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Breaking the cycle?

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| 8 |

General discussion

The aim of this thesis was to improve our knowledge of the intergenerational transmission of depressive/anxiety disorders and to shed light on possibilities to decrease the risk that these disorders pass on from one generation to the next. In the first part of this thesis, we examined the onset and course of mood/anxiety disorders in the context of parental depression/anxiety (Chapters 2, 3, 4, 5). The second part of this thesis reviewed existing programs aiming to prevent the onset of mood/anxiety disorders in offspring and focused on help-seeking in offspring already suffering from these conditions (Chapters 6, 7). In this final chapter we discuss the main findings, methodological considerations, potential clinical implications, and opportunities for future research.

OVERVIEW OF MAIN FINDINGS

Onset of mood/anxiety disorders in offspring

Chapter 2 showed that offspring of depressed/anxious patients are at very high risk to suffer from a similar disorder as their parents: in our cohort the cumulative incidence estimate for offspring mood/anxiety disorders was 38% at age 20 and 65% at the age of 35. Similar long-term follow-up studies in offspring of treatment-seeking depressed/anxious patients report comparable high cumulative incidence rates in offspring^{1,2}, confirming our conclusion that suffering from a mood or anxiety disorder is the rule rather than the exception for these children. This is about two to three times as high as reported in another large Dutch community sample of persons aged 25-44 years assessed with the same diagnostic interview as in our study.³ With some exceptions^{e,g,4}, previous studies have mainly discussed offspring vulnerability in terms of odds ratios or relative risk. As a high relative risk can be negligible when the absolute risk is low⁵, it is important that researchers also provide information on absolute risk and discuss their findings. This information is essential to make well-informed clinical and policy decisions.

Our cohort of offspring may not be representative of the population of offspring of patients who receive specialized treatment. Not all families approached take part in the ARIADNE study which may have affected the representativeness of the sample. For example, research suggest that parents who feel overburdened more often decline to participate in research.⁶ This factor is likely to be related to lower levels of family functioning and the presence of two affected parents in a family. It is therefore possible that families with these characteristics are underrepresented in our sample which may have led to an underestimation of offspring risk. On the other hand, female offspring were slightly overrepresented in our offspring cohort which may have resulted in overestimation of risk. In addition, one should bear in mind that our sample consists of offspring of treatment-seeking depressed/anxious patients. The risk estimates presented above can therefore not automatically be extrapolated to all offspring exposed to parental depression/anxiety. It is conceivable that the parents in our sample were relatively severely affected^{7,8} which may be associated with increased offspring risk.⁹⁻¹¹ It has, however, not previously been tested whether method of recruitment influences risk rates of psychopathology in offspring.⁴ A precise comparison of our cumulative risk

estimates with those found in similar longitudinal community studies^{12,13} cannot be carried out, mainly due to different approaches (i.e., trans-diagnostic versus disorder-specific). In any event, a rough comparison suggests that estimates of offspring risk in these studies are similar rather than lower.^{12,13} We tentatively conclude that our study does not markedly overestimate offspring risk for mood/anxiety disorder.

Another issue the reader should be aware of is that this study focuses on the intergenerational transmission of mood/anxiety disorders, in other words, on whether children develop problems similar to those of their parents. It is likely that offspring face other (additional) psychiatric or other problems that were not assessed in our study.¹⁴⁻¹⁶ A comprehensive review¹⁶ suggests that this may be especially true for offspring of parents with depression: they were found to be at risk of a broad spectrum of problems (e.g., depression, anxiety, conduct disorder) while studies on offspring of parents with anxiety indicated higher rates of offspring anxiety disorder, but not of other disorders. A recent study in younger children (age 5 years) found that children exposed to parental common mental disorder appear to be at elevated risk not only of anxiety, but also of aggressive, hyperactive and inattentive behavior.¹⁴ A study in adults considering a wide range of psychiatric disorders in both parents and offspring indicate that parental mood disorder as well as parental anxiety is associated with a broad spectrum of offspring problems (e.g., depression, panic disorder, antisocial personality disorder).¹⁵ For the present study these results imply that, considering the broad array of psychiatric diagnostic outcomes, offspring risk is likely to be higher than presented.

