment of bipolar disorder with family focused treatment for adolescents and pharmacotherapy

Ingredient	Units	Description
Medical officer salary	17.5	21 50-minute sessions over 9 months
Medical officer salary	24	2 hours per month for supervision
Psychiatrist salary	24	Supervision – 2 hours per month, group of 10 medical officers
Medical officer salary	16.2	Initial training to conduct intervention
Medical officer salary	8	Annual refresher training
Psychiatrist salary	16.2	Initial training of health workers, 24 health workers per training
Psychiatrist salary	8	Annual refresher training of health workers, 24 health workers per training
Haloperidol	Varies	Use daily with lithium if manic episode develops. Do not use with anti-depressant.
Lithium carbonate	365	Daily mood stabilizer treatment for all with bipolar disorder
Fluoxetine	Varies	Use daily with lithium if depressive episode develops
Serum lithium test	First year: 4 Subsequent years: 2	Needed when taking lithium carbonate. Baseline, 1 week, every 3 months for 1 year, then every 6 months
Serum prolactin test	3	Needed when taking haloperidol. Monthly tests for duration of manic episode (12 weeks)
Serum electrolytes test	2	Needed when taking haloperidol. Every 6 months.
Serum creatinine test	First year: 5 Subsequent years: 2	Needed when taking lithium carbonate. Baseline, 1 week, every 3 months for 1 year, then every 6 months
Thyroid function test	First year: 3 Subsequent years: 2	Needed when taking lithium carbonate. Baseline, 1 month, then every 6 months
Psychologist salary	40	Training for trainers/supervisors (initial). Includes 16 trainees.
Psychologist salary	8	Training for trainers/supervisors (annual refresher training). Includes 16 trainees.
Psychiatrist salary	40	Master trainer – training supervisors (initial)
Psychiatrist salary	8	Master trainer – training supervisors (annual)
Travel to group session	21	1 unit per adolescent per session

Suicide prevention

Universal school-based suicide prevention

All adolescents enrolled in a school will receive a school-based suicide prevention intervention. This intervention is modeled on the Saving and Empowering Young Lives in Europe (SEYLE) trial conducted in 10 European countries.[59] Students participate in 5 hours of in person class sessions that lectures and interactive activities. These sessions are be led by a health worker, under supervision from a psychologist. Effectiveness data are drawn from the SEYLE trial.[36,59]

Table A9: Unit counts for costing of universal school-based suicide prevention

Ingredient	Units	Description
Health worker salary	5	5 hours of in person sessions in class (23 students)
Health worker salary	15.4	Initial training to conduct intervention
Health worker salary	8	Annual refresher training
Psychologist salary	15.4	Initial training of health workers, 24 health workers per training
Psychologist salary	8	Annual refresher training of health workers, 24 health workers per training
Health worker salary	24	Supervision – 2 hours per month
Psychologist salary	24	Supervision – 2 hours per month, group of 10 health workers
Materials printing	1	1 booklet per student
Psychologist salary	40	Adaptation of educational materials to country, per country. Include initial adaptation then repeat every 5 years.
Psychologist salary	40	Training for trainers/supervisors (initial). Includes 16 trainees.
Psychologist salary	8	Training for trainers/supervisors (annual refresher training). Includes 16 trainees.
Psychiatrist salary	40	Master trainer – training supervisors (initial)
Psychiatrist salary	8	Master trainer – training supervisors (annual)

Education and follow up for individuals treated for self-harm

Intervention with individuals after a suicide attempt can effectively reduce the probability of future attempts. This intervention includes a 1-hour information session with adolescents treated for self-harm at a hospital. These adolescents then receive 9 brief follow up contacts over the following 18 months. The information sessions and follow up contacts are conducted by non-specialist health workers with supervision from a primary care doctor. This intervention and the associated effectiveness data are modeled on the WHO SUPRE-MISS trial.[60]

Table A10: Unit counts for costing of education and follow up for individuals treated for self-harm

