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ORIGINAL PAPER

# Examining selection bias in a population-based cohort study of 522 children with familial high risk of schizophrenia or bipolar disorder, and controls: The Danish High Risk and Resilience Study VIA 7

**Mette Falkenberg Krantz[1,2,4] · Carsten Hjorthøj[1,4,10] · Ditte Ellersgaard[1,4] · Nicoline Hemager[1,2,4] · Camilla Christiani[1,2,4] · Katrine Søborg Spang[3,4] · Birgitte Klee Burton[3] · Maja Gregersen[1,2,4] · Anne Søndergaard[1,2,4] · Aja Greve[4,5,7] · Jessica Ohland[1,4] · Preben Bo Mortensen[4,9] · Kerstin Jessica Plessen[1,4,8] · Vibeke Bliksted[4,5,7] · Jens Richardt Møllegaard Jepsen[1,3,4,6] · Anne A. E. Thorup[1,2,3,4] · Ole Mors[4,5,7] · Merete Nordentoft[1,2,4]**

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## Abstract

**Purpose** Knowledge about representativity of familial high-risk studies of schizophrenia and bipolar disorder is essential to generalize study conclusions. The Danish High Risk and Resilience Study (VIA 7), a population-based case–control familial high-risk study, creates a unique opportunity for combining assessment and register data to examine cohort representativity.

**Methods** Through national registers, we identified the population of 11,959 children of parents with schizophrenia (FHR-SZ) or bipolar disorder (FHR-BP) and controls from which the 522 children participating in The VIA 7 Study (202 FHR-SZ, 120 FHR-BP and 200 controls) were selected. Socio-economic and health data were obtained to compare high-risk groups and controls, and participants versus non-participants. Selection bias impact on results was analyzed through inverse probability weights.

**Results** In the total sample of 11,959 children, FHR-SZ and FHR-BP children had more socio-economic and health disadvantages than controls ($p < 0.001$ for most). VIA 7 non-participants had a poorer function, e.g. more paternal somatic and mental illness ($p = 0.02$ and $p = 0.04$ for FHR-SZ), notifications of concern (FHR-BP and PBC $p < 0.001$), placements out of home ($p = 0.03$ for FHR-SZ), and lower level of education ($p \leq 0.01$ for maternal FHR-SZ and FHR-BP, $p = 0.001$ for paternal FHR-BP). Inverse probability weighted analyses of results generated from the VIA Study showed minor changes in study findings after adjustment for the found selection bias.

**Conclusions** Familial high-risk families have multiple socio-economic and health disadvantages. In The VIA 7 Study, although comparable regarding mental illness severity after their child's birth, socioeconomic and health disadvantages are more profound amongst non-participants than amongst participants.

**Keywords** Familial high-risk · Severe parental mental illness · Socio-economy · Representativity · Generalizability

## Introduction

Schizophrenia and bipolar disorder are severe mental disorders with major implications for the affected individuals and their relatives. Both illnesses are complex psychiatric brain disorders influenced by interacting genetic and environmental factors [1]. A positive family history of either of these disorders is the largest single risk factor for developing the same illness or other psychiatric disorders [2]. Due to their tenfold increased risk of having these disorders compared to control children, children of parents with schizophrenia or bipolar disorder constitute an important population when studying antecedents and risk factors [2]. Additionally, their partially shared aetiology [3–5] makes it appropriate to study them side-by-side. Previous familial high-risk studies have documented that children at familial high risk of schizophrenia or bipolar disorder have increased levels of early psychiatric symptomatology [6–11], neuro- and socio-cognitive deficits [12–23] and neuromotor impairments [12, 13, 24, 25], generally to a higher extent among children at familial high-risk of schizophrenia than of bipolar disorder. Finally, the parental

✉ Mette Falkenberg Krantz
Mette.Falkenberg.Krantz@regionh.dk

Extended author information available on the last page of the article

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**Key Summary Points**

Children with familial high risk of schizophrenia or bipolar disorder, and their parents, are more disadvantaged than controls regarding socio-economy, health, family level of function, and child school life.

Families participating in The VIA 7 Study have fewer preventive interventions, fewer notifications of concern and their children are less frequently placed outside of the home compared to non-participants, and thus the VIA 7 population may to some degree represent better functioning families than familial high-risk families in general.

socioeconomic disadvantage is associated with a higher risk of schizophrenia [26]. Most familial high-risk studies have limitations such as large age spans, use of convenience samples and lack of sufficient matching [13, 27]. This hampers the generalizability of the findings. Analyses concerning representativity are essential to be able to generalize conclusions to the entire target population [28]. Lack of representativity may occur through selection bias and it may occur in spite of register-based recruitment from the general population, leading to poor external validity[28]. Further, it is a known problem from epidemiological research that participants tend to have a higher level of functioning than non-participants e.g. concerning social status, level of education and health [29–32].

The first wave of The Danish High Risk and Resilience Study, VIA 7 (hereafter The VIA 7 Study), was conducted to examine early development, risk and resilience factors in children of parents with schizophrenia or bipolar disorder. The study participants constitute a register-based cohort with a narrow age span, where children with familial high risk of schizophrenia are matched to controls with no such parental diagnosis. The VIA 7 Study presents a unique possibility to examine representativity, as the Danish national registers [33, 34] can be utilized to compare participants to non-participants regarding e.g. socioeconomic and health-related factors of relevance for later child development. Concerns about recall bias can thus be avoided, and group differences as well as differences between participants and non-participants can be examined. This allows for the nationwide estimation of disadvantages amongst children with familial high risk. Further, register data can be used to weight the findings of The VIA 7 Study through the use of inverse probability weighting [35–37]. Thus, in addition to examining cohort representativity, VIA 7 Study results in domains such as motor function and neurocognition can be adjusted to take any selection bias into account and thus examine how results from the VIA 7 Study would appear if no selection bias had been present in the study.

### Objectives

We aimed to describe socioeconomic and health-related characteristics of children with familial high risk of schizophrenia (FHR-SZ) or bipolar disorder (FHR-BP), compared with population-based controls (PBC). We further aimed to compare participants of The VIA 7 Study to eligible non-participants to examine representativity of The VIA 7 Study across familial high-risk status, hypothesizing that children with FHR-SZ or FHR-BP in the general population would have more severe disadvantages across multiple domains than those already observed in the VIA 7 cohort. Finally, we aimed to create a register-based weighting of results from The VIA 7 Study to examine if VIA 7 Study findings would be altered in light of the possible selection bias.

## Methods

The VIA 7 Study is a register-based nested case–control study of a cohort of 7-year-old children with one or two parents with schizophrenia (schizophrenia spectrum psychosis, 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 bipolar disorder (ICD 10-codes F30 and F31 or ICD 8-codes: 296.19 296.39), and population-based controls. Diagnostic information about parents, and information used for matching on age, sex and municipality of the children was obtained through national registers (Supplementary Table 1). Controls were matched to children with FHR-SZ, while the FHR-BP children were un-matched, however, comparable to the two other groups in terms of sex and age. Eligible children were included from the register extract from which we sorted them chronologically by age. Only families whose children were age-appropriate when there was available assessment capacity in the project were contacted. The design of the study and the extensive assessment battery has been presented elsewhere[38]. Data collection was conducted between January 1, 2013 and January 31, 2016. The national registers provide anonymous data according to risk group, which nationwide cohorts such as The VIA 7 Study can use. Socioeconomic and health-related register information regarding The VIA 7 Study participants and non-participants was obtained until the child's 7th birthday (Supplementary Table 1) to examine characteristics according to the risk group and to compare participants to non-participants. Register data were analysed between March 1 and November 1, 2020.

A total of 11,959 children and their biological parents were identified in the register extract. Up to 10 control children were included in the extract per high-risk child to make the best match. A total of 410 FHR-SZ, 214 FHR-BP and 319 PBC children and their parents were invited. Of these, 202 FHR-SZ (49.27%), 120 FHR-BP (56.07%) and 200 PBC (62.70%) constituting a total of 522 children and their parents participated in The VIA 7 Study (Fig. 1 Flowchart).

## Statistical methods

Statistical analyses were performed at the Statistics Denmark research database platform, using Stata/ MP version 16.1. The risk groups of the total sample and of The VIA 7 Study participants were compared using chi-square tests. Pairwise comparisons of risk groups were performed. The participants were compared to non-participants, applying a chi-square test and *t* test. Due to the register-based nature of the data, there were only a few missing data, except for maternal smoking during pregnancy, in which case a separate "missing or unknown" category was constructed. No adjustment was made for multiple comparisons since this would increase the risk of type II errors. Because siblings existed in the cohort, we accounted for the non-independent nature of data by applying a clustered sandwich estimator of variances, using a sibling-ID as a cluster variable. Inverse probability weights (IPW) [35] were estimated as the inverse of the estimated probability of participation in the VIA 7 study after fitting a binary logistic regression model of participation depending on the socioeconomic and health variables in which non-participants and

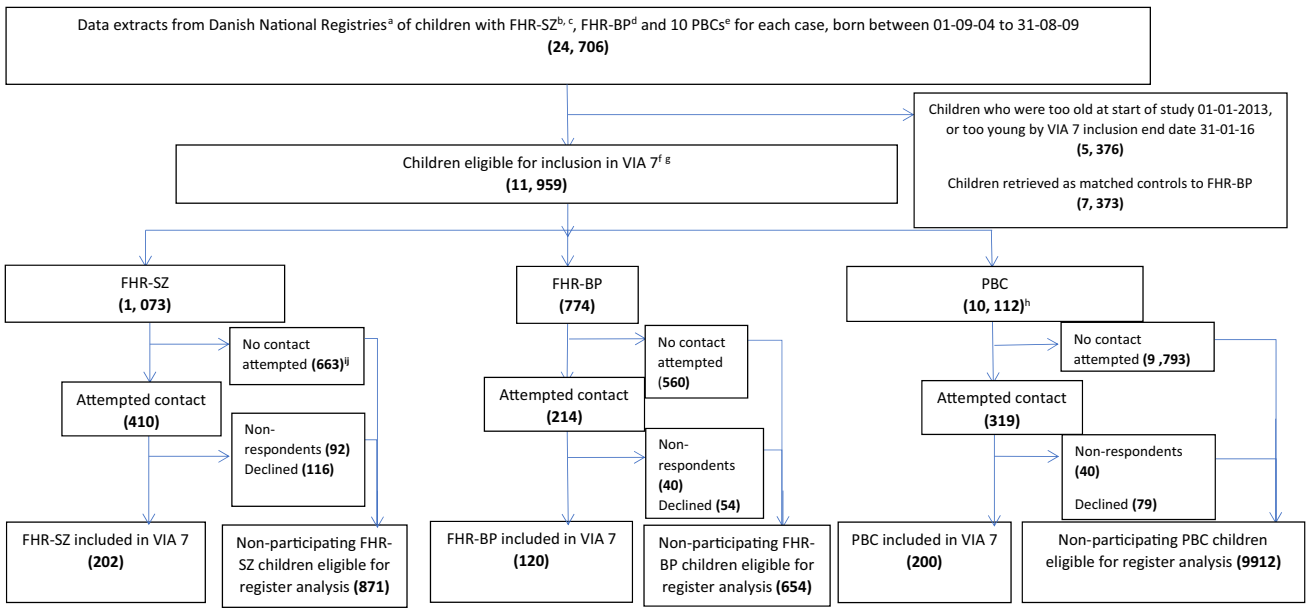


**Fig. 1** Flowchart. [a]Danish National Registries: Danish Civil Registration System and Danish Psychiatric Central Research Register. Based on the Danish Psychiatric Central Research Register, adults with a diagnosis of schizophrenia spectrum psychotic illness, (defined as schizophrenia, delusional 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 schizophrenia spectrum disorders. [c]Double diagnosed parents: Parents with diagnoses of 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 diagnoses of schizophrenia spectrum disorders or bipolar disorder. [f] Research protection: As of May 2011, legislation was enacted to protect individuals´ phone numbers from being called for participation in scientific research. Therefore, there were eligible children who were not contacted and enrolled in VIA 7. [g]Added siblings: In very few ($n < 5$) cases, parents in the control group consented to participate on the condition that the sibling of the included child could also participate. These siblings fulfilled inclusion criteria and were thus included. [h]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, there are 38 BP-controls among the 200 total controls. 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. [j]Reasons for not attempting contact: Families were invited chronologically by child's age from the extract which listed all eligible children. It was never the intent to include all children and families and thus, only children with the best exact age match to the study design were included and only when there was available assessment capacity in the project.

participants differed significantly. These were used to compare results (Supplementary Table 2) with and without such weighting.

