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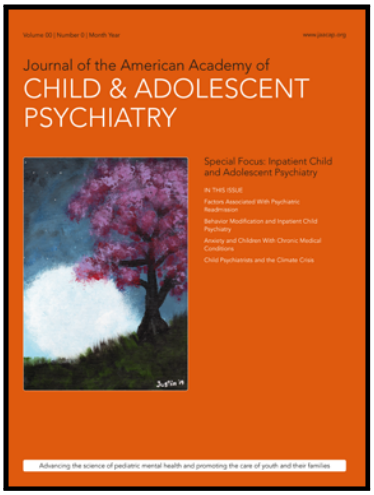

Systematic Review and Meta-analysis: Depressive Symptoms and Risky Behaviors Among Adolescents in Low- and Middle-Income Countries

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Systematic Review and Meta-analysis: Depressive Symptoms and Risky Behaviors Among Adolescents in Low- and Middle-Income Countries
RH = The DERAIL study

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Abstract

Objective: Several studies conducted in high-income countries have found an association between depressive symptoms and risky behaviors among adolescents. Evidence from low- and middle-income countries (LMICs), where 90% of the world's adolescents live, remains scarce. The objective of this review was to systematically review the evidence examining the association between depressive symptoms and risky behaviors among adolescents in LMICs.

Method: We searched 15 electronic databases for published or unpublished cohort and case-control studies about adolescents in LMICs. We applied no restrictions on date or language. The primary outcome was the association (odds ratio [ORs]) between depressive symptoms and risky sexual behavior and substance use. Secondary outcomes included delinquency, adverse school behavior, self-harm, and suicidal behavior. We pooled the ORs from all studies using the random-effect model. We assessed the quality of the studies using the Newcastle-Ottawa scale, and the strength of the overall body of evidence using GRADE. The study protocol was registered on PROSPERO (CRD42019131262).

Results: The searches yielded 31,148 potentially relevant studies. After screening, we included 33 records in the systematic review, of which 30 comprised the meta-analysis. All studies encompassed a total of 35,918 adolescents living in 17 LMICs: 5 from Africa, 7 from Asia, and 5 from Latin America and the Caribbean. We found that adolescents with depressive symptoms are more likely to engage in risky sexual behavior (OR 1.3, 95% CI: 1.1-1.5) and substance use (OR 1.8, 1.4-2.2) compared to non-depressed adolescents. Results for the secondary outcomes showed a similar pattern, with higher delinquency (OR 3.2, 1.8-5.6), self-harm (OR 4.4, 1.3-14.4), and suicidal behavior (OR 6.6, 2.3-18.9) among adolescents with depression compared to healthy adolescents.

Conclusion: This study suggests that adolescents with depression in LMICs carry a double burden: they both suffer from depression, and are at an increased risk of engaging in risky behaviors. This combination may lead to further psychological and physical health problems that persist over the life course, and may impose a health burden on society as a whole. Taken together, these findings

highlight the urgent need for scalable and sustainable approaches to prevent and/or treat depression among adolescents in resource-poor settings.

Key words: depressive symptoms, risky behaviors, adolescents, low- and middle-income countries

Introduction

Adolescence is a time when individuals start to make vital decisions – about their own health, education, friendships and intimate relationships, and entrance into the labour market – within a context of diminishing parental involvement and heightened peer influence.[1] This period is often marked by a rise in risky behaviors such as unprotected sex and substance use, especially when adolescents are with peers.[2] Externalizing problem behaviors such as aggressive and rule-breaking behaviors also show an increase in prevalence during adolescence.[3] Many of these behaviors increase the risk of a range of negative long-term outcomes such as substance abuse, HIV, teenage pregnancy, imprisonment, or in the worst cases, premature death.[4]

Adolescence is also the period in which the incidence of depression peaks, with half of lifetime onset by age 14 and with adolescent women being especially affected.[5] Depression is associated with difficulties in cognitive functioning, poorer school performance, deterioration of social relationships, and worsened long-term decision-making.[6,7] In its most severe form, depression can also lead to self-harm and suicide.[8]

Several longitudinal studies have found an association between depressive symptoms during adolescence and risky sexual behaviors such as unprotected sex, teenage pregnancy, and sexually transmitted infections (STIs).[9–12] Depressive symptoms have also been associated with alcohol and drug use, and with subsequent onset of substance use disorders.[13–16] Further complicating matters, individuals often engage in multiple risky behaviors at the same time. For example, adolescents who use drugs and alcohol are more likely to engage in risky sexual behavior.[17,18]

Most studies that have explored this association rely on data from so-called WEIRD societies (Western, Educated, Industrialized, Rich, and Democratic), making it difficult to generalise to low- and middle-income countries (LMICs).[19] The bulk of the evidence conducted in LMICs has been

cross-sectional, and thus, the temporal relationship between past depressive symptoms and future risky behaviors cannot be determined.[20–29]

Evidence from LMICs, where 90% of the world's adolescents live, remains relatively scarce.[30] This project — 'Depressive symptoms and Risky behaviors among Adolescents In Low- and middle-income countries' (the DERAIL study) — aims to contribute to closing this gap by identifying and systematically reviewing all relevant literature reporting on the association between depressive symptoms and risky behaviors among adolescents living in LMICs, with the goal of providing a quantitative summary estimate of the extent to which these are associated. In doing so, this review identifies existing adolescent cohort studies in LMICs, an area that continues to be under-represented in research studies.[31]

Method

Search Strategy and Selection Criteria

We followed the PRISMA guidelines.[32] A protocol for the study is available on PROSPERO (CRD42019131262). We searched for both published and unpublished studies reporting on the association between depression and risky behaviors in the following electronic databases: Child Development & Adolescent Studies, Cochrane Database of Systematic Reviews, Cumulative Index to Nursing and Allied Health Literature, Embase, Global Health, MEDLINE, PsycINFO, Scopus, Social Science Citation Index/Web of Science, WHO Library Database, and World Bank's Library. Additionally, we searched grey literature databases using OpenGrey, as well as the British Library for Development Studies, Eldis, and GoogleScholar. The search was conducted on April 22, 2019. We applied no restrictions on date, language, or publication status to the searches.

