Offspring of parents with mood disorders: time for more transgenerational research, screening and preventive intervention for this high-risk population

Dominique Maciejewski[a,b], *Manon Hillegers*[a], *and Brenda Penninx*[b]

Purpose of review
Offspring of parents with mood disorders (major depressive and bipolar disorder) are at increased risk for developing mood disorders. In this review, an overview regarding the intergenerational transmission of mood disorders, screening, and preventive intervention is given for this vulnerable group.

Recent findings
Offspring of parents with depression have a 40% chance of developing a depression, whereas offspring of parents with bipolar disorder have a 10% chance of developing a bipolar disorder by adulthood. Studies into the intergenerational transmission of mood disorders show that children of parents with mood disorders have increased biological dysregulation and neuropsychosocial impairments. Although there is a clear need for early identification of those at the highest risk, there are few systematic attempts in mental health care to screen children of parents with mood disorders. Lastly, preventive interventions seem to be effective in reducing depressive symptoms of children of parents with depression; however, those effects are small and short-lived.

Summary
Offspring of parents with mood disorders constitute a vulnerable group at high risk of mood disorders. More research needs to be conducted regarding mechanisms of the intergenerational transmission. Moreover, screening and preventive interventions for these offspring should be systematically evaluated and implemented.

Keywords
intergenerational transmission, offspring of parents with mood disorders, prevention, screening

INTRODUCTION

One of the strongest risk factors for developing a mood disorder (i.e., major depressive disorder and bipolar disorder) is having a parent with a mood disorder. The high risk for this offspring population, that is children of parents with a mood disorder, is due to both genetic as well as environmental vulnerability factors. However, although the risk of having a parent with a mood disorder has been demonstrated [1], studies addressing different pathways of the intergenerational transmission that increase risk or promote resilience are still limited. This review aims to give an overview of longitudinal cohort studies in offspring of parents with mood disorders, to summarize the risk of mood disorders, to review literature about biological and neuropsychosocial factors related to the intergenerational transmission of mood disorders, and to review current screening practices as well as recent findings of intervention studies for offspring of parents with mood disorders. This review closes with a short description of a new project in offspring of parents with mood disorders.

LONGITUDINAL COHORT STUDIES IN OFFSPRING OF PARENTS WITH MOOD DISORDERS

Longitudinal studies in offspring of parents with mood disorder are needed to better understand the development of mood disorders in this high-risk group. Only through longitudinal studies, as opposed to cross-sectional designs, can the development of mood disorders and direction of risk/resilience factors in this population be studied. Which *longitudinal* offspring studies have been conducted

[a]Department of Child and Adolescent Psychology and Psychiatry, Erasmus Medical Center, Rotterdam, The Netherlands and [b]Department of Psychiatry, Amsterdam Public Health Research Institute, VU Medical Center, Amsterdam, The Netherlands

Correspondence to Dominique Maciejewski, Department of Psychiatry, Amsterdam Public Health Research Institute, VU Medical Center, Oldenaller 1, 1081 HJ Amsterdam, The Netherlands.
Tel: +00 31 20 7884691; e-mail: d.maciejewski@ggzingeest.nl

Curr Opin Psychiatry 2018, 31:349–357
DOI:10.1097/YCO.0000000000000423

KEY POINTS

- Offspring of parents with depression have a 40% chance of developing a depression, whereas offspring of parents with bipolar disorder have a 10% chance of developing a bipolar disorder by adulthood.
- Offspring of parents with mood disorders show more biological dysregulation and neuropsychosocial impairment compared with offspring of controls.
- There is a clear need for screening in offspring of parents with mood disorders.
- Preventive interventions for offspring of parents with mood disorders seem to be effective, but effects are small and short-lived.

so far? Through a systematic literature search with the keywords ('offspring' OR 'COPMI' OR 'intergenerational') AND ('depress*' OR 'bipolar' OR 'manic' OR 'mood disorder'), we identified 12 longitudinal studies in offspring of parents with major depressive and bipolar disorder (Table 1).

The sample sizes of the offspring of parents with mood disorders at baseline ranged between 129 and 701 with a mean sample size of 264, indicating that most of the available offspring studies are rather small-scaled. Of the 12 studies, 67% of the studies included a control group of offspring of nonaffected parents. However, 33% of these studies included a relative small control group ($n < 100$). Including a control group in longitudinal cohort studies is important to provide a baseline against which development and association with risk and resilience factors can be compared. Six of the identified studies included parents with a major depressive and/or dysthymic disorder, three included parents with a bipolar disorder, and another three included both parents with major depressive disorder as well as parents with a bipolar disorder. The latter studies however are limited by small sample sizes for each of these disorders, likely under-powering the comparison between offspring of those two diagnostic categories and limiting the ability to conduct cross-diagnostic research. Diagnostic information about the biological coparents is available in 67% of the studies. However, in three of these eight studies, the coparent was predominantly assessed *indirectly*, for instance via the Family History Research Diagnostic Criteria method, which possibly leads to an underestimation of psychiatric diagnoses [30]. In another two studies, diagnostic information about the coparents was missing for more than one-third of the coparents. Thus, only 25% of the studies have directly assessed psychopathology in most or all coparents. Therefore, we have limited knowledge about the (additional) impact of coparent psychopathology on offspring of parents with mood disorders. In addition, recruitment strategies for the biological parents differed between studies, resulting in a variation in severity and level of comorbidity in the proband and the co-parent. To summarize, although there are longitudinal high-risk offspring studies available with convergent findings regaring the increased risk for mood disorders, there are methodological shortcomings and differences between studies that limit their ability in studying the intergenerational transmission of mood disorders.

FINDINGS OF RISK OF MOOD DISORDERS IN OFFSPRING STUDIES

Do offspring of parents with mood disorders really constitute a high-risk group? Studies suggest that having a parent with a major depressive or bipolar disorder greatly increases the risk of mood disorders in offspring. For instance, a study in offspring of parents with bipolar and major depressive disorders found that rates of mood disorders were significantly elevated (35% for offspring of bipolar patients and 26% for offspring of depressed patients) compared with offspring of parents without a psychiatric disorder (13%) [21]. A meta-analysis summarizing results from 33 offspring studies among 1482 offspring of parents with major depressive and 1492 offspring of parents with bipolar disorder supports these findings by showing that 40% of offspring with a depressed parent developed a depressive disorder during adulthood and 10% of offspring with a bipolar parent developed a bipolar disorder during adulthood [1]. The risk of suffering from a depression was increased 2.4 times among offspring of parents with a major depressive disorder. The risk of developing a bipolar disorder in offspring of parents with bipolar disorder was even increased 4.1 times. These data emphasize that offspring of parents with mood disorders are at great risk of suffering from mood disorders themselves. However, what are the reasons that offspring of parents with mood disorders have such a high risk to develop mood disorders? In the following, we will review studies that address biological and neuropsychosocial factors in the intergenerational transmission of mood disorders.

