The role of genetic liability in the association of urbanicity at birth and during upbringing with schizophrenia in Denmark

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Abstract

Background: The association of greater urbanicity at birth and during upbringing with increased risk of schizophrenia remains unexplained. Studies have raised the possibility that the association is driven by familial selective factors such as genetic liability. We used a population-based nested case-control study to assess whether polygenic risk score (PRS) for schizophrenia was associated with urbanicity at birth and at age 15, as well as to assess whether PRS and parental history of mental disorder together explained the association between urbanicity and schizophrenia.

Methods: Data were drawn from Danish population registries. Cases (n=1,692) who were born since 1981 and diagnosed with schizophrenia between 1994 and 2009 were matched to controls (n=1,724) with the same sex and birthdate. Genome-wide data were obtained from the Danish Neonatal Screening Biobank and PRSs were calculated based on results of a separate, large meta-analysis.

Results: Those with higher PRS were more likely reside in the capital compared to rural areas at age 15 (OR=1.19, 95%CI=1.00-1.41), but not at birth (OR=1.09, 95%CI=0.94-1.26). Adjustment for PRS produced almost no change in the excess risk of schizophrenia associated with urbanicity at birth, but slightly attenuated that of urban residence at age 15. The association between urbanicity at birth and schizophrenia remained after adjustment for PRS and parental history together (p=.016), but that for urbanicity at age 15 was fully attenuated (p=.148).

Conclusions: Genetic liability may be more influential in the association between urban upbringing and schizophrenia than in the association with urbanicity at birth.

Introduction

      The association between urbanicity and schizophrenia is long-established (March *et al.*, 2008). Initial findings of greater first admission rates for schizophrenia in urban centers (Faris and Dunham, 1939) were subject to debate as to whether they reflected causal effects of urban residence on mental health or resulted from selection of ill or prodromal persons into more urban areas (Eaton, 1974, Freeman, 1994, Lapouse *et al.*, 1956, Pedersen, 2015). Subsequently, a number of studies found that risk for schizophrenia is greater among those born or raised in more urban areas (Lewis *et al.*, 1992, Marcelis *et al.*, 1998, Mortensen *et al.*, 1999, Pedersen and Mortensen, 2001a). Some reported that risk increased with the degree of urbanization of the place of birth or upbringing (Lewis *et al.*, 1992, Pedersen and Mortensen, 2001b), and Pedersen and Mortensen (2001) reported a dose-response relationship between the duration of urban residence during upbringing and schizophrenia risk in Denmark (Pedersen and Mortensen, 2001a). These associations cannot be readily explained by selection of individuals into urban areas because individuals do not generally choose where they are born or raised. In addition, previous studies have shown that the finding persists after adjustment for family history of schizophrenia and other mental disorders, suggesting that they are not simply artefacts of selection of ill parents into more urban areas (Pedersen and Mortensen, 2001b). Although a few studies have reported discrepant findings (Suvisaari *et al.*, 2000), evidence for this risk factor is generally regarded as strong, and is often invoked to illustrate the importance of the social environment in the etiology of schizophrenia (van Os *et al.*, 2010, van Os *et al.*, 2005).

      A number of potential explanations for the urbanicity association have been investigated, including exposure to infections, environmental toxins, obstetric complications, vitamin D deficiency, cannabis, social processes, and stress (Kelly *et al.*, 2010, Padhy *et al.*, 2014). Unfortunately, explanations have not been clearly identified, as results for many candidate mechanisms are mixed (McGrath and Scott, 2006). One alternative explanation is that the association is induced by familial factors that increase both schizophrenia risk and the probability that a person will be born or raised in an urban area (Pedersen and Mortensen, 2006b). This possibility is supported by two findings. First, using information from Danish registries, Pedersen and

Mortensen (2006) found that the place of birth of an individual's nearest oldest sibling was associated with schizophrenia above and beyond the individual's own place of birth or upbringing (Pedersen and Mortensen, 2006a). For example, among individuals brought up in rural areas, those whose older sibling was born in the capital had about 1.6 times the risk of schizophrenia as those whose older sibling was born in a rural area (Pedersen and Mortensen, 2006a). Second, a recent Swedish register-based study found that the association between population density during upbringing and schizophrenia was attenuated after accounting for unobserved familial factors within extended and nuclear families (Sariaslan *et al.*, 2015). These findings are not completely incompatible with a causal effect of urbanicity; for example, they could be explained by exposures that accumulate in the family prior to an individual's birth (Pedersen and Mortensen, 2006b). However, they are also compatible with a scenario in which the association is induced by another familial factor, such as genetic susceptibility. There is evidence for genetic effects on features of residential location during adulthood, such as urbanicity and deprivation (Sariaslan *et al.*, 2016, Whitfield *et al.*, 2005). If some genes that increase schizophrenia risk also predispose towards living (and raising children) in more urban locations, for example by influencing personality characteristics (Jokela *et al.*, 2008), or if the chances of reproduction among those with genetic risk are greater in more urban areas, a spurious association between urbanicity and schizophrenia could result (Jablensky and Kalaydjieva, 2003). Controlling for family history would not entirely remove this influence because many people with schizophrenia do not have an affected first degree relative and family history captures only the end of a continuum of genetic risk (Yang *et al.*, 2010). To our knowledge, no studies have assessed whether differences in genetic risk might explain the associations of urbanicity at birth and during upbringing with schizophrenia using measures of genetic liability other than family history. Here, we measure genetic susceptibility using polygenic risk scores for schizophrenia, which provide individual-level continuous indices of genetic risk, in a population-based nested case-control study in Denmark.

