Childhood Depressive Disorders

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The three original papers are

1. Wesselhoeft R, Sørensen MJ, Heiervang ER, Bilenberg N. Subthreshold depression in children and adolescents – a systematic review. Journal of Affective Disorders, July 2013; 151: 7-22.

2. Wesselhoeft R, Pedersen CB, Mortensen PB, Mors O, Bilenberg N. Gender-age interaction observed in incidence rates of childhood emotional disorders. Psychological Medicine 2015; 45: 829-839.

3. Wesselhoeft R, Heiervang ER, Kragh-Sørensen P, Sørensen MJ, Bilenberg N. Major depressive disorder and subthreshold depression in prepubertal children from the Danish National Birth Cohort. Comprehensive Psychiatry 2016; 70: 65-76.

INTRODUCTION

Global Burden of Disease

Major Depressive Disorder (MDD) is a frequent and painful mental disorder with a global point prevalence estimate of 4.7% (Ferrari et al., 2013b). At any point in time in 2010, there were more than 298 million people suffering from MDD globally (Ferrari et al., 2013a). The World Health Organization (WHO) has attempted to quantify the health effects of different diseases and injuries in the Global Burden of Disease study (World Health Organization, 2008). By summing the years of life lost and the years lived with disability due to a given disorder, Disability-adjusted life years (DALYs) are assessed. DALYs is an absolute measure of health loss and subsequently quantifies the disorder's contribution to the Global Burden of Disease. The Global Burden of Disease study (World Health Organization, 2008) as well as a more recent worldwide study (Murray et al., 2012) consider MDD to be among the five leading causes of disability in Europe and North America. Globally, MDD is ranked the 11th leading cause of DALYs, and the condition displays an ascending order in rank (Murray et al., 2012).

Apart from the disability and health loss that MDD represents for the affected individual, it has severe socioeconomic consequences. In Europe, the cost of depression is estimated to comprise 1% of the total economy (gross domestic product) in 2004, making it the most costly brain disorder in Europe (Sobocki et al., 2006). Hence, there are both ethical and financial motives for preventing the development of MDD (Kessler, 2012).

Prevention

Preventive interventions aim to reduce the number of incident (new) cases of disorders, as opposed to treatment interventions that aim to reduce prevalent (current) cases (Mrazek and Haggerty, 1994). Preventive interventions can be directed at either entire populations (universal prevention) or subgroups who are at increased risk for developing mental disorders (indicated or selective prevention) (Mrazek and Haggerty, 1994). Indicated preventive interventions target subjects who present early signs or symptoms of a given disorder but have not reached diagnostic threshold (Mrazek and Haggerty, 1994). Selective preventive interventions target individuals who are at increased risk for a disorder due to biological, psychological or social risk factors (Mrazek and Haggerty, 1994).

Prevention research is challenged by the need for large sample sizes in order to demonstrate an efficacy of particularly universal and selected preventive intervention (Munoz et al., 2010). Therefore, prevention research in depression (and other areas of mental health) focus increasingly on indicated prevention targeting at subjects with a high short-term risk (Munoz et al., 2010).

A literature review finds that 22% to 50% of cases of depression could be prevented each year (Munoz et al., 2010). Another review states that only half of US workers with MDD actually receive treatment, and treatment rates are even lower in developing countries (Kessler, 2012). Hence, there is a large potential for preventing incident cases and also treat prevalent cases of this burdensome and costly condition.

The majority of mental, emotional and behavioural disorders have a childhood or youth onset, which warrants the importance of very early intervention (O'Connell et al., 2009). Interventions aimed at children and adolescents may preferably prevent or else delay the onset of a disorder (O'Connell et al., 2009). A delay of MDD onset is a goal in itself due to the poor prognosis of childhood onset MDD (Korczak and Goldstein, 2009, van Noorden et al., 2011).

Childhood seems to be a window of opportunity for prevention of mental, emotional and behavioural disorders (O'Connell et al., 2009). Supporting this, a Cochrane review examined psychological and educational preventive interventions in childhood and adolescence, and found persisting results of effective prevention of early depression onset (Merry et al., 2011).

Classification

The classification of mental disorders is usually based on either the Diagnostic and Statistical Manual of Mental Disorders (DSM) (American Psychiatric Association) or International Classification of Diseases (ICD) (World Health Organization). The versions available at the moment are DSM-V (American Psychiatric Association, 2013) and ICD-10 (World Health Organization, 2004). For the purpose of this thesis, we used both classification systems; DSM-IV-TR (American Psychiatric Association, 2000) (paper 3) and ICD-10 (World Health Organization, 2004) (paper 2).

A diagnosis of depression is based on three essential components; a certain quantity of depressive symptoms, persistence of symptoms over a given period of time, and significant functional impairment. All three components are required for assignment of a depressive disorder diagnosis in both DSM-IV and ICD-10, but there are important differences described thoroughly in 'Biology of depression' (Gruenberg et al., 2005).

In Denmark the clinical classification of mental disorders is based on the ICD-10 Classification of Mental and Behavioural Disorders: Diagnostic Criteria for Research (ICD-10-DCR) (World Health Organization, 1993). When comparing the DSM-IV-TR Major Depressive Episode and the ICD-10-DCR Depressive Episode, they have eight symptoms in common; depressed mood, loss of interest (anhedonia), decreased energy or increased fatigue, sleep disturbance, appetite and/or weight disturbance, recurrent thoughts of death or suicide, diminished ability to think or concentrate, psychomotor agitation or retardation (Table 1). In addition, ICD-10-DCR has two items; reduced self-esteem and self-confidence, and unreasonable feelings of self-reproach or excessive and inappropriate guilt. In DSM-IV-TR these items are joined in one; feelings of worthlessness or excessive or inappropriate guilt.

	DSM-IV-TR Major Depressive Episode	ICD-10-DCR Depressive Episode
Clinical significance	Symptoms cause clinically significant stress or impairment in social, occupational or other important areas of functioning.	Some difficulty in continuing with ordinary work and social activities, but will probably not cease to function completely in mild depressive episode; considerable difficulty in continuing with social, work or domestic activities in moderate depressive episode; considerable distress or agitation, and unlikely to continue with social, work, or domestic activities, except to a very limited extent in severe depressive episode.
Duration of symptoms	Most of the day, nearly every day for at least 2 weeks.	The depressive episode should last for at least two weeks.
Severity	Five or more of the following symptoms; at least one symptom is either depressed mood or loss of interest or pleasure: (1) Depressed mood1 (2) Loss of interest (3) Significant weight loss or gain or decrease or increase in appetite2 (4) Insomnia or hypersomnia (5) Psychomotor agitation or retardation (6) Fatigue or loss of energy (7) Feelings of worthlessness or excessive or inappropriate guilt (8) Diminished ability to think or concentrate, or indecisiveness (9) Recurrent thoughts of death, recurrent suicidal ideation, or suicide attempt	Most typical symptoms: Depressed mood, loss of interest or pleasure, and decreased energy or increased fatigability Other common symptoms: (1) Diminished ability to think or concentrate (2) Reduced self-esteem and self-confidence (3) Unreasonable feelings of self-reproach or excessive and inappropriate guilt (4) Psychomotor agitation or retardation (5) Recurrent thoughts of death or suicide (6) Sleep disturbance (7) Change in appetite and weight change For mild depressive episode, two of most typical symptoms of depression and a total of at least four symptoms are required. For moderate depressive episode, two of three of most typical symptoms of depression and a total of at least six depressive symptoms are required. For severe depressive episode, all three of the most typical symptoms are present and a total of at least eight depressive symptoms are required. In addition depression can be described with a specifier: 'with somatic symptoms'.
Specific for children and adolescents	1Depressed mood can be replaced by irritable mood. 2Consider failure to make expected weight gains instead of weight loss	

Table 1 Diagnostic criteria for Depressive Episodes; DSM-IV-TR versus ICD-10-DCR

Revised by permission from Alan M. Gruenberg (Gruenberg et al., 2005)

Some symptoms are mandatory (core symptoms) for a depressive episode in both DSM and ICD. In DSM-IV-TR one symptom has to be either depressed mood or anhedonia. In ICD-10-DCR, at least two symptoms have to be either depressed mood, anhedonia or decreased energy/increased fatigue.

Both classification systems require that the symptoms are present simultaneously and persist for at least two weeks. Also, they require that the condition leads to clinical significant impairment, but only DSM-IV-TR has a clinical significance criterion. In ICD-10-DCR the level of impact on work and activities (together with the number of depressive symptoms) determines the type of the specific depressive episode (mild, moderate or severe). Using DSM-IV-TR on the other hand, one initially determines if the criteria for a major depressive episode are present, and then severity is specified (mild, moderate or severe).

Despite these differences between DSM and ICD, the depressive episode criteria show a high level of concordance in adults (DSM-IV vs. ICD-10) (Andrews et al., 1999). The criteria for children and adolescents however, differ on important areas; In the DSM-IV, irritable mood may replace depressed mood for children and adolescents. A Danish study assessing a clinical sample of 199 children with both ICD-10 and DSM-IV depressive episode criteria found that only 75% of children with DSM-IV MDD also fulfilled the criteria for ICD-10 Depressive Episode (Sorensen et al., 2005). The remaining 25% did not meet the ICD-10 requirement of two core symptoms. Only one child (4%) met the ICD-10 criteria but not the DSM-IV criteria, implying that DSM-IV criteria are more inclusive than ICD-10 criteria regarding depression in children.

In conclusion, the classification of mental disorders is characterised by a descriptive categorical approach where a disorder is considered either present or not present. This descriptive method has the advantages of a unified description of phenomenology, and the clear division of individuals into two categories; healthy or ill. The nature of many mental disorders however challenges this dichotomous approach. Some psychiatric disorders (e.g. autism spectrum disorders) seem to have a more dimensional phenomenology, which limits the utility of only two categories. Both classification systems address conditions not fulfilling the criteria for a clinical depressive disorder. DSM-IV-TR includes the following research criteria (provided for further study): Minor Depressive Disorder and Recurrent Brief Depressive Disorder, and the ICD-10 includes Recurrent brief depressive disorder as a distinct diagnosis.

The depressive spectrum

The arguments for a dimensional rather than a categorical approach to depressive disorders are increasing. Cross-sectional (Lewinsohn et al., 2000) as well as longitudinal (Judd et al., 2000, Angst and Merikangas, 1997, Angst et al., 2000) community-based studies in adults support the idea of a depressive spectrum, where subclinical depressive conditions – also called subthreshold depression (SD) - is placed on a continuum of severity with clinical depression. Also, a world wide study concludes that SD is best perceived on a continuum with more severe depressive episodes, based on shared risk factor profile and health status (Ayuso-Mateos et al., 2010).

Support for the continuum hypothesis also comes from adult studies demonstrating that SD carries an elevated risk for development into MDD (Cuijpers, 2004, Shankman et al., 2009, Klein et al., 2009, Fergusson et al., 2005, Angst and Merikangas, 1997). Functional disability is increased in adults with SD although less than in MDD (Cuijpers, 2004, Judd et al., 2000, Rapaport et al., 2002), and health care use and health status is affected; either at

MDD level (Ayuso-Mateos et al., 2010) or somewhat lower (Cuijpers, 2004, Judd et al., 1997, Lewinsohn et al., 2000). It has also been argued that the frequent relapse and fluctuating intensity of symptoms in MDD support a dimensional view (Judd et al., 1997, Kessing, 2007).
In the 1960's the taxometric method, a statistical method for distinguishing categorical and continuous variables, was developed by Paul Meehl and colleagues (Ruscio et al., 2006). The method gained special interest from the field of psychology and psychiatry and includes 13 different statistical procedures that are to be executed in conjunction (Meehl, 1999, Meehl, 1995). A quantitative review of taxometric research in personality and psychopathology finds that dimensional models generally are more liable, also for mood disorders (Haslam et al., 2012). A population-based taxometric analysis of depression in children and adolescents supports this finding of a dimensional latent structure (Hankin et al., 2005).
Existing literature reviews of the nature of SD have so far focused on late adolescence, adults or the elderly (Cuijpers and Smit, 2004, Judd et al., 2002, Meeks et al., 2011) or have not been performed systematically (Kovacs and Lopez-Duran, 2010, Kessler et al., 2001). They demonstrate a lack of consensus regarding criteria used for defining SD, but even so generally support the continuum hypothesis.

Depressive disorders in children

Clinical features

The onset of depressive disorders is not restricted to a certain point in life. There is increasing evidence of the existence of preschool depression (Luby et al., 2003a, Luby et al., 2009a, Luby et al., 2009b), and since the 1980's, there has been solid evidence for childhood onset MDD (Kovacs et al., 1984, Kashani et al., 1981). The clinical features of childhood MDD are markedly similar to that of adulthood MDD (Kovacs, 1996). The same is seen in pre-school MDD, although minor developmental modifications are in place mainly regarding duration (Luby et al., 2003a, Luby et al., 2003b, Gaffrey et al., 2011).
Still, DSM-III-R added irritable mood as a symptom that could replace depressed mood in MDD for children and adolescents (American Psychiatric Association, 1987), in order to enclose developmentally appropriate criteria. This option is maintained in the DSM-IV (American Psychiatric Association, 1995) and DSM-5 (American Psychiatric Association, 2013). Yet, a recent study on a population-based sample of depressed children and adolescents finds that even though irritability is a common symptom of depression, it rarely occurs in the absence of depressed mood (Stringaris et al., 2013). When groups of depressed children with either depressed mood or depressed and irritable mood were compared, they showed the same level of development and depression severity, questioning the importance of the DSM modification (Stringaris et al., 2013).
Likewise, the utility of the symptoms increased weight and appetite included in the criteria for depression have been questioned; A study found that the validity of these symptoms was low for depressive children and adolescents as opposed to decreased weight and appetite, probably because the former symptoms are part of a natural development in children and adolescents (Cole et al., 2012).
Depressive mood and irritability are the most frequent symptoms of depressive disorders in childhood and adolescence (Yorbik et al., 2004, Goodyer and Cooper, 1993, Sihvola et al., 2007), and in preschool age (Luby et al., 2009a). The symptom presentation is highly comparable in depressed children and adolescents, but adolescents are reported to experience more hopelessness, fatigue, hypersomnia and suicidality (Yorbik et al., 2004). The presence of the depressive symptom guilt predicts a longer duration of a depressive episode in children and adolescents (Birmaher et al., 2004).
The symptoms most specific for preschool MDD separating it from other psychiatric disorders in childhood seem to be worthlessness or guilt (Luby et al., 2009a). Anhedonia tends to be a marker of severity in preschool depression (Luby et al., 2003a, Luby et al., 2004), and it increases time to recovery in treatment resistant depressed adolescents (McMakin et al., 2012).

Course and outcome

A literature review of clinical studies states that childhood onset MDD displays high recurrence and more often switches to bipolar disorder than adult onset MDD (Kovacs 1996). In addition, pre-adult onset MDD is associated with more suicidal attempts than adult onset MDD (van Noorden et al., 2011). When comparing the course of illness between subjects with childhood onset MDD and adult onset MDD, the former have longer depressive episodes, more suicidality, and more frequent hospitalization (Korczak and Goldstein, 2009). Comparisons with subjects presenting adolescent onset MDD place them intermediate to childhood and adult onset MDD on these parameters (Korczak and Goldstein, 2009). Latency for treatment is longer for childhood onset MDD than for adult onset MDD (Korczak and Goldstein, 2009). This is consistent with a large study uncovering a general delay in treatment seeking of early onset mental disorders, as well as a lower overall probability of seeking help (Wang et al., 2005).
MDD with childhood onset has similar duration (in average 17 months), recurrence risk and recovery rates of the index depressive episode, as MDD with adolescent onset (Birmaher et al., 2004). However, girls seem to have more recurrent depressive episodes than boys, and there is a trend for them having also longer episodes (Birmaher et al., 2004).

