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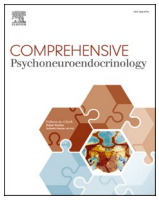

Pubertal timing, sex hormone levels, and associations between early life adversity and accelerated development amongst 11-year-old children of parents with schizophrenia or bipolar disorder and controls: The Danish high risk and Resilience study via 11

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ABSTRACT

Background: Children of parents with severe mental illness have several known risk factors for altered pubertal timing. Pubertal timing is important for children's physical and emotional development. We aimed to examine pubertal timing and associations between pubertal timing, early life adversity and child problem behavior including psychiatric diagnoses among children of parents with schizophrenia or bipolar disorder and controls.
Methods: Self-reported Tanner stage (mean age 11.9, range 10.87–12.67), sex hormone levels, home environment, placement out of home, and problem behavior including psychiatric diagnoses of children at familial high-risk (FHR) of schizophrenia (FHR-SZ), bipolar disorder (FHR-BP) and population-based controls (PBC) were assessed.
Results: A total of 465 children participated in the study (Tanner assessment N = 417, sex hormones N = 293). Assessed with self-reported Tanner, no difference in pubertal timing was found between groups ($p = 0.09$). Hormone levels did not differ between groups except for inhibin B (mean (SD) = 55.86 (29.13) pg/mL for FHR-SZ girls vs 84.98 (47.98) pg/mL) for PBC girls ($p < 0.001$)) and for follicle stimulating hormone (FSH) (mean (SD) = 5.82 (1.45) U/L for FHR-BP girls vs 4.54 (1.68) U/L for PBC girls ($p < 0.001$)). FHR children who were placed out of home (17 children, 3.8% of participants) had higher Tanner stages than those living at home ($p < 0.001$). Timing was not associated with level of problem behavior or psychiatric diagnoses.
Conclusions: FHR children did not differ from controls in pubertal timing. Early life adversity assessed as placement out of home may be associated with accelerated pubertal timing among children of parents with schizophrenia or bipolar disorder.

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1. Introduction

Pubertal onset and progression represent the transitional phase where the hypothalamic-pituitary-gonadal axis is activated, resulting in several developmental changes such as increased serum levels of sex steroids, breast development in girls, genital growth in boys, pubic hair development, a longitudinal growth spurt and advanced bone age in both sexes. Further, pubertal onset is followed by a comprehensive mental development. Puberty is often associated with mood swings and behavioral changes, and approximately 50% of the overall presence of lifetime mental illness has presented before the end of puberty [1]. Early but also late pubertal timing is associated with a higher risk of mental health problems [2–6] such as overall increased levels of psychopathology [2,3], depressive symptoms [2] and behavioral problems [2,7]. Previous studies of particularly girls (age 8–18) have found parental mental illness to be associated with early pubertal timing [8,9].

Factors such as early life adversity [10] and insufficient caregiving have been found to increase risk of early puberty [11–13]. It has been argued that through evolution, plasticity in developmental trajectories has been beneficial to support child adaptation to early experiences [14]. This could be slowing down development in a low-stress family environment and speeding up development in adverse environments where chances for long-term survival are more uncertain [14]. This stress acceleration theory suggests that a range of neural structures, functional profiles and molecular compositions occurring in brain regions of relevance for emotion expression, learning and memory may be altered through early life adversity such as family dysfunction or socio-economic disadvantage [14]. Through these mechanisms, early life adversity leads to stress and decreased plasticity in crucial regions such as the amygdala and prefrontal cortex, causing 1) accelerated puberty but also 2) increased risk of mental illness [14].

Further, physiological attributes such as increasing body fat mass and prenatal exposure to tobacco promote earlier pubertal onset [15,16]. These mentioned factors are more likely to be affected amongst children of parents with mental illness [17–23].

To our knowledge, only two previous studies have examined pubertal timing amongst children of parents with schizophrenia or bipolar disorder versus controls, and pubertal timing was not the main focus for these studies [24,25], nor did they contain sex hormone data. One of the two studies showed the pubertal onset in the VIA cohort [25] but detailed timing was not presented.

Examining pubertal timing in these populations is important since a larger proportion of these children are affected in their emotional, behavioral and social development compared with controls and pubertal timing plays a central role in brain function and neurological and mental development [26]. Therefore, the developmental problems experienced by these children may in part be caused by differential pubertal timing.

2. Objectives

We aimed to.

1) examine pubertal timing and compare puberty stages through self-reported Tanner staging as well as sex hormone development in a cohort of 465 11-year-old children of parents with schizophrenia or bipolar disorder and population-based controls [27,28],
2) test the stress acceleration hypothesis in a familial high-risk context by examining the correlation between early life adversity and pubertal onset,
3) test the association between pubertal timing and problem behavior and presence of any psychiatric disorder.

We hypothesized that.

1) children of parents with schizophrenia or bipolar disorder exhibited earlier pubertal onset than controls,
2) early life adversity was associated with accelerated pubertal timing,
3) part of the increased prevalence of problem behavior and psychiatric diagnoses found among these children is related to early pubertal timing.

3. Methods

3.1. The study cohort

The Danish High Risk and Resilience Study - VIA is a population-based, multisite, prospective cohort study of children of parents with a schizophrenia spectrum diagnosis (hereafter denoted children at risk of schizophrenia), or with a diagnosis of bipolar disorder(hereafter denoted children at risk of bipolar disorder), and population-based controls (hereafter denoted "children not at risk") with none of the two disorders among their parents [27,28]. Participants were identified, and controls matched to the group of children at risk of schizophrenia, through national registers. Children were assessed at age 7 (The VIA 7 Study, N = 522 (202 children at risk of schizophrenia, 120 children at risk of bipolar disorder, 200 children not at risk)) and at age 11 (The VIA 11 Study, N = 465 (179 children at risk of schizophrenia, 105 children at risk of bipolar disorder, 181 children not at risk)) (Fig. 1).