Our aims were to (1) estimate the association between polygenic risk score and urbanicity to assess whether those born and raised in more urban areas have greater genetic susceptibility to schizophrenia; and

(2) assess whether the associations of urban birth and upbringing with schizophrenia are explained by differences in genetic risk.

Method

Study population

Danish population registry data were used to create a population-based nested case-control study. Three population registries were linked using a unique personal identifier assigned to all Danish residents: the Danish Civil Registration System (Pedersen *et al.*, 2006), the Danish Neonatal Screening Biobank (Norgaard-Pedersen and Hougaard, 2007), and the Danish Psychiatric Central Research Register (Mors *et al.*, 2011). The Civil Registration System was established in 1968 and contains dates of birth and death, place of birth and residence, and links to parents and siblings Danish residents are required to notify the government of address changes within five days; in Denmark it is unlikely that this mandatory information is not reported (Pedersen *et al.*, 2006). The Neonatal Screening Biobank contains dried blood spot samples collected at birth from nearly all newborns born in Denmark since 1981. The Psychiatric Central Register contains all inpatient psychiatric diagnoses since 1969 and outpatient and emergency room visits since 1994. Diagnoses are those made by the treating clinician and are recorded as ICD-8 and ICD-10 codes. Denmark has free, universal healthcare coverage and no private psychiatric hospitals, making it extremely likely that severe mental disorder is captured in the registry. The study was approved by the Danish Data Protection Agency and the Danish Scientific Ethics Committee.

The study population included all singleton births from 1981 through 2000. This population was linked to the Psychiatric Central Register to identify incident cases of ICD-10 F20 schizophrenia first assigned from 1994 through September 2009. Cases were each matched to one randomly selected control with the same sex and birthdate who had not yet been diagnosed with schizophrenia at the time of the case's diagnosis. DNA was extracted from the bloodspots, whole-genome amplified (in triplicate using the QiagenREPLI-g mini kit and the 3 separate reactions were pooled), and genotyped with Illumina Human 610-Quad BeadChip array or Illumina

Infinium CoreExome beadchip (Agerbo *et al.*, 2012, Meier *et al.*, 2015). Details of genotyping and quality control have been published (Agerbo *et al.*, 2012, Agerbo *et al.*, 2015, Borglum *et al.*, 2014, Meier *et al.*, 2015). Related individuals, outliers (> +/- 4 sd) with respect to the first 10 principal components, and those whose sex in the Civil Registration System was inconsistent with genotype were removed, leaving 1,692 cases and 1,724 controls forming 1,549 complete matched pairs.

Polygenic Risk Score estimation

A meta-analysis was conducted of all Psychiatric Genetics Consortium samples (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014), excluding the Danish sample, yielding a training sample of 34,600 cases and 45,968 controls. Single Nucleotide Polymorphisms (SNPs) were retained if their minor allele frequency was >= 10% and imputation information score >= 0.9 in both the training and target samples. Indels and SNPs in the extended MHC region, except for rs7746199, were excluded. Missing SNPs were imputed using the 1000 Genomes Project reference panel (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014). Approximately 100,000 SNPs were selected from among those not in linkage disequilibrium (R2 values <= .1 in 500kb windows), preferentially retaining those that were most associated in any region. PRSs were calculated in the Danish sample using a p-value cutoff of <.05 following previous work (Agerbo *et al.*, 2015, Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014, Wray *et al.*, 2014). A PRS is a weighted sum of schizophrenia risk alleles, where the weights are the log odd ratios of disorder from the training sample. Higher PRS is associated with an increased risk of schizophrenia (Agerbo *et al.*, 2015).

Urbanicity

We considered urbanicity at two time points: birth and age 15. Urbanicity at birth was measured using the mother's address on each individual's birthdate. Urbanicity at age 15 was used as a proxy for urbanicity during upbringing and was measured according to the individual's address on his/her 15th birthday. Urbanicity

was categorized by municipality into five levels, in keeping with prior studies: capital (Copenhagen), capital suburb, provincial city (city with >100,000 residents), provincial town (city with >10,000 residents), and rural areas. Those born or living in rural areas were used as reference groups. For analyses of urbanicity at age 15 we omitted those with a matching (onset) date before age 15, leaving 1,620 controls, 1,595 cases, and 1,456 complete pairs. These analyses also include an extra urbanicity level to accommodate those who lived in Greenland or abroad at age 15.