Ingredient	Units	Description
Health worker salary	3.25	1-hour information session and 9, 15-minute follow up contacts
Computer	1	Assume useful life of 5.4 years, 1 per health worker
Internet platform	0	Use of Skype is free for internet calls
Internet access	2.25	Cost of 1-hour internet access for health worker to conduct video calls
Health worker salary	15.4	Initial training to conduct intervention
Health worker salary	8	Annual refresher training
Psychologist salary	15.4	Initial training of health workers, 24 health workers per training
Psychologist salary	8	Annual refresher training of health workers, 24 health workers per training
Health worker salary	24	Supervision – 2 hours per month
Psychologist salary	24	Supervision – 2 hours per month, group of 10 health workers
Psychologist salary	40	Adaptation of educational materials to country, per country. Include initial adaptation then repeat every 5 years.
Psychologist salary	40	Training for trainers/supervisors (initial). Includes 16 trainees.
Psychologist salary	8	Training for trainers/supervisors (annual refresher training). Includes 16 trainees.
Psychiatrist salary	40	Master trainer – training supervisors (initial)
Psychiatrist salary	8	Master trainer – training supervisors (annual)

Intervention coverage and effectiveness

The effectiveness of the interventions are given in the terms they were listed in the referenced sources, including risk ratios, odds ratios, and hazard ratios. These ratios all describe the relationship between the chance that something happens with an intervention versus the chance that it happens without the intervention. For all of them, a value of 1 means that the intervention has no effect, a value greater than 1 means the outcome is more likely to happen with the intervention, and a value less than 1 means that the outcome is less likely to happen with the intervention. The difference between the three measures lies in how they quantify the chance that something happens: as a risk, an odds, or a hazard.

A risk that something happens is the same as its probability of happening, such as 20% for an event that you expect to happen 1 out of every 5 times. Risks, and risk ratios, are generally the easiest measure of relative probability for people to understand.

The odds that something happens are calculated as the probability that something happens divided by the probability that it does not happen. For an event that you expect to happen 1 out of every 5 times (i.e. a 20% probability or 20% risk of the event), the odds of that event are 0.2 / 0.8 = 0.25. The odds and risk of an event are very similar at lower probabilities, but they diverge as the probability of the event increases. When the probability of an event exceeds approximately 10%, odds ratios will tend to exaggerate the effect of the intervention compared to a risk ratio (i.e. make a value less than 1 smaller and make a value greater than 1 bigger).

The hazard rate is the number of events (usually deaths) that happen over a time period within the population, divided by the number of individuals within the population that survived to the start of that

time period. For hazard ratios that look at the whole course of patient follow-up as the base time period, as do those cited in this model, hazard ratios and risk ratios are practically the same.

Universal prevention of anxiety and depressive disorders

Secondary school attendance rates by country and sex were gathered from the UNESCO Institute for Statistics.[61] Where country-specific data were not available, we used the average school attendance rate (by sex) for all countries within their World Bank income group. These countries are Afghanistan, Algeria, Bangladesh, China, Democratic Republic of the Congo, Iraq, Japan, Kenya, Nigeria, Sudan, Tanzania, Uganda, and Vietnam. We assumed that 20% of all adolescents in schools, regardless of health condition, would receive the intervention to prevent anxiety and depression, with a range between 10% and 50% in sensitivity analysis.

For anxiety, the effect of the intervention endures for six months after the intervention ends, with a relative risk of developing anxiety over those six months of 0.25 (minimum 0.10, maximum 0.65).[50] We therefore assume the effect holds constant at this level until the participants turn 20, then tapers off over the next six months to a null effect. To calculate the new probability of developing anxiety from a healthy state, we multiply the base probability by this risk ratio.

For depression, the effect of the intervention lasts for 12 months, but it changes over the course of those months as shown in *Table A19*.[50] After 12 months, empirical evidence suggests that there is no lasting benefit of intervention. Because adolescents receive this intervention annually, we assume the intervention effect holds constant until participants turn 20, at which point the benefits begin to decay. The effects are adjusted in a straight line between each subsequent time point until the participants turn 21 and the effect reduces to null.

Table A19: Relative risk of developing depression with preventive intervention

Months after intervention	Relative risk of developing depression	Minimum	Maximum
0	0.41	0.24	0.69
3	0.35	0.24	0.53
9	0.46	0.35	0.62
12	1	1	1

For combined anxiety and depression, the effect of the intervention similarly ends after 12 months and changes over the course of those months as shown in *Table A20*, using the effect sizes for "internalizing disorder," an umbrella term for mental health conditions, including both anxiety and depression.[50]

Table A20: Relative risk of developing both anxiety and depression with preventive intervention

Months after intervention	Relative risk of developing anxiety and depression	Minimum	Maximum
0	0.39	0.26	0.59
3	0.35	0.24	0.53
9	0.49	0.37	0.64
12	1	1	1

Indicated prevention of depression

For indicated prevention of depression, we assumed that 20% of all adolescents in schools, regardless of health condition, would be screened for warning signs of depression, with a range between 10% and 50% in sensitivity analysis. Of those, we used the probability of depression to determine the proportion of those who would go on to develop depression.[22]

Table A21: Relative risk of developing both anxiety and depression with indicated preventive intervention

Months after intervention	Relative risk of developing anxiety and depression	Minimum	Maximum
0	0.32	0.14	0.73
6	0.34	0.2	0.59
12	1	1	1

Treatment of anxiety disorders

For anxiety disorders, we assume that 20% of all adolescents with anxiety receive some form of treatment, varied between 10% and 50% in the sensitivity analysis.

