Major depressive disorder and subthreshold depression in prepubertal children from the Danish National Birth Cohort

Wesselhoeft, Rikke; Heiervang, Einar R; Kragh-Sørensen, Per; Juul Sørensen, Merete; Bilenberg, Niels

Published in:
Comprehensive Psychiatry

DOI:
10.1016/j.comppsych.2016.06.012

Publication date:
2016

Document version
Final published version

Document license
CC BY-NC-ND

Citation for published version (APA):

Terms of use
This work is brought to you by the University of Southern Denmark through the SDU Research Portal. Unless otherwise specified it has been shared according to the terms for self-archiving. If no other license is stated, these terms apply:

- You may download this work for personal use only.
- You may not further distribute the material or use it for any profit-making activity or commercial gain.
- You may freely distribute the URL identifying this open access version.

If you believe that this document breaches copyright please contact us providing details and we will investigate your claim. Please direct all enquiries to puresupport@bib.sdu.dk
Major depressive disorder and subthreshold depression in prepubertal children from the Danish National Birth Cohort

Rikke Wesselhoeft¹*, Einar R. Heiervang², Per Kragh-Sørensen³, Merete Juul Sørensen⁴, Niels Bilenberg⁵

¹Research Units of Department of Child and Adolescent Mental Health Odense and E-mental Health Odense, Mental Health Services in the Region of Southern Denmark, University of Southern Denmark, Denmark
²Institute of Clinical Medicine, University of Oslo and Oslo University Hospital, Oslo, Norway
³Institute of Clinical Research, University of Southern Denmark, Denmark
⁴Regional Centre for Child and Adolescent Psychiatry, Aarhus University Hospital, Risskov, Denmark
⁵Department of Child and Adolescent Mental Health Odense, Research Unit (University function), Mental Health Services in the Region of Southern Denmark, University of Southern Denmark, Denmark

Abstract

Background: Subthreshold Depression (SD) is an impairing condition that might convert into Major Depressive Disorder (MDD). Still, the characteristics of childhood SD are largely unknown.

Purpose: We aim to examine how SD in children differs from MDD regarding symptom profile, comorbidity, functional impairment and associated life stressors. We will examine the frequency of childhood SD and MDD and compare previous mental health between groups.

Basic procedures: This is a two-phase nested case–control study within the Danish National Birth Cohort (DNBC) (N = 4500). Mothers completed the online Development and Well-Being Assessment (DAWBA) regarding their child aged 8–10 years.

Main findings: A total of 3421 children participated (response rate 76%); 35 children were diagnosed with MDD and 55 with SD. Anhedonia, irritability and worthlessness/guilt were more frequent in MDD than SD, and anhedonia was rare in non-depressed children (1.2%). Comorbid anxiety and conduct disorders were equally common in the groups. Children with MDD had higher functional impairment caused by the depressive condition than children with SD, but overall functional impairment was the same.

Life stressors, including maternal depressive symptoms, were equally frequent for children with MDD and SD. Emotional problems and functional impairment at age 7 years predicted later SD and MDD. SD was twice as common as MDD in the DNBC (point prevalence 1.0% vs. 0.5%).

Principal conclusions: Children with SD and MDD display striking similarities. They differ mainly by the number of depressive symptoms and depression-related functional impairment.

Both SD and MDD at age 8–10 years were preceded by emotional symptoms and functional impairment at age seven years. This indicates a continuity of childhood depressive conditions but also a window of opportunity for prevention of MDD.

© 2016 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

1. Introduction

Major Depressive Disorder (MDD) is a frequent and distressing mental disorder [1], representing one of the top five contributors to the global burden of disease in Europe and North America [2,3]. Childhood onset MDD shows a high recurrence [4] and adolescents with MDD have a 40% risk of a recurrent depressive episode within two years [5]. Therefore, youth with MDD have a high risk for multiple depressive episodes during the crucial period of development. MDD is associated with more suicidal attempts if onset occurs in youth compared to adulthood [6]. Furthermore, youth with MDD are seven times more likely to complete suicide than non-depressed youth [7] and suicide is on the top five leading causes of death among adolescents [8,9].

Children and adolescents who have a family history of depression [10] or are exposed to environmental stressors [11] show an increased risk for depression. However, adolescent depression is more genetic in origin compared...
to childhood onset depression [12,13] and environmental stressors play a larger role in triggering childhood depression [12,14]. Also, the prevalence and incidence rates of depression rise prominently in adolescence [15,16], indicating that childhood rather than adolescence is a possible ‘window of opportunity’ for prevention of MDD [17].