Comorbidity

Comorbid psychiatric disorders are frequent for children with depression (estimated 66% in a large national survey) (Ford et al., 2003), with anxiety disorder, oppositional defiant disorder and conduct disorder being the most common (Ford et al., 2003, Angold et al., 1999, Costello et al., 2006). Comorbid anxiety disorder increases the severity of symptoms in depressed children and adolescents (Axelson and Birmaher, 2001) and any comorbid disorder predicts earlier recurrence (Dunn and Goodyer, 2006). Also, comorbid oppositional defiant disorder or conduct disorder may worsen the outcome (Loeber et al., 2000) or increase functional impairment for the depressed child or adolescent (Kovacs et al., 1988). In adults, MDD with comorbid disorders also lead to more serious outcomes with more distress and more severe and recurrent psychiatric episodes (Merikangas et al., 2003, Cyranowski et al., 2012).
The high co-occurrence of depression and anxiety disorders is probably based on shared genetic vulnerability (Hettema, 2008) and personality traits, rather than shared environmental risk factors (Middeldorp et al., 2005, Franic et al., 2010).

Prevalence

Literature search

In order to identify studies reporting gender-specific prevalence rates of MDD in children and adolescents, a literature search of reviews and meta-analyses was conducted in 2012 (Table 2). An overview of 26 important studies (from the period 1993-2012) originating from the literature search is listed in Table 3. Four

studies examined post-pubertal samples (defined as 12 years or older), seven studies examined pre-pubertal samples, and 15 studies examined samples across puberty (12 reported age-specific analyses). The studies were characterised by variability regarding the use of diagnostic groups and prevalence measures.

((("epidemiology"[Subheading] OR "epidemiology"[All Fields] OR "prevalence"[All Fields] OR "prevalence"[MeSH Terms]) AND ("depressive disorder"[MeSH Terms] OR ("depressive"[All Fields] AND "disorder"[All Fields]) OR "depressive disorder"[All Fields] OR "depression"[All Fields] OR "depression"[MeSH Terms]) AND ("gender identity"[MeSH Terms] OR ("gender"[All Fields] AND "identity"[All Fields]) OR "gender identity"[All Fields] OR "gender"[All Fields])) AND ((Meta-Analysis[ptyp] OR Review[ptyp] OR systematic[sb]) AND ("infant"[MeSH Terms] OR "child"[MeSH Terms] OR "adolescent"[MeSH Terms]))

Search performed September 6th 2012: 101 hits

Table 2 Literature search prevalence studies

Pre-pubertal and post-pubertal prevalence rates

When looking at MDD prevalence rates for samples spanning across puberty, one-year-prevalence estimates ranged between 1.7% (Roberts et al., 2009) and 5.4% (Vicente et al., 2012a), and point prevalence estimates ranged between 0.7% (Ford et al., 2003) and 1.6% (Anselmi et al., 2010) (Table 3). Estimates of 3-6-months-prevalence for any depressive disorder ranged between 1.6% (Breton et al., 1999) and 2.2% (Costello et al., 2003b). Prevalence studies exploring pre-pubertal prevalence rates of depressive disorders are increasing, and 19 studies using quite different prevalence measures were identified. Pre-pubertal MDD one-year-prevalence was estimated in three studies ranging between 1.4% (Merikangas et al., 2010a) and 3.4% (Vicente et al., 2012b). Point prevalence estimates for MDD was examined in three studies showing high variability. One study reported an estimate of 4.6% (Kroes et al., 2001), and two studies using the same instrument reported estimates between 0.07% (Heiervang et al., 2007) and 0.27% (Ford et al., 2003). Point prevalence for any depressive disorder was in four studies ranging between 0.14% (5-7-year-olds) (Ford et al., 2003) and 0.9% (11-year-olds) (Gomez-Beneyto et al., 1994), and one study again reported high estimates of 6.7% for 6-8-year-olds (Kroes et al., 2001). The prevalence estimates of this study are weighted estimates in a study experiencing a low response rate (57.5%) (Kroes et al., 2001). Based on the literature search, 16 studies reporting post-pubertal prevalence rates were identified (Table 3). One-year-prevalence estimates for post-pubertal MDD ranged between 3.2% (12-15-year-olds) (Merikangas et al., 2010a) and 13.8% (15-16-year-olds) (Kessler and Walters, 1998). MDD point prevalence was reported between 1.87% (Ford et al., 2003) and 2.99% (Lewinsohn et al., 1998). Point and 3-6-months prevalence for any depressive disorder after puberty were reported in five studies and ranged between 0.4% (12-year-olds) (Costello et al., 2003b) and 3.1% (16-year-olds) (Costello et al., 2003b). These results are in line with a large-scale study of US adolescents from 2012 (not included in reviews at the time of our literature search) reporting a one-year-prevalence of 8.2% and a one-month-prevalence of 2.6% (Kessler et al., 2012).

Generally, these findings support the view of depression being more frequent after puberty than before (Costello et al., 2011). They are also in line with a systematic review presenting significantly higher odds ratio (OR) for MDD prevalence in adulthood (point prevalence 4.7%) than before the age of 18 years (point prevalence not reported) (Ferrari et al., 2013b).

Author year	Journal	Design and methods	Aims	Prevalence or incidence rates (tot=total, F=female, M=male)	Equal pre-pubertal frequency	Higher pre-pubertal frequency for girls	Higher pre-pubertal frequency for boys	Higher post-pubertal frequency for girls
(Sarkar et al., 2012)	Soc Psychiatry Psychiatr Epidemiol	India, cs, N=1.851/135, mean 10.03y, c-KSADS-screen, t-KSADS	1. prevalence 2. risk factors	Point prevalence: Any D 3.13% MDD 0.81%	No gender difference (p=0.684)			
(Vicente et al., 2012a)	Soc Psychiatry Psychiatr Epidemiol	Chile, cs, N=792, 4-18y, c/p-DISC, c-DISC(>11y)	prevalence	One-year-prevalence: MDDtot 5.4% (1.1) MDDM 2.8% (1.1) MDDF 8.1% (2.3) MDD4-11y 3.3% (1.2) MDD12-18y 7.8% (2.0)		MDD more frequent in girls at all ages		MDD more frequent in girls at all ages
(Vicente et al., 2012b)	Journal Child Psychology Psychiatry	Chile, cs, N=1558, 4-18y, c/p-DISC, c-DISC(>11y)	prevalence	One-year-prevalence: MDDtot 5.1% (0.9) MDDM 3.1% (0.9) MDDF 7.0% (1.0) MDD4-11y 3.4% (1.1) MDD12-18y 6.9% (1.5)	MDDF 3.6% MDDM 3.4%			MDDF 11.1% MDDM 3.0%
(Ballard et al., 2012)	Am J Psychiatry	USA, cs, N=541, 3-6y, p-PAPA, c/p-PAPA	continuity	3-month prevalence: Any D3y 1.3%(0.6-2.0) Any D6y 5.4%(3.7-7.9)	no gender difference			
(Wichstrøm et al., 2012)	Journal Child Psychology Psychiatry	Norway, cs, N=2.475, 4-year-olds, SDQ, PAPA	prevalence	3-month prevalence: MDDtot 0.3% (0.1-0.5) Any Dtot 2.0% (1.6-2.7)	MDDF 0.1% (0-0.6) MDDM 0.4% (0.2-1.0)		Any DF 1.5% (0.5-2.5) Any DM 2.6% (1.6-4.1) Any DOR=1.8 (p=0.04)	
(Merikangas et al., 2010a)	Pediatrics	USA, cs, N=3.042, 8-15y, c/p-DISC	1. prevalence 2. social and demographic correlates	One-year-prevalence: MDDtot 2.4% (0.5) MDD8-11y 1.4% (0.4) MDD12-15y 3.2% (0.7)	MDDF 3.2% (0.7) MDDM 1.6% (0.5) (p=0.06)			
(Merikangas et al., 2010b)	J Am Acad Child Adolesc Psychiatry	US, cs, N=10,123, 13-18y, c-CIDI, p-SAQ	1. prevalence 2. overlap of disorders 3. sociodemographic correlates	Lifetime prevalence: MDDorDOtot 11.7% (0.9) MDDorD13-14y 0.4% (1.3) MDDorD15-16y 12.6% (1.3) MDDorD17-18y 15.4% (1.4)				Lifetime prevalence: MDDorDHF 15.9% (1.3) MDDorDIM 7.7% (0.8)
(Anselmi et al., 2010)	Soc Psychiatry Psychiatr Epidemiol	Brazil, cs, N=4.452, 11-12y, SDQ, DAWBA	prevalence	Point prevalence: MDDtot 1.6% (0.4-3.6)				
(Roberts et al., 2009)	Journal Child Psychology Psychiatry	USA, cs, N=4.175/3.134; 11-17y, c-DISC, p-interviews	1. risk and protective factors 2. prospective study	One-year-prevalence: MDDtot 1.7% (1.3-2.1) One-year incidence: MDDtot 1.4% (0.9-1.8) Any mood11-12y 0.2% (0.2-1.3) Any mood13-15y 2.3% (1.5-3.1) Any mood16-17y 2.7% (1.4-4.0)				MDDOR=4.2 (1.9-9.9) Any DOR=3.0 (1.6-5.6)
				Any D11-12y 0.71% (0.28) Any D13-15y 2.53% (0.32)				
(Kroes et al., 2001)	J Am Acad Child Adolesc Psychiatry	The Netherlands, cs, N=1.317, 6-8y, CBCL, p-DICA	1. prevalence 2. comorbidity	Generalized point prevalence rates: MDDtot 4.6% Any Dtot 6.7%				
(Breton et al., 1999)	Journal Child Psychology Psychiatry	Canada, cs, N=2.400, 6-14y, c/p-DISC	prevalence	6-month prevalence (p-DISC and impairment): Any D6-14y 1.6% (1.1-2.3) AnyDis-by 1.0% AnyD9-11y 1.3% AnyD12-14y 2.7%			NB: pre-pubertal boys have a higher rate of Any D than post-pubertal boys: OR=4.5	(c-DISC): Any D12-14y OR=6.6 (2.1-20.9)
(Almqvist et al., 1999)	Eur Child Adolesc Psychiatry	Finland, cs, N=5.813/4.435, 8-9y, p/t-Rutter questionnaire, CDI, Isle of Wight interview	1. prevalence 2. treatment needs	3-month prevalence: Depressiontot 6.2% (0.02)		DepressionF 4.7% (0.02) DepressionM 7.8% (0.02)		
(Angold et al., 1998)	Psychological Medicine	USA (Great Smoky Mountains Study), cs/hm, N=4.500/1.073, 10-15y, CBCL, CAPA	1. onset of female preponderance 2. pubertal status vs. age 3. pubertal timing vs. stage 4. puberty change vs. level	Girls had higher prevalence rates for MDD, and D-NOS than boys after puberty (Tanner III), while boys had higher prevalence rates before that			Any DOR=0.46 (p=0.02)	Any DOR=2.5 (p=0.04)
(Kessler and Walters, 1998)	Depression and anxiety	USA, cs, N=1.769, 15-24y, m-CIDI	1. prevalence 2. excentine increased relative risk	Reports for 15-16y: Lifetime prevalence: MDDtot 14.6% (2.6) MinorDtot 8.1% (1.7) One-year prevalence: MDDtot 13.0% (2.5) MinorDtot 6.5% (1.6) One-month prevalence: MDDtot 7.0% (1.8) MinorDtot 2.6% (0.9)				Reports for 15-16y: Lifetime prevalence: MDDF 23.4% (4.4) MDDM 5.7% (1.9) One-year prevalence: MDDF 21.5% (4.2) MDDM 4.4% (1.5) One-month prevalence: MDDF 12.4% (3.3) MDDM 1.5% (0.9)
(Lewinsohn et al., 1998)	Clinical Psychology Review	USA (Oregon Adolescent Depression Project), cs, 1.709, 14-18y, c-KSADS, LIFE	1. phenol-menology 2. epidemiology 3. psychosocial characteristics 4. comorbidity 5. assessment 6. treatment	Point prevalence: MDD14-18y 2.9% Lifetime prevalence: MDD14-18y 20.8% One-year incidence: MDDinf 7.8% MDDfirst 7.1%				Point prevalence: MDD14-18yF 3.4%; MDD14-18yM 2.0% Lifetime prevalence: MDD14-18yF 24.0%; MDD14-18yM 11.6% (significance nr)
(Costello et al., 1996)	Arch Gen Psychiatry	USA, cs/hrc, 3.896/1.015, 9/11/13y, CBCL/CAPA	1. developmental pathways 2. prevalence 3. risk factors 3. generalizability	3-month prevalence: MDDtot 0.03% (0.03; cases=5) D-NOStot 1.45% (0.46)				
(Gomez-Beneyto et al., 1994)	Acta Psychiatr Scand	Spain, cs, 1.127, 9/11/15y, CBCL, KSADS	1. prevalence 2. impairment 2. service use	Point prevalence: Any Dtly 8.7% (6.5) Any D11y 0.9% (0.5) Any D15y 2.5% (1.9)			Boys were prevalent over girls for ages 9 and 11	Girls rates were higher at age 15 in all disorders except tics and overanxious disorder!
(Cohen et al., 1993)	Journal Child Psychology Psychiatry	USA, cs, N=776, 10-20y, DISC	prevalence		Prevalence per 100 youths: MDD10-13yF 2.3% (0.9) MDD10-13yM 1.8% (0.8)			Prevalence per 100 youths: MDD14-16yF 7.6% (1.6) MDD14-16yM 1.6% (0.8)
(Fergusson et al., 1993)	J Am Acad Child Adolesc Psychiatry	New Zealand (Christchurch), cs, 961-986, 15y, c/p-DISC	1.prevalence 2. comorbidity 3. treatment	One-year prevalence: MDDorDOtot 6.6%-7.7%				More girls (p<0.001)

Table 3 Overview prevalence studies of childhood and adolescent depression

Abbreviations:

Aff D (affective disorder); Any D (any depressive disorder); Any emotional D (any emotional disorder); Any mood D (any mood disorder); c (child report); CAPA (Child and Adolescent Psychiatric Assessment); CBCL (Child Behavior Checklist); CDI (Children's Depression Inventory); CIDI (Composite International Diagnostic Interview); cl (clinical sample); cs (community sample); DAWBA (Development and well-being assessment); DD (dysthymia); DICA

(Diagnostic interview for Children and Adolescents); DISC (Diagnostic Interview Schedule for Children); D-NOS (depression not otherwise specified); hrc (high risk community); KSADS (Kiddie – Schedule for Affective Disorders and Schizophrenia); LIFE (Longitudinal Interval Follow-up Evaluation); m (modified version); MinorD (minor depression); Other dep (other depression); p (parent report); PAPA (Preschool Age Psychiatric Assessment); SAQ (self administered questionnaire); SDQ (Strengths and Difficulties Questionnaire); t (teacher report); YSR (Youth Self Report)

Gender-specific prevalence rates

The literature search identified 20 studies comparing the prevalence between boys and girls. Overall results regarding gender-specific prevalence rates before and after puberty are listed in Table 3. Six studies did not separate the gender-specific rates according to puberty. Ten studies examined gender-specific prevalence rates before puberty, and 11 studies examined gender-specific rates after puberty.

Six studies reported gender-specific prevalence rates in samples consisting of both children and adolescents (age span 4-18 years). Only one study found a difference between boys and girls, reporting a higher prevalence for girls (statistical significance not reported) (Vicente et al., 2012a).

Of the ten studies comparing male and female pre-pubertal rates, only five reported significance levels. Two studies reported findings for both MDD and any depressive disorder (Wichstrom et al., 2012, Sarkar et al., 2012), leading to twelve results. Six studies compared MDD prevalence estimates; four of them finding no difference between genders. One study found a male preponderance (Almqvist et al., 1999), and one a female preponderance (statistical significance not reported) (Vicente et al., 2012a).

When comparing the prevalence of any depressive disorder, four studies found higher rates for boys, and two studies found no difference between boys and girls.

Gender-specific prevalence rates in children aged 12 years or older were explored in 11 studies; all of them reporting prevalence to be higher for girls than boys. Hence, prevalence studies of adolescent depressive disorder unanimously find a female preponderance (Zahn-Waxler et al., 2008, Thapar et al., 2012, Angold and Worthman, 1993), like also reported for adults (Ferrari et al., 2013b). This is also reported by a large-scale study of US adolescents estimating lifetime prevalence estimates of 15.9% for females and 7.7% for males (Merikangas et al., 2010b). Prior to puberty, on the other hand, there is an inconsistency regarding the gender distribution of depressive disorders. Some literature reviews indicate a 1:1 distribution (Hyde et al., 2008, Naninck et al., 2011), and some indicate either no difference or a minor male preponderance (Cyranowski et al., 2000, Angold et al., 1998).