Parental characteristics

History of mental disorder in one or both parents before the matching date was gathered from the psychiatric registry and diagnoses were categorized hierarchically as follows: broad schizophrenia or bipolar disorder (ICD-10 F20-F29, F30-F31, or corresponding ICD-8 diagnoses (Pedersen *et al.*, 2014)), another mental disorder (another ICD-10 F diagnosis or corresponding ICD-8 diagnosis), and none. Paternal age at the time of each individual's birth was gathered from the CRS and categorized as follows: <=20, 21-25, 26-30, 31-35, 36-40, >40, and missing (due to a missing paternal link in the register, n=42). Parental place of birth was obtained from the civil registry and categorized as: both parents born in Denmark, only one parent born in Denmark, and both parents born abroad, in Greenland, or unknown.

Analysis

Conditional logistic regression among the matched pairs was used to estimate incidence rate ratios (IRRs) of schizophrenia and 95% confidence intervals (CIs). Matched analyses adjust for age, sex, and date of birth by design. The mean PRS for each level of urban birth and residence was estimated in the entire sample, adjusted for the first 10 principal components as well as age, sex, and year of birth. Associations between PRS and being born or residing in an urban vs. a rural area were estimated using logistic regression in the entire sample and adjusted for the first 10 principal components and age, sex, and year of birth (Model 1), as well as

other covariates (Models 2 and 3). PRSs were standardized and adjusted for ancestry using the first 10 principal components. Analyses were conducted using SAS version 9.4 (SAS Institute, Carey, NC).

Results

The sample consisted of 1,692 schizophrenia cases who were born in Denmark between 1981 and 2000, and 1,724 controls matched on age, sex, and date of birth. Characteristics of the 1,549 complete matched pairs are displayed in Table 1. PRS, urbanicity at birth, residence in the capital at age 15, parental psychiatric history, parental place of birth, and paternal age were associated with incidence of schizophrenia, similar to prior studies of the entire Danish population (Cantor-Graae and Pedersen, 2007, Mortensen *et al.*, 1999, Pedersen and Mortensen, 2001a, Petersen *et al.*, 2011). Details of the association between the PRS and schizophrenia in a subset of this cohort have been published previously (Agerbo *et al.*, 2015).

Figure 1 displays mean PRS, adjusted for ancestry, age, sex, and year of birth, according to urbanicity at birth and at age 15. PRS was highest among those born in the capital, decreased with decreasing urbanicity, and was lowest among those born in rural areas. The mean PRSs for each level of urbanicity at age 15 were similar to those for urbanicity at birth.

Table 2 shows the associations of PRS and parental history with being born or residing (at age 15) in the capital compared to a rural area, under different model adjustments. Regarding place of birth, each standard deviation increase in the PRS was associated with slightly greater odds of being born in the capital compared to a rural area, although estimates were not significantly different from unity (Table 2, top). Regarding place of upbringing, each standard deviation increase in PRS was associated with a 1.24-fold (95%CI=1.05-1.47) increase in the odds of residing in the capital compared to a rural area at age 15. This estimate changed only slightly after adjustment for parental history of mental disorder (Model 2 OR=1.20, 95%CI=1.02-1.42) and barely changed after further adjustment for paternal age and parental place of birth (Model 3 OR=1.19, 95%CI=1.00-1.41).

Versions of Figure 1 and Table 2 calculated among cases and controls separately are provided in the Supplement. However, these results may possibly be influenced by collider-stratification bias (Cole *et al.*, 2010).

Associations between urbanicity and schizophrenia under different adjustments are displayed in Table 3. The first column (Model 1) displays associations adjusted for age, sex, and date of birth by the matched design, as in Table 1. Compared to birth in rural areas, birth at higher levels of urbanicity was associated with greater risk of schizophrenia, with the exception of birth in provincial cities. The greatest risk was for birth in the capital (IRR=1.67, 95%CI=1.31-2.15). Residence in the capital at age 15 was also associated with greater risk of schizophrenia compared to residence in rural areas (IRR=1.58, 95%CI=1.20-2.09). Adjustment for PRS (Model 2) resulted in almost no change in the IRRs for urban birth. This adjustment produced slight changes to the estimates for urban residence at age 15, although residence in the capital was still significantly associated with schizophrenia (IRR=1.47, 95%CI=1.10-1.97). The overall associations between urbanicity and schizophrenia were still present under this adjustment (birth p=.001; age 15 p=.037). Further adjustment for parental history of mental disorders (Model 3) resulted in change in a number of estimates. Estimates for birth in the capital (IRR=1.54, 95%CI=1.18-2.02) and capital suburb (IRR=1.25, 95%CI=0.99-1.59) were appreciably attenuated, the latter to non-significance. However, the overall association for urbanicity at birth was still present (p=.016). The estimate for residing in the capital at age 15 was attenuated to non-significance (IRR=1.32, 95%CI=0.97-1.78), as was the overall association between urbanicity at age 15 and schizophrenia (p=.148). In the final adjustment (Model 4), which included paternal age and parental place of birth, the overall association between urbanicity at birth and schizophrenia remained (p=.028). Only birth in the capital (IRR=1.51, 95%CI=1.16-1.98) and provincial towns (IRR=1.26, 95%CI=1.03-1.54) were associated with schizophrenia. Urbanicity at age 15 was not associated with schizophrenia (p=.151). There were no statistical interactions between PRS and urbanicity at birth (p=.208) or age 15 (p=.140).