Preventive interventions are recommended to target individuals presenting with subclinical level symptoms (indicated prevention) or individuals exposed to important risk factors (selective prevention) [18]. A subclinical level of depressive symptoms, also called Subthreshold Depression (SD), is a precursor condition to MDD in adults [19,20] and in adolescents [21–23]. A worldwide study finds that adults with SD and MDD display similar risk factor profiles and health impairment [24], while a recent meta-analysis finds the same mortality for the two conditions [25]. Also, a prospective study finds that children with subclinical psychiatric conditions have a risk for adverse outcomes in adulthood that is similar to that of children with clinical psychiatric disorders [26]. The authors recommend that children with subclinical psychiatric conditions are targeted in preventive interventions to reduce future impairment, distress and societal costs [26].

The phenotypic characteristics of childhood SD are however poorly described [27], making it difficult to recognize and intervene towards this condition. The definitions used for SD vary between studies, but the DSM-IV research criteria for minor depressive disorder have been widely accepted [28]. Although MDD and SD differ mainly on the number of depressive symptoms present (≥5 or 2–4, respectively) from the same pool of nine depressive symptoms [28], the possible combinations are multiple. Also, some symptoms may be more associated with threshold than subthreshold depression. The symptom of markedly diminished interest or pleasure (anhedonia) predicts severity, non-response and non-remission in depressed adults [29], as well as longer time to remission in depressed adolescents [30]. Anhedonia may therefore be a ‘severity marker’ associated with more severe depressive conditions or indicating a severe course. Similarly, depressed individuals with insomnia have an increased risk of suicidal behavior [31,32], and insomnia and irritability are found to be the most treatment resistant symptoms in pediatric MDD [33]. Only three studies have so far compared the symptom profiles for childhood MDD and SD [27]. Our study will contribute to this gap in the literature.

In order to initiate selective preventive interventions towards children at risk for MDD, we need to know more about the environmental stressors that these children experience. Risk factors for depression differ throughout development, but childhood seems to be a particularly sensitive period, where exposure to stressors initiates a developmental trajectory, rendering the individual vulnerable to development of depression also as an adult [34]. The majority of putative risk factors seem to be disorder-specific in youth, and living with a single parent or staying at a foster home is mainly associated with depression [35]. In addition, experiencing Stressful Life Events (SLE) increases the risk for onset of depression [36] and for recurrent depression [37], while it lowers the response to treatment [38]. When children experience physical health problems like epilepsy, asthma and other chronic illnesses, they have an increased risk for developing depression [39,40]. Similarly, having comorbid or previous anxiety disorders [41], or living with a depressed mother [42], increases the risk for childhood MDD. These stressors are also found to increase the risk for adolescent SD converting into MDD [43]. This suggests that full-blown MDD is likely to develop in children with SD, who are exposed to a certain amount of stressors.

In order to identify (and eventually prevent) these children at risk for developing MDD, we need more knowledge of the phenotypic presentation of childhood SD and the exposure to stressors, before the incidence of depression increases significantly with puberty onset. The aim of this study was to describe childhood SD and MDD in a population-based Danish birth cohort. Focusing on depressive symptoms, functional impairment, comorbid disorders, and associated life stressors, we compared children with SD and MDD with each other and with non-depressed children. Furthermore, we examined the frequency of SD and MDD in the birth cohort, and the predictive value of poor mental health scores at age seven years for depressive disorders at age 8–10 years.

We hypothesized that children with SD would display less depressive symptoms, comorbidity and impairment than children with MDD, but still higher than non-depressed children [27]. We expected that anhedonia would be more frequent in children with MDD than with SD, serving as a severity marker. Based on the literature, we expected SD to be a more frequent condition in children than MDD [27]. Finally, we expected a dose–response relationship between experienced life stressors and depressive symptoms, assuming that the developmental pathways for SD and MDD would be identical, with the important difference that children with MDD would have experienced more cumulative stressors at the time of evaluation.

2. Material and methods

2.1. Participants

More than 100,000 pregnant women were recruited to the Danish National Birth Cohort (DNBC) from 1996 to 2002 [44]. Through interviews and questionnaires, they have repeatedly reported on the physical and psychological wellbeing of themselves and their child. In order to assess a pre-pubertal sample, we included DNBC children born in the years 2000–2003. The study is approved by the Danish Data Protection Agency (j.nr. 2010-41-4477).

2.2. Study design and measures

The study had a two-phase case–control design nested within the DNBC (Fig. 1) [45]. Phase 1 was a screening
phase, where mothers responded to a mental health screening questionnaire regarding their child as part of the seven year DNBC follow up assessment (N = 21,906). Phase 2 was a diagnostic assessment phase divided into a pilot study and a main study, where 4500 participants were invited and children with depressive disorders were identified. The pilot study (N = 500) was performed in order to identify optimal screening criteria for depressive disorders. For the main study, a random comparison group was sampled (N = 1500), before a group of screen-positive children (N = 2500) was sampled. This sampling procedure was chosen to minimize selection bias by adhering to the ‘basic rules’ for control selection outlined by Rothman et al. (“Controls should be selected such that the exposure distribution among them will estimate without bias the exposure distribution in the source population”) [45].

