

Depression and risk-taking among adolescents in low- and middle-income countries



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Abstract

Depression and risky behaviours often co-occur and represent two critical – but often overlooked – public health concerns. This co-occurrence is particularly important during adolescence, a time when individuals make vital decisions with often long-lasting consequences for their health, overall well-being, and life chances.

The literature has explored the relationship between depression and risky behaviours mostly among adolescents in high-income countries. Therefore, it is an open question whether these findings can be generalised to low- and middle-income countries, where resources and conditions differ vastly. Examining this relationship is particularly important in low-resource settings, where poverty and everyday stressors may make adolescents even more vulnerable to the negative impacts of depression and risky behaviours.

This thesis aimed to contribute to closing this research gap by pursuing four research objectives across five empirical studies. The first objective was to examine predictors of depression in a socio-economically disadvantaged rural community in South Africa, where most of the studies in this thesis are situated. Using a large cohort study of adolescents, Chapter 2 found significant and persistent effects of several risk factors on depressive symptoms. Many of these risk factors are common in low-resource settings, implying that a higher share of adolescents might be at risk of developing depression.

This enhanced understanding of the contextual influences on depression led me to my second objective, which was to explore the relationship between depression and risky behaviours from different angles. To achieve this objective, I conducted two empirical studies. Chapter 3 presents the results from a systematic review and meta-analysis of the effect of depression on risky behaviours among adolescents in low- and middle-income countries. In line with the evidence from high-income countries, I found that adolescents with depression are more likely to engage in risky behaviours than non-depressed adolescents. Related to this objective, and given the evidence for a potential bidirectional relationship, Chapter 4 aimed to disentangle the direction of effect between depression and risky behaviours. The results from this chapter suggested that the relationship is complex and possibly dependent on specific individual characteristics.

These findings informed my third objective, which moved beyond questions of associations to examining possible mechanisms underlying this relationship. To achieve this objective, Chapter 5 used a six-wave cohort study of adolescents to explore whether the relationship between depressive symptoms and risky behaviours is mediated through

executive function. Results from the longitudinal mediation model showed that executive function did not mediate the association between depression and risky behaviours. However, I found that persistent depressive symptoms over four years were associated with poorer executive function in the next year, with the largest effect sizes observed for working memory.

The fourth and final objective was to bring the evidence from all chapters together and explore possibilities for interventions targeting depression and risky behaviours among adolescents in low-resource settings. To this end, a smartphone application called the Kuamsha app was developed. Chapter 6 described the development of this app, which was co-constructed with more than 170 adolescents from rural South Africa and Uganda. While more evidence is needed to test the intervention's efficacy in reducing depressive symptoms and risky behaviours, preliminary results of early user testing showed that the Kuamsha app was acceptable in terms of usability and engagement.

Overall, the findings in this thesis highlight the importance of studying depression and risky behaviours jointly, a relationship that has so far remained relatively unaddressed among adolescents in low- and middle-income countries. The results from this thesis also provide hope that interventions targeting depression can result in a virtuous cycle of increasing returns and promote adolescents' health in low-resource settings – a critical goal for global health research.

Acknowledgements

This thesis would not have been possible without the help and support of many people. In particular, I would like to thank my supervisor, Prof. Alan Stein, for your ongoing support and all the opportunities you have given me over these years. As someone who transitioned from the field of economics to psychiatry, it would have been very easy to get lost. But you believed in me from day one, and over time and many bike rides, you made me believe that I had something to contribute to this field.

Huge thanks to my co-supervisor, Prof. Stefan Dercon. Thank you for your guidance over so many years (beginning as my supervisor during the MSc), for inspiring me to ‘diversify my portfolio’ and try out new things, and for your help with the next steps of my career.

Thank you to my funder, la Fundación del Pino, who provided a generous two-year fellowship to support my DPhil; and to the MRC Newton Fund and the Wellspring Philanthropic Fund, who also supported my work.

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My work benefited immensely from feedback and conversations with many colleagues and friends: Prof. Sarah-Jayne Blakemore, Prof. Andrea Cipriani, Prof. Michelle Craske, Ms Meghan Davis, Dr. Marta Favara, Prof. Mina Fazel, Prof. Daniel Freeman, Prof. Carol Graham, Dr Emma Kilford, Prof. Willem Kuyken, Dr Mahreen Mahmud, Ms Zamakhanya Makhanya, Dr. Cora Mezger, Dr Bianca Moffett, Dr Kate Orkin, Prof. George Patton, Prof. Audrey Pettifor, Dr Hannah Ritchie, Prof. Katherine Sorsdahl, Prof. Ernesto Talvi, and Dr. Samantha Vanderslott. Thank you all. I feel very lucky that I have the chance to be surrounded by a group of such talented and inspiring individuals.

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Many thanks to the adolescents in Uganda and South Africa who were integral to the design and development of the app. I am indebted to Ms Christine Nabulumba and Sisters Meriam Meritze and Princess Makhubela for their dedication to this project and for going out of their way to recruit participants, even in the most challenging circumstances during the COVID-19 pandemic.

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Many thanks to Prof. Crick Lund and the team at CPMH for inviting me to do a research visit in beautiful Cape Town and giving me the inspiration I needed to finish this thesis.

To Marianne and Richard Moxon, thank you for providing me with a home away from home.

To my friends, near and far, thank you for all the fun times that kept me sane. To Adrianela, Luciérnaga, Martulius and Dama, thank you for always having my back and for making me laugh over all these years.

I send my love and big thanks to Max for being there every step of the way, helping shape my ideas (and graphs), and reminding me that one writes better after a day in the mountains.

Most of all, I am grateful to my family, without whom none of this would have been possible. Special thanks to my siblings, Carmen and Juan, and my parents, Carmen and Jose Juan, for their undying support and love. It is to them that I dedicate this thesis.

Declaration

The work described in my thesis was carried out between October 2018 and September 2022 under the supervision of Professor Alan Stein and Professor Stefan Dercon. I hereby declare that this thesis entitled *“Depression and risk-taking among adolescents in low- and middle-income countries”* is the result of my own work.

Several of the chapters have content that is either published, undergoing peer review, or in preparation for publication (see page viii for a list of associated manuscripts). For all the empirical studies that contributed to this thesis, I have acted as the leading author with no more input or advice than would be considered appropriate or acceptable for a thesis. A summary of my contributions to each study is listed on the following page.

I confirm that no part of my thesis has been accepted or is currently submitted for any degree, diploma or certificate, or other qualification at the University of Oxford, any other university or similar institute of learning.

Chapters 2 and 5 contain secondary data analysis from the *Swa Koteka* study, or HIV Prevention Trial Network study 068 (HPTN 068). Permission to use this data for these analyses was provided by the HIV Prevention Trials Network. Chapter 4 used data from the National Income Dynamics Study (NIDS) which is freely available for download via the NIDS website.

My thesis does not exceed the prescribed word limit of approximately 50,000 words and contains less than 150 figures.

I have no conflict of interest to declare.

Summary of contributions

Chapter	Contribution
Chapter 1	<i>Introduction</i> I conceived the scientific scope and conducted the full write-up. This chapter does not contain any analysis and has not been published or prepared for publication.
Chapter 2	<i>Risk factors for depression: evidence from a six-wave cohort study (reference [8] below)</i> I conceived the study idea, developed the study protocol, and conducted the literature review to identify the risk factors to be included in the model. Data was already collected as part of the <i>Swa Koteka</i> study. I cleaned data, ran the analysis, and conducted the full write-up. Co-authors commented on the manuscript and subsequent revisions. This chapter benefited from the helpful comments of Prof. Michelle Craske and Prof. George Patton.
Chapter 3	<i>Effect of depression on risk-taking: a systematic review and meta-analysis (reference [1] below)</i> I conceived the study idea, developed the study protocol, and registered the review on PROSPERO. I conducted the search, compiled the results, and eliminated the duplicates. The responsibility of reviewing title and abstracts for inclusion was shared between Lucy Desborough and me, and we both reviewed all full-text documents. I extracted the data, and Lucy checked for accuracy. I conducted the analysis, wrote the first draft of the manuscript, and prepared the figures and tables. Co-authors commented on the manuscript and subsequent revisions. This chapter benefited tremendously from my discussions with Prof. Andrea Cipriani.
Chapter 4	<i>Depression and risk-taking: exploring the direction of effects</i> I downloaded the data via the NIDs website and cleaned the dataset. I generated the hypotheses, conducted the analysis, and conducted the full write-up.

Chapter 5 *Depression, risky behaviours, and executive function: testing a mediation model (references [2] and [9] below)*

Together with Dr. Emma Kilford, I conducted a review on adolescents neurocognitive development in Western and Sub-Saharan Africa. This review helped to frame parts of the introduction section of this chapter.

I led all the other sections, including conceiving the study idea, cleaning the data, conducting the analysis, and writing the manuscript. This chapter benefited from the insightful comments of Prof. Sarah-Jayne Blakemore.

Chapter 6 *Developing a digital intervention to deal with depression and risky behaviours (reference [7] below)*

This chapter is part of the “*DoBat and Ebikolwa n’empisa*” research programmes, co-led by Prof. Alan Stein, Prof. Kathleen Kahn, and Dr. Munshi Sulaiman.

My key responsibility, among others, was to guide the app development process. As part of this work, I received ethical approval to conduct the formative work, designed the instrument guides, trained fieldworkers, organised discussions with adolescents, read all the transcribed interviews, summarised findings, and developed a game design documents outlining the platform’s main features and guiding principles. The app was developed in collaboration with *Seamons*, an app development company. This process entailed organising weekly meetings for over a year, along with coordination of further formative work and user-testing.

I conducted the full write-up.

Chapter 7 *Discussion and conclusions*

I conceived the scientific scope and conducted the full write-up. This chapter does not contain any analysis and has not been published or prepared for publication.

Publications

Publications based on this thesis:

- [1] **Pozuelo, J. R.**, Desborough, L., Stein, A., & Cipriani, A. (2021). Systematic review and meta-analysis: depressive symptoms and risky behaviors among adolescents in low-and middle-income countries. *Journal of the American Academy of Child & Adolescent Psychiatry*, 61(2), 255-276.
- [2] **Pozuelo, J. R.**, Kilford E.J. (2021). Adolescent Neurocognitive Development in Western and Sub-Saharan Africa. *Tropical Medicine & International Health*, 26(11), 1333-1344.

Publications that complement this thesis:

- [3] Graham, C., & **Pozuelo, J. R.** (2022). Do High Aspirations Lead to Better Outcomes? Evidence from a Longitudinal Survey of Adolescents in Peru. *Journal of Population Economics*. 1-39.
- [4] **Pozuelo, J. R.**, Stein, A., Blakemore, S. J., Kahn, K., Dercon, S., & Pettifor, A. (2020). Cash transfers in adolescence: a developmental perspective. *The Lancet Child & Adolescent Health*, 4(3), 177-178.

Manuscripts submitted:

- [5] **Pozuelo, J. R.***, Moffett, B.D*, ... ,Kahn, K., Stein, A. (*submitted*). Digital delivery of Behavioural Activation therapy to overcome depression and facilitate social and economic transitions of adolescents in South Africa (the DoBAAt study): protocol for a pilot randomised controlled trial. [* shared first authorship]. *Under review in BMJ open*.
- [6] Rowe, K, **Pozuelo, J. R.**, Nkosi, S.K., Santos, A., Wagner, R., Scerif, G., & Stein, A. (*submitted*). AHEAD Study: a pilot randomised controlled trial of a music intervention aiming to improve executive function in adolescents with HIV. *Under review in AIDS Care*.

Manuscripts in preparation:

- [7] **Pozuelo, J. R.**, Davis, M., Moffett, B.D., O'Mahen, H.A., Craske, M., Stein, A., van Heerde, A. (*in preparation*). Kuamsha app: a gamified storytelling app to treat depression among adolescents in low-resource settings.
- [8] **Pozuelo, J. R.**, Stein, A., Craske, M., Patton, G., Kahn, K., Pettifor, A. (*in preparation*). Risk factors for depression among adolescents in rural South Africa: evidence from a six wave cohort study.
- [9] **Pozuelo, J. R.**, Stein, A., Mahmud, M., Kahn, K., Pettifor, A., Blakemore, S.J. (*in preparation*). Examining the relationship between depressive symptoms, executive function, and risky behaviours: testing a mediation model in a cohort study of adolescents in Africa.

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List of abbreviations

ACASI	Audio Computer Assisted Self Interview
CD	Coefficient of Determination
CDI-S	Children's Depression Inventory-short form
CES-D	Centre for Epidemiologic Studies Depression Score
CFI	Comparative Fit Index
CI	Confidence Interval
CPI	Consumer Price Index
DALYs	Disability-Adjusted Life Years
DSM	Diagnostic and Statistical Manual of Mental Disorders
EF	Executive Function
GRADE	Grading of Recommendations, Assessment, Development and Evaluation
HDSS	Health and Socio-Demographic Surveillance Systems
ICD	International Classification of Diseases
IPV	Intimate Partner Violence
LMICs	Low- and Middle-Income Countries
MVP	Minimum Viable Product
NIDS	National Income Dynamics Study
NOS	Newcastle-Ottawa Scale
OCS-EF	Oxford Cognitive Screen - Executive Function
ORs	Odds Ratio
OxTREC	Oxford Tropical Research Ethics Committee
PHQ-9	Patient Health Questionnaire
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RMSEA	Root Mean Square Error of Approximation
SD	Standard Deviation
SEM	Structural Equation Model
SRMR	Standardized Root Mean Square Residual
STIs	Sexually Transmitted Infections
TLI	Tucker Lewis Index
WEIRD	Western, Educated, Industrialized, Rich, and Democratic
WHO	World Health Organization

Chapter 1. Introduction

Depression and risky behaviours are leading causes of preventable morbidity and mortality among adolescents. Together, they also exert a substantial economic toll since they often result in lower productivity and large public health expenditures (Chisholm et al., 2016; Erskine et al., 2015; GBD, 2021; Gouda et al., 2019; James et al., 2018; Thapar et al., 2022; Whiteford et al., 2013).

Evidence from high-income countries has found that adolescent depression plays an important role in the development and maintenance of risky behaviours such as unsafe sex and substance use (Brown et al., 2006; DiClemente et al., 2001; Dixit & Crum, 2000; Kessler et al., 1996; Kumpulainen, 2000; Lehrer et al., 2006; Marmorstein, 2009; Seth et al., 2011; Swendsen et al., 2000; Williams & Latkin, 2005; Wolitzky-Taylor et al., 2012). This combination can result in a negative spiral of further psychological and physical health problems that persist throughout the lifespan.

Most studies that have explored the relationship between depression and risky behaviours rely on data from high-income countries and it is, therefore, an open question whether it is possible to generalise these findings to low-resource or culturally diverse settings. Exploring this relationship is particularly important in low- and middle-income countries (LMICs), where 90% of the world's adolescents live, socioeconomic adversities associated with depression are prevalent, and access to mental health resources remains very limited (Erskine et al., 2015; Saraceno et al., 2007).

This thesis studies the relationship between depression and risk-taking among adolescents in LMICs across five empirical studies. This introductory chapter summarises the thesis' rationale, research objectives, and empirical studies. Next, I describe the core constructs of adolescence, depression, and risky behaviours adopted in this thesis, as well as the significance of studying the relationship between depression and risky behaviours during this transitional life period. The last section provides an overview of the different conceptual models underlying the relationship between depression and risky behaviours.

THESIS OVERVIEW

Rationale

Exploring the relationship between depression and risky behaviours is particularly important among adolescents in LMICs, where poverty and other social determinants of mental health such as exposure to violence, inequality, and forced migration are common (WHO, 2014). Accumulating evidence shows that depression is strongly socially determined (Lund et al., 2018). For example, poverty and depression interact in a vicious cycle, with a higher prevalence of depression in conditions of poverty (Ridley et al., 2020).

Despite this, many low-income countries spend a small share of their already limited budgets on mental health (as low as 2 cents per person per year) (see Figure 1.1) (WHO, 2015). These low levels of government mental health expenditures have resulted in treatment gaps of over 80% in many LMICs (Chisholm et al., 2016; Thornicroft et al., 2017). The lack of available, effective treatment makes adolescents in LMICs disproportionately affected by the burden of depression (Patel et al., 2007, 2008).



Figure 1.1 Government mental health expenditures by country income groups
 Note: The figure shows the annual median expenditure per capita (US\$, 2016).
 Source: Mental Health Atlas (2015)

Adolescents in LMICs may also be more vulnerable to the negative consequences of risky behaviours than their counterparts in high-income countries. In many LMICs, the public health and welfare institutions are often insufficiently resourced to provide adequate healthcare (Ortiz-Ospina & Roser, 2020). While this type of support is far from perfect in high-income countries, there is a range of programmes, such as rehabilitation programmes, health-related curricula in schools, training opportunities, or peer support groups, which promote adolescent health and well-being (Patton et al., 2016). This lack of safety nets in LMICs means that adolescents who might be struggling with substance use problems or a teenage pregnancy lack the support they need.

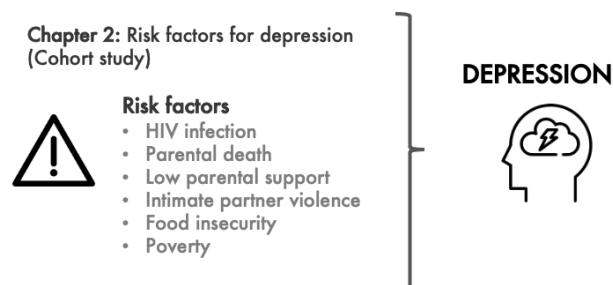
This thesis focuses on adolescents because, despite growing acknowledgement of the importance of adolescent depression and the

potential of investing in this formative period, this population group remains severely neglected (Kieling et al., 2011). Furthermore, given that depression often has its first onset in adolescence, the early identification and treatment of emergent depression and risky behaviours can potentially reduce chronicity and sequelae for individuals (Herrman et al., 2022). Investments in adolescent mental health also have the potential to support socioeconomic transitions and contribute to breaking the cycle of poverty and depression in LMICs (Lund et al., 2011).

The combination of depression, risky behaviours, and poverty during adolescence can result in further psychological and physical health problems that persist over time, putting adolescents at a lifelong disadvantage. Increasing our understanding of this relationship among adolescents in LMICs is an essential starting point to grasp the magnitude of the problem, develop treatment programmes, monitor progress, and inform policy. Ultimately, this thesis aims to deliver rigorous evidence on a topic of immediate necessity.

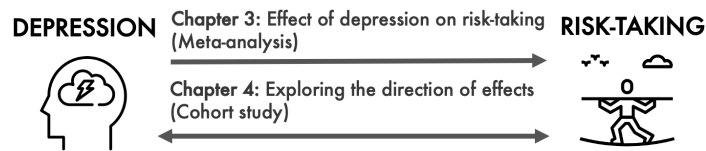
Research objectives and empirical studies

This thesis aimed to contribute to closing this research gap by pursuing four research objectives across five empirical studies. The first objective of this thesis was to examine predictors of depression among adolescents in a socio-economically disadvantaged rural community in South Africa, where most of the studies in this thesis are situated. As part of this objective, Chapter 2 used data from a longitudinal cohort study to examine the role of several risk factors in predicting depressive symptoms.

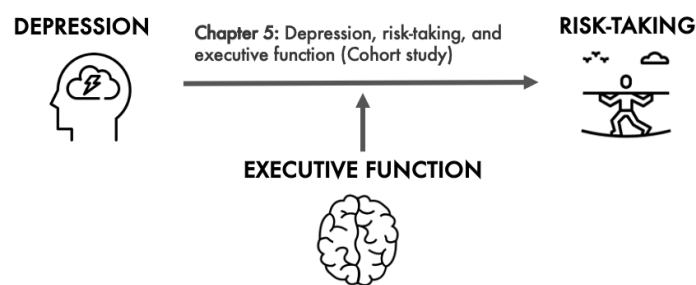


After examining the contextual influences on depression, the second objective of my thesis was to explore the relationship between depression and risky behaviours from different angles. To achieve this objective, I conducted two empirical studies. Chapter 3 comprises a systematic review and meta-analysis of the effect of depressive symptoms on risky behaviours among adolescents in LMICs. Given the evidence of a potential bidirectional relationship, Chapter 4 sought to further scrutinise this relationship by examining the direction of effect between depression and risky behaviours using data from a nationally

representative cohort study of adolescents in South Africa.



Once the relationship was established, the third objective of my thesis was to examine the possible pathways by which depression might influence risky behaviours. As part of this objective, Chapter 5 explored whether the relationship between depressive symptoms and risky behaviours is mediated through executive function, a potential mechanism that has recently received increasing attention.



The fourth objective of my thesis was to bring the evidence from all chapters together and explore possibilities for innovative interventions targeting depression and risky behaviours among adolescents in low-resource settings. To this end, a smartphone application called the Kuamsha app was developed. Chapter 6 describes the user-centred development of this app, which was co-constructed with more than 170 adolescents from rural South Africa and Uganda.

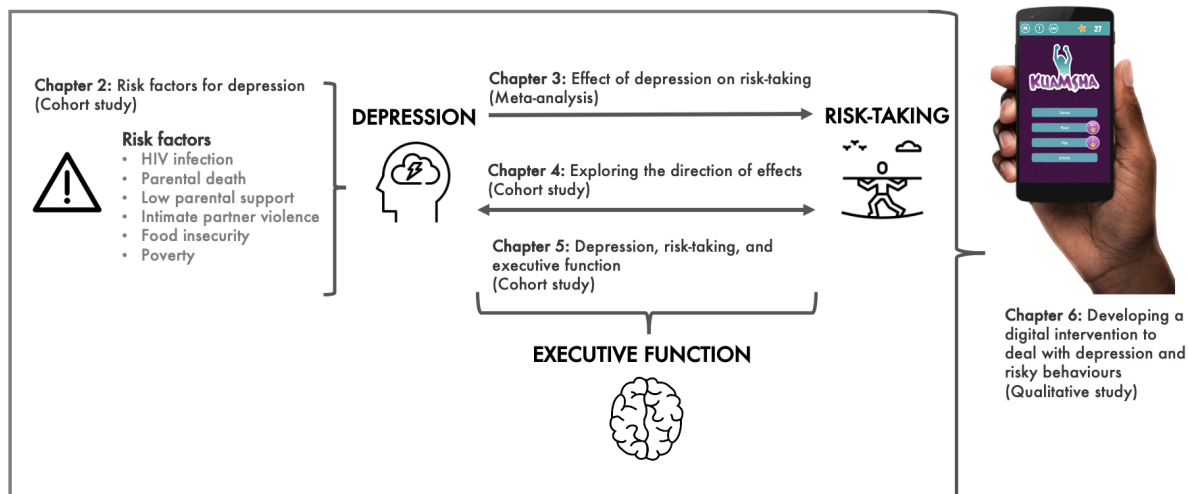


Figure 1.2. Diagrammatic summary of the thesis

The following sections describe the concepts of adolescence, depression, and risky behaviours adopted in this thesis and their significance.

ADOLESCENCE

Definition

Adolescence is broadly defined as the period of life between puberty and adult independence (Blakemore & Mills, 2014; Lerner & Steinberg, 2004). However, the timing of puberty and the transition to adulthood vary between individuals, as well as across time and between cultures. For example, in many high-income countries, the end of the period considered adolescence is frequently 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 (Blakemore, 2018).

In response, an expanded definition of adolescence has been proposed, spanning the ages of 10–24 years (Sawyer et al., 2018). This thesis adopts this broad definition of adolescence as it is more inclusive and aligns more closely with the development trajectories of today's adolescents.

A period of development and opportunities...

Adolescence is a unique stage of life characterised by substantial biological, physical, social, and cognitive development (Sawyer et al., 2018). It is a time when individuals start to develop their self-identity, acquire the necessary skills to navigate future challenges, and make vital decisions – about their health, education, relationships, and entrance into the labour market – within a context of less parental control and heightened peer influence (Patton et al., 2016).

Many brain regions undergo structural and functional development during adolescence, with prefrontal and parietal cortices being the latest to mature (in the mid-twenties) (Luna et al., 2010, 2015; Tamnes et al., 2017). Higher-level cognitive processes such as executive function and social cognition continue to develop throughout adolescence (Blakemore & Choudhury, 2006; Pozuelo & Kilford, 2021). These processes form the cognitive building blocks of our everyday behaviours: the ability to set and maintain goals, ignore distractions, empathise with others and regulate our emotions, and they are associated with a range of socioeconomic outcomes (Diamond, 2013; Kilford et al., 2016).

Aside from neurocognitive development, adolescence is a period for social development, during which social factors increase in salience and value (Blakemore & Mills, 2014; Crone & Dahl, 2012). Compared with children, adolescents often start spending more time with peers than with family members, placing more value on what their peers think about them, and becoming increasingly self-conscious, sensitive to

social exclusion, and influenced by their peers (Blakemore & Mills, 2014; Pozuelo et al., 2020).

This transitional period is also characterised by increases in reward sensitivity, which predisposes adolescents toward new experiences (i.e. novelty- and sensation-seeking) and to be more biased to take risks (Casey et al., 2008; Steinberg, 2007; Steinberg et al., 2018). While some of this risk-taking can result in adverse outcomes (the focus of this thesis), increases in reward sensitivity can also drive positive risk-taking such as travelling to a new country, speaking up in class, or trying a new sport, which can help to foster exploration, learning and creativity, and establish autonomy (Duell & Steinberg, 2019).

Many of these changes, such as heightened sensitivity to social cues and increases in reward-seeking, likely confer adaptive benefits to the development of independence and survival and are observed in humans and adolescents of other species (Spear, 2000, 2011).

...and of vulnerabilities

While adolescence is a time of exploration and opportunities, it is also a time of vulnerability, with half of all lifetime cases of mental health disorders having their onset by age 14 (Kessler et al., 2005b, 2007).

The burden associated with depressive disorders rises sharply in adolescence, accounting for more disability-adjusted life years (DALYs) than any other mental health condition (Figure 1.3) (GBD, 2021; Whiteford et al., 2013).

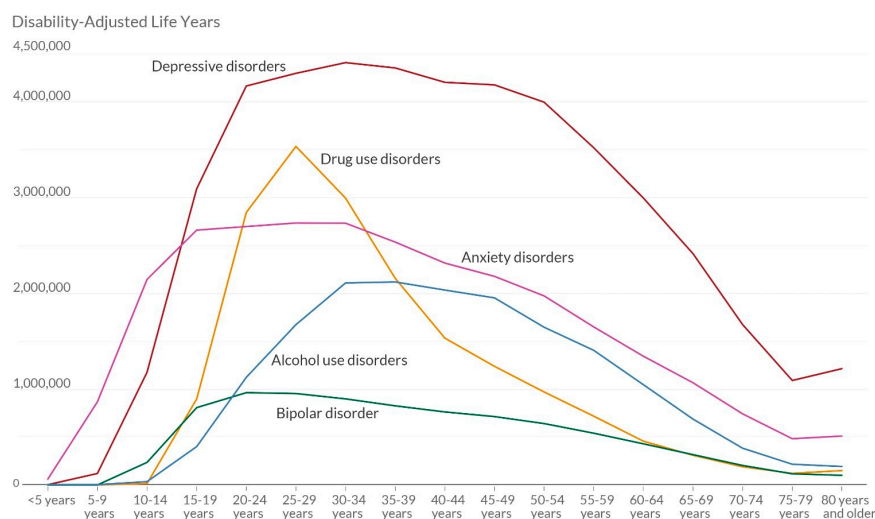


Figure 1.3. DALYs for various mental and substance use disorders in 2019

During this time, adolescents often begin experimenting with alcohol, drugs, sex, and rule-breaking, especially when they are with peers (S. Blakemore & Mills, 2014)(Steinberg, 2007). This experimentation might lead some young people down a path of self-harming behaviours, which can result in adverse life outcomes that last over their lifespan (Steinberg, 2007).

The following sections briefly describe both of these vulnerabilities and highlight the importance of studying depression and risky behaviours during this transitional life period.

DEPRESSION DURING ADOLESCENCE

Definition and measurement

Depression is a highly heterogeneous condition that affects how people feel, think, and behave. It is defined as a cluster of specific symptoms that need to be present almost every day for at least two weeks. These symptoms must affect how well an individual can keep up with normal daily life functioning (e.g. taking care of household responsibilities, getting dressed, studying) and must represent a change from how the individual was functioning before symptom onset. The symptomatic expression of depression is similar in adolescents and adults, as is the criteria for depression (Lewinsohn et al., 2003).

There are two main classification systems for guiding the diagnosis of depression: the International Classification of Diseases and the Diagnostic and Statistical Manual of Mental Disorders (APA, 1994; WHO, 1993). Both systems define depression similarly and classify depressive episodes as mild, moderate, and severe based on the number of symptoms, severity, and degree of functional impairment.

Standardised diagnostic interviews are often considered the gold standard for depression diagnosis in clinical psychiatry research (Levis et al., 2018). However, they take time to conduct and require extensive training, making them expensive and often not feasible to use.

In many LMICs, where most health workers do not have the training or time to administer complex diagnostic interviews, depressive symptoms scales are frequently used instead to assess the severity of symptoms and as screening tools to identify individuals who may have depression (Ali et al., 2016). As its name suggests, these scales measure “depressive symptoms” and do not provide a clinical diagnosis (a clinical interview would be necessary to confirm whether a depressive disorder is present). While these screening tools are likely to inflate the prevalence of depression, some scales are reliable and valid instruments to identify depression, particularly for more severe cases (Levis et al.,

2019; Löwe et al., 2004).

In this thesis, I focus on this broader definition of depression, which includes depressive symptomatology. Thus, most chapters rely on validated screening tools to measure depressive symptom severity (the exception is Chapter 3, which also included studies that ascertained depression using standard operationalised diagnostic criteria).

Prevalence

Data from the United States shows that the incidence of depression peaks during adolescence, with the prevalence of depression rising from 4.8% in early adolescence to as high as 18.5% by age 17 (Figure 1.4). (NIMH, 2017). The overall prevalence of depression among adolescents stands at around 6%, which is similar to the reported prevalence among adults (Thapar et al., 2012).

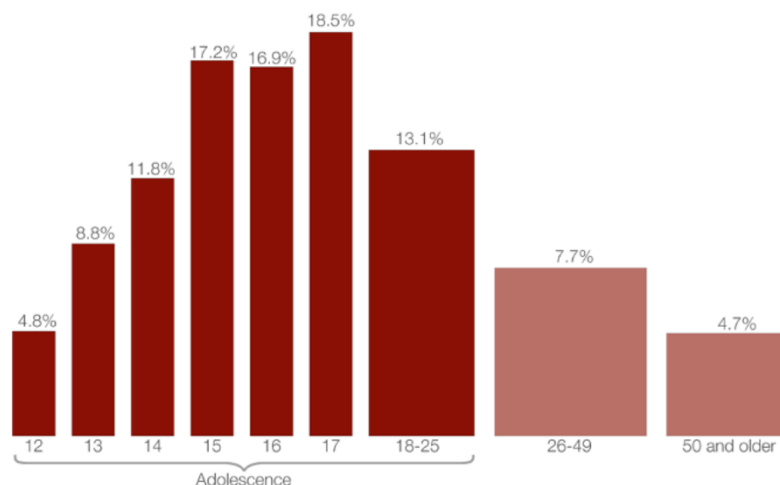


Figure 1.4. Past year prevalence of major depressive episodes by age
Data source: National Institute of Mental Health. Data for the U.S. in 2017.

Several studies show that depression is twice as common in females than males, and this gender gap first emerges in early adolescence (Platt et al., 2021). This sex difference might be partly explained by hormonal and pubertal changes associated with adolescence, as well as differences in help-seeking behaviours and reporting of symptoms (Thapar et al., 2012).

There is a paucity of data and global comparisons of the prevalence of depression in adolescents from LMICs (Thapar et al., 2022). The research published to date has shown wide variations in point prevalence rates ranging from 1.8% to as high as 39.4% (Jorns-Presentati et al., 2021; Kieling et al., 2011; Yatham et al., 2018). This wide range is partly explained by methodological differences, such as the instrument used to assess depression and sample representativeness.

Despite this variability, many factors suggest that the burden of depression is highest in LMICs. First, 90% of the world's adolescents live in LMICs (United Nations, 2019). This suggests that, even if the prevalence of depression is comparable to that reported among adolescents in high-income countries, the total number of affected individuals will be substantially greater in these countries (Thapar et al., 2012). Second, LMICs have very low levels of average public expenditure on mental health (see Figure 1.1), resulting in a significant shortage of mental health professionals and large treatment gaps (Kakuma et al., 2011; WHO, 2015). For example, less than 5% receive any minimally adequate treatment for depression in many LMICs (Thornicroft et al., 2017). Third, risk factors for depression (e.g., poverty, violence, and forced migration) are overrepresented in LMICs, which may result in higher rates of depression among adolescents in LMICs compared to high-income contexts (Fleitlich-Bilyk & Goodman, 2004; Haushofer & Fehr, 2014; Lund et al., 2014; Thapar et al., 2012). Fourth, low levels of mental health literacy and high levels of stigma prevent some individuals in LMICs from seeking care (Alonso et al., 2008; Sorsdahl & Stein, 2010). These barriers, coupled with the devastating consequences of poverty, make adolescents in LMICs disproportionately affected by the burden of depression (Patel et al., 2007, 2008).

Significance

Depression is not only common, but it can place a heavy burden on individuals and their families and exerts a substantial economic toll. The global cost of mental health conditions in 2010 was estimated at US\$2.5 trillion, and these costs are expected to increase to US\$6 trillion by 2030 (Bloom et al., 2011).

Depression in adolescence is concerning not only because it occurs during a critical developmental period but because it is associated with high rates of recurrence and potential chronicity across the lifespan. Adolescents with depression are three times more likely to have depression in adulthood than healthy adolescents (Johnson et al., 2018). In its most severe form, depression may lead to suicide, which claims more than 120,000 lives of adolescents annually (GBD, 2021).

Left untreated, depression has a marked negative effect on executive function and social cognition, two higher order cognitive functions that allow us to control and coordinate our thoughts and behaviour and build successful relationships (Snyder, 2013; Weightman et al., 2014). As a result, individuals with depression may have a diminished ability to think, concentrate, make decisions, empathise, and regulate emotions. Further, adolescent depression has been associated with a greater risk for substance use, poor sexual health, and delinquency (Pozuelo et al., 2021). It affects interpersonal relationships, interferes with schooling,

and predicts a significant reduction in future income as it can prevent people from working, making it difficult for individuals to get back to work, and diminishing their productivity when they do work (Fletcher, 2010; Lund et al., 2013; Ridley et al., 2020; Thapar et al., 2022).

RISKY BEHAVIOURS DURING ADOLESCENCE

Definition and measurement

Research about risk-taking has included various “risky behaviours” such as unsafe sex, substance use, reckless driving, or gambling. This makes it challenging to narrow down the concept to a simple, helpful definition (Schulenberg, 2010). The concept of risky behaviours also differs significantly among individuals and across cultures, as do the opportunities to engage in certain types of behaviours (Duell et al., 2018).

While there are many different definitions and types of risky behaviours, the common trait is that these behaviours often involve a lag between the reward or pleasure they provide and the possible negative consequences of the behaviour. They also involve some level of uncertainty, as not everyone that engages in risky behaviours faces harmful effects.

Risky behaviours can be categorised into several dimensions (Leigh, 1999). First, a distinction can be made between positive and negative risk-taking behaviours. While negative risky behaviours are possibly harmful to oneself and society, positive risky behaviours foster innovation and can be particularly constructive, especially during adolescence (Duell & Steinberg, 2019). Second, risky behaviours may be classified according to the type of risk (e.g., financial, health, ethical, social). Research has shown that an individual’s degree of risk-taking tends to be domain-specific: one might be risk-averse in the financial domain but risk-seeking in the health domain (Weber et al., 2002). Third, risky behaviours may also differ in the degree of harm they cause. Some behaviours carry an identifiable and immediate risk (e.g. death by speeding or playing Russian roulette) while others have more “hidden” long-term effects (e.g., smoking). Fourth, risky behaviours are also largely dependent on the particular context in which a decision is made (e.g., in affective “hot” vs “cold” contexts, such as with or without friends) (Blakemore & Robbins, 2012).

In this thesis, I define risky behaviours as voluntary, observable behaviours that contribute to disability and premature death and impose a health burden on society (Jeffery, 1989; Roth et al., 2018). Most chapters focus on risky behaviours in the health domain, such as substance use and risky sex (except Chapter 3, which also includes delinquency). These behaviours are characterised as having more

hidden long-term effects and typically occur in motivational-affectively salient or ‘hot’ situations, where peer pressure and social norms often play important roles in driving these behaviours. Throughout the thesis, I use the terms risk-taking and risky behaviours synonymously.

Measuring risky behaviour accurately is challenging, partly because of self-reporting biases. Research has primarily relied on four different methodologies. First, some studies rely on biological markers (e.g. breathalyser readings, urine, blood samples, accelerometers). While this is the most objective way of measuring risky behaviours, it is complex, costly, and may lead to high misclassification rates (Corno & de Paula, 2019). Second, the criminology literature often uses official criminal records, administrative data, driving violations, etc. However, these datasets only include a small fraction of all the actual offences, which can be problematic (Thornberry & Krohn, 2000). Third, laboratory studies have also measured risk-taking using behavioural tasks, such as the Balloon Analogue Risk Task and the Iowa Gambling Task (Brevers et al., 2013; Lejuez et al., 2002). However, some reviews have found that laboratory risk-taking measures do not always predict real-life risky behaviours (i.e., they generally have low external validity) (Charness et al., 2020; Frey et al., 2017). Fourth, most studies use self-reported questionnaires on risky behaviours (e.g. frequency of alcohol consumption, condom usage, involvement in criminal behaviours, etc.). While this method has been criticised as unreliable and subject to underreporting and recall bias, novel approaches such as the random response technique and audio computer-assisted self-interviewing (ACASI) can reduce reporting bias (Des Jarlais et al., 1999; Langhaug et al., 2010).

Several chapters of this thesis rely on self-report elicitation methods. When available, I triangulate self-reported data with collateral informants’ reports and objective outcomes associated with risky behaviours (e.g., HIV infection, being a drug-dependent patient, or teenage pregnancy) to increase the validity and reliability of the findings.

Prevalence

There are wide variations in the prevalence of risky behaviours across and within cultures. These differences can be explained by several factors, including differences in socioeconomic status, social norms, religion, country policies, and opportunities to engage in these risky behaviours. For example, individuals living in Muslim countries might be less exposed to alcohol. The observed difference in prevalence rates may also be partly explained by methodological differences, such as the reference periods, item wording, sampling strategy, and the quantity and frequency used to categorise behaviour as “risky” (e.g., drinking a sip of alcohol vs engaging in heavy episodic drinking). Complicating

matters even further, individuals often engage in more than one risky behaviour simultaneously. For example, adolescents who use alcohol are more likely to engage in risky sexual behaviour (Ngoc Do et al., 2020; Tapert et al., 2001). This makes it challenging to obtain total prevalence estimates since adding the prevalence for each type of behaviour would result in double-counting individuals.

Although there are uncertainties around these estimates, epidemiological research has repeatedly found that risky behaviours first appear during the early stages of adolescence and often persist into adulthood (Gardner & Steinberg, 2005; Patton & Viner, 2007; Sawyer et al., 2012; Steinberg, 2007). Some risky behaviours, particularly those related to aggressive and rule-breaking behaviours, peak during adolescence and gradually decline thereafter (see Figure 1.5) (Moffitt, 1993).

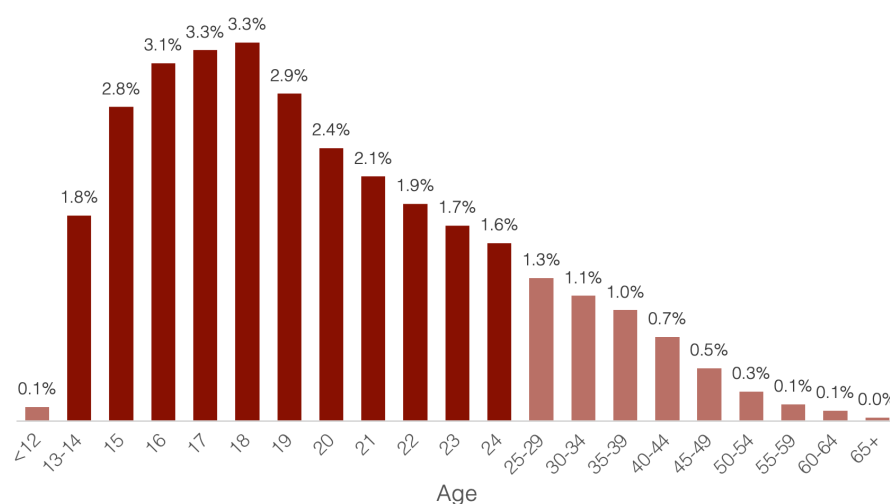


Figure 1.5. Arrest rates by age
Data source: Uniform Crime Reports, FBI. Data for the U.S. (2001)

The most commonly used substances during adolescence are tobacco and alcohol, and these substances typically precede the subsequent use of illicit drugs (Degenhardt et al., 2016). Data from a school-based survey of over 300,000 adolescents in 73 LMICs found that 1.5% of adolescents drank alcohol regularly (≥ 20 days) in the last month, and 3% of adolescents engaged in binge drinking. The same survey found that 1.2% of adolescents reported smoking regularly (≥ 20 cigarettes in the last month), and 1.5% reported smoking marijuana (de la Torre-Luque et al., 2021). Other reviews have found higher prevalence rates (Ma et al., 2018; Xi et al., 2016).

Risky sexual behaviour is also common among adolescents in LMICs, although there are significant differences by country, age, sex, marital status, and type of behaviour (Hindin & Fatusi, 2009). A study on sexual

behaviour in 59 countries found that less than a third of adolescents in many sub-Saharan African countries reported using a condom during their last sex act (Bearinger et al., 2007; Wellings et al., 2006). While recent data shows that the use of condoms among adolescents is increasing (rising from 19% to 28% between 1993 and 2001 in 19 African countries), it is still too low to contain the spread of sexually transmitted infections (Dehne & Riedner, 2001; Wellings et al., 2006). A study analysing Demographic and Health Surveys from 38 diverse countries found a high prevalence of multiple sexual partners, particularly among males (20% in males vs 10% among females) (Khan & Mishra, 2008). A narrative review explored recent trends in transactional sex – the exchange of sex for money, gifts, or favours – across 28 countries and found a high prevalence in many LMICs (with rates of 70% or higher in Uganda, Malawi, and Tanzania) and early age of onset (around 15 years) (Krisch et al., 2019).

Significance

The consequences of risky behaviours can be severe and expand beyond those that engage in these behaviours. Substance use, which includes smoking, alcohol and drug use, kills 11.8 million people each year (Roth et al., 2018). This exceeds the total number of deaths from all types of cancers and corresponds to one in five deaths globally (Ritchie & Roser, 2019). A small share (3%) are direct deaths, which includes dying from a drug overdose. The rest are indirect deaths, which result from risky behaviours acting as risk factors for other illnesses, such as lung cancer, heart disease, and risk of suicide.

Unsafe sex can result in sexually transmitted diseases and teenage pregnancy. Adolescents account for 21% of new HIV infections globally (IHME, 2019). Teenage pregnancy and childbirth complications are the leading cause of death among adolescent females aged 15–19 years, with most deaths occurring in LMICs (WHO, 2020).

Figure 1.6 shows the number of deaths attributed to different risky behaviours globally. The percentages and different colours show the distribution of deaths between LMICs (dark red) and high-income countries (light red). As shown, most deaths occur in LMICs, which is expected given that most of the world lives in this group of countries.

The negative consequences of risky behaviours impact not only those who engage in these behaviours but also family members, peers, and the wider society. In some instances, the effects result from physical proximity, such as road accidents, secondhand smoke, and disease transmission. In others, the impact of these behaviours may be more indirect, such as through the adverse effects on productivity, healthcare cost, and the increase in violence and crime (de Walque, 2013).

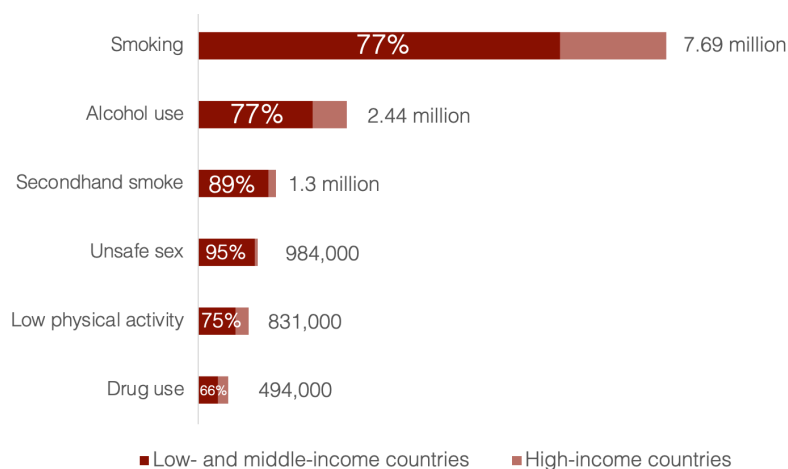


Figure 1.6. Number of deaths by risk factor, World, 2019
 Source: Our World in Data using IHME, Global Burden of Disease (2019)

DEPRESSION AND RISKY BEHAVIOURS: A COMPLEX RELATIONSHIP

Several theories have attempted to explain why depression may play an important role in the development and maintenance of risky behaviours. First, the ‘self-medication’ hypothesis (H1) suggests that individuals with depression might engage in risky behaviours as a coping mechanism to seek relief from their symptoms and escape cognitive awareness (Khantzian, 1985, 1997). While this framework originated in the addiction literature, others have expanded this to include other risky behaviours, such as risky sexual behaviours (Mckirnan et al., 2010).

Second, depression is associated with a range of negative cognitive biases that change an individual’s belief about oneself, their world, and their future, and thus increase their vulnerability to engage in risky behaviours (H2) (Beck, 1979). According to Beck’s cognitive theory, individuals with depression often view themselves as worthless and feel hopeless; they also have low self-esteem and self-efficacy and have difficulty viewing themselves as individuals who could succeed. These negative self-concepts and the lack of hope for the future might make an individual believe that they have nothing to lose and be more present-biased, making them more prone to engage in behaviours that feel good in the short term, possibly as a coping mechanism (Graham & Pozuelo, 2022; Khantzian, 1985, 1997). Negative self-concepts might also make an individual less assertive and, therefore, more likely to succumb to peer pressure and less likely to stand up to a partner who demands unprotected sex. It might also make adolescents with depression more likely to affiliate with risk-taking peers (Fergusson et al., 2003).

Third, depression affects an individual's ability to exercise their executive function, making it harder to take the time to think before acting, stay focused despite distractions, evaluate the short- and long-term consequences of one's behaviour, or adapt flexibly to changing environments (Snyder, 2013). Poorer executive function, in turn, predicts risky behaviour engagement (H3) (Brock et al., 2011; Chabris et al., 2008; Gray-Burrows et al., 2019; Lejuez et al., 2003; Miller et al., 2011; Moffitt et al., 2011; Reynolds et al., 2019; Robson et al., 2020; Ross et al., 2016; Sutter et al., 2013). This hypothesis may be particularly relevant during adolescence, given that self-regulation is still developing during this time (especially in emotionally charged contexts) (Botdorf et al., 2017).

Adding to the complexity, evidence from high-income countries suggests that the reverse is also true: risky behaviours result in higher depressive symptoms, suggesting a bidirectional relationship. While the exact mechanisms supporting this evidence are not fully understood, some studies have proposed that risky behaviours could directly induce depressive symptoms like feelings of worthlessness, fatigue, and sleep disturbance (H4) or indirectly cause depression by affecting neurotransmitter pathways (H5) (Banerjee, 2014; Fergusson et al., 2009; Gobbi et al., 2019; Quattrocki et al., 2000). Risky behaviours might also increase some risk factors for depression (e.g., job loss, HIV infection, violence exposure), which could, in turn, induce the onset of a depressive episode (H6) (Swendsen et al., 2000).

Another set of hypotheses suggests that depression and risky behaviours share common aetiologic factors, such as genetic vulnerability, puberty, and exposure to a disruptive family environment (H7) (Swendsen et al., 2000; Zhou et al., 2017). These models argue that depression and risky behaviours do not drive each other but rather, might be the product of some common underlying cause. Figure 1.7 provides an integrated overview of these hypotheses.

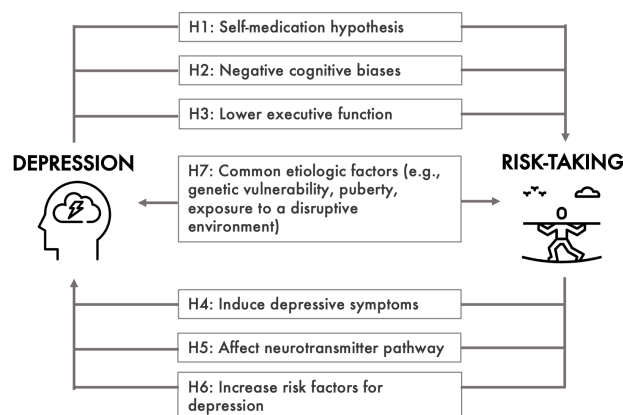


Figure 1.7. Integration of hypotheses on the relationship between depression and risk-taking

While several competing theories have attempted to explain this relationship, there is no single perspective that adequately captures the complexity of this relationship. Some of these hypotheses are not mutually exclusive; thus, the mechanisms may be a combination of different factors. Further, the fact that not all individuals who are depressed engage in risky behaviours suggests that there are moderators (e.g., poverty) that might influence the strength and direction of this relationship.

Given the limited evidence on the relationship between depression and risky behaviours among adolescents in LMICs, this thesis did not focus on one particular theoretical framework; instead, it drew on several conceptual models to guide the analysis and test my hypotheses. The rationale for doing this is that most of the existing theoretical frameworks have been primarily informed by studies conducted in high-income countries, thus restricting the extent to which the results can be generalised to diverse global contexts where resources differ vastly (Henrich et al., 2010; Wahid et al., 2021).

Chapter 2. Risk factors for depression: evidence from a six-wave cohort study¹

Chapter in context

Background. A better understanding of what factors give rise to depression can help to inform prevention strategies and more effective treatments for depression. Most of the studies contributing to this evidence are from high-income countries, thus possibly restricting the extent to which the results can be generalised to contexts where resources and circumstances differ.

