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## RELATED ARTICLES

I. Kapornai, K., & Vetró, A. (2008). Depression in children. *Current Opinion in Psychiatry*, *21*(1), 1-7. **(IF:2,599)**

II. Kapornai, K., Gentzler, A. L., Tepper, P., Kiss, E., Mayer, L., Tamas, Z., et al. (2007). Early developmental characteristics and features of major depressive disorder among child psychiatric patients in Hungary. *Journal of Affective Disorders, 100*(1-3), 91-101. **(IF:3,144)**

III. Vetró, Á., & Kapornai, K., (2008). A pszichopathológia fejlődése in Vetró, Á. (Ed.) *Gyermek és Ifjúságpszichiátria Medicina*, Budapest

IV. Vetró, Á., Baji, I., Benák, I., Besnyő, M., Csorba, J., Daróczy, G., Dombovári, E., Kiss, E., Gádoros, J., Kaczvinszky, E., Kapornai, K., Mayer, L., Rimay, T., Skultéty, D., Szabó, K., Tamás, Zs., Székely, J., Kovács, M.. (2009) „Risk factors in childhood onset depression" research design, implementation, proceeding: history of 13 years: experience in grant preparation, writing organization in relation to an American NIMH Grant. *Psychiatria Hungarica*, 24(1), 6-14.

V. Kiss, E., Kapornai, K., Tamás, Zs., Baji, I., Rimay, T., Mayer, L., Gádoros, J., Barr, C., Kovacs, M., Vetró, Á. And the International Consortium for Childhood-Onset Depression: Characteristics and risk factors of childhood-onset depression in Hungarian child and adolescent population. *European Psychiatric Review*, in press.

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## Summary

**Introduction:** Identification of early risks for childhood onset major depression (COD) can play a significant role in the intervention and prevention to reduce the severity, duration and long-term consequences of major depressive disorder (MDD). Although some investigators have studied the role of perinatal problems and developmental delay in the development of different psychiatric disorders in children and in depressed adults, the number of available studies investigating the effects of these early risk factors in relation to early onset internalizing psychopathology (COD and anxiety disorders) is limited. From other atypical childhood characteristics, early difficult temperament has been well documented as risk for psychopathology later in life. **Hypothesis:** 1.a) Perinatal problems, developmental delay, and difficult temperament are more frequent in children with COD than in community control kids and 1.b) in their unaffected siblings. 2.a) Early atypical childhood characteristics would render children vulnerable to earlier onset and more severe first episode of major depressive disorder in children. 2.b) A stable, intact, two-parent family early on will act as a protective factor and attenuate the negative impact of atypical childhood characteristics on the onset of COD. 3) Early atypical childhood characteristics would render children vulnerable to earlier onset of first internalizing disorder (i.e., the age at which the first episode of MDD or comorbid dysthymia or anxiety disorder began). **Method:** Participants were children (ages 7–14) with MDD, their unaffected (up to 18 years of age) siblings and community control kids from elementary schools. Diagnoses (via DSM-IV criteria) and onset dates of disorders were finalized "best estimate" psychiatrists, and based on multiple information sources. Mothers provided developmental data in a face-to face structured interview (COD kids and unaffected siblings) and via self-rated version of the same interview about controls. Depressive symptoms were measured by CDI (community controls). **Results:** Early neurodevelopmental characteristics (perinatal problems, delayed motor development, difficult temperament) elevated the risk for COD. Difficult temperament predicted earlier onset of MDD and first internalizing disorder, but its effect was ameliorated if the family was intact during early childhood. Further, the importance of difficult temperament decreased as a function of time. Perinatal problems and developmental delay did not impact onset ages of disorders, and none of the early childhood characteristics associated with MDD episode severity.

**Conclusions:** Children with MDD may have added disadvantage of earlier onset if they had a difficult temperament in infancy. Early caregiver stability may attenuate some adverse effects of difficult infant temperament. Thus improving the support for mothers dealing with infants after perinatal/neurodevelopmental problems and/or with difficult early temperament could have positive effect in the prevention of emotional disorders later in childhood.

# 1. Introduction

A growing body of literature confirms that major depressive disorder (MDD) is common and persistent illnesses in young people (Ryan, 2005; Birmaher et al., 1996; Nobil et al., 2003) is associated with significant impairment in school achievement, interpersonal functioning and increased risk of suicidal behavior and substance use. Based on epidemiologic studies, depression affects about 0.3%-1.4% of preschoolers (Egger and Angold, 2006; Stalets and Luby 2006), 1-2% of prepubertal children and about 3-8% of adolescents, with equal prevalence prior to adolescence in girls and boys (Birmaher et al., 1996, Costello et al., 2003; Lewinsohn et al., 1993; Zalsman et al, 2006). Thus, identification of specific risks for childhood onset major depression (COD) can play a significant role in the early intervention and prevention to reduce the severity, duration, and long-term consequences of this serious disorder.

## *1.1 Vulnerability factors in childhood onset depression*

Numerous individual and familial vulnerability factors have been documented as risks for elevated depressive symptoms and disorder (Kapornai & Vetró, 2008). Among individual vulnerability factors, differences in temperamental and cognitive characteristics, in emotion regulation and in neurobiological regulation, as well as non-affective psychopathology (anxiety) have been extensively identified as possible risk for depression in children (Birmaher et al., 1996; Garber, 2006; Zalsman et al, 2006). Familial risks involve both genetic factors (e.g., familial or parental history of mood disorder, specific gene polymorphisms) and psychosocial factors (e.g., quality of attachment, marital discord, poor family support, dysfunctional parenting practices) which may contribute to the development of depression in the child. Also, there are several other environmental factors (parental loss, divorce, physical/sexual abuse, illness or death of family member) which have been found to have depressiogenic effect (Mayer et al., 2008; Paykel 2003), including early adverse events (e.g., perinatal problems, maltreatment). It is most likely that the accumulation and/or interaction among multiple risks from different domains of vulnerability factors (individual/familiar; biological/environmental) play role in the development of depression (Kapornai & Vetró, 2008).

Thus, in my work I was particularly interested in early neurodevelopmental characteristics (perinatal complications, neurodevelopment problems, and atypical early temperament) that may mirror individual physiological vulnerability to onset and severity of

major depression, and in other biological and environmental factors (age, stable family background) that could have moderating effect in the development of COD.

## *1.2. Early neurodevelopmental characteristics and internalizing psychopathology*

### 1.2.1. Internalizing psychopathology

Problem behavior in children and adolescents can be distinguished into internalizing disorders, which reflects the child's internal distress (e.g., anxiety and depression), and externalizing disorders, which brings the child into conflict with others (e.g., rule-breaking, aggressive behavior and ADHD) (Oldehinkel et al.,2004). These two broad dimensions of psychopathology originally generated from multivariate statistical analyses of different child behavior checklists (Kovacs & Devlin, 1998). In this empirically derived classification, dimensions of „internalizing versus externalizing" behaviors accounted for most signs and symptoms of psychopathology in juveniles (see Achenbach and Edelbrock, 1978). Disorders usually classified as internalizing are listed in the DSM-IV (American Psychiatric Assocoation., 1994) under the anxiety and depressive disorders. There are three types of depressive disorders (major depressive disorder, dysthymic disorder, atypical depressive disorder) and more than 10 anxious diagnostic entities in the DSM classification system (e.g., separation anxiety, generalized anxiety, specific phobia, social phobia, obsessive compulsive disorder, posttraumatic stress disorder).

Current research indicates that there is a strong relationship between early onset depression and anxiety disorders (Axelson and Birmaher., 2001). About 25-50% of depressed youth have comorbid anxiety disorders and about 10-15% anxious youth have depression. Regarding the comorbidity between depressive and anxiety disorders, retrospective and prospective longitudinal researches also indicate that there is a temporal relationship between the two, with anxiety predating depression (Cole et al., 1998; Kovacs et al.,1989).

### 1.2.2. Perinatal and neurodevelopmental problems and internalizing psychopathology

Based on previous researches obstetric-perinatal problems have been defined as preterm birth, delayed labor, atypical birth weight, caesarian section, and special care after birth (e.g., Allen et al., 1998), and neurodevelopmental difficulties as delayed standing, walking, speaking (e.g., van Os et al., 1997). Although some investigators have studied the role of obstetric-perinatal problems and developmental delay in the development of schizophrenia, obsessive compulsive disorder, bipolar disorder or attention deficit hyperactive disorder in children (e.g., Cannon et al., 2002; Geller et al., 2008; Kinney et al., 1998;

Matsumoto et al., 1999; Milberger et al., 1997, Verdoux et al., 1997), and in depressed adults (e.g., Guth et al., 1993; Preti et al., 2000), the number of available studies investigating the effects of these early risk factors in relation to early onset internalizing psychopathology is limited.

According to Preti et al., (2000), adult patients with histories of mood disorder had significantly lower birth weight (for their gestational ages) than did matched normal controls. Furthermore, Guth et al. (1993) found that obstetric complications were more common among cases with early-onset mood disorder than among those with late-onset. Vocisano et al., (1996) reported that inpatients with prolonged, severe, and functionally impairing MDD had higher frequencies of birth related problems and physical disorder in infancy than did less severely depressed outpatients. Additionally, in a birth cohort study, Gale and Martyn (2004) found that low birth weight (LBW) was associated with self-reported depressive symptoms in women during adulthood. Also, adults with childhood-onset affective disorders have been found to attain motor milestones later, and score higher on perinatal insults and lower on gross motor skills (Jaffee et al., 2002; van Os et al., 1997).

The effect of low birth weight and developmental milestones was also investigated in childhood psychopathology. For example, in a population sample of 3344 children and adolescents Liu et al. (2001) concluded that LBW and delayed early childhood development may predict the occurrence of behavioral and emotional problems (measured by Child Behavior Checklist) in later childhood and adolescence. The lower birth weight recently was investigated in relation to genetic susceptibility on depressive symptoms in children using a sample of 2046 twins (aged 8-17 years) (Rice et al., 2006). As Rice et al (2006) found, the effect of lower birth weight for gestational age on depressive symptoms is greater in children with genetic risk, although they emphasized that the association between birth weight and depression does not imply causality. Indeed, there are conflicting results about the link between LBW and early onset depression. A recently reported finding suggested that LBW predicts depression only in adolescent girls (Costello et al., 2007) and there are reports of negative findings in the literature (e.g., Allen et al., 1998; Buka et al., 1993; Najman et al., 2005). For example, findings of associations between perinatal problems and anxiety but not mood disorders (e.g., Allen et al., 1998; Cohen et al., 1989), and findings of positive relationships but lack of diagnostic specificity (e.g., Hirshfeld-Becker et al., 2004).

