



## Preventive strategies for adolescent depression: What are we missing? A focus on biomarkers



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### ABSTRACT

Adolescent depression is an important global issue with several unmet needs that still must be addressed and, to date, there are only few effective preventive strategies to reduce the burden of this disorder worldwide. In this mini-review, the evidence and potential ways to improve an early detection will be discussed as well as prompt interventions by focusing on a better understanding of the risks underlying the developing of adolescent depression from both a sociodemographic and a biological perspective.

### 1. The global burden of adolescent depression

Depression is one of the leading causes of health-related disability worldwide and a major contributor to the global burden of disease (World Health Organization, WHO). This burden has become even more evident in the past year, which has been characterized by the worldwide COVID-19 pandemic that has put a strain on the mental health of the global population.

The onset of depression usually occurs during pubertal age and teen depression is indeed one of the leading causes of disability among adolescents. The World Health Organization has estimated that about 10–20% of adolescents experience at least one depressive episode; generally, adolescence mental health conditions account for 16% of the global burden of disease and injury in people aged 10–19 years. Moreover, depression has been considered the first cause of suicide among youth (Adolescent Mental Health, WHO, 2018).

As it happens in adulthood, depression is more prevalent in girls (around 20%) than in boys (around 6%). Furthermore, adolescents suffering with depression are more likely to develop drugs abuse and suicide attempts (statistics from “National survey on drug use and health”, 2016).

Half of all mental health conditions start by age 14, but most cases are undetected and untreated. The burden of teen depression is worsened by the difficulties in obtaining diagnosis and treatment, especially in low and middle-income countries (LMIC) where the situation is critical since they account for more the 90% of world's children and adolescents and

for over the 75% of the global suicides deaths (McKinnon et al., 2016). The main reasons for the under-diagnosis of depression in LMIC are, for examples, shortages of mental health workers, lack of research capacity, and stigmatization of mental illness preventing adolescents from seeking help, all factors that increase the gap between high-income countries (HICs) and LMICs in the Global Mental Health (Wainberg et al., 2017).

The lack of prevention and early intervention for adolescent depression, and in general mental health conditions, can lead to chronicity of these disorders throughout adulthood, affecting both physical and mental health and deeply diminishing prospects to lead satisfying lives as adults.

Importantly, we also need to mention that the incidence of depression in children and adolescents has rapidly grown during the COVID-19 pandemic (Nearchou et al., 2020; Loades et al., 2020). For example, an overall increase in mental distress has been observed by Pierce and colleagues in people aged 16 years and older in the UK in 2020 compared with the previous year; they observed that the mean population score of the 12-item General Health Questionnaire (12-GHQ) increased from 11.5 in 2018–19 to 12.6 in April 2020, and this increase was not merely a continuation of former increasing trend (Pierce et al., 2020). Similar results have been shown also in Italian students aged 18–30 years old who reported on average worse depressive symptoms during lockdown compared to six months before (Meda et al., 2021). COVID-19 lockdown has negatively also impacted children mental health: anxiety, depression and stress have been observed to be increased in children after the school closure due to the pandemic (Tang et al., 2021). Similarly, Bignardi and

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colleagues showed that during lockdown children's depression symptoms have increased substantially compared to pre-lockdown period in the UK (Bignardi et al., 2020).

## 2. Understanding the risk for developing depression in adolescence

Adolescence represents a temporal window where depressive symptoms become to be manifested, therefore it is also a crucial period for improving preventive strategies. Furthermore, adolescence is known to be a vulnerable temporal frame for brain developmental trajectories, since it is characterized by significant changes in the structure and connectivity of the brain, as well as changes in cognition and behavior (Cousins and Goodyer, 2015). In this context, identifying adolescents at risk for developing depression might become a milestone in preventive strategies, since it would allow to act before the individual develop a clear symptomatology.