Objectives. This chapter used data from a large longitudinal cohort study in rural South Africa to:

- (1) Examine the role of several risk factors in predicting high depressive symptoms among adolescents; and
- (2) Examine whether the effects of risk factors on depression dissipate over time.

Findings and implications. Results from fitting a two-way fixed effects model showed that experiencing intimate partner violence, low parental support, and being food insecure were associated with a statistically significant increase in depression severity and depression caseness. Further, the effect of some risk factors was associated with persistent depression, with adolescents remaining on a higher depression score even three years after experiencing these risk factors. These risk factors are overrepresented in low-resource settings, making adolescents living in these contexts more vulnerable to depression. However, they are also potentially modifiable and thus can be targeted through interventions. With depression being one of the leading causes of illness among adolescents, this chapter suggests that treatment alone might not be enough to address this problem at scale. Increasing efforts to identify depression early in adolescence should be a priority.

¹ This chapter has been adapted from the following paper:

Pozuelo, J. R., Stein, A., Craske, M., Patton, G., Kahn, K., Pettifor, A. (*in preparation*). Risk factors for depressive symptoms among adolescents in rural South Africa: evidence from a six wave cohort study.

INTRODUCTION

The incidence of depression peaks during adolescence, with the cumulative probability of depression increasing from 5% in early adolescence to as high as 20% by late adolescence (Thapar et al., 2012). The burden of adolescent depression is highest in low- and middle-income countries (LMICs), where 90% of the world's adolescents live, shortages of mental health workers are widespread, and stigma or lack of mental health awareness prevents adolescents from seeking care (Alonso et al., 2008; Rathod et al., 2017; Thapar et al., 2012; WHO, 2015). Left untreated, depression affects interpersonal relationships, interferes with schooling, disrupts economic productivity, and is associated with an enormous economic burden (Chisholm et al., 2016; Thapar et al., 2012).

Depression can occur for a variety of reasons, and thus, a range of biological, psychological, and environmental factors have been associated with a higher likelihood of developing depression (Herrman et al., 2022). Adding to the complexity, many individuals exposed to risk factors do not develop depression, suggesting that the interaction between these risk factors and an individual's vulnerability also plays an important role in the development of depressive episodes (Hankin & Abela, 2005; Monroe & Simons, 1991).

While the aetiology of depression is complex and multifactorial, a better understanding of what factors give rise to depression can help identify adolescents at elevated risk of depression. Selective and indicated approaches that target a specific subgroup of individuals are more cost-effective in preventing depression than universal programmes that address an entire population (Kieling et al., 2019). However, identifying individuals for whom preventive interventions are likely to be effective is still a significant challenge. This problem is even larger in many LMICs given the economic pressures they face and the overburdened healthcare sector (Herrman et al., 2022).

In addition to the limited financial resources, there is also an existing knowledge gap regarding risk factors for adolescent depression in LMICs (Jörns-Presentati et al., 2021). Most of the studies contributing to this evidence are from high-income countries, thus restricting the extent to which the results can be generalised to diverse global contexts where resources differ vastly (Wahid et al., 2021). For example, a recent meta-analysis exploring psychological and contextual risk factors for first-onset depression among adolescents globally included 19 cohort studies, of which only two were from an upper-middle-income country (China) (Pedersen et al., 2022). Similar trends have been found in other reviews (Cairns et al., 2014; Köhler et al., 2018; Stirling et al., 2015).

Evidence from previous studies has established an association between depression and prior exposure to acute stressful events (e.g. parental death and exposure to violence) and chronic adversity (e.g. HIV, poverty, food insecurity, and negative family environment) (Cairns et al., 2014; Köhler et al., 2018; Pedersen et al., 2022; Sorsdahl et al., 2011; Stirling et al., 2015; Thapar et al., 2012). Many of these risk factors are overrepresented in poor-resource settings, making adolescents living in these contexts likely more vulnerable to depression (Patel et al., 2010). However, few longitudinal studies have identified risk factors for depression among adolescents in LMICs – particularly in rural contexts.

This chapter aims to contribute to closing this gap by using a large longitudinal cohort study to examine the role of several risk factors in predicting high depressive symptoms among adolescent females in rural South Africa. I included a range of variable risk factors identified in the literature and specific to a rural sub-Saharan African context, including being diagnosed with HIV, parental death, negative family environment, exposure to trauma, food insecurity, and poverty. Exploring this relationship is particularly important among adolescent females given the high burden of depression and associated risk factors (Kessler, 2003). For example, adolescent females in South Africa are infected with HIV at 3-4 times the rate of adolescent males (Pettifor et al., 2005). Females are also considerably more likely to be victims of intimate partner violence and to face more food insecurity than men (Jung et al., 2017; Oram et al., 2022). As a secondary objective, I explored whether the effects of risk factors on depression dissipated over time.

METHODS

Study context

Data were drawn from a longitudinal cohort of adolescent females living in rural South Africa. This data was collected as part of the *Swa Koteka* study, or HIV Prevention Trial Network study 068 (HPTN 068), a phase 3 randomised controlled trial that explored whether providing cash transfers to adolescents – conditional on school attendance – reduced the risk of acquiring HIV.

The study was embedded within the Agincourt Health and Socio-Demographic Surveillance Systems (HDSS), a large demographic surveillance unit located in Mpumalanga province, near the border with Mozambique (Figure 2.1 presents a map of the study location).

The Agincourt HDSS comprises 31 villages with approximately 150,000 inhabitants. Before 1994, it was part of the Gazankulu Homeland area, and, as with other previous homeland areas in South Africa, infrastructure development is still poor. Electricity is available in all villages, but its use is limited by cost. There is very little piped water to

dwelling, sanitation is rudimentary, and few roads have been tarred. Free primary and high school education is available, but the quality remains low, and graduates have limited further educational and employment opportunities. Money sent home by migrant workers and social grants, including the old-age pension and child support grants, remain vital sources of income for households (Kahn et al., 2012).

There is a high prevalence of depression amongst adolescents in South Africa and a paucity of mental health and social care services (Flisher et al., 2012; Mokitimi et al., 2018). As a result, depression is rarely diagnosed in primary care, and suicide attempts amongst adolescents are not infrequent presentations at district hospitals, although data is lacking (Rathod et al., 2018).

Within the subdistrict in which this study was conducted there are two health centres, six clinics, and three district hospitals within a 60km radius. Combined across these facilities are three clinical psychologists, several social workers, primary healthcare nurses, and generalist medical officers. The province has three full-time public sector psychiatrists and no specialist inpatient psychiatric units. Inpatient mental health care is provided at three designated district and secondary hospitals primarily run by medical officers. Several Registered Counsellors have been trained in tertiary institutions, but as yet, no posts have been made available to them in the study area. Local NGOs providing social services include GRIP (Greater Rape Intervention Programme) and VEPs (Victim Empowerment Prevention programmes) that deal with interpersonal and sexual violence, and Right to Care which provides support to persons living with HIV/AIDS. There are no specialist child or adolescent mental health services.



Figure 2.1. Map of study setting

Participants and study procedures

A total of 2,537 adolescents were enrolled in the original study. Participants were seen at baseline in 2011 and annually for up to six waves, the last of which was in 2018. To be included, participants had to be 13–20 years old, enrolled in school grades 8–11 of the South African educational system, and not married or pregnant at baseline. Participants exited the study once they graduated from high school, which explains the largest part of the reduction in sample size over time.

Monthly cash transfer amounts were the same for all beneficiaries, 100 rands for the adolescents and 200 rands for the parent or guardian (~25% of monthly income). The last two visits (Wave 5 and Wave 6) were post-intervention (cash transfers were no longer disbursed) and included all adolescents regardless of whether they had graduated from school.

The median time lapse between waves was 1.13 years. A detailed description of the study design can be found in the main paper (Pettifor et al., 2016a).

No intervention effect was found on HIV acquisition or other secondary outcomes (including mental health); thus, the trial arms are pooled in this chapter (Pettifor et al., 2016a; Pettifor et al., 2016b).

Questionnaires were translated from English to Shangaan and back-translated again, with further testing during fieldworker training prior to the survey.

Institutional Review Board approval for this study was obtained from the University of North Carolina at Chapel Hill, the University of the Witwatersrand Human Research Ethics Committee, and the Provincial Department of Health's Research Ethics Committee. I obtained approval for the secondary analysis for this study from the Oxford Tropical Research Ethics Committee (OxTREC).

Measures

Depression

Depressive symptoms were determined at all waves, although different measures were used. Depression at Wave 1 was measured with the short form of the Children's Depression Inventory (CDI-S), a 10-item scale designed to assess depressive symptoms among children and adolescents (Kovacs, 2003). The reduced scale has been previously used with adolescents in South Africa (Cluver et al., 2007; Sharer et al., 2015). I dichotomised the total score using a cut-off point of ≥ 7 to classify participants at risk of depression, following previous literature (Binagwaho et al., 2016).

Depressive symptoms from Wave 2 onwards were assessed using the Centre for Epidemiologic Studies Depression Score (CES-D), a 20-item measure designed to measure depressive symptomatology in the general population (Radloff, 1977). The internal consistency of CES-D was good (Cronbach's $\alpha = 0.8$). The CES-D has been validated for adolescents in various settings, including South Africa (Baron et al., 2017; Pretorius, 1991). I dichotomised the total score using a cut-off of ≥ 16 to identify individuals at risk for clinical depression. In the remainder of this chapter, CES-D scores of 16 or greater will be referred to as "depression caseness."

Risk factors

Risk factors were selected based on the literature but were constrained by their availability in the study dataset. When deciding on the list of risk factors, I prioritised risk factors that are modifiable (i.e., variable risk factors) and prevalent in low-resource settings (i.e., higher exposure prevalence). In total, I focused on the following six risk factors:

HIV status. Determined at all visits by administering HIV tests at all visits. A detailed description of laboratory procedures can be found elsewhere (Pettifor et al., 2016a). A binary variable was created, equalling 1 if the respondent was HIV positive (0 if HIV negative).

Intimate partner violence (IPV). Physical IPV was measured at all visits using the 6-item World Health Organization scale (Garcia-Moreno et al., 2006). The scale assessed six different types of physical violence, such as slapping, choking, or being threatened with a weapon. Participants were asked whether this had happened in the past 12 months. A binary variable was created that encoded whether respondents experienced those types of physical violence in the previous year.

Parental death. Measured using a categorical variable showing whether the adolescent had lost their mother or father in the previous year. Data was available at all visits except for the last year (Wave 6).

Low parental support. 8 items asked respondents about the relationship quality with their primary caregiver. Adolescents were asked how often their primary caregivers tried to find out who their friends were, how they spent their free time, where they went after school, and how they spent their money. Response options range from always (score of 0) to never (score of 2). Additional questions were asked about how much the caregiver cared about her, how close she felt to the caregiver, and how often they discussed sensitive issues such as sexual relationships and HIV. A scaled score was created by averaging responses to all the items, with higher scores indicating lower parental support. The measure had acceptable internal consistency reliability ($\alpha = 0.71$). I also constructed a binary variable called 'Lack of parental support', equalling 1 if the

participant scored in the lower tercile. Data was available at all visits except for the last wave (Wave 6).

Food insecurity. Measured at all visits using a binary variable indicating that respondents were worried about not having enough food to eat at some point in the past year.

Poverty. Participants' caregivers were asked about monthly household consumption, including expenses for food (items grown, purchased, or borrowed) and non-food items (personal items, transportation, etc.). I constructed a measure of total household per capita expenditures by summing up total per-capita food and total per-capita non-food expenditures and taking the natural log. I then divided this variable into deciles to create a categorical variable. I also constructed a binary variable called 'Extreme Poverty', which is equal to 1 if the individual's monthly income was below the International Poverty Line (\$1.90 per day in international dollars). All total expenditure categories were adjusted for monthly inflation (base of December 2016) using South Africa's Consumer Price Index (CPI) for Mpumalanga province. Data was available at all visits except for the last year (Wave 6).

Covariates

I controlled for covariates that have been found to predict depression, including age, level of education, and a household asset index. The household asset index was constructed from the question 'How many durable goods (e.g., radio, television, and cellphone) does the household currently own?'. There were 27 specific durable goods queried, and the household reported the total number of each good they owned. I constructed an equal weights index using all items.

Statistical analysis

To assess the effect of risk factors on depression, I specified a two-way fixed effects model, which includes time and individual fixed effects. The Hausman test supported the choice of a fixed effects model against random effects or a mixed model ($P < 0.0001$).

Time fixed effects control for omitted variables that vary over time but are constant across individuals (e.g., this would include general macroeconomic trends during a particular year). Individual fixed effects control for time-invariant characteristics that may be correlated with the explanatory variables (Wooldridge, 2010). In the context of this study, this includes time-invariant risk factors such as genes, past life events, stable personality traits, or family history.

My first objective was to examine the role of several risk factors in predicting high depressive symptoms among adolescent females in rural South Africa. I specified two different models to explore this.

In Model 1, I specified a two-way linear fixed effects regression using the depression continuous score as the dependent variable and each risk factor as the explanatory variable. I also applied robust standard errors to account for heteroskedasticity. I estimated regression equations of the following form:

$$DepressionScore_{it} = \alpha_i + \gamma_t + \beta_1 RiskFactor_{it} + \beta' \mathbf{X}_{it} + \varepsilon_{it} \quad (1)$$

For $i=1,2,\dots,N$ and $t=1,2,\dots,6$, and where $RiskFactor_{it}$ was each of the six risk factors listed above, $\mathbf{X}_{it}$ is a vector of time-varying controls detailed above, α_i and γ_t are unit and time fixed effects, respectively, and ε_{it} is an unobserved error term.

In Model 2, I estimated a conditional fixed-effects logistic regression using the dichotomised score (depression caseness) as the dependent variable. I estimated regression equations of the following form:

$$logit(DepressionCaseness_{it}) = \alpha_i + \gamma_t + \beta_1 RiskFactor_{it} + \beta' \mathbf{X}_{it} + \varepsilon_{it} \quad (2)$$

For $i=1,2,\dots,N$ and $t=1,2,\dots,6$, and where $RiskFactor_{it}$ was each of the six risk factors, $\mathbf{X}_{it}$ is the set of controls specified above, α_i and γ_t are unit and time fixed effects, respectively, and ε_{it} is an unobserved error term.

As part of my secondary objective, I explored whether the effects of risk factors on depression dissipate over time. To do this, I examined movements in depression scores before, during, and after each risk factor. Following a similar methodology as Clark et al. (2008), I identified individuals who experienced all six risk factors and traced the evolution of their depression scores over time (Clark et al., 2008).

To conduct this type of analysis, individuals had to be observed before and after the risk factor in question so that their depression scores could be traced. As such, individuals who had the risk factor at Wave 1 were dropped from the analysis. Further, I only considered the first onset of each risk factor (i.e., when they first occurred). For example, if an individual experienced IPV in Wave 2 and then again in Wave 5, I dropped the individual's observations from Wave 5 onwards. This did not apply to permanent risk factors such as HIV and parental death. I specified the following model:

$$DepressionScore_{it} = \alpha_i + \beta' \mathbf{X}_{it} + \lambda_{-3}Y_{-3,it} + \lambda_{-2}Y_{-2,it} + \lambda_{-1}Y_{-1,it} + \lambda_0Y_{0,it} + \lambda_1Y_{1,it} + \lambda_2Y_{2,it} + \lambda_3Y_{3,it} + \varepsilon_{it} \quad (3)$$

Where α_i are individual fixed effects, $\mathbf{X}_{it}$ is the set of time-varying controls specified above, and ε_{it} is an independently and identically distributed random error term. All the Y s are binary variables indicating that the individual was a given number of periods away from

experiencing the risk factor in the respective period. For example, $Y_{-3,it}$ takes the value of 1 if the individual will experience the risk factor in 3 years, and $Y_{-2,it}$ takes the value of 1 if the individual will experience the risk factor in 2 years. Similarly, $Y_{2,it}$ takes the value of 1 if the individual experienced the risk factor 2 years ago, and so forth. Individuals who did not experience the specific risk factor have 0s in all Y terms and act as the counterfactual group (or pure controls) on which the estimation of impacts is based.

I controlled for the same covariates as in the first two models and included individual fixed effects to effectively follow the same individual over time.

All analyses were conducted using Stata/MP 14 (StataCorp, 2015).

RESULTS

The six waves of the study were used. Excluding those individuals with only one assessment of depressive symptoms, the sample for the following analyses included 2,454 adolescents.

The number of repeated measurements on each participant varied from two to six, with most participants (81%) having at least four assessments. Table A2.1 in the appendix shows the share of participants who had at least a given number of assessments.

By the last wave (Wave 6), 821 participants were lost to follow-up, resulting in an attrition rate of 33.5%. I tested for differential attrition across those who were followed up and those who dropped out by regressing a range of baseline observable characteristics on an indicator variable for attrition (=1 if adolescents were lost to follow-up in Wave 6, =0 otherwise). Results in Table A2.2 show no statistically significant differences in depressive symptoms, risk factors, and most other covariates individually or jointly (F statistic=0.1) across the two groups. I found a statistical difference in one covariate (educational level), where participants who dropped out had achieved a higher school grade at baseline. I included this as part of the covariates across all models.

Table 2.1 shows the characteristics of study participants at Wave 1. The average age was 15.5 years old. On average, participants had 8.4 years of schooling, and more than a third had repeated a school grade. Most households were relatively poor: the average household size was 6.2 members, most households received government grants, and more than a third of participants' parents had no formal education. Over half (62%) lived in extreme poverty, and more than a third (34%) were food insecure in the past year. HIV prevalence was low, which is not surprising given that participants had to be HIV negative at baseline to be included in the study. On average, 17% of participants had

experienced IPV, and 25% had lost one or both parents.

Table 2.1 Characteristics of study participants at Wave 1

Variable	All (n=2,454)	Not depressed (n=2,010)	Depressed (n=444)	P-value
<i>Individual characteristics</i>				
Average age (range)	15.5 (13 – 21)	15.4	15.9	<0.001
Average years of schooling (range)	8.4 (7 – 10)	8.4	8.4	0.186
Ever repeated a school grade	34.6%	31.3%	49.7%	<0.001
Employed	16.0%	13.6%	26.6%	<0.001
Ever pregnant	8.8%	7.3%	15.9%	<0.001
Has savings	25.1%	24.1%	29.6%	0.019
Main caregiver is not parent	26.1%	26.2%	25.5%	0.737
<i>Household characteristics</i>				
Average household size (range)	6.2 (2 – 20)	6.19	6.23	0.758
Average number of government grants received (range)	2.7 (0 – 14)	2.69	2.83	0.188
Mother without formal education	38.3%	38%	42%	0.105
Father without formal education	39.0%	39%	41%	0.494
Household asset index (range)	0.23 (0 – 1)	0.23	0.23	0.232
<i>Risk factors (prevalence)</i>				
HIV positive	2.9%	2.6%	4.3%	0.11
IPV	17.4%	13.9%	33.0%	<0.001
Parental death	24.9%	24.5%	26.7%	0.354
Low parental support	38.2%	40.0%	30.0%	<0.001
Extreme poverty	62.2%	62.0%	63.1%	0.68
Food insecurity	34.2%	32.5%	41.9%	<0.001

Table 2.1 also compares these same characteristics according to depression status. The p-values for a t-test for differences in means are reported in the last column. At baseline, participants with high depressive symptoms were more likely to be older, have repeated a school grade, be employed, and have had a child. There were no statistically significant difference in the household characteristics.

The prevalence and incidence of high depressive symptoms across all waves are shown in Table 2.2. On average, 18.1% of the sample were depressed at baseline, with the highest prevalence in Wave 2 (32.5%) and the lowest in Wave 6 (9.2%). The average prevalence of high depressive symptoms over the six waves was 23%. This prevalence is substantially higher than that reported by the National Income Dynamics Study (NIDS) for adolescents in this region of South Africa.

NIDS was the first nationally representative panel survey in South Africa, which measured depressive symptoms using the 10-item CES-D (the short version of the scale used in this study) (Southern Africa Labour and Development Research Unit, 2018). NIDS data reports a prevalence of high depressive symptoms of 13% among adolescent females (14–24 years) living in Mpumalanga and Limpopo provinces (both located close to the study site) during that same period (2012 – 2017).

Table 2.2. Prevalence and incidence of high depressive symptoms

	Wave 1	Wave 2	Wave 3	Wave 4	Wave 5	Wave 6
Sample size	2,454	2,270	1,865	893	1,918	1,634
Point prevalence (95% CI)	18.1% (17 – 20)	32.5% (31 – 34)	26.2% (24 – 28)	24.6% (22 – 28)	27.1% (25 – 29)	9.2% (8 – 11)
Incidence	-	23.4%	11.6%	12.7%	13.7%	5.1%

Note: Prevalence at Wave 1 is calculated with CDI (cut-off score = 7). CES-D was used for all other waves (cut-off score = 16).

The average incidence over the six waves was 13.3%. More than half of the sample (59%) were above the cut-off on at least one assessment occasion over the six-wave period, and 16% on at least three occasions (this was calculated among those participants for whom at least 4 observations were available). The most endorsed items were the (absence of) positive affect across all assessment time points. The second most endorsed items were somatic symptoms such as low energy, sleep disturbance, and reduced appetite. Prior studies in low-resource settings have shown similar symptomatology, particularly regarding somatic manifestations (Patel et al., 2001).

Depression severity over time is shown in Figure 2.2. The distribution of severity of depressive symptoms is similar to that found in cross-sectional studies with adolescents in Nigeria, Kenya, and South Africa (Adeniyi et al., 2011; Fatiregun & Kumapayi, 2014; Osborn et al., 2020; Strydom et al., 2012).

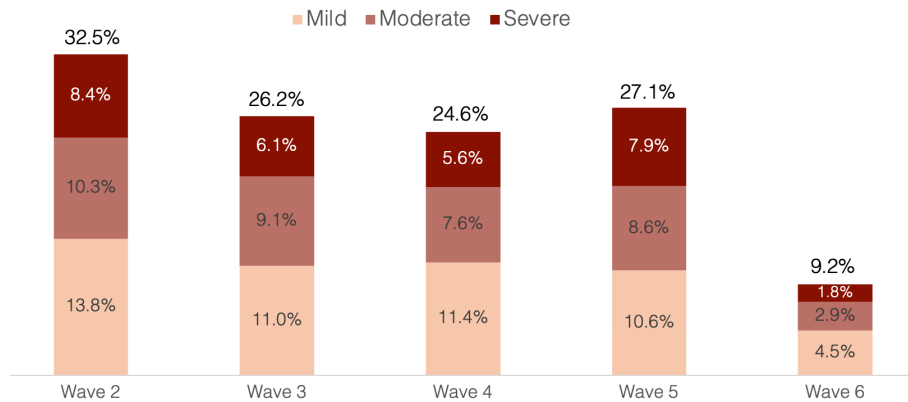


Figure 2.2. Severity of depressive symptoms over time

Note: Severity of depression was based on the 20-item Centre for Epidemiologic Studies Depression Score (CES-D) scale (CES-D) and summarised into mild (score between 16 –20), moderate (score between 21 – 25), and severe (score between 26 – 60).

Figure 2.3 shows that prevalence rates of high depressive symptoms vary by age, peaking at 18 years when prevalence reached 30%. In line with this, findings from a recent large-scale epidemiological meta-analysis also showed that depressive disorders were most common at age 19 (Solmi et al., 2021).

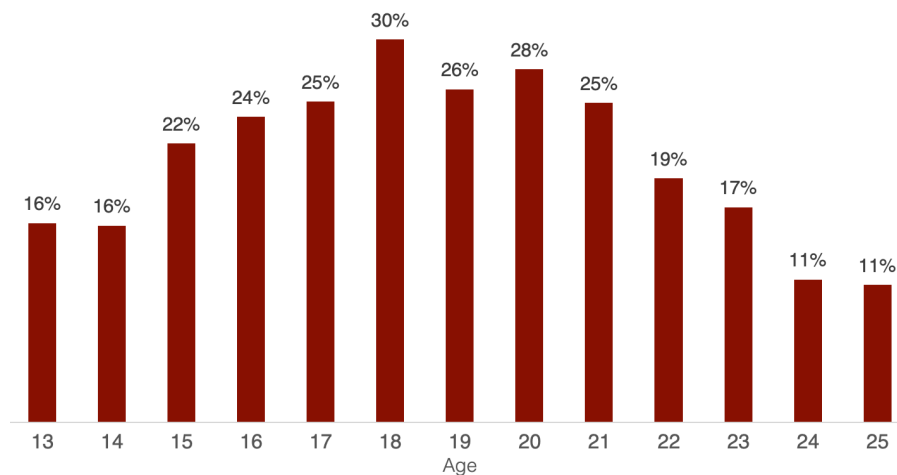


Figure 2.3. Prevalence of high depressive symptoms by age

I observed a downward trend of risk factors over time: respondents experienced 1.8 risk factors per person in Wave 1, on average, and this average decreased over time, reaching 0.6 average risk factors per person in Wave 6. This is consistent with the evidence from the study area, which shows that standards of living have substantially increased since 2001 (Kabudula et al., 2017). On average, adolescents with

depression were more likely to have more risk factors than non-depressed adolescents, and this difference was statistically significant across all waves (Figure A2.1 in the appendix).

The estimates of the multivariate two-way fixed effect models are shown in Table 2.3. The left-hand part of the table shows the estimates for the depression score (Model 1), and the right-hand side uses the dichotomised score (=1 if CESD $\geq$ 16) to measure depression caseness (Model 2).

Results show that experiencing IPV, low parental support, and being food insecure were associated with a statistically significant increase in both the depression score and depression caseness. The effect sizes were largest for IPV in depression caseness (OR = 1.79; 95% CI, 1.52-2.10) and depression score (experiencing IPV increased depression score by 2.03 points on the CES-D scale). Being infected with HIV, losing a parent, and changes in monthly expenditures were not associated with depression. The complete regression output can be found in Table A2.3 in the appendix.

Table 2.3. Multivariate two-way fixed effect model

	Model 1: Depression score		Model 2: Depression caseness	
	β coefficient	(95% CI)	Odds Ratio	(95% CI)
HIV positive	-0.09	(-1.04, 0.85)	0.96	(0.64, 1.44)
Intimate partner violence	2.03	(1.61, 2.44)***	1.79	(1.52, 2.10)***
Parental death	0.33	(-0.42, 1.08)	1.18	(0.82, 1.70)
Low parental support	1.37	(0.83, 1.92)***	1.38	(1.08, 1.75)*
Food insecurity	1.00	(0.63, 1.37)***	1.24	(1.07, 1.45)**
Consumption deciles	-0.04	(-0.10, 0.03)	1.00	(0.97, 1.03)

Note: All variables except low parental support and consumption deciles are binary variables. All regressions included time and individual fixed effects. Each regression also controlled for age, level of education, and a household asset index constructed from information on ownership of a range of durable goods. The stars represent statistical significance as follows: *** p<0.001, ** p<0.01, * p<0.05.

As a secondary objective, I explored whether the effects of risk factors on depression dissipate over time. Figure 2.4 illustrates depression scores before, during, and after these risk factors. Point estimates are displayed along with their 95% confidence intervals. The horizontal line is at zero, which corresponds to no effect on depression score compared to one year prior to when the risk factor occurred. The coefficients used to construct this figure are shown in Table A2.4 in the appendix.

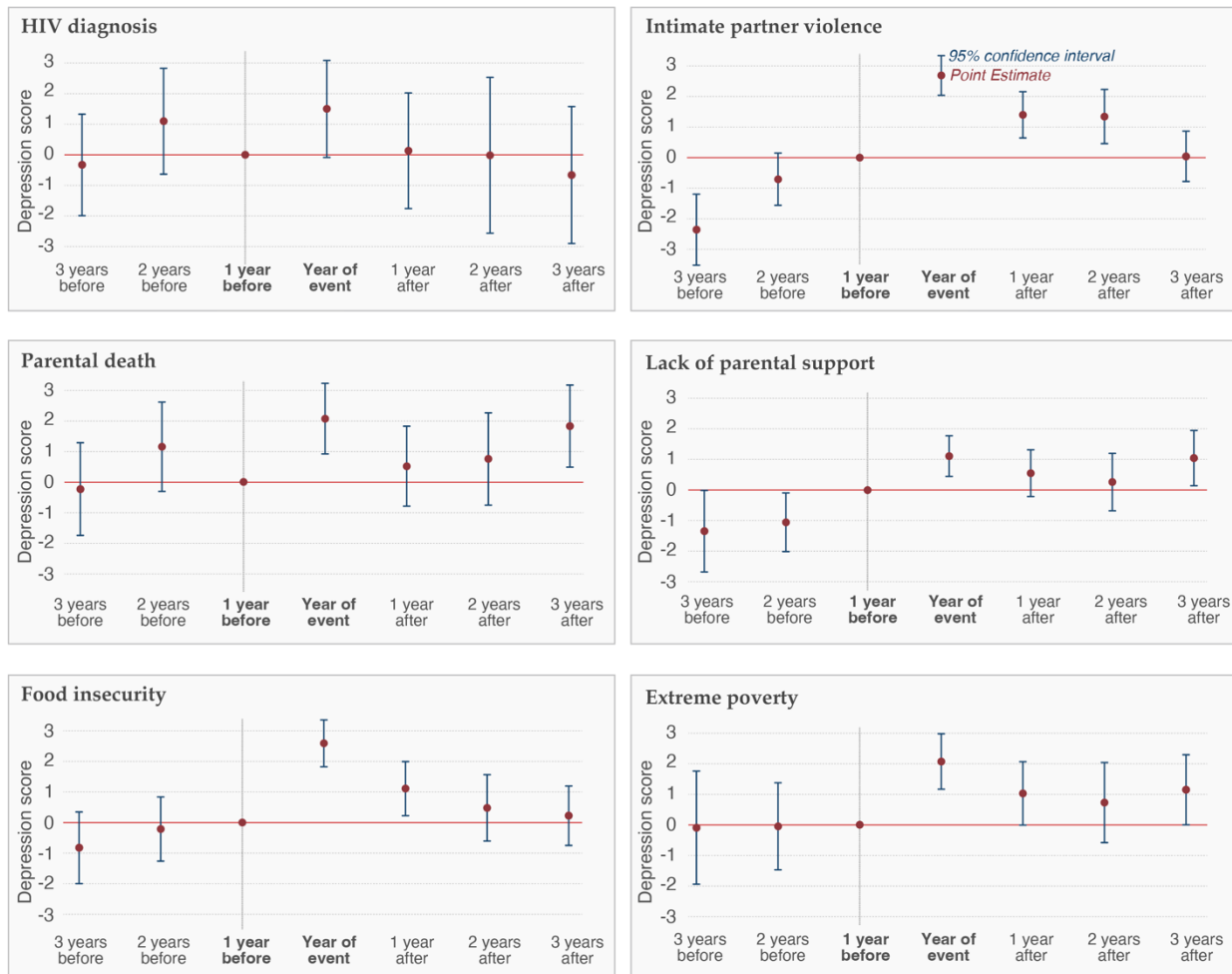


Figure 2.4. Effect of risk factors on depression score over time

Note: Extreme poverty is a binary variable equal to 1 if the individual's monthly income was below \$1.90 per day in international dollars. Lack of parental support is a binary variable equal to 1 if the parental support score was in the lower tercile. All regressions control for individual fixed effects, age, level of education, and a household asset index constructed from information on ownership of a range of durable goods. Point estimates are displayed along with their 95% confidence intervals. The horizontal line is at zero, which corresponds to no effect on depression score compared to one year prior to when the risk factor occurred.

The figure shows a positive association between risk factors and depression scores. The strongest impact often appears in the short term, around the same time when the risk factor was experienced. The magnitude of this association is largest for IPV, which is consistent with the previous results.

The analysis also reveals longer-lasting effects of IPV and food insecurity, with adolescents remaining on a higher depression score even two or three years after experiencing these risk factors. There also seems to be a significant association between parental death and

depression score three years after losing a parent. However, this might be driven by the smaller sample size in that period ($n=221$). The effects of low parental support and extreme poverty dissipated over time, with adolescents returning to the baseline depression score after one year.

Consistent with the previous findings in Model 1, I did not find any association between HIV and depression scores. This might be explained by the small number of participants who got HIV during the six-wave period, which is unsurprising given that this was an HIV prevention trial.

CONCLUSION

Using a cohort study with six waves of data, I examined the role of several risk factors in predicting high depressive symptoms in an understudied and underserved population: adolescent females in rural South Africa. Three results stand out. First, I observed a high prevalence of elevated depressive symptoms among the study sample (up to 32.5% in Wave 2 and an average prevalence of 23% over the six waves). Second, I found that experiencing IPV, low parental support, and becoming food insecure were associated with a statistically significant increase in depression severity and depression caseness. Third, the effect of some of these risk factors was associated with persistent depression, with adolescents remaining on a higher depression score even three years after experiencing these risk factors.

These results are consistent with previous studies with adolescents in LMICs. With regards to IPV, a systematic review of cohort studies found a positive association between IPV and depression (Devries et al., 2013). The pooled odds ratio (ORs) from six studies (2 of which were conducted in LMICs) was 1.97 (95% CI 1.6–2.5), which is similar to what I found (ORs = 1.79; 95% CI, 1.52–2.10). Further, a cohort study in Ghana found that lower family involvement was associated with higher depressive symptoms among adolescents (Roche et al., 2016). Lastly, a systematic review of 115 studies in LMICs (11 of which were cohort studies) found a positive association between poverty and common mental disorders among late adolescents and adults (≥ 18 years). However, the consistency and strength of the association changed depending on the dimension of poverty that was assessed. While dimensions such as food insecurity showed a strong association (food insecure individuals were up to three times as likely to have depression), other poverty indicators like expenditures were more equivocal (Lund et al., 2010). This is in line with my results, with clear evidence of an association between food insecurity and depression (ORs=1.24; 95% CI 1.1–1.5), but no association between monthly household consumption and depression.

The lack of association between depression and becoming diagnosed with HIV contrasts with previous evidence. Studies from sub-Saharan Africa have shown that the diagnosis of HIV can be a risk factor for depression, with a prevalence of nearly two times higher among individuals living with HIV compared to HIV-uninfected subjects (Ciesla & Roberts, 2001; Collins et al., 2006; Maj et al., 1994). Similarly, I find no significant effects of parental death on depression. This is at odds with existing evidence from previous case-control studies conducted in Tanzania, Ethiopia, and Uganda, which found that orphans were more likely to be depressed during the first years following the death of a parent (Bhargava, 2005; Makame et al., 2002; Sengendo & Nambi, 1997).

This chapter has several limitations. First, I explore the association between depression and risk factors using observational evidence; thus, the results do not imply causation. To mitigate the risk of confounding, I specified a two-way fixed effects model which controls for any time-invariant characteristic that may be correlated with the independent variables (by including individual fixed effects) and for omitted variables that vary over time but are constant across individuals (by including time fixed effects). Thus, this model eliminates two significant sources of confounding. In addition, all the models included a range of covariates which have been found to predict depression (e.g., age, level of education, and socioeconomic status). I also explored the effect of risk factors over time by only including those individuals who did not have the risk factor in the first period, mitigating the risk of reverse causality.

Second, this chapter did not include important risk factors such as parental depression and genetic disposition. However, while I cannot quantify the effects of these time-invariant risk factors on depression, the two-way fixed effects model controls for them.

Lastly, I relied on self-report measures to ascertain depression and most risk factors (except HIV), which might induce recall or reporting bias. Nevertheless, all sensitive questions were asked using Audio Computer Assisted Self Interview (ACASI), which has been shown to reduce reporting bias (Cullen & Mahmud, 2021). Further, the CES-D has been validated among adolescents in South Africa and has demonstrated good psychometric properties when compared with diagnostic instruments (Baron et al., 2017; Pretorius, 1991). Similarly, food insecurity reported by the adolescents was also positively correlated with food insecurity as reported by the adolescent's caregivers ($P < 0.001$). In addition, previous evidence on IPV suggests that under-reporting is a much more significant threat to validity than over-reporting of violence, implying that, if anything, the association I find between IPV and depression is a conservative estimate (Ellsberg et al., 2008).

Despite these limitations, this chapter has important implications. First, the results show that the burden of depression is high in low-resource settings such as the one where this study is based. I find a significantly higher prevalence of depression than that found in other studies, including a nationally representative cohort study of adolescent females in rural South Africa that relied on the same depression measure as the one I use in this chapter (Southern Africa Labour and Development Research Unit, 2018). These high prevalence rates, coupled with the limited access to evidence-based treatments for depression in these settings, imply that a high share of adolescents lack the support they need (Rathod et al., 2017).

Second, this chapter found significant and persistent effects of risk factors which are common in LMICs, particularly in a rural context. For example, 80% of all people in extreme poverty live in rural areas (World Bank, 2020). Rural areas also have poorer measures of crime, health, and public goods compared to urban areas within developing countries (Gollin et al., 2017). This means that a higher share of the population might be at risk of developing depression (i.e. higher exposure prevalence) (Cuijpers et al., 2021; Patel et al., 2010).

Lastly, many of the risk factors in this study are modifiable and thus can be targeted through interventions. For example, experimental studies have shown that positive income shocks lead to mental health improvements (for a comprehensive review, see Ridley et al., 2020). Interventions to prevent violence in LMICs have also shown promising results, as well as mental health interventions that reduce both IPV and depression (Ellsberg et al., 2015; Tol et al., 2019).

With depression being one of the leading causes of illness and disability among adolescents, this chapter suggests that treatment alone might not be enough to address this problem at scale. Increasing efforts to identify depression early in adolescence should be a priority in low-resource settings where resources are already scarce (Kieling et al., 2019).

Future research should explore possible moderators and mediators by which these risk factors may influence depression, for example, by examining the cognitive vulnerabilities triggered following the occurrence of risk factors (e.g., attributional style, rumination, etc.) (Kuyken et al., 2006).

More research on possible bidirectional associations between risk factors and depression is needed. This is important both conceptually and for policy purposes. For instance, if poverty precedes episodes of mental illness, then interventions might be better directed towards reducing poverty (e.g., through cash transfer programs or prioritising economic growth). On the other hand, if evidence shows that depression occurs before poverty, this would strengthen the case for more

evidence-based mental health treatments in LMICs. A better understanding of the directionality and strength of the association between depression and risk factors would promote an effective allocation of resources, inform the design of interventions, and ultimately improve mental health outcomes among adolescents in low-resource settings.

Chapter 3. Effect of depression on risk-taking: a systematic review and meta-analysis²

Chapter in context

Background. Chapter 2 revealed a high burden of depressive symptoms among adolescents in low-resource settings. This makes adolescents who live in these contexts more vulnerable to the negative consequences of depression. Studies conducted in high-income settings have identified risky behaviours as one potential consequence of depression. No systematic review to date has examined the association between depressive symptoms and risky behaviours among adolescents in LMICs, where 90% of the world's adolescents live.

Objectives. The objective of this chapter was to:

- (1) Identify and systematically review all relevant literature reporting on the association between depressive symptoms and risky behaviours among adolescents living in LMICs; and
- (2) Provide a quantitative summary estimate of the extent to which these are associated.

Findings and implications. Consistent with the evidence from high-income countries, this review found that adolescents in LMICs with depressive symptoms are more likely to engage in risky behaviours such as risky sexual behaviours and substance use, compared to non-depressed adolescents. This chapter, therefore, suggests that depressed adolescents in LMICs carry a double burden; in addition to suffering from depression, they may be at an increased risk of experiencing the negative consequences of the associated risky behaviours. This combination may lead to further psychological and physical health problems that persist over the life course.

² This chapter has been adapted from the following paper, attached in the appendix:

Pozuelo, J. R., Desborough, L., Stein, A., & Cipriani, A. (2021). Systematic review and meta-analysis: depressive symptoms and risky behaviors among adolescents in low-and middle-income countries. *Journal of the American Academy of Child & Adolescent Psychiatry*, 61(2), 255-276.

INTRODUCTION

Adolescence is a time when individuals start to make vital decisions – about their health, education, friendships and intimate relationships, and entrance into the labour market – within a context of diminishing parental involvement and heightened peer influence (Sawyer et al., 2012). This period is often marked by a rise in risky behaviours such as unprotected sex and substance use, especially when adolescents are with peers (Blakemore & Mills, 2014). Externalising problem behaviours such as aggressive and rule-breaking behaviours also increase during adolescence (Moffitt, 1993). These behaviours 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 (Steinberg, 2007).

Adolescence is also the period in which the incidence of depression peaks, with half of all lifetime onset by age 14 and adolescent females being especially affected (Kessler et al., 2005a). Depression is associated with difficulties in cognitive functioning, poorer school performance, deterioration of social relationships, and worsened long-term decision-making (Cotrena et al., 2016; Snyder, 2013). In its most severe form, depression can also lead to self-harm and suicide (Thapar et al., 2012).

Several longitudinal studies have found an association between depressive symptoms during adolescence and risky sexual behaviours such as unprotected sex, teenage pregnancy, and sexually transmitted infections (STIs) (Brown et al., 2006; DiClemente et al., 2001; Lehrer et al., 2006; Seth et al., 2011). Depressive symptoms have also been associated with alcohol and drug use and subsequent onset of substance use disorders (Dixit & Crum, 2000; Kessler et al., 1996; Kumpulainen, 2000; Wolitzky-Taylor et al., 2012). Complicating matters even further, individuals often engage in multiple risky behaviours simultaneously. For example, adolescents who use drugs and alcohol are more likely to engage in risky sexual behaviour (Ngoc Do et al., 2020; Tapert et al., 2001).

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) (Henrich et al., 2010). The bulk of the evidence conducted in LMICs has come from cross-sectional data, and thus, the temporal relationship between past depressive symptoms and future risky behaviours cannot be determined (Agardh et al., 2012; Bajunirwe et al., 2018; Dibaba et al., 2013; Kimbui et al., 2018; Kunzweiler et al., 2018; L'akoa et al., 2013; Peltzer, 2004; Smit et al., 2006; Taşkıran et al., 2017; Wilson et al., 2012).

Evidence from LMICs, where 90% of the world's adolescents live,

remains relatively scarce and, to date, no systematic review has been previously carried out on this topic (Saxena et al., 2006). This project — “Depressive symptoms and Risky behaviours 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 behaviours 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 (Ward et al., 2018).

METHODS

Search Strategy and Selection Criteria

I followed the PRISMA guidelines (Moher et al., 2009). A protocol for the study is available on PROSPERO ([CRD42019131262](https://www.crd42019131262)). I searched for both published and unpublished studies reporting on the association between depression and risky behaviours 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. I also searched grey literature databases using OpenGrey, the British Library for Development Studies, Eldis, and Google Scholar. I conducted the search on April 22, 2019, and applied no restrictions on date, language, or publication status to the searches.

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

I 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 between the start of puberty and the point at which an individual attains a stable, independent role in society (Blakemore & Mills, 2014). However, as explained in Chapter 1, the timing of puberty and the transition to adulthood vary across time and between cultures. In response to this, an expanded, more inclusive definition of adolescents (10-24 years) has been proposed to better capture the current patterns of adolescent development (Sawyer et al., 2018). I used this expanded definition when screening articles.

The core search consisted of terms related to depression (depression or depressive disorder), risky behaviour (risk-taking or risk behaviour or risky sexual behaviour or substance use or delinquency or adverse school behaviour or self-harm or suicidal behaviour), 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 the appendix in Table A3.1.

Studies were included if they met the following criteria:

- (1) Cohort studies that measured depression at baseline and then recorded the incident risky behaviours during follow-up. I also included case-control studies that compared the prevalence of depressive symptoms between adolescents who engaged in risky behaviours (cases) and adolescents who did not engage in risky behaviours (controls).
- (2) Studies that recruited adolescents aged 10 to 24 years at baseline living in LMICs as defined by the World Bank (see Table A3.2 for the full list of countries, available in the appendix).
- (3) Studies that ascertained depression using standard operationalised diagnostic criteria (DSM-III onwards and ICD-10 onwards) and validated screening tools (e.g., CES-D, PHQ-9).
- (4) Studies that measured risky behaviours using biological markers and self-reported measures (see outcome section for further details).
- (5) Studies that controlled for the outcome variable (risky behaviours) at baseline and potential confounders (e.g., age, sex, socioeconomic status).

Cross-sectional studies were excluded because of their methodological limitations. I also excluded randomised trials for two reasons. First, given the limited evidence on the relationship between depression and risky behaviours, and the fact that risky behaviours may only manifest years later, I believed that a review of observational studies was first needed to support a theoretical framework and provide supplementary information to understand better the mechanisms underlying any plausible causal relationship (Shrier et al., 2007). 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 behaviours. While similar in nature, I see this and the main objective of this chapter as two different questions.

Further, I excluded studies that reported suicidal ideation (without attempt) as thoughts are not behaviours. I also excluded studies that recruited HIV-positive adolescents where the transmission route (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 the

consequence of risky behaviour.

In cases where multiple studies used the same data, I 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 by colleagues fluent in the respective language or using Google Translate (and subsequently cross-checked by a native speaker). I checked reference lists to identify relevant studies and hand-searched these.

I compiled the search results and eliminated the duplicates. Together with another reviewer, we independently screened the title and abstracts of retrieved references and obtained the full text of all potentially eligible studies. Next, we 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 handle the screening process was carried out using Covidence, an advanced systemic literature review software (Veritas Health Innovation, n.d.).

Outcomes measures

Primary outcomes

Despite the negative long-term consequences of risk behaviours, there is no consensus on how to define these behaviours. The concept of risky behaviours may also differ greatly among individuals and across cultures, as do the opportunities to engage in certain behaviours (e.g. individuals living in Muslim countries might be less exposed to alcohol) (Duell et al., 2018).

Research about risk-taking has included a wide variety of “risky behaviours,” making it difficult to narrow down the concept to a simple, helpful definition. In this review, I define risky behaviours as voluntary, observable behaviours that contribute to disability and premature death and impose a health burden on society (Jeffery, 1989; Roth et al., 2018).

Specifically, I focus on the following two primary outcomes:

Risky sexual behaviours: Any sexual behaviour that increases an individual’s risk for STIs or unwanted pregnancies. I included studies that measured such behaviours using biological markers (e.g., STIs, pregnancy) or self-reported indicators of the following variables:

number of unprotected sex episodes, total number of partners, whether the person ever had an unintended pregnancy, teenage pregnancy, the age of first coital debut, the age difference with the sexual partner, and whether the person ever engaged in transactional sex.

Substance use: Any use of alcohol or other recreational drugs. I included studies that measured substance use using biological markers (e.g., Breathalyser 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, and whether the person ever experienced any alcohol or substance dependence symptoms.

Secondary outcomes

Delinquency: Any behaviour that is illegal or not acceptable to most people. I included studies that measured such behaviour 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, and whether the person was ever incarcerated.

Adverse school behaviours: Any behaviour that disrupts teaching in the classroom or an individual's school performance. I searched for studies that measured these behaviours 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 the previous academic year, grade retention. Behaviours 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. I searched for studies that measured experiences of intentional self-harming behaviours (e.g., cutting, burning, biting, scratching skin).

Suicidal behaviour: The act of trying to take one's own life voluntarily and intentionally. I searched for studies that measured suicidal behaviour using questionnaires and standardised interview assessments or scales of the following variables: suicidal attempts, the total number of suicides ever attempted, and whether a person died from suicide.

Data extraction and quality assessment

I extracted the data, and a second reviewer independently cross-checked

these data for accuracy against the original studies. All discrepancies were reconciled by team discussion. Data on study characteristics, depression assessments, risky behaviour assessments, and results were extracted using Microsoft Excel.

Together with the second reviewer, we both independently assessed the quality of the studies using the Newcastle-Ottawa Scale (NOS) using two different scales for cohort and case-control studies, respectively (Wells et al., 2015). 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 software version 3 (Borenstein et al., n.d.). The incidence of each type of risky behaviour in depressed and non-depressed adolescents was estimated using odds ratios (ORs). When several odds ratios were reported within a study, I used the estimate from the model that adjusted for the maximum number of covariates. I pooled the ORs from all studies using the random-effects model since considerable heterogeneity was expected (DerSimonian & Laird, 1986). Random-effects models assume that the true treatment effect differs from study to study (i.e. there is a distribution of true effect sizes), which allows generalising to a range of populations (Cheung et al., 2012). Forest plots were used to present the pooled ORs and 95% CIs. The between-study heterogeneity was tested using Cochran Q and quantified by the I^2 statistic (Higgins et al., 2003).

I carried out subgroup analyses for studies that reported separate results for females and males. As part of the protocol, I included a subgroup analysis comparing depression severity (high vs low), but most studies did not report this information. I 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 behaviour (biological markers or diagnostic interviews vs self-report measures).

RESULTS

The electronic searches yielded 31,148 potentially relevant studies, as Figure 3.1 shows. In total, 25,863 studies were excluded in the first screening phase (title and abstract), and 668 were excluded in the second screening phase (full text). I included 33 records in the systematic review, of which 30 comprised the meta-analysis. All studies encompassed 35,918 adolescents living in 17 different LMICs: 5 from

Africa, 7 from Asia, and 5 from Latin America and the Caribbean.

