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A systematic review of the association between biological markers and environmental stress risk factors for adolescent depression

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Contributors

BAK, VM, HLF, AA, RK, JRS, and CK conceived the idea for the review. ZZ, GAP, BAK, JRS, RK, CK, HLF, VM, developed the review protocol. ZZ, AW, NG and VZ conducted the search with input from GAP and supervision from VM and BAK. ZZ, AW, NG and AW performed extraction with help from GAP. ZZ and VM wrote the first draft of the manuscript with input from AW. All authors critically appraised and edited the manuscript. All authors contributed to revision and finalization of the manuscript.

Conflict of interests

VM has received research funding from Johnson & Johnson, a pharmaceutical company interested in the development of anti-inflammatory strategies for depression, but the research described in this paper is unrelated to this funding. All other authors declare that they have no competing interests.

Summary

Introduction—Although the aetiology and pathophysiology of depression are multifactorial, to date most studies have examined either biological or environmental mechanisms without looking at the integration of both; with most studies conducted in high-income countries (HICs). Therefore, we conducted a systematic review of worldwide studies investigating the relationship between biological and environmental stress risk factors for major depressive disorder (MDD) in adolescence.

Methods—We searched MEDLINE (via Ovid), PsycINFO, Cochrane Database of Systematic Reviews, Web of Science (Core Collection), Lilacs, African Journals Online and Global Health for prospective and cross-sectional studies that examined the association between biological markers and environmental stress risk factors in MDD during adolescence.

Findings—Of 11,089 articles identified, 21 were included, with only two from middle-income countries. Increased inflammation, telomere length and brain abnormalities, including blunted reward-related activity, white matter disruptions, and altered volume of limbic brain regions, were associated with increased risk for MDD mainly in the context of early life adversity. There is little evidence suggesting that the neurobiological changes investigated were associated with MDD in the context of recent life stress.

Interpretation—The developmental trajectory of depression appears to start with early life adversities and occurs in the context of immune and brain abnormalities. Understanding these biopsychosocial processes will help to improve our ability to detect individuals at risk of developing depression in adolescence. However, generalizability is limited by few studies examining both biological and environmental stress risk factors and a lack of studies on adolescents and young adults in low-and-middle-income countries (LMICs).

Keywords

Adolescence; depression; Major Depressive Disorder; MDD; risk factors; biomarkers; inflammation; cortisol; MRI; brain; early life adversity; child maltreatment; youth; young people

1. Introduction

Although the aetiology and pathophysiology of depression are complex and multifactorial, to date, most studies investigating risk factors for depression have examined either biological or environmental mechanisms without looking at the integration of both.[1–4] A better understanding of the association of biomarkers with environmental risk factors, particularly environmental stress, is paramount for the development of better prevention and treatment strategies. The literature on biological and environmental mechanisms of depression has mainly focussed on adults;[4–6] however, it is becoming evident that given the high incidence of depression in the first decades of life and chronicity throughout life, adolescence presents a window of opportunity to develop effective prevention strategies and reduce the burden associated with this disorder.[7]

The association between environmental stress risk factors of psychiatric disorders and biological risk factors has emerged over recent decades. For example, experience of

childhood traumatic events, which is a widely acknowledged risk factor for depression and other psychiatric disorders, has been linked to increased levels of inflammatory markers such as C-reactive protein (CRP) or interleukin (IL)-6.[5] Indeed, increased levels of immune markers have now been widely reported in patients with depression, suggesting a possible role of the immune system in the aetiology of this disorder.[5,8] The interaction between environmental stress risk factors and alterations in biological pathways can help us to understand why some individuals may be at higher risk of developing psychiatric disorders and why others may be more resilient. There are several potential pathways through which biological and environmental risk factors may work together to increase risk for depression. One pathway is that stressful contexts can modulate and/or interact with biological systems to influence development of depression.[5,9] For example, Miller and colleagues found that higher inflammatory markers were only associated with depression in adolescents exposed to childhood adversity.[10] In line with diathesis-stress frameworks, findings of moderation suggest that some biological vulnerabilities (e.g., increased inflammation) may only lead to the development of depression within stressful environmental contexts, but not in contexts of low stress.[11] A second potential pathway is a mediational pathway, in which exposure to a stressor leads to altered development of biological mechanisms, which in turn increase risk for developing depression. For example, reduced insular surface area was reported to mediate the association between childhood maltreatment and depression relapse in adults.[9] Furthermore, lifetime trauma-associated ventral anterior cingulate cortex connectivity was linked to the severity of affective symptoms in young adults.[12] Animal models reveal that early life stress can lead to inflammation which can in turn lead to brain abnormalities, including structural and connectivity changes, as reported in the last two studies.[5,9,12,13]. We propose that the interaction between stressful environmental factors, including early and lifetime adversities, and consequent specific alterations in biological mechanisms is particularly relevant for the development of depression. It is therefore important that associations between environmental risk factors and biological markers are assessed to better understand what contributes to development of depression and identify more effective prevention strategies. In the current paper, we consider any studies that examined associations between both biological and environmental risk factors and depression, including studies that examined either moderating or mediating pathways.

Biological markers have been increasingly investigated with the aim to better guide and develop interventions and prevention strategies.[14,15] Although various biological mechanisms have been explored and examined, no biomarker has been clearly identified or validated for risk or presence of depression in adolescence and young adulthood.[2,3,16] Most studies investigating risk factors for depression have been conducted in adults.[4,6] A number of theories explaining biological pathways underpinning depression in adults have been proposed, including a monoamine theory, increased activation of the immune system, and abnormalities of the hypothalamic-pituitary-adrenal (HPA) axis.[4,17,18] Other potential biomarkers have been suggested based on neuroimaging studies (e.g., fronto-limbic dysregulation with hyperactivity in limbic brain structures and hypoactivity in the prefrontal cortex).[19,20] Other associated biomarkers include endocannabinoids,[21,22] neurotrophic factors,[23] polyunsaturated fatty acids (PUFAs),[24] hormones,[25] telomere length,[26] and vitamin D,[27] but these associations lack consistency across studies and populations.