It is well established that demographic, behavioral, interpersonal, and cognitive risk factors are involved in the vulnerability to depression in adolescents; for example, childhood trauma experiences have been shown to increase the risk of the onset of depressive symptoms already during adolescence (Heim et al., 2008). Given the presence of several risk factors for depression, prediction models have been developed during the last years to obtain a valid tool able to predict the risk for depression as well as for the onset on a widescreen. An accurate risk prediction model could enable primary care doctors to early identify adolescents at risk of depression that may benefit from interventions and therefore refer them to appropriate level of interventions (Richardson and Katzenellenbogen, 2005). Models able to predict depression have been mainly developed in adults and are mostly limited to patients who experienced chronic medical condition or used to predict the recurrence of depression (Fernandez et al., 2018). With the aim to satisfy the need to develop tools for a risk prediction also in other populations, such as adolescents, as part of the IDEA (Identifying Depression Early in Adolescence) project (Kieling et al., 2019) a risk score was developed in a Brazilian cohort to predict the risk of developing depression in late adolescents among teen-agers with no previous diagnosis of depression (Rocha et al., 2021). By using this risk score, adolescents have been recruited and group based on the current presence of depression or on the high or low risk of developing it. The IDEA risk score was validated in Nepal, a middle-income country setting; this prediction model displayed a sensible power to discriminate between individuals who developed depression in late adolescence and those who did not (Brathwaite et al., 2021).

These results clearly suggested that this prediction model can play a key role in the early identification of vulnerable adolescents and that can be used in other low and middle-income countries to reduce the burden of depression and allow wider screening in the poorest settings worldwide.

## 3. The potential of identifying biomarkers for novel preventive strategies

Hence, since the identification of adolescents at risk of developing depression might be a turning-point in the battlefield against depression, what are we missing? What might be the milestone for identifying successful preventive strategies?

To date there are no specific biological signatures or markers associated with an enhanced risk of developing depression and the identification of such biomarkers could be the missing link towards the implementation of novel preventive strategies. However, the last three decades have witnessed the study of several hypotheses of the pathophysiology of depression, from the mono-aminergic hypothesis of depression to those highlighting the involvement of stress and HPA axis and the role of inflammation and immune system activation.

A biomarker is defined as a characteristic that can be objectively measured and evaluated as an indicator of normal biologic processes,

or pathogenic processes, or pharmacologic responses to a therapeutic intervention (Biomarkers Definitions Working, 2001). Identifying possible biomarkers will pave the way not only for identifying the risk for developing the disorder, but also for the prediction of antidepressant response, since about 20% of depressed patients fail to respond to any pharmacological interventions (Mora et al., 2018). As a consequence, the discovery of such biomarkers would lead to the achievement of important goals, such as: i) a clear biological identification of the presence of depression ii) the identification of subjects at risk for the onset of the disorder and the subsequent implementation of preventive strategies, both pharmacological and not iii) the improvement of the efficacy of treatment and the discovery of new targets for the development of novel antidepressant drugs, paving the way for the progress of precision medicine in psychiatry.

## 4. Biological markers and signatures underlying adolescent depression

### 4.1. Inflammation

Recent studies have presented and discussed possible biological markers underpinning adolescent depression. Inflammatory mechanisms have been suggested to play an important role in the pathogenesis of depression. Increased levels of peripheral inflammatory cytokines have been widely observed in depressed adult patients, as summarized in a series of meta-analyses (Osimo et al., 2019, 2020; Kohler et al., 2017; Leighton et al., 2018). Indeed, there is emerging evidence that individuals with depression show elevated serum or plasma concentration of inflammatory cytokines, such as the Interleukins IL-6, IL-10, IL-12, IL-13, IL-18, and the Tumor necrosis factor alpha (TNF- $\alpha$ ), compared to healthy controls (Himmerich et al., 2019) and that increased inflammatory signatures are associated with a higher risk of developing depression (Raison et al., 2006).