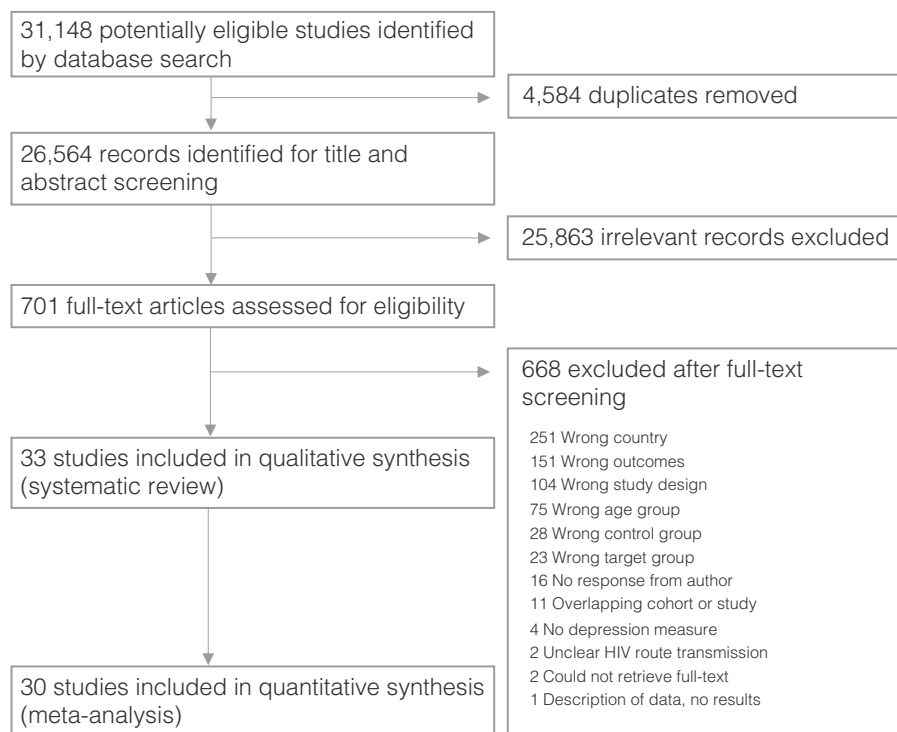


Figure 3.1. Study selection

Overall, I found:

- 7 records reporting on the association between depressive symptoms and risky sexual behaviour (Adair et al., 2011; Brophy et al., 2018; Castilla-Puentes, 2012; Freitas et al., 2008; Hall et al., 2018; Nduna et al., 2010; Victora et al., 2008);
- 10 records reporting on the association between depressive symptoms and substance use (Adair et al., 2011; Arellanez-Hernandez et al., 2004; Başay et al., 2016; Borges et al., 2018; Brophy et al., 2018; Charfi et al., 2018; Effat et al., 2016; Kazour et al., 2015; Niraula et al., 2009; Victora et al., 2008);
- 4 records reporting on the association between depressive symptoms and delinquency (Bejarpas, 2017; Kiliç, 2011; Zhou et al., 2014; Zhou et al., 2012);
- 3 records reporting on the association between depressive symptoms and self-harm (Barrocas et al., 2015; Kinyanda et al., 2005; Zhang et al., 2016); and
- 11 records reporting on the association between depressive symptoms and suicidal behaviour (2 of which were included in the systematic review) (Bella, 2012; Çetin, 2001; Cluver et al., 2015; Fidan et al., 2011; González et al., 2012; Li et al., 2008; Liu et al., 2005, 2019;

Ramalingam et al., 2016; Vieira et al., 2018; Zhao & Zhang, 2015).

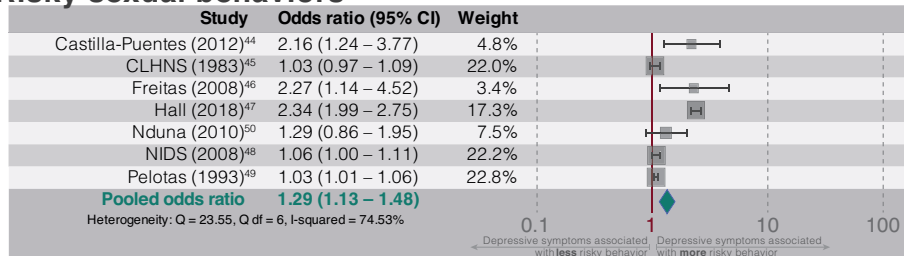
Three studies reported on both risky sexual behaviour and substance use separately (Adair et al., 2011; Brophy et al., 2018; Victora et al., 2008). One study included in the systematic review reported an index of risky behaviours (combining behaviours such as unsafe sexual practices, violent behaviours and rule-breaking) (Auerbach et al., 2010). I did not find any study reporting on the association between depressive symptoms and adverse behaviours in school. Table A3.3 and Table A3.4 show the characteristics of the included studies and a list of all excluded studies with reasons – both available in the appendix.

Regarding the study design, 12 were cohort studies, and 21 were case-control studies. I 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. I conducted the analysis whenever the data was open access (the Philippines and South Africa) and asked the study team to carry out the analysis whenever it was not freely available (Brazil). Further, 10 studies assessed depressive symptoms using standard operationalised 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 neighbours) to minimise informant discrepancies and measurement errors (Li et al., 2008; Zhao & Zhang, 2015).

With regards to 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 A3.3 shows the total score, and Table A3.5 shows the score for each dimension – both available in the appendix).

Primary outcomes: To estimate the extent to which depressive symptoms were associated with increased odds of engaging in risky behaviours, I pooled results for each type of risky behaviour. First, adolescents with depressive symptoms were more likely to engage in risky sexual behaviour than non-depressed adolescents (ORs=1.29, 95% CI: 1.13-1.48, $I^2=74.5\%$; Figure 3.2). Second, adolescents with depressive symptoms were at an increased odds of engaging in substance use compared to adolescents without depressive symptoms (ORs=1.76; 1.42-2.19, $I^2=77.33\%$; Figure 3.2).

Risky sexual behaviors



Substance use

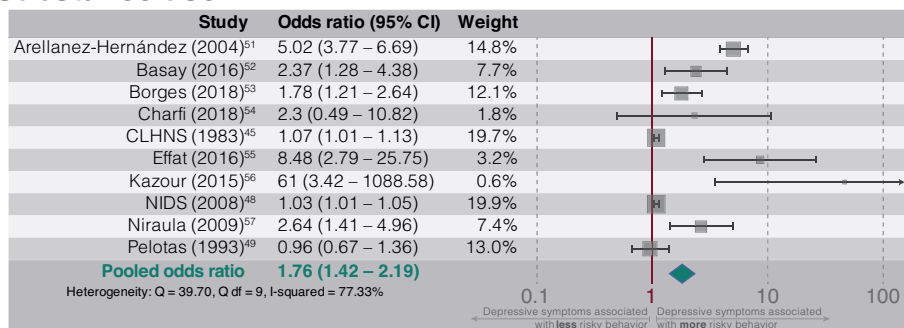
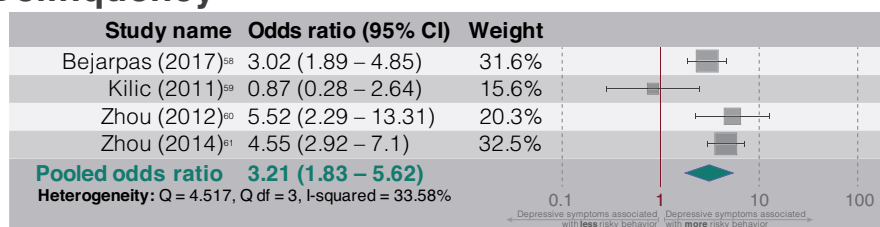


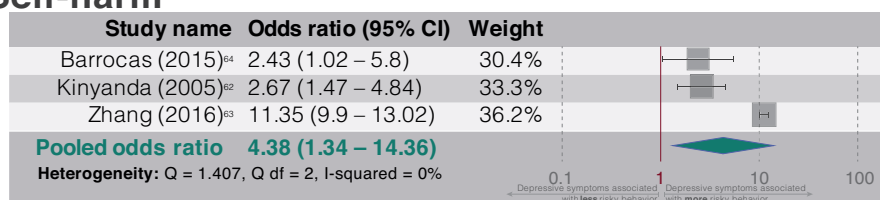
Figure 3.2. Forest Plots for Risky Sexual Behaviour and Substance Use (Random-Effects Model)

Secondary outcomes: The forest plots for the secondary outcomes are shown in Figure 3.3. Results for the secondary outcomes showed a similar pattern to the primary outcomes, with higher delinquency (ORs=3.21, 1.83-5.62, $I^2=33.58\%$), self-harm (ORs=4.38, 1.34-14.36, $I^2=0.0\%$), and suicidal behaviour (ORs=6.56, 2.28-18.86, $I^2=0.0\%$) among adolescents with depression compared to non-depressed adolescents.

Delinquency



Self-harm



Suicidal behavior

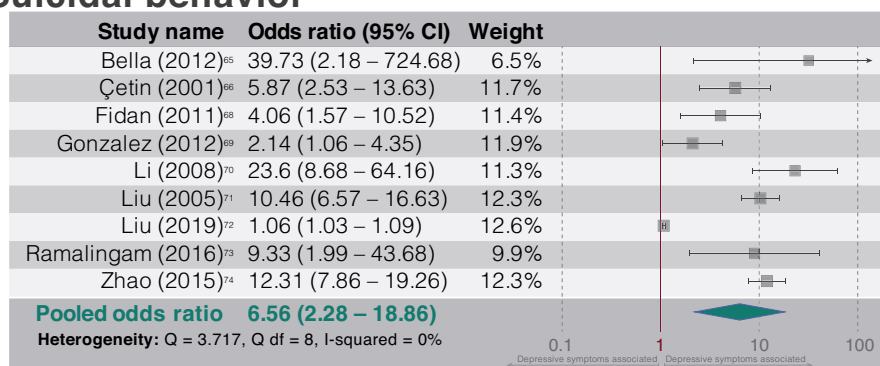


Figure 3.3. Forest Plots for Delinquency, Self-Harm, Suicidal Behaviour (Random-Effects Model)

Figure A3.1 in the appendix presents the results of the subgroup analyses for the primary outcomes. The difference between females and males was statistically significant for risky sexual behaviour (p -value=0.001), showing a larger ORs in the female subgroup than in males. 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 A3.6 in the appendix. I 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 ORs in case-controls) and risky behaviours measures, with biological markers/diagnostic interviews resulting in significantly larger ORs 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 (Cluver et al., 2015), another reported a risk ratio without the absolute numbers (Vieira et al., 2018), and another study reported an index of risky behaviours (Auerbach et al., 2010). All three studies reported a positive association between depressive symptoms and risky behaviours, in line with the results of this meta-analysis.

Interestingly, Auerbach (2010) conducted a multilevel modelling analysis to examine two hypotheses: whether depressive symptoms resulted in more risky behaviours and the reverse model (i.e., whether risky behaviours 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 behaviours.

Finally, following GRADE's guidelines regarding observational studies, I initially rated the quality of evidence as low (Balslem et al., 2011). I did not find any evidence to downgrade or upgrade the certainty of the evidence, and thus it was kept as low quality (further details can be found in Table A3.7 in the appendix).

CONCLUSION

This review found that adolescents in LMICs with depressive symptoms are more likely to engage in risky behaviours than non-depressed adolescents. These findings are consistent with the evidence from high-income countries (Brown et al., 2006; DiClemente et al., 2001; Dixit & Crum, 2000; Kessler et al., 1996; Kumpulainen, 2000; Lehrer et al., 2006; Seth et al., 2011; Wolitzky-Taylor et al., 2012). To my knowledge, this is the first systematic review and meta-analysis of the effect of depressive symptoms on risky behaviours among adolescents in LMICs.

The literature search was as comprehensive as possible and included published and unpublished studies across 15 databases and registries. In addition to relying on results from peer-reviewed studies, I conducted novel analyses of longitudinal cohort studies of adolescents from LMICs. Further, this review focused on cohort and case-control studies and only included studies that controlled for potential confounders. I assessed the quality of the studies using the Newcastle-Ottawa Scale. I 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 included nationally representative samples,

increasing the external validity of the results. Moreover, I included a range of risky behaviours (sexual, substance, delinquency, etc.) instead of focusing on a single behaviour. All included studies encompassed 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.

Several mechanisms could explain these findings. One view referred to as the 'self-medication' hypothesis suggests that adolescents with depression might engage in risky behaviours such as substance use as a coping mechanism to seek relief from their symptoms or to experience emotions (Khantzian, 1985, 1997). A second perspective states that changes in cognitive functions associated with depression (e.g. inhibitory control and reward processing) may result in a higher risky behaviour engagement (Cella et al., 2010; Snyder, 2013; Zhang et al., 2013). 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 behaviours (Beck, 1979; Giovenco et al., 2020; Nolen-Hoeksema et al., 2007; Shrier et al., 2001). Beyond individual-level mechanisms, environmental factors – such as affiliations with substance use or deviant peer groups – might precipitate the onset of depression and make adolescents more prone to engage in risky behaviours (Fergusson et al., 2003). These mechanisms are not mutually exclusive, and thus the mechanisms may, in fact, be a combination of all four. A better understanding of the mechanisms at play will help to inform policy and guide interventions targeting adolescent health.

This review has some limitations. First, it explores the association between depressive symptoms and risky behaviours using observational evidence; thus, the results do not allow definitive conclusions on causality. Given the limited number of adolescent cohort studies in LMICs, this review combined cohort and case-control studies in an effort to expand the search strategy and make it as comprehensive as possible (Ward et al., 2018). While I found a significant difference across study designs (with larger odds ratios in case-control studies), similar results were observed for cohort studies, reinforcing the validity of the findings. To mitigate the risk of confounding, I considered the most important potential confounders in advance (when preparing the protocol) and only included studies that controlled for covariates known to affect depressive symptoms and risky behaviours (e.g., age, sex, socioeconomic status). Second, significant heterogeneity was observed across studies in many outcomes. I believe this was partly because odds ratios were computed by combining different behaviours (for example, risky sexual behaviours pooled together teenage pregnancy, unsafe sex, and multiple partners). I decided *a priori* to combine these behaviours, given that they tend to co-occur and share similar antecedents. I also performed subgroup analysis to explore

possible sources of heterogeneity according to sex, study design, and the elicitation method used to assess depression and risky behaviours. In most of these cases, heterogeneity was reduced considerably. Third, several studies ascertained depression and risky behaviours using self-report measures, which may result in recall bias and 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 participants' ages, such as the Mini-International Neuropsychiatric Interview for Children and Adolescents (MINI-KID) and the Children's Depression Inventory (CDI). In addition, I found no significant difference across depression measures (diagnostic interviews vs self-report questionnaires), which indicates 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 and are considerably more cost-effective than structured clinical interviews (Stuart et al., 2014). Further, several studies relied on objective measures of risky behaviours (e.g., being a drug-dependent inpatient or pregnant), increasing the validity and reliability of the findings. Lastly, evidence from observational studies is considered low quality according to the GRADE framework; thus, the confidence in the effect estimate is limited.

Despite 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 behaviours, they are at an increased risk of suffering from the negative consequences of their behaviours. 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 increase the health burden on society significantly. In turn, this implies that a comprehensive assessment of the burden of depression — in itself already the leading cause of disability globally — would need to consider the negative consequences of risky behaviours associated with depressive symptoms (WHO, 2017).

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 (Fleitlich-Bilyk & Goodman, 2004; Haushofer & Fehr, 2014; Lund et al., 2014; Thapar et al., 2012). 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 (Rathod et al., 2017; WHO, 2015). As a result, access to evidence-based treatments remains very limited in LMICs (Holmes et al., 2018). These

findings, combined 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 is more likely to engage in risky behaviours.

Third, risky behaviours in LMICs can result in poor living conditions, especially in low-resource settings. In many developing countries, the capacity of the public health and welfare institutions is often insufficiently resourced, which means that adolescents living in these contexts lack the support they need (Ortiz-Ospina & Roser, 2020). While this type of support is far from perfect in high-income countries, there is 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 (Patton et al., 2016). This lack of safety nets in LMICs makes adolescents even more vulnerable to the negative impacts of risky behaviours.

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

Chapter 4. Depression and risk-taking: exploring the direction of effects

Chapter in context

Background. In Chapter 3, I reported on a meta-analysis that found that adolescents in LMICs with depressive symptoms are more likely to engage in risky behaviours than non-depressed adolescents. Additionally, there is evidence from high-income countries suggesting that the reverse is also true, risky behaviours result in higher depressive symptoms. Together these studies provide evidence for a bidirectional relationship between depression and risky behaviours, but few studies have investigated reciprocal prospective relationships between depression and risky behaviours among adolescents in LMICs.

Objectives. This chapter aims to use data from a nationally representative cohort study of adolescents from South Africa to:

- (3) Test the directionality of the relationship between depression and risky behaviours over time; and
- (4) Explore how this relationship varies by type of risky behaviour and socioeconomic status.

Findings and implications. The results from the structural equation model showed that the direction of effect varied between different type of risky behaviours. In particular, I found that smoking predicted future depression and that depression predicted subsequent adolescent pregnancy. However, the effect sizes for these associations were relatively small in magnitude. In contrast to previous studies and to the findings from Chapter 3, I did not find any relationship between depression and alcohol use (in either direction). More longitudinal studies of adolescents in LMICs are needed to enhance our understanding of the complex relationship between depression and risky behaviours.

INTRODUCTION

Although previous studies have established an association between depression and risky behaviours, there is still some disagreement about the relationship's exact nature, magnitude, and directionality (Banerjee, 2014; Cella et al., 2010; Fergusson et al., 2009; Khantzian, 1985, 1997; Quattrocki et al., 2000; Snyder, 2013; Swendsen et al., 2000; Zhang et al., 2013). This is partially due to the difficulty of empirically disentangling cause and effect in this relationship. For instance, it is unclear whether the relationship is unidirectional (running from depression to risky behaviours), bidirectional (running in both directions), or driven by some third variable.

Understanding the direction of effect is important both conceptually and for policy purposes. For instance, if episodes of depression precede risky behaviours, then interventions might be better directed towards identifying and treating individuals with depression in the first place. If depression is not a cause but a consequence of risky behaviours, then interventions aimed at reducing depression might not reduce risky behaviours. Lastly, if evidence shows that depression and risky behaviour co-occur – with no clear evidence on temporal sequence – then resources would be better allocated to developing integrated treatments that target both depression and risky behaviours (Curry et al., 2011; Degenhardt et al., 2013; Lewinsohn et al., 1999; Moffitt, 1993).

Several competing theories attempt to explain this relationship. Some hypotheses imply that depression results in more risky behaviours. For example, the 'self-medication' hypothesis suggests that individuals with depression might engage in risky behaviours as a coping mechanism to seek relief from their symptoms (Khantzian, 1985, 1997). It has also been proposed that depression is associated with impairments in executive function (such as lower inhibitory control), which may result in higher risky behaviour engagement (Cella et al., 2010; Snyder, 2013; Zhang et al., 2013). Another set of hypotheses predicts effects in the opposite direction, with risky behaviours preceding the incidence of depression. According to these views, risky behaviours could cause depressive symptoms like feelings of worthlessness, fatigue, and sleep disturbance or indirectly by affecting neurotransmitter pathways (Banerjee, 2014; Fergusson et al., 2009; Gobbi et al., 2019; Quattrocki et al., 2000). Risky behaviours might also increase the probability of experiencing risk factors for depression (e.g., job loss, HIV infection, violence exposure), and could thereby lead to depression. The third set of hypotheses states that depression and risky behaviours share common etiologic factors, such as genetic vulnerability, puberty, and exposure to a disruptive family environment (Swendsen et al., 2000; Zhou et al., 2017).

Several reasons may account for the mixed evidence. First, many clinical studies that have explored this relationship have relied on samples from a hospital in-patient population (e.g., psychiatric wards, drug-dependent inpatients, juvenile offenders) rather than large representative samples (Hovens et al., 1994; King et al., 1996; Rosenberg et al., 2001). Treated samples are biased in several ways, thus restricting the extent to which the results can be generalised to other populations (Swendsen et al., 2000).

Second, most studies that have explored this association rely on data from high-income countries, making it difficult to generalise to LMICs (DiClemente et al., 2001; Dixit & Crum, 2000; Kumpulainen, 2000; Lehrer et al., 2006; Wolitzky-Taylor et al., 2012).

Lastly, the bulk of the evidence from LMICs comes from cross-sectional studies and, therefore, cannot determine the temporal relationship between depression and risky behaviours (Agardh et al., 2012; Bajunirwe et al., 2018; Dibaba et al., 2013; Kimbui et al., 2018; Kunzweiler et al., 2018; L'akoa et al., 2013; Peltzer, 2004; Smit et al., 2006; Taşkıran et al., 2017; Wilson et al., 2012).

In this chapter, I aim to contribute to overcoming these challenges by using a nationally representative cohort study of adolescents from South Africa. Structural equation modelling techniques were used to test the directionality of the relationship between depression and risky behaviours across three time points. As a secondary objective, I explored how this relationship varied by type of risky behaviour and socioeconomic status.

METHODS

Data

I used data from the National Income Dynamics Study (NIDS), the first national panel study of individuals in South Africa. NIDS started in 2008 with a nationally representative sample covering more than 28,000 individuals. Since then, five survey waves have been conducted every two years. The study design and sampling method are described in the technical report (Leibbrandt et al., 2009). The data is freely available for download via the NIDS website (nids.uct.ac.za).

This chapter used data for adolescents (15–24 years old) from the first three waves, covering 2008–2012. I excluded the last two waves to focus on the period between mid-to-late adolescence (i.e., the median age was 23 years old in Wave 3). Most participants were transitioning from high school to tertiary education during this time. They thus were at a critical juncture in making vital choices – ranging from education and relationships to health behaviours – within a context of less parental

involvement and more influence from their peers (Sawyer et al., 2012).

The analysis uses a balanced panel which includes only those 15–24 years old adolescents in Wave 1 who responded to all the relevant questions in all waves. The total sample size was 2,368.

Measures

Depressive symptoms were assessed using the short version of the *Center for Epidemiologic Studies Depression Scale* (CES-D), a 10-item self-reported measure designed to assess depressive symptoms in the past week (Radloff, 1977). This shortened measure correlates very highly with the original measure (CES-D20) and has shown comparable accuracy in classifying participants with depressive symptoms (Zhang et al., 2012). The instrument includes five items on somatic symptoms, three on depressed affect, and two on positive affect. Responses are scored on a 4-point Likert scale, ranging from “rarely or none of the time” to “all of the time.” Scoring is reversed for the positive affect statements. The total score ranges from 0 to 30, with higher scores indicating greater severity of symptoms. This measure has been validated for adolescents in various settings, including South Africa (Baron et al., 2017; Pretorius, 1991). I defined a latent variable measuring depression, with all ten items of the CES-D loading into a single factor. Coefficients alpha for the ten items constituting the depression latent variable ranged from 0.6 to 0.8 over the three-wave period.

Risky behaviours. I focused on three types of risky behaviours:

- (1) *Adolescent pregnancy:* Females (n=1,341) were asked about the total number of children they had given birth to. I constructed a measure by adding the number of biological children alive and living with them, biological children that were alive but not living with them, and the number of children who were born alive but passed away later. I also included those who were pregnant at the time of assessment.
- (2) *Cigarette smoking:* This was measured as a continuous variable measuring the average number of cigarettes smoked per day. This variable was based on the following question: “On average, how many cigarettes per day do you smoke?”.
- (3) *Alcohol use:* This was measured as an ordinal variable capturing the number of standard drinks consumed on a drinking day. This variable was based on the following question: “On a day that you have an alcoholic drink, how many standard drinks do you usually have? A standard drink is a small glass of wine; a 330 ml can of regular beer, a tot of spirits, or a mixed drink.” Possible answers were on a six-point Likert scale ranging from ‘1 = 1 or 2 standard drinks’ to ‘6 = 13 or more standard drinks.’

Covariates. The following set of variables was introduced in the models as potential confounders: sex, age, education level, and monthly household income per capita. Using South Africa's Consumer Price Index (CPI), income was adjusted for inflation (base of 2010) (World Bank Group, n.d.). The characteristics were selected based on the literature as covariates known to be associated with depression and risky behaviours (Tian et al., 2021).

All questionnaires were available and administered in South Africa's eleven official languages.

Statistical analysis

A cross-lagged structural equation model was employed to conceptualise and test whether depressive symptoms and risky behaviours were reciprocally related over time. The data analyses were performed in three stages.

First, I assessed the validity of the measurement model for the latent variable measuring depression. I evaluated the goodness-of-fit using multiple indices, including one absolute fit index (the Root Mean Square Error of Approximation, RMSEA) and two incremental fit indices (Comparative Fit Index and Tucker Lewis Index, CFI and TLI). The criteria for an acceptable fit of the model were as follows: a $RMSEA \leq 0.08$ (with $RMSEA \leq 0.5$ indicating a close fit), a $CFI \geq 0.90$, and $TLI \geq 0.9$ (Hu & Bentler, 1999).

Second, I tested a cross-lagged structural equation model (SEM) to analyse the relationship between depressive symptoms and each type of risky behaviour. I ran three separate SEM models: depression and adolescent pregnancy (Model 1), depression and smoking (Model 2), and depression and alcohol (Model 3).

Depression and risky behaviours were allowed to be correlated at baseline, as well as the error terms associated with these at later time points. Error terms of the same items assessed on different occasions were also modelled as correlated (e.g., item 1 of the CES-D measured on all three waves were correlated). Cross-lagged effects were constrained to be equal across time. I performed a sensitivity analysis for unconstrained models where cross-lagged effects were not constrained to be equal. I found that constraining paths did not significantly weaken the fits for any of the three models and thus kept the constraints for the parsimony of the models. The path diagram for Model 2 (depression and smoking) is depicted in Figure 4.1.

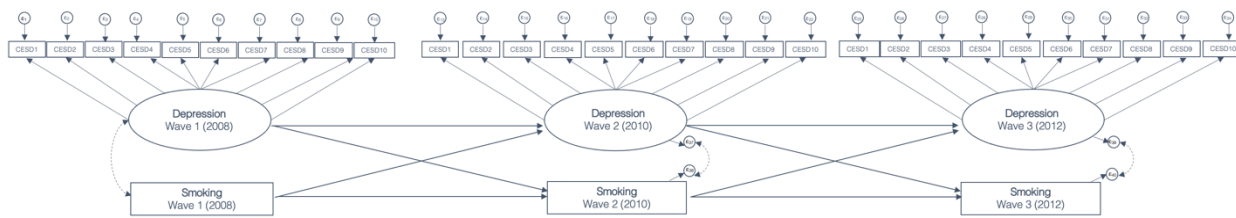


Figure 4.1 Path diagram for Model 2 (depression and smoking)

Note: Ellipses represent unobserved latent variables, and rectangles represent observed variables. Circles represent error residuals. Straight arrows capture direct effects (regression coefficients), and curved, dashed arrows account for bidirectional 'correlational' relationships. Error terms of the same items assessed on different occasions were modelled as correlated but omitted from the diagram. Sex, age, years of education, and monthly expenditures are omitted from the diagram but considered as possible confounders in the estimation of the model. The same model was fitted to study the relationships between depression and alcohol and depression and teenage pregnancy.

Third, I examined whether the magnitude of the coefficients changed depending on an individual's socioeconomic status. I relied on South Africa's food poverty line, defined as the level of consumption below which individuals cannot purchase sufficient food to provide them with at least 2,100 kilocalories per person per day. The value of the food poverty line was R561 per person per month in 2019 (which corresponds to £30 in that same year) (Stats SA, 2019). I created a binary variable equal to 1 if the individual's monthly income was below the food poverty line.

All the models were adjusted for baseline covariates and estimated using the maximum likelihood estimation method. I took into account NIDS' survey design and adjusted the estimation by poststratification weights and applied robust standard errors. I followed standard procedures for estimating SEM models with complex survey data and assessed model fit using two indices: Coefficient of Determination (CD) and the Standardized Root Mean Square Residual (SRMR) (with values <0.08 indicating a good model fit) (Bollen et al., 2013; Hu & Bentler, 1999).

All effects are reported as standardised regression coefficients, allowing meaningful comparisons across models. All analyses were conducted using Stata/MP 14 (StataCorp, 2015).

RESULTS

Table 4.1 shows the main descriptive statistics across all three waves. Female respondents made up a slightly higher proportion of the sample (57%). The average age across the three waves was 19.3 (Wave 1), 21.4 (Wave 2), and 23.3 (Wave 3). Most of the sample was Black (90%), followed by Coloured (9%), Asian/Indian (1%), and White (0.5%). Levels of education were relatively high: 96% of the sample attained

primary, and 38% had achieved secondary by wave 3. Most adolescents were single, lived with several household members, and less than a third were employed by wave 3. Monthly household expenditure per capita was low, with 42% of the sample living below South Africa's 'food poverty line' in Wave 1.

Table 4.1 Sociodemographic characteristics

	Wave 1 (2008)	Wave 2 (2010)	Wave 3 (2012)
Female	56.6%	56.6%	56.6%
Age (range)	19 (13 – 24)	21 (15 – 27)	23 (17 – 28)
Married	3.6%	4.6%	7.8%
Lost a parent	38.2%	42.9%	50.1%
Employed	13.9%	17.1%	29.3%
Enrolled in education	60.9%	39.2%	21.0%
Years of education	9.5	10.1	10.5
Household size	6.1	6.4	5.8
Monthly household income per capita (in rands)	739	875	1146
Share below food poverty line	42.4%	42.1%	27.4%

Note: Total sample size: 2,368. All variables are binary variables except age, years of education, household size, and monthly household income per capita. Employment includes full-time and part-time work, self-employment, casual work, and work on their plot or garden. The food poverty line is defined as the amount of money that an individual will need to afford the minimum required daily energy intake. Using South Africa CPI index, income was adjusted for monthly inflation (base of 2010).

The average score, prevalence of high depressive symptoms, and incident depression across all waves are shown in Table 4.2. Overall, the average score remained relatively stable over time. To estimate the prevalence of high depressive symptoms, I dichotomised the total score using a cut-off of ≥ 10 , consistent with previous studies (Andresen et al., 1994). The overall prevalence was highest at Wave 1, with more than a quarter of the sample scoring above the cut-off. The average prevalence of high depressive symptoms over the three waves was 23%. This prevalence is high compared to estimates from LMICs, which are scarce and highly variable (Yatham et al., 2018). It is also significantly higher than that found in nationally representative samples in high-income countries, with point prevalence ranging from 1% to 6% (Costello et al., 2003; Ford et al., 2003; Kessler & Walters, 1998; Lewinsohn et al., 1998). However, most of these studies measured depression using standardised diagnostic interviews (rather than rating scales such as the CES-D, which tend to elevate prevalence compared to rates based on diagnostic criteria) (Levis et al., 2019).

Table 4.2. Depressive symptoms: score, prevalence, incidence

	Wave 1 (2008)	Wave 2 (2010)	Wave 3 (2012)
CES-D average score (standard deviation)	7.12 (4.2)	6.56 (3.9)	6.58 (4.1)
Prevalence of high depressive symptoms	26.6%	19.5%	22.4%
Incidence	-	14.0%	17.1%

Note: Total sample size: 2,368. The prevalence of high depressive symptoms was calculated using a cut-off of 10 in the short version of the CES-D.

More than half of the sample (53%) were depressed (i.e., ≥ 10 on CES-D) on at least one assessment occasion over the three-wave period, and 12% were depressed on at least two occasions. Distributions of the CES-D scores for each year are presented in Figure A4.1 in the appendix, showing a right-skewed distribution.

On average, poorer and relatively older adolescents were more likely to be depressed (p -value <0.05). Contrary to what is often reported, I found no statistically significant difference in the prevalence of depression between males and females.

Table 4.3. Prevalence of risky behaviours over time

	Wave 1 (2008)	Wave 2 (2010)	Wave 3 (2012)
Share of females who are adolescent mothers (n=1,341)	35.7%	54.6%	67.5%
Average number of children (std. dev)	0.45 (0.7)	0.77 (0.8)	1.02 (0.9)
Share that smokes cigarettes	9.8%	10.5%	13.9%
Average cigarettes per day (std. dev)	0.57 (2.6)	0.66 (2.6)	0.89 (2.8)
Share that drinks alcohol	19.8%	22.5%	33.1%
Average standard drinks (std. dev)	0.43 (1.2)	0.48 (1.2)	0.77 (1.5)

Table 4.3 shows the prevalence of risky behaviours over time. Adolescent pregnancy was relatively common: more than a third of females had given birth to a child in Wave 1. Overall, 14% of the sample smoked, and a third drank alcohol by wave 3. There were significant differences by sex, with males being more likely to smoke and drink (Figure A4.2 in the appendix). These prevalence rates were lower than those found in the South African Youth Risk Behaviour Survey, a cross-sectional national prevalence study among secondary school students (21% smoked and around half drank alcohol) (Department of Health, 2003). On average, poorer and relatively older adolescents were more likely to engage in risky behaviours.

Cross-sectionally, all three types of risky behaviours were positively correlated, particularly smoking and drinking ($\rho=0.4$). Overall, there was a weak correlation between depressive symptoms and risky behaviours within each wave ($\rho=0.1$) (Table A4.1 in the appendix).

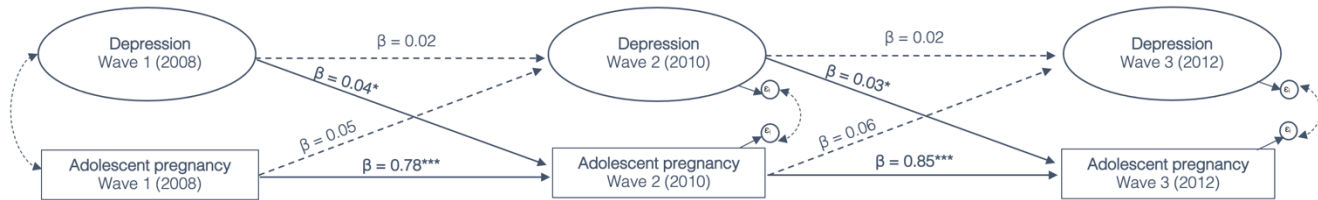
Table 4.4. Fit indices for the measurement model

	RMSEA	CFI	TLI
Depressive symptoms (using CES-D 10 items)	0.06	0.81	0.78
Depressive symptoms (using CES-D 8 items) *	0.04	0.92	0.91

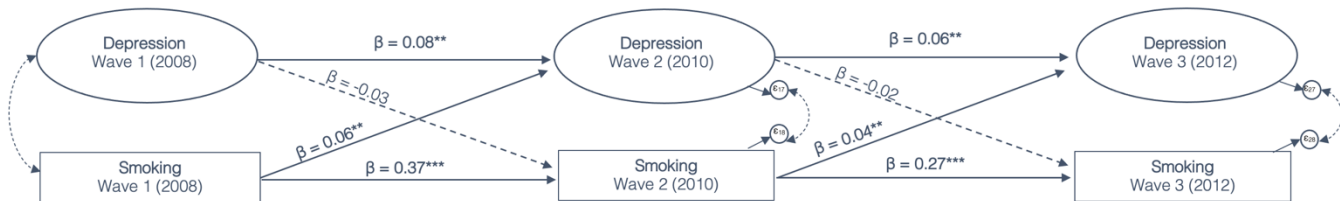
Note: Sample size=2,368. RMSEA= Root Mean Square Error of Approximation; CFI=Comparative Fit Index; TLI=Tucker Lewis Index. *The two positively worded items of the CES-D ("I felt hopeful about the future" and "I was happy") were excluded.

Table 4.4 presents the model fit indices for the measurement model. The indices suggest an inadequate model fit, with CFI and TLI below the criteria for acceptable fit. One possible reason is that the two positively worded items ("I felt hopeful about the future" and "I was happy") do not perform adequately in this sample. Both items exhibit a weak correlation with the rest of the items and – of even more concern – in the wrong direction (e.g., feeling hopeful was positively correlated with feeling depressed). This has been previously noted in a study by Lund and Cois (2018), which also used NIDS data to construct a latent variable measuring depression (Lund & Cois, 2018). Given this, both of these items were excluded from the measurement model, which resulted in an adequate fit. All factor loadings were highly significant ($p\text{-value}<0.001$), with standardised path estimates ranging from 0.32 to 0.70 for all CES-D items across the three-wave period.

Model 1. Depression & Adolescent Pregnancy (females only; n=1,297)



Model 2. Depression & Cigarette Smoking (n=2,209)



Model 3. Depression & Alcohol use (n=2,231)

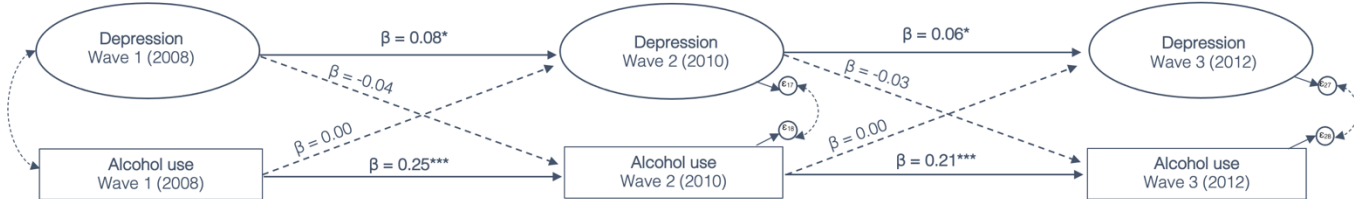


Figure 4.2 Standardised structural model

Note: β = Standardised linear regression coefficient. The stars represent statistical significance as follows: * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$. Solid lines are statistically significant, while dash lines represent nonsignificant pathways. Ellipses and rectangles represent unobserved latent and observed variables, respectively. Circles represent error residuals. Straight arrows capture direct effects (regression coefficients), and curved, dashed arrows account for bidirectional 'correlational' relationships. Relationships between depression (latent variable) and the eight categorical indicators are omitted from the diagram but considered in the measurement model. Similarly, age, years of education, and monthly expenditures are omitted from the diagram but considered as possible confounders in the estimation of the model. Sex was also introduced in Model 2 and Model 3 as a potential confounder.

Results from the structural equation model are shown in Figure 4.2. Table A4.2 in the appendix shows the same coefficients expressed in units of standard deviations, along with standard errors, statistical significance, and fit indices. The model fit indices suggest an adequate model fit (SRMR=0.04, CD=0.9 for all three models). Four results stand out.

First, I found relatively high temporal stability in depression and risky behaviours over the three waves. That is, the future values of these variables were largely predicted by the values in the previous time points. For example, someone who smoked in Wave 1 had a 40% probability of also being a smoker in the following wave (Model 2). Second, the cross-lagged path between smoking and subsequent depression was positive and significant, although effect sizes were relatively small in magnitude ($\beta \leq 0.1$). Third, the association between depression and risky behaviours at the following time point was positive and significant for adolescent pregnancy, yet again with relatively small effect sizes. Fourth, I did not find any cross-lagged effects between depression and alcohol use in either direction.

To further explore the relationship between depression and risky behaviours, I examined whether the magnitude of the coefficients changed depending on an individual's poverty status at Wave 1. Overall, I found higher temporal stability in risky behaviours for adolescents living below the food poverty line. For example, a poor adolescent who smoked in Wave 1 had a 50% probability of also being a smoker in the following wave (vs 30% for non-poor adolescents). Similarly, a poor adolescent who drank alcohol in Wave 2 had a 30% chance of drinking in the next wave (vs 10% for non-poor adolescents). I did not observe any statistically significant difference in the cross-lagged effects in any of the three models (Table A4.3 in the appendix).

CONCLUSION

This study aimed to further clarify the nature of the relationship between depression and risky behaviours. To reach this objective, I used data from a large nationally representative cohort study of adolescents in South Africa. NIDS' waves of data collection include detailed data on depressive symptoms, different types of risky behaviours and other health and socioeconomic outcomes over time, making this dataset the first of its kind in a low- and middle-income country. The relationship between depressive symptoms and risky behaviours was estimated using structural equation modelling. This flexible and powerful approach allows the inclusion of latent (unobserved) variables into the model and simultaneous estimation of all the relationships between variables.

The results from this chapter suggest that the direction of effect between depression and risky behaviours varies between different types of risky behaviour. In particular, I found that smoking predicted future depression and that depression predicted subsequent adolescent pregnancy. However, the effect sizes for both these associations were relatively small in magnitude (less than 0.1 standard deviations). In contrast to previous studies and to the findings from Chapter 3, I did not find any cross-lagged effects between depression and alcohol use in

either direction. Lastly, I found high stability of depression and risky behaviours over time, and this was higher for adolescents living below the poverty line. This suggests that adolescents from low-resource settings who engage in risky behaviours are more vulnerable to suffering the adverse consequences of risky behaviours in the long-term.

This study has at least three limitations. First, this chapter relies on a non-experimental design. As such, the estimates cannot be interpreted as proof of the presence or absence of causal relationships between depressive symptoms and risky behaviours. Issues like omitted variable bias and mismeasurement of variables could have resulted in biased estimates. For example, recall or reporting bias could have affected self-reported measures of depression and risky behaviours. This might explain why I found a lower prevalence of some risky behaviours compared to other national surveys conducted with adolescents in South Africa (Department of Health, 2003). To mitigate the risk of confounding, I controlled for important variables identified in the literature as predictors of depression and risky behaviours (sex, age, education, socioeconomic status). Further, the repeated measure design allowed me to establish a temporal sequence between the variables of interest, minimising the possibility of reverse causality. While this chapter was not intended to establish causality, it provides information about some conditions that are necessary to determine causality (e.g., the strength of the temporal relationship and determination of temporal precedence).

Second, the positively worded items of the CESD-10 did not perform adequately in this sample, which led me to exclude these items from the structural equation model. This was previously noted in a previous study, which also used NIDS data to construct a latent variable measuring depression (Lund & Cois, 2018).

Third, the length of time between survey waves (two years) might have reduced the chance of detecting a true effect between the variables of interest. This long gap is especially problematic in this sample, given the many changes that occur during adolescence (Sawyer et al., 2012). Depression and risky behaviours are known to affect each other in the short term, but these effects might not last in the long term.

In conclusion, and considering these limitations, a definitive conclusion on the direction of effect between depression and risky behaviours cannot be made. The results from this chapter suggest that the direction of effect might differ depending on the type of risky behaviour, with potentially different mechanisms at play. More longitudinal studies of adolescents with higher frequency data are needed to shed light on the complex relationship between depression and risky behaviours. An enhanced understanding of possible mediators and moderators in this

association is essential to develop more targeted and effective interventions. Lastly, and given the high levels of temporal stability observed in the study sample, our findings underscore the importance of early screening for depression and risky behaviours among adolescents to disrupt, if not prevent, a negative spiral of worsening outcomes over time.

Chapter 5. Depression, risky behaviours, and executive function: testing a mediation model³

Chapter in context

Background. The previous chapters found that depression predicts future engagement in risky behaviours. An important next step is to explore the potential mechanisms by which depression may influence engagement in risky behaviours. Executive function (EF) is one potential mechanism that has recently received increasing attention. No study to date has explored the relationship between depression, EF, and risky behaviours using a cohort study of adolescents in a LMIC context.

Objectives. This chapter used data from a six-wave cohort study of female adolescents in rural South Africa to:

- (5) Explore the extent to which persistent depressive symptoms predict future EF; and
- (6) Examine whether the relationship between depressive symptoms and risky behaviours is mediated through EF.

Findings and implications. Persistent depressive symptoms over a four-year period were negatively associated with EF in the following year, with the largest effect sizes observed for working memory. Results from the longitudinal mediation model showed that EF did not mediate the association between depression and risky behaviours, suggesting that other mediators may be at play. The findings of this chapter suggest that more attention should be directed to the association between depression and EF. Specifically, more research is needed to understand how EF deficits may arise, and the role that this may play in predicting treatment response and other long-term outcomes.

³ This chapter has been adapted from the following papers:

Pozuelo, J. R., Kilford E.J. (2021). Adolescent Neurocognitive Development in Western and Sub-Saharan Africa. *Tropical Medicine & International Health*, 26(11), 1333-1344.

Pozuelo, J. R., Stein, A., Mahmud, M., Kahn, K., Pettifor, A., Blakemore, S.J. (*in preparation*). Examining the relationship between depressive symptoms, executive function, and risky behaviours: testing a mediation model in a cohort study of adolescents in Africa.

INTRODUCTION

The previous chapters found that depression predicted future engagement in risky behaviours among adolescents in LMICs (also published in Pozuelo et al., 2021). The combination of depression and risky behaviours might lead some young people down a path of self-harming behaviours with potentially lasting consequences for their health and overall wellbeing (Steinberg, 2007). Adolescents in LMICs might be particularly vulnerable given the overburdened healthcare sector and poorly funded social protection systems (Ortiz-Ospina & Roser, 2020; WHO, 2018).

With the relationship between depression and risky behaviours among adolescents in LMICs established, an important next step is exploring potential mechanisms by which depression may influence risky behaviours. Two types of mechanisms are important: mediators and moderators. Mediators are intermediate factors that explain the relationship between the independent variable (depression) and the dependent variable (risky behaviours). Moderators modify the strength or the direction of this relationship (Kraemer et al., 2001). Identifying possible moderators and mediators allows moving beyond questions of associations to addressing more nuanced issues such as what are the most effective interventions, under which set of circumstances, and for whom (Kazdin, 2007).

Executive function (EF) is one potential mechanism that has recently received increasing attention. EF is a broad umbrella term that describes the higher-level cognitive processes that allow us to control and coordinate our thoughts and behaviour. These processes form the building blocks of our everyday behaviours and are associated with various social and economic outcomes (Diamond, 2013). EF is often defined in terms of three core domains: (i) *working memory*: the ability to hold and manipulate information; (ii) *inhibition*: the ability to exercise self-control and resist temptations; (iii) and *shifting*: the ability to adapt quickly and flexibly to new circumstances (Miyake et al., 2000). Together, these processes enable individuals to sustain attention, regulate emotion, consider the consequences of different behaviours, and plan future actions.

The relationship between depression, EF, and risky behaviours may be particularly relevant during adolescence, given the cognitive changes that occur during this time. EF, and the brain regions that support it, continue to develop throughout adolescence, with prefrontal and parietal cortices being the latest to mature (in the mid-twenties) (Luna et al., 2010, 2015; Tamnes et al., 2017). This development occurs in the context of parallel developments in other neurocognitive systems, such as social cognitive ability and motivational-affective processing (Kilford et al., 2016). It has been proposed that the continued development of

these neurocognitive systems might play a role in the progression of depression and risky behaviours during adolescence (Casey et al., 2008; Davey et al., 2008; Ross et al., 2016; Spinella, 2007; Steinberg, 2008).

While the exact neurocognitive mechanisms underlying depression and risky behaviours are not fully understood, evidence suggests that EF may be a possible mechanism in the relationship between depression and risky behaviours. This hypothesis is based on two findings. First, depression has been associated with poor EF, with similar effect sizes across the three EF domains (Cohen's d ranged from $d=0.32$ - 0.97) (Snyder, 2013). EF impairments are more significant in patients with more severe depression and persist even in patients whose depressive symptoms have remitted (Rock et al., 2014). While most of the evidence comes from studies with adults, similar results have been found among adolescents (Baune et al., 2014; Kyte et al., 2005).

Second, poor EF predicts engagement in risky behaviours. A cohort study tracking 1,000 individuals in Dunedin, New Zealand from birth to early midlife showed that individuals with lower inhibitory control at age 3 were more likely to start smoking at an earlier age, drop out of school, become unplanned teenage parents, and be convicted of criminal offence three decades later (odds ratios ranged from 1.7 to 2.3) (Moffitt et al., 2011). Other observational studies found similar results (Brock et al., 2011; Chabris et al., 2008; Gray-Burrows et al., 2019; Lejuez et al., 2003; Miller et al., 2011; Reynolds et al., 2019; Robson et al., 2020; Ross et al., 2016; Sutter et al., 2013). Taken together, these two findings suggest that EF may be a candidate mediator in the relationship between depression and risky behaviours.

The evidence exploring the relationship between depression, EF, and risky behaviours is scarce and comes primarily from studies conducted with adolescents in high-income countries. Experimental studies evaluating integrated treatments for co-occurring depression and risky behaviours have suggested that EF may be a mediator underlying the changes in symptoms and behaviour (Babowitch & Antshel, 2016; Rao, 2006). Further, three large-scale randomised controlled trials in Chicago found that a program that delivered Cognitive Behavioural Therapy reduced risky behaviours such as crime and school dropout. Among the different mechanisms of change tested, the authors found that the program helped adolescents exercise EF and develop emotional regulation strategies (Heller et al., 2017). Another experimental study found that reward processing partially mediated the effect of the treatment on depressive symptoms and substance use (Boger et al., 2014).

Findings from observational cohort studies have reached similar conclusions. A cohort study of over 1,000 adolescents in Arizona and Pennsylvania found that depressive symptoms predicted future crime

and that this relationship was partially mediated by self-control (Remster, 2013). Another cohort study conducted in Texas found that adolescents with high depressive symptoms were more likely to use marijuana, with evidence that impulsiveness moderated this pathway (Wasserman et al., 2021). These studies focused exclusively on one EF domain (inhibition), which was often measured using self-reported scales rather than at the behavioural level.

The evidence from studies exploring the relationship between depression, EF, and risky behaviours among adolescents in LMICs is limited and suffers from at least three limitations, which this chapter seeks to address. First, most studies on adolescents in LMICs have either looked at each factor individually (depression, EF, or risky behaviours) or a combination of two. Overall, these studies draw two conclusions: adolescent depression predicts future risky behaviour engagement, and lower executive function is associated with risky behaviours (Pozuelo et al., 2021; Rosenberg et al., 2018; Rowe et al., 2021a; Spies et al., 2018; Wray et al., 2020). No study to date has looked at all three factors combined.

Second, many studies conducted in LMICs are cross-sectional and have small sample sizes (Agardh et al., 2012; Bajunirwe et al., 2018; Dibaba et al., 2013; Kimbui et al., 2018; Kunzweiler et al., 2018; L'akoa et al., 2013; Peltzer, 2004; Smit et al., 2006; Taşkıran et al., 2017; Wilson et al., 2012). Thus, they often have low statistical power and cannot establish temporal precedence between variables.

Third, most studies of cognition with adolescents in LMICs have mainly focused on individuals with neurocognitive deficits due to diseases (e.g., HIV, malaria) and relied on measures of fluid intelligence (such as IQ tests or academic performance) as a proxy for EF (Pozuelo & Kilford, 2021). To date, few cohort studies have looked at the effect of depression on the different EF domains using a comprehensive cognitive test battery.

Given this research gap, this chapter aims to understand the complex relationship between depression, EF, and risky behaviours in a LMIC context. Exploring this relationship is particularly important among adolescents in LMICs given the high burden of depression (particularly among females) and the fact that EF is more likely to be compromised in low-resource settings as a result of high adversity exposure (Evans & Kim, 2013; Thapar et al., 2012; Wray et al., 2020). Further, interventions tackling risky behaviours, such as education campaigns and rehabilitation programmes, are scarce in many LMICs, making adolescents even more vulnerable to the negative impacts of risky behaviours (de Walque, 2013).

This chapter used data from a six-wave cohort study of female adolescents in rural South Africa to test two hypotheses. First, I explored the extent to which depressive symptoms predict future EF and investigated potential differential effects across each EF domain (working memory, inhibition, and shifting). I hypothesised that depressive symptoms would be associated with lower EF scores, with similar effect sizes across domains, as previously reported (Snyder, 2013).

Second, I examined whether the relationship between depressive symptoms and risky behaviours was mediated through EF. I hypothesised that depressive symptoms would be associated with poorer EF, which, in turn, would result in higher risky behaviour engagement. As part of this second hypothesis, I also tested a moderated mediation model with three moderators of interest: poverty, number of friendships, and parental support. These candidate moderators were selected as previous studies have demonstrated them to be associated with depression, EF, and risky behaviours (Blakemore, 2019; Cacioppo et al., 2010; Coyne, 1976; Delay et al., 2013; Evans & Kim, 2013; Hames et al., 2013; Lund et al., 2010; Platt et al., 2013; Thapar et al., 2012; Tian et al., 2021; Wray et al., 2020). I hypothesised that the association between the variables of interest might be stronger among individuals living in poverty, socially isolated, and with less parental support.