At age 7 [27] (mean age 7.84, age range 6.91–8.41), assessments were made concerning early development and fetal exposures. At both age 7 and 11 [28], socio-economic and early life adversity characteristics obtained from interviews with the primary caregiver (defined as the caregiver who spent the most time with the child) were collected, such as: parents' highest level of education and civil status, placement out of home (whether in foster or institutional care), parental single caregiver status, caregiver level of functioning, and level of stimulation and support in the child's home environment. The home environments were assessed through the use of a semi-structured interview (MC- and EA-HOME [29–32]) and total scores were used dichotomously to identify adequate from inadequate home environments ad modum [32]. Dichotomizing this data is relevant since the assessments are constructed to identify the "good-enough" home environments rather than to identify top-scorers. Caregiver's level of functioning was assessed with the Personal and Social Performance Scale (PSP) [33]. Child problem behavior was assessed (by the primary caregiver) with the Child Behavior Checklist (CBCL) total score [28]. The Kidde-SADS-PL interview was used to assess whether children fulfilled criteria for any psychiatric diagnosis [34]. Child height and weight were measured in the VIA 11 Study [28].

At age 11 (mean age 11.9, age range 10.87–12.67), children reported their pubertal stage after brief education and instruction from the assessor, through the use of the Tanner Stages [35,36] B1-5 for girls (breast stage), PH1-6 for boys and PH1-5 for girls (pubic hair stage), and G1-5 for boys (genital development). The children were shown illustrations (line drawings) of the Tanner stages and were asked to designate the illustration that matched their stage the most. Pubertal onset was defined as having reached a Tanner stage of 2 or more within any stage [25]. Mean values for risk groups were based on the highest self-reported Tanner stage measured in any of the Tanner assessments for each child. Since height and BMI can affect pubertal timing [37–40], information concerning height and BMI was also assessed. Height and weight were assessed three times and the mean values used. For assessment of sex hormone levels, blood samples were drawn between 8 a.m. and 2 p.m. and typically at 11.30. Blood samples were drawn from an antecubital vein by the laboratory staff at the research sites (Copenhagen (Gentofte Hospital) and Aarhus (Skejby Hospital)), centrifuged, and serum was stored at −20° Celsius until analysis. Reasons for non-participation included children not consenting to a blood draw, or that children could only participate in weekends when the laboratory was closed.

The examiners at both assessments were medical doctors, psychologists, and research nurses. Assessments at age 7 took place from

January 1st, 2013 to January 31st, 2016 and at age 11 from March 1st, 2017 until June 30th, 2020. Assessments took place at research facilities located in Copenhagen or Aarhus, Denmark. The home environment assessments took place in the children's homes. Examiners received formal training in the assessment battery and child examiners were blinded to the family's risk status. VIA 11 data was collected and managed using REDCap (Research Electronic Data Capture) [41]. The study was approved by the Danish Committee on Health Research Ethics and informed consent was obtained from all participants.

3.2. Hormone analyses

Serum concentrations of testosterone, androstenedione, dehydroepiandrosterone sulfate (DHEAS), estrone sulfate, estradiol, and estrone were determined by using isotope-dilution online-TurboFlow-liquid chromatography tandem-mass-spectrometry (LC-MS/MS) methods as previously reported in detail for androgens [42,43] and for estrogens [44]. For estrogens, isotope diluted serum samples were purified by liquid–liquid extraction before loading on the LC-MS/MS system, which was equipped with a heated electrospray ionization source running in