Moreover, high levels of inflammation are associated also with reduced response to antidepressant medications. The recent meta-analysis of Liu and colleagues showed reduced baseline levels of IL-8 and C-reactive protein (CRP) in depressed patients who become responders; on the other hand, no differences were observed in other pro-inflammatory cytokines, such as L-1 $\beta$ , IL-2, IL-4, IL-5, IL-10, IL-12 and TNF- $\alpha$  between patients who were subsequent responders and non-responders (Liu et al., 2020). Furthermore, Cattaneo and colleagues showed evidence of inflammasome activation and glucocorticoid resistance in both drug-free depressed patients and treatment resistant depression (TRD) patients treated with antidepressant drugs. They also identified a panel of mRNAs that could be used as a significant predictors of classification of depressed patients as TRD or responder group; this panel of biomarkers is represented by six genes accounting also for inflammatory molecules such as IL-1  $\beta$ , IL-6 and TNF- $\alpha$  (Cattaneo et al., 2020).

Although several studies have focused on the role of inflammatory biomarkers in adult depression, a smaller number of studies focused their attention on adolescence and childhood. In the meta-analysis recently published by Colasanto and colleagues focused on subjects younger than 18 years, depression was associated with higher levels of CRP and IL-6 (Colasanto et al., 2020). In the meta-analysis by D'Acunto and colleagues, focusing on studies in children and adolescents up to age 18, they reported higher TNF- $\alpha$  in individuals with depressive disorders versus control subjects (D'Acunto et al., 2019). Furthermore, Miller and Cole showed that adolescents girls at risk of developing depression due to family history or cognitive vulnerability who experienced a depressive episode were more likely to have elevated CRP at a 6-month follow-up, and that high levels of IL-6 were associated with increased depression risk at follow-up (Miller and Cole, 2012). Similar results were also reported by Khandaker and colleagues, showing high levels of IL-6 in association with greater depression risk compared to low levels of IL-6 (Khandaker et al., 2014). Lastly, Moriarty and colleagues observed that

increases in TNF- $\alpha$  predicted increases in depressive symptoms, whereas CRP, IL-6, IL-8, and IL-10 did not have significant within-person effects on change in total depressive symptoms (Moriarty et al., 2020).

A limitation of most of these studies is that they have explored the biological risk factors for depression in adolescence and young adulthood in high-income countries, whereas a very limited number of studies have been conducted in low-and-middle income countries' populations. This represents an important bias since 90% of the world's adolescents live in LMICs, and findings from HICs might not be generalisable across different socio-economic settings (Kieling et al., 2011). The paucity of studies focused on LMICs has been showed also by the very recent systematic review published by Zajkowska and colleagues in the context of the IDEA project (Kieling et al., 2019), focusing on subjects aged between 10 and 25 years old in both HICs and LMICs. Out of twenty-one studies eligible for the inclusion criteria, they identified only two studies conducted in LMIC adolescents. Besides the lack of studies conducted in LMIC, Zajkowska and colleagues shed light on the association of both environmental and biological risk factors for the onset of depression, as their findings support the importance of the interaction of several biological risk factors, including high inflammation, with the experience of childhood trauma in increasing the risk for future depression among adolescents and youth (Zajkowska et al., 2021). As a matter of fact, a growing body of literature has shown that exposure to early life stress is a vulnerability factor for the onset of depression through the entire lifespan (Mandelli et al., 2015; Widom et al., 2005; LeMoult et al., 2020). Nevertheless, it is also important to mention that different and specific types of childhood trauma can differently mediate the risk of developing depression; in addition, the effects of different childhood maltreatments differ between adolescents and adults (Infurna et al., 2016; Shapero et al., 2014). The association between inflammation and environmental risk factors with depression has been observed also in adulthood, as shown in the recent systematic review of Gill and colleagues, which investigated the association between the inflammatory biomarkers in depressed patients with an history of adverse childhood experiences (ACE) compared to depressed patients without ACE. Specifically, IL-6 was shown to be elevated in MDD patients with a history of ACE compared to those who did not experience childhood maltreatment (Gill et al., 2020). Hence, it is reasonable to believe that combining environmental risk factors – such as early life adversities – and biological markers – as inflammatory signatures-might provide a more comprehensive methodology for identifying the risk of developing depression and subsequently implementing preventive strategies.