METHODS

Participants and study setting

Data were drawn from a longitudinal cohort of female adolescents living in Mpumalanga province, in rural northeast South Africa (same cohort study that was used in Chapter 2). This data was collected as part of the *Swa Koteka* study, a randomised controlled trial which aimed to measure the effect of providing cash transfers on the risk of acquiring HIV (Pettifor et al., 2016a; Pettifor et al., 2016b).

A description of the study setting and study participants can be found in Chapter 2, and a detailed description of the study procedures can be found in the main trial publication (Pettifor et al., 2016a). In summary: the study enrolled 2,533 adolescent females aged 13 to 20 years attending high school in the study area. Participants completed the baseline assessment in 2011, and five follow-up waves were conducted after that (a total of six waves). The median time lapse between waves was 1.13 years.

The study setting is rural with poor infrastructure and is characterised by high poverty levels, unemployment, outmigration, and HIV

prevalence (27% of adolescent women aged 20-24 years are HIV positive) (Gómez-Olivé et al., 2013; Sartorius et al., 2014).

Executive function was measured once during the six-wave cohort study in 2015 (Wave 5). This was done using the Oxford Cognitive Screen – Executive Function (OCS-EF) software, which has been validated in this population and context (Rowe et al., 2021b). The tasks measured different EF domains and included stimuli adapted for the cultural context (e.g., using African American women's faces and images of common fruits and vegetables). A total of 1,057 adolescents completed the cognitive assessments, which is the sample I focus on in the current study.

Institutional Review Board approval for the original cash transfer study was obtained from the University of North Carolina at Chapel Hill, the University of the Witwatersrand Human Research Ethics Committee, and the Provincial Department of Health's Research Ethics Committee. Approval for the secondary analysis for this study was obtained from the Oxford Tropical Research Ethics Committee (OxTREC).

Measures

Persistent depressive symptoms (independent variable, measured from Wave 1 to Wave 4). Depressive symptoms were determined at all waves, although different measures were used. Depressive symptoms at Wave 1 were measured with the short form of the Children's Depression Inventory (CDI-S), a 10-item scale designed to assess depressive symptoms among children and adolescents (Kovacs, 2003). The reduced scale has been previously used with adolescents in South Africa (Cluver et al., 2007; Sharer et al., 2015). The measure had acceptable internal consistency reliability ($\alpha = 0.7$). I dichotomised the total score using a cut-off point of ≥ 7 to classify participants at risk of depression (Binagwaho et al., 2016).

Depressive symptoms from Wave 2 onwards were assessed using the Centre for Epidemiologic Studies Depression Score (CES-D), a 20-item measure designed to measure depressive symptomatology in the general population (Radloff, 1977). The CES-D has been validated for adolescents in various settings, including South Africa (Baron et al., 2017; Pretorius, 1991). The measure had good internal consistency reliability ($\alpha = 0.8$). I dichotomised the total score of the CES-D using a cut-off of ≥ 16 to identify individuals at risk for clinical depression (Weissman et al., 1977).

I constructed the independent variable – which I defined as '*persistent depressive symptoms*' by counting how many times an individual was above the cut-off over the first four-wave period (i.e., from Wave 1 to Wave 4). The score ranged from 0 (never depressed) to 4 (depressed at

every wave). I only included individuals with data on depression in all four waves to construct this measure ($n=647$).

Executive function (latent mediator variable, measured at Wave 5). EF was measured using a cognitive test battery administered via tablets by trained fieldworkers and was implemented in Wave 5. The battery was designed to be culturally unbiased, brief (~30 mins), and ensured an implementation that was standardised across all participants. The battery included seven different tasks: two tasks measured shifting (geometric trails task and visuospatial rule-finding task), two tasks measured inhibition in affective contexts (Iowa Gambling Task and Emotional Go/No-go task), and three tasks measured working memory (digit recall task, figure recall task, and selection task). A description of each task and indicator included in the model can be found in Table A5.1 in the appendix. All indicators were constructed so that a higher score indicated better performance in each task.

Risky behaviours (latent dependent variable, measured at Wave 6). The dependent variable was risky behaviour engagement at Wave 6. I included different risky behaviours, including having multiple partners, engaging in unprotected sex, transactional sex (i.e., exchange of money, favours, or gifts for sexual relations), binge drinking, and drunk sex (seven variables in total). A detailed description of the specific questions and how these measures were constructed can be found in Table A5.2 in the appendix.

Moderators (measured at Wave 1). I focused on three candidate moderators measured at Wave 1. These included poverty status (=1 if the individual's monthly income was below \$1.90 per day in international dollars), number of close friendships, and perceived parental involvement. A description of the specific questions and how these measures were constructed can be found in Table A5.3 in the appendix.

Covariates (measured at Wave 1). I controlled for a range of sociodemographic characteristics typically associated with risky behaviours: age, education level, and household socioeconomic status (an asset index constructed from information on ownership of a range of durable goods). I also controlled for the study arm and anxiety, which was measured using a short version of the Revised Children's Manifest Anxiety Scale (Reynolds & Paget, 1983). A description of the specific questions and how these measures were constructed can be found in Table A5.3 in the appendix.

Statistical model

I used structural equation modelling to test both hypotheses. The analysis was performed in three stages.

First, as part of Model 1, I examined the extent to which persistent depressive symptoms over Waves 1 to 4 were associated with worse EF at Wave 5. I fitted a three-factor measurement model of EF to explore differential effects by each domain (working memory, inhibition, shifting). All three factors were allowed to be correlated with each other. I hypothesised that depressive symptoms were associated with lower EF scores, with similar effect sizes across EF domains. The conceptual model for this model is presented in Figure 5.1

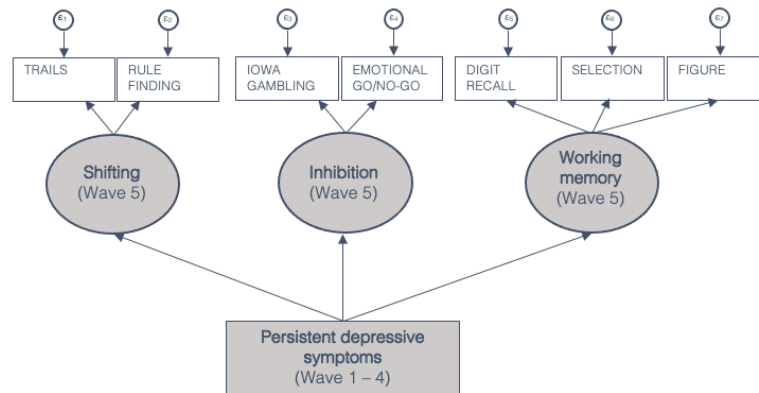


Figure 5.1. Path diagram for Model 1

Association between persistent depressive symptoms and EF domains

Note: Ellipses represent unobserved latent variables, and rectangles represent observed variables. Circles represent error residuals. All factors were allowed to be correlated with each other (not shown in the diagram).

Second, as part of Model 2, I specified a longitudinal mediation model to explore whether EF mediated the relationship between depressive symptoms and risky behaviours. The longitudinal nature of the study allowed me to establish a temporal ordering of variables, where depressive symptoms over the first four waves (Wave 1 to 4) preceded both EF assessment (Wave 5) and risky behaviours (Wave 6).

I modelled a latent model representing executive function, with all seven tasks loading into a single factor (I included one indicator per task). Similarly, I defined a latent variable measuring risky behaviours, with all seven measures loading into a single factor. I allowed the error terms of binge drinking and drunk sex to be correlated. As part of this model, I included the baseline value of the confounders listed above. I hypothesised that depressive symptoms would be associated with poor EF, which, in turn, would result in higher risky behaviour engagement. The conceptual model is shown in Figure 5.2.

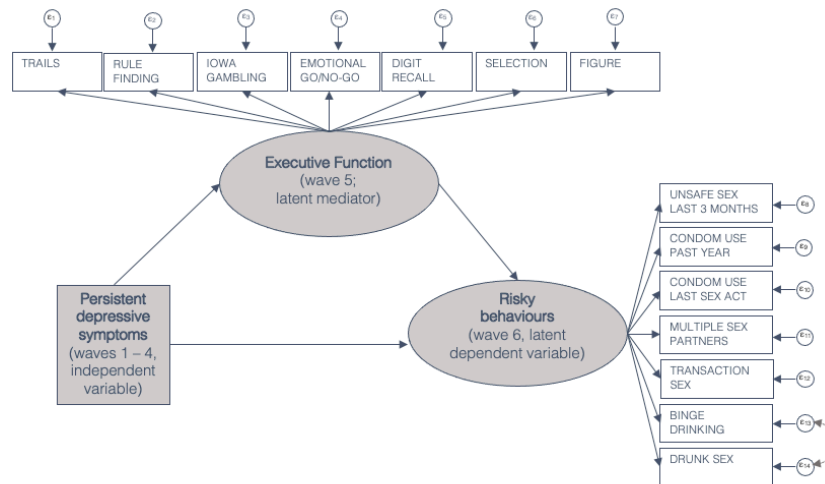


Figure 5.2. Path diagram for Model 2
Association between persistent depressive symptoms, EF, and risky behaviours

Note: Ellipses represent unobserved latent variables, and rectangles represent observed variables. Circles represent error residuals. Error terms of binge drinking and drunk sex were allowed to be correlated. Age, education level, household socioeconomic status, study arm, and anxiety are omitted from the diagram but considered as possible confounders in the estimation of the model.

Third, I tested a moderated mediation model with three independent moderators of interest: poverty, number of friendships, and parental support. I specified a first-stage moderation, whereby I explored the moderation effect of each of these variables on the path from the independent variable (depressive symptoms) to the mediator (EF). I included the same covariates as in Model 2. I hypothesised that the direct effect of depressive symptoms on executive function might be stronger among individuals living in poverty, those who are socially isolated, and those with less parental support. The moderated mediation model for poverty is depicted in Figure 5.3 (similar models were run for the other two moderators of interest).

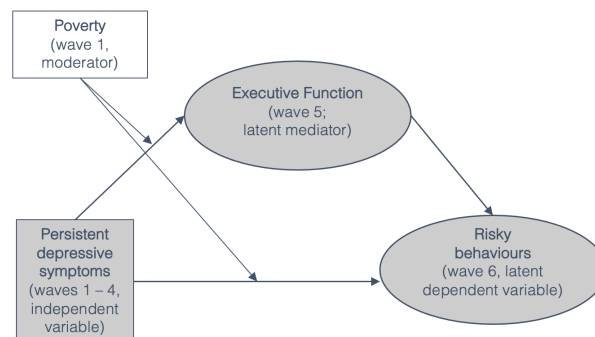


Figure 5.3. Path diagram for Model 3
Moderated-mediation model for poverty

Note: Ellipses represent unobserved latent variables, and rectangles represent observed variables. Circles represent error residuals. Error terms of binge drinking and drunk sex were allowed to be correlated. Age, education level, household socioeconomic status, study arm, and anxiety are omitted from the diagram but considered as possible confounders in the estimation of the model.

I conducted a series of sensitivity analyses to examine the robustness of the results. First, I performed cross-lagged analyses using structural equation modelling to investigate the directionality of effects between depression and EF. More specifically, I investigated if depressive symptoms at Wave 4 predicted poorer EF at Wave 5 or if poor EF at Wave 5 increased vulnerability to depression at Wave 6. I used the CES-D score as a measure of depression. Second, I ran the mediation model (Model 2) without covariates. Third, I ran Model 2 only for the control group ($n=537$ individuals who did not receive the cash). Fourth, I added depression severity at Wave 5 as a covariate. This allowed me to test whether persistent depressive symptoms in Waves 1 – 4 predicted EF at Wave 5 independent of the CES-D score at Wave 5. Fifth, I ran Model 2 excluding Wave 1, which measured depressive symptoms using a different scale than that in Wave 2 to 4.

To correct for missing values within the data, I employed the full information maximum likelihood estimation method, which is more efficient than other missing data methods such as listwise deletion or mean substitution (Allison, 2003). Under this method, missing values are not imputed or replaced; instead, it uses all available data to estimate the maximum likelihood estimates.

Bias-corrected bootstrapped standard errors with 1,000 replications were computed to construct the 95% confidence intervals of the indirect effect. Using bootstrapping methods to estimate the indirect (or mediating) effect has been recommended as it does not impose the assumption of normality in the sampling distribution and provides distributions of values for calculating confidence intervals around indirect effect sizes (Preacher & Hayes, 2008).

I assessed the goodness of fit of the models using a range of indices, including the model chi-square (χ^2), Root Mean Square Error of Approximation (RMSEA), Comparative Fit Index (CFI) and Tucker Lewis Index (TLI). The criteria for an acceptable model fit were as follows: a $RMSEA \leq 0.08$ with a non-significant p-close; and a CFI and TLI > 0.90 (Hooper et al., 2007; Hu & Bentler, 1999).

All effects are reported as standardised coefficients to allow meaningful comparisons across variables. I used the following benchmark to interpret the magnitude of the effects: small (0.05–0.10), moderate (0.1–0.25), and large (> 0.25) (Mehmetoglu & Venturini, 2021). The unstandardised model estimates are shown in the appendix. All analyses were conducted using Stata/MP 14 (StataCorp, 2015).

RESULTS

This chapter included 1,057 adolescents and all six waves of data collection. By the last wave, 269 participants were lost to follow-up, resulting in an attrition rate of 25%. I tested for differential attrition across those who were followed-up and those who dropped out by regressing a range of baseline observable characteristics on an indicator variable for attrition. Results in Table A5.4 in the appendix show no statistically significant differences in depressive symptoms, risky behaviours, and all other covariates individually or jointly (F statistic=0.69) across the two groups. I could not compare EF scores since the cognitive test battery was only assessed at Wave 5. Study attrition rates in other cohort studies cite factors such as unhealthy lifestyles or psychological distress as common attrition predictors, but those do not seem to play a role in this study (Gustavson et al., 2012).

Table 5.1. Characteristics of study participants at Wave 1

	All sample (n=1,057)
Average age (range)	14.62 (13 – 20)
Average years of schooling (SD)	7.67 (0.65)
Ever repeated a school grade	28.95%
Employed	13.75%
Food insecure	31.43%
Parental death	26.89%
Median household size (range)	6 (2 – 20)
Mother without formal education	33.26%
Father without formal education	36.07%
Living below poverty line	61.74%
Close friendships (SD)	2.43 (2.41)
Perceived parental involvement score (SD)	1.15 (0.37)

Note: SD=standard deviation. Employment was a categorical variable=1 if the participant answered yes to the following question: “Did you do any work for pay or family gain, including payment in kinds such as food or housing? Food insecurity was a categorical variable=1 if the participant answered yes to the following question: “In the past 12 months, have you been worried about having enough food for you or your family”. A description of how the moderator variables (poverty status, friendships, and parental involvement) were constructed can be found in Table A5.3 in the appendix.

Table 5.1 shows the characteristics of study participants at Wave 1. The average age was 14.6 (range: 13 – 20). On average, participants had 7.7 years of schooling, and more than a quarter had repeated a school grade. The median household size was six members; more than a third of the participants’ parents had no formal education. Around a quarter of adolescents had lost a parent, and one-third had experienced food insecurity in the past year. Regarding the moderators, more than half (61.7%) lived below the poverty line and adolescents reported having around two close friendships. The perceived parental involvement score

was negatively skewed, implying that most scores tended to be on the upper side of the distribution.

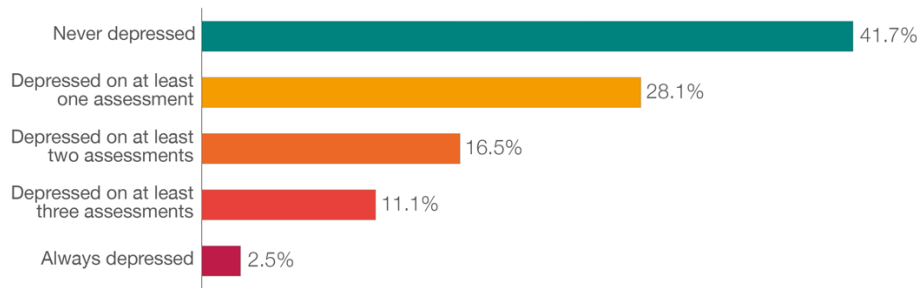


Figure 5.4. Persistent depressive symptoms over the first four waves (n=647)

Figure 5.4 shows that persistent depressive symptoms were common. By Wave 4, more than half of the sample (n=377, 58.3%) had been depressed (i.e., ≥ 16 on the CES-D) on at least one assessment occasion between Wave 1 and Wave 4. A small proportion (n=16, 2.5%) were above the cut-off in all four waves. Older adolescents with fewer years of education and higher anxiety scores were more likely to have high depressive symptoms ($p < 0.0001$). Contrary to what is often reported, I found no statistically significant difference in depressive symptoms by socioeconomic status in this population (Table A5.5 in the appendix).

Summary statistics for the EF tasks in Wave 5 are presented in Table 5.2. There were ceiling effects (negatively skewed distribution) for the trails, selection, and figure tasks. Overall, older adolescents had lower EF scores and those with more years of education performed better. These differences were statistically significant in two EF domains (switching and working memory) but not in the inhibition domain. Socioeconomic status was not associated with EF performance (Table A5.5 in the appendix).

Table 5.2. Summary statistics of EF tasks measured at Wave 5

EF task	Indicator	Mean (SD)	Median (IQR)	Range (min, max)	Shape of distribution
Trails task (n = 963)	Switch accuracy cost	0.58 (0.32)	0.57 (0.29, 0.86)	(0, 1)	Negative skew
Rule-finding task (n = 1,056)	Proportion of accurate moves	0.48 (0.23)	0.46 (0.30, 0.65)	(0, 1)	Normal
Iowa Gambling task (n = 1,057)	Net score in the last 30 trials	0.30 (0.58)	0.13 (-0.07, 1)	(-1, 1)	Bimodal
Emotional Go/No-go task (n = 1,054)	D-prime	2.11 (0.97)	2.15 (1.53, 2.77)	(-1.58, 4.87)	Normal
Digit recall task (n = 1,028)	Backwards digit span	3.62 (1.53)	4 (3, 4)	(0, 9)	Normal
Selection task (n = 1,021)	Invisible accuracy	0.73 (0.23)	0.77 (0.63, 0.9)	(-0.87, 1)	Negative skew
Figure recall task (n = 1,045)	Recall accuracy	0.79 (0.15)	0.82 (0.7, 0.9)	(0.03, 1)	Negative skew

Note: A description of each task and indicator included in the model can be found in Table A5.1 in the appendix. All indicators were constructed so that a higher score indicated better performance in each task.

Table 5.3 shows the prevalence of risky behaviours at Wave 6. Most of the sample had engaged in unsafe sex (combining all three measures into one showed that 82% of the sample had engaged in unprotected sex). Around 10% had had multiple sex partners and the same proportion engaged in sex while drunk. A few more reported engaging in transactional sex (13%) and binge drinking (17%). Older adolescents with higher anxiety and lower socioeconomic status were more likely to engage in risky behaviours (Table A5.5 in the appendix).

Table 5.3. Prevalence of risky behaviours at Wave 6

	Percent / Mean (SD)
Unprotected sex in the last 3 months (n = 788)	28.8%
General condom use with partner during last year (n = 668)	1.8 (1.4)
Condom use with partner during last sex act (n = 668)	50.9%
Multiple sex partners (n = 676)	9.6%
Transactional sex (n = 677)	12.7%
Binge drinking (n = 782)	16.6%
Drunk sex (n = 613)	9.6%

Note: A detailed description of the specific questions and how these measures were constructed can be found in Table A5.2 in the appendix.

Results of Model 1 are presented in Figure 5.5. Table A5.6 in the appendix provides the corresponding parameter estimates (unstandardised and standardised) and standard error estimates. Persistent depressive symptoms over Waves 1 to 4 were associated with worse EF at Wave 5. Keeping other factors constant, I found that a one standard deviation increase in persistent depressive symptoms was associated with a 0.25 standard deviation decrease in shifting and a 0.28 standard deviation decrease in working memory (moderate-to-large associations). The coefficient for inhibition was not significant (p -value = 0.053). This model fit the sample data reasonably well as indicated in the goodness-of-fit statistics: RMSEA = 0.035, CFI = 0.90, TLI = 0.82. The large sample size might justify the significant chi-square ($\chi^2_{15} = 34.73$).

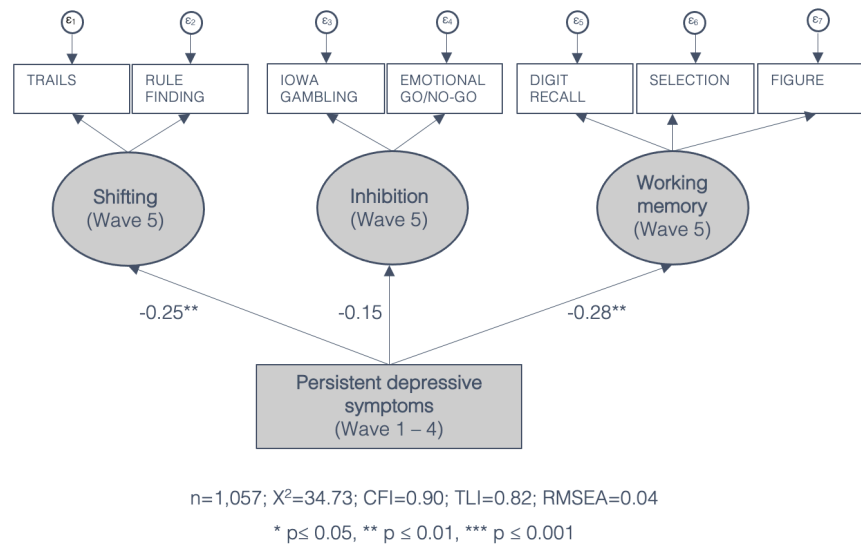


Figure 5.5. Results for Model 1
Association between persistent depressive symptoms and EF domains

Note: Ellipses represent unobserved latent variables, and rectangles represent observed variables. Circles represent error residuals. The model was estimated using the full information maximum likelihood estimation method. All effects are reported as standardised regression coefficients to allow meaningful comparisons across coefficients.

Results from the mediation model (Model 2) are presented in Figure 5.6. Table A5.7 in the appendix provides the unstandardised and standardised coefficients. The overall goodness-of-fit statistics were satisfactory (RMSEA = 0.035, CFI = 0.86, TLI = 0.83). Consistent with Model 1, I found a large and highly significant negative association between persistent depressive symptoms and the one-factor model of EF (standardised coefficient = -0.29). In addition, a one standard deviation increase in persistent depressive symptoms was associated with an increase in risky behaviour engagement by 0.17 standard deviations. However, I did not find any evidence of a mediation effect, as shown by the insignificant indirect effect for the depression $\rightarrow$ EF $\rightarrow$ risky behaviour pathway (estimate = -0.003 , 95% bias-corrected bootstrapped confidence interval = $-0.01, 0.01$).

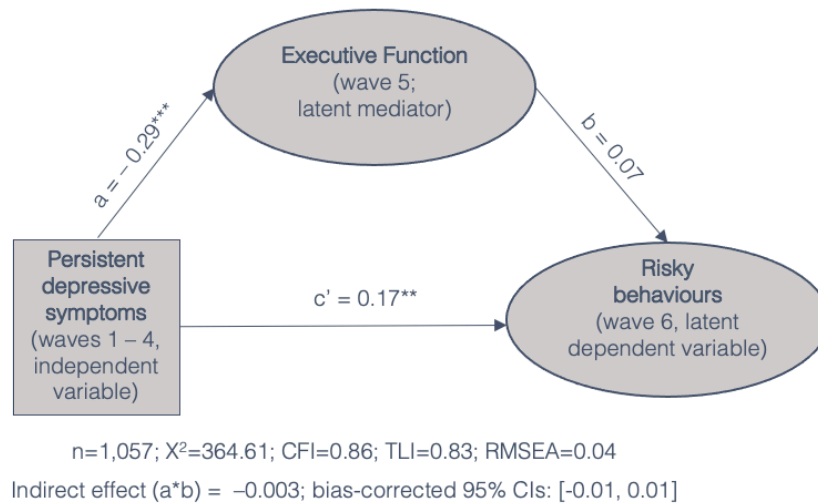


Figure 5.6. Results for Model 2
Association between persistent depressive symptoms, EF, and risky behaviours

Note: Ellipses represent unobserved latent variables, and rectangles represent observed variables. Circles represent error residuals. The model was estimated using the full information maximum likelihood estimation method. Age, education level, household socioeconomic status, study arm, and anxiety are omitted from the diagram but considered as possible confounders in the estimation of the model. All effects are reported as standardised regression coefficients to allow meaningful comparisons across coefficients.

Table A5.8 in the appendix shows the results from the moderated mediation model (Model 3). I did not find any moderating effects of poverty, friendships, or parental support. Consistent with the previous results, I found that adolescents in poverty were more likely to engage in risky behaviours and found no significant differences in EF performance. Further, the number of close friendships or parental support was not associated with EF or risky behaviour engagement.

Results for these robustness tests are shown in Table A5.9 in the appendix. In testing the directionality, I found support for a relationship running from depression to EF and not vice versa. The results and the overall study conclusions remained the same when running the model without covariates, only for the control group, and excluding Wave 1 from the analysis. I found that persistent depressive symptoms in Waves 1 to 4 predicted EF in Waves 5, independent of the depression score at Wave 5. This ruled out the possibility that depressed participants might have been less motivated to do well in the EF tasks.

CONCLUSION

This chapter had two main objectives. First, I aimed to examine the extent to which persistent depressive symptoms over four years were associated with EF in the next wave. Second, I aimed to test a longitudinal mediation model whereby I hypothesised that high

depressive symptoms would be associated with lower EF, which, in turn, would predict more risky behaviours in the following period. The results partially supported my hypotheses. Specifically, I found that persistent depressive symptoms over Waves 1 to 4 were associated with worse EF at Wave 5, with the largest effect sizes observed for working memory. However, I did not observe any mediating effect of EF on the association between persistent depressive symptoms and risky behaviours.

This is the first study to test a mediation model between depressive symptoms and risky behaviours using a large cohort of adolescents in a low-resource setting. I explored this relationship using a comprehensive and validated battery of EF tasks (Rowe et al., 2021b). The model included a range of risky behaviours instead of focusing on a single behaviour. Further, I used structural equation modelling to estimate the model, allowing me to incorporate latent variables to measure EF and risky behaviours, thus reducing bias due to measurement error (Christ et al., 2014). Structural equation modelling also enabled me to estimate all the relationships between the variables simultaneously, as opposed to the traditional series of sequential regression analyses used in mediation analyses (Baron & Kenny, 1986). This provides a more effective and direct way of modelling complex relationships between variables and testing mediation (Iacobucci et al., 2007). I used bootstrapping methods to calculate the indirect effect, which does not impose the assumption of normality in the sampling distribution (Preacher & Hayes, 2008). Further, the longitudinal design of the study allowed me to establish the temporal ordering of variables between the antecedent variable (persistent depressive symptoms), the mediator (EF), and the outcome (risky behaviours). The importance of temporal precedence when testing mediation has been emphasised, and longitudinal mediation models have been considered an essential step in advancing mediation methods (MacKinnon et al., 2013).

This chapter has several limitations. First, the use of observational data did not allow me to determine whether these associations are causal in nature. While I controlled for some important potential confounders, other unobserved variables might have influenced my results. As mentioned in the previous chapter, while the association between depression and risky behaviours is well established, it is still unknown whether the relationship is unidirectional (running from depression to risky behaviours), bidirectional (running in both directions), or the product of some third variable (Pozuelo, 2022). This exploratory study tested one possible model but did not test alternative models.

The second limitation relates to possible measurement errors. Depressive symptoms and risky behaviours were measured using self-reported measures, which may have resulted in recall or reporting bias error. However, these questions were asked using Audio Computer-

Assisted Self Interview (ACASI), where participants listened to pre-recorded survey questions through headphones and selected their responses on a tablet computer. This method has been shown to reduce reporting bias (Cullen & Mahmud, 2021). Further, depressive symptoms were measured using validated measures, which have demonstrated good psychometric properties when compared with diagnostic instruments and when used with adolescents in South Africa (Baron et al., 2017; Cluver et al., 2007; Kovacs, 2003; Pretorius, 1991; Sharer et al., 2015). Additionally, self-reported risky behaviours were positively correlated with objective measures of risky behavioural outcomes such as HIV infection (determined by administering HIV tests) and pregnancy. Related to this limitation, depressive symptoms in Wave 1 were measured using a different scale (CDI-S) than in Waves 2 to 4 (CES-D). CDI-S was again reintroduced in Waves 3 to Wave 5, allowing me to estimate the within-individual association between both measures. I found a positive and statistically significant correlation between both measures ($\rho = 0.54$, $p < 0.0001$). The same results were obtained when re-running the model excluding Wave 1 (Table A5.9 in the appendix).

Third, the time lapse between waves could have impacted the precision of my coefficient estimates. Depressive symptoms were assessed over four years during mid-adolescence (when adolescents went from 14.6 in Wave 1 to 17.6 years old in Wave 4, on average), while EF and risky behaviours were measured during late adolescence (when adolescents were 19.8 and 22 years old on average). Many biological, physical, cognitive, and social changes happen during this time, which I cannot fully capture with this cohort study. Thus, this long interval might have prevented me from finding a mediating effect. However, the attrition rate of 25% is on the low end compared to other cohort studies, and I found no significant differences across adolescents who were followed up and those who dropped out (Gustavson et al., 2012). Future research should consider using higher-frequency data to explore this relationship further.

Fourth, this chapter could not distinguish between non-affective and affective task conditions (“cool” and “hot” EF), despite the extensive literature describing a possible relationship between hot EF, depression, and risky behaviours (Carlson et al., 2013; Loewenstein & Lerner, 2003; Roiser et al., 2011; Ross et al., 2016; Schweizer et al., 2020; Steinberg, 2005; Zelazo & Cunningham, 2007). This was not possible due to the poor goodness-of-fit of the measurement model when specifying a hot-cool model (RMSEA=0.06, CFI=0.70, TLI=0.5). These results are consistent with a confirmatory factor analysis conducted with this cognitive battery, showing that the three-factor EF model had the best local and global fit compared to the two-factor hot-cool model (Rowe et al., 2021b).

Despite these limitations, this chapter has important implications. These findings suggest that adolescents with persistent depressive symptoms are at an increased risk of having lower EF. This is important given that executive functions are associated with a range of social and economic outcomes, including educational attainment, job success, higher income, social functioning, and criminal behaviour (Diamond, 2013).

The fact that I did not observe a mediating effect of EF in the relationship between persistent depressive symptoms and risky behaviours suggests that other mediators may be at play. One plausible pathway relates to how depression changes an individual's belief about oneself, their world, and their future (Beck, 1979). According to Beck's cognitive theory, individuals with depression often view themselves as hopeless, worthless, and have low self-esteem and self-efficacy, and have difficulty viewing themselves as individuals who could succeed in life. These negative self-concepts and lack of hope for the future might make an individual believe that they have nothing to lose and be more present-biased, making them more prone to engage in behaviours that feel good in the short term, possibly as a coping mechanism (Graham & Pozuelo, 2022; Khantzian, 1985, 1997). Negative self-concepts might also make an individual less assertive, and therefore more likely to succumb to peer pressure and/or less likely to stand up to a partner who demands unprotected sex. It might also make adolescents with depression more likely to affiliate with risk-taking peers (Fergusson et al., 2003). Further, the fact that not all individuals who are depressed engage in risky behaviours suggests that there are moderators (in addition to the ones I tested) that influence the strength and/or direction of this relationship.

Depression and risky behaviours often co-occur during adolescence and represent two critical – but often overlooked – public health concerns (Kessler et al., 1996; Thapar et al., 2012). It is important to understand why depressed adolescents are more likely to engage in risky behaviours than their non-depressed peers because of the adverse outcomes associated with depression and risky behaviours. This is particularly important for adolescents living in low-resource settings, which are insufficiently resourced to provide adequate care for adolescents in need. For example, less than 5% of adolescents receive any minimally adequate treatment for depression in many LMICs, and access to health promotion programmes such as rehabilitation programmes or peer support groups also remains limited (Patton et al., 2016; Thornicroft et al., 2017). Adding to the complexity, there are multiple (potentially interacting) mechanisms through which high levels of adversity might impact neurocognitive development, including poor nutrition, lack of stimulating learning conditions, and increased exposure to both physical and psychosocial environmental stressors (Evans, 2004; Fergusson et al., 2013; Johnson et al., 2016; Walker et al., 2011).

The findings of this chapter suggest that more attention should be directed to the association between depression and EF. Specifically, more research is needed to understand how EF deficits may arise, the role that these deficits may play in predicting treatment response, and in determining other long-term outcomes. Overall, this study can be viewed as a first step in exploring potential mechanisms of change in the pathway leading from depression to risky behaviours. Further cohort studies with large and diverse samples in LMICs are needed to explore this relationship in more detail. A better understanding of how different factors interact would inform policy, promote an effective allocation of resources, and guide interventions targeting adolescent health in resource-poor settings.

Chapter 6. Developing a digital intervention to deal with depression and risky behaviours

Chapter in context

Background. The previous chapters found that high depressive symptoms predict risky behaviours among adolescents in LMICs. Based on these results, treatments targeting depression may be effective at reducing both depressive symptoms and risky behaviours. Given the limited access to effective interventions in LMICs, innovative, scalable treatment delivery options are needed. Digital mental health interventions offer an unprecedented opportunity to increase access to care in LMICs. However, few interventions have been specifically developed for use or rigorously evaluated with adolescents in a rural sub-Saharan African context.

Objectives. This chapter:

- (1) Describes the user-centred development of the Kuamsha app, a gamified storytelling app designed to treat depression among adolescents in Uganda and South Africa; and
- (2) Summarises preliminary results of early user testing.

Findings and implications. The Kuamsha app was developed using multiple user-centred design methods to ensure that it was useful, culturally relevant, and usable for the targeted population. More than 170 individuals from rural South Africa and Uganda were involved in the development process. Two larger studies are currently underway to examine the intervention's feasibility, acceptability, and efficacy in reducing depressive symptoms and risky behaviours. Preliminary results of early user testing show that the Kuamsha app is acceptable in terms of usability and engagement.

INTRODUCTION

Depression is underdiagnosed and undertreated worldwide, particularly in LMICs given the very low levels of public expenditure on mental health (Kakuma et al., 2011; WHO, 2015). For example, fewer than 5% of individuals needing treatment in LMICs receive any minimally adequate treatment for depression (Thornicroft et al., 2017). Low levels of mental health literacy and high levels of stigma prevent individuals from seeking care (Alonso et al., 2008; Sorsdahl & Stein, 2010). These barriers, coupled with the devastating consequences of poverty, make adolescents in LMICs disproportionately affected by the burden of depression.

With the increase in smartphone ownership and access to the internet, digital interventions such as smartphone applications ('apps') that treat depression are a promising strategy to increase access to care in LMICs (Naslund et al., 2017; Tomlinson et al., 2013). This is particularly the case for adolescents, given that they make up the vast majority of Internet users (ITU, 2020). Digital mental health interventions offer several advantages. They have the potential to be *delivered at scale*, with low (or zero) marginal costs for each additional individual that accesses them (Muñoz, 2010; Paganini et al., 2018). They may help *overcome stigma* as individuals can access them discreetly using their device (Naslund & Deng, 2021). They are *flexible and convenient*, as users can choose when, how, and where to access them. In LMICs, where individuals might have to travel long distances to access the most proximate healthcare facility, the portability of digital technologies can save travelling time and reduce expenses for individuals with depression. They may also help reduce the pressure on already overstretched healthcare systems (Saxena et al., 2007). Digital interventions open the possibilities for more *tailored psychological treatments* and allow for a more continuous monitoring (Mohr et al., 2013). In particular, digital technologies can provide warning signs for suicide risk to enable appropriate action to be taken. Mental health apps may also *empower individuals* by making them feel more in control of their health and raise *societal awareness* of mental health issues (Borghouts et al., 2021; Lim & Nekmat, 2008).

Despite the many potential advantages of digital mental health interventions, studies that have evaluated their effectiveness among adolescents have yielded mixed results (Eilert et al., 2022; Lehtimäki et al., 2021). Many studies are characterised by low adherence and high attrition rates, with significantly lower engagement rates outside the context of empirical studies (Baumel et al., 2019; Linardon & Fuller-Tyszkiewicz, 2020). For example, it is estimated that only 3.3% of users continue to engage with mental health apps after 30 days (Baumel et al., 2019). While some commercial smartphone apps attract more users, many have not been rigorously evaluated and show little fidelity to evidence-based treatments (Huguet et al., 2016; Schueller & Torous,

2020). Further, few digital interventions have been specifically developed for use or rigorously evaluated with adolescents in sub-Saharan Africa (Lehtimäki et al., 2021).

This chapter describes the design and development process of the Kuamsha app, a smartphone app that delivers Behavioural Activation therapy. The app was developed as part of the “*DoBat and Ebikolwa n’empisa*” research programmes, which aim to develop scalable psychological treatments to address depression amongst adolescents in low-resource settings. The Kuamsha app was developed using multiple user-centred and participatory action research design methods to ensure that it was useful, culturally relevant, and usable for the targeted population.

This chapter is structured as follows: First, I describe the Kuamsha app’s main components that resulted from the user-centred design. Second, I discuss the study methods used to develop the app, including the four developmental phases. Third, I summarise the main findings for each phase and describe how the user-centred design approach informed specific components of the app.

THE KUAMSHA APP

Drawing from the findings of the formative work, the Kuamsha app (meaning “activate” in Swahili) was developed using a narrative game format. Under this approach, the app teaches the principles of Behavioural Activation using storytelling techniques and game design elements (e.g., plot, user-choice, in-app points, personalisation).

Treatment model

The treatment model was based on Behavioural Activation, a psychological therapy that was developed from extensive experimental literature on instrumental reinforcement and motivation. In essence, low levels of positive reinforcement contribute to a lack of motivation and avoidance of daily tasks that in turn contribute to negative mood and rumination. Reciprocally, negative mood and rumination lead to avoidance and lack of positive reinforcement. Behavioural Activation counteracts this cycle by helping people to re-engage with meaningful activities (Jacobson et al., 2001).

During the therapy, individuals learn to set goals, make plans and problem solve, establish routines, and reduce avoidance through simple diaries and planning exercises. They also learn to confront barriers to engagement by tackling repetitive negative thoughts and breaking down and resolving problems. Together, Behavioural Activation provides individuals with simple, structured skills to overcome depression.

Behavioural Activation was chosen for several reasons. First, it is an effective psychological therapy that is relatively simple to deliver, easily understood by patients, and less costly than Cognitive Behavioural Therapy (Ekers et al., 2014; Richards et al., 2016). Behavioural Activation was also found to be as effective as antidepressant medication (Dimidjian et al., 2006). Further, it has been effectively adapted for use with adolescents, in low-income and diverse cultural settings, and in a digital format (Arjadi et al., 2018; Huguet et al., 2018; Martin & Oliver, 2019; Patel et al., 2017; Tindall et al., 2017).

Whilst there were already some smartphone apps available that deliver Behavioural Activation therapy for depression (e.g. Mobilyzel, Moodivate, Behavioral Appivation, Boost Me), none of these apps had been developed for adolescents in a sub-Saharan African context (Burns et al., 2011; Dahne et al., 2017a; Dahne et al., 2017b; Ly et al., 2015; Stiles-Shields et al., 2019). As such, these apps contain elements that are not feasible for use in low-resource settings: they are data-intensive, are only available in Apple's iOS platforms for use in iPhones (which are expensive), or are intended to be used in conjunction with a licensed clinician.

Peer-supported app

Evidence suggests that digital interventions incorporating some form of human support (e.g., via phone, texts, face-to-face visits) are more effective than purely self-administered platforms (Lehtimäki et al., 2021; Weisel et al., 2019). Often referred to as coaches or peer mentors, human supporters are not mental health specialists and do not deliver psychological interventions directly. Instead, they are trained lay workers who provide low-intensity and time-limited support to help users understand the digital intervention's content and overcome barriers to engagement. In sub-Saharan Africa, task-sharing using non-specialist workers has been increasingly employed to deliver physical and mental health treatment services (Galvin & Byansi, 2020; Singh & Sachs, 2013). Limited research has investigated the potential for lay workers to supplement digital mental health interventions (Arjadi et al., 2018).

Given this evidence, the Kuamsha app was designed to be supported by brief weekly phone calls from peer mentors. The primary role of the peer mentors was to support adherence and compliance to the app and to troubleshoot technical problems related to the use of the app or the smartphone. Importantly, peer mentors were trained to *not* provide counselling or psychosocial support outside of their role in supporting engagement with the app. To that end, the training and weekly calls were highly standardised to support treatment fidelity and scalability.

As part of this work, a training platform was developed in collaboration with local experts and stakeholders in Uganda and South Africa to guide the peer component of the intervention. This workstream is currently being tested in both study sites, and the results from this piloting will be published as soon as it is available.

Kuamsha app's main components

The following section describes the app's main components. Example wireframes of the Kuamsha app are shown below in Figure 6.2.

1. *Gamified and narrative format*

The Kuamsha app consists of a choice between two storylines, the Song Contest and the Football Match. Each storyline consists of six tailored modules ('episodes') played in sequential order. Both storylines allow participants to play the role of a young person who faces difficulties during their everyday life. Each story was developed in collaboration with an academic story-writer, drawing heavily on the findings from the formative work. A summary of each module is shown in Tables A6.1-A6.2 in the appendix.

A key principle of the game is that the player is drawn into the narrative through interactive choices. During each module, participants can make choices that determine the main character's actions and the plot's outcomes (thus, allowing them to see the consequences of these actions). To keep complexity manageable, story branches quickly merge with the main storyline through a branch-and-bottleneck structure (Figure 6.1) This approach allows the player to construct a relatively distinctive and personalised story while ensuring consistency across users (Ashwell, 2015).

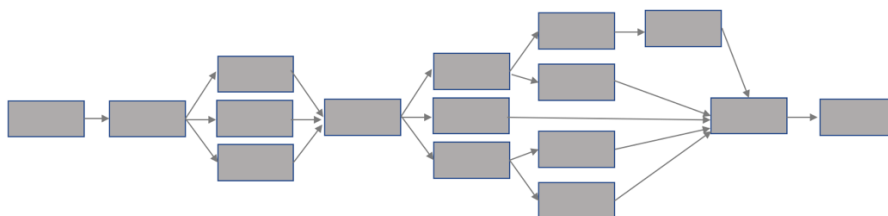


Figure 6.1 Branch-and-bottleneck game structure

The storylines cover different Behavioural Activation skills such as identifying and engaging in meaningful activities in a gradual, systematic, and sustained way. Other skills include developing and following a basic routine (e.g., getting enough sleep), targeting rumination, problem-solving, effective communication, and identifying someone who might help you when you are feeling stuck.

To ensure that players reflect on the game and understand the concepts and their choices, each module ends with a summary of lessons learned. These take the form of multiple-choice responses, which are saved as part of the game data for later analysis and potential review by peer mentors.

Each module takes 15-20 minutes to complete, and adolescents are expected to complete six modules (i.e., one story) within the 10-week intervention period. Participants can complete both stories during the intervention period if they wish.

2. Choosing a meaningful goal and putting Behavioural Activation skills into practice

After completing the first module, participants are asked to think of a goal to work on over the 10-week intervention period. This goal should be something that is important to them but is also realistic and achievable. For example, adolescents could try to learn a new skill, make new friends, or improve their relationships with someone.

Each module is followed by a homework activity where the participant is encouraged to reflect on the Behavioural Activation principles outlined in each module and think about ways to apply them to their own lives. Participants are asked to report how often they completed the homework activities and to rate their mood as they did them. These homework activities are an essential part of Behavioural Activation therapy and focus on increasing feelings of accomplishment and pleasure, and bringing users closer to their goals.

3. Mood monitoring

Participants are asked to monitor their mood at different times in the Kuamsha app. The mood monitoring is presented with a slider using a happy and unhappy emoji (both emojis were tested with the target population). A text with the words “Happy” and “Unhappy” was added to accompany the emojis. Numbers in the slider were intentionally omitted to keep it simple. The users get in-app points every time they complete mood monitoring and short feedback on how their mood is progressing. This mood rating system is also used for risk assessment and monitoring.

4. Log-in code

Kuamsha is password-protected, so users must enter a password each time they use the app. This was implemented to ensure that their information was kept private if they were to share the phone with friends or family members (which was reported to be very common among the study participants).

5. Emergency button

Kuamsha includes an emergency number for adolescents to call if they feel extremely sad or think about hurting themselves. In South Africa, adolescents are transferred to a toll-free National Suicide Hotline to receive support. In Uganda, adolescents are connected to a mental health professional from the study team with specialised training in adolescent mental health. The study team is notified whenever an adolescent calls this emergency number.

6. Language selector

The Kuamsha app is available in three different languages: Shangaan (Xitsonga), Luganda, and English. The text underwent two rounds of translation by clinical psychologists. Peer mentors also reviewed it to ensure that the language would be understandable for adolescents.

7. Onboarding process

When adolescents open the app for the first time they are introduced and guided through its main components. This onboarding process aims to teach adolescents how to interact with the interface, choose their preferred language, locate the emergency button, and select one of the stories.

8. Absorbing activities

The Kuamsha app includes two different absorbing activities or ‘mini-games’ designed to teach the principle of absorption (a state of immersion involving focused attention and departure from everyday thoughts) (Teilegen, 1985). The app includes two different absorbing activities related to each storyline. One is a music-absorbing activity, which consists of a rhythm game where users tap the screen in time with the music. The other is a football-absorbing activity, where users practice taking shots on goal while avoiding distractors. The difficulty of these ‘mini-games’ increases steadily as players engage with these activities. Players can also adjust the game's difficulty to their preferred level of challenge.

9. Notifications

Users are reminded to report their progress on their weekly activities via notifications. Notifications are sent up to four times a week, but users are allowed to disable this function.

10. Technical specifications

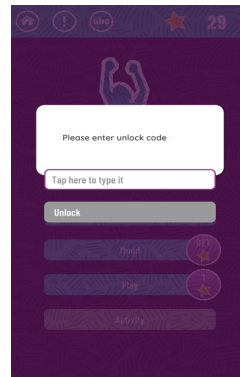
The study team partnered with *Seamonsster*, one of Africa's leading serious gaming companies, to develop the app. *Seamonsster* has a wealth of expertise in developing educational games for adolescents in the African continent and specialises in creating visually engaging content and immersive technologies.

The Kuamsha app was specifically developed for the Samsung A2 android device. It was built in Unity, a cross-platform engine popular for mobile game development. The app has two critical dependencies. One is Ink, a plugin that allows players to interact with the stories via multiple choice answers or text fields. The other is Firebase, which captures player data on an online database and tracks users' engagement with the app.

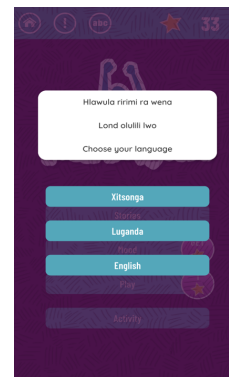
To reduce potential problems with internet access during therapy sessions, the Kuamsha app is offered in both online and offline modes. The app only requires an internet connection when it is accessed for the first time, during which the app automatically downloads the modules to the device's internal storage. After that, the users can complete all modules at any other time, regardless of the internet signal. Further, the graphics elements were reduced to use little storage space and increase the app's stability and performance.



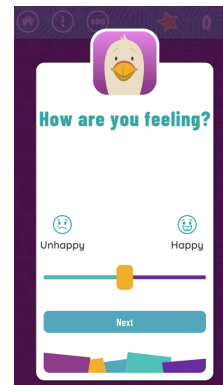
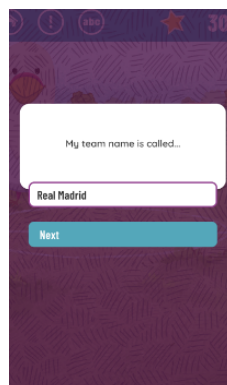
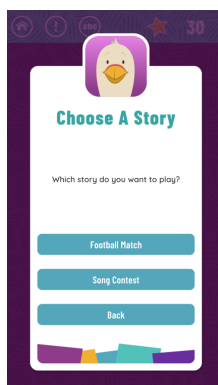
Home screen



Log-in code



Language selector



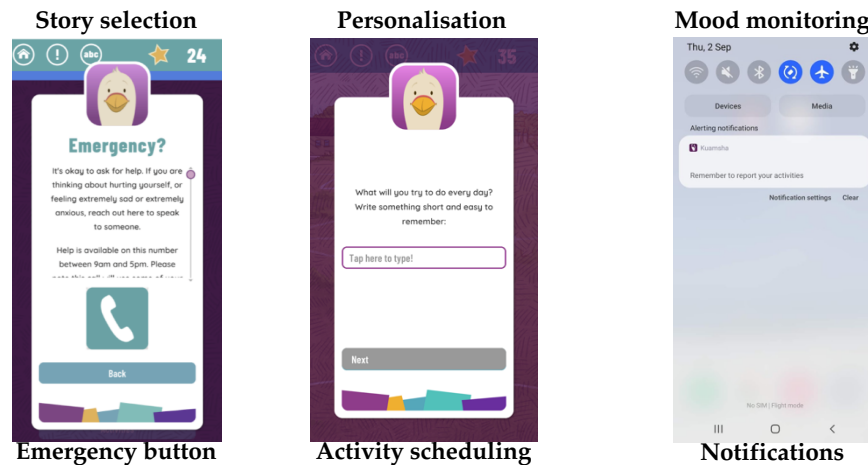


Figure 6.2. Wireframes of the Kuamsha app

METHODS

In this section, I describe the study setting, study participants, and the developmental phases of the app.

Ethical considerations

The study was reviewed and approved by institutional review boards in South Africa (the University of the Witwatersrand Human Research Ethics Committee, Ehlanzeni District, and Mpumalanga Provincial Departments of Health and Education), in Uganda (Makerere University School of Public Health and the Uganda National Council for Science and Technology), and in the United Kingdom (Oxford Tropical Research Ethics Committee, OXTREC).