Inconsistencies in the literature is not surprising, given not only sampling differences, but the various ways in which studies have defined depression (i.e., clinical diagnoses, operational criteria, self-rated scales), ascertained early developmental problems (e.g., retrospective reports of adults, pediatric records, contemporaneous ratings), and quantified key variables

(e.g., event counts, severity scales). Therefore, investigating perinatal problems and other early developmental problems in larger, carefully diagnosed samples using different design in method could serve additional information to improve our knowledge about role of these factors in the development of depression (Kapornai et al., 2007; Kiss et al., 2009).

### 1.2.3. Temperament and internalizing psychopathology.

Although theorists differ in their definitions of temperament and in determination of its dimensions, there is a shared assumption that temperament consists of biologically rooted individual differences in behavioral tendencies that are present early in life and are relatively stable across situations and time (Doussard-Roosevelt et al., 1997; Vetró and Kapornai, 2008). For example, temperament is believed to reflect neurophysiological regulatory capacities (e.g., Rothbart and Bates, 1998), while Buss and Plomin (1984) define temperament as a set of inherited personality traits that are genetic in origin and that appear in infancy (Buss and Plomin, 1984). Twin and adoption studies also suggest that individual differences in infant and child temperament are genetically influenced. However, there is also common understanding among developmental scientists that environmental factors (perinatal events, nutrition, illness, parenting style), including impact of the child's behavior on the environment, may influence the development of the child and thus contribute to his or her expressed temperament. Based on behavioral genetic studies which are intended to estimate the extent to which genetic and environmental factors contribute to temperamental variability, genes account for approximately 20-60% of the variability in most temperament dimensions, while nonshared environments (environmental influences that are unique to each individual) account for the remaining 40-80% of the variance (see, Saudino, 2005). There is little evidence about the influence of shared environmental factors (environmental influences that are shared by family members) on some dimensions of temperament (rhythmicity, soothability, shyness, activity).

Research in infant temperament originally was stimulated by work of Thomas and Chess in the New York Longitudinal Study (NYLS) (Thomas and Chess, 1977). Based on their data of 138 infants from 85 families they posited 9 temperamental dimensions (activity, rhythmicity, approach or withdrawal to unfamiliarity, adaptability, happy or irritable mood, intensity, responsiveness, distractibility, attention-span persistence). Each dimension ranges from high to low, and an individual infant could be placed anywhere on each of the nine dimensions. Infants who were placed high on given dimensions could place high on others as well. From these clustering, Thomas and Chess collapsed the findings across dimensions and posited 3 categories of temperament: easy, slow to warm up and difficult (Vetró and

Kapornai, 2008). Temperamentally difficult infants are typically irregular in their biorhythm, they are prone to intense reactions and adapt slowly to change, and show withdrawal to novelty. Similarly, Rothbart (1989) proposed that infant temperament was comprised of differences in the degree to which infants reacted and regulated their reactivity. Whereas reactivity itself was the response to external stimuli, regulation was the manner in which the infant returned to homeostasis. Regulation could be best measured by the time it took the infant to soothe after the initial reaction. Although Fox (1998) emphasized that infants may be born with individual differences in reactivity, their regulatory capacities are far from complete at birth, infants with difficult temperament (low rhythmicity, intense reactivity, difficulty in soothing) were most likely to develop emotional and behavioral problems in later childhood. Indeed, the link between difficult temperament in infancy and in early childhood and later behavioral problems has been well documented in the literature (Goldsmith and Lemery, 2000; Keenan et al., 1998; Maziade et al., 1989; Mehregany, 1991, Rubin et al., 2003;). For example, in relation to internalizing psychopathology, early difficult temperament as biological regulatory problems including persistent crying and atypical sleeping and/or feeding patterns has been associated with subsequent internalizing symptoms and disorders in childhood (e.g., Keenan et al., 1998; Maziade et al., 1989) and adults with childhood-onset affective disorders have been found to be rated as more difficult babies compared to individuals with adult-onset depression (Jaffee et al., 2002). Specifically, Jaffee et al. (2002) investigated a representative birth cohort (Dunedin Multidisciplinary Health and Development Study) from childhood to adulthood, using DSM-IV diagnoses of MDD. The infant temperament was categorized as “easy” or “difficult” based on mothers’ report on a 3-point scale (0, “easy all of the time” to 2, “very difficult to manage”) whether their child had been difficult to manage as a baby. Furthermore, early low rhythmicity (sleep and eating irregularity) were also reported as predictive factor in childhood and adolescent internalizing psychopathology (Ong et al., 2006). In this study, maternally reported irregular sleep rhythmicity predicted adolescent onset MDD and anxiety disorders in an at risk population of offsprings of depressed parent. To evaluate the early temperament rhythmicity of the child up to 6 years of age, the authors used items regarding the eating and sleeping habits from the Dimensions of Temperament Survey (Lerner at al., 1982) with modified time framing to enhance the accuracy of retrospective recall of the parent. However, there was positive association between the depression and sleep irregularity in adolescent, they didn’t find such association regarding childhood onset MDD and the low eating rhythmicity was predictive for childhood onset anxiety only.

Notwithstanding the well documented link between early temperament and emotional problems later in childhood, the association between early difficult temperament and childhood onset depression is far from clear and could be moderated by other factors (parental attitude) as well (Rothbart, 1981; Wasserman et al., 1990). Similarly, it was postulated by Fox (1998) that although temperament seems to be biologically based, learning to regulate emotional expressions (which is key element in the development of internalizing psychopathology) depends on caregiver input and socialization. Additionally, the cognitive social learning theory acknowledge the importance of biological (genetic, neurophysiologic) factors in emotional development, the role of learning process of emotion regulation (highly depend on family factors such as parental behavior, parent- child relationships, caregiver changes) in the development is also emphasized (Vetró and Kapornai, 2008).

### *1.3. Factors which may have influence on the link between early neurodevelopmental characteristics and depression*

In line with theories detailed above and with suggestions that early risk factors should be studied in models that examine multiple and interactive effects (e.g., Goodman, 2002), in my work several factors are considered which could moderate the association between early childhood characteristics and COD. For example, the child's sex emerged as possible moderator factor, given that neonatal health or motor skill problems have been found to relate to depression or anxiety for boys but not for girls (Reinherz et al., 1999; Sigurdsson et al., 2002). Also, there are some indications that marital partner changes early during a child's life may be one factor in child depression (Kasen et al., 1996; Najman et al., 2005; Phillips et al., 2005). For example, in relation to family status, Kasen et al., (1996) have found elevated risk for depression in boys from families with single mother, while in families with step-parent the girls had higher risk for depression. These results also highlighted the importance of multiple interactive effects of different vulnerability factors. Furthermore, mother's age at birth of the child suggested as influencing factor as well, because relatively younger (Jaffee et al., 2001) and older maternal ages are associated with increased rates of complications for offspring (Gray et al., 2004; van Katwijk & Peeters, 1998). Finally, parents' educational level, and household size are those variables which are usually used as proxy measures for socioeconomic status, which also may affect the development of depressive symptoms and disorder in children (Vetró and Kapornai, 2008).

### *1.4. Aims and hypotheses*

Based on the findings from the literature detailed above, I intended to explore the role of early neurodevelopmental and temperamental problems in the development of childhood onset depression using different study design (case-control studies using different control samples, cross sectional study of children with COD) in a large, representative national sample of Hungarian children. The aims of my work were: 1) to test whether depressed children differed from community controls and/or unaffected siblings in terms of early neurodevelopmental and temperamental characteristics; 2) to examine how early atypical neurodevelopment and difficult temperament affect the features of major depression (age of onset, severity) in COD children; and 3) given that MDD often presents with comorbid dysthymic and anxiety disorders (generally emerge earlier than does MDD), to examine whether early neurodevelopmental and temperamental problems have affect on these diagnoses as well. More specifically, I hypothesized:

1.a) Perinatal problems, developmental delay, and difficult temperament are more frequent in children with COD than in community control kids.

1.b) Perinatal problems, developmental delay, and difficult temperament are more frequent in children with COD than in their unaffected siblings.

2.a) Perinatal problems, developmental delay, and difficult infant temperament would render children vulnerable to earlier onset and more severe episodes of major depressive disorder.

2.b) a stable, intact, two-parent family early on will act as a protective factor and attenuate the negative impact of atypical childhood characteristics on the onset of COD.

3.) Given that the effects of early neurodevelopmental problems may not be specific to MDD I hypothesized that perinatal problems, developmental delay, and difficult infant temperament would render children vulnerable to earlier onset of first internalizing disorder (i.e., the age at which the first episode of MDD or comorbid dysthymia or anxiety disorder began).

## 2. Methods

***Participants***

In the present work I report on three different studies using different samples (MDD probands, their unaffected siblings, community controls from school based sample) from a large Hungarian study (Vetró et al., 2009; Kiss et al., in press) (a part of a Program Project in

Pittsburgh, NIMH grant #MH056193, ended in June, 2007) of genetic and psychosocial risk factors in childhood-onset depression (COD study) (Figure 1.). The recruitment procedures and the descriptions of the different samples I used in my different exploratory studies are detailed below.