We found that a parental history of depression/anxiety is also a risk factor for the onset of depression/anxiety in adulthood (Chapter 4). This suggests that the influence of a parental history is not limited to the first two decades of life. Previous research has consistently demonstrated that subclinical states often precede the development of full-blown episodes.¹⁷⁻²⁰ Our study, taking parental history into account, shows that the presence of subclinical symptoms should be considered as the more powerful marker among the clinical variables that were investigated. Nowadays several indicated preventive interventions exist that could be helpful for adults already showing symptoms.²¹⁻²⁵ Notably, these indicated interventions do not explicitly address the family context, in contrast with selective preventive interventions specifically developed for children and adolescents with affected parents. A parental history of depression/anxiety is likely to be present in a substantial subset of adults with subclinical symptoms. Whether this subgroup may benefit from family-contextual components added to these interventions (e.g., issues related to growing up with a depressed/anxious parent) is yet unclear, and certainly is an interesting question to address in future research.

A parental history in persons with depressive/anxiety disorders

ARIADNE studies the offspring of depressed/anxious patients taking the parent as its starting point which is referred to as the 'top-down' or 'high-risk' approach.^{26,27} Studies starting with depressed/anxious persons and examining rates of psychiatric disorders in their parents

or other relatives (i.e., ‘bottom-up’ approach) also show evidence that depressive/anxiety disorders run in families.²⁸⁻³⁰ Although the studies in this thesis do not apply this latter approach, they provide some indications in support of the previous findings. Chapter 4 shows clear differences in the proportions of parental history in persons who never had a depressive/anxiety disorder (45.6%), persons with a remitted depressive/anxiety disorder (65.3%) and persons with a current depressive/anxiety disorder (71.4%). In Chapter 5, we describe the six-year course of depression/anxiety in offspring with a parental history of depression/anxiety. We also select a comparison group of young adults with a lifetime depressive/anxiety disorder but without a parental history of these conditions. This comparison group, however, turned out to be relatively small (i.e., 25% reported no parental history). Perhaps not surprisingly since it aligns with studies on child-onset and adolescent-onset depression reporting that the vast majority has affected parents.^{31,32} Together, these findings indicate that a substantial number of depressed/anxious persons grow up in families where a parent has depression/anxiety. This familial aggregation should receive clinical attention.

Risk and protective factors influencing the onset of mood/anxiety disorders in offspring

It is important to state that not all offspring of depressed/anxious patients will experience negative outcomes.^{33,34} Chapter 2 indicates that mood/anxiety episodes occur in many, but not all, offspring. Offspring risk probably varies. We therefore investigated whether psychiatric characteristics, family context and offspring characteristics contribute to individual differences in offspring risk for mood/anxiety disorders. A female preponderance in mood/anxiety disorder was observed in our high-risk sample which concurs with what is consistently found in population-based samples.³⁵⁻³⁷ Substantial efforts have been made to unravel the underlying mechanisms of this heightened risk in females, but exact determinants remain speculative.^{38,39} Although this was not addressed in this thesis, gender differences in pubertal development, coping styles, social roles and childhood adversity are potential candidates³⁸ which need to be addressed by future research. Other important factors independently contributing to individual differences in offspring risk were parental age of onset and so called ‘familial loading’: we found children of parents who reported a disorder onset before the age of twenty and children with two affected parents to be at increased risk for mood/anxiety disorders which is in line with results of two longitudinal studies.^{40,41} This finding may be explained by the increased genetic and environmental risk associated with these features which may reinforce one another.

In terms of possible protective factors, balanced family functioning was found to diminish offspring risk for future mood/anxiety episodes. Results of a 20-year follow-up study of offspring of treatment-seeking depressed patients shows a marginally significant association between low family cohesion and depression in offspring.⁴² Interestingly, this study also shows that family discord factors do not have added predictive value above parental depression only, in predicting depression and anxiety in offspring. This would suggest that when it comes to identifying persons vulnerable developing these conditions in the future, parental depression

is the better marker, but this needs more research. Our samples were not suitable to clarify this issue: the ARIADNE sample does not include a control group of offspring without affected parents while the NESDA sample has no measure of family functioning. Nevertheless, our findings indicate the importance of strengthening family functioning as target of preventive or treatment interventions in offspring.

The association between parental gender, familial loading and the onset of mood/anxiety disorders in offspring

In our high-risk sample we found no evidence of differential effects of mothers versus fathers on the onset of mood/anxiety in offspring (Chapter 2, 3). These findings accord with recent longitudinal^{43,44} and cross-sectional work¹⁴ as well as with a meta-analysis⁴⁵ showing that maternal as well as paternal depression/anxiety are associated with depression/anxiety and that parents' gender seems to have little or no effect. So all in all, there is little evidence to substantiate the claim of differential effects of mothers versus fathers on offspring risk for a mood/anxiety disorder. Note, however, that this conclusion does not preclude the possibility that, for example, same sex dyads (e.g., mother-daughter) have specific influences.^{e.g.46}

