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Alcohol Intake in Early Pregnancy and Risk of Attention-Deficit/Hyperactivity Disorder in Children Up to 19 Years of Age

a cohort study

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11 **Title: Alcohol intake in early pregnancy and risk of Attention-Deficit Hyperactivity Disorder**
12 **(ADHD) in children up to 19 years of age: a cohort study.**

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34 Abstract

35 *Background:* Little is known about maternal alcohol intake in early pregnancy and the risk of
36 Attention-Deficit Hyperactivity Disorder (ADHD) in the children beyond 5-years of age. We
37 examined the association between alcohol binge drinking and weekly alcohol intake in early
38 pregnancy and the risk of ADHD in the children followed from birth to 19 years of age.

39 *Methods:* We included 48,072 children born between 1998 and 2012, whose mothers participated
40 in the Aarhus Birth Cohort. Maternal alcohol intake was obtained from a self-administered
41 questionnaire completed in early pregnancy. ADHD-diagnoses were retrieved from the Danish
42 Psychiatric Central Research Register and the Danish National Patient Register. Crude and
43 adjusted hazard ratios (aHR) of ADHD according to alcohol binge drinking or weekly intake of
44 alcohol were calculated using Cox regression.

45 *Results:* Compared to children of women with no binge drinking episodes, we observed an aHR
46 for ADHD of 0.91 (95% CI 0.76-1.08), 0.73 (95% CI 0.56-0.96), and 0.77 (95% CI 0.57-1.06)
47 among children of women reporting one, two and three or more binge drinking episodes,
48 respectively. Among children of women drinking less than one drink per week, one drink per
49 week, two drinks per week and three or more drinks per week, we observed an aHR for ADHD of
50 0.87 (95% CI 0.74-1.03), 0.63 (95% CI 0.40-0.98), 1.30 (95% CI 0.89-1.92), 0.78 (95% CI 0.38-
51 1.59), respectively when compared to children of women not drinking on a weekly basis.

52 *Conclusion:* We found no evidence that binge drinking or low alcohol intake in early pregnancy
53 was associated with the risk of ADHD in the children.

54

55 **Keywords**

56 Pregnancy; Binge Drinking; Low-Moderate Alcohol Consumption; ADHD diagnosis; Prenatal
57 Exposures

58 **Abbreviations**

59 ADHD: Attention-Deficit Hyperactivity Disorder

60 aHR: Adjusted hazard ratios

61 BMI: Body-mass-index

62 CI: Confidence intervals

63 HR: Hazard ratio

64 ICD-10: International Classification of Diseases, 10th revision

65

66 Introduction

67 Attention-deficit-hyperactivity-disorder (ADHD) is characterized by inattention, hyperactivity,
68 and impulsivity, and is one of the most common neurodevelopmental disorders in childhood
69 worldwide (Polanczyk et al., 2015). The diagnostic prevalence of ADHD has tripled over the last
70 decades (Atladottir et al., 2015), currently affecting 3% of the populations in the Nordic countries
71 (Nylander et al., 2013, Suren et al., 2013, Madsen et al., 2015). Besides being associated with
72 various comorbidities (e.g., autism and disruptive mood dysregulation disorder) (Biederman,
73 2005, Usami, 2016), ADHD has a negative impact on the quality of life in children and
74 adolescents (Klassen et al., 2004). In the long term, children with ADHD attain poorer academic
75 achievements, occupational rank and job performance compared to their peers (Usami, 2016). The
76 heritable nature of ADHD is described (Biederman, 2005, Banerjee et al., 2007, Thapar et al.,
77 2013, Sciberras et al., 2017), but 10-40% of the heritability variance may be explained by
78 environmental exposures including perinatal risk factors (Banerjee et al., 2007, Sciberras et al.,
79 2017).

80 Alcohol consumption is common among Scandinavian women of reproductive age (Stoltenberg,
81 2014, Jensen et al., 2017). It has been shown that one out of four Danish women of 25-34 years
82 regularly engage in binge drinking (five or more drinks on a single occasion as defined by the
83 Danish Health Authority (Strandberg-Larsen and Grønbaek, 1999)). Further, one out of six
84 consume seven or more drinks per week on average, thereby exceeding the official
85 recommendation for low-risk drinking for women (Jensen et al., 2017, Christensen et al., 2010).
86 The proportion of Danish women drinking one drink or more per week on average in early
87 pregnancy has decreased from 24% in 1998 to 1% in 2013 (Kesmodel et al., 2016). Still, 35-40%
88 report binge drinking in very early pregnancy (Iversen et al., 2015, Kesmodel et al., 2016).