The proportion of adolescents receiving the intervention cannot exceed the proportion of people in the country with access to the internet.[62] We assume that as long as at least 66.6% of people in the country have access to the internet, an equal proportion of adolescents will receive each of the three treatments (internet-based self-help, internet-based individual CBT, and in-person group CBT). For countries with less than 66.6% of people having access to the internet, we assumed that ⅓ of adolescents with access to the internet would choose to attend each of the internet-based treatments, and the balance would choose to attend an in-person CBT group. These relative proportions are varied individually between 0 and a maximum of 1—for the in-person treatment—or the country internet coverage—for the internet treatments—in the sensitivity analyses.

The documentation for the effectiveness of these interventions reported the odds ratio of remission as shown in *Table A22*.[35,51]

Table A22: Odds ratio of anxiety remission for treatment compared to control group

Treatment	Odds ratio of remission	Minimum	Maximum
In-person group CBT	7.86	3.83	16.12
Internet-based individual CBT	3.22	0.96	10.75
Internet-based guided self help	5.41	2.26	12.9

We calculated the new probabilities of remission, given an intervention, based on the odds ratios and baseline probabilities of remission using the following equation:

$$\mathrm{Pr}_2(x) = \frac{OR_x * \frac{\mathrm{Pr}_1(x)}{1-\mathrm{Pr}_1(x)}}{(1+OR_x) * \frac{\mathrm{Pr}_1(x)}{1-\mathrm{Pr}_1(x)}} \quad (7)$$

Where $\Pr_1(x)$ and $\Pr_2(x)$ represent the old and new probabilities of *x*, respectively, and OR_x is the odds ratio of x with vs. without the intervention.

Treatment of depressive disorders

For the treatment of mild depressive disorder, we assume a 20% coverage rate of treatment (minimum 10%, maximum 50%). Regardless of modality of delivery, receiving treatment for mild depression improves the chance of remission by a risk ratio of 4.35 (minimum 2.50, maximum 7.69).[54] Furthermore, receiving treatment reduces the probability of a relapse for those who have ever had depression by a risk ratio of 0.64 (minimum 0.42, maximum 0.98).[54]

For severe depression, we assume that adolescents receive both CBT and medication.[56] We assume a coverage rate of 20% (minimum 10%, maximum 50%) and an OR of remission of depression of 3 (minimum 1.58, maximum 5.79).

Treatment of bipolar disorder

For the treatment of bipolar disorder, the only significant effect of the intervention was an increased 2-year hazard ratio of recovery from a depressive state of 1.85 (minimum 1.04, 3.29).[58] We assumed a 20% coverage rate of bipolar disorder treatment (minimum 10%, maximum 50%).

Suicide prevention

For suicide prevention in schools, we assume 20% coverage of adolescents in school (minimum 10%, maximum 50%). As with the probability of developing depression after a preventive intervention, the effectiveness of the intervention changes over time, as shown in *Table A23*.[59] These odds ratios were applied using equation (6) to the probability of committing suicide.

Table A11: Odds ratio of death by suicide with preventive intervention

Months after intervention	Odds ratio of death by suicide	Minimum	Maximum
3	0.78	0.42	1.44
12	0.45	0.24	0.85
24	1	1	1

For providing a suicide prevention intervention in hospitals to adolescents who self-harmed, we calculated the monthly incidence of non-lethal self-harm by subtracting the country-, age-, and sex-specific incidence of death by self-harm (that is, suicide) from the overall monthly incidence of self-harm in the 2019 GBD. This statistic might double-count adolescents who self-harm more than once per month; furthermore, it is likely that most cases of self-harm do not lead to hospitalization. We therefore assume that 41% of instances of self-harm lead to hospitalization (minimum 35%, maximum 49%), based on an English study that compared the number of self-harm cases found through an intensive data gathering process with the number found in routine hospital records.[63] Limited data from low- and middle-income countries are available to inform these assumptions. Among those who presented at a hospital, we then assumed a 20% coverage rate of the intervention (minimum 10%, maximum 50%).