#### 4.2. HPA axis

Above to biomarkers related to inflammation, also stress related biomarkers have been widely investigated in the context of depression. Indeed, depression has also been hypothesised as a stress-related disorder and an hyperactivity of the hypothalamic–pituitary–adrenal (HPA) axis, in particular elevated levels of the stress hormone cortisol, have been suggested to mediate the link between the experience of stressful events and the onset of depression (Burke et al., 2005). For this reason, researchers focused their attention on HPA axis activity by measuring cortisol levels in saliva and in blood samples of adolescents, as possible biological mechanisms involved in the onset of depression and as possible biomarkers for adolescent depression risk. However, studies conducted so far reported heterogenous results, as both elevated and blunted levels of cortisol secretion during childhood and adolescence have been linked to the subsequent onset of MDD. For example, elevated morning cortisol levels have been linked to increased vulnerability in developing depression during adolescence (Adam et al., 2010; Vrshek-Schallhorn et al., 2013; Owens et al., 2014), whereas Keenan and colleagues found that 10- to 12-years-old girls who exhibited a blunted cortisol response to a laboratory stressor and who had low absolute levels of cortisol secretion at age 12 experienced a subsequent increase in depressive symptoms (Keenan et al., 2013). A possible explanation of

such inconsistencies might be the different developmental stages at which participants were assessed across the studies, as it is known that pubertal development is characterized by changes in cortisol production. For example, in the study of Colich and colleagues, cortisol hypo-reactivity predicted MDD onset in girls at an early pubertal stage, whereas cortisol hyperactivity predicted MDD onset in those who were later in pubertal development (Colich et al., 2015). Similarly, King and colleagues observed that pubertal stage interacted with the severity of early life stress (ELS) to predict the cortisol awakening response (King et al., 2017).

A very interesting role of puberty in the association between HPA axis reactivity and early life stress has been proposed by Gunnar and colleagues, and it is known as the “pubertal stress recalibration” (Gunnar et al., 2019; DePasquale et al., 2019). Accordingly, given the idea that during infancy the HPA axis is able to calibrate different environmental conditions, Gunnar and colleagues proposed that a similar pattern of calibration might occur also during puberty, which is believed to be a second window of plasticity during which the HPA axis could recalibrate. This hypothesis might represent a further explanation of discrepancies in the studies investigating the levels of cortisol in puberty and adolescence.

#### 4.3. Brain circuits

It is known that stress influences the growth of brain circuit and, although this topic is beyond the scope of the present review, it is noteworthy to mention that increasing body of studies supports the hypothesis that exposure to early life stress has a detrimental impact on the developing central nervous system (Dannowski et al., 2012). For example, functional magnetic resonance imaging studies showed that adolescent depression is associated with the hyperactivation of the amygdala and of the subgenual anterior cingulate cortex (Henje Blom et al., 2016), and other neurocircuits are involved in the complex physiopathology of the disorder in adolescence (Hulvershorn et al., 2011). Moreover, abnormalities in neural processing of rewards in depressed adolescents have been widely observed in literature (Forbes and Dahl, 2012; Kerestes et al., 2014; O'Callaghan and Stringaris, 2019).