We also searched databases with longitudinal cohort data of adolescents from LMICs (e.g. National Income Dynamics Study in South Africa, the Pelotas Birth Cohort Study in Brazil, Cebu Longitudinal Health and Nutrition Survey in the Philippines, the Young Lives study).

We included articles that recruited adolescents aged 10 to 24 years old, which is in line with the definition of adolescence put forth by Sawyer et al. (2018). Earlier studies defined adolescence as the period of life between the start of puberty and the point at which an individual attains a stable, independent role in society.[2] However, the timing of puberty and the transition to adulthood vary across time and cultures. For example, in many high-income countries, the end of the period considered as adolescence is frequently being extended as adolescents tend to undertake more years of education and live with their parents for longer, sometimes well into their twenties. In other cultures, children are expected to get married and become financially independent as soon as they reach puberty or even earlier. In response to this, an expanded, more inclusive definition of adolescents (10-24 years) has been proposed, and this is an important step towards making adolescents more visible for policymakers, donors, and researchers.[33]

Our core search consisted of terms related to depression (depression or depressive disorder), risky behavior (risk-taking or risk behavior or risky sexual behavior or substance use or delinquency or adverse school behavior or self-harm or suicidal behavior), adolescents (adolescent or young adult or school age), and study setting (developing or low income or low- and middle-income country). The main search strategy for Medline is presented in Table S1, available online.

Studies were included if they met the following criteria: (1) cohort studies that measured depression at baseline, and then recorded the incident risky behaviors during follow up. We also included case-control studies that compared the prevalence of depressive symptoms between adolescents who engaged in risky behaviors (cases) and adolescents who did not engage in risky behaviors (controls);

(2) Studies that recruited adolescents aged 10 to 24 years at baseline living in LMICs as defined by the World Bank (see Table S2, available online); (3) Studies that ascertained depression using standard operationalized diagnostic criteria (DSM-III onwards, and ICD-10 onwards) and validated screening tools (e.g. CES-D, PHQ-9); (4) Studies that measured risky behaviors using biological markers and/or self-reported measures (see Outcome section for further details); (5) Studies that controlled for the outcome variable (risky behaviors) at baseline and potential confounders (e.g. age, sex, socioeconomic status).

We excluded cross-sectional studies because of their methodological limitations. We also excluded randomised trials for two reasons. First, given the limited evidence on the issue and the fact that risky behaviors may only manifest years later, we believed that a review of observational studies was first needed to support a theoretical framework and provide supplementary information to better understand the mechanisms underlying any plausible casual relationship.[34] Second, randomised trials cannot study what happens to adolescents once they become depressed (as a trial that induces depression would not be feasible or ethical). Instead, randomised trials will only be able to measure whether reducing depression also reduces risky behaviors. While similar in nature, we see this and our main objective as two different questions.

Further, we excluded studies that reported suicidal ideation (without attempt) as thoughts are not behaviors, and studies that recruited HIV positive adolescents where the route of transmission (vertical or horizontal) was not stated. This was done to err on the side of caution, as it would be incorrect to consider being born with HIV a risky behavior.

In cases where multiple studies used the same data, we included the study with the larger sample size or the most recent publication, with the sample size taking precedence. Further, non-English-language studies were translated either by colleagues fluent in the respective language or using the

Google Translate (and subsequently crosschecked by a native speaker). We checked reference lists to identify relevant studies and hand search these.

Search results were compiled, and duplicates eliminated by a single researcher (JRP). Two reviewers (LD and JRP) independently screened the title and abstracts of retrieved references and obtained the full text of all potentially eligible studies. The same reviewers independently read the selected full texts and decided on the final suitability of each article for inclusion. Disagreements were resolved through discussion and consensus. Reasons for exclusion of articles after full-text examination were recorded. Authors of the included studies were contacted when key information was missing.

Records were managed through Mendeley, a software for managing bibliographies. The procedure to manage the screening process was carried out using Covidence,[35] an advanced systemic literature review software.

Outcomes measures

Primary outcomes

Despite the negative long-term consequences of risk behaviors, there is no consensus on how to define these behaviors. The concept of risky behaviors may also differ greatly within individuals and across cultures, as do the opportunities to engage in certain types of behaviors (e.g. individuals living in Muslim countries might be less exposed to alcohol).[36]

Research about risk-taking has included a wide variety of "risky behaviors," making it difficult to narrow down the concept to a simple, useful definition. In this review, we define risky behaviors as voluntary, observable behaviors that contribute to disability and premature death, and that impose a health burden on society as a whole.[37,38] Specifically, we focus on the following two primary outcomes:

Risky sexual behaviors: any sexual behavior that increases an individual's risk for sexually transmitted infections (STIs) or unwanted pregnancies. We included studies that measured such behaviors using biological markers (e.g. STIs, pregnancy) or self-reported indicators of the following variables: number of unprotected sex episodes, total number of partners, ever had an unintended pregnancy, teenage pregnancy, age of first coital debut, age difference with partner, ever engaged in transactional sex.

Substance use: any use of alcohol or other recreational drugs. We included studies that measured substance use using biological markers (e.g. Breathalyzer readings, urine and blood samples), diagnostic interviews, or self-reported measures of the following variables: alcohol use (frequency, age at onset, binge drinking episode), tobacco use (frequency, age at onset), illicit drug use, including but not limited to, cannabis, cocaine, heroin, and opioid, ever experienced any alcohol or substance dependence symptoms.

Secondary outcomes

Delinquency: any behavior that is illegal or not acceptable to most people. We included studies that measured such behavior using official police records or self-reported measures of the following variables: participation in delinquent acts, including but not limited to, violence, bullying, gang membership, reckless driving, drug trade, theft, frequency of delinquent activity, age at which first delinquent act occurred, delinquency charges, ever incarcerated.

