Common mental disorders in young adults born late-preterm

K. Heinonen,[1*] E. Kajantie,[2,3,7] A-K. Pesonen, [1] M. Lahti, [1] S. Pirkola,[2,4] D. Wolke,[5] A. Lano,[7] S. Sammallahti, [1, 2,7] J. Lahti, [1,6] S. Andersson, [7] J. G. Eriksson,[2,8,9,10] K. Raikkonen[1]

Affiliations:

1. Institute of Behavioural Sciences, University of Helsinki, Helsinki, Finland
2. National Institute for Health and Welfare, Helsinki, Finland
3. Department of Obstetrics and Gynaecology, Oulu University Hospital and University of Oulu, Oulu, Finland
4. University of Tampere, School of Health Sciences, Tampere, Finland
5. Department of Psychology, University of Warwick, Coventry, UK
6. Folkhälsan Research Centre, Helsinki, Finland
7. Children's Hospital, Helsinki University Hospital and University of Helsinki, Helsinki, Finland
8. Department of General Practice and Primary Health Care, University of Helsinki, Helsinki, Finland
9. Vasa Central Hospital, Vasa, Finland
10. Unit of General Practice, Helsinki University Hospital, Helsinki, Finland

***Address for correspondence**: Kati Heinonen, Institute of Behavioural Sciences, P.O. Box 9, 00014 University of Helsinki, Helsinki, Finland, kati.heinonen@helsinki.fi, Tel: +358-2941 29514, Fax +358-2941 29520

Funding source:

Study baseline and childhood follow-up was financially supported by the Bundesministerium für Forschung und Technik (Federal Goverment of Germany, Ministry of Science and Technology) program grants PKE 4 and JUG 14 (FKZ's 0706224, 0706564, and 01EP9504) to Drs Klaus Riegel, Dieter Wolke, and Barbara Ohrt; Adulthood follow-up was financially supported by the Academy of Finland program grants (to Drs Eriksson, Raikkonen and Kajantie); The work by Aulikki Lano was supported by Foundation of Pediatric Research; The work by Dr Heinonen and Dr. J. Lahti was supported by Academy of Finland post-doctoral grant; Dr Eriksson was supported also by grant from Samfundet Folkhälsan and Dr Andersson from Päivikki and Sakari Sohlberg Foundation and Finska Läkaresällskapet.

Conflicts of Interest: The authors have no conflicts of interest to disclose.

Word count: 3813

Abstract (Max 250/250)

Background

Results of adulthood mental health of those born late-preterm (34+0-36+6 weeks+days of gestation) are mixed and based on national registers. We examined if late-preterm birth was associated with a higher risk for common mental disorders in young adulthood when using a diagnostic interview, and if this risk decreased as gestational age increased.

Methods

800 young adults (Mean =25.3years, SD=0.62), born 1985-1986, participated in a follow-up of the Arvo Ylppö Longitudinal Study. Common mental disorders (mood, anxiety and substance use disorders) during the past 12 months were defined using Composite International Diagnostic Interview (Munich version). Gestational age was extracted from hospital birth records and categorized into early-preterm (<34+0, n=37), late-preterm (34+0-36+6, n=106), term (37+0-41+6, n=617) and post-term (≥42+0, n=40).

Results

Those born late-preterm and at term were at a similar risk for any common mental disorder (odds ratio [OR]=1.11; 95% confidence interval [CI] 0.67-1.84), for mood (OR=1.11; 95%CI, 0.54-2.25), anxiety (OR=1.00; 95%CI, 0.40-2.50) and substance use (OR=1.31; 95% CI, 0.74-2.32) disorders, and comorbidity of these disorders (*p*=0.38). While the mental disorder risk decreased significantly as gestational age increased, the trend was driven by a higher risk in those born early-preterm.

Conclusion

Using a cohort born during the advanced neonatal and early childhood care, we found that not all individuals born preterm are at risk for common mental disorders in young adulthood –those born late-preterm are not, while those born early-preterm are at a higher risk. Available resources for prevention and intervention should be targeted towards the preterm group born the earliest.

Each year 14.9 million births worldwide are preterm (<37+0 weeks+days of gestation) (Blencowe *et al.* 2012). Of these births 70% are late-preterm (34+0–36+6 weeks+days of gestation) (Davidoff *et al.* 2006; Engle *et al.* 2007). While those born at the most severe end of birth weight and gestational length distribution of preterm birth are at an increased risk of mental disorders (Johnson & Marlow 2011; Treyvaud *et al.* 2013; Van Lieshout *et al.* 2015) it remains less clear if this risk also characterizes those born late-preterm.We are aware of only a handful of studies that have examined mental disorders among those born late-preterm (Linnet *et al.* 2006; Moster *et al.* 2008; Talge *et al.* 2010; D'Onofrio *et al.* 2013; Harris *et al.* 2013; Rogers *et al.* 2013; Lahti *et al.* 2014), and only three have extended follow-ups into adulthood (Moster *et al.* 2008; D'Onofrio *et al.* 2013; Lahti *et al.* 2014). These Scandinavian register studies demonstrate an inconsistent pattern of risks. In the first study, late-preterm birth was associated with an increased risk of schizophrenia, disorders of psychological development, behavior and emotion (Risk ratios (RRs): 1.3 to 1.5), but not with autism spectrum disorders (Moster *et al.* 2008); in the second study, it was associated with an increased risk of psychotic/bipolar disorder, autism spectrum disorders and attention deficit hyperactivity disorder (ADHD) (Hazard ratios (HR): ~1.2 to ~1.3), but not with substance use disorder or suicide attempts (D'Onofrio *et al.* 2013); and in the third study, it was associated with an increased risk of suicide (HR: 2.01), but not with substance use, psychotic, mood, anxiety or personality disorder or suicide attempt (Lahti *et al.* 2014).

In all these studies diagnoses of mental disorders were extracted from registers carrying data on inpatients hospitalizations, outpatients care, disability benefits or cause of death. While the severity of mental disorders is highly correlated with receiving treatment, up to 50% of individuals in developed countries with mental

disorder go untreated and, hence, remain unidentified by the registers (Demyttenaere *et al.* 2004; ten Have *et al.* 2013). Furthermore, of those receiving mental health treatment, up to 14% neither meet the criteria for mental disorders nor report other indicators of need for treatment (Bruffaerts *et al.* 2015).