Related to this, we found that offspring with two affected parents were at increased risk of developing a mood/anxiety disorder. A similar study shows that offspring risk for depression more than doubled when both parents are affected (i.e., interaction effect).⁴¹ As suggested by the authors, an explanation could be that in these families there is no second parent who may (partly) take a compensatory role buffering negative effects associated with the other parent's depression.⁴¹ We were not able to examine interaction effects in our high-risk sample since healthy comparison parents were not included in our study. In response to our letter (Chapter 3), Lewis and colleagues⁴⁷ addressed this question in two large prospective population-based studies in adolescents. Contrary to the study mentioned above⁴¹, these results support an independent, additive relationship between paternal and maternal depressive symptoms.⁴⁷ Similar additive effects were reported earlier with regard to adolescent functioning.⁴⁸ These results indicate that the combined effects of paternal and maternal depressive symptoms do not escalate into a more than doubled risk for offspring. Nevertheless, it is clear that in clinical practice as well as in future research the mental health of both parents should be taken into account. Especially, since marital resemblance appears to be more common among persons with psychiatric disorders⁴⁹⁻⁵¹, probably mainly due to assortative mating.⁵¹

The association between parental history and the course of depression/anxiety in offspring

Depressive and anxiety disorders tend to run a recurrent or chronic course.⁵²⁻⁵⁴ Unlike the onset of these conditions, research is inconclusive as to whether parental depression/anxiety also predicts a less favorable disorder course.^{13,32,55-58} Notably, a parental (or family) history was not considered in the vast majority of studies examining putative predictors of course outcomes in depressed/anxious persons.⁵⁹⁻⁶¹ In our nine-year prospective study we found a

parental history of depression/anxiety to increase the risk for recurrence in adults with a remitted depressive/anxiety disorder at baseline (Chapter 4). This association was independent of clinical and treatment factors in our model, in line with previous studies.^{55,62,63} A parental history also emerge as risk factor for the most persistent forms of depression/anxiety, but the earlier age of onset typical for persons with a parental history⁶⁴⁻⁶⁶ predominantly contributed to this association. In a similar longitudinal study in adults over 18 a family history was not found to be related to persistent depression.⁶⁷ This study did not address chronicity, however, given a much shorter follow-up period (i.e., three years) than our study. Prospective studies in younger samples^{55,56} find that parental history is related to chronicity. The potential role of age of onset in this association is, however, not considered and therefore remains unclear, although age of onset would show less variation in young samples. Contrary to our findings in Chapter 4, the results presented in Chapter 5 do not corroborate the premise that a parental history may signal a less favorable disorder course. In this chapter, we compare the six-year course in depressed/anxious persons with a parental history with the course in persons without a parental history. Notably, the small sample size of the latter limits our ability to draw strong conclusions.

The long-term course in offspring with a history of depression/anxiety

The onset of depression/anxiety in offspring is often used as endpoint in existing studies on families living with parental depression/anxiety. Far less is known about how these offspring fare after onset of a depressive/anxiety disorder. In general terms, it has been stated that research on depression/anxiety should include repeated follow-up measurements to capture the fluctuating course typical of these diseases.^{8,68} In our six-year follow-up study we found that 59% of young adult offspring with a history of depression/anxiety also suffered from these conditions during follow-up. The remaining 41% of offspring did not. This suggests that stable recovery is possible, at least when defined as not fulfilling the diagnostic criteria anymore. Appropriate comparison of these rates with those found in other studies is difficult due to heterogeneous methodology. Longer recall periods between assessments^{69,70} and using a sample of early-onset cases⁷¹ could be explanations for the lower respectively higher recurrence rates found in other samples. Furthermore, variability in symptom severity and disability was found in offspring who suffered from depression/anxiety during follow-up as well as in offspring who recovered. This supports previous work performed in non-high risk samples stating that syndromal recovery does not necessarily coincide with restoration of psychosocial functioning.⁷²⁻⁷⁴ It is, therefore, important to evaluate functioning when assessing the effectiveness of preventive or therapeutic interventions for depression/anxiety in clinical practice as well as for research purposes.