## Results

### Differences between risk groups and controls in the total sample of 11,959 children and their parents

Significant differences regarding socio-economy, health and family function were identified between familial high-risk groups and PBCs in the total sample (Table 1a). Substantial disadvantages were shown for children in both familial high-risk groups and were most prominent for FHR-SZ versus PBC children in the majority of cases. Apgar score, birth weight and gestational age were lower for the familial high-risk groups ($p$ (SMD) = 0.02 (0.08) for FHR-SZ vs PBC for Apgar, $p$ (SMD) < 0.001 (0.17) for FHR-SZ vs PBC for birth weight and p (SMD) = 0.003 (0.10) for FHR-SZ vs PBC and $p < 0.001$ (− 0.13) for FHR-BP vs PBC for gestational age), and maternal smoking during pregnancy was more frequent amongst the familial high-risk groups ($p < 0.001$ for all pairwise comparisons). The familial high-risk children received more preventive interventions such as support from the municipality ($p < 0.001$ for all pairwise comparisons), and the interventions had a longer duration than for the PBCs ($p < 0.001$ for all pairwise comparisons). Notifications of concern (according to Danish legislation, individuals and particularly professionals are obliged to report to the municipality if they become significantly concerned about the wellbeing of a child) were more common ($p < 0.05$ for all pairwise comparisons), as was school support and placement out of home amongst familial high-risk children ($p \leq 0.01$ for all pairwise comparisons).

Familial high-risk children had more hospital service use than PBC ($p$ (SMD) < 0.01 (− 0.17) for bed days regarding somatic illness for FHR-SZ vs PBC and $p$ (SMD) = 0.02 (0.09) for FHR-BP vs PBC, and $p$ (SMD) = 0.005 (0.09) for somatic outpatient treatment for FHR-SZ vs PBC, and $p < 0.001$ for both familial high-risk groups vs PBC for outpatient treatment days in mental health facilities).

Parents in the familial high-risk groups had lower levels of education ($p < 0.001$ for all pairwise comparisons), were more frequently unemployed ($p < 0.001$ for all pairwise comparisons), had a lower income ($p < 0.001$ for all pairwise comparisons for familial high-risk vs PBC) and were more frequently unmarried (defined as never been married) or divorced ($p \leq 0.01$ for all pairwise comparisons). They also had more contact with hospital services than PBCs ($p < 0.001$ for all pairwise comparisons between familial high-risk and PBC for bed days and outpatient days). Parents in the familial high-risk groups were more frequently diagnosed with alcohol or substance use disorders, had higher mortality rates, and a larger proportion did not have child custody ($p \leq 0.00$ l for all pairwise comparisons between familial high-risk and PBC). The largest differences were found among fathers where 75.1% had child custody in the FHR-SZ group, 82.8% in the FHR-BP group and 94.8% in the PBC group.

### Differences between risk groups in The VIA 7 Study sample of 522 children and their parents

The VIA 7 Study sample analyses (Table 1b) showed the same pattern, however, with less significant results: The familial high-risk families were disadvantaged, however, mostly to insignificant levels, in measures concerning pregnancy and birth. Significantly more mothers belonging to the FHR-SZ group smoked during pregnancy ($p < 0.001$). The FHR groups had a higher prevalence of preventive child interventions ($p \leq 0.003$ for both familial high-risk groups vs PBC), notifications of concern ($p < 0.001$ for FHR-SZ), child school support ($p = 0.02$ for FHR-SZ vs PBC), child placement out of home ($p < 0.001$ for both FHR groups vs PBC) and child illness ($p$ (SMD) = 0.01 (−0.25) for FHR-SZ vs PBC for somatic illness bed days, and $p$ (SMD) ≤ 0.03 (− 0.22 for FHR-SZ vs PBC and 0.30 for FHR-BP vs PBC) for mental illness outpatient treatment for both familial high-risk groups vs PBC). Also. for parental socio-economic factors such as level of education, income and employment, families belonging to the FHR groups were more disadvantaged ($p < 0.001$ for the majority of the measures included, with few exceptions in the FHR-BP group). Further, FHR families were disadvantaged regarding child custody ($p < 0.05$ for both familial high-risk groups vs PBC except for mothers with schizophrenia), parental illness ($p < 0.05$ for the majority of the measures included, including somatic illness), and substance abuse ($p < 0.001$ for both familial high-risk groups vs PBC).

### Differences between VIA 7 participants and non-participants

Analysis between the 522 participating children and the 11,437 non-participants showed that the VIA 7 cohort was not significantly different with respect to the majority of the measures but differed significantly for some (Table 2).

A significantly higher prevalence amongst non-participants was found for: Maternal smoking during pregnancy ($p = 0.002$ for FHR-BP and $p < 0.001$ for PBC), living in sparsely populated areas ($p < 0.001$ for FHR-SZ, $p = 0.003$ for FHR-BP and $p < 0.001$ for PBC), child

**Table 1** Characteristics of children of parents with schizophrenia (FHR-SZ), bipolar disorder (FHR-BP) and population-based control (PBC) children and their parents in the total eligible register-based sample (Table 1a) and in the VIA 7 cohort (Table 1b)

| | FHR-SZ | FHR-BP | PBC | Pairwise comparison, FHR-SZ vs PBC, *p* value (chi-square or *t* test) (SMD)[a] | Pairwise comparison, FHR-BP vs PBC, *p* value (chi-square or *t* test) (SMD) | Pairwise comparison, FHR-BP vs FHR-SZ, *p* value (chi-square or *t* test) (SMD) |
|---|---|---|---|---|---|---|
| **a: Total eligible register-based sample (*n* = 11 959)** | | | | | | |
| **Children** | *n* = 1073 | *n* = 774 | *n* = 10 112 | | | |
| Female *n* (%) | 520 (48.6) | 386 (49.9) | 4907 (48.5) | 0.97* | 0.47* | 0.55* |
| Apgar score after 5 min, mean (SD) | 9.80 (0.81) | 9.84 (0.71) | 9.85 (0.66) | **0.02*** **(0.08)**[d] | 0.62* (− 0.02) | 0.27* (0.05) |
| Birth weight, grams, mean (SD) | 3400.33 (636.67) | 3458.07 (676.31) | 3501.64 (604.82) | **< 0.001*** **(− 0.17)** | 0.06* (− 0.07) | 0.06* (0.09) |
| Gestational age, mean (SD) | 276.03 (15.29) | 275.63 (15.89) | 277.41 (14.03) | **0.003*** **(− 0.10)** | **< 0.001*** **(− 0.13)** | 0.58* (− 0.03) |
| Preterm births, *n* (%) | | | | | | |
| Preterm births, born before 37 completed weeks of gestation | 86 (8.08) | 74 (9.72) | 652 (6.54) | 0.07* | **< 0.05*** | 0.25* |
| Very preterm births, born before 32 completed weeks of gestation | 12 (1.1) | 11 (1.4) | 97 (1.0) | 0.65* | 0.25* | 0.58* |
| Mother did not smoke during pregnancy, *n* (%) | 601 (58.1) | 504 (67.4) | 8112 (83.5) | | | |
| Mother quit smoking during the 1st trimester | 33 (3.2) | 28 (3.7) | 220 (2.3) | | | |
| Mother smoked throughout pregnancy | 395 (38.2) | 209 (27.9) | 1344 (18.8) | | | |
| No information regarding mothers smoking status | 6 (0.6) | 7 (0.9) | 44 (0.5) | **< 0.001*** | **< 0.001*** | **< 0.001*** |
| Degree of urbanization (DEGURBA), *n* (%) | | | | | | |
| Child lives in densely populated area | 269 (27.6) | 217 (29) | 2712 (27) | | | |
| Child lives in intermediate density area | 345 (35.4) | 253 (33.8) | 3504 (34.9) | | | |
| Child lives in thinly populated area | 360 (37.0) | 279 (37.2) | 3832 (38.1) | 0.79* | 0.53* | 0.76* |
| Any preventive interventions, *n* (%) | 195 (18.2) | 85 (11) | 201 (2) | **< 0.001*** | **< 0.001*** | **< 0.001*** |

**Table 1** (continued)

| | FHR-SZ | FHR-BP | PBC | Pairwise comparison, FHR-SZ vs PBC, *p* value (chi-square or *t* test) (SMD)[a] | Pairwise comparison, FHR-BP vs PBC, *p* value (chi-square or *t* test) (SMD) | Pairwise comparison, FHR-BP vs FHR-SZ, *p* value (chi-square or *t* test) (SMD) |
|---|---|---|---|---|---|---|
| Days of preventive interventions, mean (SD) | 127.33 (381.01) | 69.51 (284.22) | 9.34 (87.23) | **< 0.001*** (**0.80**) | **< 0.001*** (**0.53**) | **< 0.001*** (**− 0.17**) |
| Any notifications of concern, *n* (%)[b] | 28 (2.6) | 8 (1) | 50 (0.5) | **< 0.001*** | 0.05* | **0.02*** |
| Child placed outside of home, *n* (%) | 117 (10.9) | 37 (4.8) | 62 (0.6) | **< 0.001*** | **< 0.001*** | **< 0.001*** |
| Special support in school[c], *n* (%) | 87 (8.1) | 33 (4.3) | 269 (2.7) | **< 0.001*** | **0.01*** | **0.001*** |
| Somatic illness, bed days, mean (SD) | 10.32 (15.27) | 9.09 (13.54) | 7.82 (14.36) | **< 0.001*** (**0.17**) | **0.02*** (**0.09**) | 0.07* (− 0.08) |
| Somatic illness, outpatient treatment days, mean (SD) | 4.95 (8.58) | 4.64 (8.81) | 4.15 (8.94) | **0.005*** (**0.09**) | 0.14* (0.06) | 0.45* (− 0.04) |
| Mental illness, outpatient treatment days, mean (SD) | 0.85 (4.90) | 0.56 (4.20) | 0.18 (2.48) | **< 0.001*** (**0.24**) | **< 0.001*** (**0.14**) | 0.19* (− 0.06) |
| **Biological Mothers** | *n* = 953[e] | *n* = 680 | *n* = 9979 | | | |
| Age by child's birth, mean (SD) | 28.97 (6.15) | 30.52 (5.46) | 30.68 (4.74) | **< 0.001*** (**0.35**) | 0.396* (− 0.03) | **< 0.001*** (**0.26**) |
| Level of education, *n* (%) | | | | | | |
| Primary and lower secondary (DISCED[d] level 2), | 453 (42.4) | 175 (22.7) | 1142 (11.3) | | | |
| Upper secondary (DISCED level 3 + 5 | 361 (33.8) | 333 (43.2) | 4451 (44.1) | | | |
| Bachelor degree, equivalent or higher (DISCED level 6 + 7 + 8) | 254 (23.8) | 263 (34.1) | 4507 (44.6) | **< 0.001*** | **< 0.001*** | **< 0.001*** |
| Employment status, *n* (%) | | | | | | |
| Employed | 409 (38.1) | 387 (50) | 8598 (85) | | | |
| Pension/early retirement | 269 (25.1) | 127 (16.4) | 139 (1.4) | | | |
| Unemployed | 317 (29.5) | 208 (26.9) | 1014 (10) | | | |
| No information | 78 (7.3) | 52 (6.7) | 361 (3.6) | **< 0.001*** | **< 0.001*** | **< 0.001*** |