BIOLOGICAL PATHWAYS IN THE INTERGENERATIONAL TRANSMISSION IN OFFSPRING STUDIES

One of the reasons for the intergenerational transmission of mood disorders is genetic disposition. Research indicates that both depression and bipolar

Table 1. Overview of cohort, index parent, and offspring characteristics from identified offspring cohort studies

	Cohort characteristics			Index parent characteristics						Offspring characteristics				
Principal investigator, project name	Time follow-up	Follow-up interval (no. assessments)	% Drop-out offspring	*N*	% Male	Diagnosis (MDD/DD or BD)	Interview	Recruitment	Info on diagnostic status coparent?	*N*	% Male	Mean age (range)	Control-group	Depression assessment (mode; informant)
Abela [2,3]	1 year	Every 6 weeks (10)	~24%	102	14%	MDD	SCID	Advertisements	No or not reported on	140	49%	9.8 (6–14)	No	K-SADS-P (I; P,C) CDI (Q; C)
Birmaher Pittsburgh Bipolar Offspring Study [4,5,6▪]	*M* = 8.4 years	Every 2 years (*M* = 3.6)	~13%	236	20%	BD	SCID	Advertisements, earlier studies, outpatient clinics	Yes, indirectly (69%) and directly (31%)	391	51%	11.9 (6–18)	Yes (*n* = 248)	K-SADS-PL (I; P,C) MFQ (Q; P,C)
Brent Familial Pathways to Early-Onset Suicidal Behavior study [7,8]	*M* = 5.6 years	Annually (NR)	41%	334	15%	MDD & BD (81% MDD, 20% BD) (57% with suicide attempt)	SCID	Earlier studies, inpatient and outpatient units, referring psychiatrists, advertisements	Yes, directly (47%) and indirectly (29%), but no info on 36%	701	52%	17.7 (10–50)	No	Depending on age: K-SADS (I; C) or SCID (I; C) – age <18 vs. age ≥18 CDI (Q; C) or BDI (Q; C) – age <14 vs. age ≥14 CDRS (I; C) or HDRS (I; C) – age <18 vs. age ≥18
Duffy Flourish Canadian High-Risk Offspring Study [9,10]	*M* = 6.3 years	Annually (NR)	5%	113	48%	BD	SADS	Earlier molecular genetic studies	Yes, directly (83%) and indirectly (17%). Coparent had to be free of lifetime major psychiatric disorder	229	40%	16.4 (7–25)	Yes (*n* = 86)	Depending on age: K-SADS-PL or SADS-L (I; P,C) BDI or BDI-Y (Q; C) – age <13 vs. age ≥13
Garber [11–13]	6 years	Annually (7)	19%[c]	185	0%	MDD/DD	SCID	Schools	No or not reported	185	44%	11.8 (NR)	Yes (*n* = 55)	K-SADS-PL (I; P,C) – baseline A-LIFE (I; P,C) – follow-ups CDRS (I; P,C) CDI (Q; P,C)
Gibb Moods in Mothers and in Children [14▪,15▪][b]	2 years	Every 6 month (5)	~11%	129	0%	MDD	SCID	Advertisements	No or not reported	129	48%	10.8 (8–14)	Yes (*n* = 126)	K-SADS-PL (I; P,C) CDI (Q; C) CDRS (I; C)
Hammen & Brennan [16,17]	8.3 years	Baseline, 5 years, 8.3 years (3)	~37%[c]	358	0%	MDD/DD	SCID	Drawn from earlier study	Yes, directly, but no info on 36%	358	51%[c]	15.2 (15)	Yes (n = 458)	K-SADS-E (I; P,C) – T1 SCID (I; C) – T2 BDI (Q; C)
Hillegers Dutch Bipolar Offspring study [18–20]	12 years	Baseline, 1 year, 5 years, 12 years (4)	23%	86	40%	BD	IDCL	Patient associations, outpatient clinics	Yes, indirectly	140	51%	16.1 (12–21)	No	Depending on age: K-SADS-PL (I; P,C) or SCID (I; C) – age <18 vs. age ≥18 GBI (Q; C) IDS (I/Q; C) YMRS (I; C)
Preisig The Lausanne-Geneva cohort study of offspring of parents with mood disorders [21]	*M* = 10.6 years[c]	Every 3 years (*M* = 4.1)	NR	145	43%	MDD & BD (44% MDD, 56% BD)	DIGS	Inpatient and outpatient clinics	Yes, directly (60%) and indirectly (40%)	260 (145 of BD parents, 115 of MDD parents)	49%	10.3 (6–17)	Yes (*n* = 112)	Depending on age: K-SADS-E (I; C) or DIGS (I; C) – age <18 vs. age ≥18

Table 1 (*Continued*)

Principal investigator, project name	Cohort characteristics			Index parent characteristics						Offspring characteristics				
	Time follow-up	Follow-up interval (no. assessments)	% Drop-out offspring	*N*	% Male	Diagnosis (MDD/DD or BD)	Interview	Recruitment	Info on diagnostic status coparent?	*N*	% Male	Mean age (range)	Control-group	Depression assessment (mode; informant)
Radke-Yarrow & Gold [22,23]	15 years	First 4 assessments every 3 years, final assessment 7 years later (5)	~34%	76	0%	MDD & BD (67% MDD, 33% BD)	SADS,SCID	Advertisements, parent groups, local clinicians	Yes, directly	148 (102 of MDD parents, 46 of BD parents)	45%[a,c]	4.5 (1.5–7)[a,c]	Yes ($n=90$)	CAS (I; C) – T1 & T2 DICA (I; C,P) – T3 & T4 SCID (I; C) – T5 SCL-90 (Q; C) – T3 & T4 BDI (Q; C) – T5
Thapar Early Prediction of Adolescent Depression [24▪▪,25]	4 years	Every 12–18 months (3)	~20%	337	7%	MDD	SCAN	General practices, advertisements	No or not reported	337	42%	12.4 (9–17)	No	CAPA (I; P,C) MFQ (Q; P,C)
Weissman Yale Family Study of Major Depression [26–28,29▪▪]	30 years	Baseline, 2 years, 10 years, 20 years, 30 years (5)	36%[c]	65	42%[a]	MDD	SADS	Outpatient clinics	Yes, directly	153	48%	17 (6–23)	Yes ($n=67$)	K-SADS-E (I; P,C) CES-CD (Q; C)