Adverse school behaviors: any behavior that disrupts the classroom or an individual's school performance. We searched for studies that measured these behaviors using administrative school data or self-reported measures of the following outcomes: number of absences in the last academic year, school abandonment, number of incomplete assignments, variation in learning outcomes with respect

to last academic year, grade retention. Behaviors such as violence in school and bullying were included as part of delinquency.

Self-harm: deliberate, self-inflicted destruction of body tissues without suicidal intent. We searched for studies that measured experiences of intentional self-harming behaviors (e.g. cutting, burning, biting, scratching skin).

Suicidal behavior: the act of trying to take one's own life voluntarily and intentionally. We searched for studies that measured this behavior using questionnaires and/or standardized interview assessment or scales of the following variables: presence of suicidal attempts, total number of suicides ever attempted, and completed suicides.

Data extraction and quality assessment

One reviewer (JRP) extracted data, and a second reviewer (LD) independently crosschecked these data for accuracy against the original studies. All discrepancies were reconciled by team discussion. We extracted data on study characteristics, depression assessments, risky behavior assessments, and results using Microsoft Excel.

Two reviewers (JRP and LD) independently assessed the quality of the studies using the Newcastle-Ottawa scale (NOS) using two different scales for cohort and case-control studies, respectively.[39] The strength of the overall body of evidence for the primary outcomes was assessed using Grading of Recommendations, Assessment, Development and Evaluation (GRADE).

Statistical analysis

Studies that met all the inclusion criteria and reported an odds ratio or provided sufficient data to calculate odds ratios were included in the meta-analysis. The analysis was conducted in

Comprehensive Meta-Analysis (CMA) software version 3.[40] The incidence of each type of risky behavior in depressed and non-depressed adolescents was estimated using odds ratios (ORs). When several odds ratios were reported within a study, we used the estimate from the model that adjusted for the maximum number of covariates. We pooled the ORs from all studies using the random-effects model since considerable heterogeneity was expected.[41] Random-effects models assumes that the true treatment effect differs from study to study (i.e. there is a distribution of true effect sizes), which allows to generalize to a range of populations.[42] Forest plots were used to present the pooled ORs and 95% CIs. The presence of between-study heterogeneity was tested using Cochran Q and quantified by the I^2 statistic.[43]

We carried out subgroup analyses for studies that reported a separate association for female and male participants. As part of the protocol, we included a subgroup analysis comparing depression severity (high vs low), but this information was not reported in most of the studies. We conducted subgroup *post hoc* analysis for the following categories: study design (cohort vs. case-control studies), type of tool to measure depression (diagnostic interviews vs. self-report measures), and type of tool to measure risky behavior (biological markers or diagnostic interviews vs. self-report measures).

Results

The electronic searches yielded 31,148 potentially relevant studies. In total, 25,863 studies were excluded in the first screening phase (title and abstract) and 668 studies were excluded in the second screening phase (full-text). Overall, we included 33 records in the systematic review, of which 30 comprised the meta-analysis (see Figure 1 for flow diagram). All studies encompassed a total of 35,918 adolescents living in 17 different LMICs: 5 from Africa, 7 from Asia, and 5 from Latin America and the Caribbean.

[INSERT FIGURE 1 AROUND HERE]

Overall, we found 7 records reporting on the association between depressive symptoms and risky sexual behavior,[44–50] 10 for substance use,[45,48,49,51–57] 4 for delinquency,[58–61] 3 for self-harm [62–64] and 11 for suicidal behavior (2 of which were included in the systematic review).[65–75] Three studies reported on both risky sexual behavior and substance use, separately.[45,48,49] One study included in the systematic review reported an index of risky behaviors (combining behaviors such as unsafe sexual practices, violent behaviors and rule breaking).[76] We did not find any study reporting on the association between depressive symptoms and adverse behaviors in school. Table 1 shows characteristics of the included studies, and Table S3, available online, shows a list of all excluded studies with reasons.

[INSERT TABLE 1 AROUND HERE]

In terms of the study design, 12 were cohort studies, and 21 were case-control studies. Overall, we included 29 studies published as full-text articles in 26 different peer-reviewed journals, 1 abstract, and 3 cohort databases with data on adolescents from the Philippines, Brazil and South Africa. We conducted the analysis ourselves whenever the data was open access (Philippines and South Africa), and asked the study team to conduct the analysis whenever it was not freely available (Brazil). Further, 10 studies assessed depressive symptoms using standard operationalized diagnostic criteria (DSM-III onwards and ICD-10 onwards) and 23 studies used self-reported screening tools. Two case-control psychological autopsy studies administered diagnostic interviews to family members of adolescents who had died by suicide (cases) and other injuries (controls). Both of these studies relied on at least two types of informants (family members, friends, or neighbour) to minimise informant discrepancies and measurement error.[70,74]

Regarding study quality, using the NOS, most studies (67%) had high methodological quality, ten studies (30%) were scored as moderate, and one study (the abstract) had low quality (Table 1 shows the total score, and Table S4, available online, shows the score for each dimension).

Primary outcomes: to estimate the extent to which depressive symptoms were associated with increased odds of engaging in risky behaviors, we pooled results for each type of risky behavior. First, adolescents with depressive symptoms are more likely to engage in risky sexual behavior compared to non-depressed adolescents (OR=1.29, 95% CI: 1.13-1.48, I^2=74.5%; Figure 2). Second, adolescents with depressive symptoms are at an increased odds of engaging in substance use compared to adolescents without depressive symptoms (OR=1.76; 1.42-2.19, I^2=77.33%; Figure 2).

Secondary outcomes: the forests plots for the secondary outcomes are shown in Figure 3. Results for the secondary outcomes showed a similar pattern to the primary outcomes, with higher delinquency (OR=3.21, 1.83-5.62, I^2=33.58%), self-harm (OR=4.38, 1.34-14.36, I^2=0.0%), and suicidal behavior (OR=6.56, 2.28-18.86, I^2=0.0%) among adolescents with depression compared to non-depressed adolescents.