Risk factors for childhood depressive disorders

Gender/puberty

When children become adolescents the prevalence rates for depression increases for both girls and boys, yet the increase is even higher for girls (Costello et al., 2011). Since the prevalence includes current cases at a given time, this could have three explanations; females have more first time onsets (incidence), they have longer depressive episodes (persistence), or they have more relapse (recurrence). It appears that the main reason for the higher female prevalence is a higher incidence (Kessler, 2003, Essau et al., 2010), although studies also find that women have more recurrent episodes (Essau et al., 2010).

Although the female preponderance of adolescent depressive disorder is a robust finding, the causal pathways are not clear. Rutter et al. propose three possible causal pathways for gender differences in psychopathology: genetic influences, consequences of being genetically male or female, and the liability to experience stressful or protecting environments and the susceptibility towards them (Rutter et al., 2003).

Twin studies support a direct genetic mechanism contributing to the increased risk for depression in adolescent girls (Silberg et al., 1999). In addition, an indirect genetic mechanism is liable, since adolescent girls and women with a family history of depression are more vulnerable to stressful environments than females without a family history (Oldehinkel and Bouma, 2011, Piccinelli and Wilkinson, 2000).

Possible biological causes of the association between female gender and depression after puberty are widely explored (Deecher et al., 2008, Naninck et al., 2011). The rise in prevalence for girls seems to be related to pubertal status rather than age (Angold et al., 1998, Patton et al., 2008) and some studies find an association with early pubertal timing (Essau et al., 2010, Joinson et al., 2011), while others do not (Boden et al., 2011). Many studies find a peak in depression around menopause and a decline after that, underlining the probable influence of gonadal steroid hormones (Deecher et al., 2008, Steiner, 2003).

Gender differences in exposure to stressful or protective environments and the susceptibility towards them is the third possible causal pathway (Rutter et al., 2003). Supporting this, adolescent girls seem to report more stressful life events than boys (Cyranowski et al., 2000), and seem to be more susceptible to them (Oldehinkel and Bouma, 2011, Hankin et al., 2007, Silberg et al., 1999). There also seems to be a difference in what is perceived as stressful environments by girls and boys, with girls being more sensitive to interpersonal events like parental divorce, and boys being more sensitive to events that threaten their position in school or at sports (Oldehinkel and Bouma, 2011). The same picture is seen in adults; women attribute their depression onset mainly to relational problems or illness in the family, while males attribute it to physical illness or problems at work (Angst et al., 2002).

Insecure parental attachment, anxious or inhibited temperament and poor coping skills also add to the risk for developing depression in primarily adolescent girls (Cyranowski et al., 2000), and might reflect 'the consequences of being genetically female', but maybe even more so the 'experienced environment and the susceptibility towards it' as suggested by Rutter et al. (Rutter et al., 2003).

Environmental risk factors

The identification of environmental causes for depression has for many years focused on depression in adults. In the adult literature, environmental risk factors are often divided into childhood maltreatment (Brown et al., 2008b, Uhrlass and Gibb, 2007, Nanni et al., 2012), and more recent stressful life events (SLE) (Kessler, 1997). Alternatively, risk factors are classified as proximal and distal risk factors for adults as well as children, but the definitions used for this are diverging (Brown et al., 2008a, Rutter et al., 2008, World Health, 2002).

A retrospective study of the consequences of childhood maltreatment (defined as; physical and sexual abuse, maternal neglect and antipathy) in women finds that maltreatment increases the risk for adult onset depression but increases the risk for a chronic course even more (Brown et al., 2007, Brown et al., 2008b). Yet, in a large population-based retrospective study of men and women, childhood adversities (12 experiences; including physi-

cal/sexual abuse and maternal neglect) increase the risk for mental disorder onset more than the risk for disorder persistence (McLaughlin et al., 2010a, Green et al., 2010). It also finds that childhood adversities cluster and constitute general risk factors for different mental disorders (Green et al., 2010), and that they predict higher disorder-related impairment (McLaughlin et al., 2010b). Two studies of the literature also draw diverse conclusions; A meta-analysis suggests that childhood maltreatment increases the risk for developing recurrent, persistent and treatment-resistant depressive episodes (Nanni et al., 2012), and a review of prospective studies finds robust evidence of child abuse and neglect leading to depression onset (Weich et al., 2009).
The evidence of a link between childhood maltreatment and adulthood MDD is however quite robust and reduced hippocampal volume is observed in adults who experienced childhood maltreatment (McCrory et al., 2010) as well as in adults with MDD (Videbech and Ravnkilde, 2004). The hypothesis is that the effect of childhood maltreatment on MDD outcome is partly mediated through the hippocampus (Dannlowski et al., 2012), which has also been demonstrated in adolescents (Rao et al., 2010, Whittle et al., 2013).
Childhood adversities seem to contribute more to the onset of childhood mental disorders than to the onset of adolescent and adult disorders. Specifically, parental death, childhood physical illness and economic adversity contribute to childhood but not to later onset disorders (Green et al., 2010). When looking at environmental risk factors for childhood onset mental disorders, the division into childhood maltreatment and SLE is rarely used. Such a division is also unlikely to make sense, while the factors would be co-occurring in a child. Instead, studies exploring risk factors for childhood MDD tend to use the overall term SLE, and when considering timing, divide them into perinatal and later occurring risk factors. Perinatal risk factors for MDD or depressive problems may include prematurity or low birth weight (LBW) (Rice et al., 2007, Nomura et al., 2007, Costello et al., 2007) and exposure to antidepressants (Gentile and Galbally, 2011).
Risk factors may also be divided into child-specific and family-specific factors (Rutter et al., 2008). Several studies suggest that chronic disease constitute child-specific risk factors for emotional problems and MDD in childhood (Hysing et al., 2007, Hysing et al., 2009, Ekinci et al., 2009, Lu et al., 2012, Loftus et al., 2011), like it is also observed for adult MDD (Anderson et al., 2001, Scott et al., 2007, Stegmann et al., 2010).
Family-specific risk factors such as household moving, parental illness or parental hospitalisation seem to contribute to development of early MDD (Mayer et al., 2009). Death of a parent also increases the risk for MDD in childhood (Mayer et al., 2009, Gray et al., 2011) as well as later in life (Laursen et al., 2007). Studies of the consequences of parental divorce display mixed findings;
Some studies indicate that parental divorce or paternal absence increase depressive symptoms in adolescence, particularly for girls (Culpin et al., 2013, Storksen et al., 2005), while others do not (Mayer et al., 2009).
Poverty has for many years been associated with child mental disorders, yet there has been a lack of prospective studies, limiting the knowledge of causal directions (Rutter, 2003). A prospective study shows that poverty increases the risk for conduct problems but not emotional problems in adolescents (Anselmi et al., 2012). This pattern is also seen in a quasi-experimental study, where the opening of a casino lead to sub-groups of families moving out of poverty (Costello et al., 2003a). The study finds that children and adolescents moving out of poverty reduce their risk for conduct and oppositional defiant symptoms but that the level of depression and anxiety symptoms stays the same (Costello et al., 2003a).
Research in environmental resilience factors (protective factors) is far less evolved than research in risk factors. Still, it is a very promising area that could hold a high potential for preventive intervention (Gladstone et al., 2011). Regarding children and adolescents, there are hypotheses of close friendships protecting from developing depressive symptoms (Brendgen et al., 2013) and social support reducing the risk for MDD (Kaufman et al., 2004).

Genetic risk factors

It is well-known that children with a family history of depression have an increased risk for developing MDD (Milne et al., 2009, Hudson et al., 2003, Weissman et al., 2005, Rice et al., 2002), often with an early onset (Weissman et al., 1987, Weissman et al., 2006). There is also growing evidence of a brain-based endophenotype for MDD (Peterson and Weissman, 2011, Dubin et al., 2012) because healthy subjects who have increased risk for MDD due to a family history and subjects with MDD show similar structural cerebral changes.
Furthermore, children with depressed first-degree relatives have a higher risk of developing SD (Lewinsohn et al., 2003) and for MDD recurrence (Weissman et al., 1999) than children without depressed first-degree relatives. A family history of depression also increases the risk for SD converting into MDD (Klein et al., 2009), and a greater number of maternal depressive episodes predicts longer SD or MDD episodes for adolescents (Kaminski and Garber, 2002)
In genetic research there has been a focus on specific genes suspected to have an influence on development of MDD e.g.; the serotonin transporter polymorphism (5-HTTLPR) (Araya et al., 2009, Uher and McGuffin, 2008, Kendler et al., 2005), the brain-derived neurotrophic factor (BDNF) val66met polymorphism (Kaufman et al., 2006, Carver et al., 2011, Verhagen et al., 2010) and the catechol-O-methyltransferase (COMT) Val158Met polymorphism (Massat et al., 2005). Results regarding the effect of these genes are diverging. There is a general consensus though, that the potential effect of these genes is influenced by the exposure to a distressing or protective environment, so-called gene by environment interaction (Kendler, 1995, Rutter et al., 2006, Thapar et al., 2007).

Gene by environment interaction

Gene-environment interaction (GxE) has been defined as 'a different effect of environmental exposure on disease risk in persons with different genotypes' (Ottman, 1996). A review of studies examining gene-environment interaction in MDD in childhood and adolescence finds that despite heterogeneous methods and results, most studies report some evidence of GxE (Dunn et al., 2011). A prospective twin study suggests a significant GxE, where children with a family history of depression had an even higher risk for depressive symptoms, when also experiencing family conflict (Rice et al., 2006). Another study of twin girls finds an increased risk for depression and anxiety in adolescents with a family history of emotional disorder if exposed to SLE (Silberg et al., 2001).
Adult studies of GxE investigating the relation between the serotonin transporter polymorphism (5-HTTLPR) and depression have presented positive (Caspi et al., 2003, Kendler et al., 2005, Wankerl et al., 2010) as well as negative results (Risch et al., 2009, Fergusson et al., 2011). Very reassuring are the findings by Belsky et

al. showing that 5-HTTLPR s/s alleles are associated with high depressive scores in a stressful environment, but that they on the other hand, are associated with low depressive scores in a protective environment (Belsky et al., 2009). Hence, 5-HTTLPR s/s carriers may generally be more susceptible to the environment, regardless the character, which adds hope for future prevention (Belsky et al., 2009). In a birth cohort study of 7-year-old children, no GxE was found for the serotonin transporter polymorphism and SLE for emotional symptoms (Araya et al., 2009). However, in female adolescents, GxE is reported for the serotonin transporter polymorphism and SLE for depression (Eley et al., 2004).

A gene-gene-environment interaction (GxGxE) is reported in children, with the serotonin transporter polymorphism and the BDNF polymorphism increasing depressive symptom scores in children, but only if exposed to maltreatment (Kaufman et al., 2006). An interesting four-way interaction (GxGxExE) also occurred in this study with social support moderating the effect of the two genotypes and maltreatment.

Diagnosis validity and reliability

Biological markers play a minor part in the diagnostic process in psychiatry, and we rely more on interviews and observations (phenomenology) when discriminating the disordered subject from the non-disordered. The use of standardized structured interviews has increased (Rutter et al., 2008), and it seems to enhance validity as well as reliability of the diagnostic assignment (McClellan and Werry, 2000).

A valid estimate can be defined as an estimate with little systematic error (bias) (Rothman et al., 2008), meaning that 'we actually measure what we think we are measuring'. A precise (reliable) estimate can be defined as an estimate with little random error (Rothman et al., 2008), meaning that 'we measure uniformly'. Both validity and reliability determines the accuracy of an interview or instrument.

The reliability of a diagnostic measure can be challenged at several stages towards the final diagnosis; information gathering (information variance), the clinical phenomenon (occasion variance), the diagnostic criteria employed by the clinician (criterion variance) and consistency/carefulness of the clinician (Shrout et al., 1987). Reliability can be evaluated between clinicians (interrater reliability) and between the repeated use of a psychometric instrument (test-retest reliability) (Spitzer and Fleiss, 1974). The measurement of test-retest reliability has the obvious limitation that the clinical phenomenon may have changed between tests. If this is the case, the test-retest reliability turns out to be low due to occasion variance, rather than actual failure to reproduce (Shrout et al., 1987).

During the 1960's there was an increased focus on the interrater reliability of psychiatric diagnoses (Spitzer et al., 1967). Cohen's Kappa was presented as a method to test interrater reliability between two raters on categorical data (Cohen, 1960). Some years later Cohen introduced the weighted Kappa, which can be used to test interrater reliability on categorical data, taking into account that some disagreements are more serious than others (Cohen, 1968). Fleiss Kappa was presented in 1971, giving the possibility of testing for interrater reliability between more than two raters on categorical data (Fleiss, 1971), and the following year the intraclass correlation coefficient was introduced, in order to measure interrater realibility on quantitative data (Fleiss and Cohen, 1973).

AIMS OF THE THESIS

The overall intention with this thesis was to explore 'the nature of' childhood depressive disorders. The literature on SD in adults underlines the severity and clinical significance of this condition and its continuous relationship with MDD. Since childhood seems to be a window of opportunity for prevention of mental disorders and childhood onset MDD has a particularly severe outcome, it is important to know more about SD in children and adolescents. If SD in children and adolescents is a precursor to MDD like in adults, the prevalence and clinical characteristics need to be determined in order to target indicated preventive intervention to subjects presenting this subclinical condition. Also, there is a need for identifying risk factors that might induce conversion of an SD condition in a child into MDD.

The specific aims of this thesis were to:

1. Examine whether the literature supports a dimensional view of depressive disorders in childhood and adolescence (paper 1)

2. Investigate whether gender influences the risk for pre-pubertal MDD (paper 2)

3. Estimate the point prevalence of SD and MDD in a pre-pubertal Danish National Birth Cohort sample (paper 3)

4. Identify and compare clinical characteristics and potential risk factors for childhood SD and MDD in a population-based sample (paper 3)

Subthreshold depression in children and adolescents – a systematic review – paper 1

Methods

The PRISMA Statement

The Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement was generated by an international group in 2009 (http://www.prisma-statement.org/) (Liberati et al., 2009a, Moher et al., 2009). The PRISMA statement was an update of the Quality Of Reporting Of Meta-analysis (QUOROM) statement that was developed in 1996 (Moher et al., 1999). The QUOROM statement had the purpose to improve the report quality of meta-analyses of randomized clinical trials. The PRISMA statement addresses both meta-analyses and systematic reviews and aims to improve the report qualities of both. In order to do so, the PRISMA statement provides a 27-item checklist and a flow diagram ensuring transparency of the study. The key characteristics of a systematic review according to PRISMA is; '(a) a clearly stated set of objectives with an explicit, reproducible methodology; (b) a systematic search that attempts to identify all studies that would meet the eligibility criteria; (c) an assessment of the validity of the findings of the included studies, for example through the assessment of risk of bias; and (d) systematic presentation, and synthesis, of the characteristics and findings of the included studies.'

We performed a systematic critical review in accordance with the PRISMA statement (Liberati et al., 2009a, Moher et al., 2009). Hence, we developed a protocol prior to the conduction of the review, describing the search strategy, inclusion criteria and intended outcomes and outcome measures (Appendix 1). Furthermore a Data Extraction Sheet (DES) was created inspired by 'Data

Extraction Template for Cochrane Reviews' (Higgins and Green, 2008).
If depressive disorders are dimensional rather than categorical conditions, we expect SD to be placed intermediate to non-depressed subjects and MDD subjects on the causal chain, constituting an MDD precursor (Figure 1). Also, we expect the phenomenology (clinical presentation) of SD and MDD to match regarding quality but differ regarding quantity. We also expect an analogous aetiology, meaning shared risk factors. Finally, we expect that the course of both disorders will be not identical, while some subjects with SD may never develop MDD, but have several similarities. Therefore the intended outcomes entered in the review protocol included clinical characteristics, risk factors, prognosis and implications (Appendix 1).