89 It is well established that high alcohol intake in pregnancy is teratogenic with the potential to
90 cause structural malformations, and motor, cognitive and behavioral deficits in the children
91 (Knopik et al., 2005, Riley et al., 2011). A number of observational studies focusing on binge
92 drinking or a low-moderate alcohol intake (often defined as an intake less than six drinks per
93 week) in early pregnancy failed to show higher risk of the core symptoms of ADHD in children up
94 to five years of age (Kesmodel et al., 2012, Underbjerg et al., 2012, Bay et al., 2012, Skogerbo et
95 al., 2012, Skogerbo et al., 2013). However, ADHD may not become evident or diagnosed until the
96 child reaches an age where the expectations exceed the child's ability and resources (Kessler et al.,

2007). Recently, studies have suggested higher risk of ADHD-symptoms in children of 11-12 years exposed to alcohol in late pregnancy (Sayal et al., 2014, Furtado and Roriz, 2016, Eilertsen et al., 2017, Pagnin et al., 2018). However, only one study has examined the association between maternal alcohol consumption in early pregnancy and ADHD-symptoms in children older than five years (Rodriguez et al., 2009). Accordingly, the objective of this study was to examine the association between binge drinking or average weekly alcohol intake in early pregnancy and the risk of ADHD in the children up to 19 years of age.

Materials and methods

Study design, setting and participant selection

The study was based on data from the Aarhus Birth Cohort which is described in depth elsewhere (Hedegaard et al., 1993, Larsen et al., 2013). In brief, from September 1989 onward, all Danish-speaking pregnant women attending routine antenatal care at the Department of Obstetrics and Gynecology, Aarhus University Hospital, Denmark, were invited to participate in the cohort. In early pregnancy (median week 11, 5-95 percentile: 8-19), women were asked to complete a self-administered questionnaire with questions on medical and obstetric history, education and lifestyle including smoking and alcohol intake before and during pregnancy. Immediately after delivery, the attending midwife completed a structured form on the course of delivery and pregnancy outcome. The information from the delivery was validated by a research midwife prior to data entry. Until 2012, a total of 81,111 women (141,939 pregnancies) had been invited to participate in the cohort. Of these, 69,728 women (111,352 pregnancies) were enrolled, leading to a response rate of 79% of all pregnancies.

Since the establishment of the cohort, different versions of the questionnaire have been used. Thus, information on binge drinking was not available for children born prior to 2 June 1998. Therefore we restricted the population to live-born singletons born between 2 June 1998 and 31 December 2012, whose mothers consented to participate and completed a questionnaire including questions on binge drinking (n=48,072). Prior to 2000, information on average weekly alcohol intake did not allow identification of women with no weekly intake. In order to differentiate women with no weekly intake and women with an intake of less than one drink/week, we did not include information on average weekly alcohol intake on children born prior to 14 February 2000 (n=6,132). As data was linked to Danish health registries using the unique personal identification

number assigned to all Danish individuals at birth (Pedersen et al., 2006), children without a valid personal identification number were excluded (n=21).

Alcohol exposures

Our main exposure was self-reported alcohol consumption defined as binge drinking (number of episodes) and average intake of alcohol (drinks per week) in early pregnancy. In Denmark, one drink is equivalent to 12 grams of pure alcohol (Strandberg-Larsen and Grønbaek, 1999). The question on binge drinking was: *'Try to think of your entire pregnancy, including the first weeks before you knew you were pregnant. How many times have you been drinking five or more drinks on a single occasion?'* Women were asked to report *'number of episodes'* as an integer value, or to tick in *'none'* or *'do not know/recall'*. Women reporting *'do not know/recall'* were coded as missing, and binge drinking was categorized as: 0, 1, 2, or >3 episodes. The question on average alcohol intake was: *'How many drinks (a drink being equal to one beer, one glass of wine, or one schnapps) do you drink per week, now that you are pregnant?'* Women were asked to report *'number of drinks per week'* as an integer value, or to tick in *'less than one drink'* or *'do not drink'*. Average weekly intake of alcohol was categorized as: 0, <1, 1, 2, >3 drinks per week.

Time to ADHD-diagnosis

The main outcome was time to first clinical diagnosis of ADHD in the child. This information was obtained from Danish health registries. We obtained information on ADHD from the Danish National Patient Register for Psychiatry, which holds diagnoses on all psychiatric in- and outpatients since 1995 (Mors et al., 2011). In Denmark, some children with mental disorders are seen in somatic hospitals. Hence, we also retrieved ADHD diagnoses from the Danish National Patient Register, which contains diagnoses from in- and outpatient contacts since 1995 (Schmidt et al., 2015). Using the International Classification of Diseases, 10th revision (ICD-10) which was introduced in Denmark in 1994 (WHO, 1992), ADHD was defined as an ICD-10 diagnosis of F90.0-F90.2, or F90.8-F90.9. We also included F98.8, as this diagnosis is used to classify inattention without symptoms of hyperactivity in Denmark (Arnglim et al., 2013, Sundhedsstyrelsen, 2018).