Study setting

The study was conducted in two different countries and settings (see Figure 6.3). In South Africa, the study was located in the Bushbuckridge sub-district of Mpumalanga Province, in rural northeast South Africa (same setting as Chapters 2 and 5). Chapter 2 found a high prevalence of depressive symptoms (up to 32.5%). As in other parts of the country, there is a paucity of mental health and social care services, particularly psychological therapies (Flisher et al., 2012; Mokitimi et al., 2018).

In Uganda, the study was carried out in the Wakiso district, a peri-urban area located approximately 30 kilometres from Kampala. Wakiso District is home to nearly 2 million people. The site combines peri-urban communities close to the Entebbe-Kampala road with relatively isolated fishing villages extending to the shores of Lake Victoria. The study area is poor, and the most common occupation is subsistence farming. Among adolescents, 50% attend secondary school and 15% of youth (18

– 30-year-olds) are neither working nor in school. The nearest specialist psychiatric resources are in Kampala, a 2-hour journey by public transportation (UBS, 2017).

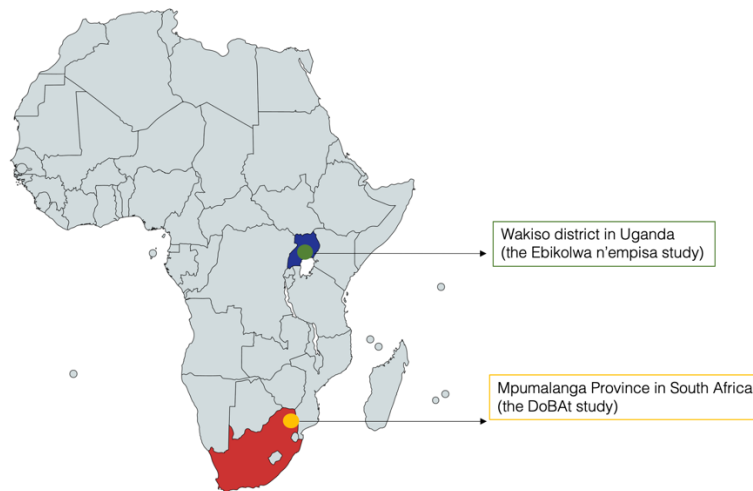


Figure 6.3. Study locations in Uganda and South Africa

In both settings, mobile phone ownership is on the rise. A census conducted at the study site in South Africa showed that more than 93% of households owned a cell phone, and 65% had a smartphone in 2019. Data from the National Population and Housing Census in Uganda suggests that the proportion of adolescents who own a mobile phone in Wakiso district is higher than 80% and increasing steadily (UBS, 2017). This digital landscape presents new opportunities to reduce the treatment gap among underserved communities in a resource-poor setting.

Study participants

The study's target population were adolescents aged between 15 and 19 years from South Africa and Uganda. Participants were balanced regarding age, sex, and social class as much as possible. To be eligible to participate, respondents needed to be fluent in Shangaan, Luganda, or English, willing and able to give informed consent or assent, and have a caregiver willing to provide consent (if under 18 years).

Other stakeholders were recruited, including caregivers of adolescents, school teachers, community stakeholders, and mental health professionals. The objective of these sessions was to elicit various views and perspectives from multiple stakeholders, contrast these perspectives with the information gathered from adolescents, and ensure that the intervention was culturally acceptable across communities.

Different recruitment strategies were followed across study settings. In Uganda, the local partner (BRAC Uganda) first obtained verbal approval from the local council chairperson and the community elders before beginning recruitment. Adolescents were recruited via BRAC's network of clubs for adolescents (Empowerment and Livelihood for Adolescents, or ELA clubs). In South Africa, the local partner (the MRC/Wits Agincourt Research Unit) consulted the Community Advisory Board and obtained their advice and approval of the project as well as key educational stakeholders. Adolescents were recruited via their schools. Field supervisors visited these facilities in both settings and provided an overview of the study and written information sheets for participants (adolescents) and parents/guardians. Adolescents willing to participate in the study were asked to return their signed assent and/or consent forms to a fieldworker who collected them at schools or ELA clubs on another occasion. Due to the challenges of the COVID-19 pandemic and limited resources, convenience sampling was deemed the most appropriate sampling method.

Study design and development phases

An iterative user-centred agile design approach was used to co-constructed the app with the study's target population (WHO, 2016; Yardley et al., 2015). Different research methods were used, including focus group discussions, in-depth interviews, participatory workshops, usability testing sessions, questionnaires, and extensive expert consultation. Discussions were framed using various elicitation techniques, including semi-structured topic guides, role-playing exercises, and card-sorting games.

The user-centred development was carried out in four phases, consisting of (1) conceptualisation, (2) prototyping, (3) product release, and (4) evaluation. An iterative feedback loop approach was used, where each phase's findings were used as inputs for the following phases and to refine previous phases. Table 6.1 summarises the development stages.

Table 6.1 Development stages

Stage	Method	Sample size	Country	Date
(1) CONCEPTUALISATION	5 focus groups with adolescents	37	South Africa	Jul – Aug 2019
	In-depth interviews with 4 adolescents from the focus group	4	South Africa	Oct 2019
	2 focus groups with caregivers (n=6) and school teachers (n=7)	13	South Africa	Dec 2019 – Jan 2020

(2) PROTOTYPING	8 usability testing sessions using other apps	8	South Africa	Feb – Mar 2020
	3 focus groups to test Kuamsha wireframes	34	Uganda	Aug 2020
	6 participatory workshops	40	South Africa & Uganda	Sept 2020 – Jan 2021
(3) PRODUCT RELEASE	24 usability testing sessions with Kuamsha app	24	South Africa & Uganda	Feb 2021
	Pre-pilot study with adolescents with depression	17	South Africa	Dec 2021 – May 2022
(4) EVALUATION	Feasibility studies in Uganda (n=31) and South Africa (n=200)	231	South Africa & Uganda	Ongoing

The objectives and types of elicitation techniques used in each phase were the following:

- (1) *Conceptualisation phase.*** The objective of this phase was to understand adolescents' needs and context, assess the feasibility of delivering Behavioural Activation using a digital platform, and decide on the app's main features. This phase included five focus groups with adolescents, four in-depth interviews with adolescents that provided helpful feedback in the focus groups, and two focus groups with caregivers and schoolteachers. The purpose of these discussions was to: (i) discuss adolescents' values, goals, struggles, social relationships, and the type of meaningful activities they engage in; (ii) learn about access and use of smartphones, and desirable content and features in apps; (iii) examine perceptions and local language terms for depression, and understand the local support systems; and (iv) understand caregivers' and teachers' views on the potential limitations of using digital tools in this population.
- (2) *Prototyping phase.*** The objective of this phase was to use the results from Phase 1 to develop a simple, scaled-down version of the app and ask adolescents to provide feedback. This phase included eight usability testing sessions, three focus groups, and six participatory workshops. In the usability testing sessions, adolescents were given smartphones and asked to interact with different apps. Facilitators observed their behaviour and asked questions as they progressed. As part of these sessions, paper-based wireframes and basic prototypes of the Kuamsha app were presented, accompanied by detailed design questions. During the focus groups, adolescents were asked to provide feedback on the story characters, artwork, and background music. The participatory workshops were all-day events where adolescents and other stakeholders were asked to give additional feedback on the app's content.

- (3) **Product release phase.** Based on the outcomes of phases 1 and 2, the objective of this phase was to build a minimum viable product (MVP) and test it with the study's target population. This phase included 24 usability testing sessions, where adolescents interacted with the Kuamsha app and were asked to provide feedback on usability, design, and recommendations for improvements. Some of these sessions were unguided, where adolescents were asked to freely explore the app and verbalise their experience and general impressions (think-aloud methodology) (Joe et al., 2015). This method was helpful in investigating whether the user interface was easy to use without much explanation. Facilitators were trained to take notes on how the app was explored, including features that adolescents did not interact with. Other sessions were guided, where the facilitator walked participants through each screen while probing for understanding. This phase also included a pre-pilot study with 17 adolescents with depression in South Africa. The entire 10-week intervention was tested, including the peer mentor component.
- (4) **Evaluation phase.** This phase includes two studies that are exploring the intervention's feasibility, acceptability, and efficacy in reducing depressive symptoms and risky behaviours. One is a feasibility study in Uganda with 31 adolescents from the general population (the *Ebikolwa n'empisa study*). The other is a randomised controlled pilot trial in South Africa with 200 adolescents with depression (the *DoBAAt study*). Both of these studies are ongoing and the results are expected by December 2022 (see Pozuelo & Stein, 2019 for a description of both studies). The outcomes of these studies will be reported as soon as they are available.

Samples of interview guides and elicitation techniques are shown in Table A6.3 in the appendix.

Analysis

Descriptive statistics summarised the participants' characteristics. Interviews and focus groups were audio recorded and transcribed verbatim, removing any potentially identifiable information to protect the privacy of the participants. I read all the transcribed interviews, summarised the main findings, and grouped these into main themes.

Data from the workshops and usability testing sessions were analysed using an instant data analysis approach (Kjeldskov et al., 2004). Under this approach, the fieldworkers were trained to record all problems that arose during the sessions. Following these sessions, the fieldworkers,

myself, and other study investigators discussed and ranked these problems. This technique reduces the time required for transcribing and analysing interviews and allows fast identification of the most critical and severe usability problems.

Lastly, I triangulated the evidence from all phases with three years' worth of meeting notes among the core study team. Using this evidence, I developed a game design document outlining the platform's main features and "guiding principles" (Yardley et al., 2015). This document was used as a roadmap for the development of the app.

RESULTS

In this section, I summarise the main findings for each developmental phase and describe how the user-centred design approach informed specific components of the app.

(1) Conceptualisation phase

In total, 50 individuals were involved in this phase, including 37 adolescents, six caregivers, and seven schoolteachers from the study site in South Africa.

Adolescents that took part in the focus group discussions were 17.1 years old on average, and the sample was evenly split between males and females. All adolescents were enrolled in school and had 9.7 years of schooling. On average, a third had part-time jobs, including selling products in the market, cutting firewood, cattle herding, gardening, and working as a hairdresser. The majority of adolescents (89%) had access to a smartphone.

Study participants were very supportive of the idea of having an app that would help them feel better:

"I like the idea of getting advice through an app because I would get the help I need, unlike if I were to get advice from a person. The app is able to advise on certain things that people don't know or cannot even give advice on. Not everyone knows what you need to do to feel better when you are feeling low" (P1 female, FG4).

"I like the idea because there are times when you don't feel like talking to anyone, or you don't have someone to talk to, so the app would be a good idea" (P5 male, UT4).

Adolescents' preferences around a mental health app revolved around four main themes: app features, cultural validity, confidentiality, and technological aspects. An excerpt of the results is presented in Table 6.2.

Among the app features, participants mentioned that the app should include stories of individuals who had been through difficult situations and narrate how they improved their circumstances. In addition, adolescents raised the sub-theme of gamification on several occasions and suggested that the app should include points and difficulty levels to increase motivation and engagement. In general, mobile games seemed to be very popular among adolescents and were already used by many as a strategy to avoid rumination and exercise attentional control: “[Games allow me] to shift my focus from the things that I don’t want to think about at that time and focus on playing that game. I don’t think about anything else when I am playing games.” (P8 female, FG3).

Table 6.2. Conceptualisation phase: Excerpt of adolescents’ preferences for app components

Theme	Subtheme	Quotes
App features	Use of stories	“The app needs to have pictures of people who have been through difficult situations and how they managed to get out of those situations.” (P3 male, FG2)
		“[The app] must include pictures or videos of people who had depression before.” (P7 female, FG1)
		“[The app] could display a person feeling low and having their friend around” (P2 female, FG4)
		“I love the comic videos that I can download on my phone and watch stories.” (P2 male, FG2)
	Gamification	“Getting points will motivate us to go back to the game and play it every day.” (P1 female, FG4)
		“If we find that we are getting help it should take us to another level.” (P8 female, FG1)
		“Personalising your character helps you to understand yourself and know yourself better” (P3 female, FG5)
Cultural validity	Aesthetics	“[The app] should show the true image of us. But now as I look to this character, I see that we are not looking the same. They used the colour for white people.” (female, ID4)
	Targeting common problems	“I would like to get advice on things like sexual activities. The app would advise us on what will happen when we engage in sexual activities at an early age.” (P4 female, FG5)
		“The app should also have pictures of the people smoking and what happens to them when they are smoking. It can also have pictures of the people who were addicted to alcohol and how they managed to stop drinking alcohol.” (P3 male, FG2)
		“[The app] will not judge you. It will be you and the app. Also confidentiality will be there. It won’t tell other people about your problems. That is nice idea (P5 female, FG1)
Confidentiality	Creating a safe space	“Getting advice through an app would be a good idea because most of the time when you tell a person or a friend your problems, they don’t keep them to themselves; they tell people. If I share my problems on the app; I will get the advice that I

		<i>need without worrying about what they will say about you to other people.” (P3 female, FG5)</i>
		<i>“There will be a problem if [other people] can get to access what I am doing on the app” (P4 male, FG2)</i>
Technological aspects	Phone data	<i>“I always run out of airtime to buy data and have to wait until month-end” (male, IDI1)</i>
	Storage	<i>“I’m always scared that [the phone] will run out of space” (female, IDI3)</i>

FG. Focus group discussion. IDI. In-depth interview.

Combining both findings, the Kuamsha app was developed using a **narrative game format** (app component #1). Under this approach, the app teaches the principles of Behavioural Activation through an engaging story. To develop the stories, the study team drew inspiration from the findings of the formative work, as well as the *Choose Your Own Adventure* children's book series and smartphone apps that use this approach (e.g., Long Live the Queen and Episode).

Questions regarding cultural appropriateness emerged several times, along with the importance of incorporating elements specific to the study's population. Adolescents wanted the story characters to look similar to them and for the app to target common problems in their community. For example, many adolescents mentioned risky behaviours – such as alcohol, smoking *dagga* (cannabis) and teenage pregnancy – as the main factors that got in the way of achieving their goals: *“A lot of young people are spending their time at taverns. They are drinking from Monday to Sunday. They are losing focus”* (P8 female, FG1). While the app was not intended to target risky behaviours specifically, the stories were designed to cover topics such as drinking alcohol and relationships to make them more relatable to the target population. Special care was also taken to ensure that the stories represented a mix of genders, ages, appearances, and social classes.

Another key theme that emerged was confidentiality. Adolescents saw the app as an opportunity to discuss their problems discreetly, without feeling judged: *“[The app] won’t criticise. That’s why if we have problems, we don’t go to our parents as we are scared. But the app won’t judge me”* (P8 female, FG1). Many participants reported using security patterns and log-in codes to avoid other people accessing their phones. This theme highlighted the need to **password-protect** the app to create a safe space (app component #4).

Within the technological aspects, adolescents discussed the lack of data and limited space as the two main barriers when using their smartphones. This theme prioritised a low-storage app and the need to explore features that would allow the user to access the app without internet connectivity. Drawing from these findings, the Kuamsha app

was made available in an **offline mode**, where users could complete the modules without an internet signal. The graphics elements were also reduced to **free space** (app component #10).

Caregivers and schoolteachers provided their views on the potential limitations of using smartphones with adolescents. The limitations concerned two main themes: adolescents' tendency to overuse and misuse phones (e.g., accessing inappropriate content). These findings helped frame how the intervention was conducted but did not directly feed into the app's design. As such, the results from these focus groups are excluded from this chapter.

(2) Prototyping phase

In total, 82 adolescents were involved in Phase 2. Three qualitative research methods were used in this phase: usability testing sessions, focus group discussions, and participatory workshops.

During the usability testing sessions (n=8), adolescents were given smartphones and asked to interact with different apps. Each of these apps targeted a different app component (e.g., mood monitoring, character personalisation, games that increased in difficulty). In addition, I designed different paper-based wireframes of other components, such as activity scheduling, getting advice, and allowing players to choose how the story unfolds (examples of these designs are shown in the appendix). These sessions had two objectives: (i) to get feedback on the different app components; and (ii) to examine adolescents' familiarity with smartphones. An excerpt of the results is presented in Table 6.3.

Overall, adolescents were familiar with smartphones and enjoyed most app components, particularly those that involved some level of **gamification** (app components #1 and #8). The sub-theme of cultural validity re-emerged when characters were asked to personalise their characters (see Table 6.3). Adolescents preferred games that were challenging but at the same time easy to understand from the beginning. This feedback led to the development of an **onboarding process**, whereby the user would be introduced to the app and its components the first time they opened it (app component #7).

When asked to monitor their mood, adolescents preferred to use emojis to describe their feelings. An initial list of 15 emojis was created. Adolescents were shown these emojis without descriptions and asked to rate what emotions were represented. This was used to choose the emojis that better captured the emotions portrayed in the **mood monitoring** (i.e., unhappy and happy) (app component #3).

Table 6.3. Prototyping phase: Excerpt of adolescents' feedback on the app's main components

Component	Quotes
Personalisation	<i>"I enjoyed personalizing my character. I decided to make my character look that way because some of the features look like mine. The character looks almost like me even though I have also added the beard to show that one day when I grow up I would like to have a beard."</i> (Male, UT4) <i>"I liked it for the fact that I got to personalise my own character and I have added all the features that are similar to mine. I wanted the character to look like me"</i> (Female, UT5)
Mood monitoring	<i>"I like the idea of rating myself and if I see that I need help, I can try new ways like going to the social workers"</i> (Male, UT1) <i>"I prefer to express my feelings through an emoji"</i> (Male, UT3) <i>"The emojis are very clear and they show clearly what they mean"</i> (Female, UT5)
Choosing how the story unfolds	<i>"It is a good game to play. It shows you that before taking a decision between going to the tavern or preparing for the exam, you need to first think of the benefits that you will get out of each decision."</i> (P1 female, UT7) <i>"It would be fun for me because I would be getting to decide how the story goes until the end."</i> (P3 female, UT8)
Absorbing games	<i>"I like this game a lot. It takes my concentration as by the time we met I was not happy but through it, now I'm starting to feel fine."</i> (Male, UT1) <i>"It is easy if you concentrate but hard to win. The more it becomes hard, the more you enjoy the game"</i> (Female, UT2) <i>"It was not difficult to play this game because you gave me instructions before I began playing, but I wouldn't have found it easy to play it on my own."</i> (Male, UT4)

UT: usability testing session.

Focus groups (n=34) were used to obtain feedback on the story characters, artwork, and background music. Adolescents were asked to list popular names in the community, and some of these names were used to name the characters in the stories. Visual designs like the one shown in Figure 6.4 were presented. For this example, adolescents were asked to spot the main differences between the images, give feedback on the overall look, feel, and design, and say whether they could relate to the characters. To mention a funny (but nevertheless insightful) anecdote, many adolescents said they could not relate because they *"did not like the way the boy's hand is touching the lady's butt."* Similarly, both storylines included a bird character which was designed to have players reflect on their choices and review what was learned in the episode. The first wireframe included an owl, inspired by Greek mythology, in which owls are considered a symbol of wisdom. During the focus groups, it

quickly became clear that owls are regarded as instruments of witchcraft in both settings (*"It is the boss of the witches"*). Both examples were good reminders of the importance of user testing and contextualization when developing an app.



Figure 6.4. Visual designs tested in focus groups

The participatory workshops (n=40) reviewed and adapted the storylines and homework activities to ensure that these were appealing to adolescents in both study sites. As part of these workshops, adolescents were asked to read through the scripts and prepare a play where they would role-play the stories. Following these discussions, modifications were made (in terms of language and content) to make the stories more locally and culturally relevant.

(3) Product release phase

The results from phases 1 and 2 provided input for developing a minimum viable product (MVP) of the Kuamsha app. Before rigorously evaluating it, the MVP was tested via usability testing sessions and a pre-pilot.

Usability testing sessions (n=24) were conducted with 12 adolescents from Uganda and 12 from South Africa. Most adolescents found the app a fun way to learn new skills and relax the mind. A note from a fieldworker in South Africa stated: *"she looked very interested and engaged because she was smiling and giggling as she was reading the story."* Some differences were noted between females and males, with males appearing to prefer the 'Football Match' story and females the 'Song Contest' story.

Aside from the general feedback, these sessions helped to highlight some parts of the app which were not intuitive and needed refinement. One issue identified was that adolescents in Uganda struggled with literacy skills at a greater level than anticipated. According to census

data from Wakiso District, 85% of adolescents in the study site area are literate (UBS, 2017). However, it became clear in these sessions that although many adolescents could read fluently, some had difficulty comprehending the text. In response, it was decided that only adolescents with an acceptable reading comprehension level would be enrolled in the feasibility study in Uganda.

Similarly, when asked to choose a goal, most adolescents set goals related to their lives, but these were rarely specific, measurable, or time-based. This highlighted the critical role of peer mentors in making sure that goals are meaningful and achievable within the 10-week intervention period. Based on these findings, the goals and weekly activities were allowed to be modified anytime the user wanted.

A pre-pilot study was conducted in the South Africa study site with 17 adolescents who screened positive for mild to moderately severe depression based on scoring between 5 and 19 on the 9-item Patient Health Questionnaire-Adolescent Version (PHQ-A). Adolescents were asked to use the Kuamsha app for ten weeks. They were also allocated to a trained peer mentor from whom they received six weekly phone calls. App engagement metrics were collected throughout this time. Table 6.4 shows the sociodemographic characteristics of study participants at baseline.

Table 6.4. Pre-pilot study: sociodemographic characteristics of study participants at baseline

Variables	All sample (n=17)
Female	88.2%
Age (range)	16.2 (15 – 19)
Grade enrolled in	10.4 (9 – 11)
Ever repeated a grade	23.5%
Married	5.9%
Has children	12.5%
Lost a parent	17.6%
Ever used a smartphone before	82.4%
Did any work for pay	0.0%
Average simple poverty scorecard (range)	43.5 (15 – 70)

The Simple Poverty Scorecard Poverty total score ranges from 0 (most likely below a poverty line) to 100 (least likely below a poverty line). More information about the tool can be found in (Schreiner, 2017).

The average age of participants was 16.2 years. Most adolescents were females, not married, and did not have children. All participants were enrolled in school, and around a quarter (24%) had repeated a school grade. None of the adolescents was employed, and the majority (82%)

had used a smartphone before. An average score of 43.5 on the simple poverty scorecard corresponds to poverty rates of 57.3%. This was computed using the South African upper national poverty line, which is set at ZAR32.57 per person per day (£2 in 2017 prices) (Schreiner, 2017).

The average PHQ-A score was 7.2 (range: 5 – 15). Two participants were moderately severely depressed (score between 10–19), and the rest (88%) were mildly depressed (score between 5–9). Seven participants (41%) endorsed the 9th item on suicidal ideation. These participants were referred to the trial psychologist to assess whether they needed any additional intervention and verify that none of these adolescents had identified means or plans to attempt suicide.

Table 6.5 shows the app engagement metrics for 16 participants (there was a problem linking the device with the game data for one participant). On average, the Kuamsha app was launched 38.4 times, and users spent 4 hours 13 mins over the intervention period. Most participants opened both stories, and the majority (75%) completed at least six modules (the recommended number of modules to be completed during the intervention). The average number of modules completed was 8.8, and several adolescents (44%) completed both stories (12 modules in total).

Adolescents' goals during the intervention period included: improving communication with friends or family, making new friends, studying more often, and exercising more. On average, participants set up 8.3 weekly activities and completed these 47.2 times.

Table 6.5. Kuamsha app engagement metrics in the pre-pilot study

	Sample with app data (N=16)
Number of logins	38.4
Total time spent on app	4hrs13min
Opened both stories	81%
Completed at least six modules	75%
Average number of modules completed	8.8
Number of set up weekly activities	8.3
Number of completed weekly activities	47.2

In general, these engagement metrics are higher than those of other apps that have been reported in the literature (Baumel et al., 2019). These preliminary results suggest that the Kuamsha app is acceptable in terms of usability and engagement. Two studies are currently underway to rigorously test the intervention's feasibility, acceptability, and efficacy

in reducing depressive symptoms and risky behaviours.

CONCLUSION

This chapter described the user-centred development of the Kuamsha app, an app designed to treat depression among adolescents in Uganda and South Africa. Kuamsha is a gamified app that uses storytelling techniques and game design elements to deliver Behavioural Activation therapy in an engaging way. Preliminary results of early user testing show that the Kuamsha app is acceptable in terms of usability and engagement.

Central to the study is an iterative co-design process with adolescents from rural South Africa and Uganda. Extensive formative research was conducted with more than 170 adolescents, who guided the development and provided feedback at each developmental phase. The user-centred development was carried out in four phases, each combining different research methods and elicitation techniques. In addition, a broad array of local stakeholders across both study settings were consulted during the development process to ensure that the intervention was culturally acceptable across communities. This iterative methodology was used to ensure the app's acceptability, cultural relevance, useability, and validity with the targeted population.

This chapter has limitations. First, a convenience sampling strategy was used to recruit adolescents from both study sites, which may have resulted in biased groups. However, the relatively large number of adolescents and stakeholders consulted may have helped minimise this bias. Second, most of the formative work was conducted with adolescents from the general population and not specifically with adolescents identified as having depression (except in the pre-pilot study). This was considered important considering that the intervention was aimed at helping adolescents across the spectrum of mental well-being to mental ill health. Although feelings of hopelessness and self-harm did arise during the discussions (particularly during one-to-one sessions), more formative work with adolescents with depression might have helped to ensure that the app is optimised to address their needs and concerns. The results from the larger studies will provide more information about the feasibility and acceptability of the Kuamsha app in this population. Third, although this study took place in two diverse settings, significant contextual differences should be considered when evaluating the implications for other sub-Saharan African populations. Fourth, the formative work revealed literacy difficulties among adolescents in Uganda. Based on these findings, a reading comprehension test was included as part of the screening criteria in the feasibility study in Uganda, which might have excluded the most vulnerable adolescents. To improve the app's scalability for adolescents

with lower literacy levels, future versions of the app should include audio voiceovers or other features to reduce the difficulty of comprehending the text.

While there has been a significant increase in digital mental health interventions in recent years, many of these platforms suffer from low uptake, slow rollout, and unsustainable business models. Further, few interventions have been rigorously designed and evaluated for adolescents in sub-Saharan Africa or are available in local languages. Given the limited access to effective interventions in rural LMICs, innovative, scalable treatment delivery options are desperately needed. Benefiting from the rapidly growing penetration of mobile devices, the Kuamsha app could help bridge the large treatment gap in rural South Africa, Uganda, and potentially other similar settings. If the feasibility studies produce promising results, they will inform the development of a further larger randomised controlled trial which could support better management of depression among adolescents in low-resource settings and could strengthen primary and community-based healthcare systems.

Chapter 7. Discussion and conclusions

In this thesis, I explored the relationship between depression and risky behaviours among adolescents in LMICs through five empirical studies. In this concluding chapter, I summarise the main findings and draw links between the results from each of the empirical studies. The last section discusses the strengths and limitations of this thesis, implications for clinical practice and policy, and directions for future research.

THESIS SUMMARY

This thesis had four objectives. First, to examine predictors of depression in a socioeconomically disadvantaged rural community in South Africa, where most of the studies in this thesis are situated. As part of this objective and Chapter 2, I used data from a longitudinal cohort study to examine the role of several risk factors in predicting depressive symptoms. There were three main findings. First, I observed a high prevalence of elevated depressive symptoms among the study sample (up to 32.5%). Second, I found that experiencing intimate partner violence, low parental support, and becoming food insecure were associated with a statistically significant increase in depression severity and depression caseness. Third, the effect of some risk factors was associated with persistent depression, with adolescents remaining on a higher depression score even three years after experiencing these risk factors.

This enhanced understanding of the contextual influences on depression led me to my second objective, which was to explore the relationship between depression and risky behaviours from different angles. To reach this objective, I conducted two empirical studies. Chapter 3 comprised a systematic review and meta-analysis of the effect of depressive symptoms on risky behaviours among adolescents in LMICs. In line with the evidence from high-income countries, this review found that adolescents with depressive symptoms are more likely to engage in risky behaviours such as risky sexual behaviours and substance use than non-depressed adolescents.

Related to this objective and given the evidence of a potential bidirectional relationship, Chapter 4 aimed to disentangle the direction of effect between depression and risky behaviours. Using data from a nationally representative cohort study of adolescents, the results presented in this chapter suggested that the direction of effect varied between different types of risky behaviour. In particular, I found that smoking predicted future depression and that depression predicted subsequent adolescent pregnancy. However, the effect sizes for these associations were relatively small in magnitude. In contrast to previous

studies and the findings from Chapter 3, I did not find any relationship between depression and alcohol use (in either direction). The results from both chapters indicated that the relationship between depression and risky behaviours is complex and possibly dependent on specific individual characteristics (e.g., sex and poverty status). Together, these findings emphasised the importance of moving beyond questions of associations to addressing more nuanced issues that explore under which circumstances a particular relationship might hold and when not.

These findings informed my third objective: to examine possible pathways by which depression might influence risky behaviours. Chapter 5 used a six-wave cohort study of adolescents to explore whether the relationship between depressive symptoms and risky behaviours is mediated through executive function. Results from the mediation model showed that executive function did not mediate the association between depression and risky behaviours, suggesting that other mediators may be at play. While I did not find a mediating effect, I found that persistent depressive symptoms over four years were associated with worse executive function in the following year, with the largest effect sizes observed for working memory. This may have important implications for developing effective interventions, which are discussed below.

My thesis's fourth and final objective was to bring the evidence from all chapters together and explore possibilities for innovative and scalable interventions targeting depression and risky behaviours among adolescents in low-resource settings. To this end, a smartphone application called the Kuamsha app was developed. Chapter 6 described the development of this app, which was co-constructed with more than 170 adolescents from rural South Africa and Uganda. The app development process was particularly innovative, as it was developed using multiple user-centred and participatory action research design methods. Drawing from the findings of the formative work, the Kuamsha app was developed using a narrative game format, in which the app teaches the principles of Behavioural Activation using storytelling techniques and game design elements. This approach might have contributed to the high engagement metrics found in the pre-pilot study. Taken together, this chapter generated new knowledge on how to ensure that mental health interventions are engaging, culturally relevant, and usable for the targeted population. While more evidence is needed to test the intervention's efficacy in reducing depressive symptoms and risky behaviours, preliminary results of early user testing showed that the Kuamsha app was acceptable in terms of usability and engagement. If the feasibility studies produce promising results, they will inform the development of a further larger randomised controlled trial which could support better management of depression among adolescents in low-resource settings and could strengthen primary and community-based healthcare systems.

Overall, in this thesis, I found that depression plays a vital role in developing and maintaining risky behaviours. These findings suggest that depressed adolescents carry a double burden; in addition to suffering from depression, they are at an increased risk of experiencing the negative consequences of the associated risky behaviours. This combination may result in further psychological and physical health problems that persist over the life course, further disadvantaging these adolescents.

STRENGTHS AND LIMITATIONS

This thesis has several strengths relating to the focus, methodology, and cohesive structure. This thesis focused on an understudied and underserved population: adolescents in LMICs. Most of the research on this topic comes from high-income countries, even though the burden of depression and risky behaviours is highest in LMICs (see Chapter 1). Evidence is necessary to both understand and target these issues. This thesis contributed to closing this gap by providing new empirical evidence on the importance of making adolescents in LMICs more visible to health professionals, policymakers, funders, and researchers.

The thesis has several methodological strengths. First, this thesis took an interdisciplinary approach to explore the relationship between depression and risky behaviours. In doing so, I relied on advanced econometric and statistical methods from the social sciences literature and applied these to the field of psychiatry. Further, several experts from different disciplines were consulted throughout the analysis and writing process, which helped to incorporate various cutting-edge approaches and ensure that the methods were appropriate for the questions at hand. Second, this thesis relied primarily on cohort studies of adolescents, which allowed me to determine the temporal relationship between depressive symptoms and risky behaviours. Third, the empirical studies had relatively large sample sizes, improving the precision of estimates. Fourth, Chapters 3 and 4 included nationally representative datasets, which helped to increase the external validity of my findings. Overall, the use of rigorous and robust methods provided the required statistical power to examine the relationship between depression and risky behaviours, and it increased confidence in my findings and their generalisability.

Another strength of my thesis is its cohesive structure, where all chapters formed different pieces of the puzzle that informed one another. By integrating the evidence from all the chapters, this thesis delivered rigorous evidence on predictors of depression, strength and consistency of the association between depression and risky behaviours, and explored possible mechanisms and pathways. It also helped inform innovative and scalable treatments that could reduce depressive

symptoms and risky behaviours.

This thesis also has several general limitations, which must be considered when interpreting the findings. First, this thesis explored the relationship between depression and risky behaviours using observational evidence, and thus, I could not infer causality. Issues like omitted variable bias and mismeasurement of variables might have resulted in biased estimates. While I included various control variables in the analyses, this thesis could not fully address all potential sources of bias. However, the repeated measure design allowed me to establish a temporal sequence between the variables of interest, reducing the possibility of reverse causality. Further, the structural equation modelling used in Chapters 4 and 5 reduced bias due to measurement error by incorporating latent variables error (Christ et al., 2014). Although further experimental work is needed, this thesis provided evidence about some necessary conditions to determine causality (such as the strength and consistency of the association and the temporal sequence of events).

The second limitation relates to possible measurement errors. Most of the chapters relied on self-report measures to ascertain depressive symptoms and risky behaviours, which might induce recall bias or measurement error. Furthermore, depressive symptoms scales were predominantly used across all chapters, which are not designed to ascertain a diagnostic status. However, most chapters relied on depressive symptom scales that were validated among adolescents in the study setting and demonstrated good psychometric properties when compared with diagnostic instruments. When available, I also triangulated self-reported data on risky behaviours with objective measures of risky behavioural outcomes (e.g., HIV infection, being a drug-dependent inpatient, or teenage pregnancy) to increase the validity and reliability of my findings.

Lastly, relying on secondary data meant that I was constrained by the available data measured in the primary studies. For example, three studies in this thesis were situated in South Africa, and thus important contextual differences should be considered when evaluating the implications for other low- and middle-income countries. Using secondary data also meant that the data was collected for purposes other than the objectives of this thesis. For example, Chapters 2 and 5 only included female participants since data was drawn from a study that aimed to explore whether providing cash transfers to adolescent females reduced the risk of acquiring HIV. Related to this limitation, most cohort studies had long gaps between survey waves, which limited the depth at which the relationship could be studied. While I could control for this in some models, this is a clear limitation of my thesis.

IMPLICATIONS AND FUTURE DIRECTIONS

This thesis has important implications. First, several chapters of this thesis (the meta-analysis and Chapters 4 and 5) found that adolescents with depressive symptoms are more likely to engage in risky behaviours than non-depressed adolescents. This implies that a comprehensive assessment of the burden of depression — already one of the most disabling and costly illnesses worldwide — would need to consider the possible knock-on effects that depression has on other outcomes such as risky behaviours (WHO, 2017).

Given this high burden, this thesis emphasises the importance of screening to identify adolescents at elevated risk of depression at an early age when intervention is likely to be more successful (Kieling et al., 2019). Early identification can help prevent a negative spiral of worsening outcomes over time and also have the potential to be an efficient strategy to support and strengthen population-level mental health (Herrman et al., 2022).

However, screening alone does not address the issue; and thus closing the existing treatment gap for mental health should be a priority (Chisholm et al., 2016). This is particularly relevant for treatments targeting adolescents, given the many changes that occur in their lives. For instance, adolescence is considered a period of heightened neural plasticity, during which the brain is particularly amenable to change and new experiences (Fuhrmann et al., 2015). This means that interventions may be especially effective during this time, offering a crucial window of opportunity for intervention (WHO, 2017).

The results from this thesis raise the possibility that treatments targeting depression may be cost-effective in reducing both depressive symptoms and risky behaviours. Recent reviews have supported this, although most of the evidence comes from studies conducted in high-income countries (Lennon et al., 2012; Sandler et al., 2014; Torrens et al., 2005).

In addition to targeting depression, this thesis found that adolescents with depression are at an increased risk of underperforming on executive function tasks. This finding is particularly relevant for adolescents in LMICs, given that executive function is known to be impaired among people living in poverty, which further disadvantages adolescents in low-resource settings (Evans, 2004; Ferguson et al., 2013; Johnson et al., 2016; Walker et al., 2011). The association between depression and executive function has implications for treatment since individuals with lower executive function show worse response and compliance to treatment (Snyder, 2013). It might also mean that interventions that target depression while simultaneously building these functions may be more effective than targeting either of them separately. For example, a review of programs for children and

adolescents aimed at developing executive functions found that programs that not only concentrated on developing these skills but also targeted adolescents' emotional, social, and physical development were more successful (Diamond & Lee, 2011; Greenberg et al., 1995).

Regarding directions for future research, this thesis consistently found a high burden of depression and risky behaviours across different settings and measures. However, as mentioned in Chapter 1, the empirical literature uses a wide range of metrics to measure depression and risky behaviours, making it often impossible to make comparisons. This can lead to inconsistent results and ultimately prevents advances in research. Future work should focus on agreeing on a set of common, psychometrically robust measures of depression and risky behaviours.

While this has already started to take place in the mental health community, similar initiatives should be developed to standardise the measurement of risky behaviours (Wolpert, 2020). Agreeing on a set of common metrics is essential to understanding the extent of the problem, comparing rates across settings, and ensuring that differences found are not simply artefacts of the way different studies have collected data.

In addition to having better data, there is a clear need for more cohort studies among adolescents in LMICs to further explore the relationship between depression and risky behaviours (Ward et al., 2018). These studies are critical to shed light on whether the relationship is unidirectional, bidirectional, or driven by some third variable. Cohort studies with high-frequency data will also improve our understanding of how different risk factors for depression and risky behaviours vary between individuals and across development. Ultimately, this may provide more insights into why adolescence is a period of high vulnerability to depression and risky behaviours, which individuals may be most at risk, and how to design effective interventions.

Further, this thesis found differential effects across different population subgroups, suggesting that depression and risky behaviours might affect some sections of the population more than others. For example, females were more likely to engage in risky sexual behaviour than males (Chapter 3). Adolescents living below the poverty line were more likely to experience recurrence of risky behaviours over time (Chapters 4 and 5). Future research should focus on these population subgroups to ensure no one is left behind. A better understanding of the mechanisms at play will help to inform policy and guide interventions targeting these vulnerable populations (Kieling et al., 2019).

This thesis mainly focused on health risk behaviours and did not consider the implications of social risks, such as the risk of social rejection by peers. Future work would likely benefit from recognising the role that social risk and social influence play in adolescent decision-

making and their mental health (Blakemore, 2018). For example, adolescents' strong sensitivity to social rejection might lead them to make decisions to avoid the risk of social exclusion, even if it means taking higher health and legal risks than they would choose in a situation without the presence of peers (Andrews et al., 2020). Interventions that mitigate the social risk of peer ostracisation and facilitate the creation of positive peer groups for adolescents may be particularly effective in reducing depression and risky behaviours (Pozuelo et al., 2020; Pozuelo & Kilford, 2021).

CONCLUSION

Around 4,000 adolescents die every average day from preventable causes such as road accidents, suicide, and HIV/AIDS (Ward et al., 2021). These deaths are related to depression and risky behaviours, which together represent leading causes of morbidity and mortality among adolescents (GBD, 2021).

Most of these deaths occur in LMICs, where 90% of the world's adolescents live, and social protection systems are poorly funded to provide adequate care (Ortiz-Ospina & Roser, 2020). This makes adolescents in LMICs more vulnerable to the negative consequences of depression and risky behaviours, putting them at a lifelong disadvantage.

Many of these deaths are preventable; thus, much of this disparity could be reduced if more efforts were directed to ensuring that adolescents in LMICs receive more timely and adequate treatments. Given the limited access to effective interventions in LMICs, innovative, scalable treatment delivery options are needed (Ersine et al., 2015).

With the increase in smartphone ownership and access to the internet, digital interventions that treat depression are a promising strategy to increase access to care in LMICs (Naslund et al., 2017; Tomlinson et al., 2013). This thesis provided preliminary evidence on the potential of a digital intervention to deal with depression and risky behaviours.

Taken together, the findings in this thesis highlight the importance of studying depression and risky behaviours jointly, a relationship that has so far remained relatively unaddressed among adolescents in LMICs. This robust relationship provides hope that mental health interventions can result in a virtuous cycle of increasing returns and, ultimately, improve adolescents' health in low-resource settings – a critical goal for global health research.

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Table A2.1 Number and share of participants who had at least a given number of assessments

Assessments	Sample size	Share
6	511	21%
≥5	1344	55%
≥4	1982	81%
≥3	2311	94%
≥2	2454	100%

Table A2.2 Testing non-random attrition across observables

VARIABLES	(1)
Depression score	-0.00
	(0.0)
Depression cut-off	0.02
	(0.0)
HIV positive	0.11
	(0.1)
Parental death	0.02
	(0.0)
Low parental support	-0.00
	(0.0)
Intimate partner violence	-0.01
	(0.0)
Extreme poverty	-0.01
	(0.0)
Food insecurity	-0.02
	(0.0)
Age	-0.00
	(0.0)
Level of education	0.03*
	(0.0)
Household asset index	0.17
	(0.1)
Employment status (=1 if work for pay)	-0.01
	(0.0)
Caregiver not parent	0.02
	(0.0)
Savings dummy (=1 if has savings)	-0.03
	(0.0)

Savings amount	-0.00
	(0.0)
Household government grants	-0.00
	(0.0)
Constant	0.16
	(0.1)
Observations	2,351
Attrition mean	0.33
R-squared	0.01
Adjusted R-squared	0.00
F test	1.56
Prob >F	0.1

Note: Robust standard errors in parentheses;

*** $p < 0.001$, ** $p < 0.01$, * $p < 0.05$

Table A2.3 Regression output for Model 1 and Model 2

Depression score:

VARIABLES	DEPRESSION SCORE					
	(1) HIV	(2) IPV	(3) Parental death	(4) Low parental support	(5) Food insecurity	(6) Consumption deciles
Age	-0.13 [0.2]	-0.12 [0.2]	-0.06 [0.2]	0.3 [0.3]	-0.03 [0.2]	-0.02 [0.2]
Education level	-0.13 [0.1]	-0.17 [0.1]	-0.26* [0.1]	-0.44* [0.2]	-0.11 [0.1]	-0.39** [0.1]
Household asset index	0.02 [0.0]	0.02 [0.0]	0.01 [0.0]	0 [0.0]	0.02 [0.0]	0 [0.0]
2.year	2.06*** [0.3]	1.97*** [0.3]	2.09*** [0.3]	1.99*** [0.4]	2.03*** [0.3]	2.21*** [0.3]
3.year	1.07** [0.4]	0.96* [0.4]	1.12** [0.4]	0.89 [0.7]	0.94* [0.4]	1.33** [0.4]
4.year	0.3 [0.5]	0.24 [0.5]	0.35 [0.6]	-0.11 [1.1]	0.1 [0.6]	0.67 [0.6]
5.year	1.57* [0.8]	1.76* [0.8]	1.58 [0.9]	0.88 [1.3]	1.46 [0.8]	1.81* [0.9]
6.year	-3.66** [1.2]	-3.35** [1.2]	-4.13** [1.4]		-4.25** [1.3]	
Risk factor (1) – (6)	-0.09 [0.5]	2.03*** [0.2]	0.33 [0.4]	1.37*** [0.3]	1.00*** [0.2]	-0.04 [0.0]
Constant	14.56*** [2.5]	14.27*** [2.5]	14.57*** [2.8]	9.63 [5.2]	12.48*** [2.6]	15.35*** [2.9]
Observations	10605	10529	9604	8014	10220	8980
R-squared	0.13	0.14	0.08	0.03	0.14	0.02
Number of individuals	2461	2460	2461	2460	2460	2461

Note: Robust standard errors in parentheses;

*** $p < 0.001$, ** $p < 0.01$, * $p < 0.05$

Depression caseness:

	DEPRESSION CASENESS					
VARIABLES	(1) HIV	(2) IPV	(3) Parental death	(4) Low parental support	(5) Food insecurity	(6) Consumption deciles
Age	0.86*	0.86*	0.84*	1.00	0.91	0.86
	[0.1]	[0.1]	[0.1]	[0.1]	[0.1]	[0.1]
Education level	1.03	1.01	1.02	1.09	1.05	1.01
	[0.0]	[0.0]	[0.1]	[0.1]	[0.1]	[0.1]
Household asset index	1.00	1.00	1.00	1.01	1.00	1.00
	[0.0]	[0.0]	[0.0]	[0.0]	[0.0]	[0.0]
2.year	3.20***	3.12***	3.27***	2.67***	3.03***	3.31***
	[0.4]	[0.3]	[0.4]	[0.5]	[0.3]	[0.4]
3.year	2.36***	2.29***	2.43***	1.65	2.10***	2.46***
	[0.4]	[0.4]	[0.4]	[0.5]	[0.4]	[0.4]
4.year	2.27***	2.25***	2.37***	1.31	1.91**	2.39***
	[0.5]	[0.5]	[0.6]	[0.6]	[0.4]	[0.6]
5.year	3.40***	3.67***	3.72***	1.95	2.97**	3.57***
	[1.1]	[1.2]	[1.3]	[1.1]	[1.0]	[1.3]
6.year	1.12	1.31	1.08		0.73	
	[0.6]	[0.7]	[0.6]		[0.4]	
Risk factor (1) – (6)	0.96	1.79***	1.18	1.38**	1.24**	1.00
	[0.2]	[0.1]	[0.2]	[0.2]	[0.1]	[0.0]
Observations	5,862	5,833	5,132	3,852	5,559	4,620
Number of individuals	1,281	1,280	1,230	1,117	1,263	1,185

Note: Robust standard errors in parentheses;

*** $p < 0.001$, ** $p < 0.01$, * $p < 0.05$

Table A2.4 Regression output for Model 3

VARIABLES	(1) HIV	(2) IPV	(3) Parental death	(4) Low parental support	(5) Food insecurity	(6) Consumption deciles
Age	-0.87*** [-0.977 - -0.760]	-0.76*** [-0.881 - -0.641]	-0.85*** [-0.971 - -0.725]	-0.93*** [-1.078 - -0.780]	-0.83*** [-0.966 - -0.684]	-0.88*** [-1.072 - -0.682]
Education level	0.48*** [0.284 - 0.677]	0.26* [0.051 - 0.476]	0.42*** [0.198 - 0.640]	0.35** [0.091 - 0.615]	0.33** [0.098 - 0.570]	0.46** [0.140 - 0.784]
Household asset index	0.03 [-0.003 - 0.056]	0.02 [-0.013 - 0.049]	0.02 [-0.009 - 0.057]	0.03 [-0.006 - 0.069]	0.04* [0.000 - 0.070]	0.01 [-0.033 - 0.060]
Three years prior (Y _{-3, it})	-0.33 [-1.989 - 1.326]	-2.35*** [-3.513 - -1.193]	-0.23 [-1.746 - 1.281]	-1.34* [-2.673 - -0.009]	-0.83 [-1.996 - 0.344]	-0.09 [-1.940 - 1.752]
Two years prior (Y _{-2, it})	1.09 [-0.634 - 2.823]	-0.70 [-1.555 - 0.148]	1.15 [-0.310 - 2.607]	-1.05* [-2.006 - -0.092]	-0.21 [-1.262 - 0.835]	-0.05 [-1.471 - 1.372]
Time of event (Y _{0, it})	1.50 [-0.087 - 3.081]	2.68*** [2.037 - 3.331]	2.07*** [0.915 - 3.220]	1.11** [0.448 - 1.774]	2.59*** [1.822 - 3.351]	2.07*** [1.162 - 2.972]
One year after (Y _{1, it})	0.13 [-1.757 - 2.021]	1.40*** [0.643 - 2.153]	0.52 [-0.790 - 1.821]	0.55 [-0.209 - 1.316]	1.11* [0.223 - 1.991]	1.02 [-0.012 - 2.059]
Two years after (Y _{2, it})	-0.02 [-2.559 - 2.528]	1.34** [0.459 - 2.227]	0.75 [-0.757 - 2.255]	0.26 [-0.674 - 1.201]	0.48 [-0.605 - 1.564]	0.73 [-0.582 - 2.033]
Three years after (Y _{3, it})	-0.66 [-2.897 - 1.575]	0.04 [-0.779 - 0.864]	1.82** [0.484 - 3.164]	1.05* [0.144 - 1.947]	0.22 [-0.747 - 1.192]	1.14 [-0.001 - 2.287]
Constant	21.92*** [20.948 - 22.902]	21.58*** [20.390 - 22.778]	22.02*** [20.880 - 23.160]	24.30*** [22.671 - 25.921]	21.71*** [20.392 - 23.027]	21.59*** [19.712 - 23.478]
Observations	10,351	8,794	8,070	6,565	6,971	3,874
R-squared	0.07	0.09	0.07	0.08	0.09	0.08
Number of individuals	2,389	2,040	1,855	1,525	1,627	936

Note: 95% confidence intervals in brackets; *** $p < 0.001$, ** $p < 0.01$, * $p < 0.05$

Table A3.1 Sample search stream strategy (Medline)

Overarching term	Query	Items found
Adolescents (#1)	adolescent / or young adult / or child / or teen / or adolescen* / or girl* / or boy* / or "young* people" / or "young* person" / or "young* adult*" / or "young* men" / or "young* women" / or youth* / or "school* age*" / or child* / or "middle school*" / or "high school*" / or "secondary school*" / or "college-age"	2,998,015
Depression (#2)	"depressive symptoms" / or "depressive symptom" / or "major depression" / or Depression / or "Depressive Disorder" / or "Depress"	505,855
Risk-taking (#3)	Risk-Taking / or "risk behavio*" / or "sensation-seek*" / or "thrill-seek* behav*" / or "reckless behavio*"	25,559
Risk sexual behaviour (#4)	"risky sexual behavio*" / or "sexual disease transmission" / or "Sexually Transmitted Diseases" / or "sexually transmitted infection*" / or STI* / or STD* / or HIV* / or "human immunodeficiency virus*" / or "unsafe sex" / or "unprotected sex" / or "casual sex" / or "early pregnanc*" / or "unplanned pregnancy" / or "unwanted pregnancy" / or "multiple partner*" / or "early coital debut" / or "impulsive sex" / or "older partner*" / or "transactional sex"	31,181
Substance abuse (#5)	"substance abuse" / or "substance use disorder" / or "drug abuse" / or "underage drink*" / or "binge drink*" / or "substance-related disorder*" / or "substance use disorder*" / or drug* / or addiction* / or dependence / or "alcohol abuse" / or opioids / or cannabis / or cocaine / or heroin / or inhalants / or "street drug"	225,060
Adverse school behaviour (#6)	"School absenteeism" / or "school dropout" / or "school absence" / or expulsion / or suspension / or truancy / or cheating / or "Skip* school*" / or absenteeism / or "miss* school" / or "irregular school attendance" / or "poor learning outcomes" / or "school performance" / or "low* school performance"	13,480
Delinquency (#7)	delinq* / or "delinquent act*" / or "juvenile delinquen*" / or crime* / or "violence" / or "bully*" / or "gang*" / or fight* / or vandalism / or "reckless driving" / or "drug dealer" / or prison / or "reckless driv*" or theft* / or robbery / or shoplift*	50,360
Self-harm / suicidal behaviour (#8)	Suicide / or suicidal / or "attempt* suicide" / or "suicidal ideation" / or self-harm	44,600
Setting (#9)	(developing or "less\$ developed" or "third world" or "under developed" or "middle income" or "low* income" or underserved or "under served" or deprived or poor\$) adj (count\$ or nation? or state? or population?)	84,373
Specific countries (#10)	"afghanistan" / or "afghan" / or "Afghanistan" / or "Afghanistan" / or "Albania" / or "Albania" / or "Algeria" / or "Algeria" / or "American Samoa" / or "American Samoa" / or "Angola" / or "Angola" / or "argent" / or "Argentina" / or "Armenia" / or "Armenia" / or "Azerbaijan" / or "Azerbaijan" / or "Bangladesh" / or "Bangladesh" / or	1,609,074