If not reported in the text, drop-out rate is calculated based on sample size of at risk offspring at first and last assessment (if that was done, it is indicated by the symbol ~). If articles differ in sample size at last assessment, information from the article with the highest sample size was taken. Demographic information related to sample size, % male, and age refers to baseline assessments, unless otherwise specified. Information about depression assessment refers to assessments specifically related to depressive or bipolar symptoms. Diagnostic information was taken from most recent article with most information about different diagnostic categories. Symbol '~' is estimation based on information provided in the article, M is mean, C is child report, P is parent report, I is interview, Q is questionnaire. Psychiatric diagnoses: BD, bipolar disorder; DD, dysthymic disorder; MDD, major depressive disorder. Instruments interviews: A-LIFE, longitudinal interval follow-up evaluation for adolescents; CAPA, child and adolescent psychiatric assessment; CAS, child assessment schedule; CDRS, Children's Depression Rating Scale; DICA, diagnostic interview for children and adolescents; DIGS, diagnostic interview for genetic studies; HDRS, Hamilton Depression Rating Scale; IDCL, International Diagnostic Checklists; IDS, inventory for depressive symptomatology; K-SADS-E, schedule for affective disorders and schizophrenia for school-age children-epidemiologic version; K-SADS-P(L), schedule for affective disorders and schizophrenia for school-age children-present (and lifetime) version; SADS, schedule for affective disorders and schizophrenia; SCAN, schedules for clinical assessment in neuropsychiatry; SCID, structured clinical interview DSM-disorders; YMRS, Young Mania Rating Scale. Instruments questionnaires: BDI, beck depression inventory; CDI, children's depression inventory; CES-CD, Center for Epidemiologic Studies Depression Scale for Children; GBI, general behavior inventory; IDS-SR, inventory for depressive symptomatology – self report; MFQ, Mood and Feelings Questionnaire; SCL-90, symptom checklist 90.

[a]No information on baseline available, only reported for follow-up sample.

[b]Study does not directly report on sample sizes at baseline and follow-up. However, there are articles from that study project that only report cross-sectional results (highest sample size of at-risk offspring is 129 across publications), and articles from that study project that only report longitudinal results (without information on attrition; highest sample size of at risk-offspring is 115 across publications). Because grant number and procedures are identical, we concluded that these studies belong to the same project. Attrition is estimated based on the highest number of at-risk offspring in the cross-sectional study part and highest number of at-risk offspring in the longitudinal study part (115 of 129).

[c]Not reported separately for at-risk and control offspring. Number reported for overall offspring sample.

disorder are heritable, with higher heritability for bipolar disorder (59% [31]) compared with major depressive disorder (37% [32]). An adoption study by Kendler *et al.* [33▪] found that genetic and familial-environmental factors were involved in the intergenerational transmission of major depression to an equal degree and that both of them acted additively on the risk of major depression in offspring. Studies are moreover now examining which specific genes are involved in depression and bipolar disorder. Although previous attempts have not always been successful [34], a recent a Genome Wide Association Study (GWAS) in 130 664 major depressive disorder cases and 330 470 controls has identified 44 independent loci that reached statistical significance in major depressive disorder [35▪▪]. GWAS analyses for bipolar disorder are generally smaller and identify fewer common genetic variants involved in the pathophysiology of bipolar disorder [36,37]. However, it is likely that in the future genetic risk variants are becoming more and more clear as sample sizes increase and GWAS scans become cheaper.

Two key biological indicators of illness risk that have been proposed for offspring of parents with mood disorders are disturbances in the hypothalamic–pituitary–adrenal (HPA)-axis and the immune system [38], which have been shown to be related to mood disorders [39,40,41▪]. Studies on inflammation have found that parental mood disorders increase inflammation in offspring [42▪,43–45,46▪,47]. For instance, a study by Plant *et al.* [42▪] showed that prenatal maternal depression was associated with elevated high-sensitivity C-reactive protein when the offspring was 25 years old. Similarly, there is evidence that HPA-axis abnormalities are associated with mood disorders [41▪]. Studies on the HPA-axis as an intergenerational transmission factor are however less conclusive. Although some found that offspring of parents with mood disorder show more HPA-axis hyperactivity as measured in salivary cortisol [48,49], others fail to find such evidence [42▪,50▪,51▪]. This could suggest that HPA-axis dysregulation is a general factor that predisposes offspring to mood disorders, rather than being a mediating factor between parental and offspring mood disorders.

All in all, these studies emphasize that biological dysregulation seems to be a mediating factor in the intergenerational transmission of mood disorders. However, many of those studies are rather small-scaled and cross-sectional. Importantly, few studies have repeatedly measured inflammatory and HPA-axis factors over time (for exceptions see [45–47,51▪]) and therefore have not been able to establish whether these dysregulations truly contribute to the increased mood disorder risk in offspring. More longitudinal studies are needed to clarify whether biological dysregulation and changes herein predispose mood disorders in offspring of parents with mood disorders.

NEUROPSYCHOSOCIAL PATHWAYS IN THE INTERGENERATIONAL TRANSMISSION IN OFFSPRING STUDIES

Apart from biological factors, several neuropsychosocial factors that increase the risk of mood disorders among offspring of parents with mood disorders have been studied. We use neuropsychosocial factors as an umbrella term to describe neurocognitive (e.g., executive functions), personal (e.g., temperament), and social factors (e.g., parental rearing). One of these neuropsychosocial factors that has been proposed to be involved in the intergenerational transmission is neurocognitive functioning, which has been shown to be related to depression in offspring and adolescents [52]. Specifically, studies suggest that offspring of parents with bipolar disorder have deficits in cognitive areas, such as executive functioning [22], attention [22,53], and memory [22,54▪]. Those deficits seem to be particularly salient for affected offspring of parents with bipolar disorder, reflecting a burden of illness in bipolar offspring, as multiple studies have failed to find an association between parental history of major depression and neuropsychological impairments in offspring [22,55,56].