Covariates

Based on a directed acyclic graph (DAG) (Williams et al., 2018), we selected a range of potential confounders a priori; maternal age at birth (<20, 20-24, 25-29, 30-34, 35-39, or >40 years), and

the following self-reported information: highest attained educational level (*none, skilled training/<3 years higher education, 3-4 years higher education, >5 years or more higher education, or other*), pre-gestational body-mass-index (BMI) (*<18.5, 18.5-24.9, 25.0-29.9, or >30.0 kg/m²*), chronic disease (*yes/no*), smoking in pregnancy (*non-smoker, cessation in pregnancy, <10 cigarettes/day, or >10 cigarettes/day*), parity (*nulliparous/multiparous*), and registered birth year (continuous). We also included information on maternal average alcohol intake prior to pregnancy, child's sex (*male/female*), and maternal diagnoses of mental or behavioral disorders (ICD-8: 290-315 and ICD-10: F10-F99) before the time of birth.

Statistical analyses

Cox regression was used to estimate adjusted hazard ratios (aHR) with 95% confidence intervals (95%CI) for first diagnosis of ADHD according to alcohol intake in early pregnancy. Children were followed from date of birth until the date of first diagnosis of ADHD, emigration, death or the end of follow-up (February 18, 2018), which ever came first. In Model 1, we adjusted for all predefined confounders. The reference group 'no binge drinking' included women with any weekly alcohol intake, and vice versa the reference group 'no weekly intake' included women with any binge drinking. Therefore, these analyses were mutually adjusted in Model 2 that also included the potential confounders from Model 1. Women totally abstaining from alcohol may be different from other women in the reference groups. Therefore, we replicated the analyses with 'total abstainers' (defined as women with no binge drinking episodes and no weekly intake) as a specific category. In the analysis on binge drinking, we used women with no binge drinking episodes but any weekly alcohol intake as the reference group, whereas women with no weekly alcohol intake but any binge drinking were used as reference group in the analysis on average weekly alcohol intake. In total, 28% of the women had more than one child in the cohort (n=13,440). To account for dependency between children of the same mother, analyses were clustered around mothers using robust standard errors; the "Huber Sandwich Estimator" (Williams, 2000). A two-sided p-value of less than 5% was considered statistically significant. Model assumptions were evaluated by log-log plots and Schoenfeld residuals. StataSE15.0 (StataCorp, 2017) was used for all statistical analyses.

Supplementary analyses

Model 1 and 2 were repeated by restricting to children of women without i) a diagnosis of mental or behavioral disorder prior to birth, and ii) self-reported chronic disease, and by stratifying by

child's sex. To account for the timing and duration of exposure, analyses were repeated by further adjustment for gestational age at questionnaire completion. Also, we restricted the analyses to women completing the questionnaire prior to 12 weeks gestation. To evaluate the sensitivity to missing values, all analyses were repeated using imputed datasets. Based on missing at random assumptions, missing values were imputed using multiple imputation by chained equations, performing 50 imputations (White et al., 2011). All complete variables from the models, the outcome variable, and the Nelson-Aalen estimator of $H(T)$ were included in the imputation models (White and Royston, 2009).

Ethical approval

The study was approved by the Danish Data Protection Agency (j.nr. 2012-41-1084, j.nr. 2012-58-0018) and the Danish Patient Safety Authority for research purposes (FSEID-00003175).

Results

The median gestational age at completion of the questionnaire was 11 weeks (5-95 percentile range: 8-19). Information on binge drinking was available for 42,862 children (11% missing). Restricted to questionnaires completed after inclusion of the abstention category for average weekly alcohol intake, information on average weekly alcohol intake was available for 41,049 children (2% missing). Women with no information on binge drinking or average weekly alcohol intake were less likely to have attained >5 years higher education compared to women, who provided this information. Also, they more often abstained from alcohol prior to pregnancy, were more likely to smoke in pregnancy, and less likely to have planned their pregnancy. Women with no information on binge drinking were more likely to have a diagnosis of a mental or behavioral disorder prior to birth than women with missing data on binge drinking. The opposite was observed among women with missing information on average alcohol intake (data not shown in table).

Characteristics of study population

The characteristics of the study population according to self-reported alcohol consumption in early pregnancy are presented in Table 1. Compared to women with any binge drinking in early pregnancy, women who did not binge were older, and had a lower average alcohol intake prior to pregnancy. Also, they were more likely to be non-smokers and multiparous. Compared to women

with any average weekly alcohol intake, women with no weekly intake were younger, had a higher BMI, and more often had a diagnosis of a mental or behavioral disorder prior to birth. They had a lower average alcohol intake prior to pregnancy, and were more likely to be non-smokers and multiparous. The lowest alcohol exposures were seen in the late period of the cohort (Table 1).

The median follow-up time was 12 years, ranging from birthday to a maximum of 19 years and eight months. Overall, 3% (n=1,346) of the children had a diagnosis of ADHD, and one fourth of the diagnosed children (n=369) were female. While 12% of the children with an ADHD-diagnosis had a mother with a diagnosis of a mental or behavioral disorder prior to birth, this applied to 8% of the children not diagnosed with ADHD (data not shown in table).

Association between alcohol consumption in early pregnancy and the risk of ADHD

The associations between binge drinking and ADHD are presented in Table 2. The highest risk of ADHD was observed among children of women who reported no binge drinking, and a significantly lower risk of ADHD was observed among children of women reporting two binge drinking episodes (aHR 0.73 95% CI 0.56-0.96). Restricting analyses to children of women without mental or behavioral disorders prior to birth (Table 2), and to children of women without chronic disease only changed estimates marginally (data not shown).