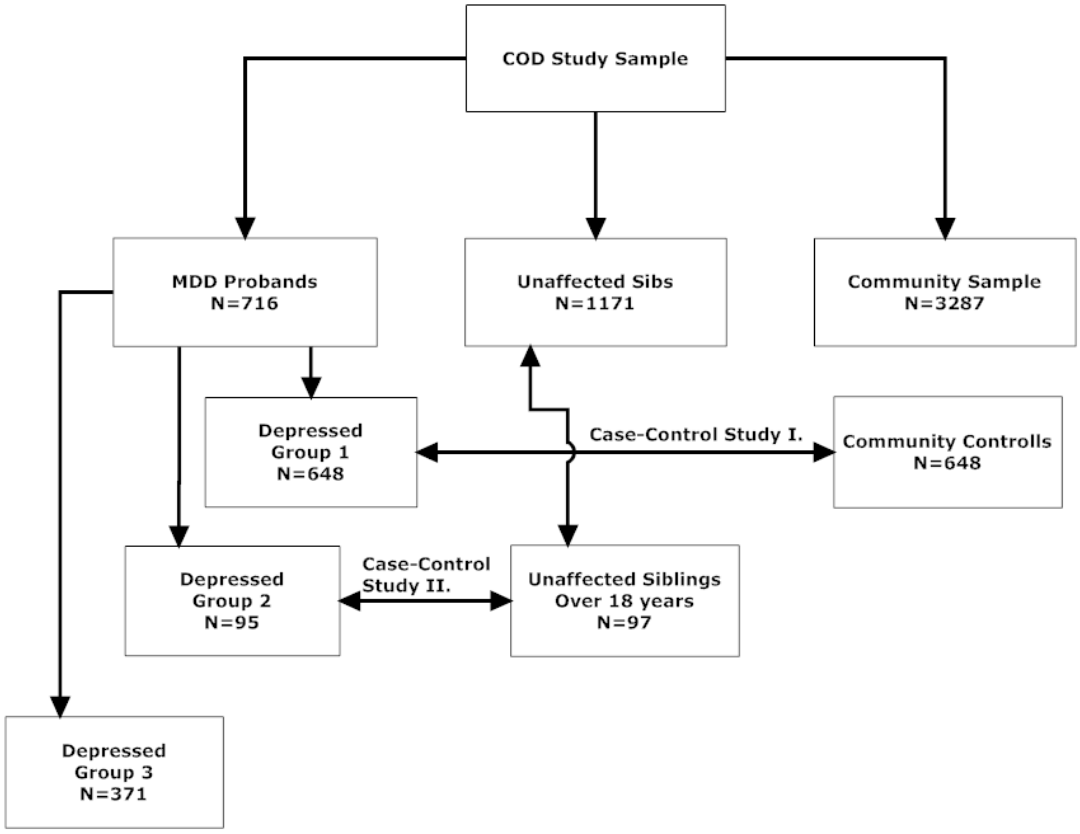



**Figure 1. Study Samples**

## *2.1 Enrollment and assessment procedures in COD study*

### 2.1.1 MDD probands

Children were recruited through 23 child psychiatric facilities (7 of which had both inpatient and outpatient units) across Hungary, serving both urban and rural areas (Vetró et al., 2009). They provided services to at least 85% of the newly registered child psychiatry cases, giving us access to a significant portion of the referred population nationwide. Children presenting at each site were scheduled for a research assessment if they met the following criteria: 7.0 years to 14.9 years old, not mentally retarded, no evidence of major systemic medical disorder, had available at least one biologic parent and a 7 –17.9 year-old sibling (required by the study's genetic component), and attained a predetermined cut-off score on one of various depressive symptom screens (e.g., the short version of the Children's Depressive Inventory; Kovacs and MHS Staff, 2003; selected items from the Child Behavior

Checklist (Achenbach, 1991). Seeking to maximize sensitivity and specificity, these initial screens were based on a previous pilot study with a different clinical sample in Hungary. A clinician-rated symptom scale was used with those patients who had been under care for a while. Further, over the course of recruitment, we adjusted the screen cut-offs, and also screening measures used, so that we could minimize false positives. Children meeting these initial criteria were scheduled for a 2-part evaluation, conducted on 2 separate occasions, about 6 weeks apart, by different clinicians. We obtained written consent for participation signed by both parents and the child, in accordance with the legal requirements in Hungary and the University of Pittsburgh, Pittsburgh, USA. All study procedures and consent forms were approved by the University of Pittsburgh's Institutional Review Board and the Board of Ethics of Human Research of the Hungarian Council for Scientific Research in order to comply with both countries' ethical rules.

The first part of the evaluation entailed administration of the "Mood Disorder Module" of a diagnostic interview (see measurement section), as well as the Intake General Information Sheet (IGIS), a comprehensive demographic and anamnestic data form. Participants also completed self-rated scales (not included in the present report). To set the proper framework and facilitate recall, evaluations started with a semistructured interview, designed to construct a "time line" for the patient from birth to the date of the assessment. The time-line anchors included major "public" events with the corresponding dates (e.g., Christmas, start of a school year) and personally relevant events (e.g., birth of a sibling, both positive and negative familial events, variables reflecting on adjustment). The time-line ("chronograph") served to identify the times when the child's symptoms became problematic and to date disorder onsets and offsets.

The second part of the evaluation involved the full diagnostic interview and the completion of additional self-rated scales, but was administered only if the child proband had met DSM criteria for mood disorder at the first evaluation. (If DSM criteria were not met, the child was assigned an "at-risk" status and entered a follow-up arm of the study). For our diagnostic interview, we used the Interview Schedule for Children and Adolescents–Diagnostic Version (ISCA-D), which is an extension of the Interview Schedule for Children and Adolescents (ISCA) (Sherrill and Kovacs, 2000). The interview, which covers the relevant Axis-I DSM-IV as well as some DSM-III disorders, was conducted by the same interviewer separately with the parent about the child, and the child about him/herself, yielding symptom ratings and diagnoses for "current" as well as "lifetime" disorders. Results of both the first and second parts of the assessments and associated documentation (e.g., psychiatric records) were subjected to a consensus diagnostic procedure (Maziade et al.,

1992). Pairs of senior child psychiatrists, trained as Best Estimate Diagnosticians (BEDs), separately reviewed all material, and then together derived consensus diagnoses. Proband status as well as onset dates of disorders, was based on best-estimate consensus. As described in connection with previous work ([Kovacs et al., 1984a] and [Kovacs et al., 1984b]), operational rules were used to define disorder onset and recovery, and "midpoint" rules were used to date onsets and offsets, if more exact dating was not possible.

The interviews were administered by child psychiatrists and psychologists who completed 3 months of didactic and practical training in the semi-structured interview technique. They were required to reach an average of 85% symptom-agreement on 5 consecutive videotaped interviews against "gold standard" interview ratings provided by the trainers. Routine monitoring and follow-up training sessions served to minimize rater drift. All interviews were audiotaped. Interrater reliability on ISCA-D symptoms was satisfactory (using audiotapes of interviews for *n*=46 pairs of raters). For MDD symptoms, kappas ranged from .64 to .88, with 80% of the coefficients at or above 0.70. For DD symptoms (using DSM-IV criteria), kappas ranged from 0.38 to 0.93, with 80% at or above 0.70. For Generalized Anxiety Disorder symptoms (the most common DSM-IV anxiety diagnosis), kappas ranged from 0.53 to 1.00, with 62.5% at or above 0.70. Similar inter-rater reliability coefficients were obtained for other ISCA-D disorders as well (e.g., Kiss et al., 2007).

The available MDD probands (n= 716) in the COD study, aged 11.8 years (SD= 2.1) on average at study entry, included 390 (54.5%) boys, and 62.2% lived in intact families (both biological parents present); the average household had 4.6 people (SD= 1.2). Reflecting the ethnic composition of Hungary, 94.4% of the sample was Caucasian and the rest were minorities, including Roma (gypsy) and Africans. Mothers had, on average, 11.3 years of education (SD=2.7); fathers had 11.2 years (SD=2.7) of schooling. Anxiety (32%) was the most common co-morbid diagnosis; altogether 50% had major Axis I. psychiatric comorbidity.

### 2.1.2 Unaffected siblings

If a child met the diagnostic criteria of major depressive disorder and become MDD proband in the COD study, the available siblings of him/her in the appropriate age range were scheduled for the same research screening procedure and in case of positive screening, for the same comprehensive diagnostic assessment procedure, described above. As the probands in the study, siblings were followed up to at least 18 years of age by sending yearly a mail-follow-up test packet (MFU). The packet (which was mailed back by the families) includes: a) parental report of interim medical and psychosocial events (short version of our SR-GIS) and

a 26-item DSM depressive symptom checklist (DSC) and b) each child's self-rated depression scale (short CDI). In case of positive screening based on this packet, the sibling was scheduled for the diagnostic assessment procedure. Unaffected siblings are the participants who have never been turned out as depressed up to their age of 18 years during the COD study. Additionally, to increase the available number of unaffected siblings we invited for assessment all the siblings over 18 years of age (not assessed earlier because of negative screenings during the study) to evaluate the existence of current as well as lifetime episode of MDD.

From the COD study, the number of available unaffected siblings over 18 years of age was 97 youngsters (for sample description see **Description of different samples** section).

### 2.1.3 Community controls

Children were recruited from 2 regions of Hungary (north-west and south-east). 1st – 8th grade elementary students were approached from 9 elementary schools in Szeged (2 schools), Győr (4 schools) and the vicinity (Kapuvár, Csorna and Szőreg, 1 school each). Children participated after receiving written consents from the parents. Testing was organized through the schools. Every child received a parental test package including all the forms and parental consent. Parents wishing to participate completed the forms at home and returned all questionnaires and the signed consent to school. Only those children were tested whose parents sent back the completed package. Children filled the questionnaires in school during class under supervision. The questions were read out loud in 1st through 3rd grades; children completed the forms by themselves in higher grades. Members of the research team or psychology/medical students were present during testing in some schools, in others teachers were instructed before distributing the questionnaires. Testing was done anonymously, child-parent pairs were identified by identical 6-digit code numbers. 5224 families were contacted initially, 62.9% of the families agreed to participate (N=3287).

## *2.2 Measurements*

### 2.2.1 Intake General Information Sheet for Children and Adolescents (IGIS) and Self-Rated General Information Sheet (SR-GIS).

The IGIS and SR-GIS are event-focused structured interviews containing fully structured, pre-coded item response choices. In IGIS the parent is interviewed about the child's socio-demographic/family background, developmental, educational, and health history, and major life events. An entire section of the IGIS is dedicated to enumerating parental caregivers for each year of the child's life. The SR-GIS is a self-rated version of the

IGIS for the parent and both versions are used for lifetime information. The IGIS was used as a structured interview in the MDD sample, and SR-GIS was used in the community controls.

Using IGIS and SR-GIS items that pertain to the child's early development history from his/her birth to toddler age, we created four indices of atypical development: *Neurodevelopmental problems* (9 items), *Perinatal Problems* (4 items), *Developmental Delay* (2 items), and *Difficult Temperament* (3 items). The construct of temperament includes multiple dimensions tapping emotional, biological, and behavioral reactivity and regulation (). Our temperament scale included a global question on how difficult it was to comfort the infant (similar to the single-item question included as part of the investigation of Jaffee et al. (2002), and because we were particularly interested in physiological vulnerability, two items measuring biological irregularity (similar to Thomas and Chess's (1977) temperament category of rhythmicity). Each scale reflects the number of "yes" responses to the corresponding items.