Discussion

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We found that genetic liability to schizophrenia, represented by the PRS, was associated with urbanicity during upbringing. Increasing PRS was associated with greater odds of residence in the capital at age 15 compared to a rural area and adjustment for PRS and parental history of mental disorder together fully explained the association between urbanicity at age 15 and schizophrenia. On the other hand, PRS was not significantly associated with urban vs. rural birth, and urbanicity at birth was significantly associated with schizophrenia after both PRS and parental history were adjusted for. To our knowledge, this is the first study to use a polygenic measure to assess the role of genetic liability in explaining differences in schizophrenia risk according to urbanicity at birth and during upbringing.

The association we found between the PRS for schizophrenia and urbanicity at age 15 may be interpreted in the context of gene-environment correlation. Mechanisms that may give rise to gene-environment correlation include a) passive, in which a child "inherits" both gene and environment; b) evocative, in which environment is evoked by a person's genetically influenced behaviors or traits; and c) selective, in which a person's genetically influenced traits cause him/her to seek out certain environments (Jaffee and Price, 2007). Both selective and passive mechanisms are relevant to the current study. Selective gene-environment correlation could occur if those with more schizophrenia risk alleles are more likely to seek out or remain in more urban areas. While individuals do not generally choose where they are raised, selection by parents could occur on the basis of personality traits, preferences, or in response to behavioral or health-related characteristics of the child. Selection by parents could give rise to passive gene-environment correlation, where individuals residing in more urban areas are more likely to inherit schizophrenia risk alleles. A recent Swedish study provides support for this notion by showing that PRS for schizophrenia was associated with living in deprived neighborhoods in mid-late adulthood among a population-based twin sample (Sariaslan *et al.*, 2016). Gene-environment correlations may also arise through evolutionary processes such as genetic drift and selection (Jaffee and Price, 2007).

Prior studies have suggested that the association between urbanicity at birth and schizophrenia has a familial basis (Pedersen and Mortensen, 2006a, Sariaslan *et al.*, 2015). That this signifies familial selection,

however, cannot be demonstrated without directly measuring the putative selective factor(s). Here we attempted to measure genetically-influenced selective factors using the schizophrenia PRS in combination with parental history. Together they appeared to explain the association between schizophrenia with urbanicity at age 15, but did not appear to explain the association between schizophrenia and urbanicity at birth. Therefore, it is possible that selective factors are more influential at later ages than they are at birth. While our results require replication, they suggest that it may be premature to conclude that the association between urbanicity and schizophrenia is entirely due to selection (Sariaslan *et al.*, 2015). A number of suspected mechanisms and constituent exposures of urban birth may themselves be familial, such as substance use (Kendler *et al.*, 2000), HPA-axis response (Federenko *et al.*, 2004), and aspects of immune function (Roederer *et al.*, 2015). Continued research including direct measurement of hypothesized mechanisms that are compatible with the familial basis for the association may be warranted (Pedersen and Mortensen, 2006b).

A small number of prior studies have investigated PRS for schizophrenia in relation to other established risk factors. Our findings are consistent with those of Sariaslan et al., who found that PRS for schizophrenia, calculated among a population-based twin sample not selected for mental disorder, predicted living in deprived neighborhoods in adulthood and that the association between schizophrenia and neighborhood deprivation in adulthood was explained by shared genetic influences (Sariaslan *et al.*, 2016), although other interpretations of their results have been put forth (Gage, (In Press)). A prior Danish study of schizophrenia PRS in relation to socioeconomic status found no evidence that PRS explained the association between parental socioeconomic status at birth and schizophrenia (Agerbo *et al.*, 2015). Power et al. reported that schizophrenia PRS was associated with ever vs. never cannabis use and quantity of use in adult twins, although French et al. did not find associations between PRS and cannabis use in 3 adolescent and youth samples (French *et al.*, 2015, Power *et al.*, 2014). Mehta et al. reported a U-shaped association between schizophrenia PRS and age at first childbirth among women, consistent with the U-shaped association between maternal age and risk of schizophrenia in offspring (Mehta *et al.*, 2016). Finally, a prior study using the current

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dataset indicated no association between schizophrenia PRS and risk of infection among controls (Benros *et al.*, 2016).

Strengths of this study include the nested case-control design, which estimates incidence in a nation-wide population-based cohort. Urbanicity was measured prospectively and independently of the outcome, without relying on self-reports or recall. The psychiatric registry provides national coverage of psychiatric diagnoses, enabling us to include information on parental history of psychiatric disorder in addition to PRS. However, this study also has a number of limitations. Although the discovery sample used in this study was large (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014), PRSs for schizophrenia tend to have low individual predictive ability (International Schizophrenia *et al.*, 2009), and they capture only proportions of variance in a trait due to common SNPs (Wray *et al.*, 2014). We cannot rule out that use of a more optimal measure of genetic liability could have fully explained the urbanicity-schizophrenia associations. However, we combined PRS with parental history information rather than relying on PRS alone. Because the Neonatal Screening Biobank started in 1981, the cohort members are relatively young and have not yet completely passed through the age period of heightened risk for schizophrenia, meaning that our findings may only apply to those with onset in young adulthood. The slightly smaller association between urbanicity and schizophrenia in this cohort compared to older cohorts may reduce the applicability of our findings to earlier cohorts. The use of a slightly smaller sample for investigation of urbanicity at age 15 may preclude direct comparability with the investigation of urbanicity at birth. Because the outcome in Table 2 is not rare, the ORs overestimate the corresponding relative risk. The psychiatric registry contains diagnoses given by treating clinicians, although studies have indicated that schizophrenia diagnoses are valid (Jakobsen *et al.*, 2008, Uggerby *et al.*, 2013). Finally, this study was conducted among a specific population and may not generalize to other settings.