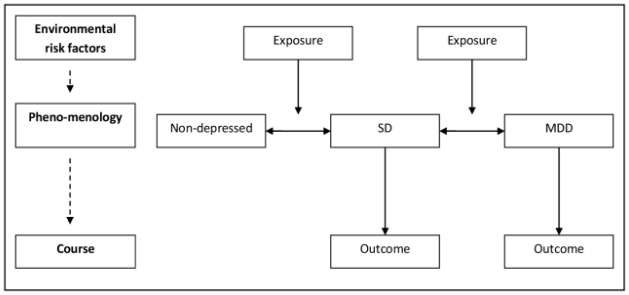

Figure 1 Causal chain of depressive disorders (genetic causes not shown)

Review process
The first author conducted the literature search assisted by the University medical librarian. The search was performed October 6th 2011 and included the electronic databases Medline (Pubmed) and PsycInfo (Ovid). The used search terms are listed in paper 1. The search was limited to reports written in English and child/infant/adolescence (PsycInfo) or all child, 0-18 years (Medline). A supplementary manual search of reference lists to the finally included reports was performed.
The review process consisted of three phases: a 1st screening phase of titles and abstracts; a 2nd screening phase of full-text papers, and a 3rd data extraction phase in which results from included reports were entered into the DES (flow chart, paper 1). Screening was preceded by tests of interrater reliability between the four reviewers (authors RW, MJS, ERH, NB), and screening and data extraction exercises were performed prior to the second and third phases.
Each report identified at the electronic search of the databases, was evaluated for inclusion by two randomly allocated reviewers. Inclusion was based on five mandatory inclusion criteria defined in the protocol (Appendix 1). Reports failing to fulfil one inclusion criterion were excluded. If fulfilment of inclusion criteria based on the abstract was unclear, the report proceeded to the 2nd screening. If fulfilment of inclusion criteria was still unclear, the authors were contacted. If there was no response after two contacts or it was still unclear whether inclusion criteria were fulfilled, the report was excluded. When disagreement on report inclusion occurred between two reviewers, a consensus decision was made in pairs or in the complete author group. The reviewer group discussed all studies included in the 3rd data extraction phase.

Assessment of risk of bias
Selection bias in a study occurs when the relation between the examined exposure and outcome is different for study participants than for those who were theoretically eligible for the study (Rothman et al., 2008). An example of selection bias is self-selection (self-referral) bias, where the reasons for self-referring to a given study may be associated with the outcome under study (Rothman et al., 2008). Self-selection bias can also occur from differential selection at start of follow up in cohort studies (e.g. 'healthy worker effect'). We classified self-selection bias as selection bias according to Szklo and Nieto (Szklo and Nieto, 2012) and not as confounding which is also suggested (Rothman et al., 2008).
Information bias is caused by measurement errors in the information needed for classification (Rothman et al., 2008). In other words, information bias leads to misclassification of exposure and/or outcome status (Szklo and Nieto, 2012). An important example of information bias is recall bias, where the outcome (healthy or ill) affects the ability to recall previous exposure, and therefore affects the information supplied regarding exposures of interest. The misclassification caused by information bias is divided into non-differential and differential. Non-differential misclassification occurs when the degree of misclassification of exposure is independent of outcome status (ill/healthy) (Szklo and Nieto, 2012). This generally leads to measures of associations pointing towards the null-hypothesis (this may not be the case when you have more than two exposure categories). Differential misclassification occurs when the degree of misclassification of exposure or outcome differs between the groups being examined. It is a more serious misclassification, because it may bias the results away from (or towards) the null-hypothesis (Szklo and Nieto, 2012).
Confounding occurs when 'the apparent effect of the exposure of interest is distorted because the effect of extraneous factors is mistaken for – or mixed with – the actual exposure effect (which may be null)' (Rothman et al., 2008). A confounder must have certain qualities to be a confounder; it must be associated with both the exposure and outcome of interest; it must be associated with outcome also in unexposed subjects; and it may not be an intermediate factor between exposure and outcome. The magnitude of confounding depends on the confounders association with the exposure of interest, and the confounders association with outcome in exposed and unexposed subjects (Rothman et al., 2008). We did not treat confounding as a bias in this review, and therefore did not assess the risk of confounding. We decided to do so, while 'a confounded association, although not causal, is real' (Szklo and Nieto, 2012), and also because confounding is important merely in causal studies which were few in this systematic review.
Reports with unacceptable risk of bias or unacceptable risk of random error (e.g. reporting on less than five subjects with SD) were excluded. Publication bias was not assessed.

Interrater reliability
The agreement between reviewers (interrater reliability) on inclusion of reports in the screening procedure was tested prior to both the 1st and the 2nd screening phase. Preceding the 1st screening phase, three consecutive interrater reliability tests were performed on title and abstracts from 25 randomly selected reports. Before initiation of the 2nd screening phase, two consecutive interrater reliability tests were performed on ten randomly selected full-text reports that had passed the 1st screening. Following each interrater reliability test, the inclusion criteria in the protocol were adjusted to inaccuracies that may have caused any disagreement.
The agreement on inclusion between the four reviewers was calculated using Fleiss' Kappa (Fleiss, 1971) (Table 4). The results

showed moderate agreement (Fleiss' Kappa 0.57) before initiation of the 1st screening phase, and substantial agreement (Fleiss' Kappa 0.77) before initiation of the 2nd screening phase (Fleiss, 1971, Landis and Koch, 1977).

	Test 1 Prior to 1st screening	Test 2 Prior to 1st screening	Test 3 Prior to 1st screening	Test 1 Prior to 2nd screening	Test 2 Prior to 2nd screening
Fleiss' Kappa	0.41	0.46	0.57	0.48	0.77

Table 4 Interrater reliability results (paper 1)

Data analysis

Screening results were entered in the Epidata software program (www.epidata.dk). Reviewer agreement was assessed by Fleiss' kappa estimates using the STATA 11 program (www.stata.com).

RESULTS – paper 1

A total of 26 reports (representing 24 studies) published between 1983 and 2011 were included in the review. All studies used the DSM classification system, but even though six studies used SD criteria resembling the research criteria for Minor Depressive Disorder (DSM-IV and DSM-IV-TR), the criteria showed great variability. The number of SD subjects in studies was generally small, with only five studies reporting on more than 100 SD cases. The majority of included studies had cross-sectional designs limiting the possibilities for causal conclusions.

SD lifetime prevalence estimates ranged from 5.3%-12.0% (MDD 1.1%-14.6%), and one-year prevalence estimates ranged from 1.0%-20.7% (MDD 0.8%-13.0%). The majority of studies comparing prevalence estimates for SD and MDD reported higher prevalence for SD.

The risk factor most widely examined regarding development of SD was female gender, which was examined in six studies. Three studies included adolescent samples, and all found higher prevalence rates for females (Sihvola et al., 2007, Oldehinkel et al., 1999, Kessler and Walters, 1998). Three studies including younger, mainly pre-pubertal samples, found no gender difference in prevalence rates for SD (Ford et al., 2003, Costello et al., 1996, Michaud-Tomson, 1996).

Potential environmental risk factors were examined in six studies, but only one study had a longitudinal design (Rohde et al., 2009). This study found 'lower parental education level' to be associated with early SD onset, and cross-sectional studies found SD to be significantly associated with 'conflicts with parents' (Jonsson et al., 2011), 'physical abuse' (Jonsson et al., 2011) and 'reduced social support' (Gonzalez-Tejera et al., 2005). Interestingly, the potential risk factors identified in cross-sectional studies were also more frequent in MDD. Adolescents with SD and MDD generally experienced more SLE than non-depressed adolescents (Krackow and Rudolph, 2008). In addition, SD and MDD youth tended to overestimate the stressfulness of non-interpersonal SLE (Krackow and Rudolph, 2008) and have a more negative self-perception at a comparable level (Hamff, 2005).

The occurrence of depressive symptoms, comorbidity and health service use was compared between children and adolescents with SD, MDD or no depressive disorder (Table 5). Depressed and irritable mood were the most frequent symptoms in both SD and MDD. Twelve comparisons were made of frequencies of depressive symptoms in SD and non-depressed. All showed significantly more symptoms in SD than in non-depressed, except for one report of suicidal acts being equally frequent in these groups (Sihvola et al., 2007). Twenty comparisons were made between the SD and MDD groups, with ten reports of an equal frequency of symptoms, and ten reports of MDD presenting a higher frequency of depressive symptoms than SD. Three studies explored suicidality, and all reported a similar frequency of either suicidal thoughts or suicidal acts in children and adolescents with SD and MDD (Goodyer and Cooper, 1993, Sihvola et al., 2007, Jonsson et al., 2011).

Anxiety disorder and conduct and oppositional defiant disorder were the most frequent comorbid disorders in both SD and MDD. Some studies reported comorbidity to be more frequent in MDD, and some reported similar frequencies (Table 5). Health service use was increased for children and adolescents with SD compared to non-depressed, and in one study even compared to subjects with MDD (Gonzalez-Tejera et al., 2005).

	Equal rates for SD and MDD	SD lower than MDD	SD higher than non-depressed
Depressive symptoms			
Depressed mood		67.4% vs. 85.7% 1	67.4% vs. 1.5% 1
Irritability	60.9% vs. 78.6% 1		60.9% vs. 1.6% 1
Depressed or irritable mood	91.0% vs. 90.7% 2		
Anhedonia	17.4% vs. 14.3% 1	42.3% vs. 76.7% 2	17.4% vs. 0.0% 1
Appetite-related symptoms		35.6% vs. 67.4% 2	
Increased appetite	63.0% vs. 64.3% 1		63.0% vs. 1.6% 1
Sleeping difficulties	74.3% vs. 88.4% 2		
Early insomnia		30.4% vs. 75.0% 1	30.4% vs. 14.2% 1
Psychomotor agitation		45.7% vs. 89.3% 1	45.7% vs. 0.8% 1
Psychomotor agitation or retardation		32.4% vs. 65.1% 2	
Fatigue		41.4% vs. 72.1% 2	
Worthlessness or excessive guilt		41.9% vs. 79.1 2	
Guilt	39.1% vs. 35.7% 1		39.1% vs. 1.6% 1
Impaired concentration	64.0% vs. 95.4% 2	43.5% vs. 71.4% 1	43.5% vs. 0.0% 1
Suicidal thoughts	31.8% vs. 53.5% 2		SD>non-depressed 2
Suicidal acts (current)	8.7% vs. 17.9% 1		8.7% vs. 0.0% 1
Suicidal acts (lifetime)	10.5% vs. 20.7% 3	2.3% vs. 11.6% 2	SD=non-depressed 2* 10.5% vs. 1.2% 3
Comorbidity			
Separation anxiety	15.2% vs. 17.9% 1		15.2% vs. 3.8% 1
Somatic anxiety		17.4% vs. 50.0% 1	17.4% vs. 10.1% 1
Generalized anxiety disorder		9.5% vs. 23.3% 2	SD>non-depressed 2
Phobias	60.9% vs. 57.1% 1		60.9% vs. 35.7% 1
Any anxiety disorder	32.0% vs. 41.8% 4	14.5% vs. 37.9% 3	SD>non-depressed 4 SD=non-depressed 3*
Oppositional defiant disorder		1.8% vs. 11.6% 2	SD=non-depressed 2*
Oppositional behaviour: - with parents - at school	28.3% vs. 46.4% 1	17.4% vs. 42.9% 1	28.3% vs. 16.3% 1 17.4% vs. 3.1% 1
Conduct disorder		22.5% vs. 37.2% 2	SD>non-depressed 2
Any disruptive disorder	26.3% vs. 25.3% 3 24.9% vs. 47.1% 4		SD>non-depressed 3 SD>non-depressed 4
Any comorbid psychiatric disorder	53.3% vs. 62.2% 4	30.6% vs. 53.5% 2	SD>non-depressed 4
Health service use			
Mental health service		6.8% vs. 32.6% 2	SD>non-depressed 2
Mental health service (lifetime)	21.2% vs. 29.1% 3		SD>non-depressed 3
Any outpatient service	36.1% vs. 12.2% 4#		
Any service	47.1% vs. 22.3% 4		
Medication	7.4% vs. 7.4% 4		
Antidepressants		1.4% vs. 4.7% 2	SD=non-depressed 2*

Table 5 Frequency of depressive symptoms, comorbidity and health service use

1 Goodyer and Cooper, 1993
2 Sihvola et al., 2007
3 Jonsson et al., 2011
4 Gonzalez-Tejera et al., 2005
SD higher than MDD
* Equal rates for SD and non-depressed

The psychopathologic outcomes of SD in childhood were examined in four prospective studies, and all showed a chronic course with either homotypic continuity (leading to depressive disorders later on) (Oldehinkel et al., 1999, Rohde et al., 2009) or both homotypic and heterotypic continuity (leading to mainly disruptive or anxiety disorders) (Jonsson et al., 2011, Johnson et al., 2009). The impairment outcomes of SD was explored in three studies, and all reported a significant increased functional impairment in a longer perspective (Johnson et al., 2009) as well as in a shorter perspective (less than two years) (Oldehinkel et al., 1999, Keenan et al., 2008).

Strengths and limitations

This critical systematic review was conducted in accordance with the PRISMA Statement and Cochrane recommendations (Liberati

et al., 2009b, Higgins and Green, 2008). The conduction of a study protocol, screening and data extraction exercises and interrater reliability tests prior to the review process, all had the purpose of minimising the risk of bias in the review. Furthermore, all reports were evaluated by two reviewers limiting bias based on individuals. Interrater reliability was in the moderate-substantial range (Landis and Koch, 1977), and any disagreements were decided upon within pairs or in consensus.
Among the most important limitations of this review are; the 1st screening of reports was based on titles and abstracts only, and we experienced that the informative quality of the abstracts was sometimes poor. We may therefore have missed eligible reports. In addition, some studies with the primary aim to prevent MDD in children and adolescents were missed, since they did not use the terms 'subtreshold, subclinical, subsyndromal or minor' which were required keywords in the search strategy. Yet, evaluating the efficacy of interventions was not a primary aim of our review, since this topic was recently explored in a Cochrane review (Merry et al., 2011).
By assessing the risk of bias for each included study, the validity of results is estimated. The most frequent bias was non-differential misclassification (information bias), which generally tends to bias the measure of associations towards the null-hypothesis (Rothman et al., 2008, Szklo and Nieto, 2012). We did not assess publication bias which potentially leads to a bias away from the null-hypothesis (Rothman et al., 2008), nor did we assess confounding, which could lead to either overestimation or underestimation of causal associations (Szklo and Nieto, 2012).
Still, the primary aim of our review was to assess similarities and differences between SD and MDD rather than actual causal associations, and we therefore trust the results presented here. The review focuses on children and adolescents below the age of 18 according to the United Nations definition of childhood (United Nations General Assembly, 1989), and relevant studies of older adolescents are therefore lacking.

Gender-age interaction observed in incidence rates of childhood emotional disorders – paper 2

Methods
Prior to the study, a literature search was performed, investigating gender-specific prevalence and incidence rates. The search strategy gave 101 hits and is listed in table 2. An overview of studies exploring gender-specific prevalence rates in the period 1993 – 2012 is listed in Table 3. Only one study was found that presented incidence rates of children and adolescents (not listed) (Carballo et al., 2011).

Study design
This is a population-based cohort study of Danish children and adolescents aged 3-18 years. Outcome variables were assignment of a clinical emotional disorder diagnosis based on in-patient and out-patient data from The Danish Psychiatric Central Register (Mors et al., 2011).

Study population
Denmark, and the other Nordic countries (Nordbotten, 2010), has a history of a wide use of registers for the original purpose of official statistics (e.g. The Danish Register of Causes of Death, The Danish National Patient Register, The Danish National Prescription Registry, The Income Statistics Register, The Danish National Birth Register) (Thygesen et al., 2011). The personal identification number, which every person alive and with a permanent residence in Denmark holds, is used in all national registers enabling accurate linkage between registers (Thygesen et al., 2011). It also enables identification of family units through generations. The registers, apart from official statistics purposes, are an important source for research in public health and health-related welfare (Thygesen and Ersboll, 2011).
The Danish Civil Registration System (CRS) was established in 1968 registering all people alive and living in Denmark at that time and forth (Pedersen et al., 2006, Pedersen, 2011). The CRS includes information on personal identification number, gender, date of birth, place of birth, citizenship, identity of parents, place of residence, identity of spouse, and updated information on vital status (Pedersen, 2011).
The source population for this study included all individuals in the CRS. The study population posed a cohort of all individuals in the CRS who were born in Denmark in the period January 1st 1992 to December 31st 2008. An additional criterion was that both parents had to be born in Denmark, leaving a total of 907,806 study participants.