Mechanisms of risk transmission

Although this was not directly addressed in this thesis, our findings warrant discussion of mechanisms underlying offspring vulnerability.⁷⁵⁻⁷⁸ Genetic factors may contribute to

increased vulnerability through biological processes.⁷⁹ But also the degree of exposure to risky environments and sensitivity to environmental risk may be partially genetically determined.⁸⁰ Furthermore, children of depressed/anxious parents are more often confronted with maladaptive behavior and cognitions associated with parental illness which is another possible way through which parental disorder exerts its effects on offspring. Finally, children of depressed/anxious parents are more likely grow up under conditions of stress and adversity (e.g., marital problems, poverty) which may predispose them to developing depressive/anxiety disorder. A recent study based on the national Swedish population register found parental genetic factors and rearing influences to affect offspring risk of depressive disorder to an approximately equal degree.⁸¹ However, such splits are rough approximations, as the environment that parents create for their children covaries with parental genes, which are only partly transmitted to their children.⁸² Furthermore, environmental effects possibly interact with genetic vulnerability in the transmission of depressive/anxiety disorders from parent to offspring.^{83,84} These examples show how tightly genetic and environmental mechanisms are entangled. Notably, the field of epigenetics is quickly growing and has provide insights to epigenetic processes in psychiatric disorders. Results should, however, be interpreted with caution as replication of findings is generally lacking.⁸⁵

With regard to the clinical course, rather than onset per se, it is suggested that different processes may be involved.^{57,59,86} Our findings may support this: we found different factors contributing to the impact of parental depression/anxiety on the onset, recurrence and persistence of depression/anxiety (Chapter 4). It should be emphasized that causal factors involved in the association between parental depression/anxiety and offspring risk are far from clear and further work is required. Such knowledge is needed to optimize prevention and treatment strategies.

Prevention programs

To prevent the intergenerational transmission of psychiatric disorders in offspring, several prevention programs have been developed in different countries in the world.⁸⁷ In Chapter 6 we identified studies testing the efficacy of prevention programs in children of parents with mood/anxiety disorders in particular. These studies report on seven unique prevention programs. All of them were delivered face-to-face and contain a psychoeducational element which is in line with previous findings on prevention programs in children of parents with mental disorders in general.^{88,89} Family-focused programs address family environmental factors thought to be linked to the intergenerational transmission of mood/anxiety disorders^{77,78} while in offspring-focused programs cognitive restructuring techniques were a central component. Our meta-analysis reveals that prevention programs reduce the onset of depression/anxiety in offspring and relieve symptoms. So it seems possible to prevent the onset of depression/anxiety in offspring or at least delay it. However, we still know little about which intervention components are critical in producing these positive outcomes as programs have been evaluated as a whole. Moreover, published papers sometimes contain incomplete

program descriptions, a problem noticed in the broader field of health sciences⁹⁰⁻⁹², which can hamper translation into clinical practice. Another issue of concern is that families with a mental illness appear to be difficult to engage in prevention activities.^{6,93} This was why a closer look was taken at the recruitment process in the studies included in our review. Most studies recruited participants via mental health clinics, media outlets, and clinicians with the latter likely to be the most successful approach. This accords with findings from a qualitative study showing that depressed/anxious parents were more willing to participate in a prevention study with their offspring when a therapist was involved.⁶ A few studies indicate that they experienced recruitment problems, but, like findings on recruitment approaches, we could not draw firm conclusions on this issue since not all studies provided sufficient information on the recruitment process. It therefore remains unclear to what extent sampling biases that may limit real-world utility of such programs exist in these studies. Our findings highlight the importance of adequately reporting on the content of prevention programs (e.g., using the TIDieR checklist), of providing a detailed description of recruitment approaches and problems experienced and of sharing program manuals. This would contribute to a solid basis for future investigation and will promote the uptake of research findings into clinical practice.

Help-seeking in offspring with a mood/anxiety disorder

Despite the high prevalence of psychiatric disorders in offspring of affected parents only few studies reported on treatment-seeking in this subgroup. Previous studies do not report on the time to initial help-seeking, an approach already embraced in studies of offspring samples.^{e.g.94-96} This outcome is highly relevant as prompt help-seeking is related to better treatment response.⁹⁷⁻¹⁰⁰ Chapter 7 addresses this issue and shows that an estimated 92% of offspring with a mood/anxiety disorder eventually contact a professional, but about a third of them delays help-seeking for more than two years after its first manifestation. These estimates are broadly comparable to those found in a Dutch community sample of adolescents¹⁰¹, and should be seen in the context of the Dutch health care system where help-seeking rates are found to be relatively high in comparison to other countries.⁹⁴ In addition, one should bear in mind the specific characteristics of our high-risk sample, that is all offspring have a parent with depression/anxiety, moreover, these parents all received treatment. Both factors may, possibly even additively¹⁰², increase the likelihood of help-seeking.^{13,103,104} In line with studies in non-offspring samples^{e.g.94,105}, we conclude that the main problem is not the failure to seek help, but the tendency to wait for a considerable period of time before seeking treatment. Promoting timely help-seeking should thus be the focus of attention.

