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1 **Common mental disorders in young adults born late-preterm**

2

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39

40 **Abstract (Max 250/250)**

41

42 **Background**

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

48 **Methods**

49 800 young adults (Mean =25.3years, SD=0.62), born 1985-1986, participated in a
50 follow-up of the Arvo Ylppö Longitudinal Study. Common mental disorders (mood,
51 anxiety and substance use disorders) during the past 12 months were defined using
52 Composite International Diagnostic Interview (Munich version). Gestational age was
53 extracted from hospital birth records and categorized into early-preterm (<34+0,
54 n=37), late-preterm (34+0-36+6, n=106), term (37+0-41+6, n=617) and post-term
55 ($\geq 42+0$, n=40).

56 **Results**

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

63 **Conclusion**

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

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

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

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

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

111

112 **METHODS**

113 The study participants come from the Finnish arm of the Bavarian-Finnish
114 Longitudinal Study (BFLS), also called the Arvo Ylppö Longitudinal Study (AYLS)
115 (Wolke *et al.* 1998; Heinonen *et al.* 2008). We identified all 1,535 infants (867 boys,
116 56.5%) born alive in the county of Uusimaa, Finland between March 15, 1985 and
117 March 14, 1986, who were admitted to neonatal wards in obstetric units, or
118 transferred to the Neonatal Intensive Care Unit (NICU) of the Children's Hospital,
119 Helsinki University Central Hospital within ten days of their birth. The population
120 ranged from severely ill preterm infants to infants born at term requiring only brief
121 inpatient observation. The gestational age in the hospitalized group ranged from 23 to
122 43 weeks. Additionally, we identified 658 (326 boys, 49.5%) infants not admitted to
123 neonatal wards or NICU. Infants were prospectively randomly recruited from 3

124 largest maternity hospitals in the study area and the neonate born after every second
125 hospitalized infant was selected. The gestational age in this control group ranged from
126 35 to 42 weeks.

127 Of the 2,193 infants of the original cohort, 2,086 were identified in adulthood based
128 on Finnish personal identification numbers. In 2009-2012, we invited 1,913 (173
129 participants address was not traceable, they lived abroad or would have needed
130 accommodation for an overnight stay) for a clinical and psychological follow-up, and
131 1,136 participated (59.4%; 51.8% of the original cohort) (Mean age = 25.5, standard
132 deviation [SD] = 0.65, Range 24.4 to 27.1 years). Of them 957 underwent the M-CIDI
133 interview. We excluded 21 because of organic mental disorder (corresponds ICD-10
134 categories F06.0-06.4: mental disorders due to brain damage and dysfunction and to
135 physical disease); 2 had missing information on the date of last substance use episode;
136 129 did not have information on gestational age or the information was evaluated as
137 unreliable; 5 participants had congenital malformations or chromosomal
138 abnormalities. Thus, the analytic sample comprised 800 participants (392 men, 49%)
139 (41.8% of those invited, 36.5% of the initial study cohort) (Supplemental Figure 1).

140 Compared with the analytic sample (n=800), those in the initial study cohort (n=1393)
141 but not included in the current study were more often men (49.0 vs 57.5%, $p<0.001$),
142 born preterm (4.6 vs 9.3% early-preterm [24+0 - 33+6 weeks+days of gestation], 23.3
143 vs 15.0% late-preterm, 77.1 vs 71.8% term, and 5.0 vs 3.9% post-term, $p<0.001$), had
144 lower birth weight for gestational age SD score (mean difference [MD]=0.20,
145 $p<0.001$), were more often admitted to hospital (63.5 vs 73.7%, $p<0.001$), had
146 younger mothers (MD=0.76 years, $p=0.001$) who had smoked more often during
147 pregnancy (14.1 vs 26.5%, $p<0.001$) and more often had parents with a lower level of

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

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

160

161 **Gestational Age and Fetal Growth**

162 Gestational age was categorized to early-preterm ($n=37$, 16 were born very preterm,
163 $<32+0$), late-preterm ($n=106$), term ($n=617$) and post-term ($n=40$). Length of
164 gestation was extracted from medical records. It was based on fetal ultrasound,
165 performed before $24+0$ weeks of gestation, of 28 (75.7%) of early-preterm, 72
166 (67.9%) of late-preterm, 395 (64.0%) of term and 20 (50.0%) of post-term
167 participants. If ultrasound was not performed, gestational age was determined from
168 the date of mother's last menstrual period.