The associations between average alcohol intake and ADHD are presented in Table 3. There was no clear pattern with association measures pointing in various directions. However, compared to children of women with no weekly alcohol intake, children of women reporting one drink per week had a significantly lower risk of ADHD (aHR 0.63 95% CI 0.40-0.98). Results among children of women without mental or behavioral disorders prior to birth (Table 3), and among children of mothers without chronic disease were comparable to those within the entire study population (data not shown).

The results from the analyses including total abstainers as a separate category are presented in Table 4. Compared to children of women not binge drinking, children of total abstainers seemed to have a higher risk of ADHD (aHR 1.17 95% CI 0.99-1.39). Similarly, higher risk of ADHD was indicated for children of total abstainers compared to children of women with no weekly alcohol intake (aHR 1.12 95% CI 0.93-1.34) (Table 4). In all analyses, we observed no significant differences according to sex of the children. Adjusting for gestational age at questionnaire

249 completion had marginal effect on risk estimates, whereas restriction to children of women
250 completing the questionnaire prior to 12 weeks of gestation slightly attenuated results towards
251 entity (supplemental Table S1). This was especially pronounced for children of women with >3
252 binge drinking episodes (aHR 1.00; 95% CI 0.68-1.46), and for children of women with a weekly
253 intake of two (aHR 1.19; 95% CI 0.72-1.99), or >3 drinks (aHR 0.89; 95% CI 0.36-2.20). Results
254 from the analyses of imputed data sets were comparable to the results from the analyses of
255 complete cases only.

256

257

258 Discussion

259 *Main results and previous studies*

260 In this study, we observed no association between binge drinking and average weekly alcohol
261 intake in early pregnancy and the risk of ADHD in children up to 19 years of age. Lower risks of
262 ADHD were indicated with binge drinking or average weekly alcohol intake up to one drink per
263 week, but we expect these patterns to represent residual or unmeasured confounding.

264 In relation to maternal alcohol intake in early pregnancy, our results are in agreement with several
265 studies on this topic (Kesmodel et al., 2012, Underbjerg et al., 2012, Bay et al., 2012, Skogerbo et
266 al., 2012, Skogerbo et al., 2013) that did not observed any significant or systematically higher risk
267 of core symptoms of ADHD. In these studies, the functional domains of ADHD were measured
268 with several different tools (e.g., the Strengths and Difficulties Questionnaire, the Behavior Rating
269 Inventory of Executive Functions, and the Test of Everyday Attention for Children at Five).
270 Similar, a study including children from Aarhus Birth Cohort born between 1990 and 1992 did not
271 show higher risk of parent- or teacher-rated ADHD-symptoms according to average weekly
272 alcohol intake at the age of 7-15 years (Rodriguez et al., 2009). However, there is a growing body
273 of evidence more consistently suggesting mildly higher risk of parent- or teacher-rated ADHD-
274 symptoms among children exposed to maternal alcohol drinking in the second or third trimester,
275 or throughout pregnancy (Sayal et al., 2014, Niclasen et al., 2014, Furtado and Roriz, 2016,
276 Eilertsen et al., 2017, Pagnin et al., 2018).

277 There may be different explanations for the abovementioned differences of findings according to
278 the timing of the maternal alcohol intake. Firstly, although the opposite has been found in
279 experimental animal studies (Bonthius and West, 1990, Schneider et al., 2011, Valenzuela et al.,
280 2012, Schambra et al., 2017), it is possible that isolated episodes of binge drinking and low
281 average weekly alcohol intake in early pregnancy do not affect the development of the human fetal
282 brain. Secondly, the majority of women drinking alcohol in early pregnancy cease to drink, or
283 decreases alcohol consumption after pregnancy recognition, and only few continue or even
284 increase their intake (McCormack et al., 2017, Pryor et al., 2017, Strandberg-Larsen et al., 2008).
285 Studies on alcohol intake in late pregnancy may therefore reflect an accumulated effect of alcohol,
286 with the possibility to affect the neurodevelopment of the fetus more profoundly. Thirdly, the
287 difference of findings may also be explained by different characteristics of women included in the
288 individual studies. Whereas the studies on maternal alcohol intake throughout pregnancy or late in

289 pregnancy have been carried out in different countries (i.e., England, Denmark, Brazil, and
290 Norway), studies on maternal alcohol intake in early pregnancy have primarily been based on data
291 from Danish women. It is well established that alcohol drinking is a common part of Danish social
292 interaction, and the majority of Danes drink in social contexts in contrast to drinking alone
293 (Bloomfield et al., 2008, Grønkjær et al., 2009, Seid et al., 2016). Although the Danish Health
294 Authority recommends alcohol abstention in pregnancy, some alcohol intake in pregnancy is
295 apparently socially accepted (Kesmodel and Kesmodel, 2011, Kesmodel and Urbute, 2019).
296 Further, in Denmark drinking in early pregnancy is not associated with social adversity
297 (Strandberg-Larsen et al., 2008, Rodriguez et al., 2009). As such, it is possible that all studies on
298 maternal alcohol intake in early pregnancy including ours to some degree may be confounded by
299 the 'healthy-drinker-effect' (Kesmodel, 2018).