Another widely studied personal factor in offspring of parents with mood disorders is temperament. Studies indicate that offspring with a depressed or bipolar parent report a more difficult temperament compared with offspring of well parents [57–59], which might further increase their risk of developing a mood disorder. Moreover, studies also suggest that emotion regulation is impaired among offspring of parents with mood disorders as they show more dysfunctional coping compared with offspring of parents without mood disorders [60–62]. Such difficulties to adequately cope with stressful life events and situations and resulting negative emotions have been shown to be related to the onset and course of mood disorders [63,64]. These factors may signal a vulnerability to mood disorders and are therefore important targets for early prevention.

Apart from neuropsychological and personal factors, environmental factors also play an important role in the development of mood disorders among offspring of parents with mood disorders. One widely studied factor is stressful life events. For instance, studies suggest that offspring of parents with mood disorders experience more stressful life

events and chronic stress than offspring of parents without mood disorders [59,65▪,66], and are more susceptible to the effect of negative life events [67,68], which might partly explain their higher risk for developing mood disorders. Another environmental factor that has important influences on the risk of mood disorders in offspring of parents with mood disorders is the parental environment, which has been shown to be impaired in offspring of parents with mood disorders, with suboptimal parenting strategies and more problematic family environments (e.g., less family cohesion, more conflict) [69–71,72▪,73▪▪,74].

Although many studies focus on risk factors in the intergenerational transmission of mood disorders, fewer studies have focused on resilience in offspring of parents with mood disorders [75]. In fact, we only identified three studies that have examined resilience to parental depression in a longitudinal fashion [24▪▪,76,77]. The few studies that are available identify some factors that seem to be protective against the development of mood disorders among offspring of parents with mood disorders. For instance, a recent study in offspring of parents with recurrent depression found that positive expressed emotion in the index parents, high coparent support, good peer relationship quality, high adolescent self-efficacy, and frequent exercise were associated with good sustained mental health in offspring [24▪▪].

In conclusion, although previous studies have shown that certain neuropsychological factors increase the risk of mood disorders in offspring of parents with mood disorders, many of these studies are cross-sectional and have a relatively small sample size. Thus, it is not clear whether a parental history of mood disorders predicts the development of neuropsychosocial impairments over time. Moreover, few studies have examined these neuropsychosocial factors in both parents and offspring. Thus, it is for instance not clear how the concordance of neuropsychosocial risk factors between parents and offspring contribute to their risk of mood disorders in offspring. In addition, few studies have focused on resilience, which is necessary to inform prevention strategies. The few studies that are available have however shown that there are potentially modifiable factors that can be targeted, such as adequate coping strategies or healthy life style.

CLINICAL IMPLICATIONS: TIME FOR SCREENING AND PREVENTIVE INTERVENTIONS

Given the high risk for offspring of parents with mood disorders to develop a mood disorder themselves, early identification of mood problems in this high-risk group is very important. However, healthcare systems that have implemented a systematic screening of offspring of parents with mood disorders are scarce. For example, in 2013 the Dutch government issued a 'child check' law requiring systematic safety checks in offspring of psychiatric patients, but implementation is largely lacking [78]. This is a missed opportunity as parents of this high-risk offspring group are in healthcare settings in which contact with the offspring could be initiated. The need for psychoeducation and prevention in high-risk offspring groups has shown to be quite large [79▪]. In an online survey that we conducted among 41 offspring of parents with mood disorders and 126 parents with mood disorders, 63% of offspring and 73% of the parents worried about the offspring's development of illness. A large proportion of both groups would be interested in screening and prevention programs.

Adequate screening instruments could detect early mood problems in offspring of parents with mood disorders. Research indicates that for instance the Patient Health Questionnaire-9 instrument can adequately predict a depressive disorder in adolescents [80]. For bipolar disorder, fewer screening instruments exist for children and adolescents and parent-report on bipolar symptoms may be superior to offspring self-report [81,82], highlighting the necessity of involving multiple informants. No recommendations exist for screening for mood problems in this high-risk population, but the US Preventive Services Task Force recommends screening for depression in the general population due to moderate net benefit of and few adverse effects due to screening [83▪]. For children and adolescents, no studies exist on the potential harms and benefits of screening [84]. As false-positive scores can – without proper follow-up – 'lead to harmful labeling, unnecessary additional testing, and inappropriate treatment' [85], it is important that a positive screening result is followed up by adequate diagnostic assessment and treatment.

Apart from and in addition to screening for mood-related problems, prevention of the onset of a mood disorder in offspring of parents with depression or bipolar disorder deserves clinical attention. Preventive interventions for depression are in general effective in reducing the incidence of depression by 25% and that they have attractive cost-effectiveness ratios [86]. However, few trials have been conducted specifically in offspring of parents with mood disorders. A recent meta-analysis summarizing seven randomized prevention intervention trials in 935 offspring of parents with a major depression indicates that preventive

interventions can prevent depression onset (risk ratio = 0.56) and decrease depressive and internalizing symptoms at postintervention (Hedges' $g = -0.20$) [87▪▪]. Interventions usually consisted of elements of psychoeducation about depression and building resilience in the child by using cognitive-behavioral therapy elements. However, effects regarding symptoms were only evident immediately after the intervention, but not at longer term follow-up. More research needs to be conducted on why these intervention programs only seem to have short-lived effects. It may be that available intervention programs are not intensive enough or could benefit from booster sessions.

THE MOOD AND RESILIENCE IN OFFSPRING PROJECT: A NEW PROJECT IN OFFSPRING OF PARENTS WITH MOOD DISORDERS

Inspired by current longitudinal offspring cohort studies and some of their methodological limitations (i.e., small sample size, few studies with control groups, few studies taking a cross-diagnostic approach, limited information about diagnostic status of the coparent), we started a new cohort study: the Mood and Resilience in offspring Project (MARIO) in which 800 offspring (ages 10–25; 200 control, 600 at-risk) will be followed over 4 years. For this offspring cohort, we will utilize existing patient cohorts in the Netherlands (NESDA [88], BiG [89], OPPER [90]) with intensive measures about biological and neuropsychosocial factors. Repeating similar rich phenotypes in the offspring allows us to link these factors between parents and offspring to get a better understanding about the intergenerational transmission of mood disorders. In addition, we aim to improve current screening in clinical practice by examining the implementation and predictive value of a screening instrument for 1500 offspring (ages 20–25) in clinical practice. Finally, in a randomized controlled trial in 350 offspring (ages 10–25), we will test the effectiveness of an online preventive intervention that adolescents can follow on their phone and will consist of psychoeducation, cognitive–behavioral therapy elements, and activation of coping.