While many studies have explored biological risk factors of depression in adults, far fewer have focused on adolescence and young adulthood, and a very limited number of studies have been conducted in low- and-middle income countries' (LMICs) populations[2,3,16] This is problematic as 90% of the world's adolescents live in LMICs, and we cannot be certain that research findings from high-income-countries (HIC) are generalisable across different socioeconomic settings.[28] Therefore, understanding what may be universal vs. context-dependent biomarkers of risk is crucial to gain a global perspective of what constitutes depression in both HIC and LMIC settings, which is paramount to inform effective prevention and intervention strategies globally.

Findings across these studies seem to mirror what has been reported in adult depression, including elevated cortisol and inflammation, and fronto-limbic dysregulation; however, they do not take into account environmental factors[2,3,16,29] and therefore provide only a partial understanding of the mechanisms leading to MDD. This is particularly relevant considering how different socioeconomic status or level of urbanization could modulate the biological response of an organism to environmental stressors.[30–32] Furthermore, of the studies that have examined younger populations, most studies to date have focussed on children and adolescents with ages <19 years old. However, as adolescence defines a period of growth and transition from childhood to adulthood, it has recently been argued that such transitions extend beyond 19 years of age, such as changes in social roles.[33] Maturational changes in the prefrontal cortex have been reported to continue beyond the age of 19.[16] Therefore, capturing social and neurobiological changes that continue to occur in adolescence and young adulthood (<25 years old) is important in understanding the wider picture underlying the biopsychosocial model for MDD which includes the transition period from childhood to adulthood across cultures.[16,33,34] To our knowledge, no review has investigated how environmental stress risk factors, , may relate to biological markers of depression in adolescence and young adulthood. Therefore, to address this gap, we conducted a worldwide systematic review of studies looking at an extensive range of biological markers for MDD in adolescents and young adults up to age 24, and their relationship with environmental stress risk factors mainly defined by adverse life experiences. We included the following biological markers in our search: HPA axis, inflammation, endocannabinoids, vitamins, PUFAs, hormones, neurotrophic factor, neurotransmitters, telomere/gene length, neuroplasticity, gene expression (including mRNA quantification) and brain-related abnormalities. We included the following environmental stress risk factors in our search: child maltreatment/ adverse childhood experiences, psychological trauma/stress, family conflicts, violence, poverty, homelessness, socioeconomic deprivation, parental mental health, life change events, refugees, armed conflicts and disasters (full list of search terms in Appendix 1). These risk factors were chosen because we decided to keep a broader perspective on the type of "stressors" included to avoid restricting too much our focus to the "usual suspect" (i.e. childhood maltreatment) and miss studies on other important stressful risk factors, such as socioeconomic deprivation, exposure to armed conflicts or natural disaster etc., particularly when trying to be more inclusive for studies coming from LMICs. We included papers in our review when they examined both one of our specified biological risk factors as well as one of our specified environmental risk factors.

2. Methods

2.1 Literature search strategy

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).[35] We searched the following electronic databases since inception until 10th January July 2021: MEDLINE (via Ovid), PsycINFO, Cochrane Database of Systematic Reviews, Web of Science (Core Collection), Lilacs, African Journals Online and Global Health. While we conducted searches in English, publication language was not a restriction. Only research published in peer-reviewed academic journals was eligible for inclusion. We performed searches with each biomarker of interest separately (HPA axis, inflammation, endocannabinoids, vitamins, PUFAs, hormones, neurotrophic factor, neurotransmitters, telomere/gene length, neuroplasticity, gene expression (including mRNA quantification) and brain-related abnormalities). A full list of search terms is reported in Appendix 1. For each search, we entered all of the search terms for Adolescent AND Depression AND environmental stress risk factors, and then entered an AND search term for each biological risk factor separately (e.g., we conducted one search with the HPA search terms and a separate search with the inflammation search terms; the terms for each biological marker were entered with "OR" between them. Given we had 12 biological markers, we ran 12 separate searches), identifying papers that examined both an environmental stress risk factor and a biological risk factor for MDD. In addition to electronic searches, we manually searched relevant systematic reviews and reference lists of the retrieved articles for eligible studies that may have been missed. The systematic review protocol has been published,[36] and is registered (PROSPERO: CRD42018103973).

2.2 Eligibility of the studies

We followed PICO model when assessing studies for eligibility. Studies were included if they met the following inclusion criteria: 1) presence of MDD through a categorical diagnostic interview or continuous measure of depressive symptoms such as a questionnaire with the cut-off value for clinical symptoms of depression reported; 2) adolescents and young adults aged 10 to 24 years old; 3) examination of one or more of the biological risk factors associated with an increased risk for developing MDD during adolescence and young adulthood: HPA axis, inflammation, endocannabinoids, vitamins, PUFAs, hormones, neurotrophic factor, neurotransmitters, telomere/gene length, neuroplasticity, gene expression (including mRNA quantification), brain function, connectivity and structure and explicit test of whether this biological risk factor was associated with MDD; 4) presence of adverse environmental stress risk factors associated with biological risk factors in the context of MDD (e.g., childhood abuse, traumatic events, family conflicts, poverty and socioeconomic deprivation, and armed conflicts); 5) explicit test of association between biological and environmental stress risk factors; 6) study design: any intervention or prevention trial, cross-sectional or longitudinal study; and 7) publication in a peer-reviewed journal.

Studies were excluded if they met at least one of the following exclusion criteria: 1) individuals included in the study/participants were limited to only specific medical

subpopulations, e.g., youth living with HIV, diabetes, intellectual disabilities; 2) investigated genetic polymorphism; 3) non-research papers (e.g., opinion pieces); 4) qualitative studies; 5) no presence of MDD; or 6) for longitudinal studies, prospective measure of depression < 6 months (for longitudinal studies). Full list of search terms is included in Appendix 1.

2.3 Analysis

Full text screenings and quality assessments were conducted by two independent reviewers until inter-rater reliability of >90% agreement was reached, following which assessments of articles for eligibility were performed independently. A third reviewer resolved any discrepancies. We used the Systematic Assessment for Quality of Observational Research (SAQOR) to assess quality of the sampling approach and depression measurement, and we used the SAQOR recommendations for equivalent GRADE rankings (see Table 1).[37] The final quality modified GRADE rating reported in our review was based on the study design and the number of SAQOR categories marked as “adequate”. All of the studies reported were observational. An observational study with a minimum of four “adequate” categories as per SAQOR, was graded as “low”. A study having less than four categories marked as “adequate” meant that the study was graded as “very low” according to the modified GRADE rating.[37] Therefore, the maximum GRADE rating for these studies was ‘low’ given that they all used observational designs.