To overcome at least some of the shortcomings related to studies employing registries, we tested if late-preterm birth was associated with increased risk for mood, anxiety and substance use disorders and comorbidity of these disorders defined by the Munich-Composite International Diagnostic Interview (M-CIDI), and if the mental disorder risk decreased according to the degree of prematurity. Our secondary aim was to test if the mental disorder risk varied according to the degree of intrauterine growth restriction.

METHODS

The study participants come from the Finnish arm of the Bavarian-Finnish Longitudinal Study (BFLS), also called the Arvo Ylppö Longitudinal Study (AYLS) (Wolke *et al.* 1998; Heinonen *et al.* 2008). We identified all 1,535 infants (867 boys, 56.5%) born alive in the county of Uusimaa, Finland between March 15, 1985 and March 14, 1986, who were admitted to neonatal wards in obstetric units, or transferred to the Neonatal Intensive Care Unit (NICU) of the Children's Hospital, Helsinki University Central Hospital within ten days of their birth. The population ranged from severely ill preterm infants to infants born at term requiring only brief inpatient observation. The gestational age in the hospitalized group ranged from 23 to 43 weeks. Additionally, we identified 658 (326 boys, 49.5%) infants not admitted to neonatal wards or NICU. Infants were prospectively randomly recruited from 3

largest maternity hospitals in the study area and the neonate born after every second hospitalized infant was selected. The gestational age in this control group ranged from 35 to 42 weeks.

Of the 2,193 infants of the original cohort, 2,086 were identified in adulthood based on Finnish personal identification numbers. In 2009-2012, we invited 1,913 (173 participants address was not traceable, they lived abroad or would have needed accommodation for an overnight stay) for a clinical and psychological follow-up, and 1,136 participated (59.4%; 51.8% of the original cohort) (Mean age = 25.5, standard deviation [SD] = 0.65, Range 24.4 to 27.1 years). Of them 957 underwent the M-CIDI interview. We excluded 21 because of organic mental disorder (corresponds ICD-10 categories F06.0-06.4: mental disorders due to brain damage and dysfunction and to physical disease); 2 had missing information on the date of last substance use episode; 129 did not have information on gestational age or the information was evaluated as unreliable; 5 participants had congenital malformations or chromosomal abnormalities. Thus, the analytic sample comprised 800 participants (392 men, 49%) (41.8% of those invited, 36.5% of the initial study cohort) (Supplemental Figure 1).

Compared with the analytic sample (n=800), those in the initial study cohort (n=1393) but not included in the current study were more often men (49.0 vs 57.5%, $p<0.001$), born preterm (4.6 vs 9.3% early-preterm [24+0 - 33+6 weeks+days of gestation], 23.3 vs 15.0% late-preterm, 77.1 vs 71.8% term, and 5.0 vs 3.9% post-term, $p<0.001$), had lower birth weight for gestational age SD score (mean difference [MD]=0.20, $p<0.001$), were more often admitted to hospital (63.5 vs 73.7%, $p<0.001$), had younger mothers (MD=0.76 years, $p=0.001$) who had smoked more often during pregnancy (14.1 vs 26.5%, $p<0.001$) and more often had parents with a lower level of

education (8.0 vs 15.9% elementary, 21.5 vs 28.7% upper secondary, 36.8 vs 33.2% lower tertiary, 33.8 vs 22.1% upper tertiary, $p<0.001$); The groups did not differ in 5 minute Apgar score ($p=0.15$). In addition, we compared those included in the current study (n=800) with those excluded due to unreliable, but existing, information on gestational age (n=128). These groups did not differ from each other in gestational age as categorized into early-preterm, late-preterm, term and post-term ($p=0.44$) or in M-CIDI diagnoses (all p's>0.18).

The study protocol at birth was approved by the ethics committees of the Helsinki City Maternity Hospital, Helsinki University Central Hospital, and Jorvi Hospital and in adulthood by the Coordinating Ethics Committee of the Helsinki and Uusimaa Hospital District. The informed consent was obtained from parents (childhood) and participants (adulthood).

Gestational Age and Fetal Growth

Gestational age was categorized to early-preterm (n=37, 16 were born very preterm, <32+0), late-preterm (n=106), term (n=617) and post-term (n=40). Length of gestation was extracted from medical records. It was based on fetal ultrasound, performed before 24+0 weeks of gestation, of 28 (75.7%) of early-preterm, 72 (67.9%) of late-preterm, 395 (64.0%) of term and 20 (50.0%) of post-term participants. If ultrasound was not performed, gestational age was determined from the date of mother's last menstrual period.

Birth weight (g) was extracted from birth records and expressed in SD units relative to sex and length of gestation, based on Finnish standards (Pihkala *et al.* 1989). Children born < -2SDs of mean birth weight were defined as small-for-gestational-age

(SGA), those born ≥-2 and ≤2SDs of the mean as appropriate-for-gestational-age (AGA), and those >2SDs of the mean as large-for-gestational-age (LGA).

Mental disorders

Mood, anxiety and substance use disorders (DSM-IV) during the past 12 months were assessed using a Finnish translation of the computerized M-CIDI (Wittchen & Pfister 1997; Andrews & Peters 1998; Wittchen *et al.* 1998; Pirkola *et al.* 2005). Mood disorders included major depressive disorder, dysthymia, and bipolar disorder. Anxiety disorders included general anxiety disorder, social phobia, panic disorder with or without agoraphobia, and agoraphobia. Substance use disorders included alcohol use disorder (dependence or abuse) and other substance use disorder (dependence or abuse). Comorbidity was defined as suffering from any disorder from more than one of the three categories (Pirkola *et al.* 2005). CIDI interview is valid and reliable (Andrews & Peters 1998; Wittchen *et al.* 1998; Jacobi *et al.* 2004; Pirkola *et al.* 2005) and has good concordance with Structured Clinical Interview for DSM Disorders (Haro *et al.* 2006). The interviews were performed by eight master's level psychology students, trained by a psychiatrist with WHO authorization (SP) and supervised by a clinical psychologist (KH). The interviewers were blind to all earlier collected information of the participants including gestational age.