CONCLUSION

Offspring of parents with mood disorders are at an increased risk of developing mood disorders in their lives: 65% of the offspring of patients have a mood disorder before the age of 35 [91▪▪]. More research needs to be conducted on biological and neuropsychosocial factors of the intergenerational transmission that explains why some of these offspring develop mood disorder symptoms, whereas others stay resilient. Moreover, more needs to be done to screen those offspring for mood disorder symptoms to signal early symptoms before they develop into a full-blown disorder. Lastly, preventive interventions, preferably using elements of psychoeducation and cognitive-behavioral therapy, need to be developed and tested so that the onset of mood disorders can be prevented.

Acknowledgements

None.

Financial support and sponsorship

The current work was supported by a grant from ZonMw (project number: 60-63600-98-021).

Conflicts of interest

B.P. received (not related to this article) research funding from Jansen Research and Boehringer Ingelheim.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- ▪ of special interest
- ▪▪ of outstanding interest

1. Rasic D, Hajek T, Alda M, Uher R. Risk of mental illness in offspring of parents with schizophrenia, bipolar disorder, and major depressive disorder: a meta-analysis of family high-risk studies. Schizophr Bull 2014; 40:28–38.
2. Abela JRZ, Skitch SA, Adams P, Hankin BL. The timing of parent and child depression: a hopelessness theory perspective. J Clin Child Adolesc Psychol 2006; 35:253–263.
3. Abela JRZ, Hankin BL, Sheshko DM, *et al.* Multiwave prospective examination of the stress-reactivity extension of response styles theory of depression in high-risk children and early adolescents. J Abnorm Child Psychol 2012; 40:277–287.
4. Birmaher B, Axelson D, Monk K, *et al.* Lifetime psychiatric disorders in school-aged offspring of parents with bipolar disorder: The Pittsburgh Bipolar Offspring Study. Arch Gen Psychiatry 2009; 66:287–296.
5. Axelson D, Goldstein B, Goldstein T, *et al.* Diagnostic precursors to bipolar disorder in offspring of parents with bipolar disorder: a longitudinal study. Am J Psychiatry 2015; 172:638–646.
6. ▪ Hafeman DM, Merranko J, Axelson D, *et al.* Toward the definition of a bipolar prodrome: dimensional predictors of bipolar spectrum disorders in at-risk youths. Am J Psychiatry 2016; 173:695–704.

Study examining dimensional predictors of bipolar spectrum disorders in offspring of parents with bipolar disorder. Results showed that dimensional measures of anxiety/depression, affective lability, and mania were strong predictors of bipolar disorder incidence in offspring of parents with bipolar disorder.

7. Brent DA, Oquendo M, Birmaher B, *et al.* Familial pathways to early-onset suicide attempt: Risk for suicidal behavior in offspring of mood-disordered suicide attempters. Arch Gen Psychiatry 2002; 59:801–807.
8. Brent DA, Melhem NM, Oquendo M, *et al.* Familial pathways to early-onset suicide attempt: a 5.6-year prospective study. JAMA Psychiatry 2015; 72: 160–168.
9. Duffy A, Alda M, Crawford L, *et al.* The early manifestations of bipolar disorder: a longitudinal prospective study of the offspring of bipolar parents. Bipolar Disord 2007; 9:828–838.
10. Duffy A, Horrocks J, Doucette S, *et al.* The developmental trajectory of bipolar disorder. Br J Psychiatry 2014; 204:122–128.
11. Gallerani CM, Garber J, Martin NC. The temporal relation between depression and comorbid psychopathology in adolescents at varied risk for depression. J Child Psychol Psychiatry 2010; 51:242–249.
12. Garber J, Keiley MK, Martin NC. Developmental trajectories of adolescents' depressive symptoms: predictors of change. J Consult Clin Psychol 2002; 70:79–95.
13. Garber J, Cole DA. Intergenerational transmission of depression: a launch and grow model of change across adolescence. Dev Psychopathol 2010; 22:819–830.

14. Tsypes A, Gibb BE. Cognitive vulnerabilities and development of suicidal ■ thinking in children of depressed mothers: a longitudinal investigation. Psychiatry Res 2016; 239:99–104.

Longitudinal study examining the association between cognitive vulnerabilities and suicidal ideation in offspring of depressed mothers. Results showed that higher levels of hopelessness and lower global self-worth predicted the onset of suicidal ideation 2 years later. Results highlight the importance of cognitive vulnerabilities in suicidal ideation.

15. Woody ML, Feurer C, Sosoo EE, *et al.* Synchrony of physiological activity ■ during mother–child interaction: moderation by maternal history of major depressive disorder. J Child Psychol Psychiatry 2016; 57:843–850.

Very interesting study examining the synchrony of physiological activity during mother–child interaction among offspring of depressed mothers and control offspring. Within-dyad analyses showed that never-depressed dyads showed respiratory sinus arrhythmia concordance, whereas dyads in which the mother had a history of depression showed respiratory sinus arrhythmia discordance. Results suggest disrupted physiological synchrony in families in which the mother has a history of depression.

16. Hammen C, Brennan PA. Depressed adolescents of depressed and nondepressed mothers: tests of an interpersonal impairment hypothesis. J Consult Clin Psychol 2001; 69:284–294.
17. Hammen C, Shih J, Altman T, Brennan PA. Interpersonal impairment and the prediction of depressive symptoms in adolescent children of depressed and nondepressed mothers. J Am Acad Child Adolesc Psychiatry 2003; 42:571–577.
18. Hillegers MHJ, Reichart CG, Wals M, *et al.* Five-year prospective outcome of psychopathology in the adolescent offspring of bipolar parents. Bipolar Disord 2005; 7:344–350.
19. Mesman E, Nolen WA, Reichart CG, *et al.* The Dutch bipolar offspring study: 12 year follow-up. Am J Psychiatry 2013; 170:542–549.
20. Wals M, Hillegers MHJ, Reichart CG, *et al.* Prevalence of psychopathology in children of a bipolar parent. J Am Acad Child Adolesc Psychiatry 2001; 40:1094–1102.
21. Vandeleur C, Rothen S, Gholam-Rezaee M, *et al.* Mental disorders in offspring of parents with bipolar and major depressive disorders. Bipolar Disord 2012; 14:641–653.
22. Klimes-Dougan B, Ronsaville D, Wiggs EA, Martinez PE. Neuropsychological functioning in adolescent children of mothers with a history of bipolar or major depressive disorders. Biol Psychiatry 2006; 60:957–965.
23. Radke-Yarrow M, Nottelmann E, Martinez P, *et al.* Young children of affectively ill parents: a longitudinal study of psychosocial development. J Am Acad Child Adolesc Psychiatry 1992; 31:68–77.
24. Collishaw S, Hammerton G, Mahedy L, *et al.* Mental health resilience in the ■■ adolescent offspring of parents with depression: a prospective longitudinal study. Lancet Psychiatry 2016; 3:49–57.