Chapter 7 also sheds light on subgroups among whom help-seeking delays are more prevalent. First, the time to initial help-seeking is found to be longer in males than in females which may relate to gender differences in expressing and sharing emotions that for men act as barrier to help-seeking.^{106,107} A second and third subgroup are offspring with a childhood-onset or an anxiety disorder. Previous investigators^{95,108} suggest that, in children, the initiative for seeking help lies with the parent or another adult who may not recognize

internalizing problems. It could also be argued¹⁰⁸ that it takes a relatively long time to self-recognize symptoms because they already appeared at young ages, which may act as barrier to help-seeking. Anxiety disorders may (initially) be perceived as less impairing compared to mood disorders^{72,109}, which may be a reason to postpone help-seeking. The predictors of initial-help seeking identified in our study are broadly in line with those found in community studies.^{e.g.94,96,101}

This suggests that, apart from their ‘at risk status’, factors generally playing a role in help-seeking may not be different for offspring characterized by parental depression/anxiety. Notably, we did not take into account parents’ previous experiences with health care, which may contribute to individual differences in help-seeking.¹¹⁰ We also examined whether offspring with mood/anxiety disorders enter secondary care and show that this is the case for about one third of offspring. A lower IQ, lower SES or comorbid mood and anxiety are relevant in predicting secondary care entrance. We find these patterns to be roughly similar to those found in the previously mentioned community sample of Dutch adolescents based on the same administrative health care data.⁹⁴

As depressive/anxiety symptoms can resolve with time, immediate help-seeking may not be necessary. The question, which was also raised by previous investigators^{e.g.94,95,111}, is whether help-seeking delays could be considered clinically relevant. Based on our own and previous findings, our answer is: yes. Our study indicates that offspring mental health problems apparently persist or reach a level at which offspring eventually perceive a need to contact a professional. The relevance of timely help-seeking is also apparent from studies demonstrating that even subthreshold forms of mood/anxiety disorder impact quality of life and symptoms easily can get worse.^{18,20,112,113} Furthermore, help-seeking delays are also seen in persons who were very severely affected.¹¹¹ Lastly, higher pre-treatment severity and a longer duration of untreated illness have been associated with a lack of treatment response and a less favorable clinical course.^{98,99,114,115} Efforts to promote timely help-seeking are therefore worthwhile, with a special focus on subgroups with long help-seeking delays.

METHODOLOGICAL CONSIDERATIONS

Several strengths and limitations of the studies included in this thesis have already been addressed in the previous chapters. In this section, the most important general methodological issues will be discussed.

The ARIADNE sample consists of 523 offspring (baseline age 13-25 years) of 366 patients who had received specialized treatment for depressive and/or anxiety disorder. Investigating the onset and course of mood/anxiety disorders and help-seeking in such a sample is of high relevance since adult mental health care provides a unique point of departure for identification and intervention aimed at children’s wellbeing.¹¹⁶ On the other hand, as we previously discussed, recruitment via mental health care facilities may limit generalizability of findings as not all depressed/anxious persons receive treatment.^{3,117} The offspring in our

study may therefore not be representative of the entire population of offspring with parental depression/anxiety.

In the present thesis we took a trans-diagnostic rather than a disorder-specific approach by grouping parental and offspring mood and anxiety disorders together into one broad category. As substantial comorbidity rates exist between mood and anxiety disorders as well as within these subcategories^{118,119} (e.g., anxiety-anxiety comorbidity) we adopted this method to increase generalizability of findings. Our own data on parental as well as offspring diagnosis support this notion of high comorbidity (Chapter 2). The downside of this method is that we do not provide a detailed picture on the intergenerational transmission of specific disorders, but in our opinion this not does outweigh the benefits of the approach we have chosen.

A major strength of this study is that diagnostic information was ascertained prospectively over multiple assessments, but baseline information may still have been biased by failure to recall past mood/anxiety episodes. Reporting of mood/anxiety episodes appeared to diminish with time¹²⁰⁻¹²³, whereby especially milder and untreated episodes may have been missed.^{124,125} The cumulative incidence of offspring mood/anxiety disorder may therefore be slightly higher than presented in Chapter 2. The same applies to age of onset and age of first help-seeking reports gathered at baseline which may be less precise. Notably, problems related to recall bias are probably tempered in our study since offspring age at baseline was relatively young.

Our study is among the largest long-term follow-up studies of offspring of depressed/anxious patients worldwide, with more than 200 offspring having been followed for more than 10 years now. A major issue of concern is that about half of the original offspring cohort dropped out in the process between the ARIADNE and NESDA study. As previously stated, due to medical ethical regulations the ARIADNE study had to be officially terminated and only afterwards could offspring be approached again to ask if they were willing to participate in the NESDA study. This was an important reason for the high dropout rates. In Chapter 2 we find that male gender, lower occupational level, lower educational level and lower IQ are negatively related to follow-up duration (i.e., age at last interview), indicating underrepresentation of these groups. These are well-known factors related to loss of follow-up in longitudinal studies.¹²⁶⁻¹²⁹ Results may be less generalizable to these groups.