Covariates and Confounders

All covariates and confounders were *a priori* selected on the basis of earlier literature. Covariates associated with either prematurity or mental health extracted from hospital

records, included sex, multiple pregnancy (singleton/multiple), parity (primiparous vs multiparous), Apgar score at 5 minutes (0-7, >7), length of stay in neonatal ward (no hospitalization, up to 7 days, 8-14 days, >14 days). Confounders associated with both prematurity and mental health, extracted from hospital records, included maternal pre-pregnancy body-mass-index (kg/m^2) (BMI), hypertensive disorder during pregnancy (hypertension, pre -eclampsia, normotension), diabetes during pregnancy (gestational diabetes, type 1 diabetes, no diabetes; none had type 2 diabetes), and maternal age at delivery (<20, 20 to 40, >40 years). Other confounders included maternal smoking during pregnancy (0, 1–10, or >10 cigarettes per day; reported at maternity ward) reported by the child's mother at study baseline, highest educational attainment of the either parent (elementary, upper secondary, lower tertiary, upper tertiary) reported by the child's mother when the child was 56 months old, maternal mental disorders (no vs yes) reported by the child's mother in conjunction with the adulthood follow-up, and self-reported highest completed or on-going educational attainment (elementary, upper secondary, lower tertiary, upper tertiary).

Statistical Analysis

Logistic regression analyses with odds ratios (OR) and 95% Confidence Intervals (CI) were used to test if late-preterm birth, in relation to (a) term birth, (b) early-preterm birth, and (c) post-term birth increased the risk of mental disorders. Linear regression analysis tested if comorbidity of mental disorders was higher in those born late-preterm than those born at term, early-preterm and post-term. The above analyses were re-run with length of gestation as a continuous variable to test if the prevalence of mental disorders and comorbidity decreased according to the degree of

prematurity. These analyses were further specified by comparing the early-term group with term-born and post-term groups. Early-preterm/late-preterm vs. term birth × SGA vs AGA interaction tested if intrauterine growth restriction modified the associations.

In all analyses, we made adjustments for all covariates and confounders, except for maternal mental disorders (Model I), and then for all of them (Model II). Missing information in covariates and confounders were dummy coded as separate category. We considered two-tailed P-values<.05 as statistically significant.

RESULTS

Twelve-month prevalence of any common mental disorder was 34.8%, and of mood, anxiety and substance use disorders 13.1%, 9.3% and 23.4%, respectively; 25.5%, 7.5% and 1.8% had suffered from a disorder in one, two or three categories, respectively. Women had more often mood, anxiety and less often substance use disorders, but their comorbidity did not differ by sex (Table 1). There were no sex differences in covariates or confounders (*p*-values >0.06).

Table 2 presents covariates and confounders by gestational age categories. Those born late-preterm differed from those born at term such that they were hospitalized more often and for a longer period after birth and their mothers had smoked more, had more often hypertensive disorders and diabetes during pregnancy; They also differed from those born early-preterm such that they were hospitalized less often and for a shorter

period after birth and more often had Apgar score > 7 at 5 minutes, and from those born post-term such that they were hospitalized more often and for a longer period after birth, were more often men, and born from multiple, multiparous or hypertensive pregnancies. Differences between those born early-preterm and post-term from the term group and from each other are presented in Table 2.

Supplemental eTable 1 presents these characteristics by mental disorders.

Late-preterm birth and mental disorders

Table 3 shows that those born late-preterm did not differ from those born at term in their risk for any common mental disorder, for mood, anxiety or substance use disorders, or their comorbidity (β's<0.04, *p*'s>0.38 for Models I and II).

When compared with those born early-preterm, those born late-preterm had lower odds for any common mental disorder (OR=0.37, 0.15 to 0.94, *p*=0.04 for Model I, P=.04 for Model II) and mood disorders (OR=0.27, 0.08 to 0.92, *p*=0.04 for Model I, P=.04 for Model II). Rates of mental disorders did not vary between those born late-preterm and those born post-term (all *p*-values>0.10).

Degree of prematurity and mental disorders

The prevalence of mood disorders (*p*=0.03, Figure 1) and comorbidity for mental disorders (*p*=0.045, Figure 2) decreased as the length of gestation increased. When we excluded those born post-term, prevalence for substance use disorders decreased as gestational age increased (*p*=0.04) (Figure 1).

Additional analyses where early-preterms were compared to those born at term demonstrated that early-preterms had higher odds for any common mental disorder (OR=3.00, 1.25 to 7.21, p=0.01 for Model I, p=0.02 for Model II), for mood (OR=4.03, 1.30 to 12.51, p=0.02 for Model I, p=0.02 for Model II) and substance use disorders (OR=3.12, 1.15 to 8.48, p=0.03 for Model I, p=0.03 for Model II), and were more likely to suffer from mental disorder comorbidity (p-values <0.03 for Models I and II); When compared to post-terms, those born early-preterm had higher odds for mood disorders (OR=7.14, 1.47 to 33.33, p=0.02 for Model I, p=0.02 for Model II) and were more likely to suffer from mental disorder comorbidity (p-values<0.04 for Models I and II).

Intrauterine growth patterns and mental disorders

Finally, analyses testing moderation by SGA/AGA status among those born late-preterm and term, and among those born early- to late-preterm and term did not reveal any significant interactions (all p-values>0.75). Compared with those born AGA, those born SGA did not have an increased risk for mental disorders with or without controlling for gestational age (all p-values>0.08).

DISCUSSION

Using a validated diagnostic interview, the current study demonstrates that 33.0% of adults born late-preterm had suffered from any common mental disorder during the previous 12 months, compared with 34.2% of those born at term. For specific

disorders, the rates were also similar: 17.4% vs 16.1% had a history of a mood, 10.1% vs. 13.1% of anxiety, and 26.8% vs. 25.0% of substance use disorders. Rates of comorbidity of these disorders were also equivalent between those born late-preterm and at term, 21.7%, 9.4% and 1.9% of those born later preterm and 25.8%, 6.6% and 1.8% of those born at term had suffered from one disorder or two or three comorbid disorders, respectively. These findings concur with previous studies that have not either identified differences in risks for mood, anxiety or substance use disorders in adulthood when these diagnoses are derived from registers (Moster *et al.* 2008; D'Onofrio *et al.* 2013; Lahti *et al.* 2014). Our findings thus add to the previous literature by showing that even when mental disorders are identified using a diagnostic interview, adults born late-preterm and at term do not differ from each other in the 12-month prevalence and comorbidity rates of common mental disorders.