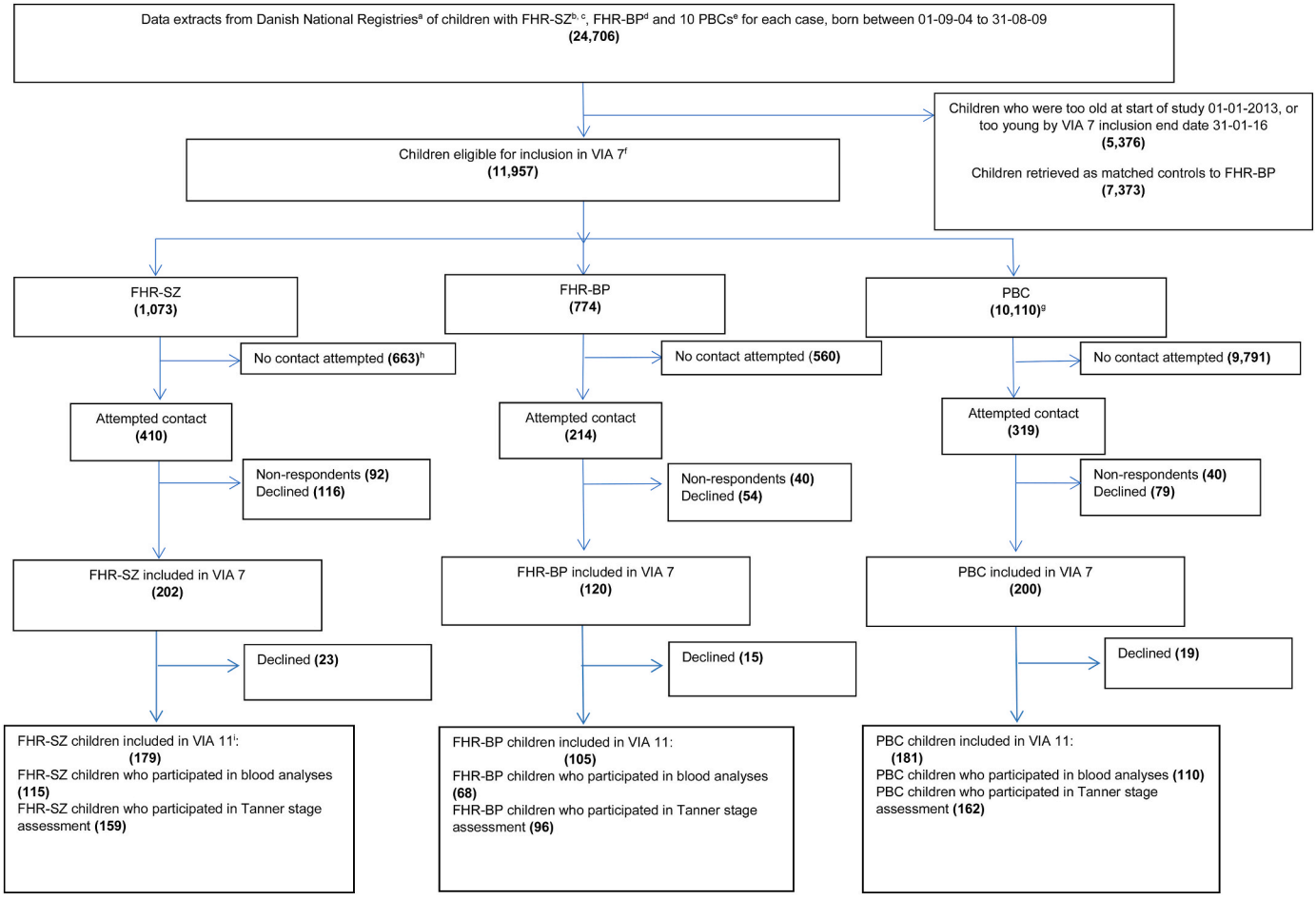

Fig. 1. Flowchart of children at familial high risk of schizophrenia (FHR-SZ) or bipolar disorder (FHR-BP) and population-based controls (PBC) in The Danish High Risk and Resilience Study VIA 11 (N = 465)

[a] **Danish National Registries:** The Danish Civil Registration System and The Danish Psychiatric Central Research Register. Based on the Danish Psychiatric Central Research Register, adults with a diagnosis of schizophrenia spectrum psychotic illness, (defined as schizophrenia, delusional disorder or schizoaffective disorder, ICD 10-codes: F20, F22 and F25 or ICD 8-codes: 295, 297, 298.29, 298.39, 298.99), or with a diagnosis of bipolar disorder (ICD 10-code F30, F31 or ICD 8-codes: 296.19 296.39) were identified. In-patient contacts could be any time between April 1, 1969, when the register was established, and the end of 2011. Out-patient contacts are registered from January 1, 1995, and onwards.

[b] **FHR-SZ:** Children of parents with a schizophrenia spectrum disorder.

[c] **Double diagnosed parents:** Parents diagnosed with schizophrenia AND bipolar disorder were assigned to the schizophrenia high-risk group in accordance with the ICD-10 hierarchy.

[d] **FHR-BP:** Children of parents with bipolar disorder.

[e] **PBC:** Population-based control children of parents with no diagnosis of schizophrenia spectrum disorder or bipolar disorder.

[f] **Research protection:** As of May 2011, legislation was enacted to protect individuals from being contacted for research purposes. Therefore, there were eligible children who were not contacted and enrolled in VIA 7.

[g] **Controls selection:** Up to 10 controls were retrieved for each child in the schizophrenia spectrum disorder group and the bipolar disorder group. Controls were matched to cases on gender, municipality, and exact age. The original intent was to only select control cases that were matched to children in the schizophrenia familial high-risk group. However, among the 200 controls, 38 are matched to children in the bipolar high-risk group.

[h] **Definition of contact:** First through letters sent to the child's address. If the family did not respond, contact by telephone was attempted (calls and text messages), if a phone number could be found.

[i] The general part of the VIA 11 flowchart is previously published in (Krantz, 2021).

Krantz, M. F. et al. (2021). Home environment of 11-year-old children born to parents with schizophrenia or bipolar disorder – a controlled, 4-year follow-up study: The Danish High Risk and Resilience Study – VIA 11. *Psychological Medicine*, 1–11. https://doi.org/DOI: 10.1017/S0033291721004487.

negative mode and with aqueous ammonium fluoride and methanol as mobile phases on the eluting column. Samples were analyzed in five batches for androgens/corticosteroids and five batches for estrogens. Beside cohort samples, each batch included calibrations samples, blanks (water) and control material in three times three levels. External quality control (UK NEQAS) for testosterone, 17-hydroxyprogesterone, androstenedione, DHEAS, and estradiol revealed excellent performance when compared with other labs using LC-MS/MS technology. The analyses of SHBG were not measured with LC-MS/MS but quality control for these was ensured with an external control program. For limits of detection and quantification, see Supplementary Table 1.

Serum concentrations of luteinizing hormone (LH) and follicle stimulating hormone (FSH) were analyzed by time-resolved fluoro immuometric assays (AutoDELFIA, PerkinElmer, Turku, Finland). The analyses were accredited by the Danish Inhibin B (Oxford-Bio-Innovation, Serotec, Oxford, UK) and anti-mullerian hormone (AMH) was determined by double antibody enzyme-immunometric assays (Immunotech, Beckman Coulter, Marseilles, France). The Accreditation Fund for medical examination was made according to a Danish approved European and International standard (the standard DS/EN ISO 15189). All hormone analyses were performed at the Dept. of Growth and Reproduction, Copenhagen University Hospital – Rigshospitalet.