In the NESDA sample a younger age, fewer years of education, not being of North European descent, having been recruited in Amsterdam and no previous participation in research were related to attrition at two-year follow-up.¹³⁰ Among the psychiatric characteristics examined, persons with a major depressive disorder, and in particular those with a comorbid depressive/anxiety disorder and higher symptom severity were underrepresented in the two-year assessment.¹³⁰ Importantly, it should be borne in mind that the NESDA study is characterized by a relatively low attrition rate.¹³⁰

A major strength of the ARIADNE study is the accuracy of the data collected regarding the presence of parental depressive/anxiety disorder: parents were recruited via

mental health care facilities because they had received treatment for these conditions and, in addition, they were interviewed about their own psychopathology (direct report) by means of a standardized psychiatric interview referred to as the “family study method”. Whether the other biological parent had a history of depression/anxiety was, however, reported by the index parent (indirect report) which is referred to as the “family history method”. Apart from the fact that self-report is preferable, an important limitation of this commonly used method is that respondents who suffer from a psychiatric disorder are more likely to report the same disorder to be present in their relatives.^{131,132} This is more of an issue in the NESDA study in which data on parental history of depression/anxiety are entirely based on indirect report of NESDA participants. Information regarding the psychiatric status of family members is thus influenced by informant’s own psychiatric history and overestimation of the degree of familial aggregation is a possible consequence.

Although extensive information on parental mental health is available for offspring of the ARIADNE cohort, these data do not provide us with a detailed picture of the timing of parental depressive/anxiety episodes. Most studies suggest that negative developmental effects of parental depression are largest early in life^{76,133}, but not all studies support the notion of timing effects^{e.g.10}. Timing of exposure to parental depression/anxiety as potential moderator merits further investigation in future studies. Addressing this question requires longitudinal study designs assessing both parents and children at regular intervals in order to precisely map if the patterns of exposure influence child development.

Most instruments used in the studies presented in this thesis have good psychometric properties in terms of reliability and validity (e.g., CIDI, BAI, IQ). For some constructs, however, single-item questions are used as indicator (e.g., parentification, suicidal ideation). Although in clinical practice such simple questions may be an attractive alternative to multi-item questionnaires (e.g., efficient, easy to implement), it has not yet been investigated if these questions are sufficient for representing the intended constructs. We can therefore not rule out that the lack of predictive power of, for example parentification, is due to this.

CLINICAL IMPLICATIONS

This thesis shows that it is more likely than not that offspring of depressed/anxious patients will develop a similar condition at some point in their life. And once affected, a parental history of depression/anxiety may be an indicator for a less favorable disorder course. These findings, together with the very large numbers of children growing up in a family with an affected parent¹³⁴, highlight the need for large-scale preventive and treatment efforts aiming to, ideally, prevent that depressive/anxiety disorders pass from one generation to the next. As most offspring experience their first episode at some point during adolescence or in young adulthood these efforts should start early in life.

How to reach offspring and their families?

One of the challenges in implementing preventive and treatment measures on any scale is to determine how the target group can be reached. Firstly, professionals working with depressed/anxious adults (e.g., psychiatrists, social workers, general practitioners) are in the position to identify these offspring via the parent. Secondly, professionals working with children and adolescents (e.g., youth care professionals, child psychologists) could play an important role here. Please note that these professionals have a less clear starting point than those serving depressed/anxious adults: in the case of the former the mental health status of parents is often unknown. The Dutch COPMIA guideline¹³⁵ (Children of Parents with Mental Illness and or Addiction; in Dutch: Richtlijn Kinderen van Ouders met Psychische Problemen) is developed to assist professionals working in youth mental health care services in the identification and intervention with families in which a parent has a mental illness. This guideline can also be useful for other professionals working with children. We recommend extra efforts to improve the implementation of this guideline as far too few professionals apply this directive.¹³⁶ Lastly, informal networks - whether or not in cooperation with professionals - can be of great value for persons with mental health problems and their families, for example friends, relatives and neighbors (see for a further elaboration on this topic¹³⁷).

In the next section, we will primarily discuss implications for adult mental health care given the unique position these professionals have in making significant contributions to offspring's mental health. Moreover, the sample of offspring on which the results of this thesis are mainly based was recruited via adult mental health care.