In a study of Medicaid patients in the United States, adolescents aged 10-17 who self-harmed experienced a 12-month mortality ratio of 46.0 (95% confidence interval minimum 29.9, maximum 67.9) compared to those who did not self-harm. For those aged 18-25, the mortality ratio was 19.2 (95%

confidence interval minimum 12.7, maximum 28.0).[64] To calculate the age-, sex-, and country-specific probability of death by suicide after self-harming, we multiplied the probability of suicide not attributable to our mental health conditions of interest (already modified by the prevention intervention in schools) by these rate ratios. To calculate the probability of death by suicide not after self-harm, we used the following equation:

$$\Pr(D_s|noSH) = \frac{[1-\Pr(SH)]* RR_{D_s|SH}}{[1-\Pr(SH)]} * \Pr(D_s) \quad (8)$$

Where D_s is death by suicide with none of our mental health conditions of interest, SH is self-harm, and $noSH$ is no self-harm. The overall probability of death by suicide in the investment case, before accounting for this hospital follow up, is therefore

$$\Pr(D_s) = [\Pr(SH) * \Pr(D_s|SH)] + \{[1 - \Pr(SH)] * \Pr(D_s|noSH)\} \quad (9)$$

This works out to the same probability of death by suicide overall, but this breakdown allows us to apply an intervention just to the proportion of people who self-harmed. The intervention risk ratio for the probability of suicide after the intervention is 0.105 (95% confidence interval minimum 0.025, 0.453).[60] The intervention includes 18 months of follow up, so we allow the effect to remain at full value until the adolescents reach 20.5 years of age and then taper to null over the next 12 months.

In the investment case as in the base case, we multiply this probability of death by suicide not due to mental health conditions by the risk ratio of death by suicide for each of our diseases of interest. This implicitly assumes that these conditions correlate the same way with self-harm as they do with suicide.

Education and employment outcomes

Education outcomes by age

Within each country, age, and sex group, we gathered the base probabilities of a person having completed a given level of education and of a person with a given level of education being employed from ILOSTAT, the International Labor Organization's online database.[65] For all data points in this section, if data were missing for a country, we filled the gaps by using the average of the indicator (by age and sex, if relevant) from the country's WHO region and World Bank income level. See *Supplementary File 3* for the estimates used for all countries included in the model.

For the levels of education completed, to allow for comparability across as many countries as possible, we used the aggregate levels from the International Standard Classification of Education (ISCED): "less than basic", "basic", "intermediate", and "advanced". We distributed any proportion of "level not stated" observations across the above categories, weighted by the existing proportions in those categories. The database did not include the probabilities of education by age and sex for China, Japan, or the Philippines, so we substituted the averages (weighted to sum to a probability of 1) from all countries within the same World Bank income level and WHO region, respectively. In all cases, we adjusted the probabilities to ensure they scaled to 1.

In the structure of the ILOSTAT database, the lowest age band begins at 15 years of age. For the purpose of employment calculations, we make the following assumptions to adjust probabilities of completed education from the age band 15-25 to ages less than 15:

- Everyone who has completed less than a basic level of education when they are over the age of 15 must not have completed less than a basic level of education before they were 15

- Everyone who has completed an intermediate or advanced degree between the ages of 15 and 25 has completed a basic degree by the age of 15
- No one has completed an intermediate or advanced degree by age 15.

Table A24 provides an example from a hypothetical country of how these assumptions would play out.

Table A12: Example adjustment of probabilities of education

Education level	Data from ILOSTAT on probability of having completed this level of education, ages 15-25	Adjusted data for probability of having completed this level of education by age 15
Less than basic	40%	40%
Basic	30%	60%
Intermediate	20%	0%
Advanced	10%	0%

For the probability of employment by education level, we use the definition of employment from the ILO: "all persons of working age who during a specified brief period, such as one week or one day, were in the following categories: a) paid employment (whether at work or with a job but not at work); or b) self-employment (whether at work or with an enterprise but not at work)."[66] We used the same education levels described above. Algeria, China, Iran, Japan, Morocco, and the Philippines all lacked these data, so we calculated and used the averages of the countries in their respective WHO regions and World Bank income levels. As 15 is the standard international start of working age, we assumed that no one under the age of 15 would be employed.