**Table 1** (continued)

| | FHR-SZ | FHR-BP | PBC | Pairwise comparison, FHR-SZ vs PBC, *p* value (chi-square or *t* test) (SMD)[a] | Pairwise comparison, FHR-BP vs PBC, *p* value (chi-square or *t* test) (SMD) | Pairwise comparison, FHR-BP vs FHR-SZ, *p* value (chi-square or *t* test) (SMD) |
|---|---|---|---|---|---|---|
| Income in DKR, mean (SD) | 273 060.20 (114,158.70) | 296 124.70 (122,110.40) | 363 717.30 (168,014.90) | **< 0.001*** **(0.55)** | **< 0.001*** **(− 0.41)** | **< 0.001*** **(0.20)** |
| Changes in civil status from 1 year before child birth until child's 7 years birthday, mean (SD) | 0.22 (0.52) | 0.27 (0.54) | 0.14 (0.40) | **< 0.001*** **(− 0.21)** | **< 0.001*** **(0.32)** | 0.06* (0.09) |
| Changes in civil status from 1 year before child birth until child's 7 years birthday, *n* (%) | | | | | | |
| 0 changes | 876 (81.6) | 600 (77.5) | 8929 (88.3) | | | |
| 1 change | 164 (15.3) | 144 (18.6) | 1011 (10.0) | | | |
| 2 changes or more | 33 (3.1) | 30 (3.9) | 172 (1.7) | **< 0.001*** | **< 0.001*** | 0.09* |
| Civil status, *n* (%) | | | | | | |
| Divorced | 183 (17.1) | 162 (20.9) | 989 (9.8) | | | |
| Married | 382 (35.6) | 359 (46.4) | 6932 (68.6) | | | |
| Unmarried | 496 (46.2) | 240 (31) | 2155 (21.3) | | | |
| Other | 12 (1.1) | 13 (1.7) | 36 (0.4) | **0.01*** | **< 0.001*** | **< 0.001*** |
| Somatic illness, outpatient days, mean (SD) | 24.85 (22.17) | 23.83 (21.28) | 20.80 (17.35) | **< 0.001*** **(− 0.23)** | **< 0.001*** **(0.17)** | 0.32* (− 0.05) |
| Somatic illness, bed days, mean (SD) | 15.44 (22.02) | 13.69 (17.31) | 9.80 (12.66) | **< 0.001*** **(− 0.41)** | **< 0.001*** **(0.30)** | 0.066* (− 0.09) |
| Mental illness, outpatient days before child's birth, mean (SD) | 27.96 (60.51) | 15.78 (41.90) | 1.17 (9.72) | **< 0.001*** **(− 1.20)** | **< 0.001*** **(0.97)** | **< 0.001*** **(− 0.23)** |
| Mental illness, bed days before child's birth, mean (SD) | 69.19 (193.65) | 24.47 (89.20) | 0.98 (16.71) | **< 0.001*** **(− 1.05)** | **< 0.001*** **(0.80)** | **< 0.001*** **(− 0.28)** |
| Mental illness, outpatient days after child's birth, mean (SD) | 26.28 (54.18) | 24.45 (39.78) | 1.20 (8.40) | **< 0.001*** **(− 1.25)** | **< 0.001*** **(1.59)** | 0.43* (− 0.04) |
| Mental illness, bed days after child's birth, mean (SD) | 29.47 (119.83) | 26.29 (121.95) | 0.41 (6.16) | **< .001*** **(− 0.75)** | **< .001*** **(0.77)** | 0.58* (− 0.03) |
| Any coercive measures, *n* (%) | 152 (14.2) | 66 (8.5) | 24 (0.2) | **< 0.001*** | **< 0.001*** | **< 0.001*** |

**Table 1** (continued)

| | FHR-SZ | FHR-BP | PBC | Pairwise comparison, FHR-SZ vs PBC, *p* value (chi-square or *t* test) (SMD)[a] | Pairwise comparison, FHR-BP vs PBC, *p* value (chi-square or *t* test) (SMD) | Pairwise comparison, FHR-BP vs FHR-SZ, *p* value (chi-square or *t* test) (SMD) |
|---|---|---|---|---|---|---|
| Mother has custody of child, *n* (%) | 1021 (96.5) | 732 (95.9) | 9989 (99.2) | **< 0.001*** | **< 0.001*** | 0.53* |
| Dead, *n* (%) | 5 (0.5) | 9 (1.2) | 9 (0.1) | **0.001*** | **< 0.001*** | 0.09* |
| Any substance abuse, *n* (%) | 173 (16.1) | 89 (11.5) | 229 (2.3) | **< 0.001*** | **< 0.001*** | **0.005*** |
| **Biological fathers** | *n* = 947[e] | *n* = 680 | *n* = 9974 | | | |
| Age by childs birth, mean (SD) | 31.91 (7.03) | 33.51 (6.49) | 32.90 (5.32) | **< 0.001*** (**0.18**) | **0.003*** (**0.11**) | **< 0.001*** (**0.23**) |
| Level of education, *n* (%) | | | | | | |
| Primary and lower secondary (DISCED level 2) | 460 (44.5) | 181 (23.6) | 1408 (14) | | | |
| Upper secondary (DISCED level 3 + 5) | 410 (39.7) | 421 (54.9) | 5793 (57.5) | | | |
| Bachelor degree, equivalent or higher (DISCED level 6 + 7 + 8) | 164 (15.9) | 165 (21.5) | 2868 (28.5) | **< 0.001*** | **< 0.001*** | **< 0.001*** |
| Employment status, *n* (%) | | | | | | |
| Employed | 527 (49.1) | 535 (69.1) | 9244 (91.4) | | | |
| Pension/early retirement | 287 (26.7) | 75 (9.7) | 124 (1.2) | | | |
| Unemployed | 195 (18.2) | 133 (17.2) | 521 (5.2) | | | |
| No information | 64 (6) | 31 (4) | 223 (2.2) | **< 0.001*** | **< 0.001*** | **< 0.001*** |
| Income in DKR, mean (SD) | 312,514.60 (302,935.10) | 354,089.90 (260,239.10) | 473,147.40 (375,526.50) | **< 0.001*** (**0.43**) | **< 0.001*** (**− 0.32**) | **0.002*** (**0.15**) |
| Changes in civil status from 1 year before child birth until child's 7 years birthday, mean (SD) | 0.22 (0.49) | 0.26 (0.50) | 0.13 (0.39) | **< 0.001*** (**− 0.21**) | **< 0.001*** (**0.31**) | 0.117* (0.07) |
| Changes in civil status from 1 year before child birth until child's 7 years birthday, *n* (%) | | | | | | |
| 0 changes | 874 (81.5) | 599 (77.4) | 8954 (88.5) | | | |
| 1 change | 166 (15.5) | 153 (19.8) | 990 (9.8) | | | |
| 2 changes or above | 33 (3.1) | 22 (2.8) | 168 (1.7) | **< 0.001*** | **< 0.001*** | 0.05* |

**Table 1** (continued)

| | FHR-SZ | FHR-BP | PBC | Pairwise comparison, FHR-SZ vs PBC, *p* value (chi-square or *t* test) (SMD)[a] | Pairwise comparison, FHR-BP vs PBC, *p* value (chi-square or *t* test) (SMD) | Pairwise comparison, FHR-BP vs FHR-SZ, *p* value (chi-square or *t* test) (SMD) |
|---|---|---|---|---|---|---|
| Civil status, *n* (%) | | | | | | |
| Divorced | 183 (17.1) | 159 (20.5) | 982 (9.7) | | | |
| Married | 384 (35.8) | 356 (46) | 6925 (68.5) | | | |
| Unmarried | 482 (44.9) | 244 (31.5) | 2162 (21.4) | | | |
| Other | 24 (2.2) | 15 (1.9) | 43 (0.4) | **< 0.001*** | **< 0.001*** | **< 0.001*** |
| Somatic illness, outpatient days, mean (SD) | 6.92 (12.77) | 6.82 (12.55) | 5.57 (12.09) | **0.001*** **(− 0.11)** | **0.006*** **(0.10)** | 0.868* (− 0.01) |
| Somatic illness, bed days, mean (SD) | 5.54 (17.94) | 3.90 (9.33) | 2.24 (8.46) | **< 0.001*** **(− 0.34)** | **< 0.001*** **(0.20)** | **0.02*** **(− 0.11)** |
| Mental illness, outpatient days before child's birth, mean (SD) | 22.55 (54.35) | 5.32 (16.27) | 0.31 (5.64) | **< 0.001*** **(− 1.18)** | **< 0.001*** **(0.71)** | **< 0.001*** **(− 0.40)** |
| Mental illness, outpatient days after child's birth, mean (SD) | 23.48 (48.71) | 11.86 (28.53) | 0.35 (3.18) | **< 0.001*** **(− 1.38)** | **< 0.001*** **(1.32)** | **< 0.001*** **(− 0.28)** |
| Mental illness, bed days before child's birth, mean (SD) | 79.01 (229.54) | 14.51 (48.27) | 0.31 (5.69) | **< 0.001*** **(− 1.05)** | **< 0.001*** **(0.98)** | **< 0.001*** **(− 0.36)** |
| Mental illness, bed days after child's birth, mean (SD) | 50.10 (187.10) | 24.20 (126.97) | 0.30 (5.33) | **< 0.001*** **(− 0.83)** | **< 0.001*** **(0.69)** | **< 0.001*** **(− 0.16)** |
| Any coercive measures, *n* (%) | 158 (14.7) | 63 (8.1) | 27 (0.3) | **< 0.001*** | **< 0.001*** | **< 0.001*** |
| Father has custody of child, *n* (%) | 795 (75.1) | 632 (82.8) | 9546 (94.8) | **< 0.001*** | **< 0.001*** | **< 0.001*** |
| Dead, *n* (%) | 22 (2.1) | 12 (1.6) | 34 (0.3) | **< 0.001*** | **< 0.001*** | 0.43* |
| Any substance abuse, *n* (%) | 334 (31.1) | 157 (20.3) | 280 (2.8) | **< 0.001*** | **< 0.001*** | **< 0.001*** |
| **b: The VIA 7 cohort (n = 522)** | | | | | | |
| Children | *n* = 202 | *n* = 120 | *n* = 200 | | | |
| Female, *n* (%) | 93 (46.0) | 56 (46.7) | 93 (46.5) | 0.93* | 0.98* | 0.91* |
| Apgar score after 5 min, mean (SD) | 9.86 (0.70) | 9.86 (0.55) | 9.90 (0.42) | 0.45* (− 0.08) | 0.47* (− 0.08) | 0.95* (0.01) |

**Table 1** (continued)

| | FHR-SZ | FHR-BP | PBC | Pairwise comparison, FHR-SZ vs PBC, *p* value (chi-square or *t* test) (SMD)[a] | Pairwise comparison, FHR-BP vs PBC, *p* value (chi-square or *t* test) (SMD) | Pairwise comparison, FHR-BP vs FHR-SZ, *p* value (chi-square or *t* test) (SMD) |
|---|---|---|---|---|---|---|
| Birth weight, grams, mean (SD) | 3460.06 (615.60) | 3457.97 (650.81) | 3531.03 (600.74) | 0.24* (− 0.12) | 0.31* (− 0.12) | 0.98* (− 0.00) |
| Gestational age, mean (SD) | 276.47 (12.15) | 275.64 (14.99) | 278.25 (13.35) | 0.16* (− 0.14) | 0.11* (− 0.19) | 0.59* (− 0.06) |
| Preterm births, *n* (%) | | | | | | |
| Preterm births, born before 37 completed weeks of gestation | 12 (6.06) | 15 (12.71) | 12 (6.15) | 0.97* | 0.07* | 0.07* |
| Very preterm births, born before 32 completed weeks of gestation | < 4 | < 4 | < 4 | 0.99* | 0.33* | 0.32* |
| Maternal smoking during pregnancy, *n* (%) | | | | | | |
| Mother did not smoke during pregnancy | 121 (62.1) | 95 (81.9) | 173 (90.6) | | | |
| Mother quit smoking during the 1st trimester | 6 (3.1) | < 5 | < 5 | | | |
| Mother smoked throughout pregnancy | 8.4 (67) | 16 (13.8) | 16 (8.4) | | | |
| No information regarding mothers smoking status | 1 (0.5) | < 5 | 0 (0.00) | **< 0.001*** | 0.17* | **0.004*** |
| Degree of urbanization (DEGURBA), *n* (%) | | | | | | |
| Child lives in densely populated area | 79 (41.4) | 49 (40.8) | 85 (42.7) | | | |
| Child lives in intermediate density area | 57 (29.8) | 41 (34.2) | 58 (29.1) | | | |
| Child lives in thinly populated area | 55 (28.8) | 30 (25) | 56 (28.1) | 0.97* | 0.64* | 0.67* |
| Any preventive interventions, *n* (%) | 24 (11.9) | 12 (10.0) | < 5 | **0.001*** | **0.003*** | 0.62* |
| Days of preventive interventions, mean (SD) | 78.08 (271.44) | 65.26 (332.16) | 3.29 (46.55) | **< 0.001*** (**0.38**) | **0.01*** (**0.30**) | 0.71* (− 0.04) |
| Any notifications of concern, n[b] | < 5 | 0 (0) | 0 (0) | **< 0.001*** | **missing** | **< 0.001*** |