Parent's contacts with mental health care as a window of opportunity for prevention and treatment in offspring

As also emphasized by others^{e.g.116,138}, a parent's entry into adult mental health care represents a unique, but yet highly underutilized, point of departure for identification and intervention aimed at children's wellbeing. In the Netherlands, the Child Check obligates professionals to inquire whether a patient has children and could provide a starting point for recognizing the needs of children of parents with mental illness.

Although parental interventions were not explicitly addressed in this thesis, we believe that the parent is the key to prevention of mood/anxiety disorders in offspring. In addition to adequate treatment of parental disorder^{9,11,139}, we therefore recommend to address parenting - an important mechanism through which parental depression/anxiety exerts its influence on offspring - as standard part of treatment. When evaluating the extent to which depression/anxiety impacts a patient's functioning in the various social roles (e.g., work, relationships), patient's role as parent should always be considered. Parenting is a sensitive topic to discuss and professionals emphasize they need additional knowledge and skills to carry out such conversations.^{140,141} 'Parenting with Success and Satisfaction' (PARSS) (in Dutch: Ouderschap met Succes en Tevredenheid) comprises a comprehensive method to support patient's rehabilitation goals in the area of parenting.¹⁴² Parenting as a focus of

recovery practice may not only benefit child's but also parental well-being¹⁴³, but this field is still in its infancy and efforts should be made to further strengthen the evidence base of such approaches.¹⁴³ Parents could additionally be offered less intensive (anonymous online) opportunities specifically designed for parents with a mental illness where they can be helped to fulfill their parenting role.^{e.g.144} Importantly, addressing parenting issues within treatment appears to fulfill a need of most parents.¹⁴²

Moreover, it is important that professionals gain insight into children's and families' well-being, strengths, vulnerabilities and needs so that they can discuss appropriate support opportunities with parents (and other family members). They should be aware that, regardless of their level of risk, many may benefit from support. Findings of the present thesis indicate that specific attention should be given to the strengthening of family functioning (Chapter 2). Our findings further emphasize the importance of taking into account both parents' mental health given that depression/anxiety in mothers as well as in fathers influence offspring well-being, probably to an equal extent (Chapter 2, 3). The characteristics found in Chapter 2 may aid professionals to identify offspring that are most likely to be in need of (preventive) support. For offspring already experiencing serious signs and symptoms, it is vital that they are identified as such, and that they receive adequate and timely care for their problems. Encouraging timely help-seeking is then the best possible advice. This is particularly relevant for male offspring, offspring with both depressive and anxiety symptoms and offspring with a symptom onset early in life: groups we find to wait a considerable amount of time before seeking help (Chapter 7). Furthermore, one should bear in mind that families in which a parent has depression/anxiety or another mental illness may be difficult to engage in prevention activities^{6,93} (see also Chapter 6). It is important that professionals are aware of possible barriers that prevent parents from talking about parenthood and the well-being of their children and how these barriers may be addressed (see a recently published paper of our own group¹⁴¹ for an overview of common barriers and possible remedies). Examples of such barriers include reluctance to bother offspring, feelings of shame and stigma and, overload of the parent.^{6,93}

One type of preventive interventions that can be offered or referred to are the offspring-focused and family-focused prevention programs specifically developed for offspring of parents with a mood/anxiety disorder (Chapter 6). They show promise in preventing new mood/anxiety episodes in offspring. However, in the Netherlands, as well as in other countries, these interventions appear to have limited reach.¹⁴⁵ It could for example be that these programs insufficiently align with the needs of this population. Further research is needed to gain insight into the reasons why before large-scale implementation of such programs should be initiated. Notably, these programs should be viewed as one of the many options to consider. As risk and needs vary widely among offspring and families, it is of great importance to offer a variety of interventions and to select those interventions that best fit individual needs. The SIK-list (Screening en Interventie Keuze Lijst) can assist professionals in this process.

Moving toward a family-focused approach

Identifying and responding to the needs of children and families in this respect is, however, not yet common practice in adult mental health care. An important reason for this is that an individual deficit approach is paramount, rather than providing family-focused care, acknowledging the pivotal role of the family.^{e.g.116,146,147} More specifically, commonly encountered barriers are concerns that talking about parenting and child's well-being may have a deleterious effect on the therapeutic alliance, or professionals feeling they have insufficient knowledge, skills or time to work with families, and a lack of (knowledge of) appropriate referral options.^{116,148-150} From the results of the present thesis it is evident that expanding efforts to carefully integrate family-focused practices in adult mental health care is highly desirable. This requires changes at organizational level (e.g., supportive resources, organizational culture, policies, procedures) as well as workplace training to equip professionals with the necessary knowledge and skills. In our University Center of Psychiatry the first steps toward embedding a family-focused approach have been taken and are described in a recently published paper.¹⁴¹ Notably, a generic COPMIA module (in Dutch: generieke module KOPP/KVO) is currently being developed and will be added to all Multidisciplinary Guidelines in Dutch mental health care in 2019. We are looking forward to the publication of this module and recommend to carefully monitor its implementation. We further advocate to incorporate education on family-focused practice into the curriculum of psychiatrists, psychologists, nurses and social workers as these students will constitute the mental health care workforce in future.