We assessed the role of genetic liability to schizophrenia, indexed by both polygenic risk score and parental history of mental disorder, in the association of urban birth and upbringing with schizophrenia risk. We found some evidence consistent with a potential role of selective migration in the association between

urbanicity and schizophrenia, especially with respect to urbanicity during upbringing. However, our results

failed to support the idea that genetic liability entirely explains the excess risk associated with urbanicity at

birth. Research is needed to identify the mechanisms or constituents that comprise this ubiquitous exposure.

Conflict of Interest: None.

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.

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Figure legends

Figure 1: Mean polygenic risk score for schizophrenia, according to urbanicity at birth and at age 15, among

3,416 schizophrenia cases and controls. Polygenic risk score adjusted for the first 10 principal components as

well as age, sex, and year of birth. Only those whose date of matching (case onset) is after the 15th birthday

and who lived in Denmark at age 15 (n=3,214) are used when considering urbanicity at age 15.

Table 1: Sample characteristics for 1549 incident cases of schizophrenia and 1549 individually age- and sex-matched controls

Characteristic	Cases N (%)		Controls N (%)		Incidence rate ratio[1] IRR (95% CI)	
Sex						
Male	859	(55.46)	859	(55.46)	-	
Female	690	(44.54)	690	(44.54)	-	
Age at matching, *median (IQR)*	20	(3.9)	20	(3.9)	-	
Polygenic risk score[2], *mean (SD)*	0.05	(0.88)	-0.23	(0.84)	1.46	(1.34,1.61)
Parental history of mental disorders						
Schizophrenia or bipolar disorder	107	(6.91)	39	(2.52)	3.23	(2.24,4.77)
Other mental disorders	355	(22.92)	167	(10.78)	2.60	(2.12,3.21)
None	1087	(70.17)	1343	(86.70)	1.00	(ref)
Urbanicity of place of birth[3]						
Capital (Copenhagen)	218	(14.07)	163	(10.52)	1.67	(1.31,2.15)
Suburb of the capital	249	(16.07)	221	(14.27)	1.38	(1.10,1.73)
Provincial cities	174	(11.23)	180	(11.62)	1.18	(0.93,1.50)
Provincial towns	436	(28.15)	414	(26.73)	1.28	(1.06,1.54)
Rural areas	472	(30.47)	571	(36.86)	1.00	(ref)
Urbanicity of residence at age 15[4]						
Capital (Copenhagen)	148	(10.16)	103	(7.07)	1.58	(1.20,2.09)
Suburb of the capital	216	(14.84)	220	(15.11)	1.10	(0.88,1.38)
Provincial cities	143	(9.82)	147	(10.10)	1.08	(0.84,1.40)
Provincial towns	422	(28.98)	392	(26.92)	1.20	(1.00,1.44)
Rural areas	523	(35.92)	584	(40.11)	1.00	(ref)
Greenland or other countries	4	(0.28)	10	(0.69)	0.47	(0.13,1.42)
Parental place of birth						
Both parents born in Denmark	1355	(87.48)	1431	(92.38)	1.00	(ref)
One parent born in Denmark	154	(9.94)	90	(5.81)	1.83	(1.39,2.42)
Other[5]	40	(2.58)	28	(1.81)	1.47	(0.91,2.43)
Paternal age at childbirth						
20 years or younger	53	(3.42)	44	(2.84)	1.36	(0.90,2.07)
21-25 years	305	(19.69)	260	(16.79)	1.32	(1.07,1.62)
26-30 years	520	(33.57)	580	(37.44)	1.00	(ref)
31-35 years	377	(24.34)	413	(26.66)	1.03	(0.85,1.23)
36-40 years	186	(12.01)	168	(10.85)	1.23	(0.97,1.56)
41 years or older	84	(5.42)	72	(4.65)	1.34	(0.95,1.88)
Missing	24	(1.55)	12	(0.77)	2.30	(1.16,4.82)

[1] IRRs are adjusted for age, sex, and date of birth by design
[2] Normalized to the sample
[3] Provincial cities = municipalities having a town with more than 100,000 inhabitants; provincial towns= municipalities having a town with between 10,000 and 100,000 inhabitants; rural areas= other municipalities in Denmark (largest town has less than 10,000 inhabitants).
[4] Only pairs whose date of matching (case onset) is after the 15th birthday (1 456 pairs).
[5] Both parents born abroad, in Greenland or missing.