Several studies have pinpointed the importance of the timing of exposure as an essential factor in considering the effects of early adversity on brain development during childhood and adolescence, as exposure to adversity that occurs during sensitive or critical periods is more likely to have significant and persistent effects on neural function (Gee, 2021; Nelson and Gabard-Durnam, 2020; Ho, 2019; Teicher and Khan, 2019; McLaughlin et al., 2019; Sheridan et al., 2020). Among early life traumas, childhood maltreatment and child-caregiver relationships have been deeply studied (Teicher et al., 2016; Tottenham, 2014). Childhood maltreatment have been shown to alter trajectories of brain development involved in emotional regulation, reward and threat detection (Teicher et al., 2016).

Furthermore, psychosocial stressors have been shown to activate inflammatory responses by increasing the production of pro-inflammatory cytokines that can in turn cross and modify the permeability of the blood-brain-barrier. Within the brain, pro-inflammatory cytokines have been shown to affect glutamate metabolism and thus increasing the release of glutamate into the synapse and preventing its re-uptake by the astrocytes. Thus, glutamatergic excitotoxicity may be one mechanism by which inflammatory cytokines effect depression-related alterations in brain circuits (Haroon and Miller, 2017; Ho et al., 2021).

Given these premises, the identification of neural biomarkers for adolescent depression might be a further step forward the implementation of preventive and therapeutic strategies for adolescent depression (Toenders et al., 2019).

#### 4.4. Epigenetic and microbiota

Recently, other areas of interest have been explored to identify other possible mechanisms underpinning the onset of depression, from

childhood to adulthood (Kennis et al., 2020; Mariani et al., 2021). As previously discussed, early life stressful experiences represent a risk factor for the future development of depression and among the possible mechanisms underlying this effect are epigenetic modifications, such as DNA methylation, histone modification, and miRNAs which have been widely described to mediate the effect of these stressful experiences and to be involved in the vulnerability for depression (Serafini et al., 2014; Januar et al., 2015). For this reason, the recent literature has focused its attention on epigenetic markers as possible biomarkers for vulnerability or resilience to depression (Lopizzo et al., 2019; Penner-Goeke and Binder, 2019; Tavakolizadeh et al., 2018) as well as for predicting antidepressant response (Mora et al., 2018).

Lastly, the past decade has witnessed a growing interest in the bidirectional communication between the gut microbiota – which is defined as the ecosystem of bacteria, viruses, archaea, and fungi – and the host's central nervous system (Dinan and Cryan, 2017; Rieder et al., 2017). The gut-brain axis has been shown to influence cognitive functioning and mood via neural, metabolic, hormonal, and immune-mediated mechanisms (Foster and McVey Neufeld, 2013). Alterations in the gut microbiota have been shown to be associated with several mental illnesses, such as depression and anxiety, as shown by a wide number of studies and literature reviews (Simpson et al., 2021; Cruz-Pereira et al., 2020; Carlessi et al., 2021; Evrensel and Tarhan, 2021). Unfortunately, to date, a paucity of studies has been conducted to better investigate the link between gut-brain axis and psychiatric disorders specifically during adolescence (Ligezka et al., 2021; Simkin, 2019); hence, further investigations are required.

## 5. Future directions

As the aforementioned literature results has shown, a general consensus has been reached by the scientific community on the involvement of inflammation, immune system, and HPA axis the pathophysiology of depression in adolescents. However, results are heterogeneous and a definitive panel of biomarkers has not been defined yet. A possible reason underlying this lack of homogeneity might be the fact that the majority of the studies is based on a candidate gene approach in spite of an hypothesis free approach.

Genome-wide studies of depression might be a more sophisticated method in the investigation of biological signatures underlying both the presence and the risk of depression through the entire lifespan (Mariani et al., 2021; Hepgul et al., 2013). The advantages of investigating the entire genome rather than focusing on specific and shortlisted molecules (such as cytokines) or hormones (as cortisol) is the opportunity of identifying novel and not yet studied biological signatures and biomarkers associated with the disorder. This might pave the way for novel approaches and novel hypothesis able to explain the complexity of the disorder, specifically in such a vulnerable temporal window as adolescence.