The Strengths and Difficulties Questionnaire (SDQ) [46] parent version was included in the DNBC 7-year follow up and served as the Phase 1 screening measure. The SDQ is a brief mental health questionnaire for children aged 4–17 years, covering four problem areas (emotional, hyperactivity/inattention, conduct and peer relationships), one area of strength (prosocial behavior), and distress and social impairment [46,47]. An SDQ total difficulties score is calculated by summing the four problem subscales, and an impact score is calculated by summing the distress and impairment items. The SDQ has been validated in different cultures, with good psychometric properties [48–50]. A child was considered screen-positive when presenting at age 7 either with an emotional subscale score or a total difficulties score ≥ 90th percentile, or with an emotional subscale score or a total difficulties score ≥ 75th percentile combined with an elevated SDQ impact score.

The Phase 2 assessment included mother reports of a second SDQ and the online version of the Development and Well-Being Assessment (DAWBA) [51] regarding their child. The DAWBA is a diagnostic assessment that covers most current child psychopathology and is validated in several settings [48,52]. It includes structured questions about symptoms and impairment related to DSM-IV criteria [53], and also open-ended questions for qualitative responses. To reduce burden on informants, only DAWBA sections for disorders most commonly reported to be comorbid with depression were assessed in this study: anxiety disorders (separation anxiety, social phobia, specific phobia, generalized anxiety, panic disorder, PTSD, obsessive–compulsive disorder), conduct disorder and oppositional defiant disorder.

Three physicians trained in child and adolescent psychiatry assigned DSM-IV diagnoses after reviewing the full DAWBA information. They were trained and attended regular supervision by one of the authors (ERH), who has documented reliability with the developer of the instrument [48]. Substantial inter-rater agreement was required before the independent rating (see Results) [54,55]. All cases with
potential depressive disorder or complex psychopathology were discussed at consensus meetings. The category SD was applied for children presenting with at least one core depressive symptom and at least one additional depressive symptom, with considerable impairment present for minimum two weeks, but not meeting full MDD DSM-IV criteria. This corresponds to the DSM-IV research criteria for minor depressive disorder, except that previous MDD was not considered an exclusion criterion [28]. From here on, the terms depressed and depressive children refer to the group including both children with MDD and SD.

The DAWBA depression section exhibits skip rules. Hence, informants are initially asked to report on depressive core symptoms within the previous month. If core symptoms are reported, informants are presented the full depression section covering all depressive symptoms, associated impairment, and open-ended questions for more detailed descriptions in their own words.

The DAWBA parent version also includes a background section covering potential life stressors; e.g. poor physical health, school problems, past year stressful life events and family stress. Parent self-report anxiety and depressive symptoms were assessed using the 10-item Everyday Feelings Questionnaire (EFQ) [56]. The EFQ has been validated in both epidemiological [56] and clinical [57] populations. The DAWBA background section was not available in Danish when the pilot study was carried out, which explains variation in some reported results related to stressors.

2.3. Data analysis

The case groups comprised children diagnosed with SD and MDD. If a child from the random sample comparison group had developed a depressive disorder in Phase 2, he/she was transferred to the appropriate case group. Attrition analyses were performed comparing gender and birth year between responders and non-responders.

The exposure odds ratios (ORs) for depressive symptoms, comorbid disorders and gender, were compared in binary logistic regression analyses. Rates of additional depressive symptoms for the SD and MDD groups were compared using Pearson’s chi-squared test and Fisher’s exact test.

SDQ scores at diagnostic assessment (Phase 2) were treated as exposure variables and dichotomized at the 90th percentile of the random sample. SDQ reported overall functional impairment was compared between depressed and non-depressed children and between children with MDD and SD using binary logistic regression. Multiple logistic regressions were performed, adjusting each SDQ score for the others (exempting total score that depends on the subscale scores).

Functional impairment due to a depressive disorder was measured by the DAWBA. Information on four areas of function (family, friendships, learning/school, and leisure) as well as distress (all coded 0, 1, 2, 3) was obtained from parents, and treated as a sum score (0–15). Comparisons were made between children with SD and MDD using two-sample t-test with equal variance.

Stressful life events (SLEs) were coded as dummy variables and analyzed on a crude level. In separate analyses, the cumulative effect of SLEs was estimated (zero, one, two or more), with no SLE as the baseline. EFQ scores were dichotomized at the 90th percentile of the distribution for mothers of random sample children.

The exposure ORs for life stressors were compared between MDD, SD and non-depressed in binary logistic regression analyses. Furthermore, life stressor sum scores were created and one-way ANOVAs were performed comparing both sum scores and logarithmic transformation of sum scores between groups. Life stressor sum scores were further compared post hoc pairwise using Bonferroni correction for t-test.