Family-focused practice within adult mental health care is not enough

Successful implementation of family-focused practices within adult mental health care services would be an important step forward, but additional measures are needed to address intergenerational risks to offspring's mental health.¹⁵¹ A broader approach to prevention and treatment of depression/anxiety - with families with parental depression/anxiety representing an important target group - is essential to lower the incidence and prevalence of these disabling conditions in the population, and so to help interrupting the cycle of intergenerational transmission. Important elements of such an approach are strategies to improve mental health literacy, to reduce stigma and to promote mental health and well-being in schools.

DIRECTIONS FOR FUTURE RESEARCH

Several potential future research questions have already been pointed out throughout this thesis. In this section we discuss the key research areas that would merit further investigation.

Chapter 2 focuses on the onset of mood/anxiety disorders in the context of parental depression/anxiety. Nonetheless, and this should be emphasized, there are also offspring who report to have acquired strengths (e.g., empathy, maturity)¹⁵² or who appear to have successfully adapted, despite experiencing parental depression/anxiety.^{33,153,154} Although some recent longitudinal work has focused on contributors to resilient outcomes^{33,153} (e.g., maintained healthy functioning in daily life, absence of mental illness, despite high-risk status), past studies have primarily focused on risk processes. Further prospective studies should be undertaken to improve our understanding of resilience promoting factors in offspring. Such studies may provide possible novel targets for preventive interventions. Level of social support, participation in leisure activities and having someone to talk to outside the family are examples of factors that received little attention so far, but certainly merit further investigation.

Prevention programs for offspring of parents with depressive/anxiety disorder have shown promise in reducing the onset of depressive/anxiety disorder in offspring. It is, however, still unclear if specific intervention ingredients are responsible for these positive results. To improve the effectiveness of prevention programs it is crucial to achieve a better understanding of the essential intervention components. This information can be used to optimize existing preventive interventions and design new approaches. This is an important area for further study.

An issue of concern is the limited reach of prevention programs.^{6,93} Future research is needed to gain insight into the reasons why only a small fraction of eligible families participate in these programs. This information may guide further research and/or implementation. Since online support opportunities offer the possibility to enhance reach, potentially have lower costs and appear to align with the needs of offspring¹⁵⁵, it may be worthwhile to develop and rigorously evaluate such online support opportunities. The Netherlands is a pioneer in this field^{144,156,157}, and valuable expertise already gained in this field should certainly be used. The development of an online preventive intervention for offspring of parents with a mood disorder is part of the recently started Dutch MARIO project (Mood And Resilience In Offspring).

Even if prevention strategies are implemented on a larger scale, there will always be offspring who develop mental health problems. Findings ways to contribute to long-term recovery in offspring is therefore of high importance. Surprisingly, this is an area that has remained unexplored to a large extent. Prospective longitudinal studies are needed to identify factors that promote recovery in affected offspring. Our findings underline the need to look beyond symptomatic recovery and to also include social and role-functioning outcomes which may be even more relevant from a patient perspective.

As previously argued, professionals working with depressed/anxious adults are in a unique position to recognize and respond to the needs of children and families. Such a family-focused approach has, however, not yet been implemented in everyday clinical practice. Several barriers have been identified that make it difficult to address the needs of children and the patient in his/her role as parent such as practitioners feeling they have insufficient knowledge or not enough time to work with families.^{116,148} Implementation research would provide important information that can help to improve the uptake of family-focused practice within adult mental health care.

CONCLUSION

This thesis shows that there is a considerable risk that children of today's depressed/anxious patients become tomorrow's patients. For a large part of offspring this happens somewhere during secondary school and in young adulthood, at an age in which many important steps in life have to be taken. Once affected, a parental history of depression/anxiety may forebode a less favorable disorder course. Our findings from Chapter 6 indicate that it may be possible to prevent the onset of depression/anxiety in offspring, or at least delay it. And in offspring already suffering from these conditions, help-seeking delays are common and could be improved. All in all, the results of this thesis highlight the need to expand efforts to interrupt the cycle of intergenerational transmission. This requires the development, implementation and evaluation of prevention and treatment strategies. We recommend to start with integrating family-focused practice in adult mental health care. If no further action is taken, the cycle will never be broken.

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