3.3. Statistical methods

For background information concerning participants, descriptive statistics were performed to estimate mean and standard deviations, and for dichotomous variables, Pearson's chi-square crosstabs obtaining N (%) and p-values were performed for all variables by risk group when overall ANOVAS were significant. Mean differences in absolute values, confidence intervals and p-values were reported for pairwise comparisons. Analyses of variance were performed using one-way ANOVAs with

Table 1
Physical and socioeconomic characteristics of 465 children at familial high risk of schizophrenia (FHR-SZ) or bipolar disorder (FHR-BP), and population-based controls (PBC).

	FHR-SZ	FHR-BP	PBC	p-value[a]	FHR-SZ vs PBC, Mean difference[b] (CI), p-value	FHR-BP vs PBC, Mean difference (CI), p-value	FHR-SZ vs FHR-BP, Mean difference (CI), p-value
Physical characteristics							
Sex, N (%)	N = 179	N = 105	N = 181		–	–	–
Female	85 (47.5)	46 (43.8)	83 (45.9)	0.83			
Age, mean (SD)	11.96 (0.26)	11.93 (0.23)	11.93 (0.02)	0.57	–	–	–
BMI boys, mean (SD)	(N = 88) 19.27 (3.01)	(N = 56) 19.17 (3.70)	(N = 90) 18.97 (3.47)	0.83	–	–	–
BMI girls, mean (SD)	(N = 80) 19.18 (3.36)	(N = 45) 18.62 (2.61)	(N = 79) 19.15 (2.82)	0.56	–	–	–
Height, mean (SD)	(N = 169) 153.42 (7.74)	(N = 101) 155.81 (7.41)	(N = 169) 155.02 (8.15)	**0.035**	1.61 (−3.28; 0.67) 0.06	0.79 (−2.72; 1.15) 0.42	2.39 (−4.33; −0.46) **0.015**
Boys, mean (SD)	152.38 (7.57)	154,21 (7.31)	154.35 (9.03)	0.217	–	–	–
Girls, mean (SD)	154.54 (7.80)	157.80 (7.13)	155.79 (7.00)	0.06	–	–	–
Height standardized, boys and girls, mean (SD)	−0.20 (0.95)	0.10 (0.91)	0.00 (1.00)	**0.035**	0.20 (−0.40; 0.01) 0.06	0.10 (−0.33; 0.14) 0.42	0.29 (−0.53; −0.06) **0.02**
Height adjusted for age, mean (SD)	153.31 (0.60)	155.80 (0.77)	155.06 (0.60)	0.347	–	–	–
Percentage meeting criteria for puberty (Tanner Stage ≥2), N (%)[c]	139 (87.4)	87 (90.6)	153 (94.4)	0.09	–	–	–
Percentage meeting criteria for puberty (Tanner Stage ≥2), N (%)[c], girls	70 (90.9)	42 (95.5)	74 (96.1)	0.358	–	–	–
Percentage meeting criteria for puberty (Tanner Stage ≥2), N (%)[c], boys	69 (84.1)	45 (86.5)	79 (92.9)	0.197	–	–	–
Tanner Stage, mean (SD)	(N = 159) 2.45 (0.93)	(N = 96) 2.53 (0.87)	(N = 162) 2.44 (0.73)	0.68	–	–	–
Socioeconomic characteristics							
Fetal tobacco smoke exposure[d]	(N = 163)	(N = 99)	(N = 177)				
Yes, on a daily basis N (%)	58 (35.6)	15 (15.2)	14 (7.9)				
Yes, but not on a daily basis N (%)	8 (4.9)	6 (6.1)	4 (2.3)	**<.001**	0.33 (0.22; 0.44) **0.00**	0.15 (−0.28; −0.02) **0.02**	0.18 (0.05; 0.31) **0.01**
Level of education of primary[e] caregiver, N (%)	(N = 171)	(N = 102)	(N = 178)				
Primary/lower secondary	47 (27.5)	18 (17.6)	26 (14.6)				
Upper secondary, vocational, short-cycle tertiary	51 (29.8)	26 (25.5)	53 (29.8)				
Bachelor degree, equivalent or higher	73 (42.7)	58 (56.9)	99 (55.6)	**0.02**	0.52 (−0.88; −0.15) **0.01**	0.01 (−0.41; 0.43) 0.97	0.52 (−0.95; −0.10) **0.02**
Home environment – level of stimulation and support at age 11, mean (SD)	(n = 158) 46.16 (5.56)	(n = 97) 46.87 (5.34)	(n = 170) 49.25 (4.37)	**<.001**	3.09 (−4.19;-1.99) **<.001**	2.39 (−3.65; −1.12) **<.001**	0.70 (−1.99; 0.58) 0.28
Proportion living in an inadequate home environment, N (%)	24 (15.0)	12 (12.2)	6 (3.5)	**<.001**	0.11 (−0.18; −0.05) **<.001**	0.09 (−0.16; −0.01) **0.02**	0.03 (−0.10; 0.05) 0.47
Placement out of home, N (%)	17 (9.6)	<5	0 (0.0)	**<.001**	0.10 (0.06; 0.13) **<.001**	0.01 (−0.06; 0.04) 0.68	0.09 (0.04; 0.13) **<.001**

[a] One-way ANOVA with posthoc LSD and Pearson chi-square for N (%).
[b] Absolute values.
[c] No adjustment for age was used because no significant difference between age at inclusion was found between groups. A supplementary ANCOVA was performed with age at inclusion as a covariate, rendering a larger difference between the FHR-SZ and PBC group (p (SE) = 0.012 (0.032)).
[d] Data from the VIA assessment at the child's age 7.
[e] The primary caregiver was defined as the adult who lived and spent the most time with the child and who participated in completing questionnaires in the VIA Study.

least significant difference (LSD) post hoc multiple comparisons. An ANCOVA was used to examine height differences after adjustment for age at study inclusion since height could be highly dependent on exact age. The cut-off value for living in an inadequate home environment was defined as 2 SD below the control group mean [45]. Dichotomization was used to describe this data in background Table 1, however, for all other calculations where the data was used, the continuous score was used in order not to lose information from dichotomization. Since some previous studies have found limitations with regards to the accuracy of self-reported Tanner, particularly with regards to the accuracy of high Tanner stages [4,5,46], we used a dichotomous measure (Tanner stage $\geq$2) to display pubertal onset but chose also to present Tanner stage as a continuous measure since this would better describe pubertal timing which was our main aim.