3. Results

3.1 Study inclusion and quality

Out of 11,089 articles, we initially identified 42 studies which included both biological and environmental stress risk factors in the context of MDD. Out of these 42 studies, 21 investigated biological and environmental stress risk factors from a joint perspective and therefore met the eligibility criteria and were included in the review (see Figure 1). Nineteen studies were conducted in high-income countries (HICs), and two in middle-income countries (Colombia and China) (see Tables 2 and 3). From the reviewed literature, several environmental stress risk factors of MDD were examined across all the eligible biomarker studies, including childhood abuse, traumatic events, peer problems, family conflicts, parental depression and socioeconomic adversity. Regarding quality, 18 studies were marked as “adequate” across four or more of the six SAQOR categories and remained at the GRADE rating for observational studies of “low” quality. The remaining studies (n=3) were downgraded to a GRADE rating of “very low” (see Table 1).[38] Characteristics of the studies are summarised in Tables 2 and 3.

3.2 Functional and structural neuroimaging

An fMRI study reported that childhood maltreatment, which included physical, sexual and emotional abuse, and physical neglect, was associated with an increase in depression symptoms only in adolescents with low left putamen activity in response to positive versus neutral images.[39] In a different study of adolescents exposed to childhood maltreatment, adolescents with MDD displayed blunted activity in response to positive emotions and reward, and this effect was strongest in MDD patients with a history of childhood maltreatment, which included acts of commission (abuse) and omission (neglect).

Specifically, adolescents with MDD and childhood maltreatment displayed reduced dorsal anterior cingulate cortex and left and right caudate activity in response to positive versus negative words during an emotional word categorisation task compared to the MDD group without maltreatment, which was in turn reduced compared to healthy controls.[40] In an electroencephalogram (EEG) study, the reward positivity event-related potential in response to social acceptance was reduced specifically in adolescents with high lifetime social stress exposure and high depressive symptoms, above the clinical cut-off for the Inventory of Depression and Anxiety Symptoms (IDAS).[41]

Two neuroimaging studies measured white matter alterations using diffusion tensor imaging (DTI) technique, specifically focussing on fractional anisotropy (FA), a DTI method used to measure white matter structural connectivity in the brain. In the first study, adolescents at high risk for MDD, by virtue of exposure to maltreatment during childhood, showed lower FA values in the superior longitudinal fasciculi and the right cingulum projecting to the hippocampus compared with healthy controls. Interestingly, the same pattern of white matter disruption was associated with subsequent MDD onset in the longitudinal follow-up.[42] Childhood maltreatment included seven subtypes of adversity such as separation/loss of caretaker, life-threatening illness/injury to the self or others, physical neglect, emotional abuse, physical abuse, witnessing domestic violence, and sexual abuse, all of which must have occurred before the age of 10 and lasted for a minimum 6 months. In the second study, recent stressful life events (past six months) were negatively associated with FA-based connectivity between right caudate and middle frontal gyrus in depressed adolescents but not in healthy controls.[43] Similarly, a structural MRI study reported that smaller hippocampal volume partially mediated the relationship between early life adversity and development of depression at follow-up. Adolescents with high early life adversity and small hippocampal volume were more likely to develop depression 3 years later. Early adversity was defined by seven subtypes of adversity including separation/loss of caretaker, life-threatening illness/injury to the self or others, physical neglect, emotional abuse, physical abuse, witnessing domestic violence, and sexual abuse, all of which must have occurred before the age of 11 and lasted for a minimum 6 months.[44] On the other hand, Redlich and colleagues,[45] did not find reduced hippocampal volume to be the mediator between childhood maltreatment, assessed with the Childhood Trauma Questionnaire (CTQ),[46] and MDD diagnosis. However, they reported that childhood maltreatment was associated with smaller hippocampal volume in both MDD and healthy adolescents, whereas no associations were found between childhood maltreatment and amygdala reactivity to negative or positive faces. Lee and colleagues did not find hippocampal or amygdala volume to be related to early life adversity or MDD diagnosis, instead there was a significant indirect effect of peer problems on MDD diagnosis and depressive symptoms through increased volume of the nucleus accumbens.[47]

Another fMRI study, conducted in a middle-income country, found that adolescents and young adults with MDD displayed significantly lower left ventromedial prefrontal cortex and greater left middle cingulate cortex stress-related activity during the Montreal Imaging Stress Task.[46] However, although depressed patients showed significantly higher CTQ scores compared with healthy controls, those neural activity patterns remained unchanged after controlling for childhood trauma.[48] In sum, these studies suggest that blunted neural

response to reward, or volumetric and white matter structural differences, mediate or moderate associations between early life stress and depression.

3.3 Inflammatory pathways and the hypothalamic-pituitary-adrenal axis

Results across studies suggest that some inflammatory markers interact with early life stress to predict depression. For example, Miller and collagues[10] used a childhood adversity index to model early life stress, which consisted of several risk factors: a) birth to a teenage mother, b) parental death or divorce before age 15, or separation from a parent for more than 1 year, c) low household education, d) limited economic resources, and e) history of affective illness in parents. They reported that the effect of increased inflammation, as measured by IL-6 and CRP, predicting subsequent depression development was only shown in the group of participants with childhood adversity, defined as the presence of two or more of the risk factors from the childhood adversity index. Similarly, Danese and colleagues[49] showed that adolescents who were depressed and experienced childhood physical maltreatment had significantly higher CRP levels compared to healthy controls. In contrast, adolescents who were depressed and without a history of maltreatment or with a history of maltreatment but not depressed, were similar in the mean CRP scores to healthy controls.

Studies of HPA markers and recent life stress have not demonstrated similar interactions for MDD onset. For example, two longitudinal studies using the same sample with different follow-up time-points for MDD onset (1 year and 2.5 years) reported that baseline stressful life events, which included domains such as close friendships, social group relations, romantic relationships, relations with family members, academic, neighbourhood conditions, job, finances, health of self, and health of family members, and higher cortisol awakening response were independently associated with MDD onset in adolescence.[50,51] Furthermore, in a logistic regression model,[52] which examined the prediction of depressive symptomatology at age 16 based on cortisol and environmental stress measures collected at age 13, neither intervening negative life events, which measured undesirable life events and difficulties, nor reported parental conflict were significant predictors of depression. Although disturbed family functioning and cortisol were significant predictors of depression, adding their interaction to the model did not improve the fit of the model.