In SR-GIS to make easier the rating for the parents, education categories (0=no qualification, 1=elementary school, 2=vocational school, 3=high school, 4=3 years college, 5=university) were used and coded on a scale of 0-5 points to evaluate the level of education of parents. Years of educations of the parents in the group of depressed kids had been recoded to correspond to the education categories of the community controls as follows: 0=0-7 years; 1=7,1-10 years; 2=11years; 3=12-14 years; 4=15 years; 5=16 years or more.

### 2.2.2 Interview Schedule for Children and Adolescents - Diagnostic Version (ISCA-D)

ISCA-D is a semi-structured interview to assess lifetime psychiatric disorders and current psychiatric status in youths up to ~age 19 to 20. It extends our earlier, symptom-based interview, which has been widely used and it has good inter-rater reliability (Sherrill & Kovacs, 2000). The ISCA-D organizes symptoms into disorders, includes most DSM-IV Axis-I diagnoses and allows assessment of "current" and "lifetime" disorders. Hungarian interviewers have achieved satisfactory inter-rater reliability (Kiss et al, 2006). The ISCA-D is completed by interviewing separately the parent (or other adult informant) about the youth, and then the youth about him/herself. For each symptom, the clinician thus has a rating derived from the adult informant interview and one from the child interview: the clinician's final rating of each symptom serves as the basis for diagnoses.

Using ISCA-D information we created an index to evaluate the MDD episode severity. This index was computed for the first episode of MDD based on 15 symptoms, each rated on a 3-point severity scale: 0 = not present; 1 = subthreshold; and 2 = threshold/clinical. If only one item was missing, that item was pro-rated. Because all children in the sample had MDD,

and the minimum of 5 symptoms rated at the "clinical" level was required for the diagnosis, the possible range for the severity score was 10 to 30.

### 2.2.3 Children depression Inventory-short version (CDI-Short Form)

The 10-item CDI Short Form was developed from the CDI that is a 27-item self-rated symptom oriented scale suitable for school-aged children and adolescents. The Short Form provides an easily measured, empirical assessment of the extent to which the child exhibits depressive symptoms. Based on data from normative sample (N=1266) CDI Short Form correlates r=0,89 with the full inventory (Kovacs M. & MHS Stuff; 1993). Its alpha reliability coefficient is equal to 0.80, indicating that is approximates the overall content of the full CDI at an acceptable level. Each item consists of three choices, keyed 0 (absence of a symptom), 1 (mild symptom), 2 (definite symptom), with higher scores indicating increasing severity. The total score can range from 0-20. The cut-off value for clinical depression is 7 points (Mayer et al., 2006).

## *2.3 Description of different samples investigated in different studies*

### 2.3.1 Depressed group 1. and community control group in case-control study I.

To compare children with depression to community control group on early neurodevelopmental characteristics (article in preparation), I included 648 MDD probands (**depressed group 1.**) from the COD study who were 15 years of age or younger at the time of the interview on behalf of matching on age to **community controls** (from elementary schools). In the depressed group 1. there were 296 (45.68%) girls and the mean age of the children at interview was 11.69 years (SD: 2.03). The girls were older (12.02, SD:2.02) than boys (11.28, SD: 1.95). Mothers' age at the interview on average was 36.57 years (SD:5.16) and mean number of members in the household was 4.63 (SD:1.15). The mean value on the 0-5 likert scale of education was 2.36 (SD:1.21) for the mothers and 2.25 (SD:1.19) for the fathers.

The **community control group** consisted of 648 kids (45.68% girls) from the available community sample (Figure 1). Based on the SR-GIS we included those who had no psychiatric hospitalization, never had taken psychiatric medication or experienced psychiatric or behavioral problems, and did not have short-CDI scores above 7 points. The community control group further was matched to depressed group 1. on age and sex. The mean age in the community controls' group was 11.69 (SD:2.03). Mothers' age at the interview on average was 38.29 years (SD:5.05) and mean number of members in the household was 4.28

(SD:0.87). The mean education level for the mothers was 3.31 (SD: 1.24) and 3.21 (SD:1.32) for the fathers.

### 2.3.2 Depressed group 2. and unaffected siblings in case-control study II.

To compare children with depression to unaffected siblings on early neurodevelopmental characteristics (article in preparation), I included 95 MDD probands (**depressed group 2.**), given their available **unaffected siblings** (N=97) over 18 years of age.

In the **depressed group 2.** children (49.5% girls) were aged on average 11.35 years (SD:1.8) and their mothers at the first interview of the child were 37.81 (SD:4.10) on average. The mean number of persons were living together in the household was 4.95 (SD:1.5) in the depressed group 2. In this sample mothers were educated on average for 11.43 (SD:2.6) years of age, while this value for fathers was 10.67 (SD: 3.6) years.

According to inclusion criteria in the comparison group of **unaffected siblings** (52.6% girls) the mean age was higher (18.3 years, SD:1.30) than in depressed group, and again, by design the mothers were also older (40.87 years on average; SD: 4.30). The mean number of members in the household was 4.79 (SD:1.5). Mothers average education level was 11.31years (SD:2.5) and fathers were educated on average for 11.13 years (SD: 2.5).

### 2.3.3 Depressed group 3. in the study of early developmental characteristics and features of MDD

During the recruitment of MDD sample in COD study, to explore the effect of early neurodevelopmental characteristics on the features (e.g., first episode onset, severity) of MDD I investigated 371 MDD probands (**depressed group 3.**) who were enrolled by December 31, 2003 (Kapornai et al., 2007). They were aged 11.7 years on average (SD = 2.0 years, range: 7.3 - 14.9 years). At study entry, mothers' ages ranged from 26 to 57 years, with a mean of 36.5 years (SD = 5.1). Mothers' years of education ranged from 6 to 21 years (M = 11.6 years, SD = 2.8). A subset of children had comorbid disorders in addition to MDD (e.g., 34.5% had an anxiety disorder, 3.5% conduct disorder; 6.2% had oppositional defiant disorder; and 15.5% attention deficit/hyperactive disorder).

## *2.4 Statistical analyses*

### 2.4.1 Case-control studies

To compare MDD probands (depressed group 1., 2.) to both community controls and unaffected siblings on neurodevelopmental variables and scales Chi2 test and Fischer exact test were used for categorical variables, and independent sample t-test for continuous variables. During the comparison the correlations between psycho-social variables and early

characteristics variables were tested by using correlation matrix with Pearson correlation coefficients method. To compare the group differences in early neurodevelopmental scales (perinatal, developmental, temperamental and total neurodevelopmental) we did analysis of covariance (ANCOVA) with controlling for psychosocial variables (sex, level of parents education, mothers' age at birth, household size). We also did separate analysis by sex to test whether the sex has influence on the associations between the early characteristics and MDD.

### 2.4.2 Early developmental characteristics and features of MDD study

We used survival analysis to examine the effects of variables on onset age of MDD or internalizing disorder. Survival analysis is useful with outcomes or events that depend on elapsed time, and can estimate how predictors may be associated with time to the event. Kaplan-Meier survival curves were generated for subgroups; log-rank tests were used to test statistical significance.

To test for relations between the predictors and the age at which children's first episodes occurred, we first conducted univariate Cox regression analyses with each risk scale and covariate. We report hazard ratios and 95% confidence intervals to indicate the risk of the outcome in any given unit of time, with one unit increase of the predictor. We also checked the proportional hazards assumption about time-dependence for each predictor variables. Second, in an initial multiple regression model, we included the three risk scales, as well as covariates with $p \leq 0.05$ in the univariate Cox models. All hypothesis-driven interaction terms were also included. We then used a backward elimination method, removing each (starting with the one with the largest p-value), and retaining covariates or interaction terms in the final model with $p \leq .05$. Thus, the final multivariate Cox regression models reflect the impact of independent variables and significant interaction terms, while adjusting for demographic factors (where $p \leq 0.05$).

To model the effects of early risk factors on the severity of the children's first depressive episode, we used GLM procedure. We examined the associations between the perinatal, developmental, and temperament problems, as well as how the interaction terms and covariates related to the severity of the MDD symptomatology.

# 3. Results

## *3.1 Case-control study I.*

### 3.1.1. Prevalence rates of neurodevelopmental variables and scores of neurodevelopmental scales in depressed group 1. and community controls

Although we did matching on age and sex between depressed group 1. and community controls, other psychosocial variables still differed between them. Specifically, based on t-test in the depressed group 1. parents were less educated on average ($p<0.0001$), mothers were younger ($p<0.0001$), and household size was larger ($p<0.0001$). On average the number of persons living in household was 4.63 (SD=1.16) in MDD sample and 4.28 (SD=0.87) in community controls. The prevalence rates of specific early developmental variables (except the variable of premature/late delivery time) and all the scores on the developmental scales were significantly higher in depressed group 1. (Table 1.). Overall, the most frequent item in the depressed group 1. was the early sleep problems (about 29% of the cases) followed by the item of usually hard to comfort (28.6%), while these items were significantly ($p<0.0001$) less common in community controls (11.11% and 5.25 % of the controls respectively). Regarding the subscales, the greatest difference between the depressed and controls emerged on the difficult temperamental scale. The psychosocial variables are not correlated significantly any of the subscales (r values ranged: from 0.0005 to 0.06 in the depressed and from 0,001 to 0,06 in the control group $p>0,13$). Whereas, in both the depressed and the control group perinatal scale is slightly correlated with early difficult temperament ($r=0.13$; $p=0.008$ and $r=0.11$; $P=0.004$ respectively) and delayed development scale ($r=0.08$; $p=0.036$ and $r=0.14$; $p=0.0003$ respectively).