Assessment of mental illness
The study population in the CRS was by the personal identification number linked to the Danish Psychiatric Central Research Register (PCRR) to obtain information of mental illness (Mors et al., 2011). The PCRR was computerized in 1969 and contains information on all admissions to Danish psychiatric in-patient facilities, and from 1995 onwards, also information on all admissions to out-patient visits to psychiatric units. The PCRR contains information on dates of admission and discharge, cause for referral, place of treatment and diagnoses assigned (Mors et al., 2011).
From 1994, the diagnostic system used in the Danish clinical departments was the ICD-10 Classification of Mental and Behavioural Disorders: Diagnostic Criteria for Research (ICD-10-DCR) (World Health Organization, 1993).
Study outcomes were specific emotional disorders according to ICD-10-DCR (Table 6). Multiple disorders were recorded if developed by the study participants, and a child may therefore appear in more than one diagnostic category.

Diagnostic groups ICD-10-DCR	Diagnostic categories (study outcomes)
Mood Disorders	F32 Depressive episode
	F33 Recurrent depressive disorder
Neurotic, stress-related and somatoform disorders	F40 Phobic anxiety disorders
	F41 Other anxiety disorders
	F42 Obsessive-compulsive disorder
Behavioural and emotional disorders with onset usually occurring in childhood and adolescence	F93 Emotional disorders with onset specific to childhood

Table 6 Study outcomes

Data analysis
By the use of competing risks survival analyses (Andersen, 1993, Rosthoj et al., 2004, Andersen et al., 2012), we estimated incidence rates and cumulative incidence of each emotional disorder. The incidence rate (or incidence density) measures the number of new outcome events that occur per person per time unit (Kirkwood and Sterne, 2003). The cumulative incidence (or risk) measures the probability of new outcome events to occur during a specified period of time (Kirkwood and Sterne, 2003).
Cohort members were followed from their 3rd birthday until emigration from Denmark, death, 19th birthday, or December 31st 2011 (whichever came first). For each emotional disorder, the

date of onset was defined as the first day of the first contact (in-patient or out-patient) given the diagnosis of interest. Analyses were made for each gender separately.
In Danish adolescents, puberty onset is observed at mean age 10 years for girls (defined as Tanner breast stage 2+) (Aksglaede et al., 2009), and at mean age 11.5 years for boys (defined as testicular volume above 3 ml.) (Sorensen et al., 2010). Therefore, cumulative incidence was examined before the 11th birthday, as an indicator of acquiring an emotional disorder before puberty. Cumulative incidence was also examined before the 19th birthday.

RESULTS – paper 2

Data on 907,806 children and adolescents was achieved. We found that pre-pubertal incidence rates for depressive and anxiety disorders were higher for boys than girls. At age 12 the pattern reversed (Table 7). The cumulative incidence for any emotional disorder on the 11th birthday was 0.52% for boys and 0.31% for girls. On the 19th birthday cumulative incidence was 2.33% for boys and 3.77% for girls. The cumulative incidence measures the probability of having been diagnosed before a certain age.

	11th birthday			19th birthday		
Disorder	Cases (N)	Males	Females	Cases (N)	Males	Females
F32-F33	207	0.05 (0.04-0.05)	0.03 (0.02-0.03)	3,433	0.96 (0.90-1.03)	2.33 (2.22-2.44)
F40-F42	1,168	0.22 (0.21-0.24)	0.16 (0.15-0.18)	3,848	1.10 (1.04-1.17)	1.55 (1.47-1.64)
F93	1,359	0.28 (0.26-0.30)	0.14 (0.13-0.15)	2,212	0.50 (0.47-0.53)	0.40 (0.37-0.43)
F40-F42 + F93	2,419	0.48 (0.46-0.51)	0.29 (0.27-0.31)	5,754	1.53 (1.46-1.59)	1.87 (1.78-1.96)
F32-F33 + F40-F42 + F93	2,594	0.52 (0.50-0.55)	0.31 (0.29-0.33)	8,602	2.33 (2.24-2.43)	3.77 (3.64-3.90)

Table 7 Cumulative Incidence at the 11th and 19th birthday (Numbers in parenthesis indicate 95% confidence intervals)

The incidence rates are listed in Figure 2-4. As expected, incidence rates for depressive disorders, anxiety disorders and emotional disorders with onset specific to childhood were higher for girls after the onset of puberty. However, before puberty, boys had higher incidence rates. At age 12, the incidence rates were equal for boys and girls.

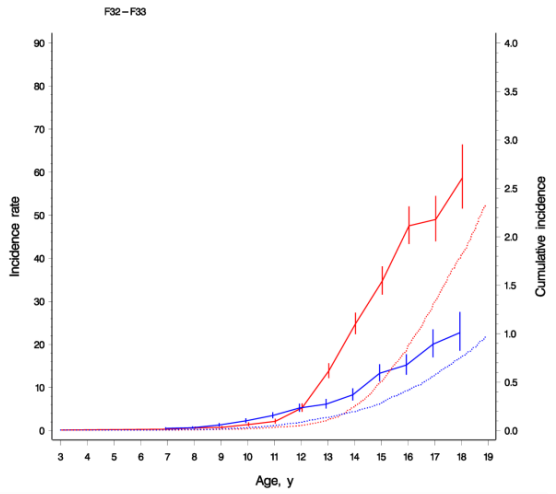

Figure 2 Age-specific incidence and cumulative incidence of depressive episode and recurrent depressive disorder

The solid lines show the age-specific incidence with the left-hand vertical axis denoting the incidence rate per 10,000 person-years, and the punctuated lines show the age-specific cumulative incidence with the right-hand vertical axis denoting the cumulative incidence in percent (females; red, males; blue). Solid horizontal lines indicate 95% confidence intervals.

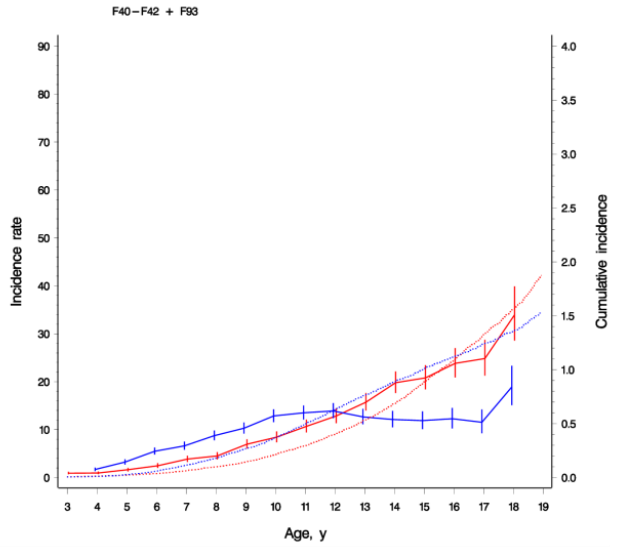

Figure 3 Age-specific incidence and cumulative incidence of any anxiety disorder and emotional disorders with onset specific to childhood

The solid lines show the age-specific incidence with the left-hand vertical axis denoting the incidence rate per 10,000 person-years, and the punctuated lines show the age-specific cumulative incidence with the right-hand vertical axis denoting the cumulative incidence in percent (females; red, males; blue). Solid horizontal lines indicate 95% confidence intervals.

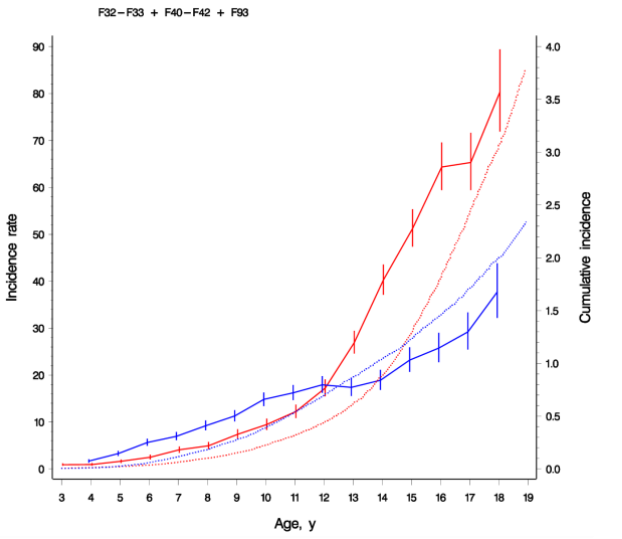

Figure 4 Age-specific incidence and cumulative incidence of any emotional disorder

The solid lines show the age-specific incidence with the left-hand vertical axis denoting the incidence rate per 10,000 person-years, and the punctuated lines show the age-specific cumulative incidence with the right-hand vertical axis denoting the cumulative incidence in percent (females; red, males; blue). Solid horizontal lines indicate 95% confidence intervals.

The null hypothesis of this study was that age-specific incidence rates for emotional disorders were identical for boys and girls before puberty, defined as before the 11th birthday. The null hypothesis was rejected due to a significant association between male gender and higher incidence for depressive disorders (F32-33; p=0.00144), anxiety disorders (F40-42, F93; p<0.00001), and any emotional disorder (p<0.00001) before the 11th birthday.

Strengths and limitations

This is a large-scale study exploring incidence rates of emotional disorders before and after puberty. Studies examining incidence rates are important, as they opposed to prevalence rates reflect new onsets only and are independent of the duration of disorder, relapses, emigration or death. Hence, they are better suited for drawing etiologic assumptions.

The incidence rates in this study are based on clinical in-patient and out-patient diagnoses, enhancing the clinical value of the results. The validity of the clinical diagnoses registered in the Danish Psychiatric Central Research Register is found to be sufficient for depressive disorders in adults (Bock et al., 2009). The coverage of PCRR is considered to be almost complete (Mors et al., 2011). Yet, reports from private practitioners and private units of child and adolescent psychiatry, which constitute a very small part of the clinical units in Denmark, are lacking.

The use of clinical in-patient and out-patient diagnoses impairs external validity. Hence, our results are not necessarily representative of non-clinical depressive conditions in the Danish child and adolescent population that could display different gender-specific incidence rates. This is possible if male gender is associated with a more severe depressive pre-pubertal phenotype or different or more severe comorbidity leading to higher referral rates to psychiatric clinics (referral bias). A decreased referral of girls with emotional disorder to mental health care, could also influence our results, if girls' depressive symptoms are more often ignored or treated in primary care due to cultural or relational matters. . While a discrepancy in referral thresholds could explain the male preponderance before puberty, it would however not explain later the female preponderance. We do not suspect that hesitancy in referring girls with depression would change dramatically after puberty, unless it was related to an actual worsening of the symptoms.

The study sample included children of parents born in Denmark. This makes the sample biologically homogeneous but limits the ability to draw any conclusions regarding children with parents born outside of Denmark.

Threshold and subthreshold depression in pre-pubertal children from The Danish National Birth Cohort – paper 3

Methods

The Danish National Birth Cohort

The children and mothers who took part in this study were collected from The Danish National Birth Cohort (DNBC) (Olsen et al., 2001). The DNBC recruited their participants in the years 1996-2002 and the primary aim was to assemble information about early life exposure influencing risk of disease across the lifespan (Andersen and Olsen, 2011). DNBC participants were included through the general practitioners, and 100,042 pregnant women accepted to participate. Participation involved telephone interviews five times during pregnancy and again shortly after birth (child age 6 and 18 months). At the child age of seven, the mother was invited to do a seven-year follow-up questionnaire online.

The DNBC interviews collected comprehensive information regarding in utero exposure (medication, smoking, alcohol, coffee etc.), home environment (pets, smoking, cleaning), job situation and psychological and physical well-being of parents, early mother-child relationship, child care etc.

Birth cohorts like the DNBC provide several obvious advantages when assessing life exposure and the development of disease. The longitudinal design gives the opportunity to collect exposure data before the onset of disease, which diminishes information bias. Hence, the time aspect in prospective cohort studies makes it possible to examine cause-effect relationships (Rothman et al., 2008). Another advantage is that cohort studies meet the 'study base principle', where individuals who develop disease, origin from the same study base, as those who do not, leading to high internal validity (Wacholder et al., 1992).

Even though the internal validity of cohort studies is often high, the external validity (generalisability) may be low, due to selection bias. Selection bias occurs when participation in a study/cohort is associated with both the exposure and the outcome of interest, and it is one of the largest methodological problems of the cohort study (Szklo and Nieto, 2012). The problem with selection bias is not the study findings, which may be valid, due to high internal validity, but the poor generalisability to the entire population (low external validity). Selection bias in cohort studies can occur at inclusion (participation bias) and at follow-up (loss to follow-up). The most harmful type of selection bias is loss to follow-up, because it diminishes the internal validity as well as external validity of the study results (Szklo and Nieto, 2012).

The extent of selection bias in the DNBC has been estimated in three studies so far (Greene et al., 2011, Jacobsen et al., 2010, Nohr et al., 2006). Like other cohort studies, the DNBC is characterized by somewhat healthier and wealthier participants than the source population. The differential participation however, has shown to be modest and the estimated effects on the risk estimates small (Nohr et al., 2006, Greene et al., 2011).

Design

The study had a two-phased case-reference design including a screening phase based on maternal reports of the Strengths and Difficulties Questionnaire, and a diagnostic phase using an online version of the Development and Well-Being Assessment. A two-phased design was chosen, because thorough assessment of infrequent disorders otherwise becomes a massive and a very expensive task. The cost-effectiveness could therefore be questioned, due to the high 'number-needed-to-examine' in order to have a sufficient number of depressive cases. Finally, the steering committee of the DNBC naturally had an interest in not burdening their cohort participants with too many interviews, increasing the risk of loss to follow-up.

Screening assessment

The DNBC seven-year follow-up survey incorporated the extended version of the mental health screening questionnaire: the Strength and Difficulties Questionnaire (SDQ) (Goodman, 2001, Goodman, 1997, Goodman et al., 2000b, Goodman, 1999). The SDQ consists of 20 items that cover four problem areas: emotional disorders, hyperkinetic disorders, conduct disorders, problems with peers, and five items on strengths: prosocial skills. It also includes five items assessing distress and social impairment (Goodman, 1999). A total SDQ difficulties score can be calculated by summing the four problem subscales (range; 0-40), and an impact score is calculated by summing the five distress and impair-

ment items (parent version range; 0-10). The SDQ has been validated in several cultures (Bourdon et al., 2005, Goodman et al., 2000c, van Widenfelt et al., 2003, Goodman and Goodman, 2012, Heiervang et al., 2007) and shows satisfactory specificity and sensitivity (Goodman, 1997, Goodman and Scott, 1999, Stone et al., 2010).

Diagnostic assessment

The screening questionnaire SDQ is often used in combination with the diagnostic interview The Development and Well-being Assessment (DAWBA) (Goodman et al., 2000a). The DAWBA includes structured questions related to DSM-IV-TR (American Psychiatric Association, 2000) and ICD-10 (World Health Organization, 2004) diagnostic criteria. Also, it includes open-ended questions in order to specify any problems described in the structured questions. The DAWBA covers most child and adolescent psychopathology (Goodman et al., 2000a) and has been validated in several cultural settings (Ford et al., 2003, Heiervang et al., 2007, Frigerio et al., 2009). However, when comparing the DAWBA to two other child psychiatric diagnostic interviews (Diagnostic Interview for Children (DISC) and Child and Adolescent Psychiatric Assessment (CAPA)), it seems to identify fewer and more severe cases (Angold et al., 2012).

The DAWBA is considered a multi-informant interview, and specific versions exist for parents, teachers and children aged 11 years or older. The assessment may be carried out as a telephone interview or online, where informants fill out the structured questions and type in replies to open-ended questions themselves. The DAWBA online version holds a computer algorithm that estimates the probability of diagnoses based on responses to the structured questions (Goodman et al., 2011). Experienced clinicians (DAWBA raters) evaluate the structured question responses, the open-ended texts, the DAWBA algorithm results and assign any final diagnoses. In this study, the category subthreshold depression (SD) was applied if considerable impairment due to depressive symptoms was present, without meeting full diagnostic criteria for MDD (at least one core symptom and one additional symptom was required).