One of the few longitudinal studies that has examined mental health resilience in offspring of parents with depression. Several factors emerged that predicted good sustained mental health in offspring, namely, index-parent positive expressed emotion, support from coparents, good-quality social relationships, youth self-efficacy, and regular physical exercise.

25. Sellers R, Collishaw S, Rice F, *et al.* Risk of psychopathology in adolescent offspring of mothers with psychopathology and recurrent depression. Br J Psychiatry 2013; 202:108–114.
26. Weissman MM, Gammon GD, John K, *et al.* Children of depressed parents: Increased psychopathology and early onset of major depression. Arch Gen Psychiatry 1987; 44:847–853.
27. Weissman MM, Warner V, Wickramaratne P, *et al.* Offspring of depressed parents: 10 years later. Arch Gen Psychiatry 1997; 54:932–940.
28. Weissman MM, Wickramaratne P, Nomura Y, *et al.* Offspring of depressed parents: 20 years later. Am J Psychiatry 2006; 163:1001–1008.
29. Weissman MM, Wickramaratne P, Gameroff MJ, *et al.* Offspring of depressed ■■ parents: 30 years later. Am J Psychiatry 2016; 173:1024–1032.

Study with a 30-year follow-up examining the association between parental depression and offspring psychopathology. Findings show that offspring of depressed had a three time higher risk for developing major depressive disorder compared with controls. Moreover, findings showed that the first onset of disorders occurred between ages 15 and 25. Lastly, results suggested that high-risk offspring had overall poorer functioning, received more treatment for emotional problems, and had an increased mortality rate compared with control offspring.

30. Andreasen NC, Endicott J, Spitzer RL, Winokur G. The family history method using diagnostic criteria. Reliability and validity. Arch Gen Psychiatry 1977; 34:1229–1235.
31. Lichtenstein P, Yip BH, Björk C, *et al.* Common genetic determinants of schizophrenia and bipolar disorder in Swedish families: a population-based study. Lancet 2009; 373:234–239.
32. Sullivan PF, Neale MC, Kendler KS. Genetic epidemiology of major depression: review and meta-analysis. Am J Psychiatry 2000; 157:1552–1562.
33. Kendler KS, Ohlsson H, Sundquist K, Sundquist J. Sources of parent-off- ■ spring resemblance for major depression in a National Swedish Extended Adoption Study. JAMA Psychiatry 2017; 75:194–200.

An adoption study showing that genetic and rearing factors influence parent–offspring resemblance for treated major depressive disorder to an equal extent and that both acted additively on the risk for major depressive disorder in offspring.

34. Ripke S, Wray NR, Lewis CM, *et al.* A mega-analysis of genome-wide association studies for major depressive disorder. Mol Psychiatry 2013; 18:497–511.
35. Wray NR, Sullivan PF. Genome-wide association analyses identify 44 risk ■■ variants and refine the genetic architecture of major depression. Nat Genet 2018. doi:10.1101/167577.

Largest Genome Wide Association Study to date examining the genes related to major depressive disorder. Analyses found 44 independent loci that reached statistical significance in genetic analyses.

36. Ferreira MAR, O'Donovan MC, Meng YA, *et al.* Collaborative genome-wide association analysis supports a role for ANK3 and CACNA1C in bipolar disorder. Nat Genet 2008; 40:1056–1058.
37. Burton PR, Clayton DG, Cardon LR, *et al.* Genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls. Nature 2007; 447:661–678.
38. Duffy A, Lewitzka U, Doucette S, *et al.* Biological indicators of illness risk in offspring of bipolar parents: targeting the hypothalamic–pituitary–adrenal axis and immune system. Early Interv Psychiatry 2012; 6:128–137.
39. Kiecolt-Glaser JK, Derry HM, Fagundes CP. Inflammation: depression fans the flames and feasts on the heat. Am J Psychiatry 2015; 172: 1075–1091.
40. Hamdani N, Doukhan R, Kurtlucan O, *et al.* Immunity, inflammation, and bipolar disorder: diagnostic and therapeutic implications. Curr Psychiatry Rep 2013; 15:387.
41. Belvederi Murri M, Prestia D, Mondelli V, *et al.* The HPA axis in bipolar ■ disorder: systematic review and meta-analysis. Psychoneuroendocrinology 2016; 63:327–342.

Important review about the relation between the hypothalamic–pituitary–adrenal (HPA)-axis and bipolar disorder. Meta-analysis showed that bipolar disorder was significantly associated with increased level of cortisol and ACTH. Analyses further showed that case–control differences in cortisol were significantly associated with manic phases.

42. Plant DT, Pawlby S, Sharp D, *et al.* Prenatal maternal depression is associated ■ with offspring inflammation at 25 years: a prospective longitudinal cohort study. Transl Psychiatry 2016; 6:e936.

Study showing that prenatal depression was significantly associated with elevated high-sensitivity C-reactive protein at age 25, highlighting the important long-term influence that maternal depression has on inflammation.

43. Duffy A, Horrocks J, Doucette S, *et al.* Immunological and neurotrophic markers of risk status and illness development in high-risk youth: understanding the neurobiological underpinnings of bipolar disorder. Int J Bipolar Disord 2014; 2:4.
44. Padmos RC, Hillegers MHJ, Knijff EM, *et al.* A discriminating messenger RNA signature for bipolar disorder formed by an aberrant expression of inflammatory genes in monocytes. Arch Gen Psychiatry 2008; 65:395–407.
45. Mesman E, Hillegers MHJ, Ambree O, *et al.* Monocyte activation, brain-derived neurotrophic factor (BDNF), and S100B in bipolar offspring: a follow-up study from adolescence into adulthood. Bipolar Disord 2015; 17:39–49.
46. Snijders G, Schiweck C, Mesman E, *et al.* A dynamic course of T cell ■ defects in individuals at risk for mood disorders. Brain Behav Immun 2016; 58:11–17.