	"Belarus"/ or "Belarus"/ or "Belarus"/ or "byelorussia"/ or "Belize"/ or "Belize"/ or "Benin"/ or "Benin"/ or "benin dahomey"/ or "benin/dahomey"/ or "Bhutan"/ or "Bhutan"/ or "bnlgldsh"/ or "Bolivia"/ or "Bolivia"/ or "Bolivia (Plurinational State of)"/ or "bosnia"/ or "bosnia and hercegovina"/ or "Bosnia and Herzegovina"/ or "Bosnia and Herzegovina"/ or "bosnia hercegov"/ or "bosnia hercegovina"/ or "bosnia hercegovina"/ or "bosnia hercegov"/ or "bosnia hercegovina"/ or "bosnia/hercegovina"/ or "bosnia/hercegovina"/ or "bosnia/hercegovina"/ or "bosnia/herzogovina"/ or "bosniaher"/ or "bosniahercegov"/ or "bosniahercegovina"/ or "bosniahercegov"/ or "bosniahercegovina"/ or "Botswana"/ or "Botswana"/ or "Brazil"/ or "Brazil"/ or "Bulgaria"/ or "Bulgaria"/ or "bur"/ or "burkina"/ or "Burkina Faso"/ or "Burkina Faso"/ or "burkina faso upper volta"/ or "Burundi"/ or "Burundi"/ or "byelorussia"/ or "c african rep"/ or "c_africa"/ or "Cabo Verde"/ or "Cabo Verde"/ or "cambod"/ or "Cambodia"/ or "Cambodia"/ or "cambodia kampuchea"/ or "Cameroon"/ or "Cameroon"/ or "cameroun"/ or "Cape Verde"/ or "cen african rep"/ or "central african empire"/ or "Central African Rep."/ or "Central African Republic"/ or "Central African Republic"/ or "ceylon"/ or "Chad"/ or "Chad"/ or "China"/ or "China"/ or "china mainland"/ or "Colombia"/ or "Colombia"/ or "Comoros"/ or "Comoros"/ or "Congo"/ or "Congo (Brazzaville)"/ or "Congo (Kinshasa)"/ or "congo brazzaville"/ or "congo brazzaville"/ or "congo brazzaville"/ or "congo brazzaville"/ or "congo brazzaville"/ or "congo brazzaville"/ or "congo dem r"/ or "congo dem rep"/ or "congo democratic rep of"/ or "congo democratic republic of"/ or "congo dr zaire"/ or "congo droc"/ or "congo kinshasa"/ or "congo rep"/ or "congo rep of"/ or "congo republic of"/ or "congo roc"/ or "Congo-Brazzaville"/ or "Congo-Kinshasa"/ or "Congo, Dem. Rep"/ or "Congo, Dem. Rep."/ or "Congo, Democratic Republic of"/ or "Congo, Rep."/ or "Congo, Rep."/ or "Congo, Republic of"/ or "cos_rica"/ or "Costa Rica"/ or "Costa Rica"/ or "costarica"/ or "Cote d'Ivoire"/ or "Côte d'Ivoire"/ or "Côte d'Ivoire"/ or "cote d'ivoire"/ or "Croatia"/ or "Cuba"/ or "Cuba"/ or "dahomey"/ or "dem rep congo"/ or "Dem. People's Republic of Korea"/ or "democratic kampuchea"/ or "Democratic People's Republic of Korea"/ or "Democratic Republic of Congo"/ or "Democratic Republic of the Congo"/ or "democratic republic of vietnam"/ or "Djibouti"/ or "Djibouti"/ or "dom_rep"/ or "Dominica"/ or "Dominica"/ or "dominica is"/ or "dominican rep"/ or "Dominican Republic"/ or "Dominican Republic"/ or "east timor"/ or "east timor leste"/ or "east timor timorleste"/ or "eastern samoa"/ or "Ecuador"/ or "Ecuador"/ or "Egypt"/ or "egypt arab rep"/ or "Egypt Arab Rep."/ or "Egypt Arab Republic"/ or "Egypt, Arab Rep."/ or "Egypt, Arab Rep."/ or "Egyt, Arab
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	Republic"/ or "El Salvador"/ or "El Salvador"/ or "eq guinea"/ or "eq_gnea"/ or "Equatorial Guinea"/ or "Equatorial Guinea"/ or "Eritrea"/ or "Eritrea"/ or "Ethiopia"/ or "Ethiopia"/ or "f st micronesia"/ or "federated states of micronesia"/ or "Fiji"/ or "Fiji"/ or "former yugoslav republic of macedonia"/ or "g bissau"/ or "g_bisau"/ or "g_bissau"/ or "Gabon"/ or "Gabon"/ or "Gambia"/ or "Gambia, The"/ or "Gambia, The"/ or "Georgia"/ or "Georgia"/ or "Ghana"/ or "Ghana"/ or "gilbert islands"/ or "Grenada"/ or "Grenada"/ or "grenada is"/ or "Guatemala"/ or "Guatemala"/ or "guatemala"/ or "Guinea"/ or "Guinea"/ or "guinea bissau"/ or "guinea equatorial"/ or "Guinea-Bissau"/ or "Guinea-Bissau"/ or "guineabissau"/ or "Guyana"/ or "Guyana"/ or "Haiti"/ or "Haiti"/ or "hondura"/ or "Honduras"/ or "Honduras"/ or "hvo"/ or "India"/ or "India"/ or "indones"/ or "Indonesia"/ or "Indonesia"/ or "Iran"/ or "Iran (Islamic Republic of)"/ or "iran islamic rep"/ or "iran islamic rep."/ or "iran islamic republic of"/ or "iran islamic republic of"/ or "Iran, Islamic Rep."/ or "Iran, Islamic Rep."/ or "Iran, Islamic Republic"/ or "Iran, Islamic Republic of"/ or "Iraq"/ or "Iraq"/ or "ivory coast"/ or "ivy_cst"/ or "Jamaica"/ or "Jamaica"/ or "Jordan"/ or "Jordan"/ or "jordan"/ or "kampuchea"/ or "Kazakhstan"/ or "Kazakhstan"/ or "kazakhstan"/ or "Kenya"/ or "Kenya"/ or "kenya"/ or "kez"/ or "kirghistan"/ or "kirgizia"/ or "Kiribati"/ or "Kiribati"/ or "korea dem people's rep"/ or "Korea, Dem. People's Rep."/ or "Korea, Dem. Rep."/ or "Kosovo"/ or "Kosovo"/ or "kyrgyz republic"/ or "kyrgyzstan"/ or "kyrgyz rep"/ or "Kyrgyz Republic"/ or "Kyrgyz Republic"/ or "Kyrgyzstan"/ or "lao"/ or "lao pdr"/ or "Lao PDR"/ or "lao people's democratic republic"/ or "Laos"/ or "Lebanon"/ or "Lebanon"/ or "Lesotho"/ or "Lesotho"/ or "Liberia"/ or "Liberia"/ or "Libya"/ or "Libya"/ or "libyan arab jamahiriya"/ or "Macedonia"/ or "Macedonia, former Yugoslav Republic of"/ or "Macedonia, FYR"/ or "Macedonia, FYR"/ or "madagas"/ or "Madagascar"/ or "Madagascar"/ or "malagasy"/ or "malagasy republic"/ or "Malawi"/ or "Malawi"/ or "Malaysia"/ or "Malaysia"/ or "maldives islands"/ or "Maldives"/ or "Maldives"/ or "Mali"/ or "Mali"/ or "marshall is"/ or "Marshall Islands"/ or "Marshall Islands"/ or "Mauritania"/ or "Mauritania"/ or "Mauritius"/ or "Mauritius"/ or "Mauritius"/ or "Mauritius"/ or "Mexico"/ or "Mexico"/ or "Micronesia"/ or "Micronesia (Fed. States of)"/ or "Micronesia (Federated States of)"/ or "micronesia fed sts"/ or "micronesia federated states of"/ or "Micronesia, Fed. Sts."/ or "Micronesia, Fed. Sts."/ or "moldavia"/ or "Moldova"/ or "Moldova"/ or "moldova moldavia"/ or "moldova republic of"/ or "mongola"/ or "Mongolia"/ or "Mongolia"/ or "Montenegro"/ or "Montenegro"/ or "Morocco"/ or "Morocco"/ or "Mozambique"/ or "Mozambique"/ or "mozambq"/ or "mritius"/ or "Myanmar"/ or "Myanmar"/ or "Namibia"/ or "Namibia"/ or "Nauru"/ or "Nauru"/ or "Nepal"/ or "Nepal"/ or "new hebrides"/ or "nicaraga"/ or "Nicaragua"/ or
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	"Nicaragua"/ or "Niger"/ or "Niger"/ or "Nigeria"/ or "Nigeria"/ or "North Korea"/ or "north vietnam"/ or "Occupied Palestinian Territory"/ or "ottoman empire"/ or "Pakistan"/ or "Pakistan"/ or "Palestine"/ or "Palestinian Territories"/ or "Panama"/ or "Papua New Guinea"/ or "Papua New Guinea"/ or "papua ng"/ or "paragua"/ or "Paraguay"/ or "Paraguay"/ or "Peru"/ or "Peru"/ or "phil"/ or "Philippines"/ or "Philippines"/ or "rep of congo"/ or "rep of s sudan"/ or "rep of south sudan"/ or "republic of moldova"/ or "republic of south sudan"/ or "rhodesia"/ or "Romania"/ or "Romania"/ or "rumania"/ or "Russia"/ or "Russian Federation"/ or "Russian Federation"/ or "Rwanda"/ or "Rwanda"/ or "s africa"/ or "s_africa"/ or "Saint Lucia"/ or "saint vincent"/ or "saint vincent and grenadines"/ or "Saint Vincent and the Grenadines"/ or "saint vincent grenadines"/ or "salvador"/ or "salvadr"/ or "Samoa"/ or "Samoa"/ or "samoa american"/ or "sao tome and prin"/ or "Sao Tome and Principe"/ or "São Tomé and Principe"/ or "sao tome prin"/ or "sao tome principe"/ or "sao tomeprincipe"/ or "Senegal"/ or "Senegal"/ or "Serbia"/ or "Serbia"/ or "sier_ln"/ or "Sierra Leone"/ or "Sierra Leone"/ or "solomon is"/ or "Solomon Islands"/ or "Solomon Islands"/ or "Somalia"/ or "Somalia"/ or "South Africa"/ or "South Africa"/ or "South Sudan"/ or "South Sudan"/ or "south sudan rep of"/ or "south sudan republic of"/ or "Sri Lanka"/ or "Sri Lanka"/ or "sri lanka ceylon"/ or "sri lanka exceilan"/ or "sri_lka"/ or "st lucia"/ or "st lucia is"/ or "st vinc and gren"/ or "st vinc gren"/ or "st vincent and grenadines"/ or "st vincent grenadines"/ or "St. Lucia"/ or "St. Lucia"/ or "St. Vincent and Grenadines"/ or "St. Vincent and the Grenadines"/ or "St. Vincent and the Grenadines"/ or "State of Palestine"/ or "Sudan"/ or "Sudan"/ or "surinam"/ or "Suriname"/ or "Suriname"/ or "Swaziland"/ or "Swaziland"/ or "Syria"/ or "syrian arab republic"/ or "Syrian Arab Republic"/ or "tadzhikistan"/ or "Tajikistan"/ or "Tajikistan"/ or "tanganyika"/ or "Tanzania"/ or "Tanzania"/ or "tanzania united republic of"/ or "tanzania/tanganyika"/ or "TFYR Macedonia"/ or "Thailand"/ or "Thailand"/ or "The former Yugoslav Republic of Macedonia"/ or "The former Yugoslav Republic of Macedonia"/ or "The Gambia"/ or "Timor"/ or "timor leste"/ or "Timor-Leste"/ or "Timor-Leste"/ or "timorleste"/ or "timorleste east timor"/ or "Togo"/ or "Togo"/ or "Tonga"/ or "Tonga"/ or "Tunisia"/ or "Tunisia"/ or "Turkey"/ or "Turkey"/ or "turkey/ottoman empire"/ or "turkmenia"/ or "turkmenist"/ or "Turkmenistan"/ or "Turkmenistan"/ or "Tuvalu"/ or "Tuvalu"/ or "Uganda"/ or "Uganda"/ or "Ukraine"/ or "Ukraine"/ or "united republic of tanzania"/ or "upp"/ or "upper volta"/ or "Uzbekistan"/ or "Uzbekistan"/ or "Vanuatu"/ or "Vanuatu"/ or "venez"/ or "Venezuela"/ or "Venezuela (Bolivarian Republic of)"/ or "venezuela rb"/ or "Venezuela, RB"/ or "Venezuela, RB"/ or "Venezuela, Republica Bolivariana de"/ or "viet nam"/ or "Vietnam"/ or "Vietnam"/ or "vietnam	
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	democratic rep"/ or "vnmn"/ or "west bank and gaza"/ or "West Bank and Gaza"/ or "western samoa"/ or "Yemen"/ or "yemen rep"/ or "Yemen, rep"/ or "Yemen, rep."/ or "Yemen, Rep."/ or "zaire"/ or "zaire congo kinshasa"/ or "zaire democratic republic of congo"/ or "zaire/dem rep of congo"/ or "Zambia"/ or "Zambia"/ or "Zimbabwe"/ or "Zimbabwe"/ or "zimbabwe rhodesia"	
Combining search terms: study setting (#11)	9 or 10	1,651,847
Combining search terms: (#12) Adolescent + Depression + Risk-taking + Study setting	1 and 2 and 3 and 11	159
(#13) Adolescent + Depression + Risk sexual behaviour + Study setting	1 and 2 and 4 and 11	94
(#14) Adolescent + Depression + Substance abuse + Study setting	1 and 2 and 5 and 11	526
(#15) Adolescent + Depression + Risky behaviour in school + Study setting	1 and 2 and 6 and 11	20
(#16) Adolescent + Depression + Delinquency + Study setting	1 and 2 and 7 and 11	255
(#17) Adolescent + Depression + Self-harm + Suicidal behaviour + Study setting	1 and 2 and 8 and 11	661
(#12 - #17)	12 or 13 or 14 or 15 or 16 or 17	1,464

Table A3.2. Low- and middle-income countries (World Bank classification 2017)

Afghanistan	Dominica	Lesotho	Samoa
Albania	Dominican Republic	Liberia	São Tomé and Príncipe
Algeria	Ecuador	Libya	Senegal
American Samoa	Egypt, Arab Rep.	Macedonia, FYR	Serbia
Angola	El Salvador	Madagascar	Sierra Leone
Argentina	Equatorial Guinea	Malawi	Solomon Islands
Armenia	Eritrea	Malaysia	Somalia
Azerbaijan	Eswatini (Swaziland)	Maldives	South Africa
Bangladesh	Ethiopia	Mali	South Sudan
Belarus	Fiji	Marshall Islands	Sri Lanka
Belize	Gabon	Mauritania	St. Lucia
Benin	Gambia, The	Mauritius	St. Vincent and the Grenadines
Bhutan	Georgia	Mexico	Sudan
Bolivia	Ghana	Micronesia, Fed. Sts.	Suriname
Bosnia and Herzegovina	Grenada	Moldova	Syrian Arab Republic
Botswana	Guatemala	Mongolia	Tajikistan
Brazil	Guinea	Montenegro	Tanzania
Bulgaria	Guinea-Bissau	Morocco	Thailand
Burkina Faso	Guyana	Mozambique	Timor-Leste
Burundi	Haiti	Myanmar	Togo
Cabo Verde	Honduras	Namibia	Tonga
Cambodia	India	Nauru	Tunisia

Cameroon	Indonesia	Nepal	Turkey
Central African Republic	Iran, Islamic Rep.	Nicaragua	Turkmenistan
Chad	Iraq	Niger	Tuvalu
China	Jamaica	Nigeria	Uganda
Colombia	Jordan	Pakistan	Ukraine
Comoros	Kazakhstan	Panama	Uzbekistan
Congo, Dem. Rep	Kenya	Papua New Guinea	Vanuatu
Congo, Rep.	Kiribati	Paraguay	Venezuela, RB
Costa Rica	Korea, Dem. People's Rep.	Peru	Vietnam
Côte d'Ivoire	Kosovo	Philippines	West Bank and Gaza
Croatia	Kyrgyz Republic	Romania	Yemen, Rep.
Cuba	Lao PDR	Russian Federation	Zambia
Djibouti	Lebanon	Rwanda	Zimbabwe

Source: World Bank (2017)

Table A3.3. Characteristics of included studies

Study	Country	Setting	Race/ ethnicity	Sample size	% of female s	Age range	Study design	Depression measure (cut-off)	Type of risky behavior	NOS	Description of the study population
Risky sexual behaviour											
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,	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

			Indian/ Asian , White)								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 $\geq$ 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 sociodemographic 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, 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, 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 behaviour	5	Case-control study conducted in Ankara, Turkey with 22 adolescents who show violent behaviour 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) 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 difference 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, 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 behaviour	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 children (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 Behaviour											
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 behaviour	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% ethnic minority, 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 (2017) ⁶⁷	Brazil	Urban	73.3% White; 26.5% Non-white	1244	58%	18 to 24	Cohort	MINI	Suicidal behaviour	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 Behaviour Checklist; YSR = Youth Self-Report Questionnaire – depression subscale. Risky behaviour measures: RBQ-A = Risky Behaviour Questionnaire for Adolescents. ^aData for 10-24 year olds was requested from corresponding author.											

Table A3.4 Excluded studies with reasons

Reason	Study
Wrong country (251 studies)	Abler 2015; Abram 2015; Adams 1999; Adrian 2016; Aiyer 2014; Akiskal 1985; Akse 2007; Al-Ansari 1997; Alvarado 2005; Andrade 2008; Arango 2018; Armistead 1992; Asselmann 2018; Auerbach 2010; Auerbach 2017; Bagge 2017; Bahk 2015; Bahk 2015; Bardone 1996; Bardone 1998; Barnes 2009; Baumann 2014; Beal 2014; Bechtold 2015; Bedi 2010; Beesdo-Baum 2013; Beghi 2013; Bekman 2010; Berk 2010; Beyers 2003; Bhatia 2011; Bhushan 2013; Biederman 2006; Bilal 2018; Bilevicius 2018; Björk 2015; Black 2009; Blonigen 2013; Boden 2011; Boersma 2014; Bogart 2007; Boschloo 2014; Brensilver 2011; Brière 2014; Brière 2017; Bruce 2017; Brunstein Klomek 2019; Burke 2012; Burns 2004; Burton 2013; Buu 2009; Cáceda 2014; Campos 2016; Caprara 2010; Carvajal 2012; Chang 2019; Chartrand 2012; Chaudhury 2016; Chavira 2010; Chen 2016; Chen 2017; Cheng 2013; Choi 2016; Cohen 2017; Colder 2017; Collishaw 2016; Cornelius 2016; Costello 2003; Cruz 2017; Culatta 2017; Dahlen 2015; Dale 2010; Davila 2009; Degenhardt 2003; Degenhardt 2011; Delorenze 2010; Dervic 2006; Dew 1997; Diamantopoulou 2010; Diaz 2019; DiClemente 2001; Donovan 2003; Dube 2003; Dumais 2005; Elkins 2006; Engelmann 2013; Ernst 2006; Farmer 2009; Fazel 2008; Felleman 2013; Felton 2015; Fendrich 2013; Fielder 2014; Fisher 2016; Fornaro 2013; Foster 2018; Gadow 2012; Gallagher 2014; Galvan 2007; Ghobadadeh 2018; Gidding 2017; Giletta 2017; Glozier 2014; Goetz 1991; Goetz 2001; Gressier 2017; Guendelman 2015; Guimond 2016; Gunn 2016; Guo 2017; Gvion 2015; Hadlaczkzy 2018; Hall 2015; Hallfors 2005; Hendin 2004; Hengartner 2018; Henquet 2006; Henrich 2004; Hien 2003; Holler 2013; Holtmann 2011; Hourani 2018; Hsieh 2018; Huang 2017; Hussong 2017; Ingoldsby 2006; Johnson 1995; Jones 2011; Jonsson 2011; Karlsson 2006; Kashyap 2015; Kedzior 2014; Kiekens 2018; Klein 2016; Kogan 2017; Kwok 2018; Lalayants 2014; Land 2003; Lansford 2008; Lau 2018; Lev-Ran 2014; Levers-Landis 2015; Lewcun 2018; Li 2012; Liang 2015; Lin 2012; Lin 2013; Lin 2016; Liu 2014; Lopez-Quintero 2018; Mackie 2011; Malamut 2017; Marsh 2016; Marshal 2011; Maser 2002; McCarty 2013; McGirr 2008; McKown 2013; McLaughlin 2014; Measelle 2006; Miller 2017; Miller 2017; Mimiaga 2015; Mojtabai 2015; Nam 2018; Nelson 2017; Nery 2009; Neumann 2003; Newton-Howes 2015; Nruham 2010; O'Donnell 2016; O'Leary-Barrett 2015; Odlaug 2013; Oldehinkel 1999; Olson 1999; Orth 2014; Otten 2010; Ouellet-Morin 2015; Ozkan 2018; Paavonen 2016; Pan 2017; Panagioti 2015; Park 2017; Parrish 2016; Pasch 2012; Pedersen 2007; Prigerson 1999; Puig-Antich 1989; Reef 2009; Reinke 2012; Ren 2018; Ribeiro 2012; Rice 2017; Roche 2011; Roy 2015; Ruchkin 2007; Saban 2010; Scafidi 1997; Scholes-Balog 2015; Schraedley 2002; Schwartz 2019; Seeley 2009; Serafini 2018; Seymour 2014; Shahar 2006; Shannon 2008; Shim 2018; Shrier 2002; Simon 2002; Simon 2013; Simons 2012; Stewart 2018; Stone 2016; Sullivan 2018; Sun 2016; Surrence 2009; Takahashi 2012; Teesson 2009; Toupin 2008; Trim 2007; Troister 2012; Tubman 1996; Tully 2010; Valencia-Agudo 2018; Vander Stoep 2011; Vrangalova 2015; Wagner 2015; Wang 2013; Weissman 1992; Wemm 2018; Weng 2017; Whiteley 2010; Wiesner 2003; Wiesner 2006; Wiesner 2006; Wilson 2012; Winokur 1998; Wittchen 2007; Womack 2016; Wong 2008; Wu 2008; Xu 2016; Yoshimasu 2016; You 2012; You 2015; Yu 2017; Yule 2018; Zappitelli 2013; Zeller 2015; Zhang 2017; Zhao 2015
Wrong outcomes (151 studies)	Abas 2013; Abdollahi 2014; Akhila 2010; Alderete 2012; AlHamid 2014; Amone-P'Olak 2013; Amone-P'Olak 2017; Anaya-Ocampo 2006; Baddock 2013; Baguma 2005; Bellieni 2013; Benner 2018; Berard 1999; Betancourt 2010; Betancourt 2010; Betancourt 2010; Betancourt 2014; Betancourt 2015; Bijker 2017; Bitew 2014; Boateng 2017; Bolak Boratav 2016; Borges 2004; Boyes 2014; Boyes 2015; Brito 2015; Burić 2018; Burleigh 2018; Byakika-Tusiime 2009; Cairns 2014; Cao 2016; Casas 2012; Cavalcante 2017; Cheng 2012; Chi 2014; Cluver 2007; Cluver 2012; Cohen 2009; Conference 2013; Cote 2014; Dai 2012; Defechereux 2016; Demir 2016; Devries 2013; Dhir 2018; Dow 2014; El Mhamdi 2013; Erskine 2016; Ezeamama 2016; Ezeamama 2016; Faisal-Cury 2017; Fatori 2013; Fontenelle 2006; Gebrezgabher 2017; Gelaye 2019; Haberer 2018; Hadjkacem 2013; Hadžikapetanović 2017; Hall 2014; Hamidi 2013; Hansrod 2015; Idaiani 2011; Imran 2014; Jasen 2013; Jewkes 2013; Joshi 2019; Kahraman 2018; Kaida 2014; Karaçam 2018; Keles 2019; Kheirabadi 2010; Khemakhem 2017; Khosravi 2015; Ko 2009; Koegler 2018; Konradt 2013; Koposov 2011; Kotan 2018; Krumme 2015; Kumar 2014; Kumar 2014; Lara 2016; Lau 2017; Lau 2018; Le 2017; Li 2019; Liang 2016; Liu 2017; Liu 2018; Lopes 2002; Lwido 2018; Martin 2016; Mayston 2014; Melo Jr 2012; Muller 2016; Munhoz 2017; Mutavi 2018; Nakasujja 2010; Nazir 2016; Niratttharadorn 2005; Norman 2012; Oğuz 2002; Panter-Brick 2011; Peng 2018; Pottinger 2009; Protopopescu 2009; Qandil 2016; Qun 2014; Ribeiro 2009; Roach 2018; Rozanov 2011; Ryu 2018; Sar 2004; Sheikmoonesi 2012; Shin 2008; Siegel 2014; Simon 2004; Slabbert 2015; Stein 2015; Sudfeld 2017; Surkan 2018; Thornicroft 1993; Tsai 2016; Tsuyuki 2019; Tu 2012; Tucci 2010; Turan 2014; Turkcapar 2015; van Heerden 2017; van Loo 2014; Vargas 2013; Velloza 2017; Wado 2014; Wang 2018; Weobong 2014; Whetten 2013; Whetten 2013; Wouters 2016; Wyatt 2017; Xie 2013; Yao 2013; Yotebieng 2017; Yu 2009; Zalwango 2016; Zegeye 2018; Zhang 2013; Zhang 2016; Zhang 2016; Zhang 2016; Zhao 2014; Zulčić-Nakić 2012
Wrong study design (104 studies)	Abdel-Khalek 1999; Abdullah 2018; Abdullah 2018; Acharya 2010; Afghah 2014; Agardh 2012; Ahmadpanah 2017; Akman 2007; Alptekin 2006; Becker 2009; Betancourt 2012; Bi 2010; Blignaut 2015; Boeckel 2014; Braham 2016; Brown 1997; Brown 2017; Burlea 2010; Chakrabarti 2004; Chang 2009; Chavez-Hernandez 2018; Chen 2013; Chowdhury 2014; Chowdhury 2014; Ciftci 2015; Conference 2013; Costa 2014; Crijnen 1999; Davis 2017; DeGraaf 2010; Dibaba 2013; Douzenis 2005; Dunlavy 2015; Edhborg 2015; Estacio 2017; Fang 2015; Farias 2013; Ghaddar 2017; Ghosh 2007; Goncalves 2017; Gupta 2008; Hadjiiski 1996; Halayem 2018; Hall 2007; Harrington 2018; Hartwig 2018; Hawton 2013; Joksimovic 2015; Kanchan 2008; Kantarci 2013; Karanikola 2018; Ke 2014; Kheirabadi 2009; Kılıç 2017; Knipe 2019; Krishnakumar 2005; Krishnakumar 2006; Kumar 2015; Kunzweiler 2016; Lari 2007; Lau 2010; Liddell 2013; Madrigal de León 2018; Makanjuola 1992; Marshall 2010; Meeus 2018; Narayanaswamy 2012; Nasiroglu 2012; Nazir 2013; Nguyen 2016; Nothling 2013; Ogbonna 2019; Okubadejo 2007; Onat 2018; Patil 2011; Podeul 2010; Polshkova 2016; Portzky 2007; Pranjić 2010; Quintana 2013; Rajapakse 2016; Reyna-Medina 2013; Rezaei 2017; Risal 2010; Rotenstein 2016; Şahin 1998; Sayil 2006; Sherman 2010; Shi 2018; Shoostari 2014; Soheyla 2016; Stein 2009; Sullivan 2004; Sutcliffe 2009; Ulusoy 2005; Ulusoy 2006;

	Unger 2011; Vásquez-Rojas 2013; Vink 2010; Vythilingum 2012; Wang 2016; Yang 2017; Zhang 2006; Zhang 2009
Wrong age group (75 studies)	Adejumo 2016; Ahmadi 2015; Alves 2016; Armes 2018; Atkinson 2011; Bozkurt 2014; Brunoni 2013; Cavicchioli 2018; Chen 1995; Chen 2014; Cheung 2008; Choi 2017; Chowdhary 2008; De Almeida 2005; DeAldaz 1987; Dedic 2010; Ebenezer 2016; Erfan 2010; Fernandez 2018; Ghorbani 2017; Govender 2012; Grover 2016; Grover 2016; Ignjatović-Ristić 2011; Incedere 2017; Javadian 2016; Jia 2010; Jia 2017; Jin 2010; Jin 2013; Kakuszi 2018; Kanmogne 2017; Kekwaletswe 2017; Kim 2011; Kinyanda 2005; Koyuncu 2015; Lee 2015; Lemos 2012; Li 2012; Li 2017; Lin 2017; Liu 2016; Liu 2017; Lyu 2018; Lyu 2019; Malbergier 2001; Manoranjitham 2010; Mao 2019; Nyongesa 2018; Peltzer 2018; Pitpitan 2012; Rabe-Jabłońska 2002; Rancić 2012; Sackey 2017; Sae-Han 2002; Sajjadi 2015; Sall 2009; Scanavino 2018; Selvi 2010; Sureka 2017; Troeman 2011; Villa-Manzano 2009; Wagner 2014; Wang 2018; Wei 2017; Wei 2018; White 2016; Xin 1992; Yang 2014; Yu 2019; Zhang 2010; Zhang 2010; Zhang 2013; Zhang 2015; Zhang 2019
Wrong control group (28 studies)	Adnams 2014; Al Ansari 2001; Atwoli 2014; Atwoli 2014; Barrimi 2014; Bhardwaj 2018; Bilginer 2017; Chan 2014; Dutta 2017; Fekadu 2015; Ferreira 2016; Ildirli 2015; Jewkes 2015; Jurma 2014; Khan 2012; Lachman 2012; Luna 2007; Ng 2015; Novaković 2006; Oginni 2015; Peltzer 2015; Prabhuswamy 2007; Rodriguez 2018; Ruengorn 2012; Shibre 2014; Spies 2018; Toska 2019; Zhang 2009
Wrong target group (23 studies)	Aloudari 2017; Ayala Velázquez 2002; Bozzini 2019; Chen 1999; Chiu 2018; Conference 2017; Espinoza-Gomez 2010; Ghoreishi 2017; Guo 2016; Kandasamy 2019; Liu 2018; MacHado 2011; Manopaiboon 1998; Murray 2015; Novakovic 2006; Novakovic 2013; Pillay 1997; Rustagi 1981; S 2010; Saab 2005; Say 2014; Sun 2015; Yaris 2005
Other —	
No separate data for 10-24 & no response from author (16 studies)	Ainsah 2008; da Silva 2006; Dedić 2010; Ekinci 2015; Ferigolo 2009; Hill 2018; Hill 2018; Kaljee 2012; Li 2012; Liu 2018; Phillips 2002; Quevedo 2011; Zhang 2011; Zhang 2013; Zhang 2019; Conner 2007
Overlapping cohort or study (11 studies)	Chen 1999; Da Silva 2006; Qandil 2016; Shibre 2015; Shin 2008; Wado 2014; Benjet 2016; Giletta 2015; Nduna 2011; Kinyanda 2004; Zhou 2012
No depression measure (4 studies)	Akbari 2015; Beguy 2014; Ruchkin 1999, Young Lives study 2013
Unclear route of HIV transmission (2 studies)	Lwidiko 2018; Toska 2019
Could not retrieve full-text (2 studies)	Jia 2005; Morshed 2016
Description of data, no results (1 study)	Nogueira 2018

Table A3.5. Newcastle-Ottawa for assessment of quality of included studies

A. Cohort studies

Study	Selection	Comparability	Outcome	Total Score	Notes
Barrocas (2015)	4	2	3	9	
Borges (2018)	4	2	2	8	Assessment not blinded.
Zhou (2012)	4	2	2	8	Self-report measure (exposure).
Auerbach (2010)	4	2	1	7	Self-report measures (exposure and outcome); No statement of lost to follow-up.
Cluver (2015)	4	2	1	7	Assessment not blinded; Some subjects lost to follow-up (<15%).
Pelotas (1993)	4	2	1	7	Self-report measure (outcome) Some subjects lost to follow-up (<15%).
CLHNS (1983)	3	2	1	6	Self-report measures (exposure and outcome) Some subjects lost to follow-up (<15%).
Hall (2018)	3	1	2	6	No control for confounding variables; Self-report measures (exposure and outcome).
Liu (2019)	3	2	1	6	Self-report measures (exposure and outcome) Some subjects lost to follow-up (<15%).
Nduna (2010)	3	2	1	6	Self-report measures (exposure and outcome); Some subjects lost to follow-up (30%)
NIDS (2008)	3	2	1	6	Self-report measures (exposure and outcome) Some subjects lost to follow-up (<15%).
Vieira (2017)	4	1	1	6	Study only controls for age and sex; Assessment not blinded; Some subjects lost to follow-up (<15%).

B. Case-control studies

Study	Selection	Comparability	Exposure	Total Score	Notes
Charfi (2018)	4	2	3	9	
Gonzalez (2012)	4	2	3	9	
Li (2008)	4	2	3	9	
Arellanez-Hernández (2004)	4	2	2	8	Self-report measure (exposure).
Basay (2016)	4	2	2	8	Assessment not blinded.
Bejarpas (2017)	4	2	2	8	Self-report measure (exposure).
Effat (2016)	4	2	2	8	Assessment not blinded.
Freitas (2008)	4	1	2	8	Assessment not blinded.
Liu (2005)	4	2	2	8	Assessment not blinded.
Bella (2012)	4	2	1	7	Self-report measure (exposure) No information on non-response rate.
Çetin (2001)	4	1	2	7	Study only controls for age and sex; Self-report measure (exposure).
Kazour (2015)	4	1	2	7	Study only controls for age and sex; Assessment not blinded.
Kinyanda (2005)	4	1	2	7	Study only controls for age and sex; Assessment not blinded.
Niraula (2009)	4	1	2	7	Study only controls for age and sex; Assessment not blinded.
Ramalingam (2016)	4	1	2	7	Study only controls for age and sex; Assessment not blinded.
Zhou (2014)	4	1	2	7	Study only controls for age and sex; Assessment not blinded.
Fidan (2011)	4	0	2	6	No description on comparability; Assessment not blinded.
Zhang (2016)	4	0	2	6	Self-report measure (exposure) No controls for confounding variables.
Zhao (2015)	3	1	2	6	Cannot rule out that controls had a history of the outcome; Study only controls for age; Self-report measure (exposure).
Kilic (2011)	3	1	1	5	No description of representativeness of cases; No control for confounding variables; Assessment not blinded; Different non-response rate
Castilla-Puentes (2012)	1	2	1	4	No description of definition or representative of cases, No information on source; No statement on non-response rate.

Table A3.6. Subgroup post hoc analysis

Subgroup category	Subgroup	Number of studies	Pooled OR (95% CIs)	I ² (%)	Test for subgroup difference (mixed-effects model)
Risky sexual behaviour					
Study design	Cohort	5	1.23 (1.07 - 1.41)	79.74	0.01
	Case-control	2	2.20 (1.43 - 3.40)	0.00	
Risky behaviour measure	Biological markers or diagnostic interviews	3	2.32 (1.99 - 2.70)	0.00	0.00
	Self-report	4	1.04 (1.02 - 1.06)	0.00	
Substance use					
Study design	Cohort	4	1.06 (0.98 - 1.14)	57.51	0.00
	Case-control	6	3.95 (2.39 - 6.53)	21.98	
Depression measure	Diagnostic interviews	4	2.07 (1.08 - 3.98)	35.61	0.633
	Self-report	6	1.74 (1.35 - 2.26)	83.93	
Risky behaviour measure	Biological markers or diagnostic interviews	7	3.41 (2.01 - 5.76)	14.36	0.00

Table A3.7. Certainty of assessment using GRADE for observational studies

Outcome (primary)	Number of participants (studies)	Effect estimate (95% CI)	Design	Study limitations [1]	Inconsistency [2]	Imprecision [3]	Indirectness [4]	Quality of the evidence (GRADE)
Risky sexual behaviour	11904 (7 studies)	OR 1.29 (1.13-1.48)	Observational studies	No serious limitations No downgrade	Moderate No downgrade	No serious imprecision No downgrade	No serious indirectness No downgrade	LOW ⊕⊕○○
Substance use	11014 (10 studies)	OR 1.76 (1.42-2.19)	Observational studies	No serious limitations No downgrade	Moderate No downgrade	No serious imprecision No downgrade	No serious indirectness No downgrade	LOW ⊕⊕○○

Notes:

Following GRADE's guidelines, we assigned an a-priori ranking of low to the strength of the overall body of evidence. This was downgraded according to four criteria (study limitations, inconsistency, imprecision, indirectness), and upgraded according to three criteria (large effect, dose-response gradient, opposing plausible residual bias or confounding).¹

[1] *Study limitations* was assessed using the Newcastle Ottawa Scale (NOS). NOS scores for assessment of quality were mostly high and moderate (see Table A5). Only one study had a low score in NOS and it contributed to less than 5% of the weight in the pooled analysis.

[2] *Inconsistency* was assessed by the presence of between-study heterogeneity using I-square statistic and extent of overlap of CIs. Small degree of heterogeneity perceptible on visual inspection. I-square for risky sexual behaviour was 74.5%, and for substance use was 77.3%. However, this was partly explained by subgroup analysis.

[3] *Imprecision* was assessed with the 95% CIs. The pooled estimate did not cross the point of no effect (OR=1).

[4] *Indirectness* was assessed by exploring whether there were any factors that limit the generalizability of the results. All studies compared the association of interest in the population of interest (adolescents in LMICs), and thus there was no threat to external validity.

We did not find any evidence to upgrade the certainty of the evidence because: the magnitude of the effects were not large enough, we could not test for dose-response gradient as none of the studies reported on the degree of exposure (i.e. depression severity), and we did not think that plausible confounding and bias would reduce the effect or suggest a spurious effect.

Table A4.1 Means, standard deviation, and correlation matrix within wave

Wave 1

Variables	Mean	SD	(1)	(2)	(3)	(4)
(1) CES-D score	7.12	4.23	1			
(2) Adolescent pregnancy	0.45	0.68	0.14***	1		
(3) Cigarette smoking	0.57	2.56	0.06**	0.03	1	
(4) Alcohol use	0.43	1.18	0.03	0.06*	0.41***	1

Wave 2

Variables	Mean	SD	(1)	(2)	(3)	(4)
(1) CES-D score	6.56	3.94	1			
(2) Adolescent pregnancy	0.77	0.83	0.07*	1		
(3) Cigarette smoking	0.66	2.62	0.03	-0.01	1	
(4) Alcohol use	0.48	1.23	0.01	-0.02	0.41***	1

Wave 3

Variables	Mean	SD	(1)	(2)	(3)	(4)
(1) CES-D score	6.58	4.07	1			
(2) Adolescent pregnancy	1.02	0.92	0.03	1		
(3) Cigarette smoking	0.89	2.81	0.01	0.00	1	
(4) Alcohol use	0.77	1.50	0.02	-0.03	0.44***	1

Note: The stars represent statistical significance as follows: * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

Table A4.2 Estimation results of the structural equation model

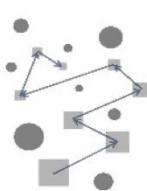
Model	Structural Relationship	β	SE	p-value
Model 1: Depression & Pregnancy (n=1,297)	Depression2 $\leftarrow$ Depression1	0.02	0.04	0.59
	Depression3 $\leftarrow$ Depression2	0.02	0.03	0.60
	Pregnancy2 $\leftarrow$ Depression1	0.04	0.02	0.03*
	Pregnancy3 $\leftarrow$ Depression2	0.03	0.02	0.04*
	Depression2 $\leftarrow$ Pregnancy1	0.05	0.03	0.11
	Depression3 $\leftarrow$ Pregnancy2	0.06	0.03	0.09
	Pregnancy2 $\leftarrow$ Pregnancy1	0.78	0.01	0.00***
	Pregnancy3 $\leftarrow$ Pregnancy2	0.85	0.01	0.00***
	SRMR = 0.04 ; CD = 0.93			
Model 2: Depression & Smoking (n=2,209)	Depression2 $\leftarrow$ Depression1	0.08	0.03	0.01**
	Depression3 $\leftarrow$ Depression2	0.06	0.02	0.01**
	Smoking2 $\leftarrow$ Depression1	-0.03	0.03	0.39
	Smoking3 $\leftarrow$ Depression2	-0.02	0.02	0.36
	Depression2 $\leftarrow$ Smoking1	0.06	0.02	0.01**
	Depression3 $\leftarrow$ Smoking2	0.04	0.02	0.01**
	Smoking2 $\leftarrow$ Smoking1	0.37	0.07	0.00***
	Smoking3 $\leftarrow$ Smoking2	0.27	0.07	0.00***
	SRMR = 0.04 ; CD = 0.86			
Model 3: Depression & Alcohol (n=2,231)	Depression2 $\leftarrow$ Depression1	0.08	0.04	0.04*
	Depression3 $\leftarrow$ Depression2	0.06	0.03	0.03*
	Alcohol2 $\leftarrow$ Depression1	-0.04	0.03	0.14
	Alcohol3 $\leftarrow$ Depression2	-0.03	0.02	0.15
	Depression2 $\leftarrow$ Alcohol1	0.00	0.03	0.92
	Depression3 $\leftarrow$ Alcohol2	0.00	0.02	0.92
	Alcohol2 $\leftarrow$ Alcohol1	0.25	0.04	0.00***
	Alcohol3 $\leftarrow$ Alcohol2	0.21	0.03	0.00***
	SRMR = 0.04 ; CD = 0.86			

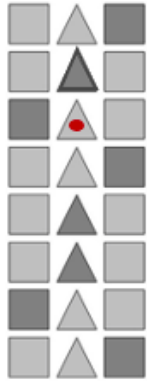
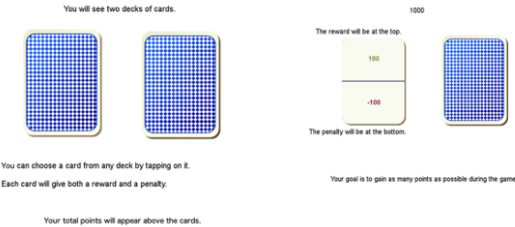
Table A4.3 Estimation results of the structural equation model by socioeconomic status

		NON-POOR	POOR
Model	Structural Relationship	β	β
Model 1: Depression & Pregnancy (n=1,297)	Depression2 $\leftarrow$ Depression1	0.02 (0.04)	0.03 (0.04)
	Depression3 $\leftarrow$ Depression2	0.02 (0.03)	0.02 (0.03)
	Pregnancy2 $\leftarrow$ Depression1	0.04* (0.02)	0.04* (0.02)
	Pregnancy3 $\leftarrow$ Depression2	0.04* (0.02)	0.03* (0.01)
	Depression2 $\leftarrow$ Pregnancy1	0.05 (0.04)	0.05 (0.04)
	Depression3 $\leftarrow$ Pregnancy2	0.05 (0.03)	0.06 (0.03)
	Pregnancy2 $\leftarrow$ Pregnancy1	0.76*** (0.01)	0.80*** (0.01)
	Pregnancy3 $\leftarrow$ Pregnancy2	0.86*** (0.01)	0.84*** (0.02)
	SRMR = 0.06 ; CD = 0.93		
Model 2: Depression & Smoking (n=2,209)	Depression2 $\leftarrow$ Depression1	0.07* (0.03)	0.08* (0.03)
	Depression3 $\leftarrow$ Depression2	0.06* (0.02)	0.05* (0.02)
	Smoking2 $\leftarrow$ Depression1	-0.03*** (0.02)	-0.03*** (0.03)
	Smoking3 $\leftarrow$ Depression2	-0.02 (0.02)	-0.02 (0.03)
	Depression2 $\leftarrow$ Smoking1	0.05* (0.02)	0.08* (0.04)
	Depression3 $\leftarrow$ Smoking2	0.05* (0.02)	0.04* (0.02)
	Smoking2 $\leftarrow$ Smoking1	0.25*** (0.07)	0.48*** (0.08)
	Smoking3 $\leftarrow$ Smoking2	0.25** (0.07)	0.22* (0.08)
	SRMR = 0.05 ; CD = 0.84		
	Depression2 $\leftarrow$ Depression1	0.13* (0.06)	0.04 (0.05)

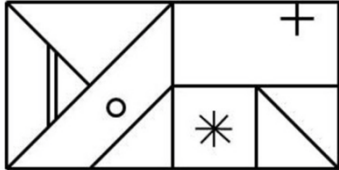
Model 3: Depression & Alcohol (n=2,231)	Depression3 $\leftarrow$ Depression2	0.03 (0.06)	0.04 (0.06)
	Alcohol2 $\leftarrow$ Depression1	-0.02 (0.05)	-0.02 (0.05)
	Alcohol3 $\leftarrow$ Depression2	-0.02 (0.06)	-0.08 (0.05)
	Depression2 $\leftarrow$ Alcohol1	-0.04 (0.03)	0.05 (0.04)
	Depression3 $\leftarrow$ Alcohol2	0.01 (0.04)	0.01 (0.05)
	Alcohol2 $\leftarrow$ Alcohol1	0.27*** (0.06)	0.20*** (0.06)
	Alcohol3 $\leftarrow$ Alcohol2	0.19*** (0.06)	0.25*** (0.06)
	SRMR = 0.05 ; CD = 0.85		

Table A5.1 Executive function tasks

Task name	Task description	Variable construction
Trails task	Respondents were presented with a series of circles and squares of different sizes and asked to draw lines to connect them in certain order. There were two baseline conditions and one set-switching condition: <i>Baseline task 1:</i> Connect circles in increasing order of size in the presence of square distractors.  <i>Baseline task 2:</i> Connect squares in decreasing order of size in the presence of circle distractors.  <i>Switch task:</i> Connect shapes alternating between circles and squares, with circles going in increasing order of size and squares in decreasing order, starting with the largest square and the smallest circle.  Respondents score 1 point for each correct connection, with a maximum score of 7 for each baseline condition and 14 for the switching condition.	We calculated the switch accuracy cost, which is given by the score in the switching condition as a percentage of the higher baseline score as follows: Switch accuracy cost = $100 * [\text{Score at Switch condition} / 2 * \max(\text{Score baseline task 2}, \text{Score baseline task 1})]$ The score was capped at 100%.
Rule-finding task	Participants were presented with three columns with alternating shapes (squares-triangles-squares), eight shapes per column. During the task, a red dot moved across the shapes following certain rules. There were five rules in total (with a total of 46 moves). The change from one rule to another was not signalled. The first four rules were only based on the position of the shape. For the fifth rule, both the position and colour of the shape were relevant.	We calculated the proportion of accurate moves as follows: Proportion accuracy of moves = $\text{Total number of accurate moves (from 0 to 46)} / \text{total number of possible correct moves (=46)}$

	 Participants were asked to predict where the dot would move next based on previous moves, measuring participants' ability to make predictions based on observing patterns and update their predictions when patterns changes. The previous position of the red dot was highlighted (see figure below). Respondents score 1 point for each move correctly predicted, with a maximum move score of 46. The first move in each new rule (where only guessing is possible) is not scored. A rule is considered acquired if a minimum of two consecutive moves within that rule are correctly predicted, with a maximum score of 5. The number of incorrect moves before each rule is acquired is also recorded.	
Iowa Gambling task	This task presented participants with two decks of cards, an advantageous, low-risk deck (low rewards, low penalties with net gain: reward of 100 points per card and 0 or -100 penalties per card) and a disadvantageous, high-risk deck (high reward, high loss with net loss: reward of 200 points per card and higher penalties of 0, -400, -500 or -600 points).  Participants are told that the goal of the game is to score as many points as possible by the end of the task. They are instructed that they may choose cards from any deck, and that they may switch decks at any time. The respondents need to infer which of the two decks is better to select to maximise long-term reward. The updated total score is shown at the top of the screen after each selection. There were 50 trials in total. The first two trials are practice trials. Respondents score a certain number of points during each trial, starting with 0 at the start. At each trial, the score balance is calculated adding the card reward and subtracting the card penalty. The advantageous deck has a total reward of 5000	We derived a Net score in the last 30 trials as follows: Net score = Proportion of advantageous choices – Proportion of disadvantageous choices in the last 30 trials

	points and a total penalty of 2500 points. The disadvantageous deck has a total reward of 10000 points and a total penalty of 12500 points. The maximum possible score is 5900 points, and the minimum possible score is -5900 points.	
Emotional Go/No-go task	Participants were presented with a series of visual stimuli: faces belonging to three different women displaying one of three different emotional expressions (happy, neutral, or fearful) and were asked to tap the screen for target images only.  Example of 'neutral face' Example of 'happy face' Example of 'fearful face' There was a practice block (6 trials) and four test blocks (36 trials each). Respondents are asked to use the stylus to tap the screen when target faces occur (go trials) while refraining from any tap for any other type of face (no-go trials). The neutral faces were always the targets in every block. In blocks 1 and 4, distractors were fearful faces (fearful blocks). In blocks 2 and 3, the distractors were happy faces (happy blocks). The ratio of go to no-go trials within each block is 2:1, making it strategically beneficial to initiate a Go response on every trial. A correct hit (tapping a target face) is followed by a low-pitched auditory tone. Respondents score 1 for each correct response – either correctly tapping a target or refraining to tap on a distractor (maximum score of 36 per block). The following reaction times are also recorded: early response (within 200ms); proper response (200 – 2000ms); repeated response (a second tap between 200 and 2000ms); late response (a response within 200ms of the next stimulus presentation).	We calculated the d-prime (d') as follows: $d' = z(\text{accuracy on go trials}) - z(\text{commission error rate}).$ Where: • <i>Accuracy on go trials</i> refers to the proportion of correct responses to 'go' trial. • <i>Commission error rate</i> refers to proportion of incorrect responses to 'no-go' trials. • <i>Z</i> means applying the z-transformation using the inverse normal distribution. Ceiling scores (0% commission errors or 100% correct hits) were converted prior to the d' calculation to avoid data loss when applying the z transformation: • 1 (100%) for go-trial accuracy was replaced with $1 - 1/(2N)$ with N being the total number of go trials in the task ($N=96$). • 0 (0%) for commission errors was replaced with $1/(2N)$ with N being the ($N=48$)
Digit recall task	Respondents are asked to repeat out loud a series of digit sequences of increasing length (from 2 to 9). Digits from 1 to 9 are used. For each sequence, the interviewer reads the digits out loud slowly	We calculated the backwards digit span , as the length (number of digits) of longest sequence

	and clearly. The task consists of two conditions: (i) the forward digit recall, for which the respondents are asked to repeat the sequence in the same order as they heard it, and (ii) the backward digit recall, for which respondents are asked to repeat the sequence in reverse order. As respondents say the digits, the interviewer uses the stylus to tap the digits on the tablet in the same order as spoken by the respondents. The accuracy is then automatically scored. Upon correct rendition of a sequence of a certain length, respondents proceed to the next level, for which the length of the sequence is increased by one. Respondents are allowed three attempts at different sequences of a certain length. Failure to correctly render any of the three sequences of a certain length finishes the assessment.	remembered and recited correctly in the backwards condition (maximum of 9)
Figure recall task	The respondent is asked to use the stylus to draw a figure composed of simple geometric shapes (see figure below) on the tablet. The task consists of a figure copy condition and a figure recall condition.  In the <i>figure copy condition</i>, the respondent is asked to copy the figure while the figure is present at the top of the screen for the duration of the copying. In the <i>figure recall condition</i> administered immediately afterwards, the respondent is asked to draw the same composite figure again, this time from memory. Timing is automatically recorded. The figure contains 20 components and respondents score a maximum of 3 for each component (1 point each for the component presence, position, and accuracy). The resulting drawings are manually scored offline after the completion of the battery by a trained expert using a dedicated figure scoring software application.	We calculated recall accuracy as follows: Recall accuracy = number of correct components (each of the 20 drawing elements scored on 3 presence, accuracy, and position) divided by total number of possible correct components (maximum 60/60)
Selection task	This task presented participants with a distribution of 60 items: 30 vegetables (10 items of each of three vegetable types) and 30 fruit (10 items of each of three fruit types).	We calculated the invisible accuracy as follows: the proportion accuracy i.e., the number of targets selected only once minus distractors selected, divided by the total number of targets (maximum 30/30)

	 Participants had to select fruits (targets), ignoring the vegetables (distractors). In the visible condition, there was sustained visual feedback highlighting items already selected. In the invisible condition, the items were highlighted briefly then the feedback disappeared meaning participants had to remember which items they had selected previously.	
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Note: The fieldworkers were prompted to select a single test condition after every EF task. The options included: no issue; participant issues (no speech, visual problems, motor problems, auditory problems, fatigue, refused or ran out of time); environmental/technical issues (technical problems, interruptions, other); examiner error. Only tasks with conditions equal to “no issue” were included in the model.