The DNBC point prevalence of SD and MDD was calculated based on the frequency of these conditions in the random sample group. SDQ scores at age seven (Phase 1) were treated as exposure variables and dichotomized at the 90th percentile of the random sample. Comparisons were made for depressed vs. non-depressed groups and for MDD vs. SD, using both unadjusted binary logistic regression, and multiple logistic regressions adjusted for other SDQ scores (except for SDQ total score).

Interrater reliability was analyzed using Fleiss’ Kappa [55]. STATA 12 or 13 was used for statistical analyses (www.stata.com).

3. Results

Of the 4500 DNBC mothers invited, 3421 filled out the SDQ and DAWBA online (response rate 76%) (Fig. 1). Participating children had a mean age of 8.98 years (SD 0.75, range 8–10 years) and 52.8% were boys. Attrition analyses showed no difference between responders and non-responders for child gender. However, mothers of children born in 2002 and 2003 were less likely to respond than mothers of children born in 2001.

Of the 1500 random sample mothers invited, 1187 responded (response rate 79%). From this random sample group 6 children met criteria for MDD, while 12 children met criteria for SD. These children were therefore transferred to the respective case groups (leading to a non-depressed group of N = 1169). In total, 35 children were diagnosed with MDD and 55 children were diagnosed with SD.

Interrater reliability between the three DAWBA raters was tested prior to independent DAWBA rating using Fleiss’ Kappa (K) [55]. Agreement among raters ranged from substantial for anxiety disorders (K = 0.64) to almost perfect for MDD (K = 0.82) and oppositional/conduct disorders (K = 0.91), according to Landis and Koch [54].

3.1. Depressive symptoms

Table 1 presents the frequency of depressive core symptoms and self-harm symptoms in children with MDD, SD and non-depressed children. All symptoms were more
frequent for children with SD or MDD than for non-depressed (p < 0.001). For both depressive groups, depressed mood was the most frequent core symptom, followed by irritability and anhedonia. Anhedonia was very rare in the non-depressed group (1%) but a frequent symptom for children with MDD (63%) and somewhat frequent for SD (31%). When we adjusted for all other clinical features listed in Table 1, anhedonia was the item that best predicted MDD status (adjusted OR 36.92; CI 110.7–434.3; p < 0.001) and anhedonia was the item that best predicted MDD status (adjusted OR 36.92; CI 110.7–434.3; p < 0.001) (Table 1). Comparing MDD and SD children, there was a trend towards more conduct or oppositional disorders in the MDD group compared to the SD group (p = 0.06), and this group also had a significantly higher SDQ conduct subscale score (p < 0.001) (Table 2).

3.2. Comorbid disorders

As expected, children with SD or MDD more often met criteria also for anxiety disorders and conduct or oppositional disorders, compared to non-depressed children (p < 0.001) (Table 1). Comparing MDD and SD children, there was a trend towards more conduct or oppositional disorders in the MDD group compared to the SD group (p = 0.06) and children with MDD and SD had the highest impact scores compared to non-depressed children (p = 0.0001) (Table 2). However, looking at the impairment caused specifically by the depressive symptoms (reported in the DAWBA depression section), the mean impact score was higher for MDD than for SD children (10.25 vs. 7.67; t = 4.35; p < 0.0001) at the time of assessment.

3.3. Distress and functional impairment

Overall functional impairment was measured by the SDQ in Phase 2. As expected, children with SD or MDD had higher impact scores compared to non-depressed children, also when adjusted for other SDQ problem areas, but there was no difference between the two depressive groups (Table 2). However, looking at the impairment caused specifically by the depressive symptoms (reported in the DAWBA depression section), the mean impact score was higher for MDD than for SD children (10.25 vs. 7.67; t = 4.35; p < 0.0001) at the time of assessment.

3.4. Life stressors

The frequency of various life stressors as outlined in the DAWBA background section was compared between depressed and non-depressed children, and between the two depressive groups (Table 3). The analyses included 60 depressive and 1111 random sample children (due to missing data on the background section). Children with MDD or SD were more likely to have a poor physical health than non-depressed children (p < 0.001), and children with MDD more frequently suffered from convulsions or epilepsy than non-depressed children with epilepsy.

---

**Table 1**

Frequency of depressive core symptoms, self-harm symptoms, comorbidity and male gender.