Other studies suggest that HPA-related markers and environmental stress risk factors independently predict depression but provide limited evidence of biological risk factors serving as moderators or mediators of recent life stress. For example, MDD at 12 months follow-up was predicted independently by baseline depressive symptoms, baseline levels of morning cortisol and evening dehydroepiandrosterone (DHEA) above the 80th percentile of the daily mean, and negative life events, which included disappointments and permanent losses, reported in the month before the MDD onset.[53] Using the same sample, the authors conducted a separate study where they looked at differences in the mean cortisol and DHEA levels between individuals at high and low risk for MDD. High risk for MDD was defined by the presence of two or more of the following risk factors: emotionality, recent undesirable life events, lifetime losses, marital/family difficulties, and parental psychiatric history. There was no difference in either cortisol or DHEA mean levels between high

and low risk adolescents. Moreover, in the subsequent follow-up analysis, none of the above-mentioned risk factors predicted MDD onset 12 months later, with the exception of morning DHEA, where adolescents with elevated morning DHEA were at significantly higher odds of developing MDD at 12 months follow-up.[54] Furthermore, another study reported higher cortisol awakening response and perceived physical and psychological stress scores in females with MDD compared with healthy controls. Physical symptoms were defined as headache, nervous agitation, insomnia, gastric problems, vertigo, cardiac symptoms, hand trembling and lack of appetite, and psychological symptoms as anxiety, anger and sadness. However, adding both stress scales as covariates to the model looking at group differences in cortisol awakening response levels, did not change the significant effect of cortisol awakening response on depression.[55] Another study failed to show that cortisol mediated the relationship between child maltreatment, which included sexual and physical abuse, and physical neglect, and subsequent MDD onset.[56]

3.4 Sleep Electroencephalography

Two studies investigated biological patterns associated with being at high risk for MDD, defined by a history of parental depression. Rao and colleagues investigated differences in sleep EEG and nocturnal urinary free cortisol measures between adolescents at high-risk for depression, by the virtue of parental depression, and the control group. High-risk adolescents showed many alterations in rapid eye movement (REM) sleep (shorter latency to REM sleep, higher number of episodes, longer duration of each episode and thus higher proportion of REM sleep, and increased REM sleep activity and density), as well as higher nocturnal urinary free cortisol compared with healthy controls. Interestingly, shorter latency to REM sleep, higher REM density, and higher nocturnal urinary free cortisol were found to predict MDD development in the sample follow-up.[57] Lastly, lower temporal coherence in ultradian sleep EEG rhythms was reported in adolescent females at high-risk for MDD, by the virtue of maternal history of depression, compared with healthy controls, although no group differences were found in any microarchitecture sleep variables including REM latency. The risk of developing MDD in the 2 year follow-up analysis increased with greater abnormality in temporal coherence and it was approximately 10 times higher in girls at high risk for MDD compared with healthy controls.[58]

3.5 Telomere length

One study from a middle-income country measured associations between leukocyte telomere length and several types of childhood trauma, including sexual, physical and emotional abuse and neglect, in adolescents with and without depression. They reported a positive association between telomere length and sexual abuse only in the MDD group. No other types of childhood trauma were associated with telomere length in either group. Further moderation analysis revealed that depressive symptoms did not moderate the relationship between childhood trauma and telomere length.[59]

4. Discussion

Our systematic review demonstrated the relevance of early life environmental stress context when examining the association of neuroimaging, inflammatory, EEG, and telomere

length markers with MDD onset in adolescents and young adults. The associations of increased inflammation and brain abnormalities with the onset of MDD in adolescence were particularly relevant in the context of early life stress. Of note, majority of the studies reporting early environmental stress refer to childhood adversity (i.e. different types of childhood trauma), which is why we refer directly to childhood adversity when reporting our findings.

The link between childhood adversity and biological changes leading to vulnerability to developing MDD in adults has been widely reported.[5,60] Therefore, finding similar patterns in adolescence and young adulthood further supports the biopsychosocial model of MDD onset and the relevance of immune and brain changes in the development of adolescent depression following experience of childhood trauma.

One proposed model to explain these findings is that early adversities lead to hyperactivation of the sympathetic nervous system and to a downstream shift in the profile of innate immune cells, contributing to increased peripheral inflammatory markers (a mediation model).[13] Previous studies have shown that an activation of the innate immune system can contribute to brain structure abnormalities, such as smaller hippocampal volume,[61,62] and a reduced functional connectivity among brain networks,[63,64] similar to the brain imaging findings reported in the adolescents with MDD and history of childhood trauma from our review.[42,44] The reduced connectivity in the superior longitudinal fasciculi and the right cingulum projecting to the hippocampus has been reported in the adolescents who will develop MDD following childhood trauma. This is complemented by the recent data that shows instead, an increased connectivity in the ventral tegmental area (VTA) and in the hippocampus, associated with resilience traits in response to early adversity in young adults.[65] The results from the studies reported in our review support the mediation framework we are proposing, whereby childhood adversity may lead to depression via changes in the brain. On the other hand, a study by Miller and colleagues supports the moderation framework, whereby increased inflammation was only associated with depression in adolescents exposed to childhood adversity.[10] Furthermore, Quevedo and colleagues, suggest that neurobiological mechanisms underlying processing of negative versus positive self-information are present in MDD with and without childhood maltreatment but are more salient in depressed, maltreated individuals.[40] Most studies reporting early life stress focus on acts of threat and deprivation together. Whilst there is evidence that such maltreatments lead to changes in biological mechanisms, and consequently may lead to depression, there is also emerging evidence suggesting that threat and deprivation may act via different biological pathways, leading to different forms of psychopathology.[66] The identification of potential biological mechanisms in the link between different types of childhood trauma and adolescent depression is particularly important. In our review, we find evidence supporting mediation and moderation frameworks, explaining the relationship between environmental stress and biological risk factors, and depression in adolescence. Altogether, these findings suggest that immune and brain markers could be potentially used for the development of prevention and treatment strategies to modify trajectories from the experience of early adversities to development of depression during the adolescent and young adulthood period.