Most DNBC members fulfilled the seven-year follow up survey online, and were expected to welcome the online DAWBA version, which was chosen for this study. Due to the use of a birth cohort sample of mothers there was no permission for approaching fathers or teachers for DAWBA information, and due to the age of included children, self-report was not an option.

Apart from information on psychopathology, DAWBA collects information on the child's physical health, school situation, SLE and family stressors in a background section. This section was not available in Danish at the time of the pilot study, but was translated into Danish by the author of this thesis in collaboration with Robert Goodman (the developer of DAWBA), for use in the main study. The level of parental distress and well-being is assessed by the Everyday Feelings Questionnaire (EFQ) (Uher and Goodman, 2010). It is a ten-item screening instrument assessing five depressive symptoms: worry and tension, fatigue and lack of energy, feeling stressed, loss of interest and unhappiness, and five items regarding psychological well-being. The EFQ is validated in epidemiological (Uher and Goodman, 2010) and clinical (Mann et al., 2012) adult samples.

Selection of participants

The prevalence rates of depressive disorders change around puberty as described earlier. Therefore it is possible that the exposure to risk factors is different before and after puberty. In order to examine children that represent somewhat equal risk factor profiles, only pre-pubertal children were selected for this study. Therefore, the sample constituted the youngest children of the DNBC, namely children born in the years 2000-2003 and subsequently aged 8-10 years at assessment. The baseline sample consisted of 21,906 children.

The two-phased study design comprised a screening phase (SDQ) and a diagnostic phase (DAWBA). The existing literature did not describe details on appropriate SDQ screening cut-offs for identifying children with a high risk for depressive disorders. The high frequency of comorbid behavioural disorders was however underlined, implying that total difficulties score might be increased (Ford et al., 2003). A pilot study was therefore conducted with the purpose of identifying the best SDQ screening criteria.

The pilot study included 380 mothers of children with high seven-year SDQ scores, and 120 mothers of children with low SDQ scores. The pilot showed that SDQ scores ≥90th percentile regarding impact, emotional problems or total difficulties were the best predictors of children having MDD at the later DAWBA assessment (sensitivity 90%).

During the pilot study, we performed a small-scale test of the validity of the DAWBA MDD diagnoses. A sample of six children with a DAWBA MDD diagnosis and six children without a MDD diagnosis were invited for a clinical assessment. Assessment with the semi-structured Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL) (Kaufman et al., 1997) was performed by blinded child and adolescent psychiatrists trained in the use of K-SADS-PL. The agreement of current MDD diagnoses between DAWBA and K-SADS-PL is listed in Table 8. The reliability between the instruments is 0.84 when using Cohen's Kappa (Cohen, 1960), which is characterised as excellent (Landis and Koch, 1977). If considering K-SADS-PL the 'gold standard', the sensitivity of DAWBA for MDD diagnosis is 100% and the specificity is 86% which is also satisfactory.

	MDD according to K-SADS-PL	Not MDD according to K-SADS-PL	Total
MDD according to DAWBA	5	*1	6
Not MDD according to DAWBA	0	6	6
Total	5	7	12

Table 8 Agreement between DAWBA and K-SADS-PL (* MDD prior to DAWBA assessment according to KSADS)

Following the pilot study, the main study included 4,000 DNBC mothers. In order to obtain a representative reference group (Rothman et al., 2008) we initially drew a random sample of 1,500 children from the study population of 21,406 (having excluded the 500 pilot study participants). Next, 2,500 children at increased risk for depressive disorders (according to the seven-year SDQ) were selected for participation. Both children with SDQ impact and emotional or total difficulties scores ≥75th percentile (N=1,298) and children with low SDQ impact but emotional or total difficulties scores ≥90th percentile (N=1,202) were selected.

Response rate

The various psychiatric disorders are assessed in different sections of DAWBA. In order to get a high response rate, we decided to leave out sections of disorders not typically comorbid to emotional disorders. Thus only sections relating to background information, depression, anxiety disorders (separation anxiety, generalised anxiety, specific phobia, social phobia, panic disorder,

agoraphobia, post-traumatic stress disorder), obsessive compulsive disorder and conduct or oppositional defiant disorders were utilized. The online DAWBA system was programmed so that first SDQ and then the DAWBA depression section appeared as the mothers logged onto the website. Subsequently the mother could choose in what order to complete the remaining sections.
The mother was invited to participate in the study by a letter posted to the home address. The letter described the purpose of the study and it contained logins to DAWBA and a link to the DNBC website describing the study in more detail. The letter also mentioned the possibility of a DAWBA telephone interview instead of an online interview, but no mothers requested this. If a mother did not login to the DAWBA within a given time frame, a reminder letter was sent up till two times.

Interrater reliability
The raters assigning DAWBA diagnoses constituted a team of three medical doctors with more than three years of clinical child and adolescent psychiatric experience. The validity of the diagnoses was ascertained at several DAWBA meetings, where cases with potential depressive disorder or complex psychopathology were discussed. The meetings were held under supervision of ERH who has considerable DAWBA experience both in research and clinical use, and documented interrater reliability with the developer of the instrument, Robert Goodman (Heiervang et al., 2007). The reliability of assigned diagnoses was assured by four interrater reliability tests performed prior to the initiation of the DAWBA rating. The agreement was tested on random cases categorised as either diagnosis probable or diagnosis possible by the DAWBA algorithm. If none of the random cases presented depressive symptoms, they were exchanged with selected cases that did before the test. Interrater reliability was calculated using Fleiss' Kappa for multiple raters (Fleiss, 1971). The results show an excellent rater agreement on MDD and conduct disorders according to Landis & Koch criteria (Landis and Koch, 1977) (Table 8). Interestingly only a good agreement is reached on anxiety diagnoses (Fleiss' Kappa 0.64), even though this category looks at any anxiety diagnosis. This reflects very well, the already described challenges in categorising children correctly according to anxiety diagnoses (Costello et al., 2005).

	1st test (N=24)	2nd test (N=15)	3rd test (N=15)	4th test (N=30)
K MDD	0.72	0.91	1.00*	0.82
K Anxiety disorders	0.72	0.64	0.64	0.64
K Disruptive disorders	0.78	0.38	0.91	0.91

Table 9 Interrater reliability results (paper 3)
(* No children received an MDD diagnosis in this test)

Data analysis
The case groups included all children with SD or MDD recruited from the pilot study and the main study. The reference group included all participating children from the random sample group, except for children fulfilling the criteria for SD or MDD. Comparisons were made between depressive children (in separate groups) and reference group children, and between children with SD and MDD. Exposure odds ratios (OR) for core symptoms, self-harm symptoms, comorbid disorders and gender were compared between depressive children and reference group children using binary logistic regression. The frequencies of all depressive symptoms were compared between children with SD and MDD using Pearson's chi-squared test and Fisher's exact test.

SDQ scores at DAWBA assessment were treated as exposure variables and dichotomised at the 90th percentile of the reference group sample. Both SDQ results at the seven-year follow-up (SDQ1) and at DAWBA assessment (SDQ2) were analysed. Comparisons between depressive and reference group children were made using both unadjusted binary logistic regression and multiple logistic regression adjusted for other SDQ problem subscales and SDQ impact.
Potential risk factors: health problems, school problems, SLE, gender, family stresses and maternal emotional well-being (EFQ), were coded as dummy variables and analysed on a crude and adjusted level. In the adjusted analyses, a potential risk factor was adjusted for all other potential risk factors. In separate analyses, the cumulative effect of SLE was estimated, by counting the number of SLE for each individual (zero, one, two or more), with zero SLE being the baseline exposure. EFQ scores were dichotomised at the 90th percentile of the distribution for parents of reference group children. Since the Danish version of the DAWBA background section was not available at the time of the pilot study, these analyses included children from the main study only.

Interrater reliability was analysed using Fleiss' Kappa (Fleiss, 1971). Data analyses were performed using STATA 12 (www.stata.com).

RESULTS – paper 3
A total of 3,421 DNBC mothers participated (response rate 76%). Children of responding mothers had a mean age of 8.98 years (standard deviation 0.75, range 8-10 years) and 52.8% were boys. MDD was diagnosed in 35 children and SD in 55 children (Figure 1 – paper 3). Twelve children from the random sample reference group had SD and six children had MDD, equivalent to an SD point prevalence of 1.0% and an MDD point prevalence of 0.5% in the DNBC (keeping in mind that some SDQ high-scorers had already been extracted for the pilot study; N=380).
The frequency of depressive symptoms and comorbid disorders were compared between depressive children and reference group children, and between children with SD and MDD. Depressive core symptoms and self-harm symptoms were more frequent for children with SD or MDD compared to children from the reference group ($p<0.001$) (Table 10). In both depressive groups, depressed mood was the most frequent core symptom (MDD 94.3%, SD 94.5%) followed by irritable mood (MDD 88.6%, SD 45.5%) and anhedonia (MDD 62.9%, SD 30.9%). The core symptom best predicting MDD was anhedonia, which occurred in 63% of MDD children and in 1% of reference group children (crude OR 139.62; CI 58.80-331.51; $p<0.001$). This finding persisted, when adjusting for other core symptoms, self-harm symptoms, comorbid disorders and gender (adjusted OR 36.92; CI 9.80-139.10; $p<0.001$). The core symptom best predicting SD status was depressed mood (crude OR 88.20; CI 27.27-285.33; $p<0.001$; adjusted OR 34.67; CI 10.17-118.18; $p<0.001$).

	MDD (N=35)		SD (N=55)		Reference group (N=1,167/1,169)	
	Frequency (%)	Crude OR	Frequency (%)	Crude OR	Frequency (%)	OR
Core symptoms						
Depressed mood	33/35=94.3 %	83.96 (19.98-352.83)***	52/55=94.5%	88.20 (27.27-285.33)***	192/1169=16.4%	1
Irritable mood	31/35=88.6 %	62.48 (21.71-179.84)***	25/55=45.5%	6.72 (3.83-11.78)***	129/1169=11.0%	1
Anhedonia	22/35=62.9 %	139.62 (58.80-331.51)***	17/55=30.9%	36.91 (16.96-80.33)***	14/1169=1.2%	1
Self-harm symptoms						
Talked about self-harm	16/35=45.7 %	40.11 (18.42-87.34)***	19/55=34.5%	25.14 (12.64-49.98)***	24/1167=2.1%	1
Newly self-harm	3/35=8.6%	36.38 (7.07-187.22)***	4/55=7.3%	30.43 (6.64-139.55)***	3/1167=0.3%	1
Ever self-harm	6/35=17.1%	48.08 (13.88-166.60)***	7/55=12.7%	33.89 (10.38-110.67)***	5/1167=0.4%	1
Comorbid disorders						
Comorbid anxiety disorders	8/35=22.9%	14.76 (6.06-35.97)***	8/55=14.5%	8.48 (3.60-19.96)***	23/1169=2.0%	1
Comorbid conduct disorder or oppositional defiant disorder	8/35=22.9%	31.19 (11.62-83.73)***	5/55=9.1%	10.53 (3.52-31.45)***	11/1169=0.9%	1
Gender						
Male gender	24/35=68.6 %	2.04 (0.99-4.20)	36/55=65.5%	1.77 (1.00-3.13)*	604/1169=51.7%	1

Table 10 Frequency of depressive core symptoms and self-harm symptoms, comorbidity and male gender (Logistic regression; *p<0.05; ***p<0.001)

SD and MDD children were more likely to have comorbid anxiety disorders and conduct or oppositional disorders than the reference group (p<0.001). The SD group had a higher frequency of boys than the reference group (p<0.05). While the pilot study was performed prior to the sampling of the reference group, we also performed these analyses with a modified reference group enhanced with an equivalent percentage of random sample pilot study participants. These results did not differ significantly from those presented here.

The frequency of all depressive symptoms was compared between children with SD and MDD (Table 2 - paper 3). The majority of symptoms were equally common in both groups. However, the following symptoms were more frequent for children with MDD: irritable mood (p<0.001), anhedonia (p<0.01) and worthlessness/guilt (p<0.05). Listings of symptom frequency within symptom groups showed almost similar ordering. Comorbid anxiety disorder occurred with similar frequency in children with SD and MDD (p=0.31; Pearson's chi-squared test), as did conduct or oppositional disorders (p=0.12; Fisher's exact test).

Only a subsample of reference group mothers reported that their child displayed any core depressive symptom (N=267), which resulted in further questions regarding: appetite/weight, sleep, psychomotor agitation/retardation, worthlessness/guilt, thoughts of death and concentration. All six symptoms were more common for the children with SD or MDD than for these reference group children (p<0.001).

SDQ results were collected at seven-year follow-up (SDQ1) and at DAWBA assessment (SDQ2) (mean time between SDQ1 and SDQ2: 20 months). These results were analysed using binary logistic regression of scores above and below the 90th percentile (reference group distribution) (Table 11). For children with current SD or MDD, all SDQ2 scores were more frequently above the 90th percentile, than they were for reference group children (p<0.001). When adjusting for other SDQ scores (omitting total score, which is dependent on subscales), a current emotional subscale score or impact score above the 90th percentile individually predicted both MDD and SD status. In addition, conduct subscale or peer subscale score above the 90th percentile predicted MDD status.

When looking at the seven-year SDQ1, our pilot study findings were confirmed; emotional subscale score, total difficulties score or impact score above the 90th percentile were good predictors of childhood depressive disorders (Table 11). In addition we found that peer problems at age seven to some degree predicted MDD and SD status, and hyperactivity problems predicted SD status at follow up.

When SDQ scores between children with SD and MDD were compared, only impact score at age seven (SDQ1) and conduct subscale score at DAWBA assessment (SDQ2) differed. Hence, children with current SD and MDD present the same level of functional impairment.

	MDD crude OR SDQ≥90th percentile (CI)	MDD adjusted OR SDQ≥90th percentile (CI)	SD crude OR SDQ≥90th percentile (CI)	SD adjusted OR SDQ≥90th percentile (CI)	Reference group OR SDQ≥90th percentile (CI)	Comparison MDD vs. SD (Pearson's chi-squared test/Fisher's exact test)
SDQ 1						
Hyperactivity subscale	4.31 (2.15-8.66)***	0.99 (0.41-2.44)	9.00 (5.13-15.79)***	4.25 (2.12-8.48)***	1	ns
Emotional subscale	9.40 (4.71-18.77)***	3.42 (1.53-7.63)**	17.18 (9.36-31.54)***	8.37 (4.27-16.39)***	1	ns
Conduct subscale	4.45 (2.22-8.94)***	1.04 (0.43-2.52)	6.92 (3.97-12.07)***	1.85 (0.90-3.78)	1	ns
Peers subscale	8.80 (4.31-17.96)***	2.41 (1.00-5.78)*	8.03 (4.54-14.20)***	2.52 (1.24-5.13)*	1	ns
Prosocial subscale	2.84 (1.36-5.90)**	0.93 (0.37-2.35)	1.73 (0.89-3.35)	0.42 (0.17-1.04)	1	ns
Total score	16.84 (8.29-34.21)***	not calculated	25.09 (13.63-46.18)***	omitted	1	ns
Impact score	49.14 (20.87-115.68)***	23.18 (8.47-63.48)***	17.09 (9.59-30.47)***	3.71 (1.77-7.80)**	1	*
SDQ 2						
Hyperactivity subscale	16.18 (7.81-33.52)***	1.18 (0.47-2.93)	15.44 (8.64-27.61)***	1.57 (0.74-3.32)	1	ns
Emotional subscale	34.35 (14.64-80.60)***	5.53 (2.13-14.37)***	45.52 (21.74-95.35)***	9.41 (4.15-21.35)***	1	ns
Conduct subscale	52.55 (18.25-151.32)***	7.06 (2.16-23.08)**	10.51 (5.96-18.52)***	1.82 (0.86-3.83)	1	**
Peers subscale	35.35 (15.06-82.98)***	2.94 (1.06-8.16)*	20.49 (11.21-37.46)***	2.09 (0.97-4.48)	1	ns
Prosocial subscale	8.74 (4.35-17.57)***	1.15 (0.46-2.83)	4.61 (2.57-8.30)***	0.88 (0.40-1.91)	1	ns
Total score	142.51 (33.72-602.19)***	not calculated	52.33 (24.15-113.40)***	omitted	1	ns
Impact score	192.62 (26.71-1447.27)***	21.83 (2.63-181.32)**	103.28 (31.89-334.49)***	18.90 (5.18-68.88)***	1	ns

Table 11 Odds ratios for SDQ scores above the 90th percentile at age seven (SDQ1) and at DAWBA assessment (SDQ2) (*p<0.05; **p<0.01; ***p<0.001, ns; non-significant)

The exposure to potential risk factors was estimated for children in the main study (Table 12). Sixty depressive children and 1,111 non-depressed reference group children participated in these analyses, because not all participating mothers had filled out background data. The background data was collected cross-sectionally but included information of exposure to events within the last year.