<table>
<thead>
<tr>
<th></th>
<th>MDD (N = 35)</th>
<th>SD (N = 55)</th>
<th>Non-depressed (N = 1169)</th>
<th>MDD vs. Non-depressed</th>
<th>SD vs. Non-depressed</th>
<th>MDD vs. SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Core symptoms</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depressed mood</td>
<td>33 (94.3)</td>
<td>52 (94.5)</td>
<td>192 (16.4)</td>
<td>84.0 (20.1–352.8)***</td>
<td>88.2 (27.3–285.3)***</td>
<td>1.8 (0.2–18.4)</td>
</tr>
<tr>
<td>Irritable mood</td>
<td>31 (88.6)</td>
<td>25 (45.5)</td>
<td>129 (11.0)</td>
<td>62.5 (21.7–179.8)***</td>
<td>6.7 (3.8–11.8)***</td>
<td>11.1 (2.3–54.3)***</td>
</tr>
<tr>
<td>Anhedonia</td>
<td>22 (62.9)</td>
<td>17 (30.9)</td>
<td>14 (1.2)</td>
<td>139.6 (58.8–331.5)***</td>
<td>36.9 (17.0–80.3)***</td>
<td>4.0 (1.3–12.3)***</td>
</tr>
<tr>
<td>Self-harm symptoms</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Talked about self-harm</td>
<td>16 (45.7)</td>
<td>19 (34.5)</td>
<td>24 (2.1)</td>
<td>40.1 (18.4–87.3)***</td>
<td>25.1 (12.6–50.0)***</td>
<td>1.5 (0.5–4.5)</td>
</tr>
<tr>
<td>New self-harm</td>
<td>3 (8.6)</td>
<td>4 (7.3)</td>
<td>3 (0.3)</td>
<td>36.4 (7.1–187.2)***</td>
<td>30.4 (6.6–140.0)***</td>
<td>3.7 (0.3–43.4)</td>
</tr>
<tr>
<td>Ever self-harm</td>
<td>6 (17.1)</td>
<td>7 (12.7)</td>
<td>5 (0.4)</td>
<td>48.1 (13.9–166.6)***</td>
<td>33.9 (10.4–110.7)***</td>
<td>2.6 (0.5–12.9)</td>
</tr>
<tr>
<td>Comorbid disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anxiety disorder</td>
<td>8 (22.9)</td>
<td>8 (14.5)</td>
<td>23 (2.0)</td>
<td>14.8 (6.1–36.0)***</td>
<td>8.5 (3.6–20.0)***</td>
<td>2.5 (0.6–10.5)</td>
</tr>
<tr>
<td>Conduct or Oppositional</td>
<td>8 (22.9)</td>
<td>5 (9.1)</td>
<td>11 (0.9)</td>
<td>31.2 (11.6–83.7)***</td>
<td>10.5 (3.5–31.5)***</td>
<td>4.4 (1.0–19.7)***</td>
</tr>
<tr>
<td>Defiant Disorder</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male gender</td>
<td>24 (68.6)</td>
<td>36 (65.5)</td>
<td>604 (51.7)</td>
<td>2.0 (1.0–4.2)</td>
<td>1.8 (1.0–3.1)</td>
<td>0.8 (0.3–2.6)</td>
</tr>
</tbody>
</table>

Logistic regression; *p < 0.05; **p < 0.01; ***p < 0.001, p = 0.06.
Table 2

<table>
<thead>
<tr>
<th></th>
<th>MDD vs. SD</th>
<th>SD vs. non-depressed</th>
<th>MDD vs. SD</th>
<th>SD vs. MDD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Crude OR SDQ ≥ 90th percentile (CI)</td>
<td>Adj OR SDQ ≥ 90th percentile (CI)</td>
<td>Crude OR SDQ ≥ 90th percentile (CI)</td>
<td>Adjusted OR SDQ ≥ 90th percentile (CI)</td>
</tr>
<tr>
<td>Hyperactivity subscale</td>
<td>6.3 (2.7)</td>
<td>5.8 (2.4)</td>
<td>2.4 (2.3)</td>
<td>1.8 (0.9)</td>
</tr>
<tr>
<td>Emotional subscale</td>
<td>6.8 (2.5)</td>
<td>6.6 (2.3)</td>
<td>2.1 (1.8)</td>
<td>1.1 (1.3)</td>
</tr>
<tr>
<td>Conduct subscale</td>
<td>4.6 (2.2)</td>
<td>4.2 (2.2)</td>
<td>1.8 (1.3)</td>
<td>0.8 (0.8)</td>
</tr>
<tr>
<td>Peer subscale</td>
<td>6.2 (2.8)</td>
<td>7.2 (2.2)</td>
<td>1.6 (0.6)</td>
<td>0.3 (0.3)</td>
</tr>
<tr>
<td>Prosocial subscale</td>
<td>5.4 (2.5)</td>
<td>5.2 (2.2)</td>
<td>1.0 (0.8)</td>
<td>0.3 (0.3)</td>
</tr>
<tr>
<td>Impact subscale</td>
<td>22.0 (5.9)</td>
<td>19.6 (5.8)</td>
<td>6.0 (6.0)</td>
<td>2.5 (2.5)</td>
</tr>
</tbody>
</table>

sd: standard deviation, CI: confidence interval.