Except for one study, the associations between biological risk factors and MDD appeared to be relatively independent from recent life stress, as they did not moderate or mediate associations between recent life stress and MDD. This was more typical for studies assessing HPA biomarkers. For example, we found that several studies consistently showed that elevated cortisol was associated with increased risk of developing MDD and the presence of MDD in adolescence, even when controlling for recent life stress.[50–52] This aligns with the previously described theory of "allostatic load" which suggests that exposure to chronic, but not acute stress, can lead to the overload of the HPA-axis' homeostatic function, which eventually can lead to the development of stress related psychiatric disorders.[67,68] Subsequently, the onset of depression as a consequence of chronic stress might be delayed and emerge many years later. Thus, cortisol could serve as a potential biomarker of being "at-risk" for developing depression at a later stage. Although this explanation seems plausible, and in line with the existing evidence on cortisol abnormalities as biomarkers of depression in adulthood,[6,15] cortisol levels are also affected by the steroid hormones which undergo pubertal changes. Therefore, using cortisol as a biological risk factor for depression in adolescence might not be as straightforward, and using inflammatory markers or brain abnormalities might be more plausible.

Contrary to most of the existing evidence, suggesting that shorter telomere length is associated with chronic stress exposure and depression,[69,70] the study reviewed here found that adolescents with history of sexual abuse and current depression had longer telomere length.[59] However, depressive symptoms did not moderate the association between abuse and telomere length. This was the first study to look at telomere length in clinically depressed Colombian adolescents. This highlights the importance of conducting more research including LMICs, to understand which risk factors are context-dependent and which ones are universal.

Our systematic review has several limitations. The total number of studies looking at biological markers and environmental stress risk factors in the context of adolescent MDD was low, which becomes particularly apparent when grouping them by each biological marker separately. This made it difficult to draw strong conclusions regarding the relationships between specific biological risk factors and specific types of environmental stress. We also acknowledge that parental depression, which was considered as an environmental risk factor in our review, can also be linked to genetic predispositions of developing depression in offspring.[71] Another limitation if our study is that we did not include institutionalisation and parenting as part of the environmental stress risk factors. Furthermore, studies included in the review were observational, and although we assessed them for quality using SAQOR with modified GRADE rankings, we cannot make GRADE-level clinical recommendations at this point in time.

Our review also revealed the sparsity of research looking at biological and environmental stress risk factors in adolescence and young adulthood in LMICs, with only two studies conducted in middle-income countries. Considering that 90% of the world's adolescents live in LMICs, bearing the greatest burden of depression, it is striking how little has been done in trying to understand the biological mechanisms underpinning MDD development in adolescence in these settings.[28,72,73] This is crucial in understanding what may be

universal vs. context-dependent biomarkers of risk. We stress the importance of expanding biomarker research in LMICs to both advance the science of adolescent depression as well as achieving the greatest public health impact.[74] In conclusion, we find evidence suggesting that co-presence of several biological risk factors including high inflammation, blunted reward-related activity, white matter disruptions, and altered volume of limbic brain regions with the experience of childhood trauma may be associated with increased risk for future depression among adolescents and youth. The combination of environmental risk factors and neurobiological markers appears necessary to gain a better understanding of the pathophysiology of depression in adolescence and to improve our ability to detect individuals at risk of developing depression in adolescence at an early stage. Going forward, more focus is needed on harmonization in assessing both early adversity and recent stressors across different study modalities, in particular, inflammation, neuroimaging, and EEG. Advancing the field for more definitive identification of risk for depression in adolescence and young adulthood will also require studying the same factors across diverse settings with greater representation of LMIC populations of adolescents and young people.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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- Inflammation and depression in youth only present in the context of child adversity
- Brain alterations mediate the link between child adversity and depression in youth
- Limited studies on environmental and biological risk factors in youth depression
- Immune and brain markers – potential for prevention and treatment of depression