Change in probability of graduation due to mental illness

We calculated the probability of a person not graduating from a specific level of education as follows:

$$\Pr(E_n) = \frac{\Pr(E_i)}{\sum_{i=n}^{3} \Pr(E_i)} \quad (10)$$

Where $\Pr(E_n)$ is the probability of *n* being their highest level of educational achievement; and 0, 1, 2, and 3 correspond to less than basic, basic, intermediate, and advanced education, respectively.

As bipolar disorder usually manifests in people older than the standard ages for secondary school, we could not find data on the reduction in secondary graduation rates due to bipolar disorder. We drew the reduction in probability of completing a tertiary (i.e. advanced) degree from a United States study of college students with bipolar disorder matched with controls on age, sex, ethnicity, handedness, and parental education levels, with a reduction in probability of completing a tertiary degree of 34%, varied by 50% in sensitivity analysis.[67] We multiplied the baseline probability of completing a tertiary degree by the complement of this reduction in probability to determine the probability of a person who experienced bipolar disorder as an adolescent graduating with an advanced degree. We then added the difference between the baseline and adjusted probability of completing an advanced degree to the probability that a person would have an intermediate degree.

Anxiety and depression do often affect adolescents in secondary school. We drew from a recent systematic review of the effects of these disorders on early school leaving. Adolescents with major depressive disorder face an odds ratio of 3.38 for leaving secondary (i.e. intermediate) school before

graduation (varied between 1.8 and 6.42 in sensitivity analysis, the confidence interval for early onset depression in that review). Adolescents with anxiety face an odds ratio of 1.4 (95% confidence interval 1.1 to 1.8) of leaving school early.[68] We used these odds ratios and the base probabilities of graduating to calculate new probabilities of graduating as in equation (6). We conservatively assumed that comorbid anxiety and depression has the same effect on graduation rates as depression alone. In our scenario analyses, we allowed for an additive effect for those who experienced both anxiety and depression as teenagers by calculating the sum of percentage change in graduation rates among those with anxiety or depression alone.[69]

For those who experienced depression and/or anxiety as an adolescent, we calculated the new probability of a given level of education being a person's maximum within each country, age, and sex group as follows:

$$\Pr(E_{0,dx}) = \Pr(E_{0,base}) \quad (11)$$

$$\Pr(E_{1,dx}) = [1 - \Pr(E_{0,base})] * [1 - \Pr(G_{2,dx})] \quad (12)$$

$$\Pr(E_{2,dx}) = \sum_{i=1}^{3} E_{i,base} * \Pr(G_{2,dx}) * \frac{\Pr(E_{2,base})}{\Pr(E_{2,base}) + \Pr(E_{3,base})} \quad (13)$$

$$\Pr(E_{3,dx}) = \sum_{i=1}^{3} E_{i,base} * \Pr(G_{2,dx}) * \frac{\Pr(E_{3,base})}{\Pr(E_{2,base}) + \Pr(E_{3,base})} \quad (14)$$

Where *G* is the probability of graduating from a given level of education, $base$ denotes parameters related to people without a mental disorder of interest during their adolescence, and dx denotes parameters related to people who experienced the disease as an adolescent.

Wage returns to education

To capture the economic effects of changes in educational attainment as an adolescent, we must convert educational attainment to expected wages. This is a tricky proposition, and the ILO does not report actual median wages by educational attainment. We rely on a World Bank working paper that calculates comparable returns on investment for an additional year of education for countries in all WHO regions and World Bank income levels.[70] We used the most recent years of data for all available countries at the highest level of granularity available for the country. The highest level of granularity was disaggregated by sex (male/female) and by level of education (primary/secondary/tertiary). For countries missing from the dataset—Algeria, China, Iran, Japan, Morocco, and the Philippines—we once again used the averages of the available data from other countries in the same World Bank income level and WHO region.

As an assumption for the baseline level of wages expected by a person with zero years of education, we used the mean of the 10th percentile of wages or consumption from the World Bank PovcalNet database.[71] If data were available for both wages and consumption, we chose the wage data. For countries with both urban and rural data, we used the weighted urban and rural data. Only Afghanistan had no income decile information, so we used the average of the available data from other countries in the same World Bank income level and WHO region.

We used the expected length of time to complete a degree in primary and secondary schools for each country from the UNESCO Institute for Statistics [72] and assumed 4 years for completion of a tertiary degree, which is the most common length in the OECD.[73] We further assume that a person does not

pursue any years of education after they complete their highest degree. We then calculate the expected wages for each income level with the standard percentage growth formula, compounded each year.[74]

$$w_2 = w_1(1 + p) \quad (15)$$

where w_1 is the base expected wage, w_2 is the wage with one additional year of education, and p is the expected return to the additional year of education as a proportion.