**Table 1. Early neurodevelopmental characteristics of depressed group 1. and community controls**

| | Depressed group 1. (N=648) | | | Community controls (N=648) | | |
|---|---|---|---|---|---|---|
| | Item endorsement | | Score Mean (SD) | Item endorsement | | Score Mean (SD) |
| **Variables** | **N** | **%** | | **N** | **%** | |
| Perinatal problem scale | | | 0.76 (0.99)* | | | 0.57 (0.88) |
| Premature/late delivery | 90 | 13.89 | | 81 | 12.50 | |
| Complications during delivery[a] | 151 | 23.30* | | 104 | 16.05 | |
| Very large/small at birth | 135 | 20.83* | | 115 | 17.75 | |
| Special care after birth[b] | 117 | 18.06* | | 75 | 11.57 | |
| Difficult temperament scale | | | 0.78 (0.92)* | | | 0.29 (0.60) |
| Recurrent feeding problems | 139 | 21.52* | | 83 | 12.81 | |
| Recurrent/chronic sleeping problems | 187 | 28.90* | | 72 | 11.11 | |
| Usually/often hard to comfort/soothe | 185 | 28.59* | | 34 | 5.25 | |
| Developmental delay scale | | | 0.23 (0.51)* | | | 0.10 (0.34) |
| Late for age when began to walk | 58 | 8.95* | | 22 | 3.40 | |
| Late to start to speak in sentences | 97 | 14.97* | | 46 | 7.10 | |
| Neurodevelopmental scale (0-9) | | | 1.78 (1.58)* | | | 0.99 (1.21) |

[a]E.g.. excessive bleeding. "cord" around the neck. Rh incompatibility
[b]E.g.. placed in incubator. under special observation
* $p \leq 0.001$

### 3.1.2. Association between neurodevelopmental scales and depression

Results of the ANCOVA analyses indicated that while controlling for all psychosocial variables (sex, parents' education, age of the mothers, household size) depression significantly associated with the perinatal (F=10.73; p=0.0011), the developmental (F=21.73; p<0.0001), the temperamental (F=90.38 p<0.0001) scales and with the total score (F=80.09; p<0.0001) as well. Further, sex of the child's also associated significantly with the developmental subscale and with the total score. Regarding the developmental subscale there was significant depression-by-sex interaction as well (F=6.09; p=0.01) even after adjusting for psychosocial factors (F=6.09; p=0.01), indicating that depressed boys scored significantly higher on developmental scale (delayed in standing, walking and talking) than depressed and control girls.

### 3.1.3. Repeated analysis by sex

The girls (12.02. SD:2.02) in the depressed group 1. were older than boys (11.28. SD: 1.95) and scored lower on developmental (0.13; SD:0.39), temperamental subscales (0.78; SD:0.92) and on the total scale (1.56; SD:1.46) than boys did (0.33; SD:0.58. 0.79; SD:0.93 and 1.95; SD:1.65 respectively). By design, in the community control group girls were also older (mean age for girls: 12.20; SD:2.02; mean age for boys: 11.28; SD:1.95). Girls had lower ratings on developmental (0.07; SD:0.28) and on total scales (0.85; SD:1.08) than boys (0.13; SD:0.39; 1.08; SD:1.30 respectively) in this group as well. The effect of sex, indicated by the depressionXsex interaction in the developmental subscale mentioned above can be seen in the results from these data as well (Table 2.)

**Table 2. Developmental delay scale in the depressed group1. and the community controls by sex**

| | **Depressed group 1.** | **Community controls** |
|---|---|---|
| Developmental delay scale in females (mean±SD) | 0.1318±0.3856 * (N=296) | 0.0709±0.2823 (N=296) |
| Developmental delay scale in males (mean±SD) | 0.3295±0.5842** (N=352) | 0.1335±0.3876 (N=352) |

* $p \leq 0.05$. ** $p \leq 0.01$.

To investigating the group (depressed vs. community controls) differences by sex, chi2 test and t-test procedures were made separately for girls and boys. Results showed that in females there were no significant differences between the depressed and controls regarding the variables of late for walk (p=0.055) and late for speak (p=0.057) and the variable of premature/late delivery was significantly more frequent in control girls (p=0.0112), however at p<0.05 level, all the other early variables and subscales were significantly differentiated between the two groups favoring the depressed sample. In males the differences between depressed and controls were not significant in relation to premature/late delivery (p=0.1267), birth size (p=0.116) and early eating problems (p=0.0921). Yet, the differences between the depressed and controls boys were significant on all neurodevelopmental subscales (at p<0.05), and further the difference on the developmental scale was greater than the difference between the depressed and control females. The depression is also associated significantly to each subscales and total scores in girls and boys as well, while controlling for psychosocial variables was conducted using ANCOVA model.

## *3.2. Case-control study II.*

### 3.2.1. Prevalence rates of neurodevelopmental variables and scores of neurodevelopmental scales in depressed group 2. and unaffected siblings

According to the inclusion criteria (>18 years of age) unaffected siblings were older than kids in the depressed group 2. Other psychosocial characteristics (sex rates, parents' education level, number of living in the household, mothers' age) were similar in the two groups. The psychosocial variables further are not correlated significantly any of the early neurodevelopmental subscales.

The prevalence rates of specific early developmental variables and specific scores on the different neurodevelopmental indices in the depressed group 2. and in the group of unaffected siblings are shown in Table 3. Overall, the highest prevalence rates were observed regarding the hard to comfort (27.4%) and the sleeping problems (18.9%) in the depressed group, while these items were far less common in unaffected siblings (13.4% and 9.3% respectively). Based on $Chi^2$ procedures, the differences on these items were statistically significant between the two groups ($p=0.01$ and $p=0,05$ respectively). The probands in the depressed group scored significantly ($p=0,021$) higher ($0.62\pm0.81$) on difficult temperament scale than youths in the group of unaffected siblings ($0.37\pm0.88$). Other early variables or indices didn't differentiate significantly between the two groups. Further the perinatal problem scale was slightly higher in unaffected siblings, however the difference was not statistically significant ($P=0.279$).

In both the depressed and unaffected siblings' group perinatal scale is correlated with the total developmental scale ($r=0.651$; $p<0.0001$ and $r=0.645$; $p<0.001$ respectively). Further, in the group of unaffected siblings the early difficult temperament scale significantly correlated with the developmental subscale ($r=0.262$; $p=0.010$) and with the total score ($r=0.642$, $p<0.0001$), while in the depressed group 2. the difficult temperament scale showed significant correlation with the total score only ($r=0.751$; $p<0.001$).

**Table 3. Early neurodevelopmental characteristics of the depressed group 2. and unaffected siblings**

| | Depressed group 2. (N=95) | | | Unaffected Siblings>18yr (N=97) | | |
|---|---|---|---|---|---|---|
| | Item endorsement | | Score Mean (SD) | Item endorsement | | Score Mean (SD) |
| **Variables** | **N** | **%** | | **N** | **%** | |
| Perinatal problem scale | | | 0.54 (0.79) | | | 0.67 (0.83) |
| Premature/late delivery | 9 | 9.50 | | 9 | 9.30 | |
| Complications during delivery[a] | 19 | 20.2 | | 17 | 17.5 | |
| Very large/small at birth | 11 | 11.6 | | 20 | 20.6 | |
| Special care after birth[b] | 15 | 15.8 | | 19 | 19.8 | |
| Difficult temperament scale | | | 0.62 (0.81)* | | | 0.37 (0.88) |
| Recurrent feeding problems | 15 | 15.8 | | 14 | 14.4 | |
| Recurrent/chronic sleeping problems | 18 | 18.9* | | 9 | 9.3 | |
| Usually/often hard to comfort/soothe | 26 | 27.4** | | 13 | 13.4 | |
| Developmental delay scale | | | 0.23 (0.47) | | | 0.18 (0.46) |
| Late for age when began to walk | 8 | 8.4 | | 5 | 5.2 | |
| Late to start to speak in sentences | 14 | 14.7 | | 12 | 12.4 | |
| Neurodevelopmental scale (0-9) | | | 1.39 (1.28) | | | 1.22 (1.18) |

[a]E.g.. excessive bleeding, "cord" around the neck, Rh incompatibility
[b]E.g.. placed in incubator, under special observation
* $p \leq 0.05$, ** $p \leq 0.01$.

### 3.2.2. Association between neurodevelopmental scales and depression

Based on ANCOVA procedure, only the difficult temperament scale differentiated significantly (F=5.556; p=0.019) between the depressed group 2. and the group of unaffected siblings. Further, significant depression status-by-sex interaction was found (F=2.908; p=0.036) in the difficult temperament scale. There were no significant associations between the group status and any of the early neurodevelopmental indices in the model.

### *3.3. Integrated results from Case-control study I. and II. regarding the difficult temperament*

The proportions of kids in the different samples with different early temperamental problems can be seen on Figure 2. All the variables referring the difficulty of early temperament were more frequent in the depressed groups than in the community controls. Although, the group of unaffected siblings was not compared to community controls, the data from case-control studies showed that early eating problems and soothability problems emerged with higher frequency in unaffected siblings, while sleeping problems were more common in community controls (11.11%) than in unaffected siblings (9.3%). The difference was the most robust regarding the item of hard to comfort/soothability, which was six times frequent in the depressed group (28.59%) comparing to community controls (5.25%) and about twice as frequent than in unaffected siblings (13.4%). Similarly, sleeping problem was far more common in the group (1.) of depressed youngsters (about 29%) than in community controls (11,11%). Investigating the difficult temperament scale, the results showed significantly higher scores in the depressed group 1. (0.78) and in the unaffected group as well (0.37) compared to the community sample (0.29), however the magnitude of the difference regarding unaffected siblings was smaller.

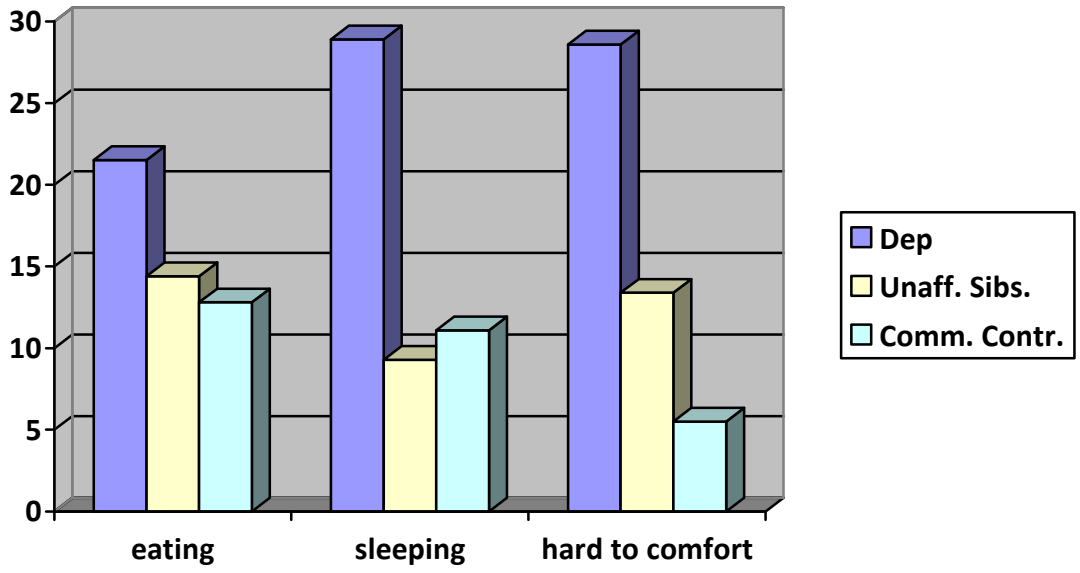



**Figure 2. Rates of variables refer to difficult temperament in the different samples**

## *3.4 Early developmental characteristics and features of MDD study*

### 3.4.1. Prevalence rates of neurodevelopmental variables and scores of neurodevelopmental scales in the depressed group 3.