169 Birth weight (g) was extracted from birth records and expressed in SD units relative
170 to sex and length of gestation, based on Finnish standards (Pihkala *et al.* 1989).

171 Children born < -2 SDs of mean birth weight were defined as small-for-gestational-age

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

174

175 **Mental disorders**

176 Mood, anxiety and substance use disorders (DSM-IV) during the past 12 months were
177 assessed using a Finnish translation of the computerized M-CIDI (Wittchen & Pfister
178 1997; Andrews & Peters 1998; Wittchen *et al.* 1998; Pirkola *et al.* 2005). Mood
179 disorders included major depressive disorder, dysthymia, and bipolar disorder.
180 Anxiety disorders included general anxiety disorder, social phobia, panic disorder
181 with or without agoraphobia, and agoraphobia. Substance use disorders included
182 alcohol use disorder (dependence or abuse) and other substance use disorder
183 (dependence or abuse). Comorbidity was defined as suffering from any disorder from
184 more than one of the three categories (Pirkola *et al.* 2005). CIDI interview is valid and
185 reliable (Andrews & Peters 1998; Wittchen *et al.* 1998; Jacobi *et al.* 2004; Pirkola *et*
186 *al.* 2005) and has good concordance with Structured Clinical Interview for DSM
187 Disorders (Haro *et al.* 2006). The interviews were performed by eight master's level
188 psychology students, trained by a psychiatrist with WHO authorization (SP) and
189 supervised by a clinical psychologist (KH). The interviewers were blind to all earlier
190 collected information of the participants including gestational age.

191

192 **Covariates and Confounders**

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

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

210

211 **Statistical Analysis**

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

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

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

227

228 **RESULTS**

229

230 Twelve-month prevalence of any common mental disorder was 34.8%, and of mood,
231 anxiety and substance use disorders 13.1%, 9.3% and 23.4%, respectively; 25.5%,
232 7.5% and 1.8% had suffered from a disorder in one, two or three categories,
233 respectively. Women had more often mood, anxiety and less often substance use
234 disorders, but their comorbidity did not differ by sex (Table 1). There were no sex
235 differences in covariates or confounders (p -values >0.06).

236

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

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

247 Supplemental eTable 1 presents these characteristics by mental disorders.

248

249 **Late-preterm birth and mental disorders**

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

253 When compared with those born early-preterm, those born late-preterm had lower
254 odds for any common mental disorder (OR=0.37, 0.15 to 0.94, $p=0.04$ for Model I,
255 $P=.04$ for Model II) and mood disorders (OR=0.27, 0.08 to 0.92, $p=0.04$ for Model I,
256 $P=.04$ for Model II). Rates of mental disorders did not vary between those born late-
257 preterm and those born post-term (all p -values > 0.10).

258

259 **Degree of prematurity and mental disorders**

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

264

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

275

276 **Intrauterine growth patterns and mental disorders**

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

282

283 **DISCUSSION**

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

287 disorders, the rates were also similar: 17.4% vs 16.1% had a history of a mood, 10.1%
288 vs. 13.1% of anxiety, and 26.8% vs. 25.0% of substance use disorders. Rates of
289 comorbidity of these disorders were also equivalent between those born late-preterm
290 and at term, 21.7%, 9.4% and 1.9% of those born later preterm and 25.8%, 6.6% and
291 1.8% of those born at term had suffered from one disorder or two or three comorbid
292 disorders, respectively. These findings concur with previous studies that have not
293 either identified differences in risks for mood, anxiety or substance use disorders in
294 adulthood when these diagnoses are derived from registers (Moster *et al.* 2008;
295 D’Onofrio *et al.* 2013; Lahti *et al.* 2014). Our findings thus add to the previous
296 literature by showing that even when mental disorders are identified using a
297 diagnostic interview, adults born late-preterm and at term do not differ from each
298 other in the 12-month prevalence and comorbidity rates of common mental disorders.