Table 2: Associations of polygenic risk score for schizophrenia with being born in the capital and living in the capital at age 15, compared to being born or living in rural areas

	Place of birth				
	Capital N (%)	Rural areas[1] N (%)	Model 1[2] OR (95% CI)	Model 2[3] OR (95% CI)	Model 3[4] OR (95% CI)
Polygenic risk score[5], *mean (SD)*	0.06 (0.89)	-0.18 (0.85)	1.14 (0.99;1.31)	1.09 (0.95;1.26)	1.09 (0.94;1.26)
Parental history of mental disorders					
Schizophrenia or bipolar disorder	32 (7.75)	34 (2.99)	2.86 (1.72;4.75)	2.79 (1.63;4.75)	2.82 (1.63;4.84)
Other mental disorders	83 (20.10)	171 (15.01)	1.55 (1.15;2.08)	1.55 (1.13;2.11)	1.50 (1.10;2.05)
No diagnosis of mental disorders	298 (72.15)	934 (82.00)	1.00 Ref	1.00 Ref	1.00 Ref
	Place of residence at age 15[6]				
	Capital N (%)	Rural areas[1] N (%)	Model 1 OR (95% CI)	Model 2 OR (95% CI)	Model 3 OR (95% CI)
Polygenic risk score[5], *mean (SD)*	0.13 (0.91)	-0.19 (0.84)	1.24 (1.05;1.47)	1.20 (1.02;1.42)	1.19 (1.00;1.41)
Parental history of mental disorders					
Schizophrenia or bipolar disorder	17 (6.14)	45 (3.71)	1.90 (1.03;3.33)	1.86 (0.98;3.36)	1.89 (1.00;3.44)
Other mental disorders	67 (24.19)	189 (15.57)	1.80 (1.30;2.48)	1.74 (1.24;2.43)	1.73 (1.22;2.43)
No diagnosis of mental disorders	193 (69.68)	980 (80.72)	1.00 Ref	1.00 Ref	1.00 Ref

[1] Municipalities in Denmark where largest town has less than 10,000 inhabitants.

[2] Model 1: Adjusted for sex, age, year of birth, and the first 10 principal components.

[3] Model 2: Model 1, plus polygenic risk score and parental history of mental disorder are adjusted for one another.

[4] Model 3: Model 2 additionally adjusted for parental place of birth and paternal age at childbirth.

[5] Normalized to the sample

[6] Only those aged 15 or older at the time of matching are considered for the analysis with place of residence at age 15.

Table 3: Associations of urbanicity at birth and during upbringing with the risk of schizophrenia under different adjustments.

	Model 1[1] IRR (95% CI)	Model 2[2] IRR (95% CI)	Model 3[3] IRR (95% CI)	Model 4[4] IRR (95% CI)
Urbanicity at birth[5]				
Capital (Copenhagen)	1.67 (1.31,2.15)	1.67 (1.29,2.17)	1.54 (1.18,2.02)	1.51 (1.16,1.98)
Suburb of the capital	1.38 (1.10,1.73)	1.35 (1.08,1.71)	1.25 (0.99,1.59)	1.25 (0.98,1.59)
Provincial cities	1.18 (0.93,1.50)	1.16 (0.91,1.50)	1.17 (0.91,1.52)	1.17 (0.90,1.52)
Provincial towns	1.28 (1.06,1.54)	1.31 (1.08,1.60)	1.28 (1.05,1.56)	1.26 (1.03,1.54)
Rural areas	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Urbanicity at age 15[6]				
Capital (Copenhagen)	1.58 (1.20,2.09)	1.47 (1.10,1.97)	1.32 (0.97,1.78)	1.30 (0.96,1.77)
Suburb of the capital	1.10 (0.88,1.38)	1.07 (0.85,1.36)	1.01 (0.79,1.28)	0.99 (0.78,1.27)
Provincial cities	1.08 (0.84,1.40)	1.02 (0.79,1.33)	0.96 (0.73,1.26)	0.97 (0.73,1.27)
Provincial towns	1.20 (1.00,1.44)	1.19 (0.98,1.43)	1.15 (0.94,1.39)	1.13 (0.93,1.38)
Rural areas	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Greenland or abroad	0.47 (0.13,1.42)	0.38 (0.10,1.20)	0.38 (0.10,1.22)	0.34 (0.09,1.12)

[1] Model 1: Adjusted for sex, age and date of birth by design.
[2] Model 2: Model 1 additionally adjusted for the polygenic risk score and the first 10 principal components
[3] Model 3: Model 2 additionally adjusted for parental history of mental disorders.
[4] Model 4: Model 3 additionally adjusted for parental place of birth and paternal age at childbirth.
[5] Provincial cities = municipalities having a town with more than 100,000 inhabitants; provincial towns= municipalities having a town with between 10,000 and 100,000 inhabitants; rural areas= other municipalities in Denmark (largest town has less than 10,000 inhabitants).
[6] Only includes pairs whose date of matching (case onset) is after the 15th birthday (1,456 pairs).