The specific variables, which comprised the 3 indices of early neurodevelopmental characteristics, had various rates in our sample (Table 4.); in general, developmental delays were least common (from about 8% to 12%) while features of difficult temperament were reported for about 24% to 32% of the cases. The 3 indices were unrelated to each other (r-values ranged from 0.02 to 0.06, $p > 0.24$), and were unrelated to mothers' age at child's birth, mothers' education level, and whether the child was reared in an intact vs. non-intact family early in life. However, boys scored higher on developmental delays ($M = 0.25$, $SD = 0.52$) than did girls ($M = 0.15$, $SD = 0.38$), $t(369) = -2.11$, $p < 0.05$.

**Table 4. Early neurodevelopmental characteristics of depressed group 3. (N=371)**

| | Item endorsement | | Score |
|---|---|---|---|
| **Variables** | **N** | **% of sample** | **Mean (SD)** |
| Perinatal problem scale (0-4) | | | 0.72 (.98) |
| Premature/late delivery | 47 | 12.7% | |
| Complications during delivery[a] | 79 | 21.3% | |
| Very large/small at birth | 70 | 18.9% | |
| Special care after birth[b] | 73 | 19.7% | |
| Difficult temperament scale (0-3) | | | 0.87 (.97) |
| Recurrent feeding problems | 88 | 23.9% | |
| Recurrent/chronic sleeping problems | 118 | 31.9% | |
| Usually/often hard to comfort/soothe | 119 | 32.2% | |
| Developmental delay scale (0-2) | | | 0.20 (.48) |
| Late for age when began to walk without help | 30 | 8.1% | |
| Late to start to speak in sentences | 46 | 12.4% | |

[a]E.g., excessive bleeding, "cord" around the neck, Rh incompatibility
[b]E.g., placed in incubator, under special observation

### 3.4.2. Onset age of MDD

A series of univariate Cox Regression models yielded significant effects for child's sex, early intact family status, and maternal age at child's birth. (See Table 2 for Hazard ratios.) At the onset of their MDD, boys (M = 10.08; SD = 2.12 years) were 1 year younger than girls (M = 11.03; SD = 2.37 years). Children exposed to changes in caregivers before age four were younger at the onset of their MDD (M = 9.68; SD = 1.96 years) than those from intact families (M = 10.60; SD = 2.30 years), and children whose mothers were 35 years and older when they gave birth had earlier onset of MDD (M = 9.14; SD = 1.89) than children with mothers in the normative age group (M = 10.57; SD = 2.30).

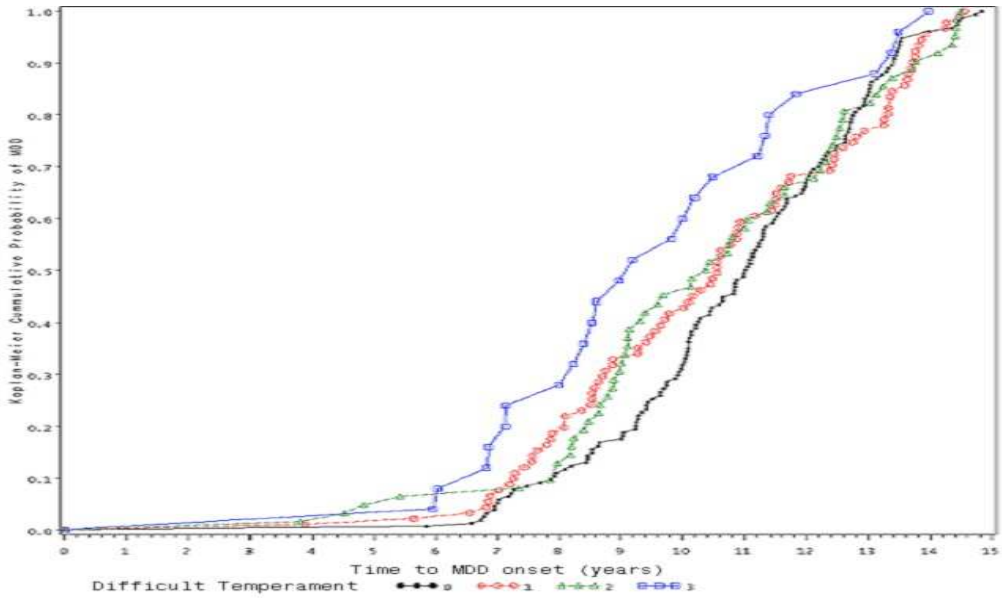
However, in the final multivariate model, mother's age at child's birth became nonsignificant, and only one interaction term was retained. The results indicate that having a difficult temperament and being a boy were associated with earlier onset of MDD (Table 5.). Furthermore, the main effect of temperament was qualified by its interaction with intact family status, and is illustrated by Kaplan-Meier survival curves (separately for intact vs. not-intact families).

**Table 5. Modeling Age of Onset of first MDD Episode (N=371)**

| | **Univariate Models** | **Final Multivariate Model** |
|---|---|---|
| **Variables** | **Hazard Ratio (95% CI)** | **Hazard Ratio (95% CI)** |
| Perinatal problems | 0.98 (0.88, 1.08) | 0.96 (.86, 1.06) |
| Developmental delay | 0.96 (0.77, 1.19) | 0.87 (.69, 1.10) |
| Difficult temperament | 1.11 (0.99, 1.23)$^{+}$ | 5.88 (2.05, 16.83)** |
| Sex (male = 1) | 1.68 (1.36, 2.08)*** | 1.75 (1.41, 2.17)*** |
| Intact family until age 4 | 0.64 (0.45, 0.91)* | 0.93 (0.58, 1.47) |
| Mother's education (years) | 0.98 (0.94, 1.01) | -- |
| Maternal age at birth (years) | | |
| 16-18 vs. 19-34 | 0.94 (0.60, 1.46) | -- |
| 35-46 vs. 19-34 | 1.73 (1.10, 2.72)* | -- |
| Temperament X Intact Family | -- | 0.65 (.45, .92)* |
| Temperament X Time | -- | 0.58 (.37, .92)* |

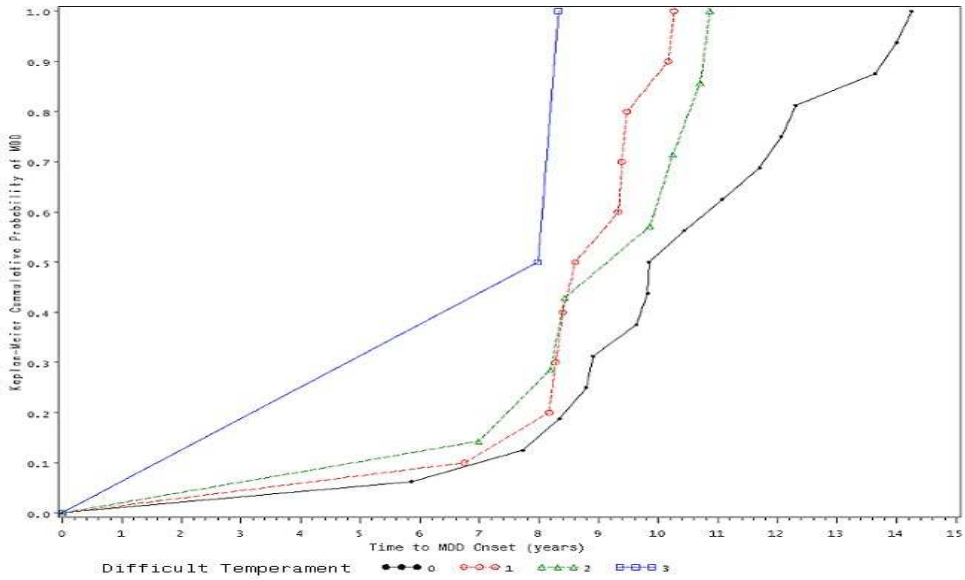
*Note*. MDD = major depressive disorder; CI = confidence interval; Cox regression analyses were used.
$^{+}p < .07$. $^{*}p < .05$. $^{**}p < .01$. $^{***}p < .001$.

For children in intact families (see Figure 1), temperament was unrelated to age at MDD onset ($\chi^2$ (3) = 3.95, p = 0.27). However, for non-intact families (see Figure 2), children with a more difficult temperament had an earlier MDD onset age than did children with fewer difficulties ($\chi^2$ (3) = 13.57, p < 0.01). Temperament also interacted with elapsed time, suggesting that its effect is not constant. Specifically, as indicated by the parameter estimate of the interaction term (-.540), the effect is attenuated across time. For example, comparing children at age 14 to children at age 7, the hazard ratio for temperament problems is decreased by exp{-.540*[log(14) – log (7)]} = 0.69.




0: no temperament difficulty; 1: minimal temperament difficulty; 2: moderate temperament difficulty
3: severe temperament difficulty

**Figure 3. Effect of Early Temperament on MDD-onset among children from Intact Families**




0: no temperament difficulty; 1: minimal temperament difficulty; 2: moderate temperament difficulty
3: severe temperament difficulty

**Figure 4. Effect of Early Temperament on MDD-onset among children from Non-Intact Families**

### 3.4.3. Severity of first episode of MDD

In a series of univariate general linear models, we found no significant associations between perinatal problems, developmental delay, difficult temperament and the severity of the first MDD episode. Only an association to child's sex was found, $F$ (1, 369) = 4.32, $p$ < 0.05, with girls showing more severe symptoms ($M$ = 20.15) than boys ($M$ = 19.36). In multivariate GLM analyses, the interactions of the three developmental indices with sex and with family status were not statistically significant and were dropped from the final model. The final model, including just the three indices and child sex, was not significant, $F$ (4, 362) = 1.60, $p$ = 0.17.

### 3.4.4. Onset age of first internalizing disorder (MDD/Dysthymia/Anxiety)

We first examined if children, who had developed dysthymic and/or anxiety disorder (Anx) in addition to MDD ($n$ = 158), differed from children with MDD only ($n$ = 213) in early risk factors. The groups did not differ in perinatal problems or developmental delays (p= .95, p= .065, respectively). However, children with comorbid DD or Anx were rated as having had a more difficult early temperament ($M$ = .99, $SD$ = 1.02) than were those without DD or Anx ($M$ = .78, $SD$ = .91), $t$ (365) = -2.10, $p$ < .05.