† Adjusted for other SDQ scores (except for total score that is dependent on SDQ subscale scores).

sd: standard deviation, CI: confidence interval.

† Adjusted for other SDQ scores (except for total score that is dependent on SDQ subscale scores).

sd: standard deviation, CI: confidence interval.

† Adjusted for other SDQ scores (except for total score that is dependent on SDQ subscale scores).

Comparison of means between MDD and SD was performed. The difference between groups remained statistically significant (F(2,1158) = 29.84, p = 0.000). However, after log transformation of the stressor sum score, the pair-wise comparison of means between MDD and SD was not statistically significant (F(2,1158) = 15.42, p = 0.000). Life stressor sum score means were also compared pairwise using Bonferroni corrected t-test. All pairs showed a statistically significant difference in means (SD vs. non-depressed p = 0.000; MDD vs. non-depressed p = 0.000; SD vs. MDD p = 0.042).

The life stressor sum score was not completely normally distributed and therefore a logarithmic transformation was performed. The difference between groups remained statistically significant (F(2,1158) = 29.84, p = 0.000). However, after log transformation of the stressor sum score, the pair-wise comparison of means between MDD and SD was not statistically significant (F(2,1158) = 15.42, p = 0.000). Life stressor sum score means were also compared pairwise using Bonferroni corrected t-test. All pairs showed a statistically significant difference in means (SD vs. non-depressed p = 0.000; MDD vs. non-depressed p = 0.000; SD vs. MDD p = 0.042).

The life stressor sum score was not completely normally distributed and therefore a logarithmic transformation was performed. The difference between groups remained statistically significant (F(2,1158) = 29.84, p = 0.000). However, after log transformation of the stressor sum score, the pair-wise comparison of means between MDD and SD was not statistically significant (F(2,1158) = 15.42, p = 0.000). Life stressor sum score means were also compared pairwise using Bonferroni corrected t-test. All pairs showed a statistically significant difference in means (SD vs. non-depressed p = 0.000; MDD vs. non-depressed p = 0.000; SD vs. MDD p = 0.042).

The life stressor sum score was not completely normally distributed and therefore a logarithmic transformation was performed. The difference between groups remained statistically significant (F(2,1158) = 29.84, p = 0.000). However, after log transformation of the stressor sum score, the pair-wise comparison of means between MDD and SD was
3.6. Mental health at age seven

Children who developed MDD or SD at age 8–10 years were more likely to have high impairment (measured by SDQ) already at age seven compared to non-depressed children (Table 4). This association persisted, when adjustments for other SDQ subscale scores were performed (MDD p < 0.001; SD p < 0.01). Similarly, an emotional subscale score at or above the 90th percentile was associated with later MDD and SD, when controlling for other subscale scores (p < 0.01 and p < 0.001 respectively). In addition, children who later developed SD were more likely than non-depressed children to have a high hyperactivity subscale score at age seven years (p < 0.001). When we compared SDQ scores at age seven years between children who later developed depressive disorders, only the functional impairment score differed between groups (Table 4), being significantly higher for children with later MDD compared to children with later SD (p < 0.05).

4. Discussion

We identified 90 children in the Danish National Birth Cohort with pre-pubertal depressive disorder. Due to the diagnostic criteria, children with MDD clearly presented more depressive symptoms (at least five) than children with SD (at least two and less than five). However, the specific
Table 4: SDQ at Phase 1 (age seven years).

<table>
<thead>
<tr>
<th></th>
<th>MDD vs. SD</th>
<th>MDD vs. non-depressed</th>
<th>SD vs. non-depressed</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Crude OR SDQ</td>
<td>Adjusted OR SDQ</td>
<td>Crude OR SDQ</td>
</tr>
<tr>
<td>Hyperactivity subscale</td>
<td>90th percentile (CI)</td>
<td>90th percentile (CI)</td>
<td>90th percentile (CI)</td>
</tr>
<tr>
<td>Emotional subscale</td>
<td>90th percentile (CI)</td>
<td>90th percentile (CI)</td>
<td>90th percentile (CI)</td>
</tr>
<tr>
<td>Peer subscale</td>
<td>90th percentile (CI)</td>
<td>90th percentile (CI)</td>
<td>90th percentile (CI)</td>
</tr>
<tr>
<td>Total score</td>
<td>90th percentile (CI)</td>
<td>90th percentile (CI)</td>
<td>90th percentile (CI)</td>
</tr>
</tbody>
</table>

sd: standard deviation, CI: confidence interval.

*p < 0.05; **p < 0.01; ***p < 0.001.