Figure 1

Figure 1
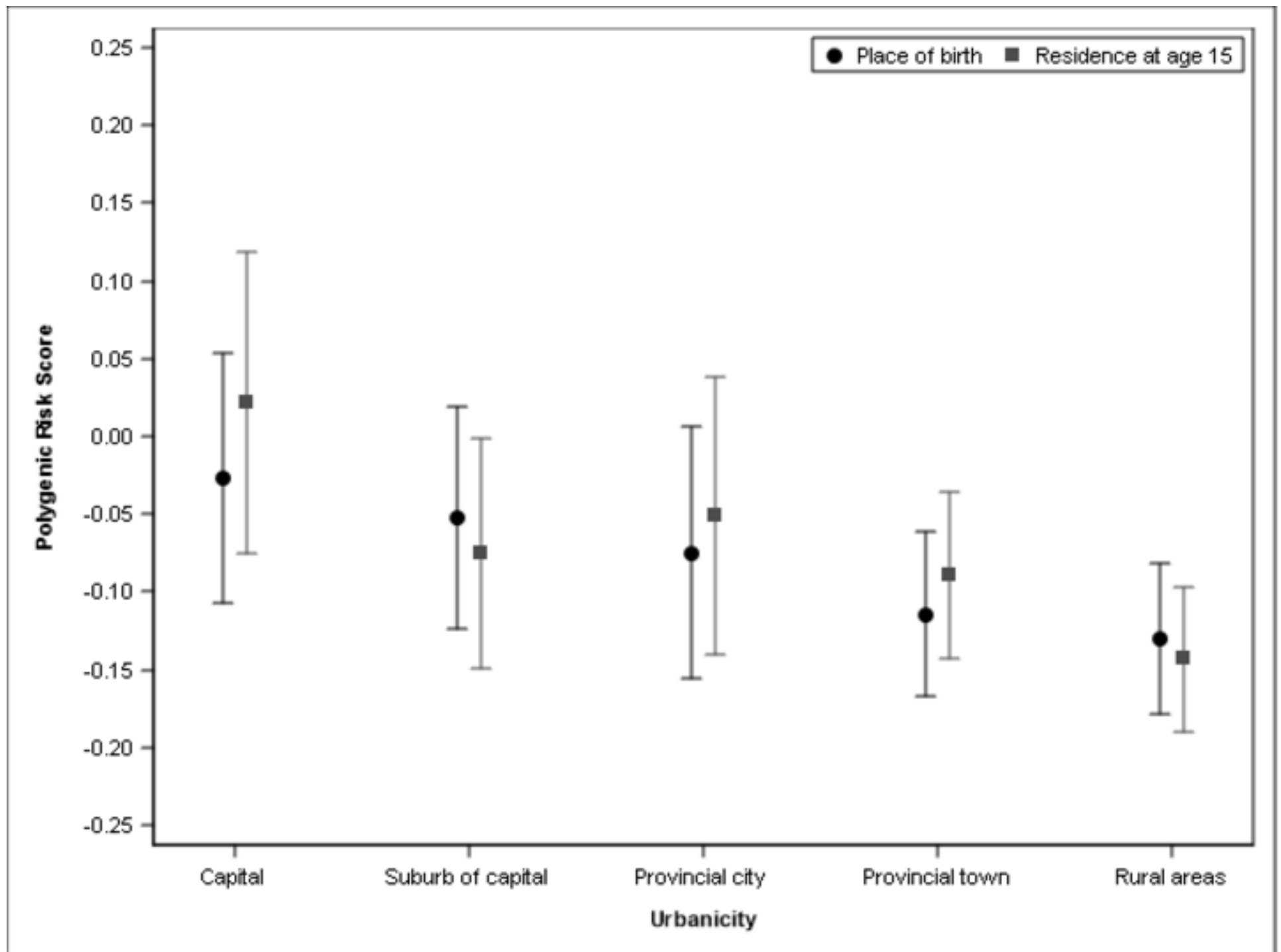
Supplementary material

The role of genetic liability in the association of urbanicity at birth and during upbringing with schizophrenia in Denmark