Expected wages by adolescent experiences of mental illness

The expected wage for a given state is calculated using the average of expected wages by education level, weighted by the probabilities that a person will have achieved that education level. For all adolescents that move out of the "healthy" state of the model, our model assumes that the above-described educational effects of adolescent illness remain over the life of the individual. In every state except the initial healthy state, therefore, the probabilities of a given education level are modified as described above. Even when a person recovers from the health effects of an adolescent mental health condition, the effects of their illness on their adolescent educational experiences remain.

Acute effects of mental illness on employment

In addition to the long-lasting effects of mental illness in adolescence, our model accounts for the short-term effects of an acute episode of mental illness by adjusting the expected productivity during an episode. For bipolar disorder, we additionally reduce the overall probability of employment, regardless of education status.

We drew the reduction in productivity from absenteeism due to anxiety, depression, and the non-euthymia states of bipolar disorder from World Mental Health survey data.[75] To calculate losses associated with presenteeism—a reduction in productivity while not absent from work—due to depression, we used the ratio from a study of 8 HIC and MIC workers.[76] We found little literature on presenteeism due to anxiety, so we conservatively assumed no presenteeism at baseline, varied to the depression base value in sensitivity analysis.[77] For bipolar disorder, systematic reviews have found productivity losses due to a 60% overall reduction in the probability of employment, but no evidence of additional losses due to presenteeism after accounting for absenteeism.[78,79]

These multipliers are applied to expected wages in all active disease states, regardless of adolescent health status.

Model outputs

For each cycle that an individual spends in a given model state, the model counts the expected monthly cost of any relevant intervention and the monthly "benefits" in terms of the intrinsic value of health in that state plus the expected value of wages. We added these costs and benefits together across all subsets of the cohort to calculate the expected costs and benefits of the intervention. To calculate the return on investment (ROI) of the interventions, we used the following equation:

$$ROI = \frac{(Benefit_{invest} - Benefit_{noinvest}) - Cost_{invest}}{Cost_{invest}} \quad (16)$$

In all runs of the model, the cost of "no investment" is always zero, as the no investment case involves no interventions.

Sensitivity analysis

For each parameter varied in our sensitivity analysis (see Supplementary File 2 for the list), we assigned a distribution, using the lognormal distribution for odds ratios, risk ratios, and hazard ratios and using the PERT distribution (an improvement on the triangle distribution, which uses the minimum, maximum, and mode to generate a smooth probability distribution) for all other parameters. In a standard Markov probabilistic sensitivity analysis (PSA), we would re-run our base case analysis, resampling each parameter from its distribution some large number of times for each country/sex/age population and intervention. Given the scope of the analysis—720 populations, 2 outcomes of interest, and 13 interventions, which would require 18,720 runs of the model per Markov resampling—however, the built-in PSA methods from the heemod package would take a prohibitively long time to run, even when taking advantage of parallelization. Instead, we used the lhs package[80] to generate a Latin hypercube sample (LHS)[81] for all parameters that varied in our sensitivity analysis. For each row of the LHS, we first generated the samples by country and sex by assigning them numeric values and then converting those to categorical and by age as a continuous variable. We then generated the LHS for the remaining variables, all of which were continuous variables. Where values differed by country, sex, and/or age at start, we ensured that the LHS drew from the appropriate distribution, based on the previously selected values in the row. For each of the 13 intervention options, we generated this LHS for 100,000 samples. We then ran the model 100,000 times per intervention, drawing the values from a random row of the appropriate LHS each time. We present the median, range, and interquartile range (the 25th and 75th percentiles) of these simulations in the results and the supplemental files.

It is important to note that these estimates differ from the base case estimates due to their methods of calculation. In the base case, each of the estimates derive from the *sum* of the costs and benefits across all populations in the model or subset. For example, the base case ROI for the treatment of severe depression in the PAHO region shows the *total* ROI for implementing the intervention among all males and females aged 10-19 in Argentina, Brazil, Colombia, Mexico, and the United States. By contrast, the PSA considers the distribution of possible ROIs when looking at a single randomly-selected permutation of sex, age at start, and country. Of these three, country drives the vast majority of differences in ROI; we therefore present all of the sensitivity analysis results by country.

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