Fair or poor general health was associated with both SD (p<0.01) and MDD (p<0.01), and children with MDD were more likely to present convulsions or epilepsy than were reference group children (p<0.05). School problems were also associated with depressive disorders: extra support in school or placement in a special class/school was associated with SD (p<0.05), and the experience of a school shift was associated with MDD (p<0.05). Mothers of children with MDD commonly indicated that more school help was needed for their child (adjusted OR 9.64; CI 2.06-45.09; p<0.01). Two children with learning disabilities at a first glance appeared to have a slightly reduced risk for MDD. This could however be based on the adjustment of factors that are closely associated with both MDD and learning disabilities (SLE, poor family function, high maternal mental disorder score) (Emerson and Hatton, 2007).

SLE did not individually seem to increase the risk for depressive disorders, except that parental separation or divorce was more frequent for children with MDD (p<0.01). However, when assessing SLE quantitatively as exposure to: no SLE, one SLE or two

or more SLE, an association was demonstrated. Children with depressive disorders were more frequently exposed to two or more SLE (MDD OR 11.12; CI 3.57-34.64; p<0.001, SD OR 4.78; CI 2.16-10.58; p<0.001), and children with MDD were more often exposed to one SLE, but at a slightly lower level (ORMDD 4.76; CI 1.58-14.33; p<0.01). This indicates a dose-response relationship where the severe outcome (MDD) is closer correlated to a more severe exposure.

Self-reported psychological health was reported to be poor by significantly more mothers of children with MDD (p<0.01), and EFQ scores were more frequently above the 90th percentile for mothers of children in both depressive groups, than mothers of reference group children (p<0.05) (Table 12).

	MDD (N=22)			SD (N=38)			Reference group (N=1,093-1,111)	
	Frequency (%)	Crude OR	Adjusted OR†	Frequency (%)	Crude OR	Adjusted OR†	Frequency (%)	OR
Health problems								
Fair/poor general health	5/22=22.7 %	10.97 (3.79-31.77)***	10.30 (2.24-47.43)**	6/38=15.6 %	7.00 (2.71-18.03)***	5.78 (1.90-17.60)**	29/1111=2.6%	1
Language/speech problems	1/22=4.5%	3.26 (0.41-25.72)	1.48 (0.04-49.11)	4/38=10.5 %	8.05 (2.56-25.37)***	1.10 (0.17-7.18)	16/1111=1.4%	1
Vision/hearing problems	1/22=4.5%	1.91 (0.25-14.73)	0.35 (0.01-8.55)	0/38=0%	omitted	omitted	27/1111=2.4%	1
Movement/coordination problems	1/22=4.5%	5.24 (0.64-42.83)	0.90 (0.02-40.44)	2/38=5.3 %	6.12 (1.29-28.94)*	3.60 (0.36-36.11)	10/1111=0.9%	1
Enuresis/encopresе	5/22=22.7 %	2.88 (1.04-7.96)*	1.68 (0.40-7.10)	3/38=7.9 %	0.84 (0.25-2.77)	0.44 (0.09-2.24)	103/1111=9.3%	1
Convulsions/epilepsy	2/22=9.1%	8.45 (1.79-39.91)**	20.24 (1.04-392.47)*	0/38=0%	omitted	omitted	13/1111=1.2%	1
Other serious disease/imp	3/22=13.6 %	5.50 (1.55-19.57)**	2.12 (0.24-19.00)	5/38=13.2 %	5.28 (1.93-14.44)**	1.45 (0.28-7.46)	31/1111=2.8%	1
School problems								
Learning disabilities	2/22=9.1%	0.97 (0.22-4.20)	0.10 (0.01-0.84)*	15/38=39.5%	6.31 (3.20-12.48)***	1.56 (0.46-5.31)	104/1111=9.4%	1
Special class/school/extra support	7/22=31.8 %	6.84 (2.70-17.30)***	3.33 (0.59-18.71)	12/38=31.6%	6.76 (3.27-13.96)***	3.92 (1.29-11.90)*	71/1111=6.4%	1
School shifts (≥1)	6/22=27.3 %	4.97 (1.89-13.05)**	4.85 (1.16-20.18)*	6/38=15.8 %	2.48 (1.01-6.12)*	1.70 (0.57-5.09)	78/1111=7.1%	1
More school help needed	9/22=40.9 %	8.05 (3.35-19.35)***	9.64 (2.06-45.09)**	14/38=36.8%	6.78 (3.39-13.58)***	1.60 (0.52-492)	88/1111=7.9%	1
SLE (past year)								
Accident/serious injury	1/22=4.5%	3.48 (0.44-27.57)	5.54 (0.45-68.73)	0/38=0%	omitted	omitted	15/1111=1.4%	1
Severe disease and hospitalisation	3/22=13.6 %	8.20 (2.25-29.83)**	3.16 (0.33-30.49)	2/38=5.3 %	2.88 (0.65-12.77)	0.83 (0.10-7.12)	21/1111=1.9%	1
Death (parent/sibling/close friend)	3/22=13.6 %	1.98 (0.57-6.83)	1.34 (0.25-7.10)	2/38=5.3 %	0.70 (0.16-2.95)	0.37 (0.06-2.20)	82/1111=7.4%	1
Loss of friendship	4/22=18.2 %	2.11 (0.70-6.34)	1.08 (0.21-5.67)	10/38=26.3%	3.39 (1.60-7.16)**	2.45 (0.99-6.07)	106/1111=9.5%	1
Economic crisis in family	3/22=13.6 %	3.03 (0.87-10.55)	0.49 (0.08-3.19)	3/38=7.9 %	1.65 (0.49-5.52)	1.06 (0.21-5.39)	55/1111=5.0%	1
Separation/divorce	4/22=18.2 %	4.03 (1.32-12.31)*	8.62 (1.92-38.68)**	7/38=18.4 %	4.10 (1.73-9.70)**	2.55 (0.81-7.96)	58/1111=5.2	1
Other serious events	10/22=45.5%	4.64 (1.98-10.92)***	1.99 (0.51-7.75)	13/38=34.2%	2.90 (1.45-5.78)**	2.02 (0.86-4.75)	169/1111=15.2 %	1
Family stresses (current)								
Parental unemployment	6/22=27.3 %	4.90 (1.87-12.89)**	1.23 (0.21-7.40)	2/38=5.3 %	0.73 (0.17-3.07)	0.38 (0.06-2.41)	78/1098=7.1%	1
Parental work situation	8/22=36.4 %	1.76 (0.73-4.24)	0.61 (0.16-2.34)	15/38=39.5%	2.01 (1.03-3.90)*	1.53 (0.66-3.58)	269/1097=24.5 %	1
Financial problems	10/22=45.5%	4.71 (2.00-11.07)***	3.11 (0.66-14.65)	6/38=15.8 %	1.06 (0.44-2.57)	0.46 (0.13-1.59)	165/1097=15.0 %	1
Marital problems (partner/expartner)	9/22=40.9 %	3.86 (1.62-9.16)**	0.94 (0.24-3.63)	13/38=34.2%	2.90 (1.45-5.77)**	1.62 (0.66-3.97)	167/1097=15.2 %	1
Parental physical health	4/22=18.2 %	1.46 (0.49-4.37)	0.22 (0.02-2.23)	8/38=21.1 %	1.75 (0.79-3.89)	0.55 (0.16-1.91)	145/1097=13.2 %	1
Sickness (mother + others)	6/22=27.3 %	1.26 (0.49-3.26)	0.49 (0.06-3.72)	15/38=39.5%	2.20 (1.13-4.28)*	1.96 (0.69-5.54)	251/1097=22.9 %	1
Parental psychological health	10/22=45.5%	9.00 (3.79-21.38)***	10.09 (2.36-43.15)**	11/38=28.9%	4.40 (2.11-9.15)***	2.07 (0.76-5.63)	93/1097=8.5%	1
Maternal EFQ≥90th percentile	12/22=54.5%	14.80 (6.21-35.27)***	5.89 (1.49-23.24)*	13/37=35.1%	6.68 (3.28-13.60)***	3.44 (1.33-8.91)*	82/1093=7.5%	1
Male gender	16/22=72.7%	2.57 (1.00-6.61)	1.16 (0.32-4.18)	26/38=68.4%	2.09 (1.04-4.18)*	1.23 (0.55-2.76)	566/1111=50.9 %	1

Table 12 Frequency and odds ratio of potential risk factors (*p<0.05; **p<0.01; ***p<0.001; † Adjusted for all other potential risk factors listed)

Strengths and limitations

The use of online DAWBA holds large possibilities of thoroughly examining large sample sizes. We therefore were able to diagnostically assess a population-based sample of almost 3,500 children. The response rate was 76% which is high compared to other population-based studies (Ford et al., 2003, Heiervang et al., 2007, Rask et al., 2012). We found prevalence estimates to be in line with existing studies. Still, we believe they are minimum estimates, because the DAWBA seems to identify fewer and more severe cases than other child diagnostic assessments, especially regarding internalising disorders (Angold et al., 2012).

The reference group was sampled randomly ahead of the main study, in order to make it representative of the exposure distribution in the source cohort population (Rothman et al., 2008). Still, a small sample (pilot study participants) had been withdrawn prior to this, making it not completely representative. However, children with psychiatric disorders apart from depressive disorders remained in the reference group directing associations towards the null hypothesis compared to studies using healthy control groups.

The use of single-informants may also lead to an underestimation, because children and adolescents usually report more internalised symptoms with superior predictive value compared to their parents (Rothen et al., 2009). The DAWBA is most reliable when used as a multi-informant instrument which was not possible in this study. Yet, a large-scale study found that teacher information did not change the clinical evaluated prevalence of emotional disorders (Ford et al., 2003). Also, reports of mental disorders seem equal between mothers and fathers (Rothen et al., 2009).

There is a documented selection by socioeconomic factors in the DNBC, like reported in other cohorts (Jacobsen et al., 2010). Subsequently, rates of exposure and outcome reported here are likely to underestimate the rates of the original Danish population. Nevertheless, studies suggest that the consequence of selection bias is smaller than earlier anticipated (Nohr et al., 2006, Greene et al., 2011, Goodman, 2013) and especially causal associations are reliable (Goodman, 2013, Lundberg et al., 2005, Wolke et al., 2009). Regarding childhood depressive disorders, the prevalence is found to be largely uninfluenced by change in socioeconomic factors (Costello et al., 2003a).

There is a risk that mothers with depressive symptoms falsely report more depressive symptoms in their child, due to their own condition (Youngstrom et al., 1999, van der Toorn et al., 2010, Najman et al., 2001). The risk for maternal reporting bias is however estimated to be small for general population samples (van der Toorn et al., 2010, Najman et al., 2001).

DISCUSSION

The purpose of this thesis was to explore different aspects of childhood depressive disorders. For this, we applied three methodological approaches: First, we examined whether the literature supports a dimensional view of depressive disorders in childhood. Second, we investigated how female gender influences the incidence of MDD in a register study based on clinical diagnoses. And third, we conducted a large-scale population-based study of prepubertal children, estimating the prevalence of SD and MDD and comparing the clinical characteristics and potential risk factors between groups.

Our systematic review of the literature supports that SD is a precursor to MDD in children and adolescents causing poor outcomes like psychopathology (homotypic and heterotypic), functional impairment and high use of health service (Wesselhoeft et al., 2013). In our study of pre-pubertal children from the DNBC, we are not yet able to address the outcomes of SD. We estimated the point prevalence of depressive disorders in the cohort however and find that SD (1.0%) is more frequent than MDD (0.5%), reflecting the literature (Wesselhoeft et al., 2013). Only three studies were identified in our review estimating the SD point prevalence in pre-pubertal samples and the diversity of the estimates is massive (0.07% - 7.3%). The most trustworthy reports present SD and MDD point prevalence estimates of 2.5% and 1.8% respectively (9-year olds)(Kashani et al., 1983) and estimates of 0.07% and 0.27% (8-10-year olds) (Ford et al., 2003). The study by Ford et al. aimed at identifying children with mental disorders in a national sample and minor emphasis was put on subthreshold mental conditions. Also, this large-scale study presented rather low prevalence estimates of MDD after puberty, and higher

MDD estimates than SD estimates, which is not the general finding in prevalence studies of SD and MDD. Kashani et al. performed clinical assessment using child report only leading to higher prevalence estimates. Our study is based on assessment with the DAWBA (similar to the Ford study), and a small pilot study indicated excellent agreement between DAWBA and K-SADS-PL on MDD diagnoses. Assignment of SD and MDD diagnoses and assessment of complicated cases in general was thoroughly discussed and supervised. We therefore believe that our point prevalence estimates represent a high internal validity, yet the external validity is somewhat biased (participation bias) leading to a possible underestimation of the true prevalence of depressive disorders in the Danish population. In comparison, another population-based study with clinical assessment (K-SADS-PL) of Danish 8-9-year old children reports a point prevalence of 0.8% for threshold affective disorders (Petersen et al., 2006).

The clinical characteristics of DNBC children with SD and MDD are largely similar. Children with SD by definition hold fewer depressive symptoms, the ranking and frequency of these individual depressive symptoms however, is almost the same. Only irritability, anhedonia and worthlessness/guilt are more common in children with MDD, supporting that the latter two symptoms may be severity indicators as demonstrated in previous studies (Luby et al., 2003a, Luby et al., 2004, Luby et al., 2009a, McMakin et al., 2012, Birmaher et al., 2004). DNBC children with SD and MDD are just as likely to have comorbid anxiety and conduct/oppositional disorders. Our findings are supported by the literature of SD in children and adolescents that also show analogous comorbidity and symptom patterns (including self-harm symptoms) for SD and MDD (Wesselhoeft et al., 2013). Some studies indicate a non-significant difference between the depressive groups, while others find a quantitative difference, where SD display characteristics between MDD and non-depressed subjects, closer to the former. The SD category in our study was applied if considerable impairment due to depressive symptoms was present, without meeting the full MDD criteria (at least one core symptom and one additional depressive symptom was required). Hence, caution is warranted regarding conclusions about current impairment level for SD. However, we are somewhat surprised that the degree of functional impairment measured by SDQ does not differ in a statistically significant way between DNBC children with SD and MDD. This is important, because marked impairment in adolescents with SD predicts an outcome almost similar to that of MDD (Oldehinkel et al., 1999) as well as longer SD episodes (Kaminski and Garber, 2002). Our review demonstrates that impairment, in terms of health service use, is increased for subjects with SD, and two out of three studies indicate that the level of health service use is in SD similar to that of MDD (Wesselhoeft et al., 2013). Hence, our results from the DNBC support a similar qualitative pattern of clinical features including impairment in childhood SD and MDD, and only few results indicate a quantitative difference.

In our register study of Danish children and adolescents, we examined gender-specific incidence rates of clinical MDD. As expected, we demonstrate higher incidence of MDD for girls after puberty compared to boys. Before puberty however, we find that boys have higher MDD incidence rates than girls. A male pre-pubertal preponderance for MDD is demonstrated before (Almqvist et al., 1999, Anderson et al., 1987, Angold et al., 1998, Gomez-Beneyto et al., 1994, McGee et al., 1992, Carballo et al., 2011), although many studies support the general consensus of an equal pre-pubertal risk for MDD (Merikangas et al., 2010a, Sarkar et al., 2012, Vicente et al., 2012b, Costello et al., 2003b, Ford et al., 2003). This observed gender-age interaction makes us speculate that the vulnerability towards psychiatric disorder may be changeable and influenced by gender and developmental stage as well as by exposure to gender-related risk and resilience factors. Our study indicates that the vulnerability towards emotional disorder is higher for boys before puberty, but that it opposed to the vulnerability of girls that changes dramatically at puberty, is more constant over time. This is supported by a prospective study of adolescents showing an increase in internalising symptoms in girls across pubertal Tanner stages and a decrease in boys (Oldehinkel et al., 2011).