**Table 1** (continued)

| | FHR-SZ | FHR-BP | PBC | Pairwise comparison, FHR-SZ vs PBC, *p* value (chi-square or *t* test) (SMD)[a] | Pairwise comparison, FHR-BP vs PBC, *p* value (chi-square or *t* test) (SMD) | Pairwise comparison, FHR-BP vs FHR-SZ, *p* value (chi-square or *t* test) (SMD) |
|---|---|---|---|---|---|---|
| Child placed outside of home, *n* (%) | 13 (6.4) | < 5 | 0 (0) | **< 0.001*** | **< 0.001*** | **< 0.05*** |
| Special support in school, *n* (%)[c] | 15 (7.4) | 4 (3.3) | 4 (2) | **0.02*** | 0.47* | 0.14* |
| Somatic illness, bed days, mean (SD) | 10.09 (15.81) | 9.52 (17.08) | 6.68 (10.48) | **0.01*** (**0.25**) | 0.07* (0.21) | 0.76* (− 0.04) |
| Somatic illness, outpatient treatment days, mean (SD) | 5.78 (11.66) | 3.88 (6.01) | 4.14 (7.86) | 0.10* (0.16) | 0.76* (− 0.04) | 0.10* (− 0.19) |
| Mental illness, outpatient treatment days, mean (SD) | 0.61 (3.64) | 0.42 (1.98) | 0.04 (0.37) | **0.03*** (**0.22**) | **0.01*** (**0.30**) | 0.58* (− 0.06) |
| **Biological mothers** | *n* = 193[e] | *n* = 115 | *n* = 198 | | | |
| Age by child's birth, mean (SD) | 29.36 (5.89) | 31.56 (5.33) | 32.10 (4.14) | **< 0.001*** (**0.52**) | 0.313* (− 0.12) | **0.001*** (**0.38**) |
| Level of education, *n* (%) | | | | | | |
| Primary and lower secondary (DISCED[d] level 2) | 69 (34.2) | 17 (14.2) | 17 (8.5) | | | |
| Upper secondary (DISCED level 3 + 5) | 72 (35.6) | 43 (35.8) | 86 (43) | | | |
| Bachelor degree, equivalent or higher (DISCED level 6 + 7 + 8) | 61 (30.2) | 60 (50) | 97 (48.5) | **< 0.001*** | 0.20* | **< 0.001*** |
| Employment status, *n* (%) | | | | | | |
| Employed | 87 (43.1) | 77 (64.2) | 186 (93.006) | | | |
| Pension/early retirement | 43 (21.3) | 13 (10.8) | < 5 | | | |
| Unemployed | 55 (27.2) | 21 (17.5) | 6 (3) | | | |
| No information | 17 (8.4) | 9 (7.5) | 5 (2.5) | **< 0.001*** | **< 0.001*** | **0.002*** |
| Income in DKR, mean (SD) | 276 756.80 (102,416.10) | 313 883.30 (125,998.20) | 392 190.20 (166,923.10) | **< 0.001*** (**0.77**) | **< 0.001*** (**− 0.50**) | **0.004*** (**0.33**) |

**Table 1** (continued)

| | FHR-SZ | FHR-BP | PBC | Pairwise comparison, FHR-SZ vs PBC, *p* value (chi-square or *t* test) (SMD)[a] | Pairwise comparison, FHR-BP vs PBC, *p* value (chi-square or *t* test) (SMD) | Pairwise comparison, FHR-BP vs FHR-SZ, *p* value (chi-square or *t* test) (SMD) |
|---|---|---|---|---|---|---|
| Changes in civil status from 1 year before child birth until child's 7th birthday, mean (SD) | 0.23 (0.56) | 0.32 (0.58) | 0.09 (0.31) | **0.001*** | **< 0.001*** | 0.20* |
| Changes in civil status from 1 year before child birth until child's 7th birthday, *n* (%) | | | | | | |
| 0 changes | 165 (81.7) | 89 (74.2) | 185 (92.5) | | | |
| 1 change | 29 (14.4) | 24 (20.0) | 13 (6.5) | | | 0.28* |
| 2 changes or more | 8 (4.0) | 7 (5.8) | < 4 | **0.004*** | **< 0.001*** | |
| Civil status, *n* (%) | | | | | | |
| Divorced | 34 (16.8) | 29 (24.2) | 12 (6.0) | | | |
| Married | 87 (43.1) | 64 (53.3) | 153 (76.5) | | | |
| Unmarried | 80 (39.6) | 26 (21.7) | 35 (17.5) | | | |
| Other | 1 (0.5) | 1 (0.8) | 0 (0.00) | **< 0.001*** | **< 0.001*** | **0.01*** |
| Somatic illness, outpatient days, mean (SD) | 23.65 (19.27) | 23.89 (21.88) | 18.59 (13.96) | **0.003*** (**− 0.30**) | **0.01*** (**0.30**) | 0.92* (0.01) |
| Somatic illness, bed days, mean (SD) | 13.87 (17.73) | 12.93 (20.96) | 8.20 (7.81) | **< 0.001*** (**− 0.41**) | **0.004*** (**0.33**) | 0.67* (− 0.05) |
| Mental illness, outpatient days before child's birth, mean (SD) | 28.18 (50.45) | 11.42 (26.15) | 0.30 (2.26) | **< 0.001*** (**− 0.73**) | **< 0.001*** (**0.66**) | **0.001*** (**− 0.38**) |
| Mental illness, bed days before child's birth, mean (SD) | 81.63 (174.30) | 24.08 (94.96) | 0.01 (0.14) | **< 0.001*** (**− 0.63**) | **< 0.001*** (**0.41**) | **0.001*** (**− 0.38**) |
| Mental illness, outpatient days after child's birth, mean (SD) | 23.77 (45.04) | 19.57 (33.41) | 0.75 (8.17) | **< 0.001*** (**− 0.67**) | **< 0.001*** (**0.81**) | 0.38* (− 0.10) |
| Mental illness, bed days after child's birth, mean (SD) | 23.77 (72.68) | 22.43 (67.58) | 0.19 (2.62) | **< 0.001*** (**− 0.446**) | **< 0.001*** (**0.521**) | 0.87* (− 0.02) |
| Any coercive measures, *n* (%) | 31 (15.3) | 12 (10) | 0 (0) | **< 0.001*** | **< 0.001*** | 0.17* |
| Mother has custody of child, n (%) | 196 (98.5) | 115 (95.8) | 198 (99.5) | 0.32* | **0.02*** | 0.14* |
| Dead, *n* (%) | 0 (0) | < 5 | 0 (0) | **missing** | 0.20* | 0.19* |

**Table 1** (continued)

| | FHR-SZ | FHR-BP | PBC | Pairwise comparison, FHR-SZ vs PBC, *p* value (chi-square or *t* test) (SMD)[a] | Pairwise comparison, FHR-BP vs PBC, *p* value (chi-square or *t* test) (SMD) | Pairwise comparison, FHR-BP vs FHR-SZ, *p* value (chi-square or *t* test) (SMD) |
|---|---|---|---|---|---|---|
| Any substance abuse, *n* (%) | 25 (12.4) | 15 (12.5) | < 5 | **< 0.001*** | **< 0.001*** | 0.97* |
| **Biological fathers** | *n* = 193[e] | *n* = 115 | *n* = 198 | | | |
| Age by childs birth, mean (SD) | 31.96 (6.38) | 35.04 (6.71) | 33.68 (4.77) | **0.002*** (**0.30**) | **0.04*** (**0.24**) | **< 0.001*** (**0.46**) |
| Level of education, *n* (%) | | | | | | |
| Primary and lower secondary (DISCED level 2) | 81 (41.1) | 18 (15.4) | 20 (10) | | | |
| Upper secondary (DISCED level 3 + 5) | 81 (41.1) | 60 (51.3) | 114 (57) | | | |
| Bachelor degree, equivalent or higher (DISCED level 6 + 7 + 8) | 35 (17.8) | 39 (33.3) | 66 (33) | **< 0.001*** | 0.33* | **< 0.001*** |
| Employment status, *n* (%) | | | | | | |
| Employed | 194 (97) | 115 (56.9) | 87 (72.5) | | | |
| Pension/ early retirement | 46 (22.8) | 8 (6.7) | < 5 | | | |
| Unemployed | 34 (16.8) | 20 (16.7) | 4 (2.0) | | | |
| No information | 7 3.5 | 5 4.2 | < 5 | **< 0.001*** | **< 0.001*** | **0.002*** |
| Income in DKR, mean (SD) | 325 711.40 (207,920.90) | 403 410.60 (292,728.10) | 480 896.60 (234,723.40) | **< 0.001*** (**0.66**) | **0.010*** (**− 0.30**) | **0.006*** (**0.32**) |
| Changes in civil status from 1 year before child birth until child's 7th birthday, mean (SD) | 0.22 (0.48) | 0.32 (0.52) | 0.07 (0.27) | **< 0.001*** (**− 0.38**) | **< 0.001*** (**0.61**) | 0.10* (0.19) |
| Changes in civil status from 1 year before child birth until child's 7th birthday, *n* (%) | | | | | | |
| 0 changes | 163 (80.7) | 89 (74.2) | 185 (92.5) | | | |
| 1 change | 33 (16.3) | 24 (20.0) | 13 (6.5) | **0.004*** | **< 0.001*** | 0.28* |
| 2 changes or more | 6 (3.0) | 7 (5.8) | < 4 | | | |
| Civil status, *n* (%) | | | | | | |
| Divorced | 35 (17.3) | 34 (28.3) | 15 (7.5) | | | |
| Married | 87 (43.1) | 62 (51.7) | 150 (75.0) | | | |
| Unmarried | 77 (38.1) | 21 (17.5) | 34 (17.0) | | | |

**Table 1** (continued)

| | FHR-SZ | FHR-BP | PBC | Pairwise comparison, FHR-SZ vs PBC, *p* value (chi-square or *t* test) (SMD)[a] | Pairwise comparison, FHR-BP vs PBC, *p* value (chi-square or *t* test) (SMD) | Pairwise comparison, FHR-BP vs FHR-SZ, *p* value (chi-square or *t* test) (SMD) |
|---|---|---|---|---|---|---|
| Other | 3 (1.5) | 3 (2.5) | 1 (0.5) | **< 0.001*** | **< 0.001*** | **.001*** |
| Somatic illness, outpatient days, mean (SD) | 4.99 (8.13) | 7.62 (17.42) | 5.08 (11.53) | 0.93* (0.01) | 0.12* (0.18) | 0.07* (0.21) |
| Somatic illness, bed days, mean (SD) | 4.46 (16.38) | 3.47 (6.07) | 1.60 (5.29) | **0.02*** **(− 0.23)** | **0.004*** **(0.33)** | 0.52* (− 0.07) |
| Mental illness, outpatient days before child's birth, mean (SD) | 15.47 (36.82) | 6.59 (17.44) | 0.11 (0.98) | **< 0.001*** **(− 0.57)** | **< 0.001*** **(0.58)** | **0.01*** **(− 0.28)** |
| Mental illness, outpatient days after child's birth, mean (SD) | 21.22 (42.78) | 15.23 (36.74) | 0.01 (0.07) | **< 0.001*** **(− 0.66)** | **< 0.001*** **(0.64)** | 0.20* (− 0.15) |
| Mental illness, bed days before child's birth, mean (SD) | 58.24 (159.02) | 17.13 (43.06) | 0.06 (0.85) | **< 0.001*** **(− 0.50)** | **< 0.001*** **(0.62)** | **0.006*** **(− 0.32)** |
| Mental illness, bed days after child's birth, mean (SD) | 56.39 (204.64) | 28.25 (99.69) | 0.44 (4.83) | **< 0.001*** **(− 0.38)** | **< 0.001*** **(0.45)** | 0.16* (− 0.16) |
| Any coercive measures, *n* (%) | 28 (13.9) | 9 (7.5) | < 5 | **< 0.001*** | **< 0.001*** | 0.08* |
| Father has custody of child, *n* (%) | 159 (79.9) | 99 (82.5) | 194 (97.5) | **< 0.001*** | **< 0.001*** | 0.57* |
| Dead, *n* (%) | < 5 | < 5 | < 5 | 0.32* | 0.12* | 0.52* |
| Any substance abuse, *n* (%) | 60 (29.7) | 23 (19.2) | < 5 | **< 0.001*** | **< 0.001*** | **0.04*** |

[a]Standard Medium Difference

[b]According to Danish legislation, individuals and particularly professionals are obliged to report to the municipality if they become significantly concerned about the wellbeing of a child

[c]Special support is only registered if the amount exceeds 9 h per week

[d]DISCED: The Danish version of the International Standard Classification of Education

[e]All included children have a mother and a father registered and the number of mothers and fathers included thus equals the included number of children. Since some of the included children have the same mother and father, the n in the table representing mothers and fathers is lower than the n for included children