However, our study revealed that the risk for these disorders decreased as gestational age increased. Indeed, when compared to those born early-preterm, those born late-preterm had lower risks for any common mental disorder and mood disorders, those born at term had lower risks for any common mental disorder, mood and substance-use disorders and mental disorder comorbidity, and those born post-term had lower risk for mood disorders and mental disorder co-morbidity. Hence the decreasing trend of mental disorder risk was driven by a higher risk for mental disorders in those born the earliest. Strikingly, nearly half of those born early-preterm had suffered from any common mental disorder during the past 12 months. While not in the direct focus of our study, these findings deserve some attention as they concur with previous studies (Indredavik *et al.* 2010; Johnson *et al.* 2010; Johnson & Marlow 2011; Nosarti *et al.*

2012; D'Onofrio *et al.* 2013; Van Lieshout *et al.* 2015) and hence increase both internal and external validity of our findings. However, of note is that in some previous studies those born the earliest/smallest have been less likely to suffer from alcohol and substance use disorders than those born at term (Strang-Karlsson *et al.* 2008; Lindström *et al.* 2009; D'Onofrio *et al.* 2013; Van Lieshout *et al.* 2015). In our study, the number of participants was, however, too small to examine more extreme groups, such as those born very preterm, separately. Thus, combining them may have masked any potential protective effects and may explain this slight controversy. This was supported by a post-hoc analyses in this sample which showed that those born very preterm did not differ (*p*-values>0.39) from those born at term, whereas those born moderately preterm (32+0 to 33+6 weeks of gestation) had a significantly higher risk (P-values<.03) for substance use disorders.

Several mechanisms may underlie the detected associations, including brain immaturity, and severity of neonatal illnesses and complications, which decrease as gestational age increases. Although abnormalities in brain structure and function are also detected among those born late-preterm (Munakata *et al.* 2013; Rogers *et al.* 2014; Kelly *et al.* 2015), brain changes have been reported to be wide among those born earliest (Bäuml *et al.* 2014). Moreover, existing studies have shown associations between brain abnormalities and behavioural and psychiatric problems in preterm children (Skranes *et al.* 2007; Rogers *et al.* 2012, 2014; Treyvaud *et al.* 2013). Further, neonatal complications and illnesses related to preterm birth may amplify the risk for neurodevelopmental adversities (Whitaker *et al.* 1997; Indredavik *et al.* 2010). The risk for neonatal illnesses and complications generally decrease as

gestational age increases (Milligan 2010; Engle 2011; Laptook 2013). Moreover, severe complications, e.g. intracranial hemorrhage, are less common among those born late than among those born earlier (Laptook 2013). Also in our sample, the length of stay in neonatal intensive care was longest and 5 min Apgar score more often below 7 in those born early-preterm suggesting more severe illnesses/complications in this group. However, as we lack neuroimaging data, we cannot determine the extent to which any potential differences in brain structure and function according to the severity of preterm birth underlie our findings.

Moreover, also less mature regulatory and communicative abilities of those born preterm (Voegtline & Stifter 2010; Wolke *et al.* 2014) may add to the risk for later mental health problems of the offspring (Hemmi *et al.* 2011). Further, although observed parenting sensitivity does not differ between those born preterm and term (Bilgin & Wolke 2015), findings suggest that those born preterm are more susceptible to parenting effects (Shah *et al.* 2013; Jaekel *et al.* 2014). Evidence that especially those born the earliest (Shah *et al.* 2013) are most affected, may potentially also explain the increased risk of mental disorders among those born early-preterm, but not among those born late-preterm. Finally, a common, not yet known, genetic or environmental risk factor may also be involved.

Our study also showed that intrauterine growth (SGA/AGA), did not add to the risk for common mental disorders at any degree of gestational age. Earlier studies among adults born with extremely or very low birth weight have suggested that SGA birth increases the risk for any non-substance use disorder (Van Lieshout *et al.* 2015) and

depression (Raikkonen *et al.* 2008). Further, SGA have been shown to be associated with risk for mental disorders at any length of gestation (Mathiasen *et al.* 2011). A difference explaining the lack of moderation by intrauterine growth pattern in our study may relate to the relatively moderate degree of SGA in our sample in comparison to the earlier studies that by design have included those born at the extreme end of birth weight and gestational age distribution in their samples.

Strengths of our study include a validated diagnostic interview. Although the prevalence rates of mental disorders in the current study may seem relatively high (Table 1), especially for any substance use disorders, they correspond earlier reported twelve-months prevalence rates among young adults which for any substance-use disorder is 30.5%, and for any mood and anxiety disorders are 11.3% and 12.4%, respectively (Blanco *et al*. 2008). Further, we had reliable and verified information on gestational age, available data on important covariates and confounders, a relatively large sample, and a long follow-up to adulthood.

There are also limitations. Two thirds of the infants participating in the AYLS were admitted to neonatal wards in obstetric units or NICU after birth. However, the majority of the admitted infants had no diagnosed illness and were on the wards for observation or because of common problems of neonatal adaptation. Moreover, those with congenital malformations or chromosomal abnormalities potentially affecting gestational age and/or mental health, were excluded. While the eligibility criteria related to hospitalization after birth enriched the number of preterm births in our sample, it is also a study limitation that restricts generalizations from our findings to