Univariate Cox regression models revealed two significant effects: boys ($M$ = 9.50, $SD$ = 2.51) had an earlier onset of MDD/DD/Anx than did girls ($M$ = 9.98, $SD$ = 2.69), and more difficult temperament was associated with earlier disorder onset. In the final model (see Table 6), child's temperament and sex remained significant, and a significant interaction between

Temperament and Intact Family was found, in the same direction as with MDD Onset-Age. Also, Temperament interacted with elapsed time, with the parameter estimate once again indicating that temperament better predicted onset-age among younger than older children.

**Table 6. Modeling Age of Onset of First Internalizing Disorder Episode (MDD/DD/Anx)**

| **Variables** | **Univariate Models** | **Final Multivariate Model** |
|---|---|---|
| | **Hazard Ratio (95% CI)** | **Hazard Ratio (95% CI)** |
| Perinatal problems | 0.98 (0.89, 1.08) | 0.95 (0.85, 1.05) |
| Developmental delay | 1.11 (0.89, 1.38) | 1.06 (0.84, 1.33) |
| Difficult temperament | 1.22 (1.09, 1.36)*** | 4.07 (1.80, 9.20)*** |
| Sex (male = 1) | 1.30 (1.06, 1.60)* | 1.36 (1.10, 1.68)** |
| Intact family until age 4 | 0.77 (0.54, 1.09) | 1.01 (.63, 1.60) |
| Mother's education (years) | 0.99 (.96, 1.02) | -- |
| Maternal age at birth (years) | | |
| 16-18 vs. 19-34 | 0.92 (0.59, 1.43) | -- |
| 35-46 vs. 19-34 | 1.58 (1.00, 2.52) $^{+}$ | -- |
| Temperament X Intact Family | -- | 0.65 (.45, .93)* |
| Temperament X Time | -- | 0.70 (.49, 1.00)* |

Note. MDD = major depressive disorder; CI = confidence interval; Cox regression analyses were used.
$^{+}$p < .10. *p < .05. **p < .01. ***p < .001.

# Discussion

My work is the first to investigate the possible impact of early neurodevelopmental difficulties on the development and features of major depressive and related internalizing disorders in a very large clinical sample of youngsters with COD. I was particularly interested in developmental characteristics that may mirror physiological vulnerability because such factors could be helpful in the early identification of cases at risk. Overall, the results complement a growing body of literature, which suggests that various atypical early childhood characteristics may affect both the risk and timing of internalizing psychopathology.

In the case-control study of depressed and community control children, as I predicted, childhood-onset depression significantly associated with greater scores on all early developmental scales, suggesting that having a history of early atypical development (perinatal problems, developmental delay, and difficult temperament) may pose elevated risk for early onset MDD. Thus, findings of my work similar to findings from research with depressed adults, which suggest that perinatal-obstetric problems may have role in the development of MDD (Gale and Martin, 2004; Preti et al., 2000). My results also concordant with results of Jaffe et al. (2002) and van Os et al. (1997) regarding the effect of perinatal problems and delayed motor development toward higher vulnerability to early onset depression. Although, I investigated the direct relationship between perinatal complications and COD, there are several other pathways thorough which early developmental characteristics may act, and it is likely that interacting effect of different domains of vulnerability factors which play role in the development of depression (Kapornai & Vetró, 2008). Although, there are clearly several other factors which are proven to have role in the development of emotional problems were not investigated in my research, on the Figure 4. I depicted some vulnerability factors from risk domains (individual, familial, environmental) of internalizing disorders including those were investigated in the present research. I also figured some possible pathways which may suggested based on findings from former and my studies.

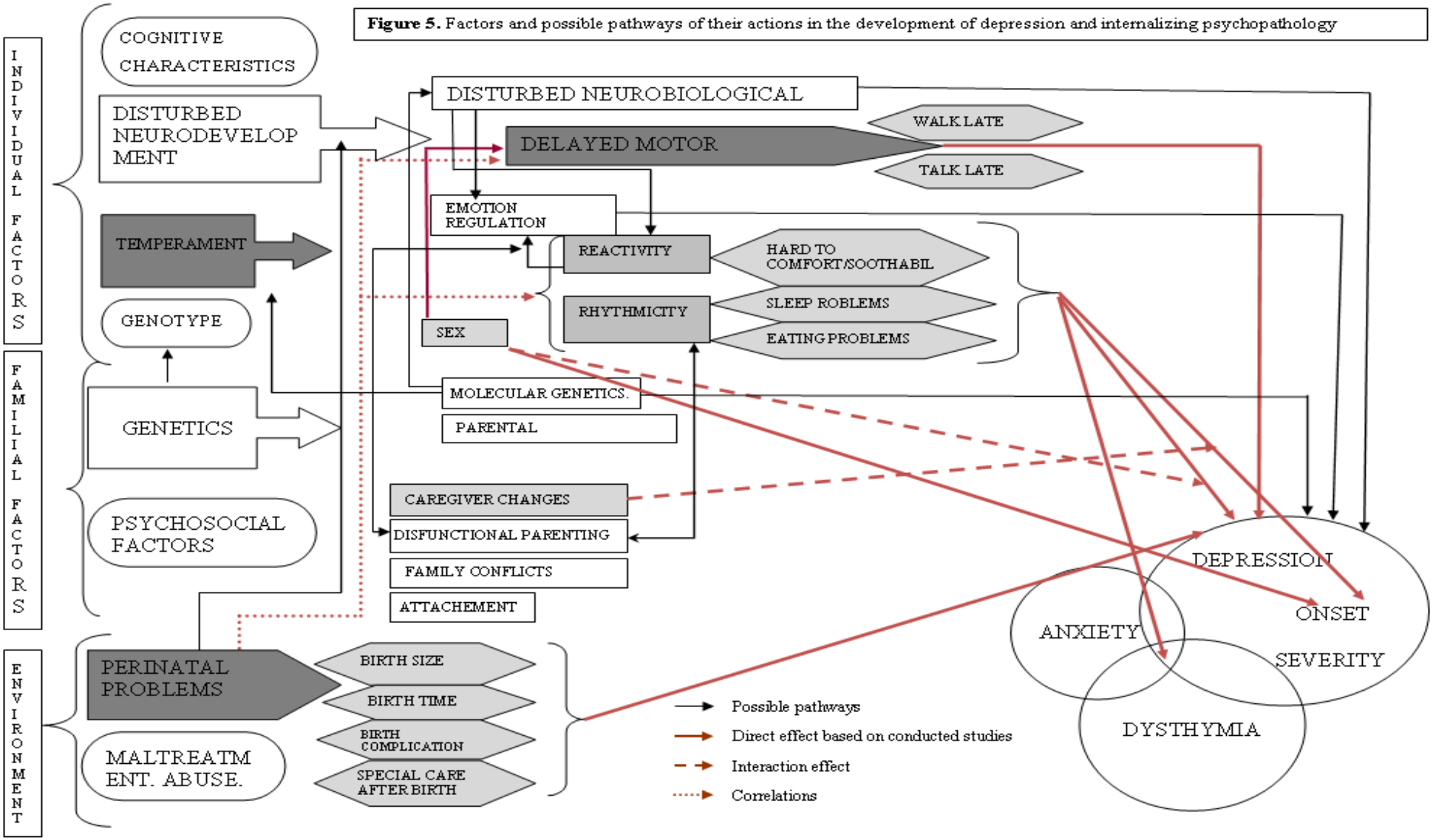



**Figure 5.** Factors and possible pathways of their actions in the development of depression and internalizing psychopathology

One possible mechanism through which perinatal problems might increase risk for depressive disorders is by altering the neurobiological regulatory systems (such as hypothalamic-pituitary-adrenal [HPA] axis function) (not investigated in the study) that govern emotion regulation and reactivity. As the correlation between perinatal scale and delayed development scale in my study indicates, perinatal problems by altering neurodevelopment, also could lead to disturbed motor development, which may than elevate the risk for COD. It is important to note, that consistent with a large body of literature on the greater vulnerability of male infants to a variety of problems (e.g., Halpern, 1997); boys in all of my samples had higher scores on developmental delay than did girls. Perinatal problem scale also correlated with difficult temperament scale suggesting other relevant pathways should be examined in the future. Namely, perinatal problems may act thorough increase the probability of difficult temperament by disturbing some neurobiological correlates of rhythmicity reactivity/emotion regulation domains of temperament. In general, other factors (illness, parenting style, social interactions) including the impact of the child behavior on the environment, may influence the psychophysiology of the child and thus contribute to the expressed temperament. Furthermore, it is also could be the case, that the perinatal problems influence on parenting early in life leads to mutual effect of temperament and dysfunctional parenting on each other, which then render children vulnerable to internalizing symptoms. Additionally, evidence has increasingly been found for interactions between temperament and parenting in psychopathology outcomes (Rothbart & Posner, 2006) The authors proposed this mechanism in the coercion model which suggests that child characteristics can influence parental reactions leading to increased risk for psychopathology. Although we had no data about the possible depressive psychopathology in the mother, in the case of infant temperament-by-parent characteristics interaction, it would be reasonable to consider the maternal depression as well. Namely, beside the genetic pathway, infant with difficult temperament and lower emotional regulatory capacity may have difficulty organizing their emotional and behavioral responses in the context of interactions with a depressed mother, leading to increasing their own risk for early manifestations of depression. Based on case-control study II. depressed probands were not differed from unaffected siblings on variables or scales of perinatal problems and delayed development, thus, in part, I failed to confirm my hypothesis 2)a. However, the lower sample sizes in case-control study II. could be a limitation to detect the possible associations between the aforementioned variables. I also failed to confirm the hypotheses regarding the effects of perinatal problems and motor skills delay on age of onset of depressive and related disorders. Although clinical or population based studies

have found that such characteristics distinguish childhood onset from adult onset affective disorders (Guth et al., 1993; Jaffee et al., 2002; van Os et al., 1997), differences in methodologies and samples may partly account for the inconsistent results. In our depressed group 3., early childhood characteristics also were unrelated to the severity of first MDD episode, despite Vocisano et al. (1996) finding a link between obstetric complications and severity of affective illness in adulthood.