[d]**p* values, bold signifies values significant at $p = 0.05$ level

**Table 2** Comparison of register-based socioeconomic and health characteristics of VIA 7 participants and non-participants amongst children with familial high-risk of schizophrenia (FHR-SZ), familial high-risk of bipolar (FHR-BP) and population-based controls (PBC)

| | FHR-SZ Non-participants, mean (SD) or *n* (%) | FHR-SZ VIA 7 Participants mean (SD) or *n* (%) | *p* value , chi-square or *t* test (SMD)[a] | FHR-BP Non-participants mean (SD) or *n* (%) | FHR-BP VIA 7 Participants mean (SD) or *n* (%) | *p* value, chi-square or *t* test (SMD) | PBC Non-participants mean (SD) or *n* (%) | PBC VIA 7 Participants mean (SD) or *n* (%) | *p* value, chi-square or *t* test (SMD) |
|---|---|---|---|---|---|---|---|---|---|
| **Children** | *n* = 871 | *n* = 202 | | *n* = 654 | *n* = 120 | | *n* = 9912 | *n* = 200 | |
| Female, *n* (%) | 427 (49.02) | 93 (46.04) | 0.44* | 330 (50.46) | 56 (46.67) | 0.44* | 4814 (48.57) | 93 (46.50) | 0.56* |
| Apgar score after 5 min, mean (SD) | 9.79 (0.83) | 9.86 (0.70) | 0.25* (− 0.09) | 9.84 (0.73) | 9.86 (0.55) | 0.68* (− 0.04) | 9.85 (0.66) | 9.90 (0.42) | 0.27* (− 0.08) |
| Birth weight, grams, mean (SD) | 3386.64 (637.55) | 3460.06 (613.95) | 0.14* (− 0.12) | 3458.09 (681.64) | 3457.97 (649.05) | 1.00* (0.00) | 3501.05 (605.02) | 3531.03 (599.13) | 0.49* (− 0.05) |
| Gestational age, mean (SD) | 275.93 (15.90) | 276.47 (12.12) | 0.65* (− 0.04) | 275.63 (16.06) | 275.64 (14.95) | 0.99* (− 0.00) | 277.39 (14.05) | 278.25 (13.32) | 0.39* (− 0.06) |
| Preterm births, born before 37 completed weeks of gestation, *n* (%) | 74 (8.54) | 12 (6.06) | 0.28* | 59 (9.18) | 15 (12.71) | 0.28* | 640 (6.55) | 12 (6.15) | 0.84* |
| Very preterm births, born before 32 completed weeks of gestation, *n* (%) | 11 | < 4 | 0.38* | 9 | < 4 | 0.81* | 96 | < 4 | 0.52* |
| Mother did not smoke during pregnancy, *n* (%) | 480 (55.11) | 121 (59.90) | - | 409 (62.54) | 95 (79.17) | - | 7939 (80.09) | 173 (86.50) | - |
| Mother quit smoking during the 1st trimester, *n* (%) | 27 (3.10) | 6 (2.97) | - | 25 (3.82) | < 4 | - | 218 (2.20) | < 4 | - |
| Mother smoked throughout pregnancy, *n* (%) | 333 (38.23) | 68 (33.66) | - | 198 (30.28) | 18 (15.00) | - | 1372 (13.84) | 16 (8.00) | - |
| No information regarding mothers smoking status, *n* (%) | 31 (3.56) | 7 (3.47) | – | 22 (3.36) | 4 (3.33) | – | 383 (3.86) | 9 (4.50) | – |
| | | | 0.67* | | | **0.002***[c] | | | **< 0.001*** |
| Degree of urbanization (DEGURBA), *n* (%) | | | | | | | | | |
| Child lives in densely populated area | 190 (24.27) | 79 (41.36) | | 168 (26.71) | 49 (40.83) | | 2627 (26.67) | 85 (42.71) | |
| Child lives in intermediate density area | 288 (36.78) | 57 (29.84) | | 212 (33.70) | 41 (34.17) | | 3446 (34.99) | 58 (29.15) | |

**Table 2** (continued)

| | FHR-SZ Non-participants, mean (SD) or *n* (%) | FHR-SZ VIA 7 Participants mean (SD) or *n* (%) | *p* value , chi-square or *t* test (SMD)[a] | FHR-BP Non-participants mean (SD) or *n* (%) | FHR-BP VIA 7 Participants mean (SD) or *n* (%) | *p* value, chi-square or *t* test (SMD) | PBC Non-participants mean (SD) or *n* (%) | PBC VIA 7 Participants mean (SD) or *n* (%) | *p* value, chi-square or *t* test (SMD) |
|---|---|---|---|---|---|---|---|---|---|
| Child lives in thinly populated area | 305 (38.95) | 55 (28.80) | | 249 (39.59) | 30 (25.00) | | 3776 (38.34) | 56 (28.14) | |
| | | | **< 0.001*** | | | **0.003*** | | | **< 0.001*** |
| Any preventive interventions, *n* (%) | 171 (19.63) | 24 (11.88) | **0.01*** | 73 (11.16) | 12 (10.00) | 0.73* | 200 (2.02) | < 4 | 0.16* |
| Days of preventive interventions, mean (SD) | 138.75 (390.72) | 78.08 (270.72) | **0.04 * (0.16)** | 70.29 (272.29) | 65.26 (331.29) | 0.86 * (0.02) | 9.47 (87.87) | 3.29 (46.42) | 0.32* (0.071) |
| Any notifications of concern, *n* (%) | 27 (3.10) | < 4 | 0.07* | 8 (1.22) | 0 (0.00) | **< 0.001*** | 50 (0.50) | 0 (0.00) | **< 0.001*** |
| Child placed outside of home, *n* (%) | 104 (11.94) | 13 (6.44) | **0.03*** | 36 (5.50) | < 4 | 0.06* | 62 (0.63) | 0 (0.00) | < 0.001* |
| Special support in school, *n* (%)[b] | 72 (8.27) | 15 (7.43) | 0.69* | 29 (4.43) | 4 (3.33) | 0.59* | 265 (2.67) | 4 (2.00) | 0.56* |
| Somatic illness, bed days, mean (SD) | 10.37 (15.18) | 10.09 (15.77) | 0.81 * (0.02) | 9.01 (12.78) | 9.52 (17.04) | 0.71* (− 0.04) | 7.84 (14.42) | 6.68 (10.45) | 0.25* (0.08) |
| Somatic illness, outpatient treatment days, mean (SD) | 4.76 (7.68) | 5.78 (11.63) | 0.13* (− 0.12) | 4.78 (9.22) | 3.88 (5.99) | 0.31* (0.10) | 4.15 (8.96) | 4.14 (7.84) | 0.99* (0.00) |
| Mental illness, outpatient treatment days, mean (SD) | 0.90 (5.15) | 0.61 (3.63) | 0.45* (0.06) | 0.59 (4.50) | 0.42 (1.97) | 0.68* (0.04) | 0.19 (2.50) | 0.03 (0.37) | 0.39* (0.06) |
| **Biological mothers** | *n* = 776[d] | *n* = 197 | | *n* = 576 | *n* = 104 | | *n* = 9783 | *n* = 196 | |
| Age by child's birth, mean (SD) | 28.88 (6.21) | 29.36 (5.89) | 0.32* (− 0.08) | 30.33 (5.46) | 31.56 (5.33) | **0.02* (− 0.23)** | 30.65 (4.75) | 32.10 (4.14) | **< .001* (− 0.31)** |
| Level of education, *n* (%) | | | | | | | | | |
| Primary and lower secondary (DISCED[c] level 2) | 384 (44.34) | 69 (34.16) | | 158 (24.27) | 17 (14.17) | | 1125 (11.36) | 17 (8.50) | |
| Upper secondary (DISCED level 3 + 5) | 289 (33.37) | 72 (35.64) | | 290 (44.55) | 43 (35.83) | | 4365 (44.09) | 86 (43.00) | |

**Table 2** (continued)

| | FHR-SZ Non-participants, mean (SD) or *n* (%) | FHR-SZ VIA 7 Participants mean (SD) or *n* (%) | *p* value , chi-square or *t* test (SMD)[a] | FHR-BP Non-participants mean (SD) or *n* (%) | FHR-BP VIA 7 Participants mean (SD) or *n* (%) | *p* value, chi-square or *t* test (SMD) | PBC Non-participants mean (SD) or *n* (%) | PBC VIA 7 Participants mean (SD) or *n* (%) | *p* value, chi-square or *t* test (SMD) |
|---|---|---|---|---|---|---|---|---|---|
| Bachelor degree, equivalent or higher (DISCED level 6 + 7 + 8) | 193 (22.29) | 61 (30.20) | **0.01*** | 203 (31.18) | 60 (50.00) | **< .001*** | 4410 (44.55) | 97 (48.50) | 0.34* |
| Employment status, *n* (%) | | | | | | | | | |
| Employed | 322 (36.97) | 87 (43.07) | | 310 (47.40) | 77 (64.17) | | 8412 (84.87) | 186 (93.00) | |
| Pension / early retirement | 226 (25.95) | 43 (21.29) | | 114 (17.43) | 13 (10.83) | | 136 (1.37) | < 4 | |
| Unemployed | 262 (30.08) | 55 (27.23) | | 187 (28.59) | 21 (17.50) | | 1008 (10.17) | 6 (3.00) | |
| No information | 61 (7.00) | 17 (8.42) | 0.27* | 43 (6.57) | 9 (7.50) | **0.004*** | 356 (3.59) | 5 (2.50) | **0.007*** |
| Income in DKR, mean (SD) | 272 198.9 (116,763) | 276 756.8 (102,416.1) | 0.61* (− 0.04) | 292 858.4 (121,198.4) | 313 883.3 (125,998.2) | 0.08* (− 0.17) | 363 142.2 (167,995.6) | 392 190.2 (166,923.1) | **0.02* (− 0.17)** |
| Changes in civil status from 1 year before child birth until child's 7th birthday, mean (SD) | 0.22 (0.51) | 0.23 (0.56) | 0.74 (− 0.03) | 0.26 (0.54) | 0.32 (0.58) | 0.29 (− 0.10) | 0.14 (0.40) | 0.09 (0.31) | 0.07 (0.13) |
| 0 changes, *n* (%) | 711 (81.63) | 165 (81.68) | | 511 (78.13) | 89 (74.17) | | 8744 (88.22) | 185 (92.50) | |
| 1 change, *n* (%) | 135 (15.50) | 29 (14.36) | | 120 (18.35) | 24 (20.00) | | 998 (10.07) | 13 (6.50) | |
| 2 changes or above, *n* (%) | 25 (2.87) | 8 (3.96) | 0.68* | 23 (3.52) | 7 (5.83) | 0.42* | 170 (1.71) | < 4 | 0.17* |
| Civil status, *n* (%) | | | | | | | | | |
| Divorced | 149 (17.11) | 34 (16.83) | | 133 (20.34) | 29 (24.17) | | 977 (9.86) | 12 (6.00) | |
| Married | 295 (33.87) | 87 (43.07) | | 295 (45.11) | 64 (53.33) | | 6779 (68.39) | 153 (76.50) | |
| Unmarried | 416 (47.76) | 80 (39.60) | | 214 (32.72) | 26 (21.67) | | 2120 (21.39) | 35 (17.50) | |
| Other | 11 (1.26) | < 4 | 0.07* | 12 (1.83) | < 4 | 0.08* | 36 (0.36) | 0 (0.00) | 0.07* |
| Somatic illness, outpatient days, mean (SD) | 25.13 (22.79) | 23.65 (19.27) | 0.40* (0.07) | 23.82 (21.19) | 23.89 (21.88) | 0.97* (− 0.003) | 20.84 (17.41) | 18.59 (13.96) | 0.07* (0.13) |
| Somatic illness, bed days, mean (SD) | 15.81 (22.90) | 13.87 (17.73) | 0.26* (0.09) | 13.83 (16.56) | 12.93 (20.96) | 0.60* (0.05) | 9.84 (12.74) | 8.20 (7.81) | 0.07* (0.13) |
| Mental illness, outpatient days before child's birth, mean (SD) | 27.90 (62.64) | 28.18 (50.45) | 0.95* (− 0.005) | 16.58 (44.15) | 11.42 (26.15) | 0.21* (0.12) | 1.19 (9.81) | 0.3 (2.26) | 0.20* (0.09) |