Figure S1, available online, presents the results of the subgroup analyses for the primary outcomes. The difference between female and male participants was statistically significant for risky sexual behavior (p-value=0.001), showing a larger OR among female adolescents compared to male adolescents. No statistically significant difference was found between groups for substance use (p-value=0.442). Results for the subgroup post hoc analysis are shown in Table S5, available online. We did not find any significant difference across depression measures (diagnostic interviews vs. self-report questionnaires). The test for subgroup differences was significant across the study design (cohort vs. case-control, with larger OR in case-controls), and risky behaviors measures, with biological markers/diagnostic interviews resulting in significantly larger OR compared to self-reported measures.

Three studies did not report poolable data and were thus not included in the meta-analysis. One study reported findings as a regression coefficient,[75] another reported a risk ratio without the absolute numbers,[67] and another study reported an index of risky behaviors.[76] All three studies reported a positive association between depressive symptoms and risky behaviors, reinforcing the results of the meta-analysis. Interestingly, Auerbach (2010) conducted a multilevel modelling analysis to examine two hypotheses: whether depressive symptoms resulted in more risky behaviors, and the reverse model (i.e. whether risky behaviors resulted in higher depressive symptoms). Using a sample of 411 Chinese adolescents and seven assessments, the results suggested that the model was unidirectional, with depressive symptoms occurring earlier than the incidence of risky behaviors.

Finally, following GRADE's guidelines, we assigned an a-priori ranking of low to the strength of the overall body of evidence.[77] Overall, we did not find any evidence to downgrade or upgrade the certainty of the evidence. The certainty in the evidence was thus assessed as low (further details can be found in Table S6, available online).

Discussion

This review found that adolescents in LMICs with depressive symptoms are more likely to engage in risky behaviors compared to non-depressed adolescents. These findings are consistent with the evidence from high-income countries.[9–16] To our knowledge, this is the first systematic review and meta-analysis of the effect of depressive symptoms on risky behaviors among adolescents in LMICs.

Our literature search was as comprehensive as possible, we searched both published and unpublished studies across 15 different databases and registries. In addition to relying on results from peer-reviewed studies, we also conducted novel analyses of longitudinal cohort studies of adolescents from LMICs. Further, this review focused specifically on cohort and case-control studies, and only included studies that controlled for potential confounders. We assessed the quality of the studies

using the Newcastle-Ottawa scale and used GRADE to assess the strength of the overall body of evidence, which is now considered an international standard. Most of the studies included were of moderate to high methodological quality, and some of them included nationally representative samples, increasing the external validity of our results. Moreover, we included a range of risky behaviors (sexual, substance, delinquency, etc), as opposed to focusing on a single behavior. All included studies encompassed a total of 35,918 adolescents living in 17 different LMICs. These 17 countries are home to 48% of the world's population, and 57% of the LMIC population (Table S7, available online).

There are several mechanisms that could explain these results. One view, referred to as the 'self-medication' hypothesis, suggests that adolescents with depression might engage in risky behaviors such as substance use as a coping mechanism to seek relief from their symptoms, or to experience emotions.[78,79] A second perspective states that changes in cognitive functions associated with depression (e.g. inhibitory control and reward processing) may result in higher risky behavior engagement. [6,80,81] Further, the presence of cognitive biases such as low self-esteem, avoidance, rumination, and hopelessness may make a depressed individual more prone to engage in risky behaviors.[82–85] Beyond individual-level mechanisms, environmental factors – such as affiliations with substance using or deviant peer groups – might precipitate the onset of depression and make adolescents more prone to engage in risky behaviors.[86] These mechanisms are not mutually exclusive, and thus the mechanisms may in fact be a combination of all four. Further research is needed to better understand the mechanisms at play, and to inform policy and guide interventions targeting adolescent's health.

Our review has some limitations. First, this study reviews the association between depressive symptoms and risky behaviors using observational evidence, and thus, the results do not allow definitive conclusions on causality to be drawn. Given the limited number of adolescent cohort

studies in LMICs, this review combined results from cohort and case-control studies in an effort to expand the search strategy and make it as comprehensive as possible.[31] While we found a significant difference across study designs (with larger odds ratio in case-control studies), similar results were observed for cohort studies, reinforcing the validity of our findings. To mitigate the risk of confounding, we considered the most important potential confounders in advance (when preparing the protocol) and only included studies that controlled for covariates that are known to affect depressive symptoms and risky behaviors (e.g. age, sex, socioeconomic status). Second, significant heterogeneity was observed across studies in many outcomes. We believe that this was, in part, due to the fact that odds ratios were computed by combining different behaviors (for example, risky sexual behaviors pooled together teenage pregnancy, unsafe sex, multiple partners); and the applied to substance use and delinquency. We decided *a priori* to combine these behaviors given that they tend to co-occur and share similar antecedents. To explore possible sources of heterogeneity, we also performed subgroup analysis according to sex, study design, and elicitation method used to assess depression and risky behaviors, respectively. In most of these cases, heterogeneity was reduced considerably. Third, several studies ascertained depression and the risky behavior outcome using self-report measures, which may result in recall bias and/or measurement error. However, most studies that relied on self-report elicitation methods used validated screening tools with good psychometric properties. Studies with younger adolescents (10–15 years) used standardised diagnostic interviews and depressive symptoms scales that were suitable for participant's age, such as the Mini-International Neuropsychiatric Interview for Children and Adolescents (MINI-KID) and the Children's Depression Inventory (CDI). In addition, we found no significant difference across depression measures (diagnostic interviews vs. self-report questionnaires), which gives some indication of the reliability of the self-report tools. This is consistent with the evidence showing that self-reported questionnaires are valid methods to identify depressive symptoms, in addition to being considerably more cost-effective than structured clinical interviews.[87] Further, several studies relied on objective measures of risky behaviors (e.g. being a drug-dependent inpatient or pregnant),

increasing the validity and reliability of our findings. Lastly, evidence from observational studies is considered low quality according to the GRADE framework, and thus, our confidence in the effect estimate is limited.