samples that may vary from ours in neonatal health characteristics. Loss of follow-up may also inevitably cause selection bias and impact generalizability of the findings further. Of the original sample, 33.1% of the hospitalized infants and 44.4% of the non-hospitalized infants participated in the follow-up in adulthood. Also, participation rates in the adulthood follow-up increased according to gestational age: of the original sample 22.3%, 33.7%, 38.2% and 39.4% of those born early-preterm, late-preterm, term and post-term participated in the adulthood follow-up, respectively. Furthermore, those who did not participate in the adulthood follow-up had more often younger mothers who had smoked more often during pregnancy, and more often had parents with a lower level of education. All these characteristics have been related to preterm birth. Hence, the preterm group that participated in the adulthood follow-up might be healthier than those born preterm in general. Whether our results generalize to samples exposed to less advanced neonatal and early childhood medical care remains also unknown. As we examined the most common mental disorders in adulthood, we cannot either determine the extent to which our findings agree with previous studies, which have shown that late-preterm birth increased the risk of other mental disorders, such as schizophrenia. Moreover, our findings do not either inform of the lifetime mental disorder risk. Finally, although we did not find any statistically significant associations, ORs for those born late-preterm were 1.11 and 1.31 for mood and substance use disorders compared to those born at term. To detect significant association with these ORs the sample size should have been over 36 000 and over 5 000, respectively. Thus, future studies detecting mental disorders using structured interviews should be conducted in at least 5000 individuals to either confirm or refute the null associations found in this study. Moreover, the sample size of the current

study also precluded us to study the less common mental disorders, such as psychotic disorders, autism spectrum disorders or adult ADHD.

CONCLUSIONS

Using a cohort born during the advanced neonatal and early childhood care we found that not all individuals born preterm are at risk for common mental disorders in young adulthood – those born late-preterm are not, while those born early-preterm are at higher risk. Available resources of prevention and intervention of common mental disorders should be targeted towards the preterm group born the earliest.

Acknowledgements:

Special thanks are due to Juha Peltola and the numerous other persons who carried out the data collection and kept the sample intact in childhood and adulthood follow-ups.

References:

Andrews G, Peters L (1998). The psychometric properties of the Composite International Diagnostic Interview. *Social Psychiatry and Psychiatric Epidemiololy* **33**, 80–88.

Bilgin A, Wolke D (2015). Maternal Sensitivity in Parenting Preterm Children: A Meta-analysis. *Pediatrics* **136**, e177-e193.

Blanco C, Okuda M, Wright C, Hasin DS, Grant BF, Liu, S-M, Olfson M (2008). Mental Health of College Students and Their Non-college-attending Peers: Results from the National Epidemiologic Study on Alcohol and Related Conditions. *Archives of General Psychiatry* ***65***, 1429–1437.

Blencowe H, Cousens S, Oestergaard MZ, Chou D, Moller AB, Narwal R, Adler A, Vera Garcia C, Rohde S, Say L, Lawn JE (2012). National, regional, and worldwide estimates of preterm birth rates in the year 2010 with time trends since 1990 for selected countries: A systematic analysis and implications. *The Lancet* **379**, 2162–2172.

Bruffaerts R, Posada-Villa J, Al-Hamzawi AO, Gureje O, Huang Y, Hu C, Bromet EJ, Viana MC, Hinkov HR, Karam EG, Borges G, Florescе SE, Williams DR, Demyttenaere K, Kovess V, Matschinger H, Levinson D, de Girolamo G, Ono Y, de Graaf R, Browne MO, Bunting B, Xavier M, Haro JM, Kessler RC (2015). Proportion of patients without mental disorders being treated in mental health services worldwide. *The British Journal of Psychiatry* **206**, 101–109.

Bäuml JG, Daamen M, Meng C, Neitzel J, Scheef L, Jaekel J, Busch B, Baumann N, Bartmann P, Wolke D, Boecker H, Wohlschläger AM, Sorg C (2014). Correspondence Between Aberrant Intrinsic Network Connectivity and Gray-Matter Volume in the Ventral Brain of Preterm Born Adults. *Cerebral Cortex* **25**, 4135-4145.

D'Onofrio BM, Class QA, Rickert ME, Larsson H, Långström N, Lichtenstein P (2013). Preterm birth and mortality and morbidity: a population-based quasi-experimental study. *JAMA Psychiatry* **70**, 1231-1240.

Davidoff MJ, Dias T, Damus K, Russell R, Bettegowda VR, Dolan S, Schwarz RH, Green NS, Petrini J (2006). Changes in the gestational age distribution among U.S. singleton births: Impact on rates of late preterm birth, 1992 to 2002. *Seminars in Perinatology* **30**, 8–15.

Demyttenaere K, Bruffaerts R, Posada-Villa J, Gasquet I, Kovess V, Lepine JP, Angermeyer MC, Bernert S, Girolamo G de, Morosini P, Polidori G, Kikkawa T, Kawakami N, Ono Y, Takeshima T, Uda H, Karam EG, Fayyad JA, Karam AN, Mneimneh ZN, Medina-Mora ME, Borges G, Lara C, Graaf R de (2004).

Prevalence, Severity, and Unmet Need for Treatment of Mental Disorders in the World Health Organization World Mental Health Surveys. *JAMA* **291**, 2581–2590.

Engle WA (2011). Morbidity and mortality in late preterm and early term newborns: A continuum. *Clinics in Perinatology* **38**, 493–516.

Engle WA, Tomashek KM, Wallman C (2007). 'Late-preterm' infants: a population at risk. *Pediatrics* **120**, 1390–1401.

Haro JM, Arbabzadeh-Bouchez S, Brugha TS, de Girolamo G, Guyer ME, Jin R, Lepine JP, Mazzi F, Reneses B, Vilagut G, Sampson NA, Kessler RC (2006). Concordance of the Composite International Diagnostic Interview Version 3.0 (CIDI 3.0) with standardized clinical assessments in the WHO World Mental Health surveys. *International Journal of Methods in Psychiatric Research* **15**, 167–180.

Harris MN, Voigt RG, Barbaresi WJ, Voge G a., Killian JM, Weaver AL, Colby CE, Carey WA, Katusic SK (2013). ADHD and Learning Disabilities in Former Late Preterm Infants: A Population-Based Birth Cohort. *Pediatrics* **132**, e630–e636.

Ten Have M, Nuyen J, Beekman A, & de Graaf R (2013). Common mental disorder severity and its association with treatment contact and treatment intensity for mental health problems. *Psychological Medicine* **43**, 2203–2213.

Heinonen K, Räikkönen K, Pesonen A-K, Kajantie E, Andersson S, Eriksson JG, Niemelä A, Vartia T, Peltola J, Lano A (2008). Prenatal and postnatal growth and cognitive abilities at 56 months of age: a longitudinal study of infants born at term. *Pediatrics* **121**, e1325–e1333.