300 Given the heritability of ADHD (Biederman, 2005, Banerjee et al., 2007, Thapar et al., 2013,
301 Sciberras et al., 2017) and the fact that a child's resilience in mental health is highly associated
302 with the mental health of the primary caregiver (Rutten et al., 2013, Hauck et al., 2013), it is
303 plausible that children of women with ADHD or other mental or behavioral disorders may have a
304 higher a priori risk of ADHD than other children. In our population, women with mental or
305 behavioral disorders prior to birth less frequently reported binge drinking or drinking on a weekly
306 basis than women without such diagnoses. It is plausible that women with mental diseases
307 deliberately abstain from alcohol, as alcohol may exaggerate their symptoms, or as health care
308 providers may encourage women in medical treatment not to drink. Also, as alcohol drinking in
309 Denmark is a highly social behavior, and as women with mental or behavioral disorders may be
310 less enticed by social interaction, it is reasonable to assume that these women less often than other
311 women engage in situations in which alcohol drinking is common or even expected. On the other
312 hand, we cannot exclude that women with mental or behavioral disorders are more aware of the
313 negative connotations of alcohol drinking and therefore more likely to underreport or even deny
314 alcohol intake which would have introduced differential misclassification potentially masking a
315 true association. However, in the analyses restricted to women without mental or behavioral
316 disorders prior to birth associations were attenuated towards the null-hypothesis, and we do not
317 expect a true association to be masked. Optimally we should have accounted for maternal ADHD
318 and not just any mental or behavioral disorder, but due to the time period in which the mothers
319 grew up, it is likely that the disorder was undetected or classified as other mental disorders, and in

our population only 1% of the mothers had a diagnosis of ADHD. Thus, some of the indicated protective effect of the prenatal alcohol exposure may be explained by maternal mental health.

Due to our formulations of the alcohol questions, the binge drinking question captured all episodes until questionnaire completion, whilst the question average weekly alcohol intake only reflected consumption after recognition of the pregnancy only. Thereby, in the supplementary analyses including 'total abstainers' as a separate category, the reference group of women with no weekly alcohol intake are likely to represent the regular, socially accepted drinkers who cease drinking after recognition of pregnancy. It is more complicated to interpret, the reference group of women with no binge drinking episodes when separating the total abstainers. However, as children of total abstainers seemed to have higher risks of ADHD when compared to children of women without binge drinking and children of women with no average weekly alcohol intake, one may infer that in a Danish setting, children of total abstainers have a higher risk of ADHD presumably due to the maternal characteristics related to total alcohol abstinence. This elucidates the importance of considering total abstainers as a specific group when investigating the potential risk of prenatal alcohol exposure.

The gestational age at questionnaire completion varied quite widely in our population. Whereas additional control for gestational age had marginal effect, restriction to children of mothers completing the questionnaire prior to 12 weeks gestation attenuated estimates towards the null. As one may assume that the information about alcohol consumption in early pregnancy collected in the first trimester was more precise due to a better recall, these findings weaken the indications of a protective effect of alcohol consumption in early pregnancy. However, it should be noted that in these analyses, the sample was halved resulting in broader confidence intervals.

Strengths and limitations

Our study was based on a sample of 48,072 children from the Aarhus Birth Cohort, which is a community-based data-collection with a high response rate. The number of missing questionnaire information was generally low. Although one-tenth of the women did not provide information on binge drinking, our supplementary analyses using imputed datasets did not indicate that missing values affected our effect estimates. Using data from Danish registers ensured that only migration could cause loss to follow-up, and the frequency of ADHD was comparable to those reported in other Nordic register studies (Madsen et al., 2015, Suren et al., 2013, Nylander et al., 2013). The

350 children in our cohort were born between 1998 and 2012, hereby not being followed for an equal
351 amount of time. However in Denmark, most children with ADHD are diagnosed by the age of 12
352 years (Pottgard et al., 2012), and when we analyzed children below versus above the age of 12
353 years, we found comparable results.