For the sex hormones, raw concentrations and standardized values (z-scores) were calculated using the Generalized Additive models for Location Scale and Shape (GAMLSS) [47], stratified by sex. Since groups did not differ in age on the overall ANOVA, no age adjustments were made for the sex hormones. To examine Tanner stage variation across groups, a histogram was produced for visual inspection.

Dropout analyses using Pearson chi-square were performed for blood sample participation by risk group and by sex of the child, for Tanner stage participation by risk group and for blood sample participation by living out of home versus living at home.

To examine how pubertal timing was related to early life adversity, a covariance analysis including level of stimulation and support at home, caregiver functioning, and prevalence of child placement was performed. To examine whether pubertal timing was associated with prevalence of problem behavior and psychiatric diagnoses, covariance analyses including level of problem behavior and prevalence of psychiatric diagnosis were performed.

All analyses were conducted using statistical software IBM SPSS, version 25.

4. Results

4.1. Sex, age and dropout analyses

The included children were comparable across study groups in terms of age which ranged from mean values of 11.93–11.96 ($p = 0.57$, SD 0.02 to 0.26) (Table 1). Dropout analyses showed that participation rates across groups for children who participated in blood samples and in self-reported Tanner stage assessment did not differ ($p = 0.50$ and $p = 0.61$), nor did participation rates differ between the sexes ($p = 0.56$) (Supplementary Table 2). A dropout analysis assessing dropout by living out of home showed that a higher proportion of children who were living out of the home had blood samples taken compared with children living with their parents ($p = 0.03$) (Supplementary Table 2).

4.2. Body mass index and height

Body mass index (BMI) for both boys and girls (N = 234 for boys, N = 204 for girls) displayed similar results across groups (mean values 18.97–19.27 for boys, 18.62–19.18 for girls).Children at risk of schizophrenia of both sexes together were shorter compared to the group of children at risk of bipolar disorder ($p = 0.015$) (mean (SD) = 153.42 (7.74) for children at risk of schizophrenia, = 155.81 (7.41) for children at risk of bipolar disorder and = 155.02 (8.15) for children not at risk) (Table 1).

4.3. Pubertal timing assessed with self-reported Tanner stage

For self-reported Tanner stage assessment, a total of 417 children (198 girls and 219 boys, 159 children at risk of schizophrenia (88.8% of VIA 11 participants), 96 children at risk of bipolar disorder (91.4%), 162 children not at risk (89.5%) participated (Fig. 1).

The risk and not at risk groups did not differ in terms of Tanner stage ($p = 0.09$) (Table 1). Histograms of Tanner stage assessment of maximum development stage in either pubic hair or sex organs showed that for both risk groups, Tanner Stage varied more with a higher proportion of familial high-risk children having Tanner Stages 1, 4 or 5 compared with children not at risk (Supplementary Fig. 1). As expected, a higher proportion of girls reported onset of puberty, compared to boys. Although not significant, more controls reported onset of puberty in both sexes compared to controls.

4.4. Early life adversity

Significant between-group differences were identified regarding all included socio-economic characteristics (Table 1). Children in both risk groups were more exposed to tobacco smoke during pregnancy than children not at risk (40.5% for children at risk of schizophrenia, 21.3% for children at risk of bipolar disorder and 10.2% for children not at risk, $p < 0.001$), parents belonging to the schizophrenia risk group had significantly lower levels of education than controls (27.5% of caregivers in the schizophrenia risk group, 17.56% in the bipolar disorder risk group and 14.6% of caregivers belonging to the control group only had primary/lower secondary school) ($p = 0.02$), and for both risk groups, a higher proportion of children lived with single caregivers compared with children not at risk (31.5% for children at risk of schizophrenia, 42.9% for children at risk of bipolar disorder and 13.9% for children not at risk) ($p < 0.001$). Further, children in both risk groups lived in homes with lower levels of stimulation and support compared with controls (mean (SD) for children at risk of schizophrenia = 46.16 (5.56), for bipolar disorder = 46.87 (5.34) and for children not at risk = 49.25 (4.37), $p < 0.001$) and a higher proportion lived in inadequate home environments, compared with controls (15.0% for children at risk of schizophrenia, 12.2% for children at risk of bipolar disorder and 3.5% for children not at risk, $p < 0.001$ for children at risk of schizophrenia vs children not at risk, $p = 0.02$ for children at risk of bipolar disorder vs). Also, a higher proportion of children at risk of schizophrenia were placed out of the home of the biological parents compared with children not at risk (9.6% for children at risk of schizophrenia versus 0% of children not at risk and <5 of children at risk of bipolar disorder, $p < 0.001$ for children at risk of schizophrenia vs children not at risk).