**Table 2** (continued)

| | FHR-SZ Non-participants, mean (SD) or *n* (%) | FHR-SZ VIA 7 Participants mean (SD) or *n* (%) | *p* value , chi-square or *t* test (SMD)[a] | FHR-BP Non-participants mean (SD) or *n* (%) | FHR-BP VIA 7 Participants mean (SD) or *n* (%) | *p* value, chi-square or *t* test (SMD) | PBC Non-participants mean (SD) or *n* (%) | PBC VIA 7 Participants mean (SD) or *n* (%) | *p* value, chi-square or *t* test (SMD) |
|---|---|---|---|---|---|---|---|---|---|
| Mental illness, bed days before child's birth, mean (SD) | 66.30 (197.85) | 81.63 (174.30) | 0.31* (− 0.08) | 24.54 (88.18) | 24.08 (94.96) | 0.96* (0.005) | 1.00 (16.88) | 0.01 (0.14) | 0.41* (0.06) |
| Mental illness, outpatient days after child's birth, mean (SD) | 871 (56.10) | 202 (45.04) | 0.46* (0.06) | 25.35 (40.79) | 19.57 (33.41) | 0.14* (0.15) | 1.21 (8.41) | 0.75 (8.17) | 0.44* (0.06) |
| Mental illness, bed days after child's birth, mean (SD) | 30.797 (128.31) | 23.77 (72.68) | 0.45* (0.06) | 26.998 (129.49) | 22.43 (67.58) | 0.71* (0.04) | 0.42 (6.21) | 0.19 (2.62) | 0.60* (0.04) |
| Any coercive measures, *n* (%) | 121 (13.89) | 31 (15.35) | 0.59* | 54 (8.26) | 12 (10.00) | 0.53* | 24 (0.24) | 0 (0.00) | 0.49* |
| Mother has custody of child, *n* (%) | 825 (96.04) | 196 (98.49) | 0.09* | 617 (95.96) | 115 (95.83) | 0.95* | 9791 (99.15) | 198 (99.50) | 0.60* |
| Dead, *n* (%) | 5 (0.57) | 0 (0.00) | 0.28* | 8 (1.22) | < 4 | 0.71* | 9 (0.09) | 0 (0.00) | 0.67* |
| Any substance abuse, *n* (%) | 148 (16.99) | 25 (12.38) | 0.11* | 74 (11.31) | 15 (12.50) | 0.71* | 226 (2.28) | < 4 | 0.46* |
| **Biological fathers** | *n* = 774[d] | *n* = 173 | | *n* = 572 | *n* = 108 | | *n* = 9778 | *n* = 196 | |
| Age by childs birth, mean (SD) | 31.90 (7.18) | 31.96 (6.38) | 0.91* (− 0.01) | 33.23 (6.42) | 35.04 (6.71) | **< 0.005*** **(− 0.28)** | 32.89 (5.33) | 33.68 (4.77) | **0.04*** **(− 0.15)** |
| Level of education, *n* (%) | | | | | | | | | |
| Primary and lower secondary (DISCED[c] level 2) | 379 (45.28) | 81 (41.12) | | 163 (25.08) | 18 (15.38) | | 1388 (14.06) | 20 (10.00) | |
| Upper secondary (DISCED level 3 + 5) | 329 (39.31) | 81 (41.12) | | 361 (55.54) | 60 (51.28) | | 5679 (57.54) | 114 (57.00) | |
| Bachelor degree, equivalent or higher (DISCED level 6 + 7 + 8) | 129 (15.41) | 35 (17.77) | 0.52* | 126 (19.38) | 39 (33.33) | **0.001*** | 2802 (28.39) | 66 (33.00) | 0.15* |
| Employment status, *n* (%) | | | | | | | | | |
| Employed | 412 (47.30) | 115 (56.93) | | 448 (68.50) | 87 (72.50) | | 9050 (91.30) | 194 (97.00) | |
| Pension/ early retirement | 241 (27.67) | 46 (22.77) | | 67 (10.24) | 8 (6.67) | | 123 (1.24) | < 4 | |
| Unemployed | 161 (18.48) | 34 (16.83) | | 113 (17.28) | 20 (16.67) | | 517 (5.22) | < 4 | |

**Table 2** (continued)

| | FHR-SZ Non-participants, mean (SD) or *n* (%) | FHR-SZ VIA 7 Participants mean (SD) or *n* (%) | *p* value , chi-square or *t* test (SMD)[a] | FHR-BP Non-participants mean (SD) or *n* (%) | FHR-BP VIA 7 Participants mean (SD) or *n* (%) | *p* value, chi-square or *t* test (SMD) | PBC Non-participants mean (SD) or *n* (%) | PBC VIA 7 Participants mean (SD) or *n* (%) | *p* value, chi-square or *t* test (SMD) |
|---|---|---|---|---|---|---|---|---|---|
| No information | 57 (6.54) | 7 (3.47) | 0.06* | 26 (3.98) | 5 (4.17) | 0.66* | 222 (2.24) | < 4 | **0.04*** |
| Income in DKR, mean (SD) | 309,439.5 (321,082.5) | 325,711.4 (207,920.9) | 0.50* (− 0.05) | 345,143.4 (253,123.4) | 403,410.6 (292,728.1) | **0.03* (− 0.22)** | 472,990.4 (377,842) | 480,896.6 (234,723.4) | 0.77* (− 0.02) |
| Changes in civil status from 1 year before child birth until child's 7th birthday, mean (SD) | 0.22 (0.50) | 0.22 (0.48) | 0.91* (− 0.01) | 0.25 (0.50) | 0.32 (0.52) | 0.15* (− 0.14) | 0.13 (0.40) | 0.07 (0.28) | **0.02* (0.16)** |
| 0 changes, *n* (%) | 711 (81.63) | 163 (80.69) | | 514 (78.59) | 85 (70.83) | | 8767 (88.45) | 187 (93.50) | |
| 1 change, *n* (%) | 133 (15.27) | 33 (16.34) | | 121 (18.50) | 32 (26.67) | | 978 (9.87) | 12 (6.00) | |
| 2 changes or above, *n* (%) | 27 (3.10) | 6 (2.97) | 0.93* | 19 (2.91) | < 4 | 0.12* | 167 (1.68) | < 4 | 0.07* |
| Civil status, *n* (%) | | | | | | | | | |
| Divorced | 148 (16.99) | 35 (17.33) | | 125 (19.11) | 34 (28.33) | | 967 (9.76) | 15 (7.50) | |
| Married | 297 (34.10) | 87 (43.07 | | 294 (44.95) | 62 (51.67) | | 6775 (68.35) | 150 (75.00) | |
| Unmarried | 405 (46.50) | 77 (38.12) | | 223 (34.10) | 21 (17.50) | | 2128 (21.47) | 34 (17.00) | |
| Other | 21 (2.41) | < 4 | 0.08* | 12 (1.83) | < 4 | **0.003*** | 42 (0.42) | < 4 | 0.25* |
| Somatic illness, outpatient days, mean (SD) | 7.37 (13.58) | 4.99 (8.13) | **0.02* (0.19)** | 6.68 (11.45) | 7.62 (17.42) | 0.45* (− 0.08) | 5.58 (12.19) | 5.08 (11.53) | 0.56* (0.04) |
| Somatic illness, bed days, mean (SD) | 5.79 (18.28) | 4.46 (16.38) | 0.34* (0.07) | 3.98 (9.82) | 3.47 (6.07) | 0.577* (0.06) | 2.25 (8.51) | 1.6 (5.29) | 0.28* (0.08) |
| Mental illness, outpatient days before child's birth, mean (SD) | 24.19 (57.55) | 15.47 (36.82) | **0.04* (0.16)** | 5.08 (16.05) | 6.59 (17.44) | 0.35* (− 0.09) | 0.31 (5.69) | 0.11 (0.98) | 0.61* (0.04) |
| Mental illness, outpatient days after child's birth, mean (SD) | 24.01 (49.99) | 21.22 (42.78) | 0.46* (0.06) | 11.25 (26.74) | 15.23 (36.74) | 0.16* (− 0.14) | 0.35 (3.22) | 0.005 (0.07) | 0.13* (0.11) |
| Mental illness, bed days before child's birth, mean (SD) | 83.83 (242.81) | 58.24 (159.02) | 0.15* (0.11) | 14.03 (49.19) | 17.13 (43.06) | 0.52* (− 0.06) | 0.32 (5.75) | 0.06 (0.85) | 0.53* (0.05) |
| Mental illness, bed days after child's birth, mean (SD) | 48.64 (182.88) | 56.39 (204.64) | 0.60* (− 0.04) | 23.46 (131.42) | 28.25 (99.69) | 0.70* (− 0.04) | 0.29 (5.34) | 0.44 (4.83) | 0.70* (− 0.03) |

**Table 2** (continued)

| | FHR-SZ Non-participants, mean (SD) or *n* (%) | FHR-SZ VIA 7 Participants mean (SD) or *n* (%) | *p* value , chi-square or *t* test (SMD)[a] | FHR-BP Non-participants mean (SD) or *n* (%) | FHR-BP VIA 7 Participants mean (SD) or *n* (%) | *p* value, chi-square or *t* test (SMD) | PBC Non-participants mean (SD) or *n* (%) | PBC VIA 7 Participants mean (SD) or *n* (%) | *p* value, chi-square or *t* test (SMD) |
|---|---|---|---|---|---|---|---|---|---|
| Any coercive measures, *n* (%) | 130 (14.93) | 28 (13.86) | 0.70* | 54 (8.26) | 9 (7.50) | 0.78* | 26 (0.26) | <5 | 0.52* |
| Father has custody of child, *n* (%) | 636 (74.04) | 159 (79.90) | 0.09* | 533 (82.89) | 99 (82.50) | 0.92* | 9352 (94.70) | 194 (97.49) | 0.08* |
| Dead, *n* (%) | 19 (2.18) | < 5 | 0.53* | 9 (1.38) | < 4 | 0.36* | 33 (0.33) | <5 (0.50) | 0.69* |
| Any substance abuse, *n* (%) | 274 (31.46) | 60 (29.70) | 0.63* | 134 (20.49) | 23 (19.17) | 0.74* | 278 (2.80) | <5 | 0.12* |

[a]Standard Medium Difference

[b]Special support is only registered if the amount exceeds 9 h per week

[c] DISCED: The Danish version of the International Standard Classification of Education

[d]All included children have a mother and a father registered and the number of mothers and fathers included thus equals the included number of children. Since some of the included children have the same mother and father, the n in the table representing mothers and fathers is lower than the n for included children

[e]*$p$ values, bold signifies values significant at $p = 0.05$ level

preventive interventions received from the municipality ($p = 0.01$ for FHR-SZ and p (SMD) = 0.04 (0.16) for days of preventive interventions amongst FHR-SZ), child notifications of concern ($p < 0.001$ for FHR-BP and PBC), child placement out of home ($p = 0.03$ for FHR-SZ), lower maternal and paternal age at time of the birth of the participating child ($p$ (SMD) = 0.02 (− 0.23) for FHR-BP and $p$ (SMD) < 0.001 (− 0.31) for PBC for mothers, $p$ (SMD) = 0.005 (− 0.28) for FHR-BP and $p$ (SMD) = 0.04 (− 0.15) for PBC for fathers), lower maternal and paternal level of education ($p = 0.01$ for FHR-SZ and $p < 0.001$ for FHR-BP for mothers and $p = 0.001$ for FHR-BP for fathers), maternal and paternal unemployment ($p = 0.004$ for FHR-BP and $p = 0.007$ for PBC for mothers and $p = 0.04$ for PBC for fathers), maternal and paternal lower income ($p$ (SMD) = 0.02 (0.17) for PBC mothers and $p$ (SMD) = 0.03 (− 0.22) for FHR-BP fathers), never married ($p = 0.003$ for FHR-BP fathers), paternal somatic illness ($p$ (SMD) = 0.02 (0.19) for FHR-SZ), and outpatient treatment days in mental health facilities before the birth of the participating child than participants ($p$ (SMD) = 0.04 (0.16) for FHR-SZ). The latter difference was no longer found after the child's birth ($p$ (SMD) = 0.46 (0.06) for FHR-SZ, $p$ (SMD) = 0.16 (-0.14) for FHR-BP and $p$ (SMD) = 0.13 (0.11) for PBC), nor were any significant differences found with respect to paternal inpatient treatment days or coercive measures (Table 2).

No significant difference was found with respect to the participation versus non-participation rates amongst families with two ill parents ($p = 0.56$) (Table 3).