Although there is a risk that our results are influenced by referral bias, we believe that they might actually reflect a valid association. Very few studies of incidence rates have been performed and prevalence estimates are influenced by duration of episodes, relapse of the given disorder, emigration and death, some of which may be related to female gender. Supporting this, female gender appears to be associated with longer depressive episodes (Essau et al., 2010, Marcus et al., 2005) and more depressive episodes in adults (Essau et al., 2010), which is also observed in children and adolescents (Birmaher et al., 2004). Furthermore, this study by far has a larger scale than previous studies (907,806 children and adolescents was included; 3,433 subjects with unipolar depressive disorder; of which 207 were younger than 11 years). While a discrepancy in referral thresholds between males and females could explain the male preponderance before puberty, it would however hardly explain the later female preponderance. Our findings, however, need to be replicated in other large-scale studies of clinical and non-clinical samples, before boys are targeted with selective prevention.

We also examined whether gender influenced the risk for depressive disorders in our pre-pubertal DNBC sample. We find no association between gender and MDD, but male gender is associated with SD at a crude level. Yet, when adjusting for comorbid disorders or other possible risk factors the association vanishes. Gender is one of the few potential risk factors appropriately explored in longitudinal designs for SD (six studies) (Wesselhoeft et al., 2013). It seems that female gender constitutes a risk factor for adolescent SD and that the risk for childhood SD is uninfluenced by gender.

In our birth cohort sample, we identified potential environmental risk factors for depressive disorders. We find that poor general health of the child is associated with both SD and MDD, and convulsions or epilepsy are associated with MDD. This is in line with previous studies that show a relation between chronic physical disorder and childhood emotional problems (Hysing et al., 2007, Glazebrook et al., 2003) and between epilepsy and MDD (Ekinci et al., 2009). It seems logical that a chronic physical disorder may influence daily living severely for a child, leading to possible emotional distress. Furthermore physical disorder is a documented risk factor for MDD in adults (Loftus et al., 2011, Scott et al., 2007, Anderson et al., 2001), maybe exerted through the impairment the physical disorder holds (Stegmann et al., 2010). Another hypothesis is that the physical disorder itself may lead to immune system changes inducing mood disorders, explaining the increased risk that severe infections and autoimmune diseases hold (Benros et al., 2013).

We used an SLE sum score as a risk indicator, which is documented useful in previous studies (Mayer et al., 2009, Christiansen et al., 2011). In our study, one SLE within the last year is correlated to MDD and exposure to two or more SLE is correlated to SD and MDD. MDD is more closely related to the more severe exposure of two or more SLE (OR 11.12) than to exposure of one SLE (OR 4.76) indicating a dose-response relationship.

Parental divorce/separation within the past year is the only SLE showing an individual effect by increasing the risk for MDD. Parental divorce obviously affects the child's daily life significantly at the time of divorce, yet the effect on emotional problems in a longer perspective might be smaller. Two prospective studies however, indicate that exposure to parental divorce or paternal absence constitute risk factors for depressive symptoms also after several years (Culpin et al., 2013, Storksen et al., 2005). We find school problems to be associated with MDD (school shifts), and SD (special class/school or extra support), but the causal directions are unclear. Our results point towards a shared risk factor profile for childhood SD and MDD, with an indication of a quantitative rather than a qualitative difference in exposure.

The term 'stressful life events' covers all sorts of stressful events and there is a need for more consensus regarding what should be considered SLE in children. Furthermore, we need to be able to divide risk factor exposure in childhood into sensible categories. The utility of the division into child-specific and family-specific risk factors is limited by the fact that these may be very difficult to separate in childhood. What might appear to be a child-specific risk factor (for instance chronic asthma) might be a consequence of a family-specific life style (for instance indoor smoking). Also in the breast-feeding period, the symbiotic relationship between mother and child limits the relevance of such a division. We advocate that the most appropriate division of risk factors (and resilience factors) is categorising them by the time of exposure. Such a division takes into account that the vulnerability towards these risk or protective factors may be fluctuating during the development of a child. Hence, we find it more rational to categorise environmental risk and resilience factors occurring in childhood or adolescence into: pre-natal, post-natal, pre-pubertal and post-pubertal. This temporal approach to risk factors reflects the use of proximal and distal environmental factors in the adult literature but is more specific, securing a consistent use.

Mothers of children with MDD report a poorer psychological health, and mothers of children with MDD or SD are more likely to present high EFQ scores (>90th percentile), than mothers of reference group children. It is well-known that children with a family history of clinical depression are more likely to develop MDD (Weissman et al., 2006) and SD (Lewinsohn et al., 2003), and that offspring of parents with a history of depression are relevant targets for selective prevention (Kaminski and Garber, 2002). It is interesting though that a high maternal score on depressive symptoms and poor well-being may be useful for identifying children at increased risk for SD or MDD, since this information is so easily collected (ten-item questionnaire). The maternal EFQ data are collected simultaneously with assessment of the child, and therefore we cannot conclude whether maternal depressive symptoms lead to childhood depressive disorder or the other way around. Based on the literature though, we assume that the former causal pathway is more likely, although we cannot say whether it would be genetic or environmental, or both. We will prospectively follow our DNBC sample and hopefully be able to answer some of these research questions when the sample is assessed again at the age of 17 years.

The findings reported in this thesis underline that SD in childhood and adolescence is a significant condition calling for attention, due to the early onset, the risk for progression into MDD and the poor outcome.

IMPLICATIONS

Indicated preventive interventions target subjects presenting a subthreshold condition in order to prevent progression into a clinical disorder (Mrazek and Haggerty, 1994). Hence, the purpose of indicated prevention in this field is to prevent subjects moving from the SD category to the MDD category in the causal chain of depressive disorders (Figure 1). This approach is fully in line with a dimensional view of depressive disorders, which this thesis supports. When targeting SD in pre-pubertal children, our findings indicate that we must seek children presenting fewer symptoms, but the same symptom pattern as presented by children with MDD. Children with SD demonstrate impairment to a level similar to children with MDD, which may be the most important clinical characteristic. Children with SD are characterised by frequent comorbid anxiety or conduct and oppositional disorders, which can also be viewed as part of the clinical picture.

We recommend that a categorical assessment as well as a dimensional assessment like a rating scale is used for the identification of SD subjects. Rating scales reflect the dimensional approach to depressive symptomatology and they may be superior to categorical assessments in terms of identifying SD subjects with increased impairment (Karsten et al., 2010). We also recommend the use of systematic assessment of the level of functional impairment.

Selective preventive interventions target individuals who are at increased risk for a clinical disorder due to exposure to a range of risk factors (Mrazek and Haggerty, 1994). This thesis indicates that selective prevention aimed at childhood MDD could effectively target children who suffer from chronic physical illness, and children whose mothers present depressive symptoms, also below clinical threshold. Selective prevention should also target children experiencing repeated SLE. Whether boys are at increased risk for pre-pubertal MDD needs to be explored further. Studies that combine indicated and selective preventive interventions towards depressive disorders in adolescents are on their way (Nauta et al., 2012). We believe that they could contribute considerably to the field in addition to prospective studies of risk and resilience factors for childhood depressive disorders.

Clinicians in child and adolescent psychiatry have a central responsibility in separating subjects who are clinically depressed from those who are not. They need however, to pay more attention to children and adolescents with subthreshold depressive symptoms who present significant functional impairment. Emphasis must be put on the risk for SD transforming into MDD, especially in those exposed to the potential risk factors found in this thesis. In order to identify children with SD in the clinic, the use of structured diagnostic assessment in combination with the use of rating scales is recommended. Pre-pubertal children with SD present the same symptom pattern, comorbidity and impairment level as children with MDD. Anhedonia and worthlessness or guilt are however symptoms more predictive of MDD, and the presence of these in a child with SD (or even a non-depressed child) should lead to increased clinical attention.

We highly recommend that the clinical assessment of a child is combined with a brief assessment of the parents' depressive symptoms. First of all, our study indicates that a high maternal depressive score might be a risk factor for development of depressive disorder in a child. Second of all, if a parent suffers from MDD, remission of this condition seems to be a prerequisite for remission of depressive symptoms in the child (Garber et al., 2009, Wickramaratne et al., 2011, Birmaher et al., 2004). Following this, we urge clinicians to assess not only the psychopathology of a child and its parents, but also the environmental risk factors this child has been exposed to, or still faces. Identification of risk

factors in a child's environment gives us valuable causal information, but indeed the presence of current risk factors may hinder remission of the depressive condition. Certainly, we are not able to eliminate all risk factors in a child's environment, but some might actually be modified.

Due to our findings, we welcome collaboration between paediatric and child and adolescent psychiatric clinics, because children with chronic physical disease are at increased risk for acquiring depressive disorders. General practitioners should also pay attention to our findings, because SD seems to be frequent in adolescents attending primary care (Gledhill and Garralda, 2012). Thus, primary care with its continuous contact with youth and low risk for stigmatisation would be an obvious setting for early identification of SD and prevention of MDD.

We propose that upcoming research in depressive disorders in children and adolescents focus on gender-specific differences. It is well-known that girls have a higher risk for MDD after puberty, but we found that more boys than girls presented pre-pubertal onset of clinical depression in a Danish population-based sample. We speculate that this difference could be based on an increased exposure to biological or environmental risk factors for boys before puberty, and/or an increased vulnerability. Therefore, studies exploring the gender distribution of large-scale pre-pubertal clinical as well as non-clinical depressive disorder are needed. If the gender-age interaction observed in paper 2 reflects an unbiased valid association, we need to have a more dynamic view of risk factors and vulnerability that may vary by age or developmental stage within each gender.

Future studies examining the prevalence or incidence of depressive disorders should analyse the rates on pre-pubertal and post-pubertal samples separately, since studies exploring these rates in samples including both children and adolescents seem unable to replicate the robust female preponderance after puberty (Table 3). Similarly, future prospective research studies aiming to identify specific risk factors for development of depressive disorders should bear possible gender differences in mind. We recommend that SLE regarding performance in school and sports as well as interpersonal events like parental divorce are highlighted, since boys and girls seem to have varied vulnerability towards these types of SLE (Oldehinkel and Bouma, 2011). Studies exploring environmental factors that protect (resilience factors) from development of depressive disorders are limited, but they show promising results (Brendgen et al., 2013, Kaufman et al., 2004). We encourage researchers to systematically assess possible resilience factors in addition to risk factors, in order to broaden this area that could naturally hold a high potential for prevention (Gladstone et al., 2011). Finally, we recommend a developmental approach to risk and resilience factors categorising them according to the child's developmental stage at the time of exposure rather than the quality of the exposure itself.

The DSM-5 has included a new diagnostic category 'other specified depressive disorder' with the intention to enhance diagnostic specificity (American Psychiatric Association, 2013). In this category however, the research criteria for Minor Depressive Disorder used in DSM-IV and DSM-IV-TR are replaced by 'depressive episode with insufficient symptoms'. The criteria are alike, except for one important change: depressed mood is now mandatory. Based on the literature, we do not find arguments for this change regarding children and adolescents. We are concerned that this change will increase the diversity of criteria used for SD in studies even more, limiting the ability to draw overall conclusions. Future prospective studies might consider using both the Minor Depressive Disorder criteria (DSM-IV-TR) and the new DSM-5 criteria and examine the outcome of both.

Childhood seems to be a window of opportunity for prevention of mental, emotional and behavioural disorders (O'Connell et al., 2009). Clinicians and researchers in child and adolescent psychiatry, as well as other professionals working with children, need to be very aware of the obligation that this provides. Interventions preventing MDD in children and adolescents seem effective (Merry et al., 2011), and even a delay of MDD onset in a child is a goal in itself due to the poor prognosis of this condition (Korczak and Goldstein, 2009, van Noorden et al., 2011). SD in children and adolescents is a precursor to MDD and therefore an important target for prevention of MDD. We provide information of what to look for in a child when identifying the SD condition, and point at risk factors that may facilitate the transformation of SD into MDD.

SUMMARY

Major Depressive Disorder (MDD) is a frequent and painful mental disorder considered among the five leading causes of disability in Western countries by the World Health Organization. MDD occurs at all ages, but childhood onset MDD has a more severe course with longer depressive episodes, more suicidality, and more frequent hospitalization, than later onset MDD. Childhood seems to be a window of opportunity for prevention of mental disorders, and subsequently prevention of MDD onset in childhood is recommended.

Feasible prevention targets either individuals who present early signs of a given disorder but have not reached diagnostic threshold (indicated prevention) or individuals who are at increased risk for a disorder due to risk factor exposure (selective prevention). Indicated prevention is rational also for depressive disorders, because subthreshold depression (SD) in adults is found to be a precursor to MDD.

The purpose of this thesis was to provide information necessary for the prevention of MDD onset in childhood. First, we examined whether the literature supports that SD is a MDD precursor also in children (systematic review). Second, we explored the risk that gender might constitute for pre-pubertal and post-pubertal onset MDD (register study). Third, we estimated the prevalence of SD and MDD in a large-scale pre-pubertal sample, and compared the clinical features of SD and MDD and potential risk factors (population-based study).

The systematic review of the literature showed that SD in children and adolescents presents analogous comorbidity and symptom patterns (including self-harm symptoms). It also supports that SD is a precursor to MDD in children and adolescents causing poor outcomes like psychopathology, functional impairment and high use of health service.

In the register study of Danish children and adolescents, we found a higher incidence of clinical MDD for girls after puberty compared to boys. Before puberty however, we demonstrated that boys had higher MDD incidence rates than girls.

The population-based study including 3,421 8-10-year old children from the Danish National Birth Cohort (DNBC) showed point prevalence estimates of 0.5% for MDD and 1.0% for SD. Children with SD by definition hold fewer depressive symptoms, but the ranking and frequency of these individual depressive symptoms was almost similar. Only irritability, anhedonia and worthlessness/guilt were more common in children with MDD. DNBC children with SD and MDD had comorbid anxiety or conduct/oppositional disorders just as frequently, and the degree of functional impairment was the same. When examining potential risk factors

for SD and MDD, we found that poor general health, more than two stressful life events (SLE) within the past year, and a high level of maternal depressive symptoms were correlated to both SD and MDD. In addition we found epilepsy/convulsions, one SLE within the past year and parental divorce/separation to be correlated to MDD.

In conclusion, the findings reported in this thesis underline that SD in childhood and adolescence is a significant condition calling for attention, due to the early onset, the risk for progression into MDD and the poor outcome. Indicated prevention aimed at MDD in childhood should target SD children who are characterised by fewer depressive symptoms but the same symptom pattern, the same level of impairment, and the same amount of comorbid anxiety and conduct/oppositional disorders, as presented by children with MDD. Selective preventive interventions could effectively target children who suffer from chronic physical illness and children whose mothers present depressive symptoms, also below clinical threshold. In addition, boys might have an increased risk for developing pre-pubertal MDD, but this has to be explored further in non-clinical samples.

We recommend that more attention is paid to children and adolescents with subthreshold depressive symptoms who also present significant functional impairment. Emphasis must be put on the risk for SD transforming into MDD, especially in those exposed to the potential risk factors identified in this thesis.

Abbreviations

World Health Organization (WHO)
Disability-adjusted life years (DALYs)
Major Depressive Disorder (MDD)
Diagnostic and Statistical Manual of Mental Disorders (DSM)
International Classification of Diseases (ICD)
ICD-10-Diagnostic Criteria for Research (ICD-10-DCR)
Subthreshold Depression (SD)
Stressful Life Events (SLE)
The Danish Civil Registration System (CRS)
The Danish Psychiatric Central Research Register (PCRR)
Odds ratio (OR)
Confidence intervals (CI)
Data Extraction Sheet (DES)

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