4.5. Sex hormone levels

A total of 293 children (139 girls and 154 boys, 115 children at risk of schizophrenia (64.3% of VIA 11 participants), 68 children at risk of bipolar disorder (64.8%), 110 children not at risk (60.8%)) had blood samples successfully drawn for hormone analyses (Fig. 1). Overall ANOVAs showed no significant differences between groups for girls (Table 2a) and boys (Table 2b), respectively (p-values from 0.121 to 0.986 for boys and from 0.229 to 0.944 for girls) except for inhibin B and FSH in girls. For inhibin B in girls, the overall ANOVA revealed significant differences (mean (SD) for children at risk of schizophrenia = 55.86 (29.13), children at risk of bipolar disorder = 73.52 (32.82), children not at risk = 84.98 (47.98), $p < 0.001$) and pairwise comparisons showed that the children at risk of schizophrenia had significantly lower levels compared to the children not at risk ($p < 0.001$) and to those at risk of bipolar disorder ($p = 0.012$). For FSH, the overall ANOVA revealed significant differences (mean (SD) for children at risk of schizophrenia = 4.38 (2.22), for children at risk of bipolar disorder = 5.82 (1.45), for children not at risk = 4.54 (1.68), $p = 0.003$) and pairwise comparisons showed that the children at risk of bipolar disorder had significantly higher levels compared with those not at risk and with those at risk of schizophrenia ($p = 0.001$ and $p = 0.002$).

4.6. Early life adversity, behavior and pubertal development

The pubertal development of children at risk of schizophrenia or

Table 2a
Sex hormone levels for 139 11-year-old female offspring at familial high risk of schizophrenia (FHR-SZ) or bipolar disorder (FHR-BP), and population-based controls (PBC).

	FHR-SZ (n = 59)	FHR-BP (n = 30)	PBC (n = 50)	p-value (ANOVA)[b]
DHEAS nmol/L, mean (SD)	1923.73 (1078.42)	1771.77 (1059.30)	1900.24 (1014.93)	0.804
DHEAS standardized	−0.05 (1.07)	−0.22 (1.04)	−0.01 (0.91)	0.672
Androstenedione nmol/L, mean (SD)	2.25 (1.03)	2.69 (1.25)	2.51 (1.46)	0.260
Androstenedione standardized	0.23 (0.98)	0.55 (1.11)	0.42 (1.03)	0.343
Testosterone nmol/L, mean (SD)	0.64 (0.25)	0.76 (0.39)	0.69 (0.36)	0.229
Testosterone standardized	0.48 (0.88)	0.70 (1.11)	0.60 (0.93)	0.573
Estrone pmol/L, mean (SD)	95.90 (52.32)	113.20 (45.89)	106.67 (67.19)	0.357
Estrone standardized	0.13 (0.94)	0.41 (0.88)	0.30 (0.91)	0.354
Estradiol pmol/L, mean (SD)	143.69 (143.28)	144.66 (79.47)	137.14 (92.11)	0.944
Estradiol standardized	0.33 (1.01)	0.55 (0.70)	0.51 (0.71)	0.411
Estrone sulfate[a] nmol/L, mean (SD)	1.39 (1.51)	1.26 (0.88)	1.38 (1.47)	0.914
SHBG[a] nmol/L, mean (SD)	72.92 (33.88) (n = 58)[c]	67.31 (27.95) (n = 28)	76.25 (31.05)	0.492
AMH[a] pmol/L, mean (SD)	24.34 (15.40) (n = 58)	22.45 (15.04) (n = 28)	27.66 (18.07)	0.356
Inhibin B[a] pg/mL, mean (SD)	55.86 (29.13) (n = 58)	73.52 (32.82) (n = 29)	84.98 (47.98)	**<0.001**
FSH[a] IU/L, mean (SD)	4.38 (2.22) (n = 58)	5.82 (1.45) (n = 28)	4.54 (1.68)	**0.003**
LH[a] IU/L, mean (SD)	3.55 (6.08)	4.25 (3.12)	2.93 (2,50)	0.441
	(n = 56)	(n = 29)	(n = 50)	

[a] No standardized version is presented due to lack of control material for standardization.
[b] Pairwise comparisons with posthoc LSD were performed between groups with significant overall p-values: In these, no significant differences were found between groups except for Inhibin B and FSH. For Inhibin B, significant differences were found between the FHR-SZ and PBC groups ($p < 0.001$) and between the FHR-SZ and FHR-BP groups ($p = 0.012$). For FSH, significant differences were found between the FHR-BP and PBC groups ($p = 0.001$) and between the FHR-SZ and FHR-BP groups ($p = 0.002$).
[c] The N for included samples varies due to results below the limit of detection and is therefore in these cases reported in the table.

bipolar disorder who had been placed out of the home (N = 17) was compared with the development of children at risk of schizophrenia or bipolar disorder who lived at home (N = 238) (Supplementary Table 3). The mean (SD) of the highest self-reported Tanner Stage of each of the children placed out of home was 3.18 (1.0) compared to 2.43 (0.9) for the children living at home ($p < 0.001$). Results remained significant after adjustment for BMI and age at inclusion (data not shown). When assessed dichotomously as having reached puberty according to Tanner staging 2 or above, no difference was found between at-risk children placed out of the home and those living at home ($p = 0.12$, data not shown) but when assessed dichotomously as having reached puberty according to Tanner staging 3 or above, 12 out of 17 children (70.6%, $p = 0.03$) had a Tanner stage of 3 or above (data not shown). As approximately half of the children placed out of home were boys and the other half were girls, numbers were too few to meaningfully explore sex hormone levels for girls respectively boys living out of home versus those who did not.

An analysis of covariance was performed to examine possible effects on pubertal development of living out of home, of living with a low level of stimulation and support at home, and of living with a caregiver with a low level of functioning. In this analysis, 3% of pubertal development could be attributed to living out of home ($p = 0.002$) and 1% to the level of stimulation and support at home ($p = 0.03$). Parental level of functioning did not explain pubertal development ($p = 0.50$) (Supplementary Table 4). Also, pubertal timing did not explain problem behavior ($p = 0.607$) (Supplementary Table 5) and pubertal timing did not explain any current psychiatric diagnoses ($p = 0.561$) (Supplementary Table 6).