Up-to-date approaches able to investigate the entire genome are represented by next generation sequencing (NGS) techniques, such as RNA-Sequencing, to identify genes significantly associated with depression (Mostafavi et al., 2014; Le et al., 2018; Chiang et al., 2019). In this context, also the aforementioned IDEA project might provide important steps forward the identification of genes' transcripts and biological pathways associated with risk of developing adolescent depression (Kieling et al., 2021). As a matter of fact, the IDEA project is not only aiming at understanding the environmental risk factors for adolescent depression, but also at unraveling the biological signatures underlying the disorder.

It is also noteworthy to consider that, apart from a biological approach in preventing adolescent depression, psychosocial and environmental approaches should be improved. The burden of adolescent depression is worsened by the fact that a little percentage of youths take advantage of existing mental health services together with the low prevalence of mental health service for adolescents and young adults.

The study of Babajide and colleagues observed a drop in the use of psychiatric services in individuals aged between 19 and 25 years old (Babajide et al., 2020). The authors blamed mainly the stigma associated with psychopathology, financial issues, and less resources available for this age group. To front the reduction in the seeking-help behaviors, the authors suggested an “integrated care” hypothesis, aimed to integrate mental health care services with general care; this union might be an important turning point for an early detection as well as for a prompt treatment of depression in adolescents and young adults. On the other hand, it is extremely desirable that the implementation of mental health services for the youngest go hand in hand with a good quality of those services. For examples, the “strengths model” on youth mental health proposed by Mendenhall and colleagues aims to provide tools to assist both youths and their families in managing mental health related disorders, also by equipping supervisors and case managers with a formal model to follow and by engaging adolescents in services designed on their own need and personal goals (Mendenhall and Grube, 2017).

## 6. Conclusions

In conclusion, as adolescence represents a vulnerable temporal window for the development of depressive symptoms, the possibility to have a unique and comprehensive panel of biological markers able to predict the onset of the disorder would allow a prompt and focused prevention and intervention. Although several biological risk factors have been so far proposed, we still do not have clear biomarkers or biological targets to develop intervention strategies. A genome-wide approach might provide successful results in terms of biological signatures able to discriminate adolescents based on the presence or risk of developing depression, rather than focusing only on already known clinical or biological risk factors.

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## Declaration of competing interest

None.

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**Valentina Zonca.** I am Valentina Zonca, I graduated in Pharmacy at the University of Milan and I am currently a PhD student in Psychological Medicine at the Institute of Psychiatry, Psychology and Neuroscience at King's College London in collaboration with the Biological Psychiatry Laboratory at the IRCCS San Giovanni di Dio Fatebenefratelli (Brescia, Italy).

I am interested in the biological mechanisms underpinning the onset of depression as well as the biological and environmental risk factors associated with the development of the disorder, such as trauma early in life. In my doctoral project, I aim to investigate the biological pathways involved in the risk of adolescent depression to early identify teenagers at risk of developing depression, specifically in low- and middle-income setting (IDEA project, funded by MQ).

Over the years, I have acquired proficiency in a variety of experimental approaches including Next Generation Sequencing (NGS) techniques and in vitro models (e.g. multipotent hippocampal progenitor cell line, primary fibroblast). I developed experimental skills in the management of several human tissues, in performing a wide panel of genome-wide and candidate-gene expression analysis. I have recently acquired experience in in vivo manipulations as well as in animal models' behavioral tests.

I have been engaged in the organization of informal and formal scientific and social activities (e.g. scientific seminars, conferences and soft skills courses) and I have supervised and still supervising bachelor and master students. I am also actively involved as a writer in the blog Inspire the Mind.

I am deeply committed to the cause of reducing the burden of adolescent depression, since I truly believe that understanding the biological signatures underlying the disorder can pave the way for the ambitious goal of reducing the burden of teen-agers depression and win the stigma associated with adolescent mental health.