In spite of these limitations, this study has important implications. First, these findings suggest that adolescents with depression in LMICs carry a double burden: they suffer from depression, and additionally, since they are more likely to engage in risky behaviors, they are at an increased risk of suffering from the negative consequences of their behaviors. This double burden may result in further psychological and physical health problems that persist over the life course (e.g. substance use disorder and sexually transmitted infections), and may impose a significant health burden on society as a whole. In turn, this implies that a comprehensive assessment of the burden of depression — already the leading cause of disability globally[88] — would need to take into account the negative consequences of risky behaviors associated with depressive symptoms.

Second, some studies have found that risk factors for depression (e.g. food scarcity, violence, and forced migration) are overrepresented in LMICs, resulting in higher rates of depression among adolescents in LMICs compared to high-income contexts.[8,89–91] Adding to the complexity, LMICs have extremely low levels of public expenditure on mental health (less than US$2 per capita per year) and many lack a mental health policy specifically devoted to adolescents.[92,93] As a result, access to evidence-based treatments remains very limited in LMICs.[94] These findings, taken together with the results from this study and the fact that nearly 90% of the world's adolescents live in LMICs, imply that a significantly higher share of adolescents are more likely to engage in risky behaviors.

Third, risky behaviors in LMICs can result in particularly poor living conditions, especially in low resource settings. In many developing countries the capacity of the public health and welfare

institutions are often insufficiently resourced, which means that adolescents living in these contexts lack the support they need.[95] While this type of support is far from perfect in high-income countries, there are a range of programmes such as rehabilitation programmes, health-related curricula in schools, training opportunities, or peer support groups that promote adolescent health and well-being.[96] This lack of safety nets in LMICs makes adolescents even more vulnerable to the negative impacts of risky behaviors.

In conclusion, given the high prevalence of depression among adolescents in LMICs and the lack of services for them, our results underline the need for targeted screening for depression and risky behaviors, in addition to scalable treatments that can promote adolescents' health and well-being. Future research should continue to focus on this important issue given the associated negative long-term consequences. This might include a special emphasis on possible moderators and mediators by which depression may influence risky behaviors. Empirically investigating this relationship might also inform policy and the design of effective interventions to prevent and/or treat depression among adolescents in resource-poor settings.

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Conceptualization: Pozuelo, Stein, Cipriani
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Project administration: Pozuelo
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Supervision: Stein, Cipriani
Validation: Desborough
Visualization: Pozuelo
Writing – original draft: Pozuelo
Writing – review and editing: Pozuelo, Desborough, Stein, Cipriani

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Figure 1 R1

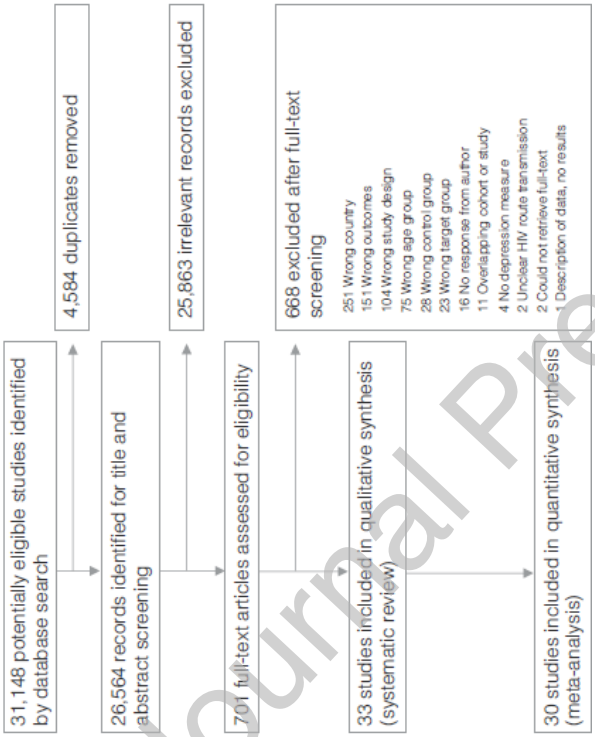

Figure 1. Study Selection

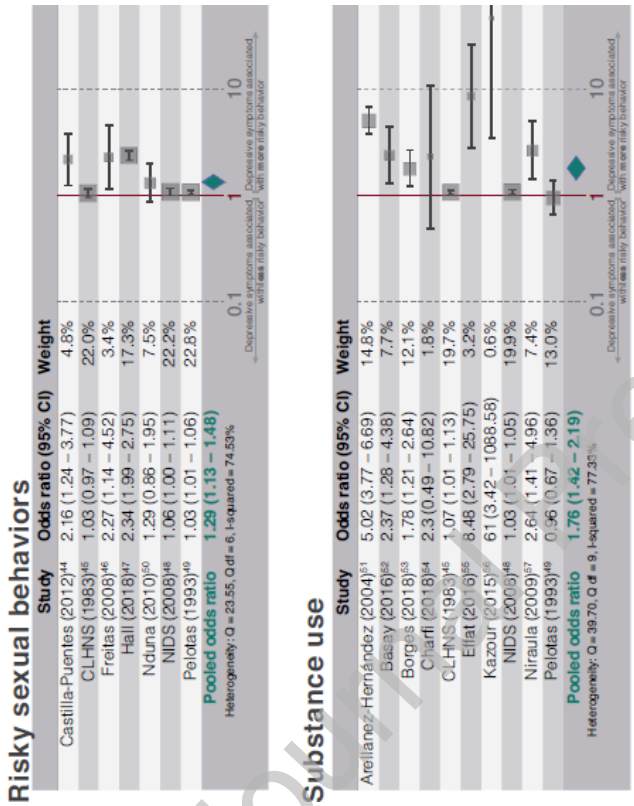

Figure 2. Forest Plot for Risky Sexual Behavior and Substance Use (Random-Effects Model)