Still, three depressive symptoms were more frequent in children with MDD than children with SD: anhedonia, irritability and worthlessness/guilt. Anhedonia was the core symptom best predicting MDD status, supporting that anhedonia is a marker of depression severity also in this age group, as observed in preschool children [58], adolescents [30] and adults [29]. Also, anhedonia, depressed mood and worthlessness/guilt are the depressive symptoms most predictive of conversion of adolescent SD into MDD [21,59]. In our study, depressed mood was the symptom best predicting SD status, whereas worthlessness/guilt was significantly higher in children with MDD than SD. Irritability was significantly more common in MDD than SD, but it was a quite common symptom in the non-depressed population (11.0%), rendering anhedonia a more efficient predictive marker (1.2% in the non-depressed population). If a child displays diminished interest and pleasure, it should initiate further examination, because the child might have MDD or be at high risk for developing MDD in the near future.

Anxiety disorders and oppositional/conduct disorders were equally frequent comorbid conditions in children with SD and MDD. Compared to SD, there was a trend for more frequent conduct and oppositional disorders in MDD, which was supported by a significantly higher SDQ conduct subscale score in the MDD group. Some studies have reported similar levels of comorbid disorders for childhood SD and MDD [60,61], while others have found less comorbid disorders in SD than in MDD [62,63].

Overall functional impairment measured by the SDQ was high in both children with SD and MDD and did not differ between depressive groups. This is an important finding, underlining the severity of SD and its comorbid conditions and the influence on everyday functioning of the child. However, distress and functional impairment caused by the depressive condition reported on DAWBA were significantly higher for children with MDD than with SD. This suggests that functional impairment due to a childhood depressive disorder could follow a dimensional pattern of severity, where SD is placed between MDD and non-depressed. This is equivalent to the dose–response relationship between depressive condition severity and functional impairment level observed in adults [64]. Lewinsohn and colleagues also showed that the level of psychosocial impairment increased as a direct function of the number of depressive symptoms in adolescents [65].

We found that children with MDD and SD experience more life stressors than non-depressed children, when looking at life stressors individually and as a sum score.
However, interpretation of these results should be conservative, considering the small sample sizes in our depressed groups. In line with previous studies poor physical health and epilepsy were associated with depressive disorders [39,40]. Children with depressive disorders had more special education at schools, although their mothers still reported an unmet need for school support. However, due to the cross-sectional design of the study, it cannot be ruled out that school problems could be a consequence of the depressive condition, rather than a risk factor for development of depression. This is a topic for future longitudinal risk factor studies. Children with SD had more learning disabilities than non-depressed children and also compared to children with MDD. This finding is supported by a meta-analysis indicating that learning disabilities cause depressive symptoms, but not MDD [66]. It is possible that children with learning disabilities develop emotional symptoms due to a challenging school situation that are not prone to further development into MDD.

The experience of stressful life events (SLEs) was more common for children with depressive disorders than non-depressed. Children with MDD had more often experienced severe disease or hospitalization, whereas children with SD had more often experienced loss of a friendship. Both depressive groups were more exposed to parental divorce or separation in the previous year compared to non-depressed children, which is in line with studies of adolescents demonstrating that parental divorce or paternal absence increases the risk for depressive symptoms [35,67,68]. The exposure to SLEs indicated a dose–response relationship, where an association with multiple SLEs was observed for children with SD, but at a lower level than the association for children with MDD. However, the summed experience of life stressors did not significantly differ between children with MDD and SD. Therefore our hypothesis that a dose–response relationship would exist between experienced life stressors and depressive symptoms could not be confirmed. Still, there were trends in this direction and testing the hypothesis on larger depressed sample sizes is recommended.

Families of depressed children were characterized by more marital problems, poor parental psychological health, unemployment, and financial problems than families of non-depressed children. Given that our comparison group was a random sample (children with hyperactivity, anxiety and conduct disorder remained in the group), this is reliable and important information. The mothers of children with SD and MDD had higher levels of anxious and depressive symptoms according to the EFQ, compared with mothers of non-depressed children. Although we cannot draw causal implications from the present cross-sectional design, several studies find that children with clinically depressed first-degree relatives have a higher risk of developing SD [69] and MDD [10]. Our study might also reflect that children seem to display depressive symptoms parallel to depressive symptoms displayed by their mother [42]. However, it is also possible that shared risk factors increase the risk for depression in both parents and children, or that the burden of caring for depressed children acts as a stressor and increases internalizing symptoms in parents. This should be explored further when working with children and families clinically.