One of the few longitudinal studies on biological dysregulation in offspring of parents with mood disorders. Study showed a subtle partial T-cell defect in offspring of parents with bipolar disorder from adolescence until adulthood.

47. Snijders G, Mesman E, de Wit H, *et al.* Immune dysregulation in offspring of a bipolar parent. Altered serum levels of immune growth factors at adolescent age. Brain Behav Immun 2017; 64:116–123.
48. LeMoult J, Chen MC, Foland-Ross LC, *et al.* Concordance of mother–daughter diurnal cortisol production: understanding the intergenerational transmission of risk for depression. Biol Psychol 2015; 108:98–104.
49. Ellenbogen MA, Santo JB, Linnen A-M, *et al.* High cortisol levels in the offspring of parents with bipolar disorder during two weeks of daily sampling. Bipolar Disord 2010; 12:77–86.
50. Schreuder MM, Vinkers CH, Mesman E, *et al.* Childhood trauma and HPA axis ■ functionality in offspring of bipolar parents. Psychoneuroendocrinology 2016; 74:316–323.

Study examining the association between childhood trauma and HPA-axis in offspring of bipolar parents and controls. Results showed that there were no differences in HPA-axis activity bipolar and control offspring. However, results showed that childhood trauma was associated with lower daytime cortisol levels in bipolar but not in control offspring, suggesting a hypoactive state of the HPA-axis in bipolar offspring in response to trauma.

51. Goodday SM, Horrocks J, Keown-Stoneman C, *et al.* Repeated salivary ■ daytime cortisol and onset of mood episodes in offspring of bipolar parents. Int J bipolar Disord 2016; 4:12.

One of the few studies that examined repeated biological markers in offspring of parents with mood disorders to study the longitudinal development of those markers. Results, however, showed no difference in HPA-axis activity between bipolar offspring and controls. In addition, HPA-axis activity showed no significant changes across a 4-year period. Lastly, results showed that daytime cortisol and evening cortisol were associated with mood disorder onset/recurrence in bipolar offspring.

52. Wagner S, Müller C, Helmreich I, *et al.* A meta-analysis of cognitive functions in children and adolescents with major depressive disorder. Eur Child Adolesc Psychiatry 2015; 24:5–19.

53. Diwadkar VA, Goradia D, Hosanagar A, *et al.* Working memory and attention deficits in adolescent offspring of schizophrenia or bipolar patients: comparing vulnerability markers. Prog Neuro-Psychopharmacology Biol Psychiatry 2011; 35:1349–1354.

54. ■ de la Serna E, Vila M, Sanchez-Gistau V, *et al.* Neuropsychological characteristics of child and adolescent offspring of patients with bipolar disorder. Prog Neuro-Psychopharmacology Biol Psychiatry 2016; 65: 54–59.

Study examining the differences in cognitive performance between offspring of bipolar parents and controls. Results showed that bipolar offspring showed significantly worse performances in processing speed and immediate recall of visual memory compared with controls. Findings suggest that those cognitive impairments could be regarded as vulnerability markers for bipolar disorder.

55. Micco JA, Henin A, Biederman J, *et al.* Executive functioning in offspring at risk for depression and anxiety. Depress Anxiety 2009; 26:780–790.

56. Wagner C, Abramson LY, Alloy LB. Brief report: executive functions in adolescent offspring of mothers with a history of depression. J Adolesc 2015; 44:32–36.

57. Bruder-Costello B, Warner V, Talati A, *et al.* Temperament among offspring at high and low risk for depression. Psychiatry Res 2007; 153: 145–151.

58. Sanches M, Scott-Gurnell K, Patel A, *et al.* Impulsivity in children and adolescents with mood disorders and unaffected offspring of bipolar parents. Compr Psychiatry 2014; 55:1337–1341.

59. Duffy A, Alda M, Trinneer A, *et al.* Temperament, life events, and psychopathology among the offspring of bipolar parents. Eur Child Adolesc Psychiatry 2007; 16:222–228.

60. Nijjar R, Ellenbogen MA, Hodgins S. Personality, coping, risky behavior, and mental disorders in the offspring of parents with bipolar disorder: a comprehensive psychosocial assessment. J Affect Disord 2014; 166: 315–323.

61. Silk JS, Shaw DS, Skuban EM, *et al.* Emotion regulation strategies in offspring of childhood-onset depressed mothers. J Child Psychol Psychiatry 2006; 47:69–78.

62. Jones SH, Tai S, Evershed K, *et al.* Early detection of bipolar disorder: a pilot familial high-risk study of parents with bipolar disorder and their adolescent children. Bipolar Disord 2006; 8:362–372.

63. Aldao A, Nolen-Hoeksema S, Schweizer S. Emotion-regulation strategies across psychopathology: a meta-analytic review. Clin Psychol Rev 2010; 30:217–237.

64. Kemner SM, Mesman E, Nolen WA, *et al.* The role of life events and psychological factors in the onset of first and recurrent mood episodes in bipolar offspring: results from the Dutch Bipolar Offspring Study. Psychol Med 2015; 45:2571–2581.

65. ■ Pan LA, Goldstein TR, Rooks BT, *et al.* The relationship between stressful life events and Axis I diagnoses among adolescent offspring of probands with bipolar and nonbipolar psychiatric disorders and healthy controls. J Clin Psychiatry 2017; 78:e234–e243.

Largest study to date examining the relation between stressful life events and Axis I diagnoses in bipolar, nonbipolar Axis I, and control offspring. Results showed that bipolar offspring showed greater independent and neutral life events compared with offspring of healthy controls. Moreover, stressful life events were associated with Axis I disorders in all offspring.

66. Ostiguy CS, Ellenbogen MA, Linnen A-M, *et al.* Chronic stress and stressful life events in the offspring of parents with bipolar disorder. J Affect Disord 2009; 114:74–84.

67. Bouma EMC, Ormel J, Verhulst FC, Oldehinkel AJ. Stressful life events and depressive problems in early adolescent boys and girls: the influence of parental depression, temperament and family environment. J Affect Disord 2008; 105:185–193.

68. Zimmermann P, Bruckl T, Lieb R, *et al.* The interplay of familial depression liability and adverse events in predicting the first onset of depression during a 10-year follow-up. Biol Psychiatry 2008; 63:406–414.

69. Belardinelli C, Hatch JP, Olvera RL, *et al.* Family environment patterns in families with bipolar children. J Affect Disord 2008; 107: 299–305.