5. Discussion

In this study of a cohort of same aged, early adolescent children of parents with schizophrenia or bipolar disorder and population-based controls, a range of physical and socio-economic factors which may affect pubertal timing were examined. We found that children at familial risk of schizophrenia or bipolar disorder differ from controls particularly regarding the socio-economic factors.

5.1. Height and BMI

Contrary to previous studies, comparisons between risk groups and children not at risks on height did not reach significance. Children at risk of schizophrenia, particularly girls, were shorter than children not at risk but to insignificant levels. The lack of significance thus stands in contrast with a previous study which found that daughters of mothers with a psychotic illness were shorter [48]. Reasons for the non-significant finding in our study could include lack of statistical power. Previous studies have found that children of parents with mental illness are overnourished and may have higher BMIs [49], which is associated with earlier puberty in girls [40,50]. We found no significant differences in BMI between groups but did see a slight tendency towards higher BMI particularly amongst children at risk of schizophrenia. The lack of significant differences between risk groups and children not at risk might reflect a certain homogeneity across groups in terms of nutrition and genetic makeup for height. A large body of evidence confirms the association between nutritional factors, particularly in childhood, and height [51], while this is to our knowledge not the case for any genetic overlap between risk alleles for schizophrenia or bipolar disorder and height. These findings represent the current stage of development at 11-year-old children and may not reflect future differential development. The lack of significant differences in height and BMI may relate to the study context of a Danish welfare model which may buffer some of the socio-economic effects of being at risk of schizophrenia or bipolar disorder and through economic and health care aid decrease nutritional differences across groups [52].

5.2. Pubertal timing

In the age-range examined, girls are on average known to be physiologically more advanced in their pubertal development than boys [53]. Our results were in line with this finding. We found a wider self-reported Tanner stage variation among at-risk children, with more children having both very low and very high Tanner stages. In analyses of percentage meeting criteria for puberty, we found no significant difference between the groups, neither in total nor for any sex analyzed separately. These findings are difficult to compare to the only other study of children at risk of schizophrenia or bipolar disorder versus controls which found that a higher proportion of children at risk of bipolar disorder and a lower proportion of children at risk of schizophrenia had high Tanner stages, because this study had mean ages which differed significantly between groups with a mean age of 12.5 for bipolar offspring, of 10.4 for

Table 2b
Sex hormone levels for 154 11-year-old male offspring at familial high risk of schizophrenia (FHR-SZ) or bipolar disorder (FHR-BP), and population-based controls (PBC).

	FHR-SZ (n = 56)	FHR-BP (N = 38[a])	PBC (n = 60)	p-value (ANOVA)
DHEAS nmol/L, mean (SD)	2232.85 (1249.70)	2493.46 (1260.86)	2642.78 (1285.98)	0.218
DHEAS standardized, mean (SD)	−0.53 (1.00)	−0.24 (0.89) (n = 37)	−0.18 (0.91)	0.121
Androstenedione nmol/L, mean (SD)	0.90 (0.39)	0.88 (0.31)	1.02 (0.45)	0.128
Androstenedione standardized, mean (SD)	−0.42 (0.70)	−0.40 (0.64) (n = 37)	−0.19 (0.77)	0.156
Testosterone nmol/L, mean (SD)	2.21 (3.68)	1.70 (2.44)	1.94 (2.85)	0.731
Testosterone standardized, mean (SD)	−0.40 (0.93)	−0.40 (0.98) (n = 37)	−0.43 (0.89)	0.986
Estrone pmol/L, mean (SD)	23.08 (12.56)	23.70 (12.86)	26.29 (15.69)	0.430
Estrone standardized, mean (SD)	−0.62 (0.71)	−0.56 (0.76) (n = 37)	−0.42 (0.81)	0.369
Estradiol[a] pmol/L, mean (SD)	9.30 (14.72)	7.56 (11.61)	9.19 (13.99)	0.805
Estradiol standardized, mean (SD)	0.32 (0.59)	0.16 (0.50)	0.27 (0.61)	0.601
Estrone Sulfate[b], mean (SD)	0.26 (0.24)	0.30 (0.24)	0.27 (0.23)	0.671
SHBG[b] nmol/L, mean (SD)	77.93 (29.19)	86.09 (33.49) (N = 37)	87.55 (36.06) (N = 57)	0.264
AMH[b] pmol/L, mean (SD)	278.29 (222.56)	285.67 (228.05) (n = 37)	346.69 (262.67) (n = 57)	0.269
Inhibin B[b] pg/ml, mean (SD)	178.32 (56.05)	180.32 (79.64) (n = 37)	171.41 (73.37) (n = 59)	0.792
FSH[b] IU/L, mean (SD)	1.94 (1.08)	2.25 (1.32) (n = 37)	2.22 (2.14) (n = 56)	0.551
LH[b] IU/L, mean (SD)	1.29 (1.19) (n = 56)	1.07 (1.10) (n = 37)	1.57 (1.47) (n = 57)	0.170

[a] The N for included samples varies due to results below the limit of detection and is therefore in these cases reported in the table.
[b] Standardized results not available.

schizophrenia offspring and of 11.7 for controls [24] and age-adjustment was not noted in this study for the Tanner results.

5.3. Sex hormones

For most sex hormones, we found no significant differences between hormone levels across the groups. We did however find that inhibin B was lower for the children at risk of schizophrenia and that FSH was higher for the children at risk of bipolar disorder. We have not been able to identify any previous studies of children at familial high-risk of schizophrenia or bipolar disorder who have examined LH and FSH levels and thus cannot compare findings. Like for pubertal timing, several competing factors may be affecting the sex hormone levels, such as fetal exposures, physical attributes and upbringing conditions [16]. We expected to see a larger proportion of children with increased sex hormone levels among children at risk of schizophrenia since this group is affected by several risk factors for early pubertal timing. We hypothesize that reasons for not finding any differences relate to opposite effects like those described below for pubertal timing.