In the DNBC random sample, we found an MDD point prevalence of 0.5% and SD point prevalence of 1.0. The prevalence of MDD and SD in pre-pubertal children is rarely compared but generally, studies find that SD is more prevalent than MDD [27]. A study of 9-year-old girls reported point prevalence estimates of 1.8% (MDD) vs. 2.5% (SD) [70]. As opposed to our study, this study included child reports at clinical assessment, which might explain the higher rates [71]. Two studies that both used the DAWBA but focused on all psychiatric disorders reported very low point prevalence rates in this age group of MDD and SD in Great Britain (0.27% vs. 0.07%) [52] and Norway (0.07% vs. 0.11%) [48]. A Brazilian study using DAWBA assessed 6-year-olds and showed a 1.3% prevalence of depressive disorders, but it was not specified how major and minor depression was defined [72]. Cohort participants usually present higher socio-economic status and health status than non-participants [45], which has also been demonstrated for the DNBC [73]. We therefore believe that the point prevalence rates reported in this study are likely to represent an underestimation of the Danish population.

Children diagnosed with MDD or SD at age 8–10 years showed functional impairment and emotional symptoms already at age seven. Functional impairment is a significant risk factor for depression also in adolescents, where Lewinsohn et al. showed that 19.4% of study participants with functional impairment developed MDD vs. 7.3% of those without functional impairment [65]. This indicates that emotional symptoms are rather persistent in children, and that early identification of children with functional impairment and emotional symptoms may represent an important window of opportunity for prevention of MDD.

4.1. Strengths and limitations

This study collected data from a reasonably large population-based sample of almost 3500 pre-pubertal children. Large-scale population-based studies are necessary in order to address subclinical conditions of rare disorders. The response rate of 76% was good compared to other Nordic population-based studies [48,74]. The comparison group was sampled randomly prior to sampling of children who were screen-positive for psychiatric symptoms, making it representative to the source population [45]. Consequently, our comparison group includes children with non-depressive psychiatric disorders like externalizing disorders and anxiety disorders as opposed to a comparison group of children that are screen-negative for psychiatric symptoms. Our findings are therefore conservative, yet reliable.

The use of parent information only is a limitation that might lead to an underestimation of the prevalence, because
children and adolescents usually report more internalizing symptoms with superior predictive value compared to their parents [71]. Another limitation is that mothers with depressive symptoms could falsely report increased depressive or behavioral symptoms about their child due to their own condition, although maternal reporting bias is estimated to be smaller for general population samples [75,76]. The association could also be in the opposite direction where a depressive child causes emotional symptoms and distress in the mother. Finally, the statistical comparisons of life stressors are numerous and include cells with few cases. Therefore conclusions about specific risk factors should be cautious.

5. Conclusion

Studies of adolescents and adults show that subjects with SD have an elevated risk for developing MDD. Our study gives no reason to believe that this would be any different in children.

We present the phenotypic characteristics of children with SD and MDD. The similarities of these two groups are striking concerning depressive symptomatology, frequency of self-harm symptoms, comorbidity, experienced life stressors and overall functional impairment. In fact, the number of depressive symptoms and the level of depression-related functional impairment represent the main differences between childhood SD and MDD.

Anhedonia stands out as being very rare in non-depressed children and it is a severity marker that should always alert the clinician. Furthermore, children with SD and MDD experience multiple life stressors, and we should keep the possibility of reducing these in mind for treatment purposes.

Children with MDD and SD at age 8–10 years show emotional symptoms and resulting impairment already at age seven. Furthermore, the incidence rates of depression rise sharply after puberty. We therefore believe that childhood would be an important time window to identify subjects with SD and target them with indicated interventions aiming to prevent the deterioration of their condition.

Acknowledgment

This study was funded by grants from the Psychiatric Research Fund of the Region of Southern Denmark, the Lundbeck Foundation and the University of Southern Denmark. The funders had no involvement in any aspect of the study.

The Danish National Research Foundation has established the Danish Epidemiology Science Centre that initiated and created the Danish National Birth Cohort. The cohort is furthermore a result of a major grant from this Foundation. Additional support for the Danish National Birth Cohort is obtained from the Pharmacy Foundation, the Egmont Foundation, the March of Dimes Birth Defects Foundation, the Augustinus Foundation, and the Health Foundation.

The DNBC 7-year follow-up is supported by the Lundbeck Foundation (195/04) and the Danish Medical Research Council (SSVF 0646).

The research secretaries Tina Ravn and Bente Anthony are acknowledged for their extraordinary help and support with the conduction of the study.

The child and adolescent psychiatrists Claudia Drechsler Christensen, Sanne Kloppenborg and Morten Ørnstrup from the Mental Health Services in the Region of Southern Denmark contributed significantly by rating the DAWBA interviews of the study.

David Gyllenberg, University of Turku, is acknowledged for his qualified feed back on a previous draft of this paper.

Inger Kristine Meder at the Danish National Birth Cohort, Statens Serum Institut, Copenhagen, is acknowledged for qualified help with the logistics.

It is due to the unique and on-going contribution of children and mothers of the Danish National Birth Cohort that this study has been achievable.

References