Figure 3 R1

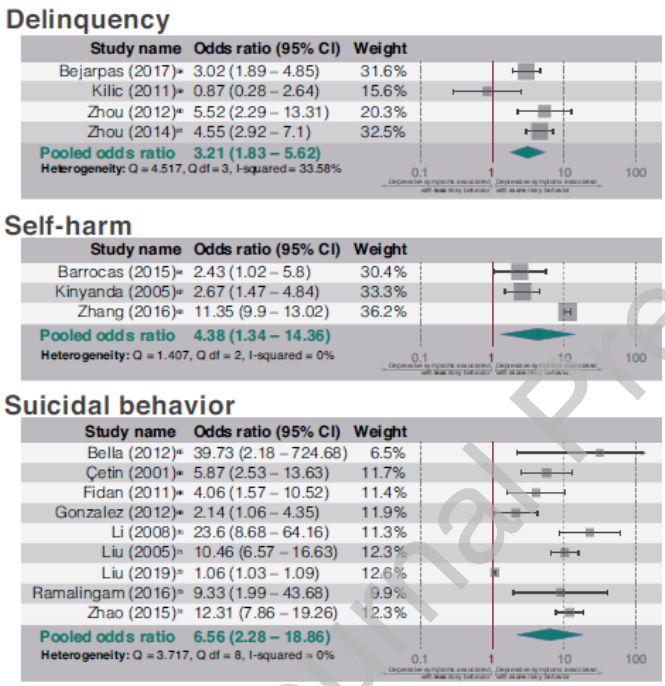

Figure 3. Forest Plot for Delinquency, Self-Harm, Suicidal Behavior (Random-Effects Model)

Table 1. Characteristics of Included Studies

Study	Country	Setting	Race/ ethnicity	Sample size	% of female participants	Age range	Study design	Depression measure (cut-off)	Type of risky behavior	NOS	Description of the study population
Risky sexual behavior											
Castilla-Puentes (2012)[44]	Bolivia	Urban	NA	645	100%	9 to 19	Case-control	CES-D (cut-off ≥16)	Teenage pregnancy	4	Case-control study conducted in La Paz, Bolivia. Subjects were 99 pregnant teens (cases) and 546 teenagers who had never been pregnant (controls).
CLHNS (1983)[45]	Philippines	Both	Filipino	915	41%	20 to 24	Cohort	CES-D (continuous score)	Unsafe sex and unplanned pregnancy	6	Cebu Longitudinal Health and Nutrition Survey (CLHNS) is the largest and longest running birth cohort study in Southeast Asia, following more than 3,000 pregnant women and their children. The study site has diverse environmental and socioeconomic conditions. For the meta-

											analysis we used data from 2005 and 2007.
Freitas (2008)[46]	Brazil	Urban	NA	220	100%	14 to 18	Case-control	HADS (depression scale cut-off ≥8)	Teenage pregnancy	8	Case-control study conducted in the city of Piracicaba (State of Sao Paulo). Subjects were 110 pregnant teens (cases) and 110 teenagers who had never been pregnant (controls). Cases were aged 14-18, primiparous, and recipient of medical assistance through the prenatal program. Controls were matched by age, residence, and family circumstances.
Hall (2018)[47]	Malawi	Rural	NA	4029	100%	15 to 24	Cohort	Depressive symptoms (cut-off ≥2)	Unintended pregnancy	6	Cohort study conducted in Mchinji District, Malawi. Over 4,000 pregnant women were followed-up and pregnancy intention and depression were

											measured. Respondents were aged 15-49, over 90% were married, and 86% had either no education or primary level.[a]
Nduna (2010)[50]	South Africa	Both	NA	1978	51%	15 to 26	Cohort	CES-D (cut-off ≥16)	Multiple partners	6	Cohort study conducted around Mthatha, South Africa. Participants were interviewed in 2002, and then again in 2004. Most participants were educated up to Grade 10 (88%), 20% had been pregnant before, and compared to men, women came from lower socioeconomic background.
NIDS (2008)[48]	South Africa	Both	Nationally representative sample (includes Black/African, Coloured, Indian/Asian, White)	677	100%	10 to 19	Cohort	CES-D (continuous score)	Teenage pregnancy	6	The National Income Dynamics Study (NIDS) is the first national household panel study in South Africa. The study began in 2008 with a nationally

											representative sample of over 28,000 individuals in 7,300 households across the country. For the meta-analysis, we used data on teenage pregnancy from Wave 3 (2012) and Wave 4 (2014).
Pelotas (1993)[49]	Brazil	Urban	Multi-ethnic population-based study, representative of Pelota's population (includes White, Black, and Brown)	3440	47%	11 to 22	Cohort	SDQ-E (continuous score)	Teenage pregnancy	7	Pelotas birth cohort is a longitudinal study that includes all live births in 1993 in the urban area of Pelotas. The economy of the study site is based on commerce and agribusiness, and has high levels of inequality, with 18.4% of respondents coming from poor families (less than US$ 100 per month). For the meta-analysis, we use data for over 3,000 individuals

											aged 11-22 with information on depressive symptoms and teenage pregnancy.
Substance use											
Arellanez-Hernández (2004)[51]	Mexico	Urban	NA	897	18%	10 to 18	Case-control	CES-D (cut-off ≥ mean + 1SD)	Illicit drug abuse	8	Case-control study conducted in Mexico City with 218 illicit drug abusers and dependents (cases) and 679 non-users (controls) matched by age, sex, and neighbourhood. Respondents were mainly single (98.5%), school-goers (71%), with lower levels of education in the cases than in the controls.
Basay (2016)[52]	Turkey	n.a.	NA	138	25%	16 to 18	Case-control	MMPI	Substance use disorder	8	Case-control study conducted in Turkey with 69 adolescents with substance use disorder (cases) and 69 adolescents with similar sociodemogra