Table A5.2 Risky behaviour variables

Variable name	Question	Variable construction
Unprotected sex in the last 3 months (general question)	Based on the following questions: A. <i>In the past three months, how many times have you had vaginal sex?</i> [number] B. <i>Of these times you had vaginal sex, how many of these times did you use a condom?</i> [number] C. <i>In the past three months, how many times have you had anal sex?</i> [number] D. <i>Of these times you had anal sex, how many of these times did you use a condom?</i> [number]	=1 if the number of times participant had vaginal sex was greater than the number of times using condom in vaginal sex ($A > B$) OR if the number of times participant had anal sex was greater than the number of times using condom in anal sex ($C > D$) =0 if otherwise ($A = B$ or $C = D$) OR if participant never had vaginal or anal sex
General condom use with partner during last year question about specific sex partners)	This section starts by asking participants to list up to three most recent sex partners since the last study visit. Participants were asked to identify partners by the initials. We then constructed a measure of unprotected sex in the last year based on the following question: <i>On average, how often would you say you have used condoms when you have sex with [initials]?</i> • 0 = Always, every time • 1 = Frequently, but not all the time • 2 = Sometimes, about half of the time • 3 = Rarely, once in a while	We created an average score using all questions about participant's sexual partners (maximum of three). This was done to allow comparisons across participants, regardless of the number of recent sex partners identified. The score ranged from 0 (if always used a condom with all partners) to 4 (if never used a condom)

	• 4 = <i>Never, none of the time</i>	
Condom use with partner during last sex act (question about specific sex partners)	This question also references the sexual partners identified by the participant. This specific measure is based on the following question: <i>Did you use a condom with [initials] the last time you had sex? [Yes/No]</i>	=1 if did not use a condom =0 if used a condom
Multiple sex partners	As above, this question also references the sexual partners identified by the participant. This specific measure is based on the following question: <i>During the time that you and [initials] have had a sexual relationship, have you had any other sexual partners? [Yes/No]</i>	=1 if had multiple sex partners at once =0 if did not have any other sex partners
Transactional sex	Based on the following questions: A. <i>Did you feel like you had to have sex with [initials] because they gave you money? [Yes/No]</i> B. <i>Did you feel like you had to have sex with [initials] because they gave you things? [Yes/No]</i> C. <i>Is part of the reason you had sex with or stayed sexually involved with [partner initials] is because he provided you with money or gifts? [Yes/No]</i> D. <i>What are the main and secondary reasons you are/were with [partner initials]? [1 = Looks/ physical attraction; 2 = Love/romance; 3 = Money/gifts/financial support; 4 = Adventure/ entertainment; 5 = Status among friends; 6 = Coercion/He forced me; 7 = Other (specify); 8 = No second reason]</i>	=1 if engaged in transactional sex (i.e., said YES to A or B or C OR main and secondary reasons to be with the partner is for money / gifts / financial support) =0 if otherwise
Binge drinking	Based on the following question: <i>On a day that you have an alcoholic drink, how many standard drinks do you usually have?</i> • 0 = <i>Never drinks</i> • 1 = <i>1 or 2 standard drinks</i> • 2 = <i>3 or 4 standard drinks</i> • 3 = <i>5 or 6 standard drinks</i> • 4 = <i>More than 6 standard drinks</i>	= 1 if 3 or more standard drinks = 0 if less than 3 standard drinks
Drunk sex	Based on the following question: <i>Have you ever had sex while you were drunk on alcohol? [Yes/No]</i>	= 1 if had sex while drunk = 0 if otherwise

Table A5.3 Moderators and covariates

Variable name	Question	Variable construction
Poverty	Participants' caregivers were asked about monthly household consumption, including expenses in food (items grown, purchased, or borrowed) and non-food items (personal items, transportation, etc.).	We constructed a poverty measure in two steps. First, we summed up the total food and total non-food expenditures within the household. In the second step, we arrived at a per capita measure of consumption by adjusting for household size. All total expenditure categories were then adjusted for monthly inflation (base of December 2016) using South Africa CPI index for Mpumalanga province. We constructed a binary variable equal to 1 if the individual's monthly income was below the extreme poverty line as defined by the International Poverty Line (\$1.90 per day in international dollars).
Number of close friendships	<i>How many close friends do you have? [number]</i>	Number
Perceived parental involvement	Based on the following questions: • How often does your primary caregiver try to find out about who your friends are? (0=Never, 1=Sometimes, 2=Always) • How often does your primary caregiver try to find out about how you spend your free time? (0=Never, 1=Sometimes, 2=Always) • How often does your primary caregiver try to find out about where you go after school? (0=Never, 1=Sometimes, 2=Always) • How often does your primary caregiver try to find out about how you spend your money? (0=Never, 1=Sometimes, 2=Always) • How much do you feel that your primary caregiver cares about you? (0= Not at all, 1=Somewhat, 2=Very)	A scale score was created by averaging responses to the 8 items, with higher scores indicating higher and better parental involvement. The measure had an acceptable internal consistency reliability ($\alpha = 0.71$).

	much) - How close do you feel to her /him? (0= Not at all close, 1=Somewhat close, 2=Very close) - How free / open do you feel to discuss issues of sex and sexuality with her /him? (0= Not at all, 1=Somewhat, 2=Very much) - How free / open do you feel to discuss issues of HIV prevention her /him? (0= Not at all, 1=Somewhat, 2=Very much)	
Age	<i>How old are you? [number]</i>	Number
Education level	Based on the following question: <i>In what grade are you currently enrolled?</i> Answer options: 8=Grade 8; 9=Grade 9; 10=Grade 10	To construct highest level of education attained we subtracted one from grade enrolled
Household socioeconomic status	The variable for asset index was constructed from the question 'How many durable goods (e.g., radio, television, and cellphone) does the household currently own?'. There were 27 specific durable goods queried and the household reported the total number of each good they owned.	We constructed an equal weights indices using all 27 items. Any household with missing data for any of the 27 items were coded as missing for the asset index.
Anxiety	Based on the following questions: <i>I worry a lot of the time</i> <i>I worry about what my carers will say to me</i> <i>I feel that others do not like the way I do things</i> <i>It is hard for me to get to sleep at night</i> <i>I worry about what other people think about me</i> <i>I feel alone even when there are people with me</i> <i>I worry about what is going to happen</i> <i>Other children/teenagers are happier than I</i> <i>I have bad dreams</i> <i>I wake up scared some of the time</i> <i>I worry when I go to bed at night</i> <i>I am nervous</i> <i>A lot of people are against me</i> <i>I often worry about something bad happening to me</i> Response options were: 0 = no; 1 = yes.	Response to the 14 items were summed and averaged, ranging from 0 (no anxiety) to 1 (high anxiety). The measure had a good internal consistency reliability ($\alpha = 0.88$).

Table A5.4 Predictors of attrition

	(1)
Age	0.01
	(0.0)
Grade attained	0.03
	(0.0)
Household size	-0.00
	(0.0)
Employment status (=1 if work for pay)	0.04
	(0.0)
Income (past 3 months)	-0.00
	(0.0)
Savings dummy (=1 if has savings)	-0.02
	(0.0)
Savings amount	-0.00
	(0.0)
Food insecurity (=1 if insecure)	0.01
	(0.0)
Consumption	-0.00
	(0.0)
Assets	0.02
	(0.1)
IPV	0.01
	(0.0)
Depression score	-0.00
	(0.0)
Unprotected sex in the last 3 months	-0.05
	(0.1)
General condom use with partner during last year	-0.01
	(0.0)
Condom use with partner during last sex act	-0.04
	(0.1)
Multiple sex partners	0.05
	(0.1)
Transactional sex	-0.11
	(0.1)
Binge drinking	0.06
	(0.1)

Drunk sex	0.02
	(0.1)
Constant	-0.04
	(0.2)
Observations	1,057
Attrition mean	0.25
R-squared	0.01
Adjusted R-squared	-0.01
F test	0.69
Prob >F	0.84

Note: Standard errors in parentheses; *** $p < 0.001$, ** $p < 0.01$, * $p < 0.05$

Table A5.5 Association between variables of interest and covariates

	Unstandardised coefficient	Standardized coefficient	Z	P> z
Persistent depressive symptoms				
Age	0.18*** (4.67)	0.21	4.77	0.000
Education level	-0.37*** (-4.14)	-0.22	-4.25	0.000
Socioeconomic status	-0.46 (-1.22)	-0.05	-1.22	0.221
Study arm	-0.1 (-1.27)	-0.05	-1.27	0.202
Anxiety	1.18*** (7.39)	0.27	7.8	0.000
Inhibition				
Age	-0.0132 (-1.01)	-0.071	-1.00	0.318

Education level	0.00388	0.011	0.16	0.876
	(0.16)			
Socioeconomic status	-0.117	-0.056	-0.92	0.357
	(-0.91)			
Study arm	-0.0677*	-0.145	-2.37	0.018
	(-2.24)			
Anxiety	-0.0114	-0.013	-0.20	0.838
	(-0.21)			
Switching				
Age	-0.0246***	-0.308	-3.80	0.000
	(-3.75)			
Education level	0.0315**	0.205	2.66	0.008
	(2.67)			
Socioeconomic status	0.0966	0.108	1.60	0.109
	(1.56)			
Study arm	0.00228	0.011	0.18	0.861
	(0.18)			
Anxiety	-0.0256	-0.066	-1.00	0.318
	(-1.00)			
Working memory				
Age	-0.214***	-0.596	-6.99	0.000
	(-4.76)			
Education level	0.276***	0.398	5.19	0.000
	(4.07)			
Socioeconomic status	-0.284	-0.070	-1.16	0.244
	(-1.16)			
Study arm	0.0734	0.081	1.33	0.183
	(1.29)			

Anxiety	0.100	0.057	0.93	0.351
	(0.94)			
Risky behaviours				
Age	0.0272**	0.165	3.06	0.002
	(3.00)			
Education level	-0.00644	-0.020	-0.40	0.691
	(-0.40)			
Socioeconomic status	-0.184*	-0.099	-2.31	0.021
	(-2.26)			
Study arm	0.0139	0.034	0.77	0.439
	(0.77)			
Anxiety	0.0801*	0.100	2.32	0.02
	(2.26)			

Table A5.6 Persistent depressive symptoms → EF dimensions (Model 1)

EF dimension	Unstandardised coefficient	Standardised coefficient	Z	P> z
Depression→ Switching	-0.022**	-0.251	-2.950	0.003
	(0.007)			
Depression→ Inhibition	-0.029	-0.149	-1.930	0.053
	(0.015)			
Depression→ Working memory	-0.084*	-0.283	-3.100	0.002
	(0.039)			

Note: n=1,057, X²=34.73; CFI=0.904; TLI=0.821; RMSEA=0.035;
Standard errors in parentheses. *** p<0.001, ** p<0.01, * p<0.05

Table A5.7 Persistent depressive symptoms → EF → Risky behaviours (Model 2)

	Unstandardised coefficient	Standardised coefficient	Z	P> z
Depression → EF	-0.0435***	-0.29	-4.95	0.000
	(-4.17)			
Depression → Risky Behaviours	0.0313**	0.167	2.80	0.005
	(2.72)			
EF → Risky Behaviours	0.0840	0.068	0.93	0.350
	(0.92)			
Covariates				
Age	0.212***	0.237	5.64	0.000
	(5.45)			
Education level	-0.379***	-0.220	-4.47	0.000
	(-4.36)			
Socioeconomic status	-0.468	-0.047	-1.27	0.203
	(-1.27)			
Study arm	-0.0979	-0.044	-1.21	0.226
	(-1.21)			
Anxiety	1.142***	0.263	7.53	0.000
	(7.19)			

Table A5.8 Moderated-mediation model (Model 3)

	Unstandardised coefficient	Standardised coefficient	Z	P> z
MODERATOR 1: POVERTY				
Depression → EF	-0.0487**	-0.32	-3.41	0.001
	(-2.92)			
Poverty → EF	-0.0250	-0.07	-1.04	0.300
	(-1.01)			

Depression*Poverty → EF	0.00851	0.06	0.47	0.640
	(0.46)			
Depression → Risky behaviours	0.0551**	0.29	3.09	0.002
	(2.87)			
EF → Risky behaviours	0.112	0.09	1.19	0.233
	(1.17)			
Poverty → Risky behaviours	0.0663*	0.15	2.35	0.019
	(2.24)			
Depression*Poverty → Risky behaviours	-0.0329	-0.17	-1.58	0.115
	(-1.52)			
MODERATOR 2: CLOSE FRIENDSHIPS				
Depression → EF	-0.0474***	-0.31	-4.47	0.000
	(-3.84)			
Friendships → EF	-0.006	-0.08	-0.88	0.378
	(-0.87)			
Depression*Friendships → EF	0.002	0.07	0.62	0.537
	-0.61			
Depression → Risky behaviours	0.0315*	0.17	2.10	0.035
	-2.05			
EF → Risky behaviours	0.087	0.07	0.95	0.342
	-0.94			
Friendships → Risky behaviours	0.001	0.01	0.08	0.934
	-0.08			
Depression*Friendships → Risky behaviours	0.000	0.00	-0.01	0.995
	(-0.01)			
MODERATOR 3: PARENTAL SUPPORT				
Depression → EF	-0.0612**	-0.40	-3.82	0.000
	(-3.02)			

Support → EF	0.0104 (0.41)	0.02	0.40	0.686
Depression*Support → EF	0.0177 (1.10)	0.14	1.17	0.241
Depression → Risky behaviours	0.0729** (3.12)	0.38	3.51	0.000
EF → Risky behaviours	0.147 (1.43)	0.12	1.47	0.143
Support → Risky behaviours	0.0308 (1.04)	0.05	1.06	0.291
Depression*Support → Risky behaviours	-0.0363 (-1.95)	-0.22	-2.10	0.036

Table A5.9 Robustness tests

	Unstandardised coefficient	Standardised coefficient	Z	P> z
ROBUSTNESS TEST #1: TESTING DIRECTIONALITY				
Depression score at Wave 4 → EF at Wave 5				
Depression score → Switching	-0.00379*** (-3.72)	-0.308	-3.69	0.000
Depression score → Inhibition	-0.00434* (-2.29)	-0.168	-2.24	0.025
Depression score → Working memory	-0.00535 (-1.44)	-0.153	-1.99	0.046
RMSEA: 0.032; CFI: 0.92; TLI: 0.85				
EF at Wave 5 → Depression at Wave 6				
Switching → Depression score	-5.462 (-0.46)	-0.087	-0.45	0.651
Inhibition → Depression score	2.613 (0.49)	0.087	0.49	0.622
Working memory → Depression score	1.530	0.054	0.48	0.634

	(0.47)			
RMSEA: 0.02; CFI: 0.971; TLI: 0.947				
ROBUSTNESS TEST #2: MODEL 2 WITHOUT COVARIATES				
Persistent depression → EF	-0.0412***	-0.264	-4.42	0.000
	(-3.86)			
Persistent depression → Risky behaviours	0.0256*	0.136	2.22	0.026
	(2.17)			
EF → Risky behaviours	0.0702	0.058	0.81	0.418
	(0.80)			
RMSEA: 0.034; CFI: 0.92; TLI: 0.90				
ROBUSTNESS TEST #3: MODEL 2 FOR CONTROL GROUP ONLY (N=520)				
Persistent depression → EF	-0.0331**	-0.247	-3.33	0.001
	(-2.76)			
Persistent depression → Risky behaviours	0.0236	0.155	1.71	0.088
	(1.70)			
EF → Risky behaviours	-0.00694	-0.006	-0.07	0.948
	(-0.07)			
RMSEA: 0.041; CFI: 0.84; TLI: 0.81				
ROBUSTNESS TEST #4: MODEL 2 WITH DEPRESSION SEVERITY AT WAVE 5				
Persistent depression → EF	-0.0384***	-0.261	-4.17	0.000
	(-3.60)			
Depression score → EF	-0.00129	-0.067	-1.29	0.198
	(-1.29)			
Persistent depression → Risky behaviours	0.0304**	0.162	2.72	0.006
	(2.64)			
EF → Risky behaviours	0.0709	0.056	0.77	0.442
	(0.76)			
RMSEA: 0.042; CFI: 0.79; TLI: 0.764				

ROBUSTNESS TEST #5: MODEL 2 WITHOUT WAVE 1				
Persistent depression → EF	-0.0440*** (-3.71)	-0.243	-4.15	0.000
Persistent depression → Risky behaviours	0.0347** (2.63)	0.158	2.71	0.007
EF → Risky behaviours	0.0723 (0.83)	0.059	0.84	0.401
RMSEA: 0.035; CFI: 0.852; TLI: 0.831				

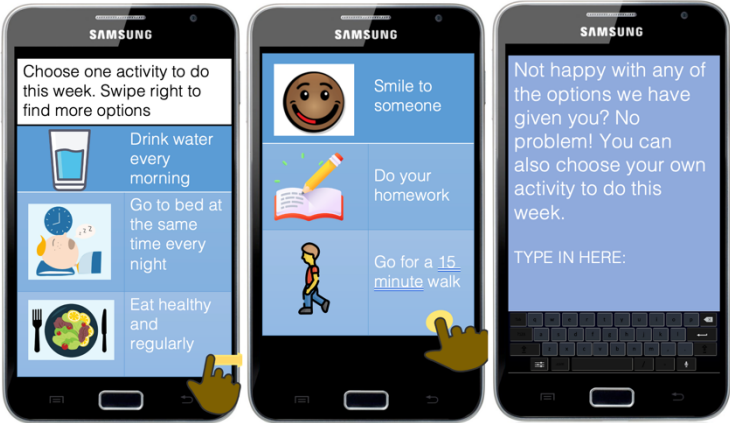
Table A6.1 The Song Contest Story

Learning module	Description of each module	BA Learning principles
Episode 1 ("Pick a team")	Students find out about a school Song Contest. The winning prize is a voucher to shop for a new outfit at the mall. User chooses the main character's name and picks two teammates to join the Song Contest. Main character gets anxious about the idea of performing in front of everyone else. Christine (teacher) talks about the benefits of stepping outside one's comfort zone and offers her support. At the end of the module, the user will be asked to set a goal to work on over the 10 weeks of intervention.	Absorption TRAP-TRAC Sleep Self-confidence Relapse prevention
Episode 2 ("Find a cool tune")	First practice session with group which didn't go well because one teammate fell asleep. Main character is frustrated and decides to ask Christine for advice. After hearing that teammate's grandmother ill, main character showed leadership and compassion in how they handled the situation.	
Episode 3 ("The Lure")	The team worked well together and made progress on the song. At the end of the practice, Prince (desirable character) invites the main character to go to the tavern. Main character is asked to think about the consequences of their actions but decides to go anyway.	
Episode 4 ("The Fallout")	The next day the main character is exhausted, hungover, and unable to concentrate. They arrive late to practice session without homework done. Teammates get annoyed. Main character decides to apologise instead of avoiding the problem and their teammates are forgiving. Main character learns about the importance of sleep and goes to sleep early.	
Episode 5 ("The Return")	Main character sleeps and feels recharged. Team is happy with the practice. Song is completed. Main character learns that they have to give a presentation if they win and asks Christine for advice. Main character learns ways to deal with being nervous and how to feel more self-confident.	
Episode 6 ("The Big Day")	Team feels nervous before the show. They perform and win the prize. Group reflects on journey.	

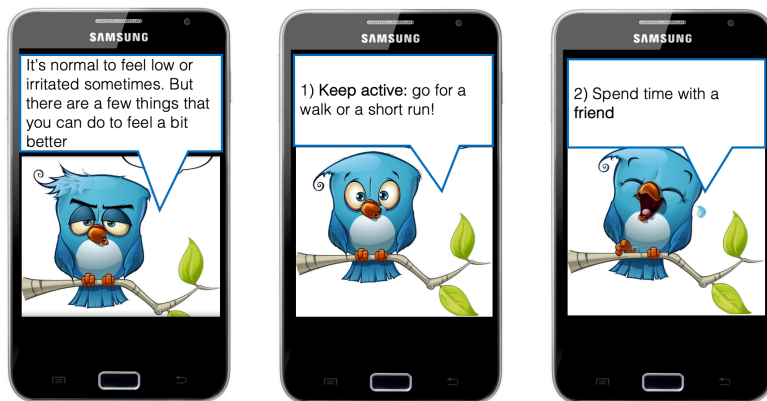
Table A6.2 The Football Match story

Learning module	Description of each module	BA Learning principles
Episode 1 ("Pick a team")	Main character is the striker for the local team. User chooses the main character's name and picks a name for the football team. User gets introduced to the football task. At the end of the module, the user will be asked to set a goal to work on over the 10 weeks of intervention.	Absorption Rumination TRAP-TRAC Problem-solving Negotiation
Episode 2 ("Game Over")	Main character misses some important shots. Shane (antagonistic character) is a discouraging main character because of their poor performance. Team loses the game. Main character leaves the match alone feeling upset and discouraged, ruminating over her performance during the match. Bird offers different, more positive perspective on performance but the main character not in a frame of mind to believe it.	
Episode 3 ("Hide away")	Main character is frustrated, misses school and gets a detention. Main character feels a bit better after friends visit her/him at her house, but apprehensive about going to school. Main character plays the football task which makes them feel energised enough to do their homework.	
Episode 4 ("That's okay")	Main character returns to school feeling more positive after a good night's sleep. Main character handles Shane well, but their mood takes a dip. Main character decides to speak with Coach Bayer after school about their performance in the match. Main character learns that mistakes can be useful opportunities to learn, instead of something to avoid. Main character practises what they've learnt and starts to feel more confident.	
Episode 5 ("Keep practising")	Main character speaks with friends before practice about what they learnt from Coach Bayer and asks for help in dealing with Shane. With their supportive presence, main character gets Shane to agree to stay away from them so that they can focus on football and winning. Main character feels confident, keeps practising, and feels ready for the re-match.	
Episode 6 ("The Big Match")	It all came together for the main character, stepping out onto the pitch with new confidence. Main character keeps calm and meets their mistakes with curiosity instead of frustration. Main character scores the winning goal.	

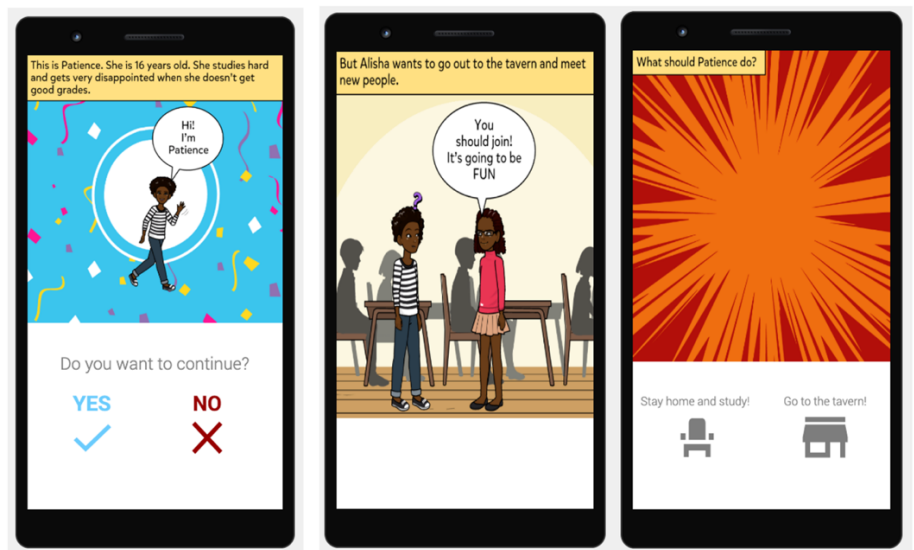
Table A6.3 Samples of interview guides and elicitation techniques

Phase	
(1) CONCEPTUALISATION	- People have different dreams. What do people your age in this community dream for their future? - Many teenagers feel sad or stressed at times. What words do people in this community use to talk about feelings depressed/low/down? - We are going to ask you about a time when you set a goal that is important to you and worked towards it. This can be any goal, small or big. What was the goal you set? Why did you decide this goal was important to you? Did you achieve your goal? - Describe an average day in your life with your phone. - What sort of things do adolescents like yourself like/dislike doing on their phone? - Imagine that if you were feeling sad and that there was a mobile phone app that could give you support and advice and connect you anonymously with people that could help. How would you feel about such an app? PROMPT: Would you rather speak to a friend in person about your problems? If you like the idea, what is appealing about it? What sort of things would the app need to have to make it useful (these can be photos, videos, music, etc.)? What would make you stop using the app?
(2) PROTOTYPING	<i>Paper-based wireframes I designed to test different components of the app:</i> - Activity scheduling 

- Getting advice through the app



- Allowing players to choose how the story unfolds



Participatory workshops – interview guides

- What did you think about the story? What did you like or not like about this story?
- Can you summarize the story?
- What did you think about the characters?
- What did you think about the setting/ place where the story happened?
- What did you think about the way this story was written and the language that was used?

Example mock-ups of the first basic prototype of the Kuamsha app

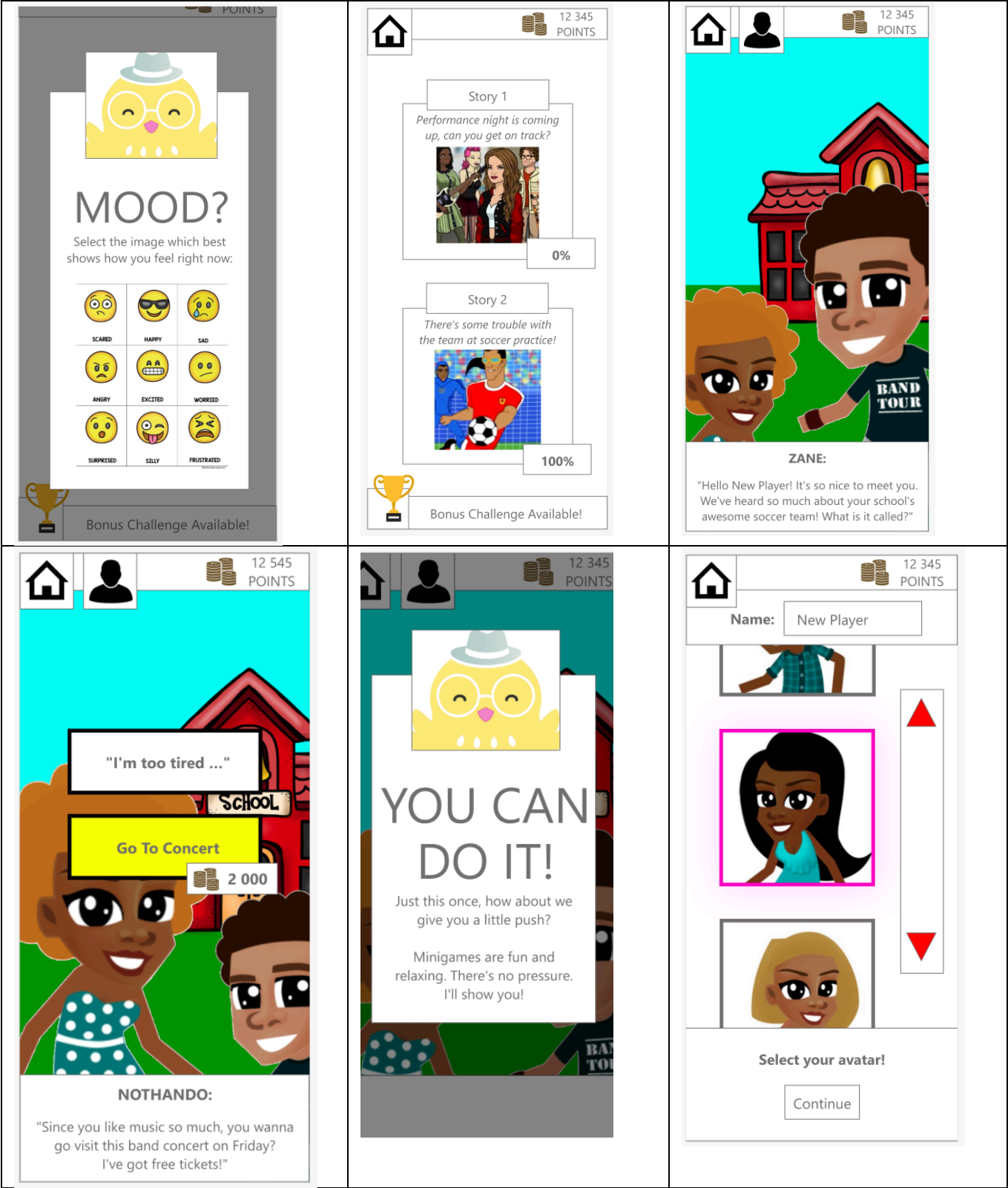
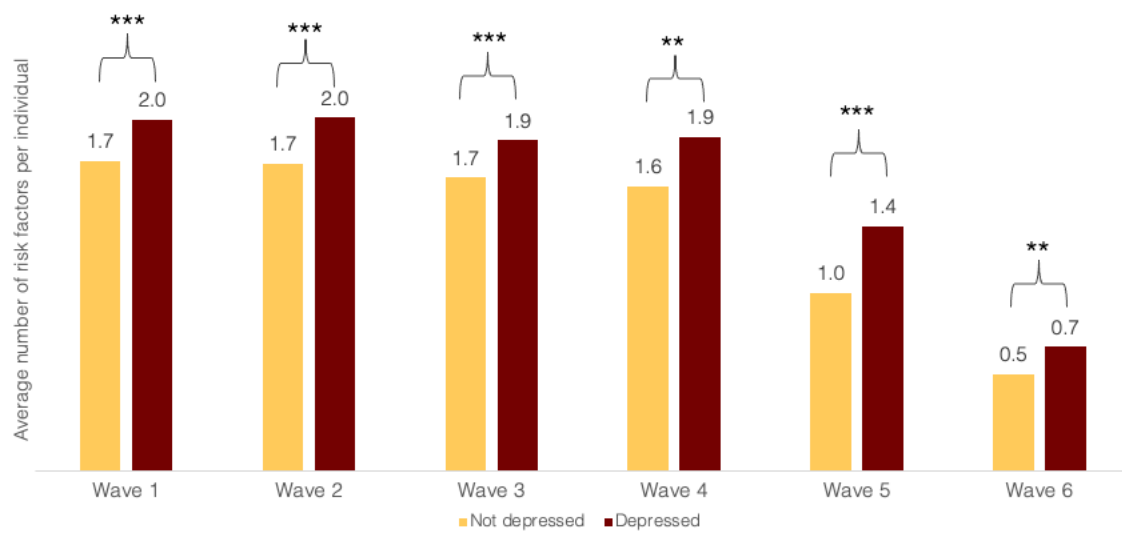


Figure A2.1 Average number of risk factors per individual by depression status

Note: *** $p < 0.001$, ** $p < 0.01$, * $p < 0.05$

Figure A3.1. Results of the subgroup analyses for the primary outcomes

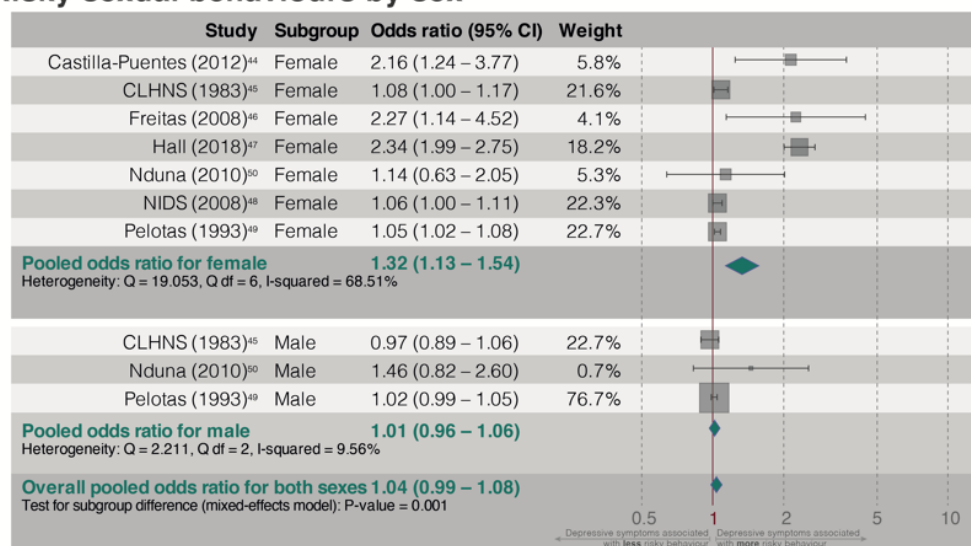
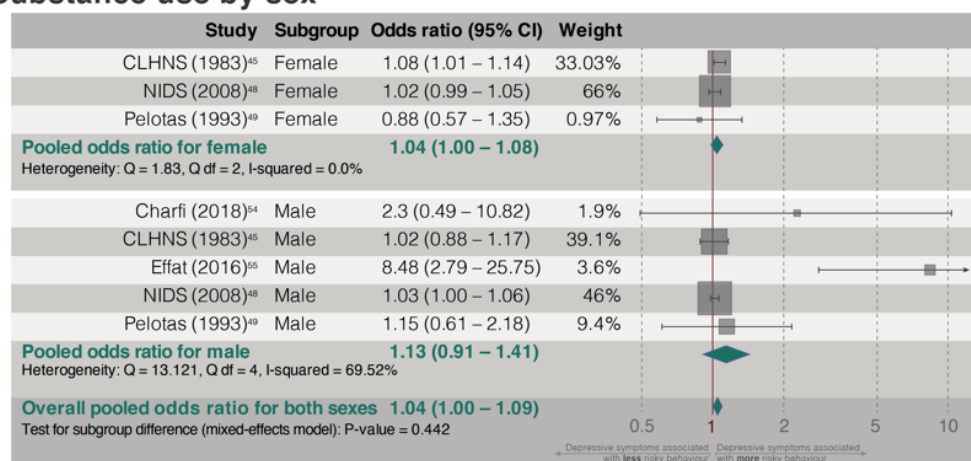
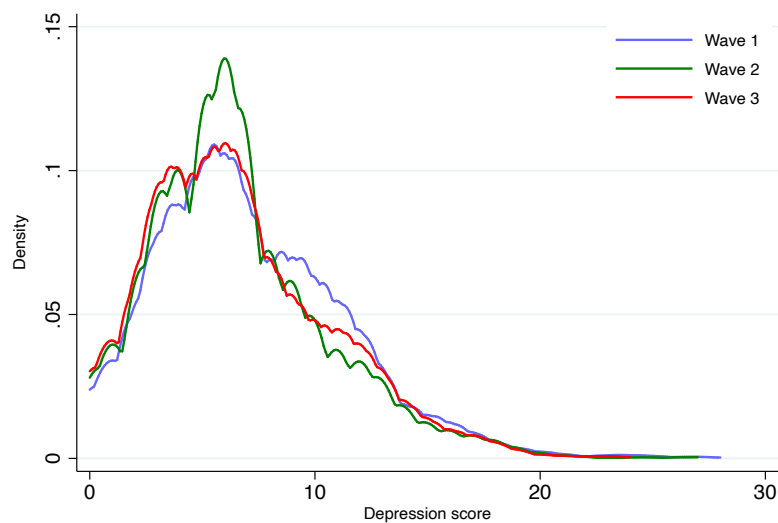
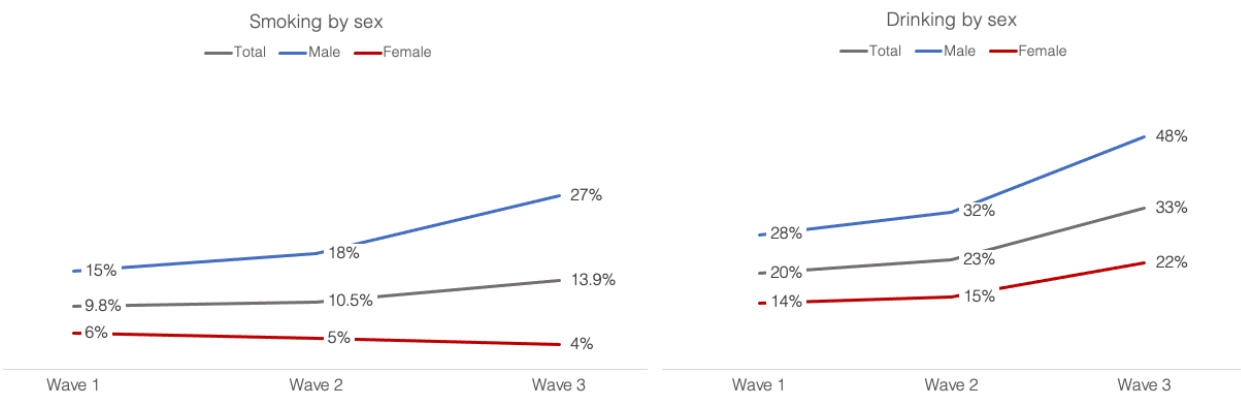
Risky sexual behaviours by sex**Substance use by sex**

Figure A4.1. CES-D score over time



Note: Kernel density plots of CES-D score over time.

Figure A4.2. Smoking and alcohol use by sex



META-ANALYSIS

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

Julia Ruiz Pozuelo, MSc^{id}, Lucy Desborough, PGCert^{id}, Alan Stein, FRCPsych^{id}, Andrea Cipriani, MD^{id}

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. This meta-analysis systematically reviewed evidence examining the association between depressive symptoms and risky behaviors among adolescents in LMICs.

Method: Fifteen electronic databases were searched for published or unpublished cohort and case-control studies about adolescents in LMICs. The primary outcome was the association (odds ratio [OR]) between depressive symptoms and risky sexual behavior and substance use. Secondary outcomes included delinquency, adverse school behavior, self-harm, and suicidal behavior. ORs from all studies were pooled using the random-effects model. Quality of studies was assessed using the Newcastle-Ottawa scale, and strength of the overall body of evidence was assessed using Grading of Recommendations, Assessment, Development and Evaluation.

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

Conclusion: This study suggests that adolescents with depression in LMICs carry a double burden: depression and 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: adolescents, depressive symptoms, low- and middle-income countries, risky behaviors

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Adolescence is a time when individuals start to make vital decisions about their own health, education, friendships and intimate relationships, and entrance into the labor 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, human immunodeficiency virus infection, 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 girls 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.^{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, adolescents 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 generalize 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 The current project, Depressive Symptoms and Risky Behaviors Among Adolescents in Low- and Middle-Income Countries (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 identified existing adolescent cohort studies in LMICs, an area that continues to be underrepresented in research studies.³¹

METHOD

Search Strategy and Selection Criteria

We followed 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 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 (eg, National Income Dynamics Study in South Africa, Pelotas Birth Cohort Study in Brazil, Cebu Longitudinal Health and Nutrition Survey in the Philippines, Young Lives study).

We included articles that recruited adolescents aged 10–24 years old, which is in line with the definition of adolescence by Sawyer *et al.*³³ 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 a longer period, sometimes well into their 20s. 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 toward making adolescents more visible for policy-makers, 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 10–24 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 (eg, Center for Epidemiological Studies Depression Scale [CES-D], Patient Health Questionnaire [PHQ]-9).
4. Studies that measured risky behaviors using biological markers and/or self-reported measures (see “Outcomes Measures” for further details).
5. Studies that controlled for the outcome variable (risky behaviors) at baseline and potential confounders (eg, age, sex, socioeconomic status).

We excluded cross-sectional studies because of their methodological limitations. We also excluded randomized trials for two reasons. First, given the limited evidence on the issue and the fact that risky behaviors may manifest only 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 causal relationship.³⁴ Second, randomized trials cannot study what happens to adolescents once they become depressed (as a trial that induces depression would not be feasible or ethical). Instead, randomized trials would be able to measure only whether reducing depression also reduces risky behaviors. While similar in nature, we see this and our main objective as 2 different questions.

Further, we excluded studies that reported suicidal ideation (without attempt), as thoughts are not behaviors, and studies that recruited human immunodeficiency virus-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 human immunodeficiency virus 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 date, with the sample size taking precedence. Further, non-English-language studies were translated either by colleagues fluent in the respective language or using Google Translate (<https://translate.google.com/>) with subsequent cross-checking by a native speaker. We checked reference lists to identify relevant studies and handsearched these.

Search results were compiled, and duplicates were eliminated by a single researcher (J.R.P.). Two reviewers (L.D. and J.R.P.) independently screened the titles 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 (<https://www.mendeley.com/reference-management/mendeley-desktop>), 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

(eg, people 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 defined 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 focused on the following 2 primary outcomes:

1. **Risky sexual behaviors:** any sexual behavior that increases an individual's risk for sexually transmitted infections or unwanted pregnancies. We included studies that measured such behaviors using biological markers (eg, sexually transmitted infections, 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 at coital debut, age difference with partner, ever engaged in transactional sex.

2. **Substance use:** any use of alcohol or other recreational drugs. We included studies that measured substance use using biological markers (eg, 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. We included on the following secondary outcomes:

1. **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.
2. **Adverse school behaviors:** any behavior that disrupts the classroom or a student'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.

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

Data Extraction and Quality Assessment

One reviewer (J.R.P.) extracted data, and a second reviewer (L.D.) independently cross-checked 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 (Microsoft Corp., Redmond, Washington).

Two reviewers (J.R.P. and L.D.) independently assessed the quality of the studies using the Newcastle-Ottawa Scale, using 2 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) or provided sufficient data to calculate ORs were included in the meta-analysis. The analysis was conducted in Comprehensive Meta-Analysis Version 3.⁴⁰ The incidence of each type of risky behavior in depressed and nondepressed adolescents was estimated using ORs. When several ORs 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, as considerable heterogeneity was expected.⁴¹ Random-effects models assume that the true treatment effect differs from study to study (ie, there is a distribution of true effect sizes), which allows generalization 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).

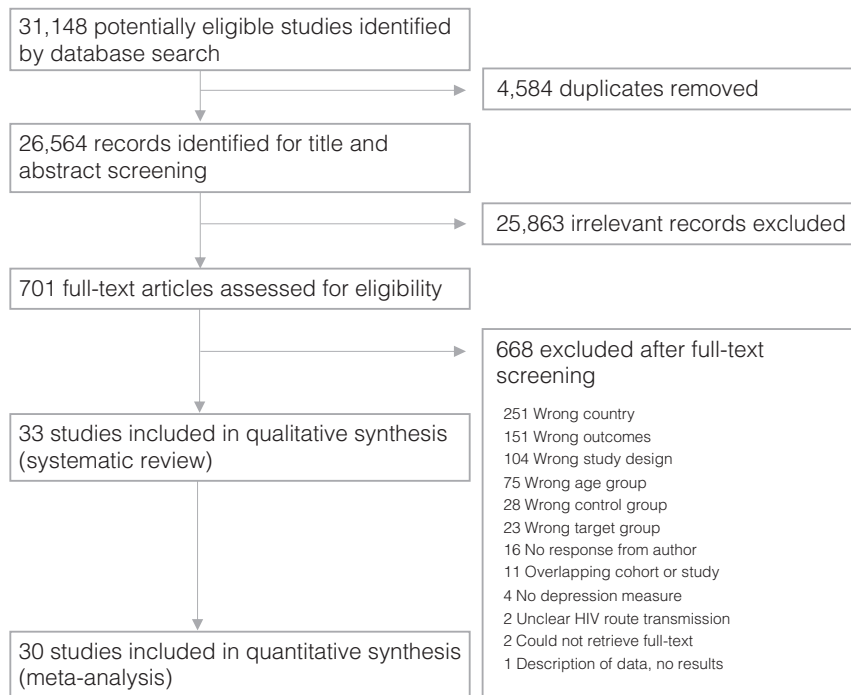
RESULTS

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 (Figure 1). 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.

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 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 presents the characteristics of the included studies, and Table S3, available online, lists all excluded studies with reasons.

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 we 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 2 types of informants (family members, friends, or neighbors) to minimize informant discrepancies and measurement error.^{70,74}

Regarding study quality, using the Newcastle-Ottawa Scale, most studies (67%) had high methodological quality, 10 studies (30%) had moderate quality, and 1 study (the

FIGURE 1 Study Selection

Note: HIV = human immunodeficiency virus.

abstract) had low quality. Table 1 shows the total score, and Table S4, available online, shows the score for each dimension.

To estimate the extent to which depressive symptoms, the primary outcome, 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 with nondepressed 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 with adolescents without depressive symptoms (OR 1.76, 95% CI 1.42–2.19, $I^2 = 77.33\%$) (Figure 2).