354
355 There are also limitations to our design. Firstly, the prenatal alcohol exposures were based on self-
356 administered questionnaires. In lack of valid biomarkers, there is no valid gold standard for
357 measuring the validity of self-reported alcohol intake, and often methods yielding the highest
358 intake are considered the most valid (Kesmodel, 2005). In pregnant women, self-administered
359 questionnaires have been shown to result in slightly lower frequencies of both binge drinking
360 (Kesmodel and Frydenberg, 2004) and average weekly alcohol intake (Kesmodel and Olsen, 2001)
361 than other methods (e.g. diaries) which may have affected our estimates. Presuming that an
362 association actually exists, denial of alcohol consumption may increase the risk of the unexposed
363 children (Kesmodel, 2018), and in our study this would have led to an overestimation of the risk of
364 ADHD among children of women not binge drinking and women with no weekly intake.
365 Secondly, ADHD may be slightly underestimated in our study, as we did not have information on
366 redeemed prescriptions of central stimulants (i.e. methylphenidate and atomoxetine) which can be
367 used to identify cases of ADHD treated in private psychiatric practices not obliged to report to the
368 national registers (Madsen et al., 2018, Christensen et al., 2019). Thirdly, participants were
369 enrolled over a 14 years period. Within this period, the proportion of women with any weekly
370 alcohol intake declined markedly, whilst the occurrence of binge drinking among Danish pregnant
371 women was relatively constant. Therefore, although controlling for birth year of the child, we
372 cannot exclude residual confounding as the factors associated with alcohol drinking in the early
373 study period may be different than those in the late study period. Further, except from birth year
374 all confounders were based on self-report, and some misclassification may have occurred; it is
375 likely that variables such as highest attained educational level and height may be overestimated,
376 whereas variables such as weight and smoking may be underestimated. Even though capturing a
377 wide range of diseases, chronic disease was dichotomized, and we cannot exclude some residual
378 confounding. However, results did not change when excluding all women with a chronic disease.
379 Overall, the results on binge drinking were less sensitive to adjustment for confounders than the
380 results on average weekly alcohol intake, but we cannot exclude that this may be due to

381 unmeasured - and yet unknown - factors intertwined with binge drinking in early pregnancy and
382 ADHD in the children.

383 Our results may be generalizable to cultural settings where maternal alcohol intake in early
384 pregnancy is socially accepted, and where access to healthcare is free of charge.

385

386 **Conclusion**

387 Our findings were most compatible with a small protective association between low maternal
388 alcohol intake in early pregnancy and the risk of ADHD in children followed from birth to 19
389 years, but results are likely to be confounded by health-related factors. However, the absence of a
390 positive dose-response association implies that low maternal alcohol intake in early pregnancy is
391 not a risk factor for ADHD in the children.

392

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400

401 **Conflicts of interest**

402 The authors have no conflicts of interest to declare.

403

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Table 1: Characteristics according to self-reported alcohol consumption in early pregnancy; Aarhus Birth Cohort, Denmark, 1998-2012.

	Total		Binge drinking (number of episodes)				Average alcohol intake (drinks/week)				
			0	1	2	>3	0	<1	1	2	>3
Maternal and child characteristics, n (%)	(n=48,072)		(n=27,264)	(n=9,038)	(n=3,964)	(n=2,596)	(n=27,279)	(n=10,974)	(n=1,427)	(n=964)	(n=405)
Age at birth*											
<20 years	866	(1.8)	(1.5)	(0.9)	(1.3)	(1.7)	(2.2)	(0.5)	(0.2)	(0.3)	(1.0)
20-24 years	5,596	(11.6)	(10.5)	(10.5)	(11.3)	(13.8)	(13.5)	(6.6)	(5.1)	(3.6)	(4.2)
25-29 years	19,030	(39.6)	(37.2)	(45.2)	(46.3)	(46.2)	(39.8)	(40.2)	(34.9)	(34.2)	(26.4)
30-34 years	13,872	(28.9)	(30.6)	(28.9)	(27.1)	(25.3)	(27.3)	(33.1)	(36.7)	(35.9)	(30.1)
35-39 years	7,443	(15.5)	(17.2)	(12.8)	(12.3)	(11.4)	(14.7)	(17.1)	(18.9)	(21.4)	(30.1)
>40 years	1,265	(2.6)	(3.0)	(1.7)	(1.6)	(1.6)	(2.5)	(2.5)	(4.1)	(4.6)	(8.1)
Highest attained educational level											
None	7,696	(17.8)	(17.2)	(15.9)	(18.8)	(22.2)	(19.4)	(13.4)	(12.8)	(11.1)	(14.1)
Skilled training/<3 years higher education	9,058	(21.0)	(19.9)	(22.1)	(22.2)	(20.7)	(19.5)	(21.2)	(16.6)	(21.7)	(20.7)
3-4 years higher education	15,338	(35.5)	(35.5)	(37.6)	(36.9)	(34.0)	(35.3)	(37.6)	(36.0)	(35.3)	(33.7)
>5 years higher education	9,113	(21.1)	(22.9)	(20.4)	(18.5)	(19.3)	(20.7)	(24.2)	(31.2)	(28.1)	(26.4)
Other	1,986	(4.6)	(4.4)	(4.1)	(3.6)	(3.8)	(5.0)	(3.5)	(3.4)	(3.8)	(5.2)
Pre-gestational BMI											
<18.5 kg/m ²	2,232	(4.8)	(5.0)	(3.8)	(3.6)	(4.2)	(4.9)	(4.2)	(3.9)	(3.6)	(5.8)
18.5-24.9 kg/m ²	33,439	(71.3)	(71.1)	(72.7)	(75.2)	(76.3)	(69.6)	(74.8)	(78.1)	(77.6)	(79.1)
25.0-29.9 kg/m ²	7,999	(17.1)	(16.6)	(17.3)	(16.4)	(14.8)	(17.4)	(16.0)	(15.0)	(15.1)	(11.3)