I examined three types of early developmental characteristics. From these only the difficult early temperament was related to the development of depression and to the earlier onset of depression as well. More specifically, depressed kids with difficult early temperament, indexed by mother-reported problems with feeding, sleeping, or soothability, more frequently were difficult baby in their infancy than community children or then unaffected siblings and had earlier onset of MDD than had children with milder or no temperamental difficulties. Furthermore, the variables that refer to difficult temperament are emerged with significantly higher frequency in unaffected siblings than in community controls as well. This result suggests a possible endophenotype variation (genetic influence) in COD and/or could be explained by the influence of shared familiar factors as it was proposed in some behavioral genetic studies in relation to rhythmicity and soothability dimensions of temperament (Saudino, 2005). Notably, Jaffee et al. (2002) have reported that infant temperament (having been a "difficult baby") distinguished young adults with childhood-onset and those with adult-onset depression. However, having had a difficult temperament also was associated with earlier DD, or anxiety disorder, as well as MDD (whichever emerged first), indicating a lack of specificity to MDD. Thus, atypical infant temperament may presage vulnerability to a range of internalizing psychiatric problems later on, underscoring that risk factors should be examined in relation to a range of disorders rather than a single condition (Kessler et al., 1997). Additionally, children who had comorbid dysthymic or anxiety disorder reportedly had more difficult temperaments than children without DD or anxiety.

If a difficult temperament prognosticates earlier onset of emotional disorder, what could be the mechanisms? As I noted earlier, toddlers with difficult temperaments may be compromised on some psychoneurophysiologic parameter related to emotionality or emotion regulation (e.g., Fox, 1994), which may interfere with the development of effective coping responses, and render them susceptible to earlier onset of disorders. Findings that depressed children, or those at risk for depression, differ from comparison peers in their neuroendocrine or physiological responses to negative experimental mood induction, do suggest the existence

of physiological or neurobiological dimensions of vulnerability to depression (e.g., Forbes, et al., 2006; Luby et al., 2003) (Figure 4.)

Genes may contribute to individual differences in both temperament and psychopathology. For example, some emerging research suggests that genetic variations associated with the phenotype of a difficult temperament may be the same that predispose an individual to develop a psychiatric disorder (e.g., Pezawas et al., 2005). Furthermore, several researches propose evidences that depression and anxiety disorders may share a genetically determined neurobiological component that could involve neural circuits that include or are modulated by serotonergic regulation. This component could contribute to the negative affectivity dimension of temperament which appears to be common in childhood onset internalizing disorders.

Notably, however, in depressed group 3. it was found that early caregiver stability may mitigate some of the ramification of an infant having difficulties in rhythmicity or in being soothed, which is consistent with the buffering effects of a positive environment (e.g., Rothbart & Bates, 1998). Intact families may have available more of the emotional or material resources needed to take care of a "difficult" child. But because parenting and parent-infant relationships are influenced by the infant's temperament as well (e.g., Kochanska et al., 2004), future research should examine whether parents from non-intact families experience more deleterious effects of having a difficult baby, and how this may impact offspring's psychopathology.

Interestingly, the effect of temperament on disorder onset was attenuated across time in the sample. This finding may reflect that our anamnestic assessment focused on the period of infancy and toddlerhood. But, it is also possible that, across development, disorder parameters, such as age of onset, are subject to a variety and varying influences of risk variables (environmental stress, puberty, genetic effect, gene-by-environment interactions) other than early characteristics. Indeed, in risk research of mental disorders, there is a growing interest in the investigation of moderating effect of genes on individuals' sensitivity to environmental risk factors (not shown in Figure 4.), known as gene–environment interactions (GXE), gene–environment correlation (rGE) (Jaffe and Price, 2007; Moffit et al, 2005), and other varieties in gene–environment interplay (Rutter et al, 2006). In the past few years, GXE studies with young people reported associations between 5-HTTLPR variation and risk for depression following adverse life experiences (Kaufman et al 2006; Eley et al 2004; Caspi et al 2003; Kendler et al 2005), and association of variation in brain-derived neurotrophic factor (BDNF) genetics with childhood-onset depression (Strauss et al 2004a, 2004b). Based on

these findings Kaufman et al. (2006) recently examined the role of 5-HTTLPR-BDNF interaction in the development of depression in maltreated children and the potential modifying effect of social support available for the child. Children with the met allele of the BDNF gene and two short alleles of 5-HTTLPR had the highest depression scores, but the vulnerability associated with these two genotypes was only evident in maltreated children. Social support was further found to be a moderator factor in this study.

Other possible interacting mechanism suggested by the results of my work was also proposed by other researchers (MacPhee & Andrews, 2006; Oldehinkel et al., 2006). In these studies dysfunctional parenting (along with the strong effect of child's self-esteem) also emerged as an important predictor for depression, but for example, the association was dependent on the temperament characteristics and the gender of the children in the population sample of preadolescents examined by Oldehinkel et al. (2006).

Several other findings are of note. First, consistent with a large body of literature on the greater vulnerability of male infants to a variety of problems (e.g., Halpern, 1997), boys in all samples had higher scores on developmental delay than did girls, and their first episode of MDD, DD, or anxiety disorder occurred at a younger age than did girls'. But once an episode of MDD had onset, girls displayed more severe symptoms than boys, consistent with findings reported for adolescents (Reinhertz et al., 1999). Thus, in my work, sex emerged as a main effect and not as a moderator variable on age of onset of MDD as I had predicted. Additionally, diagnostic comorbidity in our patients was associated with reports of more difficult infantile temperaments. Notably, I reconfirmed prior reports (e.g., Kovacs, 1989) that, if depressed juveniles have comorbid anxiety disorders, the anxiety disorders will tend to onset earlier than the depressive disorder.

The finding in depressed group 3., that older maternal age at the child's birth (compared to maternal age between 19 and 34 years at childbirth) conferred earlier onset of MDD to their offspring, partly confirm those of Reinhertz et al. (1993). Reinhertz et al. (1993) found that older parental age at childbirth was associated with an increased risk of depression in female adolescent offspring. Maternal age at childbirth, however, was unrelated in our analyses to any of the early risk factors and failed to enter the final predictive models. This finding suggests that older maternal age affects offspring's psychopathology through other variables not examined in this study.

## Limitations

Beside the unique strengths in sampling (very large clinical sample, which is representative to Hungary) and design (parallel investigations using case-control and cross-sectional design), my study has several limitations. The depressed and school-based community controls were not well matched geographically because the former group was recruited across Hungary thorough multiple sites, whereas the latter group was recruited from schools in some midsize cities. The control sample in the case-control study I. consisted of families who agreed to participate in the study in response to written invitation. This raises the possibility of un-known self-selection bias (Mayer et al., 2009). However, the depressed sample likewise included self-selected families willing to participate. Data ascertainment format (face-to-face interview versus mailed questionnaires) also may carry some sources of bias in responses (Mayer et al, 2009). Further, the lack of psychiatric control group limited the information to be draw regarding the specificity of the early neurodevelopmental characteristics in depression.

Additionally, because the anamnestic data on our patients were obtained retrospectively from their mothers, inaccuracies and biases in recall are of concern. In spite of its drawbacks, however, the retrospective reporting of perinatal and early developmental events has been an important component of various clinically oriented investigations (e.g., Buka et al., 2004; Foley et al., 2001; Lewis & Murray, 1987; Sanderson et al., 1998). Research has shown that the reproducibility and validity of maternal recall of perinatal events can vary from very good to poor (e.g., Foley et al., 2001; Launer et al., 1992; Tomeo et al., 1999) and is affected by the type of the data being sought and the method of acquisition (Buka et al., 2004). Data gathering procedures in my research had been designed with several features in mind, which have been recently recognized as facilitating (although not guaranteeing) the accuracy of retrospective recall (Buka et al., 2004), including face-face-interviews by clinically trained assessors, use of “common” rather than medical terms and phrases, and focusing on fairly frequently occurring events and readily observable and reportable signs (eating and sleeping habits). The finding of an interaction effect between child temperament and family status also argues against an overall bias in maternal recall because the association was evident only for a subgroup of participants.

Further limitation is that mothers reported on both their children’s early development and psychiatric history, introducing shared method (within-reporter) variance. However, this source of bias was reduced by the fact that a child’s final psychiatric diagnosis was: a) based

both on parental and child report, b) determined on two occasions by different clinical interviewers, and c) subjected to two "best estimate" child psychiatrists independently, who also had access to psychiatric and mental health records. While questions could also be raised about the accuracy of dating the onsets of disorders, two features of the design support my findings. First, the method of obtaining clinical history and onset dates (including the use of "time-lines" with culturally standard and personally meaningful marker events, visual aids, verbal summaries, and cross-links of information) has been shown to be the preferred approach for collecting various types of retrospective data (e.g., Caspi et al., 1996). And, second, my clinically referred sample did not have protracted illness, which is likely to reduce errors in dating; the average time elapsed between the age of onset of MDD and the date of the psychiatric evaluation was 1.14 years (SD = 1.34 years), and for about 67% of the sample, it was within one year.

It could be argued that the portion of youths in my sample of depressed group 3. who were not raised by both biological parents between birth and 4 years of age (9.4%) constitutes a very small segment of the sample. Although high rates of intact families have also been found in other pediatric samples, including those of Najman et al., 2005 (82% intact) and Hirshfeld-Becker et al., (2004) (86% intact), it would be informative to replicate my study with a sample that includes more single-parent or blended families. Another extension of my study could include other environmental factors in the analyses, such as parenting behavior given the information from earlier research on temperament-environment interactions in adaptive and maladaptive emotional development (e.g., Bates et al., 1998; Kochanska, 2004) and in depression as well (MacPhee & Andrews, 2006; Oldehinkel et al., 2006).

## Respective findings and clinical implications

My results are concordant with results in research of adult depression, while extend evidences regarding the possible link between neurodevelopmental and temperamental adversities and the development of major depression in childhood, by suggesting the effect of difficult infant temperament on the age of onset of first depressive episode. Also, my research is the first to investigate the possible impact of early neurodevelopmental difficulties on the development and features of major depressive and related internalizing disorders in a very large, nationally representative clinical sample of youngsters with MDD. My findings highlight that, even in a vulnerable sample, the putative negative effects of early infant characteristics are not immutable, but can be ameliorated by family resources. Thus

improving the support provided by health professionals for mothers dealing with infants after perinatal complications and/or with difficult temperament could have positive effect in the prevention of emotional disorders later in life. Further, the impact of some early child characteristics on features of juvenile psychopathology seems to be attenuated by the passage of time.

Additionally, in clinical practice, psychiatrists typically have access only to parents' reports of early child characteristics and are unlikely to have documents of early development. Based on our findings, careful interviewing of parents can yield data that may illuminate some aspects of children's clinical history.

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