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, 95% CI 1.83–5.62, $I^2 = 33.58\%$), self-harm (OR 4.38, 95% CI 1.34–14.36, $I^2 = 0.0\%$), and suicidal behavior (OR 6.56, 95% CI 2.28–18.86, $I^2 = 0.0\%$) among adolescents with depression compared with nondepressed 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 ($p = .001$), showing a larger OR among female adolescents compared with male adolescents. No statistically significant difference was found between groups for substance use ($p = .442$). 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 ORs in case-controls) and risky behaviors measures, with biological markers/diagnostic interviews resulting in significantly larger ORs compared with 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 3 studies reported a positive association between depressive symptoms and risky behaviors, reinforcing the results of the meta-analysis. Interestingly, Auerbach *et al.*⁷⁶ conducted a multilevel modeling analysis to examine 2 hypotheses: whether depressive symptoms resulted in more risky behaviors and whether risky behaviors resulted in higher depressive symptoms. Using a sample of 411 Chinese adolescents and

TABLE 1 Characteristics of Included Studies

Study Risky sexual behavior	Country	Setting	Race/ethnicity	Sample size, n	Female participants, %	Age range	Study design	Depression measure (cutoff)	Type of risky behavior	NOS	Description of study population
Castilla-Puentes, 2012 ⁴⁴	Bolivia	Urban	NA	645	100	9–19	Case-control	CES-D (cutoff ≥ 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 - Adair <i>et al.</i> , 2011 ⁴⁵	Philippines	Both	Filipino	915	41	20–24	Cohort	CES-D (continuous score)	Unsafe sex and unplanned pregnancy	6	Cebu Longitudinal Health and Nutrition Survey (CLHNS) is largest and longest running birth cohort study in Southeast Asia, following >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 <i>et al.</i> , 2008 ⁴⁶	Brazil	Urban	NA	220	100	14–18	Case-control	HADS (depression scale cutoff ≥ 8)	Teenage pregnancy	8	Case-control study conducted in 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 <i>et al.</i> , 2018 ⁴⁷	Malawi	Rural	NA	4,029	100	15–24	Cohort	Depressive symptoms (cutoff ≥ 2)	Unintended pregnancy	6	Cohort study conducted in Mchinji District, Malawi. Pregnancy intention and depression were measured among

(continued)

TABLE 1 Continued

Study	Country	Setting	Race/ethnicity	Sample size, n	Female participants, %	Age range	Study design	Depression measure (cutoff)	Type of risky behavior	NOS	Description of study population
Nduna <i>et al.</i> , 2010 ⁵⁰	South Africa	Both	NA	1,978	51	15–26	Cohort	CES-D (cutoff ≥ 16)	Multiple partners	6	>4,000 pregnant women on 2 different occasions. Respondents were aged 15–49, >90% were married, and 86% had either no education or primary level. ^a Cohort study conducted around Mthatha, South Africa. Participants were interviewed in 2002 and again in 2004. Most participants were educated up to grade 10 (88%), 20% had been pregnant before, and compared with men, women came from lower socioeconomic background.
NIDS - Brophy <i>et al.</i> , 2018 ⁴⁸	South Africa	Both	Nationally representative sample (includes Black/African, Coloured, Indian/Asian, White)	677	100	10–19	Cohort	CES-D (continuous score)	Teenage pregnancy	6	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 >28,000 participants 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 - Victora <i>et al.</i> , 2008 ⁴⁹	Brazil	Urban	Multiethnic population-based study, representative of Pelota's population (includes White, Black, and Brown)	3,440	47	11–22	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

(continued)

TABLE 1 Continued

Study	Country	Setting	Race/ethnicity	Sample size, <i>n</i>	Female participants, %	Age range	Study design	Depression measure (cutoff)	Type of risky behavior	NOS	Description of study population
Substance use Arellanez-Hernández <i>et al.</i> , 2004 ⁵¹	Mexico	Urban	NA	897	18	10–18	Case-control	CES-D (cutoff $\geq$ mean + 1 SD)	Illicit drug abuse	8	Case-control study conducted in Mexico City with 218 illicit drug abusers and dependents (cases) and 679 nonusers (controls) matched by age, sex, and neighborhood. Respondents were mainly single (98.5%), school-goers (71%), with lower levels of education in cases than in controls.
	Turkey	NA	NA	138	25	16–18	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 sociodemographic 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 <i>et al.</i> , 2018 ⁵³	Mexico	Urban	Representative sample of adolescents in Mexico City	1,071	NA	12–17	Cohort	WMH-CIDI	Any substance use disorder (alcohol, drugs, or tobacco)	8	Cohort study conducted in Mexico City with >3,000 adolescents at baseline in 2005 and >1,000 adolescents in the 8-year follow-up. The survey was designed to be representative of

(continued)

TABLE 1 Continued

Study	Country	Setting	Race/ethnicity	Sample size, n	Female participants, %	Age range	Study design	Depression measure (cutoff)	Type of risky behavior	NOS	Description of study population
Charfi et al., 2018 ⁵⁴	Tunisia	Urban	NA	53	0	19–24	Case-control	TEMPS-A	Illicit drug abuse	9	adolescents aged 12–17 in the area. About two-thirds of the adolescents lived with both parents; four-fifths were students; 1 in 10 had social burdens such as being married, having a child, or being employed during the school year. Case-control study conducted in Sfax, Tunisia, with 50 drug addicts (cases) and 50 nonusers matched by age, marital status, socioeconomic level, and education level (controls). ^a
CLHNS - Adair et al., 2011 ⁴⁵	Philippines	Both	Filipino	1,755	46	20–24	Cohort	CES-D (continuous score)	Alcohol use	6	See Adair et al. ⁴⁵ entry above for description of the cohort. For the meta-analysis, we used data from 2005 and 2007.
Effat et al., 2016 ⁵⁵	Egypt	Both	NA	161	0	12–18	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 cases had poorer academic performance than the controls and had a significantly higher family history of psychiatric illness and history of drug abuse.
Kazour et al., 2015 ⁵⁶	Lebanon	Urban	NA	60	NA	15–24	Case-control	HAMD (NA)	Illicit drug abuse	7	Case-control study conducted in Beirut, Lebanon, with 61 heroin-dependent inpatients

(continued)

TABLE 1 Continued

Study	Country	Setting	Race/ethnicity	Sample size, n	Female participants, %	Age range	Study design	Depression measure (cutoff)	Type of risky behavior	NOS	Description of study population
NIDS - Brophy <i>et al.</i> , 2018 ⁴⁸	South Africa	Both	See Brophy <i>et al.</i> ⁴⁸ entry above	3,505	52	14–24	Cohort	CES-D (continuous score)	Alcohol use	6	See Brophy <i>et al.</i> ⁴⁸ entry above for description of cohort. For the meta-analysis, we used data on alcohol use from wave 3 (2012) and wave 4 (2014).
Niraula <i>et al.</i> , 2009 ⁵⁷	Nepal	Rural	Hill native; Brahmin/Chhetry; Newar; Others.	183	NA	15–24	Case-control	CES-D (cutoff determined using ROC curve)	Illicit drug abuse	7	Case-control study conducted in Dharan, Nepal, with 102 drug abusers (cases) and 81 nonusers (controls). Respondents were mainly male, had <12 years of education, were not married, and came from upper-lower socioeconomic status. ^a
Pelotas - Victora <i>et al.</i> , 2008 ⁴⁹	Brazil	Urban	See Victora <i>et al.</i> ⁴⁹ entry above	3,191	53	18–22	Cohort	MINI	Alcohol and illicit drug use	7	See Victora <i>et al.</i> ⁴⁹ entry above for description of cohort. For the meta-analysis, we used data for >3,000 participants aged 18–22 with information on depression and substance use.
Delinquency Bejarapas and Soleimani, 2017 ⁵⁸	Tajikistan	NA	NA	240	50	13–19	Case-control	Scl-90-R (continuous score)	Committing a crime	8	Case-control study conducted in Tajikistan with 120 delinquents (cases) and 120 nondelinquent adolescents matched by age, neighborhood, education level, and

(continued)

TABLE 1 Continued

Study	Country	Setting	Race/ethnicity	Sample size, n	Female participants, %	Age range	Study design	Depression measure (cutoff)	Type of risky behavior	NOS	Description of study population
Kiliç, 2011 ⁵⁹	Turkey	Urban	NA	41	0	12–15	Case-control	CDI (NA)	Violent behavior	5	socioeconomic background (controls), Case-control study conducted in Ankara, Turkey, with 22 adolescents who showed violent behavior at school (cases) and 10 nonviolent peers (controls). Both groups came from low socioeconomic backgrounds with low levels of parental education.
Zhou et al., 2012 ⁶⁰	China	Urban	Asian; Han people	476	0	14–17	Cohort	YSR (NA)	Committing a crime	8	Cohort study conducted in Chongqing, China, with juvenile offenders (all male) serving sentences of at least 1 year and nonoffenders from the same community. Juvenile offenders were more likely to have a low level of education, come from single-parent households, and live separately from their family compared with community adolescents. There was no statistical difference between household income, religious belief, and ethnicity across the 2 groups.
Zhou et al., 2014 ⁶¹	China	Rural	Asian	409	0	15–17	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 nonoffenders matched by gender and age (controls). Cases had been convicted of various offenses ranging

(continued)

TABLE 1 Continued

Study	Country	Setting	Race/ethnicity	Sample size, <i>n</i>	Female participants, %	Age range	Study design	Depression measure (cutoff)	Type of risky behavior	NOS	Description of study population
Self-harm											
Barrocas <i>et al.</i> , 2015 ⁶⁴	China	Both	Asian	617	51	15–17	Cohort	K-SADS-PL	Nonsuicidal self-injury	9	Cohort study with 617 adolescents enrolled in grade 10 at baseline and followed for 2 years. Respondents were from an urban school in Changsha and a rural school in Liuyang (Hunan province, China).
Kinyanda <i>et al.</i> , 2005 ⁶²	Uganda	Urban	NA	188	NA	15–24	Case-control	BDI (cutoff ≥ 11)	Deliberate self-harm	7	Case-control conducted in Kampala, Uganda, with 50 cases of deliberate self-harm and 138 controls matched by age and sex. Respondents were mainly male, had low educational attainment, and were single. ^a
Zhang <i>et al.</i> , 2016 ⁶³	China	Both	Asian	3,957	53	11–20	Case-control	Scl-90-R (continuous score)	Self-harm behavior	6	Case-control conducted in Linyi, China, with 1,092 cases of self-harm and 2,865 controls. Both groups were students from junior and senior high schools in rural and urban areas. Most respondents had no siblings (79%), one-third came from a family with high parental education (high school or higher), and 40% of the sample

(continued)

TABLE 1 Continued

Study	Country	Setting	Race/ethnicity	Sample size, n	Female participants, %	Age range	Study design	Depression measure (cutoff)	Type of risky behavior	NOS	Description of study population
Suicidal behavior Bella, 2012 ⁶⁵	Argentina	Urban	NA	59	NA	10–16	Case-control	DIS	Suicide attempt	7	had low family income (<1,000 yuan per month).
											Case-control study conducted in Cordoba, Argentina, with 25 adolescents hospitalized for a suicidal attempt and 34 controls without such history. ^a Most respondents were enrolled in school, and compared with controls, cases were more likely to smoke, drink alcohol, and have tried other drugs.
Çetin, 2001 ⁶⁶	Turkey	Urban	NA	83	62	14–20	Case-control	BDI (cutoff ≥ 17)	Suicide attempt	7	Case-control conducted in Ankara, Turkey, with 33 adolescents who attempted suicide (cases) and 50 healthy controls. Most of the sample lived with family (90%). Compared with controls, cases were more likely to have higher number of siblings and family members and were mostly the older children in birth order.
Fidan et al., 2011 ⁶⁸	Turkey	Both	NA	60	82	14–22	Case-control	BDI (cutoff ≥ 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

(continued)

TABLE 1 Continued

Study	Country	Setting	Race/ethnicity	Sample size, n	Female participants, %	Age range	Study design	Depression measure (cutoff)	Type of risky behavior	NOS	Description of study population
González <i>et al.</i> , 2012 ⁶⁹	Cuba	Urban	NA	128	NA	10–18	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 neighborhood. Compared with controls, cases were more likely to have a family history of psychiatric illness and come from a broken family.
Li <i>et al.</i> , 2008 ⁷⁰	China	Both	Asian (representative sample)	205	41	15–24	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 with 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 <i>et al.</i> , 2005 ⁷¹	China	Rural	Asian (representative sample)	284	40	12–18	Case-control	YRBS (NA)	Suicide attempt	8	Case-control study conducted in rural prefecture of Shangong Province, China, with 142 suicide attempters and 142 healthy controls matched by age, gender, and school class. Most respondents came from a family of

(continued)

TABLE 1 Continued

Study	Country	Setting	Race/ethnicity	Sample size, <i>n</i>	Female participants, %	Age range	Study design	Depression measure (cutoff)	Type of risky behavior	NOS	Description of study population
Liu et al., 2019 ⁷²	China	Both	Asian (representative sample)	5,451	48	12–16	Cohort	YRBS (continuous score)	Any suicidal behavior	6	farmers with low parental education. Compared with controls, suicide attempters reported more negative life events during the past year, shorter sleep duration, and poorer physical health. Cohort study conducted in Shandong province, China, with 5,451 adolescents followed for 1 year. Compared with nonsuicidal adolescents, suicidal adolescents were more likely to report having a history of cigarette smoking and alcohol drinking.
Ramalingam et al., 2016 ⁷³	India	Both	NA	100	70	13–18	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, and were single (83%), and one-third were students while 38% were unskilled workers.
Zhao and Zhang, 2015 ⁷⁴	China	Rural	Asian	315	47	15–24	Case-control	HAM-D (continuous score)	Death by suicide	6	Case-control psychological autopsy study in several rural counties in 3 Chinese provinces (Liaoning, Hunan, and Shandong) with 141 suicide cases and 174 community controls matched by age and residence. Most respondents were single (77%), had an average of 8 years of education, and came from an

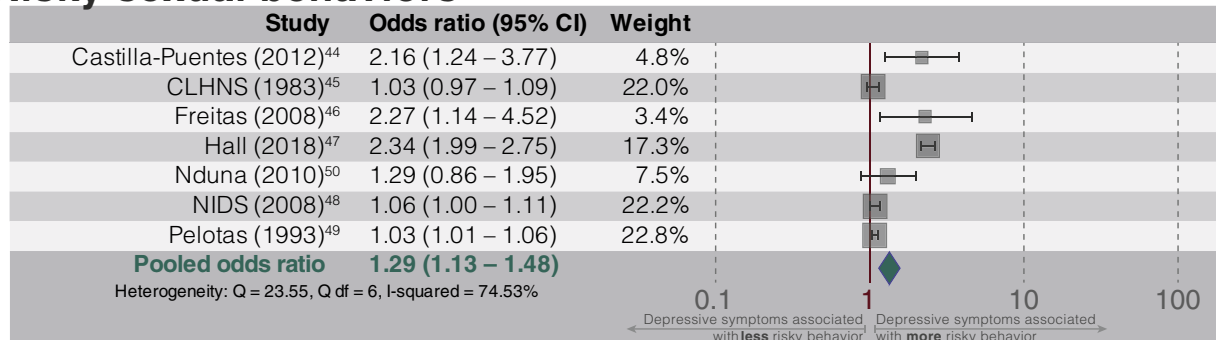
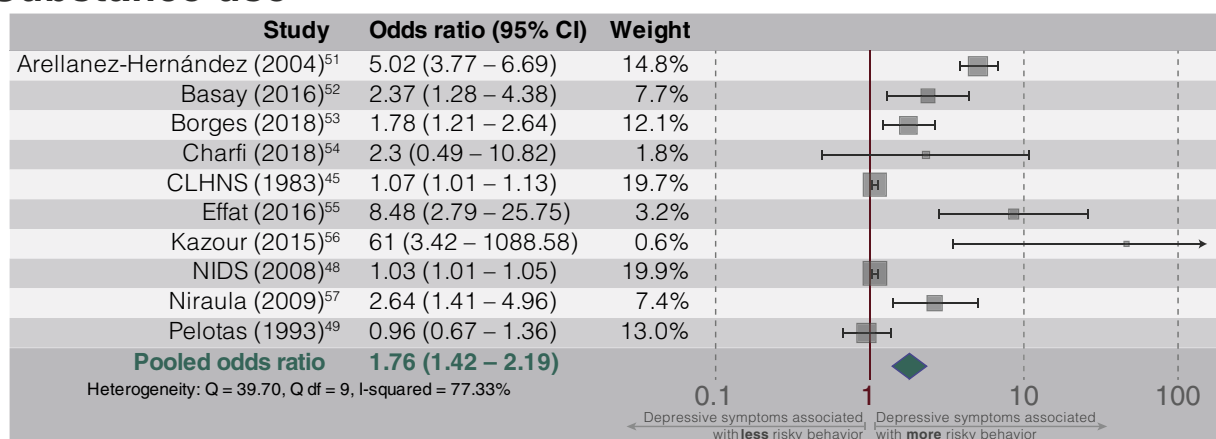
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TABLE 1 Continued

Study	Country	Setting	Race/ethnicity	Sample size, n	Female participants, %	Age range	Study design	Depression measure (cutoff)	Type of risky behavior	NOS	Description of study population
Systematic review											
Auerbach <i>et al.</i> , 2010 ⁷⁶	China	Urban	97.1% Han people; 1.7% other ethnic group; 1.2% participants did not report ethnicity	411	50	14–19	Cohort	CES-D	RBO-A	7	Cohort study conducted in Hunan, China, with 411 high school students. The sample was predominantly Han ethnicity (97.1%) and came from nuclear families (89.3%).
Cluver <i>et al.</i> , 2015 ⁷⁵	South Africa	Both	NA	3,515	56	10–18	Cohort	CDI	Suicide attempt	7	Cohort study conducted in 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, 3 meals a day, and toiletries to be able to wash every day.
Vieira <i>et al.</i> , 2018 ⁶⁷	Brazil	Urban	73.3% White; 26.5% Mixed	1,244	58	18–24	Cohort	MINI	Suicidal behavior	6	Cohort study conducted in Pelotas, Brazil, to assess 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, 45% as middle socioeconomic status, and 3% as low socioeconomic status.

Note: A diagnosis of depression was used in studies that ascertained depression using structured clinical interviews (eg, MINI). BDI = Beck Depression Inventory; CDI = Children's Depression Inventory; CES-D = Centre for Epidemiologic Studies Depression Score; DIS = Diagnostic Interview Schedule; DRS = Depression Self-Rating Scale; EPSIS I = European Parasuicide Study Interview Schedule I; HADS = Hospital Anxiety and Depression Rating Scale; HAM-D = Hamilton 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; NA = not available; NOS = Newcastle-Ottawa scale (total score); RBQ-A = Risky Behavior Questionnaire for Adolescents; ROC = receiver operating characteristic; Scl-90-R = Symptom checklist; SDQ-E = Strengths and Difficulties Questionnaire–emotional subscale; 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.

^aData for 10- to 24-year-olds was requested from corresponding author.

FIGURE 2 Forest Plot for Risky Sexual Behavior and Substance Use (Random-Effects Model)**Risky sexual behaviors****Substance use**

Note: Please note color figures are available online.

7 assessments, the results suggested that the model was unidirectional, with depressive symptoms occurring earlier than the incidence of risky behaviors.

Finally, following GRADE 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

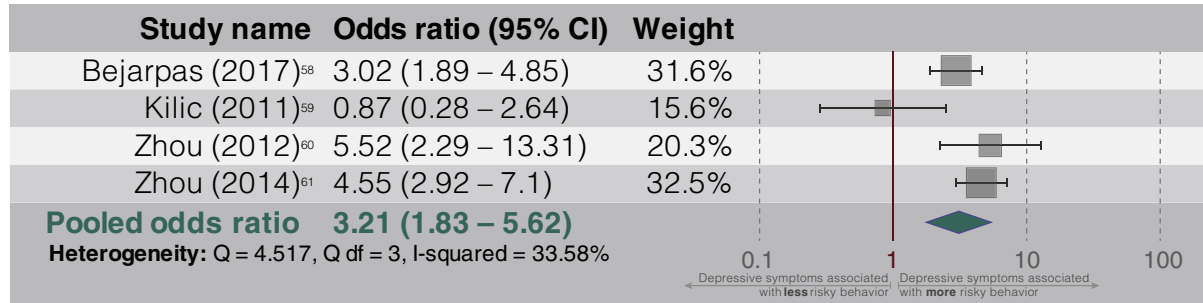
This review found that adolescents in LMICs with depressive symptoms are more likely to engage in risky behaviors compared with nondepressed adolescents. These findings are consistent with the evidence from high-income countries.^{9–16} To our knowledge, this is the first systematic review and meta-analysis 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 included only 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 (eg, sexual, substance use, delinquency, self-harm, suicidal), as opposed to focusing on a single behavior. All included studies encompassed 35,918 adolescents living in 17 different LMICs. These 17 countries are home to 48% of the world population and 57% of the population of LMICs (Table S7, available online).

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

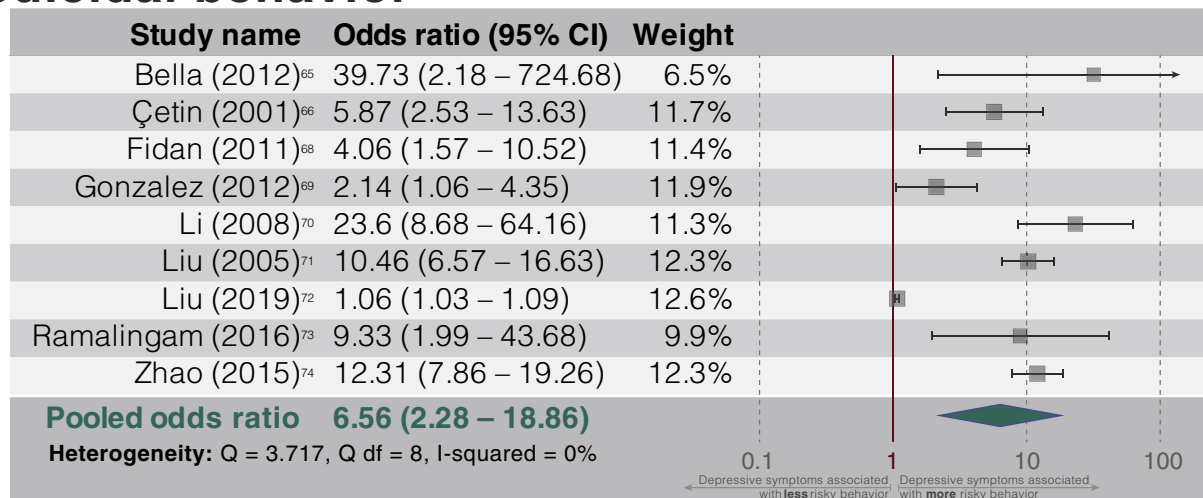
Delinquency



Self-harm



Suicidal behavior



Note: Please note color figures are available online.

Several mechanisms 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 (eg, inhibitory control and reward processing) may result in higher engagement in risky behavior.^{6,80,81} Further, the presence of cognitive biases,

such as low self-esteem, avoidance, rumination, and hopelessness, may make a depressed person 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 adolescents' 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 ORs 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 included only studies that controlled for covariates that are known to affect depressive symptoms and risky behaviors (eg, age, sex, socioeconomic status). Second, significant heterogeneity was observed across studies in many outcomes. We believe that this was due in part to the fact that ORs were computed by combining different behaviors (eg, risky sexual behaviors pooled together teenage pregnancy, unsafe sex, and multiple partners). 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 analyses 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 standardized diagnostic interviews and depressive symptoms scales that were suitable for the 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 (eg, 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.

Despite these limitations, this study has important implications. First, these findings suggest that adolescents with depression in LMICs carry a double burden: they experience symptoms of depression, and because they are more likely to engage in risky behaviors, they are at an increased risk of experiencing the negative consequences of their behaviors. This double burden may result in further psychological and physical health problems that persist over the life span (eg, 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, which is 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 (eg, food scarcity, violence, forced migration) are overrepresented in LMICs, resulting in higher rates of depression among adolescents in LMICs compared with adolescents in high-income contexts.^{8,89–91} Adding to the complexity, LMICs have extremely low levels of public expenditure on mental health (less than USD \$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 number 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 public health and welfare institutions are often insufficiently resourced, which means that adolescents living in these countries lack the support they need.⁹⁵ While this type of support is far from perfect in high-income countries, there are a range of program, such as rehabilitation program, 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 living in LMICs 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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Formal analysis: Pozuelo, Cipriani

Investigation: Pozuelo, Desborough

Methodology: Pozuelo, Cipriani

Project administration: Pozuelo

Software: Pozuelo, Desborough

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Validation: Desborough

Visualization: Pozuelo

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RESEARCH ARTICLE

Adolescent health series: Adolescent neurocognitive development in Western and Sub-Saharan African contexts

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Abstract

The transitional period of adolescence has long been associated with physical, social and behavioural change. During this time, adolescents start to develop their own self-identity, make important life decisions and acquire the necessary skills to successfully transition to adulthood. More recently, advances in brain imaging technology have enabled increased understanding of structural and functional changes in the human brain during this developmental period, and how they relate to social, emotional, motivational and cognitive development. The ability to integrate these developing cognitive processes in increasingly complex social contexts is a key aspect of mature decision-making, which has implications for adolescent health, educational, economic and social outcomes. Insights from the field of developmental cognitive neuroscience could increase our understanding of this influential stage of life and thus inform potential interventions to promote adolescent health, a critical goal for global health research. Many social changes occur during adolescence and the social environment shapes both brain and cognitive development and the decisions adolescents make. Thus, it is important to study adolescent neurocognitive development in socio-cultural context. Yet, despite evidence from Western studies that socio-cultural and economic factors impact on adolescent neurocognitive development, existing studies of adolescent neurocognitive development in sub-Saharan Africa are relatively scarce. We summarise research findings from Western and sub-Saharan African contexts and highlight areas where research is lacking. Longitudinal studies from more diverse global samples will be needed to build a comprehensive model of adolescent development, that characterises both commonalities in developmental trajectories, as well as the way these can meaningfully differ between both individuals and contexts.

KEYWORDS

adolescence, brain development, cognition, decision-making, emotional regulation, social cognition, social context

Sustainable Development Goals: No poverty; Zero Hunger; Good Health and Well-being; Quality Education; Gender equality; Reduced Inequalities

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INTRODUCTION

Adolescence can be defined as the period of life between the biological changes of puberty and the individual attainment of a stable, independent role in society [1,2]. However, the timing of both pubertal onset and adult role transition vary both between and within cultures [3]. In response to this, it has recently been argued that a broader, more inclusive definition of adolescence, spanning the ages of 10–24 years, most accurately conceptualises contemporary global patterns of adolescent development [4]. Adolescents constitute approximately one-third of the total population of sub-Saharan Africa (SSA), a region which is projected to have more adolescents than any other in the world by 2050 [5]. Yet, there is very little existing research into brain and cognitive development among adolescents living in this region.

Globally, developmental research has historically largely focused on infancy and the early years [2], and SSA is no exception – much of what is known about neurocognitive development comes from studies of young children [6–12]. However, adolescence is a unique stage of life, characterised by substantial physical, behavioural, social and neurocognitive change relative to early childhood and adulthood. During this time, adolescents develop their self-identity and make important decisions which impact on their long-term health, economic, social and educational opportunities and outcomes [3,13]. Adolescence can be considered a sensitive period for social development, during which brain and behaviour become increasingly adapted to one's unique social environment and individuals show heightened sensitivity to developmentally relevant social experiences [1,14]. In adolescence, this manifests as a re-orientation towards peers [14,15], as individuals explore and develop their own socially integrated self-identity and align their behaviour with the social norms of those they identify with [16–18]. Many of the changes occurring in adolescence, such as heightened sensitivity to social cues and interactions, and increased exploration of novel environments, likely confer adaptive benefits to the development of independence and survival and are observed in both humans and adolescents of other species [19,20]. However, they can also confer vulnerability. Key aspects of adult health behaviour emerge or are intensified during adolescence, from exercise and nutritional habits [21], to engagement in health risks such as substance use and unsafe sex [13,22,23], and the majority of lifetime mental illness begins before the age of 25 [24,25]. Thus, understanding this influential stage of life is a critical goal for global health research.

This review outlines key developmental changes in brain and cognitive development in human adolescence and how this knowledge can increase our general understanding of adolescent behaviour and decision-making, in addition to potential applications for adolescent health in SSA. Given that adolescence is a period of social reorientation [14,26], it is important to study adolescent neurocognitive development within socio-cultural context [1,27]. However, existing studies of adolescent neurocognitive development in SSA are

relatively scarce. We review key findings of extant research and highlight areas where evidence is lacking. Where there is a paucity of existing research, we use relevant research from Western contexts to speculate on the impact of challenges faced by adolescents growing up in SSA on cognitive development. Caution should however be exercised when applying the findings from research conducted in high-income, Western countries. We discuss these limitations, in addition to methodological and logistical challenges involved in studying adolescent neurocognitive development in SSA, a region with large socio-cultural, economic and environmental variation. Finally, we make some suggestions as to how taking a developmental cognitive neuroscientific perspective can increase our understanding of adolescent health behaviour and how these principles might be harnessed when designing interventions targeting adolescents' health and well-being.

ADOLESCENT NEUROCOGNITIVE DEVELOPMENT

Structural brain development

The human brain undergoes substantial structural and functional reorganisation during adolescence. Although the overall volume of the brain does not change after late childhood, there is converging evidence that cortical white matter volume increases throughout childhood and adolescence and this increase continues until the thirties, while cortical grey matter volume shows concomitant decreases in volume during adolescence, before stabilising in the mid-twenties [28,29]. While the precise relationships between these structural changes and underlying biological mechanisms are still debated [30–32], they are consistent with histological evidence of continued cellular reorganisation during adolescence [33–35]. These neurodevelopmental processes, such as axonal growth, myelination and synaptic reorganisation, are thought to facilitate developmental changes in connectivity within and between brain regions, resulting in alterations in the way information is integrated throughout the brain [36,37]. One of the brain regions that has received considerable research focus is the prefrontal cortex (PFC), one of several areas of the brain that undergoes prolonged development throughout adolescence [34,38,39]. The PFC is involved in a wide range of cognitive processes, including social cognition, cognitive control and motivational-affective processing. These processes form the cognitive building blocks of our everyday behaviours: the ability to set and maintain goals, ignore distractions, empathise with others and regulate our emotions.

Social cognitive development

Adolescence is characterised by social change, in which social factors increase in salience and value [1,40]. Compared with

children, adolescents form more complex and hierarchical peer relationships and are more sensitive to acceptance and rejection by their peers [41–44]. An adolescent's social world is thus often unstable and changeable, for example, it is only later in adolescence that friendships become more stable and characterised by reciprocity [45]. Furthermore, self-reported friendship quality predicts mental health resilience and well-being longitudinally in young people (14–24 years) [46], highlighting the importance of social functioning in this period of development.

Although the factors that underlie these social changes are likely to be multi-faceted, it is notable that adolescence is also a period of pronounced structural and functional development of the 'social brain' [47–49]. This refers to a network of brain areas, including dorsomedial regions of the PFC, that are associated with social cognitive abilities [49–51]. Social cognition encompasses a wide range of processes which enable us to understand and interact with one another, from face processing to more complex social inferential processes such as understanding others mental states and using the perspectives of others to guide our actions [51,52]. Thus, social cognitive abilities play a critical role in the successful negotiation of complex social interactions and decisions [53]. These abilities, and the brain networks that support them [48,49], continue to develop into early adulthood and occur in the context of parallel developments in other neurocognitive systems such as cognitive control and motivational-affective processing [47].

Development of cognitive control

Cognitive control can be defined as the ability to actively guide behaviour and involves the coordination of a heterogeneous set of sub-processes that focus attention on goal-relevant information, while inhibiting goal-irrelevant information [54–56]. Studies indicate continued maturation of the component processes that make up cognitive control throughout adolescence and into early adulthood, as well as a steady increase during this period in the ability to co-ordinate these processes to guide thoughts and actions in a goal-directed manner [57,58]. These sub-processes, such as inhibitory control, performance monitoring, attentional shifting and working memory (WM) are supported by integrated brain networks including the dorsolateral PFC [59,60] and there is considerable evidence for developmental changes in PFC recruitment during cognitive control tasks over the course of adolescence [57,58].

Cognitive control processes can be engaged in the absence of socio-emotional, motivationally relevant information or 'cold' contexts. However, many of the everyday scenarios in which cognitive control is employed are characterised by motivational-affectively salient, or 'hot' situations and outcomes [61]. Social interactions represent a key source of motivational-affective responses, particularly during adolescence: social cues can elicit robust emotional

responses, and those around us can be a salient source of potential rewards and punishments [62–65]. Successful navigation of these 'hot' situations involves the integration of cognitive control with mechanisms of social cognition, emotional responsiveness and motivation and is facilitated by the extensive connectivity of the PFC with many other brain regions, including areas of the social brain network and sub-cortical brain structures such as the amygdala and striatum [40]. These regions are implicated in multiple, distinct neural circuits which show temporal variation in their maturational trajectories, both within and between circuits, and become increasingly integrated during development [14,40].

Emotional regulation

Emotional regulation describes the monitoring, evaluation and modification of our emotional states and involves both the explicit strategic regulation of emotional responses, and more automatic, implicit regulatory processes that operate largely outside of our awareness [66]. Despite conceptual differences, both types of emotional regulation processes involve a network of extensively interconnected brain regions, including the PFC, amygdala and striatum [67]. These connections facilitate both the top-down regulation of affective responses by cognitive control and the bottom-up modification or disruption of cognitive control processes by affective information [67] and show marked maturational changes during adolescence [68–70]. Experimental studies of emotional regulation in typically developing adolescents indicate continuing developmental improvements in both implicit and explicit regulation and it has been hypothesised adolescence may be an important period for the development of adaptive emotional regulation, a key predictor of mental health and socio-economic outcomes [66].

Value-based learning and decision-making

Adolescence is characterised by changes in learning and decision-making, including value-based decision-making, in which potentially rewarding or costly choices are made based on the perceived value and risk of the outcomes. Experimental studies suggest that different components of value-based decision-making show different developmental trajectories [71]. Children as young as 8 are able to estimate risk probabilities and reward values on developmentally adapted tasks [72,73]. However, the ability to use this information to make advantageous choices in 'hot' contexts characterised by high levels of emotion, reward or arousal, shows a more protracted course of development [71]. Adolescents are more likely to take risks in pursuit of a potentially rewarding outcome with 'hot' risky decision-making paradigms, indicating a peak in risk-taking during adolescence [71,74]. Delay discounting (the tendency to prefer smaller,

immediate rewards over larger but delayed rewards) has also been shown to decrease as a function of age during adolescence [75–78].

Obtaining a rewarding outcome elicits robust activation of dopaminergic regions, such as the striatum [79], and it has been hypothesised that developmental changes in the dopamine system during adolescence may result in heightened reward sensitivity [80]. Both cross-sectional and longitudinal neuroimaging studies have found that, compared with children and adults, adolescents show increased striatal reactivity when receiving rewards [81–86], and studies using risky decision-making paradigms are mostly consistent with the hypothesis that adolescents are biased to take risks due to heightened reward sensitivity [83,85,87,88].

Although adolescents are often stereotyped as prone to take risks that can result in harmful outcomes, such as substance use and dangerous driving, increases in reward sensitivity can also drive adaptive risk-taking, exploration and learning [89]. When outcomes are unknown, such as in changing or novel environments, taking risks can facilitate learning through the acquisition of new information about the world around us, which can be used by adolescents to inform future decision-making [90]. Computational studies of value-based learning and decision-making suggest that adolescence is characterised by reductions in sensitivity to negative feedback and increases in sensitivity to reward [68,91,92], which may contribute to the observed increase in reward-approach and subsequent learning behaviour [93]. For example, adolescents (12–16 years) have been shown to preferentially seek rewards rather than avoid punishments on a probabilistic learning task, whereas adults learned to seek and avoid both equally [94].

In addition to changes in reward and punishment sensitivity, there is also evidence that in some ‘hot’ contexts adolescents do not engage regulatory prefrontal regions to the same extent as adults [95–97]. However, we should not assume this characterises all instances of value-based decision-making in adolescence. Studies suggest that heightened reward sensitivity in adolescence can result in an enhanced ability to flexibly up-regulate cognitive control in a goal-directed manner relative to children and adults [97–100], indicative of the complex relationship between motivational-affective processing and cognitive control. Indeed, in contexts in which exploration of novel environments is associated with opportunity, adolescents (16–17 years) exhibit more optimal behaviour and learning strategies than adults [101]. Some risk-taking behaviours are strategic in nature and may in fact be dependent on the ability to engage cognitive control processes to achieve one's goal, even in the face of potential loss, such as auditioning for a desired role in a play or standing up to a bully [102]. Furthermore, when considering the optimality or rationality of a decision, it is important to take into account not just the degree of risk involved, but also the existence of differences between what adults and adolescents ascribe relative value to [1,102].

Social context

Many of the decisions that adolescents make are taken in social contexts and it has been proposed that the risk of social rejection may be weighted more strongly by adolescents than other risks (such as health or legal risks) and therefore that engaging in risk-taking behaviour may sometimes be seen as the rational choice [1,103]. Behavioural and neuroimaging studies indicate that social context, particularly the presence of peers, has a greater impact on adolescent behaviour, including risky decision-making, in comparison to adults [104–107]. Studies of social context in adolescence have largely focused on the detrimental impact of peer influence on experimental tasks involving risky and reward-related decisions [104,108,109]. However, social context can also have positive effects on adolescent behaviour, and studies indicate a facilitative effect of peers on feedback-learning [110], group decision-making [111] and engaging in prosocial behaviour [112,113]. We discuss the potential implications of this for adolescent health and well-being in the final section of this review.

INDIVIDUAL DIFFERENCES IN ADOLESCENT NEUROCOGNITIVE DEVELOPMENT

Research has so far predominantly focused on characterising average neurocognitive development in adolescence. While this has been essential in furthering understanding of typical patterns of development, the precise timings and trajectories of structural and functional brain development, and how this relates to behaviour, show substantial and meaningful variation between individuals [114,115]. Understanding sources of individual variation, such as genetics, puberty hormones, socio-economic status, culture and exposure to environmental stressors, will be fundamental in developing a more nuanced understanding of adolescent neurocognitive development across contexts.

In addition to direct social contexts, such as the presence of peers, adolescent decision-making and behaviour also vary according to the context of our broader social environment. Societal expectations of adolescents differ greatly across cultures, as do definitions of behaviours that are considered high-risk or socially unacceptable and opportunities to engage in different types of risky behaviours [116].

An advantage of experimental assessments of value-based decision-making is that they can be used to assess the propensity to take risks, or learn from experience, in a controlled choice environment and thus can be a useful tool for cross-cultural research into the underlying mechanisms of risky decision-making. A study of adolescents from 11 different countries found that laboratory tasks yielded more consistent patterns of developmental effects across cultures than self-report measures of risk behaviours [116]. Despite the existence of variation between countries, there were also similarities which suggest that risk-taking tendencies peak

in the late teenage years in young people growing up in both Western and Non-Western countries [116,117]. However, further work is needed to understand *how* cultural differences contribute to variation in developmental trajectories of risky behaviours.

Adolescence can be thought of as a period of learning and adaptation, in which neurocognitive networks develop and are moulded through reciprocal interactions between brain, body, behaviour and the environment [118]. The brain requires environmental input to complete development, and it has been hypothesised that adolescence is a period for the 'biological embedding of culture', whereby sensitivity to the social environment promotes optimal development according to the specifics of one's local context [119]. Given that SSA is characterised by marked variation in socio-cultural and economic environments both within and between countries, this should be taken into account when considering adolescent neurocognitive development and applying findings from Western studies to adolescents in SSA contexts [120]. Yet to date, very few studies have investigated the effects of culture on neurocognitive development [121].

In the next sections, we discuss evidence on adolescent neurocognitive development in SSA and highlight areas in which evidence from other countries suggests future research may be relevant, before discussing some of the ongoing challenges faced when conducting research in this region.

ADOLESCENT NEUROCOGNITIVE DEVELOPMENT IN SUB-SAHARAN AFRICA

Challenges in studying cognitive development in SSA

Most studies of adolescent cognitive development (including the research reviewed above) have been conducted in so-called WEIRD societies (Western, Educated, Industrialized, Rich, and Democratic) [122], which account for only 10 per cent of the world's adolescents, limiting the generalisability of study results. However, investigating neurocognitive development in SSA often involves both logistical and methodological challenges, which may provide some insight into why there is limited research in this area.

The availability of MRI units is currently scarce or non-existent across SSA [123] and therefore unsurprisingly so has been developmental neuroimaging research among adolescents in the region. A recent study, which used locally adapted neuroimaging to investigate neurocognitive development in a South African cohort of 2–3-year olds, found evidence of similar associations between the brain and cognition to those observed in studies in high-income countries [12]. However, to build a comprehensive and generalisable model of adolescent neurocognitive development, studies of adolescence from diverse global samples including SSA are needed. Neuroimaging studies can provide key insights into

the development of neurobiological mechanisms underlying complex aspects of behaviour and increase our understanding of the developmental trajectories associated with risk and resilience outcomes. They also have the potential to improve the predictive utility of some behavioural assessments of cognition on future outcomes [124].

There is also a marked paucity of culturally appropriate and standardised measures of cognition among adolescents in SSA [125]. Yet, tasks developed in high-income countries might not be appropriate in an SSA context, challenging the validity of the results, particularly measures that yield standardised performance norms. Systematic differences between research settings can also result in differences in cognitive task performance that do not necessarily reflect cognitive function. Many tasks have been developed and validated to assess a given underlying cognitive construct in high-income settings. However, to yield a valid and accurate assessment, these tasks are often reliant on the availability of trained assessors and a distraction-free environment, which might not be available in low-resource settings [126].

Cross-cultural studies using tasks developed in high-income countries have generally shown lower scores in cognitive tasks among African samples compared to Western samples [127–130]. Differences in language, culture, ethnicity, education and context can lead to several type of biases and affect the validity of measures, both within and between countries. Given the linguistic and cultural diversity of SSA countries, this presents a challenge [131–134]. Furthermore, many cognitive tests require basic literacy and numeracy skills and were developed with individuals who were familiar with test demands through school exposure. This can be a barrier for SSA, the region with the highest out-of-school rate across all age groups, where nearly nine of ten individuals between the ages of 6 and 14 do not meet minimum proficiency levels in reading and maths [135].

Despite these challenges, there is evidence to support the value and effectiveness of adapting and validating cognitive tasks for different cultural contexts. In the next section, we discuss existing research into adolescent cognitive development in SSA, including studies which have successfully adapted cognitive tasks within SSA contexts, in addition to highlighting areas in which future research is needed.

Existing research

Many adolescents in SSA are exposed to negative life experiences such as poverty, malnutrition, early life stress and diseases such as HIV and malaria [136–138]. While a discussion of the effects of adversity is beyond the scope of this review, there are multiple, potentially interacting, mechanisms through which high levels of adversity might impact on neurocognitive development including, but not limited to, poor nutrition, lack of stimulating learning conditions and increased exposure to both physical and psychosocial environmental stressors [139–142]. Thus, the majority of studies of cognition in SSA to date have focused on childhood poverty

and nutrition [6–12], and cognitive impairment as a result of disease [143–146].

One of the few longitudinal studies measuring cognitive development among adolescents in SSA is the Young Lives project, a longitudinal study of child poverty conducted in Ethiopia, India, Peru and Vietnam (totalling 12,000 participants across all sites) [147]. These data were used to investigate the relationship between stunting, a delay in physical growth during childhood as a result of poverty, malnutrition and/or infectious diseases and cognitive development in children aged 8–15 years [148]. Consistent with previous research, child growth was an important predictor of subsequent school outcomes [148]. However, some of the negative effects of stunting on cognition were partially reversible: 36% of children showing stunting at age 8 caught up in terms of growth with their peers by age 15, and those who caught up in physical growth had smaller deficits in cognitive scores than those who did not [148]. These results highlight the importance of nutrition for cognitive development in both the early years and adolescence.

While studies of the impact of exposure to high levels of environmental adversity on cognition are of crucial importance, there are few studies investigating adolescent neurocognitive development in larger community samples of young people, which is important to build a comprehensive picture of typical developmental trajectories in adolescents growing up in SSA contexts. The majority of existing studies of cognition in typically developing adolescents in SSA have focused on ‘cold’ aspects of cognition, such as fluid intelligence, academic abilities and aspects of cognitive control such as WM and inhibition. These studies are largely cross-sectional and typically have focused on the influence of factors such as education and family environment on cognition in children and early adolescents (5–14 years), or the adaptation of ‘Western’ cognitive tasks to SSA contexts. For example, Holding et al. (2018) developed a cognitive test battery for use among children and adolescents (7–18 years) in three cultural settings (Bangladesh, Ghana and Tanzania) [149]. The tasks, which assessed aspects of cognitive control such as WM and inhibition, were systematically adapted to the different cultural contexts — including heavy piloting of both the content and the administration [149]. Scores were similar across sites and instruments presented adequate psychometric properties. Similar results were found using culturally adapted cognitive tasks with a school-age sample in Zambia, Cameroon, South Africa and the Democratic Republic of the Congo [127–130] and a recent study found that associations between different aspects of cognitive control in Nigerian adolescents (12–21 years) resembled those predicted by existing models of executive functions derived from Western studies [150].

These studies highlight the importance of adaptation and validation of cognitive tasks within cultures, and the value in doing so for assessments of ‘cold’ aspects of cognition. In contrast, very little is known about the development of socio-affective and motivational processing and the influence of ‘hot’ contexts on cognitive control and decision-making

among adolescents in SSA. Extensive adaptation and validation will also be needed to create appropriate assessments of the development of these aspects of cognition. In addition to being essential in informing our understanding of typical adolescent socio-affective development in SSA, this research may be particularly relevant to understanding the effects of exposure to psychosocial stressors — such as socio-economic instability and inequality, sparse or unstable caregiving, abuse and violence — on adolescent cognition.

Given the high HIV burden in many SSA countries, many adolescents have suffered adversity during development including the death and illness of primary caregivers, reduced frequency and/or quality of caregiver interaction, and the impact of negative stigma of HIV status on the family and child [151,152]. Early life stress, including childhood trauma, exposure to violence and maternal deprivation can result in altered neurocognitive development of affective and motivational processing during adolescence [153,154]. These changes can impact on an individual's ability to navigate the developmental changes of adolescence and may create vulnerability to later mental health difficulties and associated negative outcomes such as poorer educational attainment and social functioning [155]. However, early adversity can also result in developmental alterations that may be adaptive in some adverse or unpredictable later environments or even represent neurocognitive markers of resilience [156–158]. Studies of socio-affective and motivational processing therefore have the potential to inform the development of preventative interventions that aim to reduce the impact of early adversity on neurocognitive development and promote adaptive changes which foster resilience during adolescence.

IMPLICATIONS OF ADOLESCENT NEUROCOGNITIVE DEVELOPMENT FOR INTERVENTION DESIGN

Increasing our understanding of adolescent neurocognitive development across contexts may give insight as to why some adolescents are successful in making the transition to adulthood, while others experience difficulties. Adolescence may represent a period of heightened neural plasticity, during which the brain is particularly amenable to change and the effects of experience and intervention [159,160]. Evidence from both global and SSA contexts suggests that incorporating perspectives from developmental cognitive neuroscience can be used to inform the design and selection of interventions to promote adolescent health and well-being and to help adolescents who may be struggling as a result of earlier environmental adversity.

Considering the influence of socio-emotional and motivational context on adolescent learning and decision-making may be particularly effective in supporting adolescents in the safe transition to adult independence. As an example, Graduated Driver Licensing, in which young drivers build up their experience gradually with extended periods of supervision in high-risk situations, such as carrying

same-aged passengers, has substantially reduced young driver casualties and crash rates in adopting Western countries [161]. Similarly, interventions encouraging adolescents to make decisions in 'cold' contexts that they will benefit from even in 'hot' contexts (such as pre-exposure prophylaxis and long-acting contraceptives) may be particularly successful [162,163]. Interventions that provide adolescents with the opportunity and support to engage in positive risk-taking, such as trying out for sports teams, or initiating new friendships may also be an effective way for adolescents to engage in exciting and novel experiences that also promote their well-being [164].

Traditional conceptualisations of risk behaviours tend to focus on health, legal or financial risks, with less consideration given to the implications of social risk, such as the risk of social rejection by one's peers and/or wider community [165]. Yet, interventions targeting risky health behaviours such as unsafe sex or binge drinking in adolescence will likely benefit from recognising the role social risk and social influence plays in adolescent decision-making and well-being [103]. While intervention research highlights the importance of avoiding or reducing situations in which high-risk behaviours such as substance misuse or criminal behaviour can be mutually reinforced through peer feedback [166–168], the positive effects of social context and positive peer influence on behaviour should not be overlooked [112,113,169–171]. Interventions that mitigate the social risk of peer ostracisation and facilitate the creation and support of positive peer groups for adolescents may be particularly effective in promoting prosocial, healthy behaviour [172]. Adolescent's heightened sensitivity to peer influence can also be harnessed as a driver of positive behavioural change. 'Grassroots' interventions, in which socially connected adolescents are supported in developing and delivering interventions, enable adolescents to identify the key issues in their community (which may differ to those defined by adults) and aim to spread behavioural change through shifting social norms. This type of intervention has been effective in reducing bullying and smoking in high-income countries [173,174], although evidence from Indonesia highlights the importance of careful adaptation to context and local resources [175].

Approaches targeting the salience of adolescents' social environments have already shown success in reducing risky health behaviours and enhancing educational outcomes within SSA contexts. A large-scale study in Botswana evaluating the delivery of information about safe sex practices to adolescent women (12–16 years) found that the intervention reduced pregnancy when delivered by peer mentors but had no effect when delivered by older teachers [176]. Other studies found that exposure to inspiring, relatable positive role significantly increase students' school performance among adolescents in Madagascar (9–15 years) [177] and Uganda (15–20 years) [178]. The heightened sensitivity of adolescents to social approval and rejection may have important implications for interventions targeting young women's engagement in transactional sex, a key contributor to the HIV epidemic

in SSA. Qualitative work suggests that young women living in rural South Africa (13–20 years) are aware of the risks associated with these relationships but may overlook these risks in the pursuit of consumer goods perceived as essential to their sense of self-worth and social status [179,180]. Given that within this cohort low self-esteem was associated with increased engagement in transactional sex [181], interventions are needed which take into account the psychosocial needs of adolescents during this developmental period [182].

Exposure to adversity during early life can impact on later brain development and cognition during adolescence and influence an individuals' ability to achieve their full potential [6]. Lower cognitive ability is associated with a range of disadvantageous real-world outcomes [183–185], highlighting the need for effective interventions for adolescents who are struggling due to disease exposure and other environmental adversities. In addition to the relevance of such interventions for educational attainment, interventions may also have implications for adolescent health. A cohort study among adolescent/young adult women (18–25 years) in rural South Africa found that individuals scoring in the bottom quintile on tasks assessing attentional switching and WM were more likely to report engaging in risky sexual behaviour, such as unprotected sex, concurrent partners and transactional sex [186]. A study from Sweden suggested that WM training can be effective in ameliorating cognitive deficits in adolescents (14–15 years) born at extremely low birth weight with low cognitive ability [187]. Given evidence from Western samples that some aspects of complex cognition, such as relational reasoning, show greatest training benefits in late rather than early adolescence, adolescence may represent a window of opportunity for interventions targeting aspects of cold cognition that show protracted development during adolescence [188].

Adolescents growing up in adverse environments may also develop protective, automatic emotional responses, such as avoidance or aggression, that may not be adaptive in the different contexts they encounter in adolescence such as school and broader social settings which can negatively impact on subsequent socio-affective development [153,154]. While alterations in the processing of threatening or uncertain information may confer adaptive advantages in unpredictable, adverse environments, they may become maladaptive later in life, particularly if the environment becomes more stable and less adverse [155,156]. Interventions that support adolescents in the development of explicit emotional regulation strategies, such as reflecting on their automatic responses to affectively charged situations, and whether or not they are adaptive to their goals in different contexts, have been effective in reducing crime and school dropout rates in disadvantaged male youth in Chicago [189]. Neuroimaging studies have also indicated that childhood maltreatment is associated with reduced activation of reward processing systems during adolescence [154,190]. Given the adaptive role of developmental changes in reward processing in adolescence, alterations or disruption to these developmental trajectories may reduce learning and exploration during this phase of

life and it has been hypothesised that a lack of a developmental increase in reward sensitivity during adolescence may be a mechanism through which early childhood adversity is predictive of later emerging depression [154,156]. If so, adolescence may represent a critical period for intervention for depression, particularly with interventions that target reward processing systems such as behavioural activation therapy [191].

CONCLUSION

Increasing our understanding of adolescent neurocognitive development and how this varies within individuals over time, between individuals and across cultures can provide insight into why adolescence is a period of elevated health vulnerability, who may be most at risk and how best to design effective interventions. However, there is still a lot we do not know about adolescent cognitive development within an SSA context. Longitudinal studies from more diverse global samples will be needed to build a comprehensive model of adolescent development, that characterises both commonalities in developmental trajectories, as well as the way these can meaningfully differ between both individuals and contexts.

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