>30.0 kg/m ²	3,229	(6.9)	(7.3)	(6.1)	(4.9)	(4.7)	(8.0)	(5.0)	(2.9)	(3.8)	(3.8)
Chronic disease (yes)	5,218	(11.4)	(11.7)	(10.6)	(8.8)	(9.9)	(11.8)	(10.0)	(9.7)	(10.4)	(11.9)
Mental or behavioural disorder (yes)*	3,869	(8.0)	(8.1)	(7.1)	(7.2)	(9.1)	(10.0)	(5.9)	(5.1)	(5.8)	(7.9)
Average alcohol intake prior to pregnancy											
<1 drink/week	21,855	(53.3)	(63.9)	(39.0)	(22.5)	(11.3)	(65.1)	(36.9)	(0.6)	(1.1)	(1.5)
1-2 drinks/week	6,550	(16.0)	(16.4)	(20.4)	(15.5)	(8.6)	(13.7)	(21.8)	(22.4)	(12.8)	(0.0)
3-4 drinks/week	5,592	(13.6)	(11.2)	(19.4)	(22.1)	(17.2)	(10.1)	(19.5)	(33.5)	(20.5)	(12.0)
5-9 drinks/week	5,245	(12.8)	(7.2)	(17.3)	(29.3)	(36.5)	(8.7)	(16.9)	(33.0)	(44.4)	(39.3)
>10 drinks/week	1,727	(4.2)	(1.3)	(3.9)	(10.6)	(26.4)	(2.4)	(4.9)	(10.5)	(21.1)	(47.1)
Smoking in pregnancy											
Non-smoker	38,095	(79.9)	(86.1)	(76.2)	(68.3)	(60.7)	(82.2)	(79.7)	(79.8)	(73.7)	(61.3)
Cessation in pregnancy	5,247	(11.0)	(6.9)	(14.9)	(20.8)	(24.9)	(10.1)	(12.1)	(13.1)	(15.0)	(12.8)
<10 cigarettes/day	2,601	(5.5)	(4.1)	(5.6)	(7.6)	(9.5)	(4.6)	(5.4)	(5.6)	(6.8)	(13.3)
>10 cigarettes/day	1,726	(3.6)	(2.8)	(3.3)	(3.2)	(4.9)	(3.1)	(2.8)	(1.4)	(4.5)	(12.8)
Planned pregnancy (yes)*	35,823	(74.5)	(77.9)	(77.1)	(72.4)	(64.1)	(74.9)	(77.1)	(76.5)	(75.6)	(65.9)
Parity (nulliparous)*	24,896	(51.8)	(45.4)	(57.0)	(66.2)	(75.7)	(53.9)	(48.0)	(47.2)	(46.1)	(41.7)
Child's gender (male)*	24,670	(51.3)	(51.1)	(51.5)	(52.9)	(50.9)	(51.1)	(51.9)	(51.0)	(50.3)	(52.6)

Birthyear*

1998-2002	15,199	(31.6)	(27.2)	(31.2)	(34.7)	(36.7)	(15.7)	(29.6)	(38.8)	(45.4)	(52.3)
2003-2007	17,476	(36.4)	(37.1)	(36.6)	(35.5)	(37.1)	(38.2)	(49.1)	(47.7)	(47.3)	(39.0)
2008-2012	15,397	(32.0)	(35.6)	(32.1)	(29.8)	(26.2)	(46.1)	(21.3)	(13.6)	(7.3)	(8.6)

Abbreviations: Body-mass-index (BMI). *Complete data. Missing data: highest attained educational level (n=4,881), BMI (n=1,173), chronic disease (n=2,142), average alcohol intake prior to pregnancy (n=7,103), and smoking in pregnancy (n=403).

Table 2: Hazard ratios for Attention Deficit Disorder according to binge drinking in early pregnancy; Aarhus Birth Cohort, Denmark, 1998-2012.

General study population								
Binge drinking	ADHD	Person-years x 10 ³	IR/10,000	Crude (n=42,862) HR	Model 1* (n=38,136) aHR 95% CI	Model 2** (n=33,529) aHR 95% CI		
0 episodes	741	313	2.4	1	1	1		
1 episode	249	108	2.3	0.95	0.91 (0.77 - 1.06)	0.91	(0.76 - 1.08)	
2 episodes	101	49	2.1	0.85	0.80 (0.64 - 1.01)	0.73	(0.56 - 0.96)	
>3 episodes	68	32	2.1	0.84	0.79 (0.61 - 1.03)	0.77	(0.57 - 1.06)	
Children of mothers without mental or behavioral disorder prior to birth								
Binge drinking	ADHD	Person-years x 10 ³	IR/10,000	Crude (n=36,451) HR	Model 1* (n=32,787) aHR 95% CI	Model 2** (n=28,802) aHR 95% CI		
0 episodes	530	265	2.0	1	1	1		
1 episode	190	94	2.0	0.99	0.91 (0.76 - 1.09)	0.91	(0.74 - 1.11)	
2 episodes	78	42	1.9	0.89	0.89 (0.70 - 1.15)	0.82	(0.61 - 1.11)	
>3 episodes	53	27	2.0	0.94	0.87 (0.64 - 1.18)	0.89	(0.63 - 1.26)	