Hemmi MH, Wolke D, Schneider S (2011). Associations between problems with crying, sleeping and/or feeding in infancy and long-term behavioural outcomes in childhood: a meta-analysis. *Archives of Disease in Childhood* **96**, 622–629.

Indredavik MS, Vik T, Evensen KAI, Skranes J, Taraldsen G, Brubakk A-M (2010). Perinatal risk and psychiatric outcome in adolescents born preterm with very low birth weight or term small for gestational age. *Journal of Developmental & Behavioral Pediatrics* **31**, 286–294.

Jacobi F, Wittchen H-U, Holting C, Hofler M, Pfister M, Muller N, Lieb R (2004). Prevalence, co-morbidity and correlates of mental disorders in the general population: results from the German Health Interview and Examination Survey (GHS). *Psychological Medicine* **34**, 597–611.

Jaekel J, Pluess M, Belsky J, Wolke D (2014). Effects of maternal sensitivity on low birth weight children's academic achievement: a test of differential susceptibility versus diathesis stress. *Journal of Child Psychology and Psychiatry* **6**, 693-701.

Johnson S, Hollis C, Kochhar P, Hennessy E, Wolke D, Marlow N (2010). Psychiatric disorders in extremely preterm children: longitudinal finding at age 11 years in the EPICure study. *Journal of the American Academy of Child and Adolescent Psychiatry* **49**, 453–463.e1.

Johnson S, Marlow N (2011). Preterm birth and childhood psychiatric disorders. *Pediatric Research* **69**, 22–28.

Kelly CE, Cheong JLY, Gabra Fam L, Leemans A, Seal ML, Doyle LW, Anderson PJ, Spittle AJ, Thompson DK (2015). Moderate and late preterm infants exhibit widespread brain white matter microstructure alterations at term-equivalent age relative to term-born controls. *Brain Imaging and Behavio*r, Epub ahead of print.

Lahti M, Eriksson JG, Heinonen K, Kajantie E, Lahti J, Wahlbeck K, Tuovinen S, Pesonen a.-K, Mikkonen M, Osmond C, Barker DJP, Räikkönen K (2014). Late preterm birth, post-term birth, and abnormal fetal growth as risk factors for severe mental disorders from early to late adulthood. *Psychological Medicine*, 1–15.

Laptook AR (2013). Neurologic and Metabolic Issues in Moderately Preterm, Late Preterm, and Early Term Infants. *Clinics in Perinatology* **40**, 724–738.

Van Lieshout RJ, Boyle MH, Saigal S, Morrison K, Schmidt LA (2015). Mental Health of Extremely Low Birth Weight Survivors in Their 30s. *Pediatrics* **135**, 452-459.

Lindström K, Lindblad F, Hjern A (2009). Psychiatric morbidity in adolescents and young adults born preterm: a Swedish national cohort study. *Pediatrics* **123**, e47–e53.

Linnet KM, Wisborg K, Agerbo E, Secher NJ, Thomsen PH, Henriksen TB (2006). Gestational age, birth weight, and the risk of hyperkinetic disorder. *Archives of Disease in Childhood* **91**, 655–660.

Mathiasen R, Hansen BM, Forman JL, Kessing LV, Greisen G (2011). The risk of psychiatric disorders in individuals born prematurely in Denmark from 1974 to 1996. *Acta Paediatrica* **100**, 691–699.

Milligan DW (2010). Outcomes of children born very preterm in Europe. *Archives of Disease in Childhood Fetal and Neonatal Edition* **95**, F234–F240.

Moster D, Lie RT, Markestad T (2008). Long-Term Medical and Social Consequences of Preterm Birth. *New England Journal of Medicine* **359**, 262–73.

Munakata S, Okada T, Okahashi A, Yoshikawa K, Usukura Y, Makimoto M, Hosono S, Takahashi S, Mugishima H, Okuhata Y (2013). Gray matter volumetric MRI differences late-preterm and term infants. *Brain and Development* **35**, 10–16.

Nosarti C, Reichenberg A, Murray RM, Cnattingius S, Lambe MP, Yin L, MacCabe J, Rifkin L, Hultman CM (2012). Preterm Birth and Psychiatric Disorders in Young Adult Life: Preterm Birth and Psychiatric Disorders. *Archives of General Psychiatry* **69**, 610–617.

Pihkala J, Hakala T, Voutilainen P, Raivio K (1989). [Characteristic of recent fetal growth curves in Finland]. *Duodecim* **105**, 1540–1546.

Pirkola SP, Isometsä E, Suvisaari J, Aro H, Joukamaa M, Poikolainen K, Koskinen S, Aromaa A, Lönnqvist JK (2005). DSM-IV mood-, anxiety- and alcohol use disorders and their comorbidity in the Finnish general population. Results from the Health 2000 Study. *Social Psychiatry and Psychiatric Epidemiology* **40**, 1–10.

Raikkonen K, Pesonen A-K, Heinonen K, Kajantie E, Hovi P, Jarvenpaa A-L, Eriksson JG, Andersson S (2008). Depression in Young Adults With Very Low Birth Weight: The Helsinki Study of Very Low-Birth-Weight Adults. *Archives of General Psychiatry* **65**, 290–296.

Rogers CE, Anderson PJ, Thompson DK, Kidokoro H, Wallendorf M, Treyvaud K, Roberts G, Doyle LW, Neil JJ, Inder TE (2012). Regional cerebral development at term relates to school-age social-emotional development in very preterm children. *Journal of the American Academy of Child and Adolescent Psychiatry* **51**, 181–191.

Rogers CE, Barch DM, Sylvester CM, Pagliaccio D, Harms MP, Botteron KN, Luby JL (2014). Altered Gray Matter Volume and School Age Anxiety in Children Born Late Preterm. *The Journal of Pediatrics* **165**, 1–8.

Rogers CE, Lenze SN, Luby JL (2013). Late preterm birth, maternal depression, and risk of preschool psychiatric disorders. *Journal of the American Academy of Child and Adolescent Psychiatry* **52**, 309–18.