70. Barron E, Sharma A, Le Couteur J, *et al.* Family environment of bipolar families: a UK study. J Affect Disord 2014; 152–154:522–525.

71. Sellers R, Harold GT, Elam K, *et al.* Maternal depression and co-occurring antisocial behaviour: testing maternal hostility and warmth as mediators of risk for offspring psychopathology. J Child Psychol Psychiatry 2014; 55: 112–120.

72. ■ Goetz M, Sebela A, Mohaplova M, *et al.* Psychiatric disorders and quality of life in the offspring of parents with bipolar disorder. J Child Adolesc Psychopharmacol 2017; 27:483–493.

Study showing that offspring of parents with bipolar disorder have a higher rate of mood and anxiety disorders compared with controls. Moreover, results showed that offspring of parents with bipolar disorder have a lower quality of life in multiple domains compared with controls.

73. ■■ Iacono V, Beaulieu L, Hodgins S, Ellenbogen MA. Parenting practices in middle childhood mediate the relation between growing up with a parent having bipolar disorder and offspring psychopathology from childhood into early adulthood. Dev Psychopathol 2017. [Epub ahead of print]

One of the few longitudinal studies examining the association between parenting practices in childhood and offspring psychopathology from childhood to early adulthood. Cross-sectional results showed that low levels of structure mediated the relation between having a bipolar parent and offspring psychopathology, whereas longitudinal analyses showed that parental control mediated the relation between having a bipolar parent and offspring psychopathology. Results emphasize the important role that parental practices have in the relation between being at familial risk for bipolar disorder and offspring psychopathology.

74. Nomura Y, Wickramaratne PJ, Warner V, *et al.* Family discord, parental depression and psychopathology in offspring: ten-year follow-up. J Am Acad Child Adolesc Psychiatry 2002; 41:402–409.

75. Reuben JD, Shaw DS. Resilience in the offspring of depressed mothers: variation across risk, domains, and time. Clin Child Fam Psychol Rev 2015; 18:300–327.

76. Pargas RCM, Brennan PA, Hammen C, Le Brocque R. Resilience to maternal depression in young adulthood. Dev Psychol 2010; 46:805–814.

77. Lewandowski RE, Verdeli H, Wickramaratne P, *et al.* Predictors of positive outcomes in offspring of depressed parents and nondepressed parents across 20 years. J Child Fam Stud 2014; 23:800–811.

78. van der Zanden R, Haverman M, van der Poel A. Resultaten van een Rondgang in de Uitvoeringspraktijk van preventie, zorg en ondersteuning voor kinderen van ouders met psychische problemen (KOPP) en kinderen van verslaafde ouders (KVO). Utrecht: Trimbos-instituut; 2016.

79. ■ Grové C, Reupert A, Maybery D. The perspectives of young people of parents with a mental illness regarding preferred interventions and supports. J Child Fam Stud 2016; 25:3056–3065.

Study examining the needs of young people of parents with mental illnesses regarding preferred interventions and supports. Findings show that almost all offspring wanted some kind of support, such as talking to a counsellor or receiving support online.

80. Richardson LP, McCauley E, Grossman DC, *et al.* Evaluation of the Patient Health Questionnaire-9 Item for detecting major depression among adolescents. Pediatrics 2010; 126:1117–1123.

81. Wagner KD, Hirschfeld RMA, Emslie GJ, *et al.* Validation of the Mood Disorder Questionnaire for bipolar disorders in adolescents. J Clin Psychiatry 2006; 67:827–830.

82. Youngstrom EA, Findling RL, Calabrese JR, *et al.* Comparing the diagnostic accuracy of six potential screening instruments for bipolar disorder in youths aged 5 to 17 years. J Am Acad Child Adolesc Psychiatry 2004; 43:847–858.

83. ■ Siu AL, Bibbins-Domingo K, Grossman DC, *et al.* Screening for depression in adults. US Preventive Services Task Force Recommendation Statement. JAMA 2016; 315:380.

US Preventive Services Task Force Recommendation statement about suggested screening practices for depression in adults. Statement recommends screening for depression in adults due to moderate net benefit and low potential harm.

84. Forman-Hoffman V, McClure E, McKeeman J, *et al.* Screening for major depressive disorder in children and adolescents: a systematic review for the U.S. preventive services task force. Ann Intern Med 2016; 164:342–349.

85. Nimalasuriya K, Compton MT, Guillory VJ. Prevention Practice Committee of the American College of Preventive Medicine: screening adults for depression in primary care: a position statement of the American College of Preventive Medicine. J Fam Pract 2009; 58:535–538.

86. Cuijpers P, Beekman ATF, Reynolds CF. Preventing depression: a global priority. JAMA 2012; 307:1033–1034.

87. ■■ Loechner J, Starman K, Galuschka K, *et al.* Preventing depression in the offspring of parents with depression: a systematic review and meta-analysis of randomized controlled trials. Clin Psychol Rev 2018; 60:1–14.

Well conducted, recent systematic review and meta-analysis on the randomized clinical trials on preventing the onset of depression in offspring of parents with depression. Results showed that preventive interventions were effective in reducing depressive and internalizing symptoms at postintervention follow-up, but not at medium and long-term follow-up. Moreover, results showed that preventive interventions were associated with a lower depression incidence.

88. Penninx BWJH, Beekman ATF, Smit JH, *et al.* The Netherlands Study of Depression and Anxiety (NESDA): rationale, objectives and methods. Int J Methods Psychiatr Res 2008; 17:121–140.

89. Collin G, van den Heuvel MP, Abramovic L, *et al.* Brain network analysis reveals affected connectome structure in bipolar I disorder. Hum Brain Mapp 2016; 37:122–134.

90. Kamperman AM, Veldman-Hoek MJ, Wesseloo R, *et al.* Phenotypical characteristics of postpartum psychosis: A clinical cohort study. Bipolar Disord 2017; 19:450–457.

91. ■■ Havinga PJ, Boschloo L, Bloemen AJP, *et al.* Doomed for disorder? High incidence of mood and anxiety disorders in offspring of depressed and anxious patients: a prospective cohort study. J Clin Psychiatry 2017; 78:e8–e17.

Well conducted study showing the risk of mood/anxiety disorders in offspring of parents with a mood/anxiety disorder. Results show that 65% of offspring of parents with a mood/anxiety disorder develop a mood/anxiety disorder themselves until the age of 35.