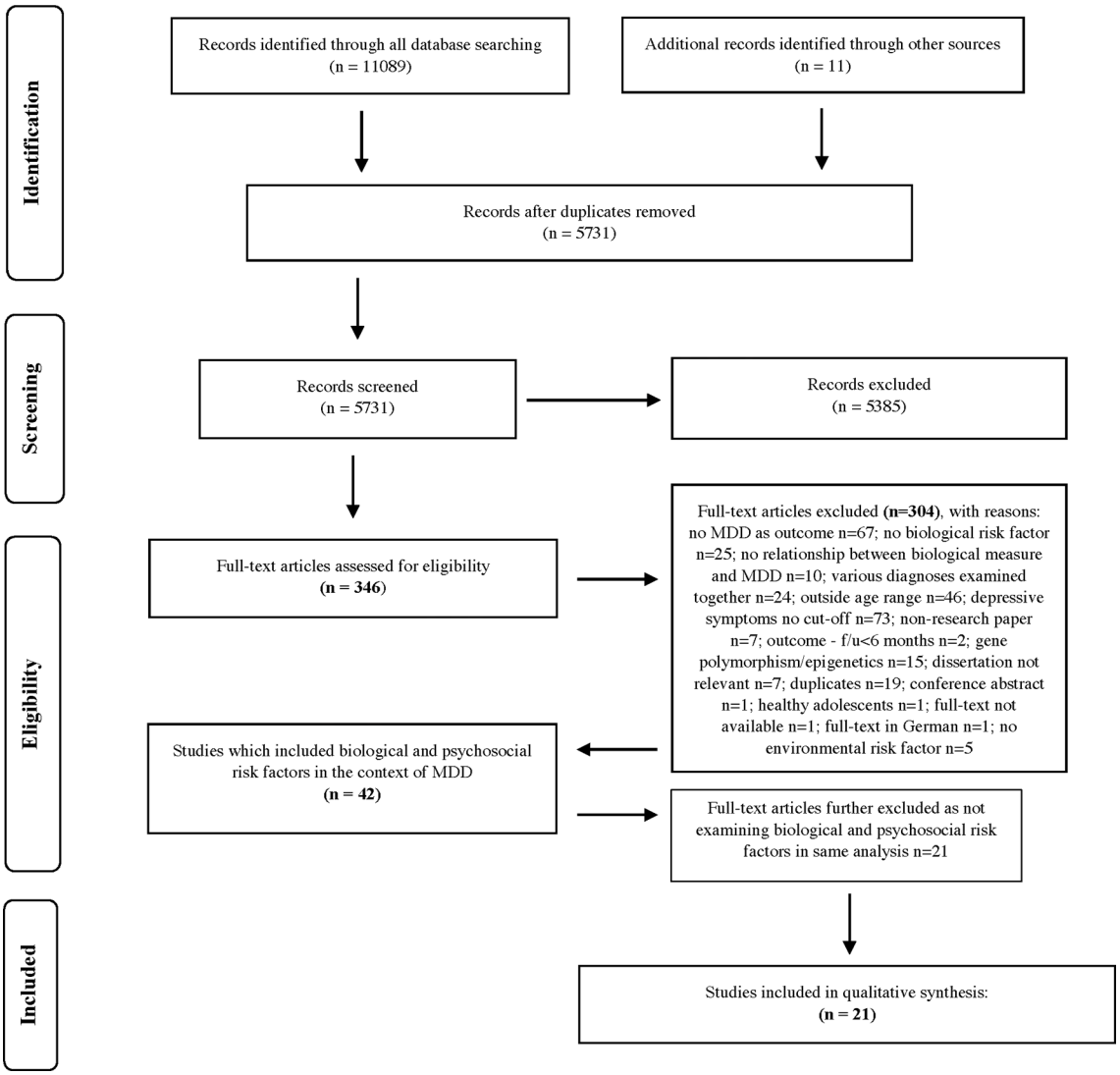

Figure 1: PRISMA Flow Diagram of Study Selection Process

Table 1:

Systematic Assessment of Quality in Observational Research (SAQOR) Quality Assessment ratings of included studies (n=21)

First author (year)	Sample	Control group/comparison group	Measurement quality	Follow-up	Distorting Influences	Reporting of data	Modified Grade Rating
Adam (2010)[50]	Adequate[1]	Inadequate	Adequate	Inadequate	Adequate	Adequate	Low
Danese (2011)[49]	Adequate	Adequate	Adequate	..	Inadequate	Adequate	Low
Dennison (2016)[39]	Adequate	Adequate	Adequate	Adequate	Adequate	Adequate	Low
Goodyer (2000)[53]	Adequate	Adequate	Adequate	Adequate	Adequate	Adequate	Low
Goodyer (2000)[54]	Adequate	Adequate	Adequate	Adequate	Adequate	Inadequate	Low
Halligan (2007)[52]	Adequate	Adequate	Adequate	Adequate	Inadequate	Adequate	Low
Huang (2012)[42]	Adequate	Adequate	Adequate	Inadequate	Adequate	Adequate	Low
Jimenez (2019)[59]	Inadequate	Adequate	Adequate	..	Adequate	Adequate	Low
Lee (2020)[47]	Adequate	Adequate	Adequate	..	Adequate	Adequate	Low
Miller (2012)[10]	Adequate	Inadequate	Adequate	Inadequate	Adequate	Inadequate	Very Low
Ming (2017)[48]	Adequate	Adequate	Adequate	..	Adequate	Adequate	Low
Morehouse (2002)[58]	Adequate	Adequate	Adequate	Inadequate	Adequate	Inadequate	Low
Pegg (2019)[41]	Inadequate	Inadequate	Adequate	..	Inadequate	Adequate	Very low
Quevedo (2017)[40]	Adequate	Adequate	Adequate	..	Adequate	Adequate	Low
Rao (2009)[57]	Adequate	Adequate	Adequate	Adequate	Adequate	Adequate	Low
Rao (2010)[44]	Adequate	Adequate	Adequate	Adequate	Adequate	Adequate	Low
Redlich (2018)[45]	Adequate	Adequate	Adequate	..	Adequate	Inadequate	Low
Shenk (2015)[56]	Adequate	Adequate	Adequate	Adequate	Adequate	Adequate	Low
Tymofiyeva (2017)[43]	Adequate	Adequate	Adequate	..	Adequate	Adequate	Low
Vrshek-Schallhorn (2013)[51]	Adequate	Inadequate	Adequate	Adequate	Adequate	Adequate	Low
Ulrike (2013)[55]	Adequate	Adequate	Inadequate	..	Adequate	Inadequate	Very Low

[1]"SAQOR, a tool developed to assess the quality of observational studies, assesses the following categories: sample, control/comparison group, quality of measurement(s) and outcome(s), follow-up, distorting influences, and reporting data. Each of the categories evaluates different criteria. For example, the "sample category" evaluates: (a) the sample representativeness, (b) the sample source, (c) the sampling method, (d) the sample size, and (e) clear inclusion/exclusion criteria. Each of the five criteria could be marked as "yes", "no", or "unclear". For the "sample category" to be marked as "adequate", a minimum of three of the five criteria needs to be met. Each of the categories listed is evaluated as being "adequate" or "inadequate". The final SAQOR outcome is based on the number of "adequate" categories, where a minimum of four out of six categories is required for the study to be marked "adequate".[6] In our review, fifteen studies met these criteria and were marked as "adequate". We then graded each study according to the modified GRADE system, which assesses the quality of evidence and strength of clinical recommendations. The GRADE system is based largely on the study design

and observational studies are graded as "low" quality.[7] The final quality modified GRADE rating reported in our review was based on the study design and the number of SAQOR categories marked as "adequate". All of the studies reported were observational. An observational study with a minimum of four "adequate" categories as per SAQOR, was graded as "low". A study having less than four categories marked as "adequate" meant that the study was graded as "very low" according to the modified GRADE rating.[6] Therefore, the maximum GRADE rating for these studies was 'low' given that they all used observational designs."