											phic characteristics without substance use disorder (controls). Subjects were aged 16-18, the majority came from a low- and middle-socioeconomic background, and most (89%) were in high school.
Borges (2018)[53]	Mexico	Urban	Representative sample of adolescents in Mexico city	1071	NA	12 to 17	Cohort	WMH-CIDI	Any substance use disorder (alcohol, drugs, or tobacco)	8	Cohort study conducted in Mexico City with over 3,005 adolescents at baseline in 2005, and over 1,000 adolescents in the 8-year follow up. The survey was designed to be representative of the adolescents aged 12 to 17 in the area. About two-thirds of the adolescents live with both parents; four-fifths are currently students; one in ten has social burdens

											such as being married, having a child, or being employed during the school year.
Charfi (2018)[54]	Tunisia	Urban	NA	53	0%	19 to 24	Case-control	TEMPS-A	Illicit drug abuse	9	Case-control study conducted in Sfax, Tunisia with 50 drug addicts (cases) and 50 non-users matched for age, marital status, socioeconomic level, and education level (controls).[a]
CLHNS (1983)[45]	Philippines	Both	Filipino	1755	46%	20 to 24	Cohort	CES-D (continuous score)	Alcohol use	6	See Row 2 for a description of the cohort. For the meta-analysis, we use data from 2005 and 2007.
Effat (2016)[55]	Egypt	Both	NA	161	0%	12 to 18	Case-control	MINI-KID	Substance use disorder	8	Case-control study conducted in Helwan, Egypt with 81 adolescents with substance use disorder (cases) and 80 adolescents who had never used drugs (controls). Most participants were living at

											their family home. The case group had poorer academic performance than the control, and also had a significantly higher family history of psychiatric illness and history of drug abuse.
Kazour (2015)[56]	Lebanon	Urban	NA	60	n.a.	15 to 24	Case-control	HAM-D (NA)	Illicit drug abuse	7	Case-control study conducted in Beirut, Lebanon with 61 heroin dependent inpatients (cases) and 61 non-users paired on age and gender (controls). Cases were predominantly male patients, and also had significantly higher rates of unemployment compared to controls.[a]
NIDS (2008)[48]	South Africa	Both	See Row 6	3,505	52%	14 to 24	Cohort	CES-D (continuous score)	Alcohol use	6	See Row 6 for description of the cohort. For the meta-analysis, we use data on alcohol use from Wave 3

											(2012) and Wave 4 (2014).
Niraula (2009)[57]	Nepal	Rural	Hill native; Brahmin/ Chhetry; Newar; Others.	183	n.a.	15 to 24	Case-control	CES-D (cut-off determined using ROC curve)	Illicit drug abuse	7	Case-control study conducted in Dharan, Nepal with 102 drug abusers (cases) and 81 non-users (controls). Respondents were mainly male patients, had less than 12 years of education, not married, and came from an upper-lower socioeconomic status.[a]
Pelotas (1993)[49]	Brazil	Urban	See Row 7	3191	53%	18 to 22	Cohort	MINI	Alcohol and illicit drug use	7	See Row 7 for a description of the cohort. For the meta-analysis, we use data for over 3,000 individuals aged 18-22 with information on depression and substance use.
Delinquency											
Bejarpas (2017)[58]	Tajikistan	n.a.	NA	240	50%	13 to 19	Case-control	Scl-90-R (continuous score)	Committing a crime	8	Case-control study conducted in Tajikistan with 120 delinquents (cases) and

											120 non-delinquent adolescents matched by age, neighbourhood, education level, and socioeconomic background (controls).
Kilic (2011)[59]	Turkey	Urban	NA	41	0%	12 to 15	Case-control	CDI (NA)	Violent behavior	5	Case-control study conducted in Ankara, Turkey with 22 adolescents who show violent behavior at school (cases) and 10 non-violent peers (controls). Both groups came from low socioeconomic backgrounds with low levels of parental education.
Zhou (2012)[60]	China	Urban	Asian; Han people	476	0%	14 to 17	Cohort	YSR (NA)	Committing a crime	8	Cohort study conducted in Chongqing, China, with juvenile offenders (all male participants) serving sentences of at least 1 year and non-offenders

											from the same community. Juvenile offenders were more likely to have a low–level of education, come from single-parent households, and to live separately from their family as compared with community adolescents. There was no statistical different between household income, religious belief, and ethnicity across the two groups.
Zhou (2014)[61]	China	Rural	Asian	409	0%	15 to 17	Case-control	DSRS (continuous score)	Committing a crime	7	Case-control study conducted in Hunan, Sichuan, and Guangdong, China with 323 male juvenile offenders (cases) and 86 non-offenders matched by gender and age (controls). Cases had

											been convicted of various offences ranging from theft and fraud to rape, assault, and homicide. Compared to controls, offenders received significantly fewer years of education and had a lower family income. Additionally, their parents also received significantly fewer years of education, and were more likely to be divorced.
Self-harm											
Barrocas (2015)[64]	China	Both	Asian	617	51%	15 to 17	Cohort	K-SADS-PL	Nonsuicidal self-injury	9	Cohort study with 617 adolescents enrolled in Grade 10 at baseline and followed up for two years. Respondents were from an urban school in Changsha and a rural school in Liuyang (Hunan province,

											China).
Kinyanda (2005)[62]	Uganda	Urban	NA	188	n.a.	15 to 24	Case-control	BDI (cut-off ≥11)	Deliberate self-harm	7	Case-control conducted in Kampala, Uganda with 50 cases of deliberate self-harm and 138 controls matched on age and sex. Respondents were mainly male participants, had low educational attainment, and were single.[a]
Zhang (2016)[63]	China	Both	Asian	3957	53%	11 to 20	Case-control	Scl-90-R (continuous score)	Self-harm behavior	6	Case-control conducted in Linyi, China with 1092 cases of self-harm and 2865 controls. Both groups were students from junior and senior high schools in rural and urban areas. Most respondents were only childs (79%), a third came from a family with high parental education (high school or higher), and 40% of the