## Results from The VIA 7 Study weighted through the use of register data

Analyzing selected VIA 7 Study results through IPW, most of the differences found in analyses of observed cases remained statistically significant (Table 4). The exceptions primarily concerning comparisons between the FHR-SZ and the FHR-BP group. Only in analyses of two variables, results changed from insignificant to significant after IPW. This was the case for the pairwise comparisons of FHR-SZ

**Table 3** Children of two parents with either schizophrenia or bipolar disorder diagnoses amongst participants in the Danish High Risk and Resilience Study VIA 7 versus non-participants, identified through national registers

| Two ill parents, *n* (%) | Non-participant family | VIA Participant family | *P* value |
|---|---|---|---|
| No | 1483 (97.25) | 315 (97.83) | 0.56* |
| Yes | 42 (2.75) | 7 (2.17) | |

**Table 4** Selected results from The Danish High Risk and Resilience Study VIA 7 for children of parents with schizophrenia (FHR-SZ), bipolar disorder (FHR-BP) or population-based controls (PBC) ($N=522$), and the corresponding results which are weighted through the use of register data regarding socioeconomics and health in the total eligible sample of 11.959 children

| VIA 7 domain and assessment | Overall ANOVA, *p* value unweighted | Overall ANOVA, *p* value weighted | FHR-SZ vs PBC, unweighted mean difference or OR (CI), *p* value (SMD) | FHR-SZ vs PBC, weighted mean difference or OR (CI), *p* value (SMD) | FHR-BP vs PBC, unweighted mean difference or OR (CI), *p* value (SMD) | FHR-BP vs PBC, weighted mean difference or OR (CI), *p* value (SMD) | FHR-SZ vs FHR-BP, unweighted mean difference or OR (CI), *p* value (SMD) | FHR-SZ vs. FHR-BP, weighted mean difference or OR (CI), *p* value (SMD) |
|---|---|---|---|---|---|---|---|---|
| Language | | | | | | | | |
| Receptive language (TROG) [1], mean difference (CI) | **0.01*** | **0.04*** | − 0.91 (− 1.54;− 0.27)**0.005*** (**− 0.28**) | − 0.88 (− 1.59;− 0.17)**0.02*** (**− 0.25**) | − 0.02 (− 0.67;0.62)0.94* (− 0.01) | − 0.04 (− 0.77;0.70)0.92* (− 0.01) | − 0.88 (− 1.58;− 0.19)**0.01*** (**− 0.27**) | − 0.84 (− 1.65; − 0.04)**0.04*** (**− 0.23**) |
| Social cognition | | | | | | | | |
| Theory of mind (Happe) [2], mean difference (CI) | **0.02*** | 0.11* | − 0.66 (− 1.16; − 0.16)**0.01*** (**− 0.26**) | − 0.54 (− 1.14; 0.06)0.08* (− 0.18) | − 0.08 (− 0.64; 0.49)0.80* (− 0.03) | 0.10 (− 0.53; 0.72)0.76* (0.03) | − 0.59 (− 1.17; − 0.01) **< 0.05*** (**− 0.23**) | − 0.63 (− 1.29; 0.02)0.06* (− 0.21) |
| Emotion recognition, percent correct answers (CANTAB) [3], mean difference (CI) | 0.43* | 0.19* | − 1.09 (− 3.12; 0.93)0.29* (− 0.11) | − 0.86 (− 3.18; 1.47)0.47* (− 0.07) | 0.25 (− 1.94; 2.45)0.82* (0.03) | 1.52 (− 0.91; 3.95)0.22* (0.14) | − 1.35 (− 3.60; 0.91)0.24* (− 0.13) | − 2.37 (− 4.95; 0.20)0.07* (− 0.20) |
| Intelligence | | | | | | | | |
| Child intelligence level (RIST) [4], mean difference (CI) | **0.03*** | **0.02*** | − 2.78 (− 4.89; − 0.66)**0.01*** (**− 0.26**) | − 2.81 (− 5.04; − 0.57)**0.01*** (**− 0.24**) | − 0.79 (− 2.95; 1.38)0.48* (− 0.08) | 0.05 (− 2.25; 2.34)0.96* (0.005) | − 1.99 (− 4.30; 0.33)0.09* (− 0.19) | − 2.86 (− 5.21; − 0.51)**0.02*** (**− 0.26**) |
| Motor function | | | | | | | | |
| Aiming and catching (Movement ABC) [5], mean difference (CI) | 0.25* | 0.92* | − 0.45 (− 1.04; 0.14)0.13* (− 0.15) | − 0.05 (− 0.68; 0.576)0.87* (− 0.02) | − 0.47 (− 1.16; 0.23)0.19* (− 0.15) | − 0.15 (− 0.87; 0.56)0.68* (− 0.05) | 0.02 (− 0.67; 0.70)0.96* (0.005) | 0.10 (− 0.63; 0.83)0.79* (0.03) |
| Balance (Movement ABC) [5], mean difference (CI) | **< 0.001*** | 0.03* | − 1.40 (− 2.10; − 0.71) **< 0.001*** (**− 0.39**) | − 1.100 (− 1.90; − 0.30)**0.01*** (**− 0.27**) | − 0.72 (− 1.54; 0.09)0.08* (− 0.20) | − 0.53 (− 1.42; 0.37)0.25* (− 0.13) | − 0.68 (− 1.45; 0.09)0.08* (− 0.21) | − 0.58 (− 1.49; 0.34)0.22* (− 0.14) |
| Manual dexterity (Movement ABC) [5], mean difference (CI) | **< 0.001*** | **< 0.001*** | − 1.46 (− 2.15; − 0.76) **< 0.001*** (**− 0.41**) | − 1.28 (− 2.06; − 0.50)**0.001*** (**− 0.32**) | − 0.75 (− 1.58; 0.08)0.08* (− 0.21) | − 0.31 (− 1.23; 0.60)0.50* (− 0.08) | − 0.70 (− 1.52; 0.11)0.09* (− 0.20) | − 0.97 (− 1.91; − 0.03)**0.04*** (**− 0.23**) |
| Emotional control | | | | | | | | |

**Table 4** (continued)

| VIA 7 domain and assessment | Overall ANOVA, *p* value unweighted | Overall ANOVA, *p* value weighted | FHR-SZ vs PBC, unweighted mean difference or OR (CI), *p* value (SMD) | FHR-SZ vs PBC, weighted mean difference or OR (CI), *p* value (SMD) | FHR-BP vs PBC, unweighted mean difference or OR (CI), *p* value (SMD) | FHR-BP vs PBC, weighted mean difference or OR (CI), *p* value (SMD) | FHR-SZ vs FHR-BP, unweighted mean difference or OR (CI), *p* value (SMD) | FHR-SZ vs. FHR-BP, weighted mean difference or OR (CI), *p* value (SMD) |
|---|---|---|---|---|---|---|---|---|
| Executive functions, emotional control (BRIEF) [6] mean difference (CI) | **< 0.001*** | **< 0.001*** | 2.00 (1.11; 2.90) **< 0.001*** **(0.44)** | 2.21 (1.15; 3.28) **< 0.001*** **(0.42)** | 1.68 (0.65; 2.72)**0.002*** **(0.40)** | 1.77 (0.51; 3.03)**0.01*** **(0.36)** | 0.32 (− 0.81; 1.45)0.57* (0.07) | 0.44 (− 0.94; 1.82)0.53* (0.08) |
| Problem behaviour | | | | | | | | |
| Externalizing problems (CBCL) [7], mean difference (CI) | **< 0.001*** | **< 0.001*** | 3.70 (2.44; 4.97) **< 0.001*** **(0.56)** | 3.41 (1.95; 4.87) **< 0.001*** **(0.49)** | 2.09 (0.68; 3.51)**0.004*** **(0.37)** | 2.70 (0.73; 4.67)**0.01*** **(0.39)** | 1.61 (− 0.03; 3.25)0.05* (0.22) | 0.71 (− 1.48; 2.90)0.52* (0.08) |
| Internalizing problems (CBCL) [7], mean difference (CI) | **0.002*** | **0.003*** | 1.73 (0.68; 2.79)**0.001*** **(0.33)** | 1.99 (0.75; 3.23)**0.002*** **(0.34)** | 1.76 (0.33; 3.19)**0.02*** **(0.32)** | 1.73 (0.04; 3.41)**0.04*** **(0.29)** | − 0.03 (− 1.55; 1.49)0.97* (− 0.004) | 0.26 (− 1.58; 2.11)0.78* (0.03) |
| Symptoms of ADHD and oppositional defiant disorder (mADHD-RS) [8–10], mean difference (CI) | **< 0.001*** | **< 0.001*** | 5.56 (3.27; 7.84) **< 0.001*** **(0.47)** | 5.59 (2.97; 8.21) **< 0.001*** **(0.44)** | 3.13 (0.50; 5.77)**0.02*** **(0.29)** | 3.66 (0.53; 6.79)**0.02*** **(0.31)** | 2.42 (− 0.50; 5.34)0.10* (0.19) | 1.93 (− 1.55; 5.42)0.28* (0.13) |
| Self-perception | | | | | | | | |
| Self-perception (I think I am) [11], mean difference (CI) | **< 0.001*** | **0.004*** | − 3.03 (− 4.58; − 1.48) **< 0.001*** **(− 0.38)** | − 3.14 (− 4.97; − 1.31)**0.001*** **(− 0.35)** | − 0.79 (− 2.44; 0.85)0.34* (− 0.11) | − 0.99 (− 3.05; 1.07)0.35* (− 0.12) | − 2.24 (− 4.07; − 0.40)**0.02*** **(− 0.27)** | − 2.15 (− 4.44; 0.13)0.07* (− 0.21) |
| Psycho-pathology | | | | | | | | |
| Any axis 1 diagnosis, present (K-SADS) [12], OR (CI) | **< 0.001*** | **< 0.001*** | 3.59 (2.12; 6.08) **< 0.001*** | 3.57 (2.00; 6.37) **< 0.001*** | 2.82 (1.55; 5.10)**0.001*** | 2.89 (1.50; 5.57)**0.001*** | 1.27 (0.77; 2.11)0.34* | 1.23 (0.69; 2.19)0.48* |
| Psychotic experiences | | | | | | | | |
| Psychotic Experiences (PE's) [13], OR (CI) | **0.01*** | 0.06* | 2.92 (1.37; 6.21)**0.005*** | 2.36 (1.02; 5.45)**0.04*** | 2.92 (1.28; 5.66)**0.01*** | 2.90 (1.16; 7.25)**0.02*** | 1.00 (0.52; 1.94)1.00* | 0.81 (0.38; 1.74)0.60* |

**Table 4** (continued)

| VIA 7 domain and assessment | Overall ANOVA, *p* value unweighted | Overall ANOVA, *p* value weighted | FHR-SZ vs PBC, unweighted mean difference or OR (CI), *p* value (SMD) | FHR-SZ vs PBC, weighted mean difference or OR (CI), *p* value (SMD) | FHR-BP vs PBC, unweighted mean difference or OR (CI), *p* value (SMD) | FHR-BP vs PBC, weighted mean difference or OR (CI), *p* value (SMD) | FHR-SZ vs FHR-BP, unweighted mean difference or OR (CI), *p* value (SMD) | FHR-SZ vs. FHR-BP, weighted mean difference or OR (CI), *p* value (SMD) |
|---|---|---|---|---|---|---|---|---|
| Level of functioning | | | | | | | | |
| Level of functioning, child (CGAS) [12], mean difference (CI) | **< 0.001*** | **< 0.001*** | − 9.64 (− 12.50; − 6.77) **< 0.001*** **(− 0.63)** | − 10.25 (− 13.45; − 7.05) **< 0.001*** **(− 0.61)** | − 4.16 (− 7.45; − 0.86)**0.01*** **(− 0.29)** | − 4.19 (− 7.95; − 0.43)**0.03*** **(− 0.30)** | − 5.48 (− 8.94; − 2.02)**0.002*** **(− 0.35)** | − 6.06 (− 10.07; − 2.06)**0.003*** **(− 0.34)** |
| Home environment | | | | | | | | |
| Level of stimulation and support (MC-HOME) [14], mean difference (CI) | **< 0.001*** | **< 0.001*** | − 4.05 (− 5.15; − 2.96) **< 0.001*** **(− 0.69)** | − 3.42 (− 4.63; − 2.21) **< 0.001*** **(− 0.58)** | − 2.33 (− 3.40; − 1.25) **< 0.001*** **(− 0.50)** | − 2.27 (− 3.43; − 1.11) **< 0.001*** **(− 0.45)** | − 1.72 (− 2.99; − 0.46)**0.01*** **(− 0.29)** | − 1.15 (− 2.53; 0.23)0.10* (− 0.18) |
| Parental level of functioning | | | | | | | | |
| Level of functioning, primary caregiver (PSP) [15], mean difference (CI) | **< 0.001*** | **< 0.001*** | − 11.24 (− 13.61; − 8.87) **< 0.001*** **(− 0.85)** | − 8.28 (− 10.77; − 5.79) **< 0.001*** **(− 0.67)** | − 9.94 (− 12.81; − 7.07) **< 0.001*** **(− 0.81)** | − 9.13 (− 12.14; − 6.12) **< 0.001*** **(− 0.73)** | − 1.30 (− 4.55; 1.96)0.43* (− 0.09) | 0.85 (− 2.43; 4.14)0.61* (0.06) |
| Level of functioning, index parent (PSP) [15], mean difference (CI) | **< 0.001*** | **< 0.001*** | − 18.32 (− 21.15; − 15.49) **< 0.001*** **(− 1.14)** | − 15.19 (− 18.21; − 12.17) **< 0.001*** **(− 1.06)** | − 15.60 (− 18.90; − 12.30) **< 0.001*** **(− 1.08)** | − 15.07 (− 18.27; − 11.87) **< 0.001*** **(− 1.11)** | − 2.72 (− 6.59; 1.15)0.17* (− 0.17) | − 0.12 (− 4.02; 3.78)0.95* (− 0.01) |
| Child lives with a single caregiver OR (CI) | **< 0.001*** | **< 0.001*** | 4.78 (2.82; 8.12) **< 0.001*** | 4.60 (2.55; 8.30) **< 0.001*** | 3.90 (2.16; 7.04) **< 0.001*** | 4.45 (2.30; 8.59) **< 0.001*** | 1.23 (0.75; 2.00)0.41* | 1.03 (0.60; 1.78)0.90* |
| Father´s level of education [16], Primary/ lower secondary education vs upper secondary education vs bachelor degree, equivalent or higher, OR (CI) | **< 0.001*** | **0.005*** | − 0.62 (− 0.94; − 0.31) **< 0.001*** | − 0.46 (− 0.80; − 0.12)**0.01*** | 0.17 (− 0.20; 0.54)0.37* | 0.16 (− 0.24; 0.55)0.43* | − 0.79 (− 1.17; − 0.41) **< 0.001*** | − 0.62 (− 1.03; − 0.21) **< 0.005*** |