¨N/A

Table 2:

Description of included studies examining neuroimaging and EEG markers and their relationship with contextual risk factors for MDD in adolescence and young adulthood (n=11)

First author (year)	Neuroimaging method/ acquisition	Biological risk factor	Environmental risk factor	Study design	Sample Size			Sample age (years)	Sample source	Outcome measure #	Study setting (HIC or LMIC) ^
					HR*	MDD (n, % or mean and SEM)	HC**				
Dennison (2016)[39]	fMR/Siemens Trio, 3T, passive viewing of affective images, FreeSurfer	Reward activity	Childhood maltreatment - physical, sexual and emotional abuse, and physical neglect	Longitudinal	21	Mean of depression symptom count at follow-up in maltreatment group: 8.6 ± 4.02, and without maltreatment group-6 ± 4.53	38	Maltreatment group: 16.7 ± 1.52; group without maltreatment: 17.1 ± 1.41	Recruited from a large community-based study, USA	DISC-IV	HIC
Huang (2012)[42]	DTI/Philip, 3T, DTI, FSL	Tract Fractional Anisotropy (FA)	Childhood maltreatment - separation/loss of caretaker, life-threatening illness/ injury to the self or others, physical neglect, emotional abuse, physical abuse, witnessing domestic violence, and sexual abuse	Longitudinal	19	MDD at follow-up-6	13	HR: 15.89 ± 2.79; HC: 16.00 ± 2.74	Not reported	K-SADS	HIC
Lee (2020)[47]	MRI/ Siemens, 3T, high-resolution structural T1 images, Freesurfer 6.0 automatic segmentation on subcortical regions	Hippocampal, amygdala and nucleus accumbens volume	Social stress - peer problems	Cross-sectional	..	78	47	MDD: 14.9 ± 1.5; HC: 14.3 ± 1.4	Participants were recruited from the Seoul National University Hospital, Korea	K-SADS	HIC
Ming (2017)[48]	fMRI/ Siemens, 3T, EPI, Montreal	Frontal activity	Early life adversity - physical and emotional abuse, emotional neglect,	Cross-sectional	..	36	36	MDD - 22.81 ± 4.25; HC - 22.19 ± 1.60	MDD - outpatient department of 2nd Xiangya Hospital, Hunan; HC -	SCID	LMIC

First author (year)	Neuroimaging method/ acquisition	Biological risk factor	Environmental risk factor	Study design	Sample Size			Sample age (years)	Sample source	Outcome measure #	Study setting (HIC or LMIC) ^
					HR*	MDD (n, % or mean and SEM)	HC**				
	Imaging Stress Task, SPM8		sexual abuse, and physical neglect						Changsha community advertisement		
Morehouse (2002)[58]	EEG/ Sleeping, FFT	Sleep Macro- & Microarchitecture	Maternal history of depression	Longitudinal	41	MDD at follow-up-6	40	HR: 13.54 ± 1.36; HC: 13.73 ± 1.06	HR: Local advertisement, local Psychiatry Outpatient Clinic; HC: local schools and friends of at-risk adolescents (USA and Canada)	K-SADS	HIC
Pegg (2019)[41]	EEG during Island Getaway Task	Event-related potentials to social acceptance & rejection	Social life stress	Cross-sectional	..	Out of a total sample of 231, 21.6% were in the clinical range for MDD symptoms	..	18.16 ± 0.41	First year college students Canada	IDAS	HIC
Quevedo (2017)[40]	fMRI/ Siemens Trio, 3T, MPRAGE & EPI, ECAT, SPM8	Reward activity	Childhood maltreatment - physical and sexual abuse, and neglect	Cross-sectional	..	44	37	MDD: 14.72 ± 1.72; HC: 14.48 ± 1.53	Minneapolis/ Pittsburgh residents (inpatient, therapist referrals, flyers, radio adverts)	K-SADS	HIC
Rao (2009)[57]	EEG Sleeping, International 10–20 system EEG electrode placement	Sleep Macro- & Microarchitecture	Parental history of depression	Longitudinal	48	MDD at follow-up-14	48	Mean ages: HR - 15.0 ± 1.5; HC - 15.2 ± 1.4	Recruited from local paediatric and mental health clinics and schools in Los Angeles and through community advertisements	K-SADS	HIC
Rao (2010)[44]	Structural MRI/GE, 1.5T	Hippocampal volume	Early life adversity - separation/loss of caretaker, life-threatening illness/ injury to the self or others, physical neglect, emotional	Longitudinal	22	MDD at baseline - 29; MDD at follow-up- 19	32	Mean ages: HR - 15.0 ± 1.7; MDD (baseline) - 14.6 ± 1.9; HC - 15.1 ± 1.6	Part of larger ongoing study performed at 2 sites - Harbor-University of California at Los Angeles Medical	K-SADS	HIC

First author (year)	Neuroimaging method/ acquisition	Biological risk factor	Environmental risk factor	Study design	Sample Size			Sample age (years)	Sample source	Outcome measure #	Study setting (HIC or LMIC) ^
					HR*	MDD (n, % or mean and SEM)	HC**				
			abuse, physical abuse, witnessing domestic violence, and sexual abuse, all of which must have occurred before the age of 11 and lasted for minimum 6 months						Center and University of Texas Southwestern Medical Center		
Redlich (2018)[45]	Structural and functional MRI/GI 3T	Hippocampal volume	Childhood maltreatment - physical, sexual and emotional abuse, and physical neglect	Cross-sectional	¨	20	21	Mean ages: MDD - 16 ± 1.03; HC - 16.57 ± 1.08	MDD - inpatient service of the Department of Child and Adolescent Psychiatry, University of Muenster, and HC - community advertisement	SCID	HIC
Tymofiyeva (2017)[43]	DTI/ GE, 3T, DTI, FSL	Tract Fractional Anisotropy (FA)	Stressful life events in the past 6 months	Cross-sectional	¨	57	41	MDD: 16.2 ± 1.3; HC: 16 ± 1.4	MDD - adolescent psychiatric clinics across San Diego County area; HC - San Diego area community advertisement	K-SADS	HIC

*High-risk for depression - definitions vary by articles, details of each reported in the Results section

**HC - healthy controls

#Outcome measure abbreviations: Diagnostic Interview Schedule for Children Version IV (DISC-IV); Inventory of Depression and Anxiety Symptoms (IDAS); Kiddie- Schedule for Affective Disorders and Schizophrenia (K-SADS); Structured Clinical; Structured Clinical Interview for Diagnostic and Statistical Manual (SCID);

^High-income countries (HICs); Low-and-middle-income countries (LMICs)

¨N/A

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Table 3:

Description of included studies examining inflammatory and other peripheral biological markers and their relationship with contextual risk factors for MDD in adolescence and young adulthood (n=11)