299

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

311 2012; D'Onofrio *et al.* 2013; Van Lieshout *et al.* 2015) and hence increase both
312 internal and external validity of our findings. However, of note is that in some
313 previous studies those born the earliest/smallest have been less likely to suffer from
314 alcohol and substance use disorders than those born at term (Strang-Karlsson *et al.*
315 2008; Lindström *et al.* 2009; D'Onofrio *et al.* 2013; Van Lieshout *et al.* 2015). In our
316 study, the number of participants was, however, too small to examine more extreme
317 groups, such as those born very preterm, separately. Thus, combining them may have
318 masked any potential protective effects and may explain this slight controversy. This
319 was supported by a post-hoc analyses in this sample which showed that those born
320 very preterm did not differ (p -values >0.39) from those born at term, whereas those
321 born moderately preterm (32+0 to 33+6 weeks of gestation) had a significantly higher
322 risk (P -values $<.03$) for substance use disorders.

323

324 Several mechanisms may underlie the detected associations, including brain
325 immaturity, and severity of neonatal illnesses and complications, which decrease as
326 gestational age increases. Although abnormalities in brain structure and function are
327 also detected among those born late-preterm (Munakata *et al.* 2013; Rogers *et al.*
328 2014; Kelly *et al.* 2015), brain changes have been reported to be wide among those
329 born earliest (Bäumler *et al.* 2014). Moreover, existing studies have shown associations
330 between brain abnormalities and behavioural and psychiatric problems in preterm
331 children (Skranes *et al.* 2007; Rogers *et al.* 2012, 2014; Treyvaud *et al.* 2013).
332 Further, neonatal complications and illnesses related to preterm birth may amplify the
333 risk for neurodevelopmental adversities (Whitaker *et al.* 1997; Indredavik *et al.*
334 2010). The risk for neonatal illnesses and complications generally decrease as

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

343

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

354

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

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

365

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

374

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

383 samples that may vary from ours in neonatal health characteristics. Loss of follow-up
384 may also inevitably cause selection bias and impact generalizability of the findings
385 further. Of the original sample, 33.1% of the hospitalized infants and 44.4% of the
386 non-hospitalized infants participated in the follow-up in adulthood. Also, participation
387 rates in the adulthood follow-up increased according to gestational age: of the original
388 sample 22.3%, 33.7%, 38.2% and 39.4% of those born early-preterm, late-preterm,
389 term and post-term participated in the adulthood follow-up, respectively. Furthermore,
390 those who did not participate in the adulthood follow-up had more often younger
391 mothers who had smoked more often during pregnancy, and more often had parents
392 with a lower level of education. All these characteristics have been related to preterm
393 birth. Hence, the preterm group that participated in the adulthood follow-up might be
394 healthier than those born preterm in general. Whether our results generalize to
395 samples exposed to less advanced neonatal and early childhood medical care remains
396 also unknown. As we examined the most common mental disorders in adulthood, we
397 cannot either determine the extent to which our findings agree with previous studies,
398 which have shown that late-preterm birth increased the risk of other mental disorders,
399 such as schizophrenia. Moreover, our findings do not either inform of the lifetime
400 mental disorder risk. Finally, although we did not find any statistically significant
401 associations, ORs for those born late-preterm were 1.11 and 1.31 for mood and
402 substance use disorders compared to those born at term. To detect significant
403 association with these ORs the sample size should have been over 36 000 and over
404 5 000, respectively. Thus, future studies detecting mental disorders using structured
405 interviews should be conducted in at least 5000 individuals to either confirm or refute
406 the null associations found in this study. Moreover, the sample size of the current

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

409 **CONCLUSIONS**

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

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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

Variable	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)
	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}
<i>Pre- and neonatal period</i>				
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^a				
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%)
<i>Childhood</i>				
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%)
<i>Young adulthood</i>				
Age	25.0 (0.65)	24.7 (0.68)	24.8 (0.70)	24.6 (0.71)
Own education^c				
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%)
<i>CIDI DSM IV mental disorders</i>				
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	<i>p</i>	OR	95%CI	<i>p</i>	OR	95%CI	<i>p</i>	OR	95%CI	<i>p</i>
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.