**Table 4** (continued)

| VIA 7 domain and assessment | Overall ANOVA, *p* value unweighted | Overall ANOVA, *p* value weighted | FHR-SZ vs PBC, unweighted mean difference or OR (CI), *p* value (SMD) | FHR-SZ vs PBC, weighted mean difference or OR (CI), *p* value (SMD) | FHR-BP vs PBC, unweighted mean difference or OR (CI), *p* value (SMD) | FHR-BP vs PBC, weighted mean difference or OR (CI), *p* value (SMD) | FHR-SZ vs FHR-BP, unweighted mean difference or OR (CI), *p* value (SMD) | FHR-SZ vs. FHR-BP, weighted mean difference or OR (CI), *p* value (SMD) |
|---|---|---|---|---|---|---|---|---|
| Mother´s level of education [16], Primary/ lower secondary education vs upper secondary education vs bachelor degree, equivalent or higher, OR (CI) | **< 0.001*** | **< 0.001*** | − 0.77 (− 1.08; − 0.45) **< 0.001*** | − 0.65 (− 0.99; − 0.30) **< 0.001*** | 0.10 (− 0.26; 0.46)0.59* | 1.89 (− 0.21; 0.59)0.36* | − 0.86 (− 1.23; − 0.49) **< 0.001*** | − 0.83 (− 1.24; − 0.42) **< 0.001*** |

*= p-values

and FHR-BP for manual dexterity (*p* (SMD) = 0.04 (− 0.23)) and level of intelligence (*p* (SMD) = 0.02 (− 0.26)).

Additionally, a few variables changed from significant to insignificant after IPW in pairwise comparisons between FHR-SZ and FHR-BP. The variables were the theory of mind, self-perception, and home environment. Also, differences between FHR-SZ and PBC in theory of mind changed from significant to insignificant (Table 4).

## Discussion

The need for register-based validation of cohort representativity and generalizability of results in psychiatric research has been highlighted in previous studies [39], but this is to our knowledge the first analysis of familial high-risk children which combines a clinically examined cohort of children at FHR-SZ or FHR-BP with population-based register data on a nationwide, larger familial high-risk sample. One key advantage of this approach is the allowance for analyses of case non-response and not only item non-response.

The children with FHR-SZ and FHR-BP and their parents were disadvantaged with regard to numerous socioeconomic and health measures. For the total sample, children with FHR-SZ, but also FHR-BP, had higher prevalence rates of prenatal and perinatal risk factors known from previous studies to be unfavorable for child development [40] such as maternal tobacco smoking during pregnancy, lower mean Apgar score, and a higher prevalence of preterm birth [41–43]. During the first seven years of life, preventive interventions had more frequently been established for familial high-risk children, and although it is positive that such interventions exist, being in need of them is not. The increased levels of notifications of concern and placement out of home illustrate that familial high-risk children, and their parents, are more likely to have severe risk factors in their family functioning as compared with controls.

Parental data showed that the familial high-risk families have multiple group-level impairments as compared with controls. As previously shown, it is likely that the accumulation of risk factors poses socioeconomic and health risks [44–48] not just for the parents but also for the children. As both mothers, fathers and children in the familial high-risk groups have various socioeconomic and health risk factors, awareness of the accumulated burden in these families is relevant for health policy makers when planning national preventive strategies.

Assessing the flowchart for participation in the VIA 7 study, participation rates were found to differ between risk groups amongst those who attempted contact, with the FHR-SZ group having the lowest rate (49.27%), the FHR-BP group having an intermediate rate (56.07%) and the PBC having the highest (62.70%). Multiple factors such as

a parental agreement to participate as well as the child's willingness to participate, logistic and practical barriers and the parental capacity to overcome these may be involved. Factors such as having parents who had split up but still shared the custody of the child and had to agree on participation could have complicated participation in the FHR groups where this situation was more prevalent than amongst controls, and the children in the FHR groups may also have been more reluctant to participate—for those who did participate, we found the frequency of psychopathology to be higher in FHR children than amongst controls and if this was also the case for the non-participating children, it may have played a role in them not wanting to participate.

Comparisons of VIA 7 study participants and non-participants demonstrated that the VIA 7 cohort is representative in most measures including parental use of mental health facilities after the child's birth. However, non-participants were exposed to more risk factors such as exposure to smoking during pregnancy, receiving preventive measures and school support, placement out of home, notifications of concern, lower parental levels of education and lower levels of income. This implies lower parental and child function and a higher degree of risk factors amongst non-participants and indicates that the differences found between PBCs and familial high-risk children in The VIA 7 Study may be even larger. While the private economy probably would not have hindered participation due to fair compensation and coverage of expenses, logistic issues may have played a role. We removed barriers and facilitated participation (e.g. by offering hotel stays and taxi rides) to also include both children and parents with severely impaired levels of functioning. By and large, we succeeded with this, considering the many measures in which participants and non-participants do not differ, including the prevalence of families with two ill parents. However, barriers such as coordination with foster parents, or with ill parents living permanently in institutions, or long distances to rural areas, may in some cases have played a role. Perhaps some of these barriers have to some degree made participation easier for families with good function and for children who had optimal conditions to perform well in the test battery. The fact that The VIA 7 Study may to some degree underrepresent children and families with lower function in spite of the huge efforts made to include them further emphasizes the need for health policy attention towards familial high-risk children.

Most of the results generated from the VIA Study remained unaltered in terms of significance after adjustment for the found selection bias through the use of IPW. The few exceptions were primarily found in comparisons between FHR-BP and FHR-SZ, but there was no consistent pattern in how weighting changed the results.

There are several implications of this study. First, the study calls for health policy awareness concerning the impairments of familial high-risk families with respect to education and work, health, family level of function, and pregnancy. Second, the study concludes that there is a selection bias towards the most well-functioning families even though a highly flexible approach to include the most severely impaired families was used.

## Strengths and limitations

This study has several important strengths. It is the largest and, in some respects, the only study of familial high-risk children who have been thoroughly examined clinically and at the same time have been identified through nationwide registers. It is a major strength that representativity could be examined through analyses of important prognostic factors identified in the registers. However, it is a limitation that not all factors of possible relevance can be obtained through the registers. A limitation to this study is also the risk of incorrect information from the Danish registers. Previous studies have shown that the Danish registers from 1990 [49] and at present time [34] have good validity but lacked validity at the time of the first validation study in 1980, which may be a small limitation for the parental lifetime mental illness information [34, 50]. Finally, private hospitals and clinics are potential sources of underreporting although reporting to the national registers has been mandatory since 2003 [34, 51].

## Conclusions

We found substantial and predominantly highly significant differences regarding socioeconomic status and health and family functioning across the three groups. We found that the VIA 7 Study is in many measures representative of the general Danish population, but does, however, underrepresent particularly individuals from rural areas with low educational levels and low-functioning children and families. Weighted adjustment for this underrepresentation only resulted in small changes in our findings from the VIA 7 Study, indicating that the conclusions generated from the VIA 7 Study are in most cases unaffected by the found selection bias.. The found underrepresentation of the most disadvantaged families further highlights the need for policy awareness towards this group as well as for research awareness to take precautions to avoid selection bias in clinical studies.

**Supplementary Information** The online version contains supplementary material available at https://doi.org/10.1007/s00127-022-02338-3.

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**Availability of data and material** According to GDPR rules, data can be accessed by researchers upon data agreement application and approval.

**Code availability** According to GDPR rules, data can be accessed by researchers upon data agreement application and approval.

## Declarations

**Conflict of interest** On behalf of all authors, the corresponding author states that there is no conflict of interest.

**Ethics approval** The Scientific Ethical Committee concluded upon approval of The VIA 7 Study that no approval of The Danish High Risk and Resilience Study was needed from their side according to Danish research legislation. The extraction of data concerning eligible participants was approved by The Danish Health Data Authority (approval number FSEID-00003828) and by Statistics Denmark (DST ID 707519). The Danish Data Protection Agency also approved the study (approval number 2007–58-0015), as did the Capital Region Authorities for Health Research (2012–58-0004). All human studies have been approved by the appropriate committees including the ethical committee which concluded that no approval was needed and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

**Consent to participate** All participants gave their informed consent prior to their inclusion in The VIA 7 Study. Parents consented on behalf of their children according to Danish legislation. For register-based anonymized data, no consent is needed according to Danish legislation upon the obtained approvals.

**Consent for publication** All participants in The VIA 7 Study were informed that data would be published without disclosing the identity of the subjects and consented to participate upon this information. For register-based anonymized data, no consent is needed according to Danish legislation upon the obtained approvals.

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## Authors and Affiliations

**Mette Falkenberg Krantz[1,2,4] · Carsten Hjorthøj[1,4,10] · Ditte Ellersgaard[1,4] · Nicoline Hemager[1,2,4] · Camilla Christiani[1,2,4] · Katrine Søborg Spang[3,4] · Birgitte Klee Burton[3] · Maja Gregersen[1,2,4] · Anne Søndergaard[1,2,4] · Aja Greve[4,5,7] · Jessica Ohland[1,4] · Preben Bo Mortensen[4,9] · Kerstin Jessica Plessen[1,4,8] · Vibeke Bliksted[4,5,7] · Jens Richardt Møllegaard Jepsen[1,3,4,6] · Anne A. E. Thorup[1,2,3,4] · Ole Mors[4,5,7] · Merete Nordentoft[1,2,4]**

1 CORE- Copenhagen Research Center for Mental Health, Mental Health Center Copenhagen, The Danish High Risk and Resilience Study VIA 7 and VIA 11, Capital Region of Denmark, Copenhagen University Hospital, Gentofte Hospitalsvej 15, opg. 15, 1. Sal., 2900 Hellerup, Denmark

2 Faculty of Health and Medical Sciences, Institute of Clinical Medicine, University of Copenhagen, Blegdamsvej 3B, 2200 Copenhagen, Denmark

3 Research Unit at Child and Adolescent Mental Health Center Copenhagen, Gentofte Hospitalsvej 3A, opg. 3A, 1. sal, 2900 Hellerup, Denmark

4 iPSYCH -The Lundbeck Foundation Initiative for Integrative Psychiatric Research, Fuglesangs Allé 26, Aarhus N, 8210 Arhus, Denmark

5 The Psychosis Research Unit, Aarhus University Hospital, Psychiatry, Palle Juul-Jensens Boulevard 175, Aarhus N, 8200 Arhus, Denmark

6 Mental Health Services, Capital Region of Denmark, Center for Clinical Intervention and Neuropsychiatric Schizophrenia Research, Mental Health Center Glostrup, Nordstjernevej 41, 2600 Glostrup, Denmark

7 Department of Clinical Medicine, Faculty of Health and Medical Services, Aarhus University, Palle Juul-Jensens Boulevard 82, Aarhus N, 8200 Arhus, Denmark

8 Division of Child and Adolescent Psychiatry, Department of Psychiatry, Lausanne University Hospital, Avenue d'Echallens 9, 1004 Lausanne, Switzerland

9 Department of Economics and Business Economics, National Centre for Register-Based Research, Aarhus University, Fuglesangs Allé 26, Bygning R2640-R2641, Aarhus V, 8210 Arhus, Denmark

10 Department of Public Health, Section of Epidemiology, University of Copenhagen, Copenhagen, Denmark