Abbreviations: Attention Deficit Disorder (ADHD), adjusted hazard ratio (aHR), and body-mass-index (BMI). *Adjusted for maternal age, highest attained educational level, chronic disease, pre-gestational BMI, smoking in pregnancy, parity, and birth year. **Adjusted for maternal age, highest attained educational level, chronic disease, pre-gestational BMI, smoking in pregnancy, parity, birth year, and average weekly alcohol intake.

Table 3: Hazard ratios for Attention Deficit Disorder according to average weekly alcohol intake in early pregnancy; Aarhus Birth Cohort, Denmark, 2000-2012.

General study population								
Average intake	ADHD	Person-years x 10 ³	IR/10,000	Crude (n=41,049) HR	Model 1* (n=35,359) aHR	95% CI	Model 2** (n=33,529) aHR	95% CI
0 drinks/week	709	282	2.5	1	1		1	
<1 drink/week	279	135	2.1	0.74	0.84	(0.72 - 0.98)	0.87	(0.74 - 1.03)
1 drink/week	24	19	1.3	0.44	0.55	(0.35 - 0.86)	0.63	(0.40 - 0.98)
2 drinks/week	34	13	2.6	0.89	1.12	(0.77 - 1.63)	1.30	(0.89 - 1.92)
>3 drinks/week	12	5	2.2	0.74	0.77	(0.41 - 1.46)	0.78	(0.38 - 1.59)

Children of mothers without mental or behavioral disorder prior to birth								
Average intake	ADHD	Person-years x 10 ³	IR/10,000	Crude (n=34,552) HR	Model 1* (n=30,234) aHR	95% CI	Model 2** (n=28,802) aHR	95% CI
0 drinks/week	493	230	2.1	1	1		1	
<1 drink/week	222	119	1.9	0.77	0.85	(0.71 - 1.02)	0.88	(0.73 - 1.06)
1 drink/week	19	17	1.1	0.45	0.57	(0.35 - 0.92)	0.64	(0.39 - 1.05)
2 drinks/week	27	12	2.3	0.93	1.14	(0.76 - 1.73)	1.29	(0.84 - 1.97)
>3 drinks/week	10	5	2.2	0.87	0.99	(0.50 - 1.94)	1.08	(0.53 - 2.20)

Abbreviations: Attention Deficit Disorder (ADHD), adjusted hazard ratio (aHR), and body-mass-index (BMI). *Adjusted for maternal age, highest attained educational level, chronic disease, pre-gestational BMI, smoking in pregnancy, parity, and birth year. **Adjusted for maternal age, highest attained educational level, chronic disease, pre-gestational BMI, smoking in pregnancy, parity, birth year, and binge drinking.

Table 4: Hazard ratios for Attention Deficit Disorder according to binge drinking and average weekly alcohol intake in early pregnancy (total abstainers included as a separate category); Aarhus Birth Cohort, Denmark, 1998-2012.

General study population						
	ADHD	Person-years x 10 ³	IR/10,000	Crude (n=42,862) HR	Model 1* (n=38,136) aHR	95% CI
Binge drinking						
Total abstainers [†]	443	176	2.5	1.40	1.17	(0.99 - 1.39)
0 episodes ^{††}	298	137	2.2	1	1	
1 episode	249	108	2.3	1.15	0.99	(0.82 - 1.19)
2 episodes	101	49	2.1	1.02	0.87	(0.68 - 1.12)
>3 episodes	68	32	2.1	1.01	0.86	(0.65 - 1.15)
	ADHD	Person-years x 10 ³	IR/10,000	Crude (n=41,049) HR	Model 1* (n=35,359) aHR	95% CI
Average intake						
Total abstainers [†]	443	176	2.5	1.04	1.12	(0.93 - 1.34)
0 drinks/week ^{†††}	266	107	2.5	1	1	
<1 drink/week	279	135	2.1	0.76	0.90	(0.74 - 1.10)
1 drink/week	24	19	1.3	0.46	0.59	(0.37 - 0.94)
2 drinks/week	34	13	2.6	0.91	1.20	(0.81 - 1.78)
>3 drinks/week	12	5	2.2	0.76	0.83	(0.43 - 1.58)

Abbreviations: Attention Deficit Disorder (ADHD), adjusted hazard ratio (aHR), and body-mass-index (BMI). *Adjusted for maternal age, highest attained educational level, chronic disease, pre-gestational BMI, smoking in pregnancy, parity, and birth year. [†]n=17,249 ^{††}n=10,015 ^{†††}n=10,030