Shah PE, Robbins N, Coelho RB, Poehlmann J (2013). The paradox of prematurity: The behavioral vulnerability of late preterm infants and the cognitive susceptibility of very preterm infants at 36 months post-term. *Infant Behavior and Development* **36**, 50–62.

Skranes J, Vangberg TR, Kulseng S, Indredavik MS, Evensen KI, Martinussen M, Dale a. M, Haraldseth O, Brubakk a. M (2007). Clinical findings and white matter abnormalities seen on diffusion tensor imaging in adolescents with very low birth weight. *Brain* **130**, 654–666.

Strang-Karlsson S, Räikkönen K, Pesonen AK, Kajantie E, Paavonen EJ, Lahti J, Hovi P, Heinonen K, Järvenpää AL, Eriksson JG, Andersson S (2008). Very low birth weight and behavioral symptoms of attention deficit hyperactivity disorder

565 in young adulthood: the Helsinki study of very-low-birth-weight adults. *American*
566 *Journal of Psychiatry* **165**, 1345–1353.

567 **Talge NM, Holzman C, Wang J, Lucia V, Gardiner J, Breslau N** (2010). Late-
568 preterm birth and its association with cognitive and socioemotional outcomes at 6
569 years of age. *Pediatrics* **126**, 1124–1131.

570 **Treyvaud K, Ure A, Doyle LW, Lee KJ, Rogers CE, Kidokoro H, Inder TE,**
571 **Anderson PJ** (2013). Psychiatric outcomes at age seven for very preterm children:
572 rates and predictors. *Journal of Child Psychology and Psychiatry* **54**, 772–779.

573 **Whitaker AH, Van Rossem R, Feldman JF, Schonfeld IS, Pinto-Martin JA, Tore**
574 **C, Shaffer D, Paneth N** (1997). Psychiatric outcomes in low-birth-weight children at
575 age 6 years: relation to neonatal cranial ultrasound abnormalities. *Archives of General*
576 *Psychiatry* **54**, 847–856.

577 **Wittchen H-U, Lachner G, Wunderlich U, Pfister H** (1998). Test- retest reliability
578 of the computerized DSM-IV version of the Munich-Composite International
579 Diagnostic Interview (M-CIDI). *Social Psychiatry and Psychiatric Epidemiology* **33**,
580 568–578.

581 **Wittchen H-U, Pfister H** (1997). *DIA-X-Interviews: Manual für screening-verfahren*
582 *und Interview; Interviewheft Längsschnittuntersuchung (DIA-X-Lifetime);*
583 *Ergänzungsheft (DIAX- Lifetime); Interviewheft Querschnittuntersuchung (DIA-X-12*
584 *Monate); Ergänzungsheft (DIA-X-12 Monate); PC-Program*. Swets and Zeitlinger:
585 Frankfurt.

586 **Voegtline KM, Stifter CA** (2010). Late-preterm birth, maternal symptomatology,
587 and infant negativity. *Infant Behavior and Development* **33**, 545–554.

588 **Wolke D, Eryigit-Madzwamuse S, Gutbrod T** (2014). Very preterm/very low
589 birthweight infants' attachment: infant and maternal characteristics. *Archives of*
590 *Disease in Childhood. Fetal and Neonatal Edition* **99**, 70–75.

591 **Wolke D, Söhne B, Riegel K, Ohrt B, Österlund K** (1998). An epidemiologic
592 longitudinal study of sleeping problems and feeding experience of preterm and term
593 children in southern Finland: comparison with a southern German population sample.
594 *The Journal of Pediatrics* **133**, 224–231.

595

Figure legends

Figure 1.

Title: The prevalence (%) of common mental disorders during the past 12 months by gestational age.

Figure 2.

Title: Comorbidity of common mental disorders during the past 12 months (%) by gestational age.

Table 1. 12-month prevalence of M-CIDI DSM-IV mood, anxiety, and substance use disorders.

Mental disorder	Men (n=392)	Women (n=408)	Men vs. Women χ^2-test, P
Any common mental disorder	134 (34.2%)	144 (35.3%)	0.74
Mood disorders	35 (8.9%)	72 (17.2%)	0.003
Dysthymia or major depressive disorder [a]	28 (7.1%)	59 (14.5%)	0.003
Bipolar disorder	7 (1.8%)	11 (2.7%)	0.38
Anxiety disorders	24 (6.1%)	50 (12.3%)	0.006
Social phobia	11 (2.8%)	15 (3.7%)	0.48
Generalized anxiety disorder	4 (1.0%)	8 (2.0%)	0.27
Other anxiety disorder	16 (4.1%)	38 (9.3%)	0.006
Substance use disorders	115 (29.3%)	72 (17.6%)	0.005
Alcohol use disorder (dependence or abuse)	111 (28.3%)	70 (17.2%)	0.006
Other substance use disorder	13 (3.3%)	4 (1.0%)	0.03
Comorbidity			0.16
One disorder	103 (26.3%)	101 (24.8%)	

Two disorders[b]	22 (5.6%)	38 (9.3%)
Three disorders	9 (2.3%)	5 (1.2%)

Note. Categories have comorbidity with each other. [a] Of total 10.0% (6.6.% men, 13.2% women, P=0.005) had major depressive disorder. [b] Mood and anxiety disorder n=19 (31.7%), mood and substance use disorder n=26 (43.3%), anxiety and substance use disorder n=15 (25,0%).