First author (year)	Analytical method used	Biological risk factor	Environmental risk factor	Study design	Sample Size				Sample age (years)	Sample source	Outcome measure[#]	Study setting (HIC or LMIC) ^
					LR[*]	HR[**]	MDD (n, % or mean and SEM)	HC[***]				
Adam (2010)[50]	Logistic regression	Salivary cortisol	Stressful life events in the past year - close friendships, social group, relations, romantic relationships, relations with family members, academic, neighbourhood conditions, job, finances, health of self, and health of family members	Longitudinal	..	230	MDD at follow-up-19		17.04 ± 0.36 (baseline)	Youth Emotion Project - participants recruited from public high schools in suburban Chicago and Los Angeles	SCID	HIC
Danese (2011)[49]	Regression analysis	Bloodspot CRP	Childhood maltreatment - physical	Cross-sectional	..	..	MDD only-8 MDD + maltreatment-13 Maltreatment only-69	84	Assessment completed at age 12	Environmental Risk (E-Risk) Longitudinal Twin Study	CDI (with cut-off score of 20 and above for clinical symptoms)	HIC
Goodyer (2000)[53]	Binary logistic regression	Salivary cortisol and DHEA	Disappointments and permanent losses 1 month prior to MDD onset	Longitudinal	..	180	MDD at follow-up-48	..	Age range 12 to 16	Secondary schools in Cambridge	K-SADS	HIC
Goodyer (2000)[54]	Backwards stepwise logistic regression	Salivary cortisol and DHEA	Recent undesirable life events, lifetime losses, marital/ family difficulties and parental psychiatric history 12 months prior to MDD onset	Longitudinal	65[a]	181	MDD at follow-up-31	..	Age range for all sample (HR+LR) - 12 to 16.5	Secondary schools in Cambridge	K-SADS	HIC
Halligan (2007)[52]	Binary logistic regression	Salivary cortisol	Undesirable life events and difficulties, and reported marital conflict 3 years prior to MDD onset	Longitudinal	..	48	MDD at follow-up-25	39	Baseline assessments completed at age 13; follow-up age	Participants were part of a prospective longitudinal study of the development of	MFQ (with cut-off score of 7 and above for clinical symptoms)	HIC

First author (year)	Analytical method used	Biological risk factor	Environmental risk factor	Study design	Sample Size				Sample age (years)	Sample source	Outcome measure#	Study setting (HIC or LMIC) ^
					LR*	HR**	MDD (n, % or mean and SEM)	HC***				
									range 15 to 17 (HR + HC)	children of postnatally depressed and well women		
Jimenez (2019)[59]	Spearman's rank-order Correlation and moderation analysis	Leukocyte telomere length	Childhood trauma - sexual, physical and emotional abuse, and neglect	Cross-sectional	..	..	40	52	21 ± 3	General population of young Colombians	CES-D	LMIC
Miller (2012)[10]	..	Serum CRP, IL-6	Childhood adversity - birth to a teenage mother, parental death or divorce before age 15; or separation from a parent for more than 1 year, low household education, limited economic resources and, history of affective illness in parental.	Longitudinal	..	147	MDD at follow-up-40	..	17.01 ± 1.33 (baseline)	Participants recruited from Vancouver, through advertisements in local media	SCID	HIC
Rao (2009)[57]	Logistic regression analysis	Nocturnal urinary free cortisol	Parental history of depression	Longitudinal	..	48	MDD at follow-up-14	48	Mean ages: HR - 15.0 ± 1.5; HC - 15.2 ± 1.4	Recruited from local paediatric and mental health clinics and schools in Los Angeles and through community advertisements	K-SADS	HIC
Shenk (2015)[56]	Multiple mediator model	Salivary cortisol	Childhood maltreatment - sexual and physical abuse, and physical neglect	Longitudinal	59*b*	51	MDD at follow-up - 27.6%	..	Mean ages: Childhood maltreatment - 16.78 ± 1.12; HC - 17.19 ± 1.20	Participants with child maltreatment - recruited from Child Protective Service agencies investigating allegations of physical neglect or contact physical or	BDI-II (a score of 21 or higher on the BDI- II was used identify clinical levels of MDD symptoms)	HIC

First author (year)	Analytical method used	Biological risk factor	Environmental risk factor	Study design	Sample Size				Sample age (years)	Sample source	Outcome measure#	Study setting (HIC or LMIC) ^
					LR*	HR**	MDD (n, % or mean and SEM)	HC***				
										sexual abuse; HC - recruited using posted flyers in a primary care outpatient medical clinic serving at-risk, adolescent females		
Vrshek-Schallhorn (2013)[51]	Cox regression model	Salivary cortisol	Stressful life events in the past year (measured 2.5 years before MDD onset) - close friendships, social group, relations, romantic relationships, relations with family members, academic, neighbourhood conditions, job, finances, health of self, and health of family members	Longitudinal	..	270	MDD at follow-up-42	..	Mean age at baseline: HR - 17.06 ± 0.39	Participants were recruited from high schools in suburban Chicago and Los Angeles	SCID	HIC
Ulrike (2013)[55]	ANOVA	Salivary cortisol	Perceived physical stress - headache, nervous agitation, insomnia, gastric problems, vertigo, cardiac symptoms, hand trembling and lack of appetite; and perceived psychological stress - anxiety, anger and sadness	Cross-sectional	..	..	63	68	Mean ages: MDD - 15.0 ± 2.3; HC - 15.4 ±2.2	Community advertisement in Trier, Germany	Kinder-DIPS	HIC

*Low-risk for depression -

[a]none or one of moderately to severe undesirable life events in past 12 months: current marital disharmony or past marital breakdown, two or more lifetime exit events (bereavement or parental separation) of personal significance to the adolescent, high emotionality (>80 percentile), and in addition absence of the parental psychiatric disorder;

[b]participants recruited from outpatient clinics for at-risk adolescents who did not meet childhood maltreatment criteria

** High-risk for depression - definitions vary by articles, details of each reported in the Results section

*** HC - healthy controls

Outcome measure abbreviations: Beck Depression Inventory (BDI); Children's Depression Inventory (CDI); Diagnostisches Interview bei psychischen Sto¨rungen im Kindesund Jugendalter (Kinder-DIPS); Kiddie-Schedule for Affective Disorders and Schizophrenia (K-SADS); Structured Clinical; Structured Clinical Interview for Diagnostic and Statistical Manual (SCID); Moods and Feelings Questionnaire (MFQ)

^ High-income countries (HICs); Low-and-middle-income countries (LMICs)

¨ N/A