5.4. Early life adversity and pubertal development

Children at risk of schizophrenia or bipolar disorder and their parents were more disadvantaged than controls in all included socio-economic measures. Findings were significant in all measures except for comparisons between children at risk of schizophrenia versus children not at risk concerning parental level of education and child placement out of the home. Factors of disadvantage which resemble these have previously been linked to altered pubertal timing in the general population [8,54] – for example, a study found that lower household socio-economic status was associated with a two and four-fold increase in early puberty in girls and boys, respectively [55]. These factors may indicate, from an evolutionary perspective as presented in the stress acceleration hypothesis, a need for the child to grow up fast, although etiological pathways are still widely unknown [14].

Previous studies have identified a range of factors which are present among children at risk of schizophrenia or bipolar disorder, e.g. early life adversity, low socio-economic status and insufficient caregiving, and which may affect pubertal timing, primarily through acceleration [10,13,15,17–23]. Some factors, e.g. lack of proper nutrition [10] may, however, delay puberty, and since several of the factors which can affect pubertal timing are more prevalent among the at-risk children in our cohort [32,56] and several of the mentioned factors are closely interconnected [10], it might cause a wider Tanner variation among at-risk children rather than accelerate group average pubertal timing.

Finally, it is also possible that most children at risk of schizophrenia or bipolar disorder in our cohort are not affected by such socio-economic factors to a degree where pubertal timing is significantly affected e.g. due to the study context of a Danish welfare state which provides support for many of the at-risk families [32]. This system may act as a buffer and decrease the degree to which at-risk families are affected by early life adversity and low socio-economic status.

Our finding concerning earlier pubertal development among children at risk of schizophrenia or bipolar disorder placed out of home is in line with previous studies linking child adversity to early pubertal timing, since it is reasonable to assume that a range of childhood adversities are represented among the children who have been placed out of home. Other studies concerning children placed in foster care in general, with no specific mention of parental mental illness, have likewise found associations between placement, the reasons for placement (e.g. early life stress and child maltreatment), and early pubertal timing in girls [57,58], particularly those who had experienced more than two disruptions in their placement. A meta-analysis concerning adverse childhood experiences and early pubertal timing in girls found small to medium effect-sizes concerning father absence, and small effect-sizes concerning sexual abuse and family dysfunction which are all possible reasons for placement in foster care [59]. Another study of both sexes concluded that placement (in orphanages) increases the risk of growth stunting but is not independently associated with early pubertal timing in girls [60]. Adding this literature, our finding supports the conclusion that a subgroup of children at risk of schizophrenia or bipolar disorder who have experienced early life adversity may also be at risk of early pubertal timing, potentially increasing the risk of negative physical and emotional development, as found in previous studies [14].

5.5. Strengths and limitations

This study is to our knowledge the first study to assess pubertal timing with sex hormone levels in a cohort of same aged, early adolescent children at risk of schizophrenia or bipolar disorder versus children

not at risk. It is a major strength that the VIA 11 Study is a well-powered follow-up study based on national registers which allowed authors to include a nation-wide cohort with children matched on age, sex and municipality code. The study adds to the sparse literature regarding pubertal development among children of parents with more severe mental illness since most studies in the field have concerned more common psychopathology like anxiety and depression. It is a strength that this study captured data concerning sex hormones and self-reported Tanner stage at the same time. To our knowledge, this is the first study to assess pubertal development through the use of sex hormone measures in this group of children. It is a limitation that not all children participated in blood analyses and that the exact time of day for the blood sample was not registered, although all were measured at daytime. Notably, a timed early morning blood sample in all subjects may have limited the minor diurnal variation. However, this also accounts for the reference material, where blood sampling in the healthy subjects was between 8 and 13 o-clock.

The main limitation in our study may be that Tanner stage assessment was self-reported and not assessed by clinicians. This approach was chosen since such examination was considered inappropriate in the study setting. A golden standard assessment of pubertal development requires a physical examination including inspection and palpation of breasts in girls and testicular volume in males. This study however decided to use a self-reported questionnaire in spite of its limitations due to the abovementioned reason, and its limitations must be taken into account when considering reliability of the results. It is also a limitation that the age range spanned from 10.87 to 12.67 although in other contexts this age span is quite small and although mean age did not differ between groups. Genetic heritability for pubertal timing may also play a role and it is a limitation that no genetic data concerning pubertal timing of parents were assessed. Further, it is a limitation that numbers of children placed out of home were few (N = 17). Thus, variation in Tanner stage among at-risk children living at home versus those who did not could represent chance findings.

6. Conclusion

Our study indicates that for most children at risk of schizophrenia or bipolar disorder, pubertal timing is in most respects in line with the timing among children not at risk. However, for at-risk children, several risk factors for abnormal pubertal timing – early as well as late - co-occur and possibly contribute to a wider variation in pubertal timing particularly among children at risk of schizophrenia. In this respect, children at risk of schizophrenia who have been disadvantaged in their family life to the extent where placement was needed may represent a subgroup with early pubertal timing. Our findings are in line with the stress acceleration hypothesis for this subgroup of children suggesting that growing up in a stressful environment may accelerate pubertal timing. If replicated in other studies, they increase clinical implications for home support of this subgroup of children since living in a severely insufficient home environment may pose a risk for early pubertal timing.

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Ethical standards

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. The study was approved by the Danish Data Protection Agency and The Danish National Committee on Health Research Ethics (Protocol number H16043682). The protocol for the study was published in Ref. [28].

Declaration of competing interest

None.

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Appendix A. Supplementary data

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