											sample had low family income (<1,000 yuan per month).
Suicidal Behavior											
Bella (2012)[65]	Argentina	Urban	NA	59	n.a.	10 to 16	Case-control	DIS	Suicide attempt	7	Case-control study conducted in Cordoba, Argentina with 25 adolescents hospitalised due to a suicidal attempt and 34 controls without such history.[a] Most respondents were enrolled in school, and compared to control, cases were more likely to smoke, drink alcohol, and have tried other drugs.
Çetin (2001)[66]	Turkey	Urban	NA	83	62%	14 to 20	Case-control	BDI (cut-off ≥17)	Suicide attempt	7	Case-control conducted in Ankara with 33 adolescents who attempted suicide (cases) and 50 healthy controls. Most of the sample lived with family (90%). Compared to controls, cases were more likely to have

											higher number of siblings and family members and are mostly the older children.
Fidan (2011)[68]	Turkey	Both	NA	60	82%	14 to 22	Case-control	BDI (cut-off ≥17)	Suicide attempt	6	Case-control conducted in Turkey with 30 cases of attempted suicide and 30 healthy controls matched by sociodemographic characteristics. Most participants lived in an urban area (80%), were in high-school (63%), and had average school performance.
Gonzalez (2012)[69]	Cuba	Urban	NA	128	NA	10 to 18	Case-control	DIS	Suicide attempt	9	Case-control study conducted in Artemisa, Cuba with 64 cases of attempted suicide and 64 healthy controls matched by age, sex, ethnicity, and neighbourhood. Compared to controls, cases were more likely to

											have a family history of psychiatric illness and come from a broken family.
Li (2008)[70]	China	Both	Asian (representative sample)	205	41%	15 to 24	Case-control	DIS	Death by suicide	9	Case-control psychological autopsy study of 114 adolescents who died by suicide (cases) and 91 who died of other injuries (controls). The survey was representative of the different economic strata in each region. Compared to controls, cases had lower levels of education and lower monthly per capita income. Most of the cases was employed in the agricultural sector, while the controls were mainly students or employed in other wage-earning job.

Liu (2005)[71]	China	Rural	Asian (representative sample)	284	40%	12 to 18	Case-control	YRBS (NA)	Suicide attempt	8	Case-control study conducted in a rural prefecture of Shangong Province, China with 142 suicide attempters and 142 healthy controls matched on age, gender, and school class. Most respondents came from a family of farmers, and with low parental education. Compared to controls, suicide attempters reported more negative life events during the past year, shorter sleep duration, and poorer physical health.
Liu (2019)[72]	China	Both	Asian (representative sample)	5451	48%	12 to 16	Cohort	YRBS (continuous score)	Any suicidal behavior	6	Cohort study conducted in Shandong province, China with 5451 adolescents followed up for one year. Compared

											with nonsuicidal adolescents, suicidal adolescents were more likely to report having a history of cigarette smoking and alcohol drinking.
Ramalingam (2016)[73]	India	Both	NA	100	70%	13 to 18	Case-control	DIS	Suicide attempt	7	Case-control study conducted in Tamilnadu, India with 50 suicide attempters and 50 controls matched by age and sex. Most participants came from an urban setting (85%), had a lower middle socioeconomic status, were single (83%), a third were students while 38% were unskilled workers.
Zhao (2015)[74]	China	Rural	Asian	315	47%	15 to 24	Case-control	HAM-D (continuous score)	Death by suicide	6	Case-control psychological autopsy study in several rural counties in three Chinese provinces (Liaoning,

											Hunan, and Shandong) with 141 suicide cases and 174 community living controls matched by age and residence. Most respondents were single (77%), had an average of 8 years of education, and came from an average socioeconomic status.
Systematic Review											
Auerbach (2010)[76]	China	Urban	97.1% Han, 1.7% other ethnic group, and 1.2% participants did not report their ethnicity	411	50%	14 to 19	Cohort	CES-D	RBQ-A	7	Cohort study conducted in Hunan, China with 411 high school students. The sample was predominantly Han (97.1%) and came from nuclear families (89.3%).
Cluver (2015)[75]	South Africa	Both	NA	3,515	56%	10 to 18	Cohort	CDI	Suicidal attempt	7	Cohort study conducted in the provinces of Mpumalanga and the Western Cape, South Africa. The sample was split evenly

											between urban and rural areas, and many lacked basic necessities such as clothes to keep warm and dry, three meals a day, toiletries to be able to wash every day.
Vieira (2018)[67]	Brazil	Urban	73.3% White; 26.5% Mixed	1244	58%	18 to 24	Cohort	MINI	Suicidal behavior	6	Cohort study conducted in Pelotas, Brazil to assess the risk factors for suicidality among adolescents. The sample was mainly white (70%) and out of school (74%). Half of the sample was classified as high socioeconomic status (SES), 45% as middle SES status, and 3% as low.

Note: NOS = Newcastle-Ottawa scale (total score). A diagnosis of depression was used amongst those studies that ascertained depression using structured clinical interviews (eg, MINI). Depression measures: BDI = Beck Depression Inventory; CDI = Children's Depression Inventory; DSRS = Depression Self-Rating Scale; CES-D = Centre for Epidemiologic Studies Depression Score; DIS = Diagnostic Interview Schedule; EPSIS I = European Parasuicide Study Interview Schedule I; HAM-D = Hamilton Depression Rating Scale; HADS = Hospital Anxiety and Depression Rating Scale; K-SADS-PL = Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children Present and Lifetime Version; MINI = Mini International Neuropsychiatric Interview; MINI-KID = Mini International Neuropsychiatric Interview for Children and Adolescents; MMPI = Minnesota Multiphasic Personality Inventory – depression subscale; SDQ-E = Strengths and Difficulties Questionnaire – emotional subscale; Scl-90-R = Symptom checklist; TEMPS-A = Temperament Evaluation of the Memphis Pisa Paris and San Diego-Auto-Questionnaire; WMH-DIDI = World Mental Health Composite International Diagnostic Interview; YRBS = Youth Self-Report of Child Behavior Checklist; YSR = Youth Self–Report Questionnaire – depression subscale. Risky behavior measures: RBQ-A = Risky Behavior Questionnaire for Adolescents.
[a]Data for 10-24 year olds was requested from corresponding author.