Table 2. Characteristics of the study sample by gestational age

	Gestational age			
	Early-preterm 24+0 - 33+6 weeks (n=37)	Late-preterm 34+0 – 36+6 weeks (n=106)	Term 37+0 – 41+6 weeks (n=617)	Post-term ≥ 42+0 weeks (n=40)
Variable	n (%)/ mean(SD)	n (%)/ mean(SD)	n (%)/ mean(SD)	n (%)/mean(SD)
Sex (men)	23 (62.2%)[c]	59 (55.7%)	299 (48.5%)	11 (27.5%) [a, b]
Pre- and neonatal period				
Intrauterine growth				
SGA	9 (24.3%)[a, c]	18 (17.0%)	27 (4.4%)	1 (2.5%)
AGA	27 (73.0%)	82 (77.4%)	568 (92.1%)	36 (90.0%)
LGA	1 (2.7%)	6 (5.7%)	22 (3.6%)	3 (7.5%)
Multiple pregnancy	3 (8.1%)[a]	12 (11.3%)	14 (2.3%)	0 (0.0%)[b]
Parity (Primiparous)	25 (67.6%)[a]	59 (55.7%)	305 (49.4%)	33 (82.5%)[a,b]
Maternal prepregnancy BMI	22.3 (3.72)	22.0 (2.53)	22.2 (3.36)	21.8 (3.05)
Maternal hypertensive disorder				
Hypertension	3 (8.1%) [a, c]	9 (8.5%) [a]	108 (17.5%)	4 (10.0%)[b]
Pre-eclampsia	7 (18.9%)	15 (14.2%)	14 (2.3%)	0 (0.0%)
Normotension	27 (73.0%)	82 (77.4%)	495 (80.2%)	36 (90.0%)
Maternal diabetes				
no OGTT	33 (89.2%)	81 (76.4%) [a]	494 (80.1%)	36 (90.0%)
normal OGTT	4 (10.8%)	14 (13.2%)	84 (13.6%)	4 (10.0%)
gestational diabetes	0 (0.0%)	3 (2.8%)	30 (4.9%)	0 (0.0%)

T1 diabetes	0 (0.0%)	8 (7.5%)	9 (1.5%)	0 (0.0%)
Maternal smoking during pregnancy				
No	27 (73.0%) [a]	86 (81.1%) [a]	542 (87.8%)	32 (80%)
1-10/ day	7 (18.9%)	18 (17.0%)	54 (8.8%)	6 (15.0%)
>10 / day	3 (8.1%)	2 (1.9%)	21 (3.4%)	2 (5.0%)
Maternal age at delivery				
< 20 years	1 (2.7%)	1 (0.9%)	8 (1.3%)	0 (0.0%)
20 to 40 years	36 (97.3%)	103 (97.2%)	598 (96.8%)	40 (100.0%)
> 40 years	0 (0.0%)	2 (1.85)	11 (1.8%)	0 (0.0%)
Apgar score 5 minutes [d]				
0-7	8 (22.2%) [a,b]	9 (8.8%)	44 (7.3%)	7 (17.9%) [a]
> 7	28 (77.8%)	93 (91.2%)	560 (92.7%)	32 (82.1%)
Length of stay in hospital/ days				
no hospitalization	0 (0.0%) [a,b]	6 (5.7%) [a, c]	275 (44.6%)	11 (27.5%) [b]
up to 7 days	13 (35.1%)	84 (79.2%)	318 (51.5%)	29 (72.5%)
8 to 14 days	7 (18.9%)	15 (14.2%)	15 (2.4%)	0 (0.0%)
> 14 days	17 (45.9%)	1 (0.9%)	9 (1.5%)	0 (0.0%)
Childhood				
Parental education				
elementary	2 (5.4%)	11 (10.4%)	47 (7.6%)	4 (10.0%)
upper secondary	10 (27.0%)	27 (25.5%)	127 (20.6%)	8 (20.0%)
lower tertiary	13 (35.1%)	35 (33.0%)	229 (37.1%)	17 (42.5%)
upper tertiary	12 (32.4%)	33 (31.1%)	214 (34.7%)	11 (27.5%)
Young adulthood				
Age	25.0 (0.65)	24.7 (0.68)	24.8 (0.70)	24.6 (0.71)
Own education [e]				
elementary	2 (5.4%)	3 (2.9%)	26 (4.3%)	2 (5.1%)

upper secondary	11 (29.7%)	37 (35.6%)	192 (31.6%)	11 (28.2%)
lower tertiary	8 (21.6%)	28 (26.9%)	168 (27.7%)	12 (30.8%)
upper tertiary	16 (43.2%)	36 (34.6%)	221 (36.4%)	14 (35.9%)
Mother's self-reported mental illness [f]	10 (31.3%)	14 (17.5%)	107 (20.8%)	5 (16.1%)
CIDI DSM IV mental disorders				
Any common disorder	17 (45.9%)	35 (33.0%)	211 (34.2%)	15 (37.5%)
Mood disorder	8 (28.6%)	15 (17.4%)	78 (16.1%)	4 (13.8%)
Anxiety disorder	4 (16.7%)	8 (10.1%)	61 (13.1%)	1 (3.8%)
Substance use disorder	13 (39.4%)	26 (26.8%)	135 (25.0%)	13 (34.2%)

a $p < 0.05$ for difference against the term born group. b $p < 0.05$ for difference against the late-preterm born group. c $p < 0.05$ for difference between early-preterm and post-term groups. d Data missing from 1 early-preterm, 4 late-preterm, 13 term and 1 post-term participants. e Data missing from 2 late-preterm, 10 term, and 1 post-term participants. f data missing from 5 early-preterm, 26 late-preterm, 102 term and 9 post-term participants.

OGTT=Oral glucose tolerance test; SGA= small for gestational age; AGA= appropriate for gestational age; LGA= large for gestational age; BMI=body-mass-index

Table 3. Risk of common mental disorders during the past 12 months in young adults born late-preterm (n=106) in comparison to those born at term (n=617).

		Mental Disorder[a]											
		Any common			Mood			Anxiety			Substance use		
		OR	95%CI	*p*	OR	95%CI	*p*	OR	95%CI	*p*	OR	95%CI	*p*
Term vs Late-preterm													
	Model I	1.11	0.67-1.84	0.68	1.11	0.54-2.25	0.78	1.00	0.40-2.50	0.99	1.31	0.74-2.32	0.36
	Model II	1.08	0.66-1.80	0.75	1.08	0.53-2.21	0.83	1.00	0.40-2.49	0.99	1.30	0.73-2.29	0.37

Note: OR=Odds Ratio; CI= Confidence interval; Model I: controlling for sex, age and maximum educational level of either parent(s), own educational level, maternal age, and pre-pregnancy body-mass-index, multiple pregnancy, parity, small for gestational age (SGA), large for gestational age (LGA), five minutes Apgar score, smoking during pregnancy, maternal diabetes, hypertension, and preeclampsia, length of hospitalization after birth; Model II further controlling for mother's self-reported mental health. Of those born at term 406 and of those born late-preterm did not had any mental disorders and were used as a comparison group.