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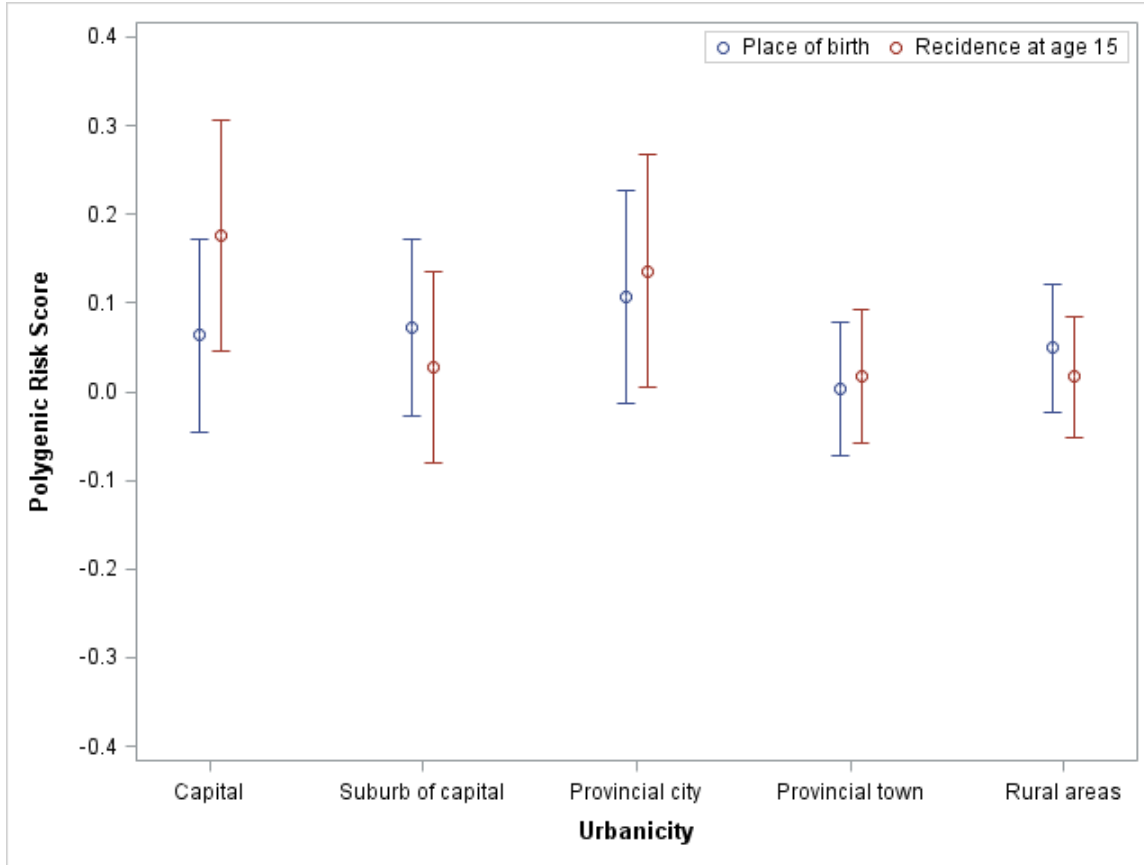
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eTable 1: Associations of polygenic risk score for schizophrenia with being born in the capital and living in the capital at age 15, compared to being born or living in rural areas, among cases.

eFigure 2: Mean polygenic risk score for schizophrenia, according to urbanicity at birth and at age 15, among 1 724 controls.

eTable 2: Associations of polygenic risk score for schizophrenia with being born in the capital and living in the capital at age 15, compared to being born or living in rural areas, among controls.

eFigure 1: Mean polygenic risk score for schizophrenia, according to urbanicity at birth and at age 15, among 1 692 cases.

Note: Polygenic risk score adjusted for the first 10 principal components. Only 1 591 cases whose date of matching (case onset) is after the 15th birthday and who lived in Denmark at age 15 are used when considering urbanicity at age 15.

eTable 1: Associations of polygenic risk score for schizophrenia with being born in the capital and living in the capital at age 15, compared to being born or living in rural areas, among cases

	Place of birth				
	Capital (n=232) N (%)	Rural areas[a] (n=518) N (%)	Model 1 OR (95% CI)	Model 2 OR (95% CI)	Model 3 OR (95% CI)
Polygenic risk score[b], *mean (SD)*	0.14 (0.89)	-0.01 (0.89)	0.98 (0.81,1.19)	0.93 (0.76,1.13)	0.92 (0.75,1.12)
Parental history of mental disorders					
Schizophrenia or bipolar disorder	29 (12.50)	21 (4.05)	3.30 (1.81,6.09)	3.67 (1.95,6.98)	3.58 (1.88,6.89)
Other mental disorders	51 (21.98)	115 (22.20)	1.15 (0.78,1.68)	1.29 (0.86,1.92)	1.25 (0.82,1.87)
No diagnosis of mental disorders	152 (65.52)	382 (73.75)	1.00 Ref	1.00 Ref	1.00 Ref
	Place of residence at age 15*				
	Capital (n=160) N (%)	Rural areas[a] (n=575) N (%)	Model 1 OR (95% CI)	Model 2 OR (95% CI)	Model 3 OR (95% CI)
Polygenic risk score[b], *mean (SD)*	0.28 (0.92)	-0.03 (0.88)	1.24 (0.99,1.54)	1.18 (0.94,1.48)	1.16 (0.92,1.45)
Parental history of mental disorders					
Schizophrenia or bipolar disorder	17 (10.63)	28 (4.87)	2.61 (1.34,4.96)	2.86 (1.42,5.61)	2.91 (1.43,5.75)
Other mental disorders	46 (28.75)	130 (22.61)	1.53 (1.01,2.29)	1.59 (1.03,2.43)	1.62 (1.04,2.48)
No diagnosis of mental disorders	97 (60.63)	417 (72.52)	1.00 Ref	1.00 Ref	1.00 Ref

*Note: Only cases aged 15 or older at the time of matching are considered for the analysis with place of residence at age 15.

Model 1: Adjusted for sex, age, year of birth, and the first 10 principal components.

Model 2: Model 1 additionally adjusted for parental history of mental disorder.

Model 3: Model 2 additionally adjusted for parental place of birth and paternal age at childbirth.

[a] Municipalities in Denmark where largest town has less than 10 000 inhabitants.

[b] Normalized to the sample

eFigure 2: Mean polygenic risk score for schizophrenia, according to urbanicity at birth and at age 15, among 1 724 controls.
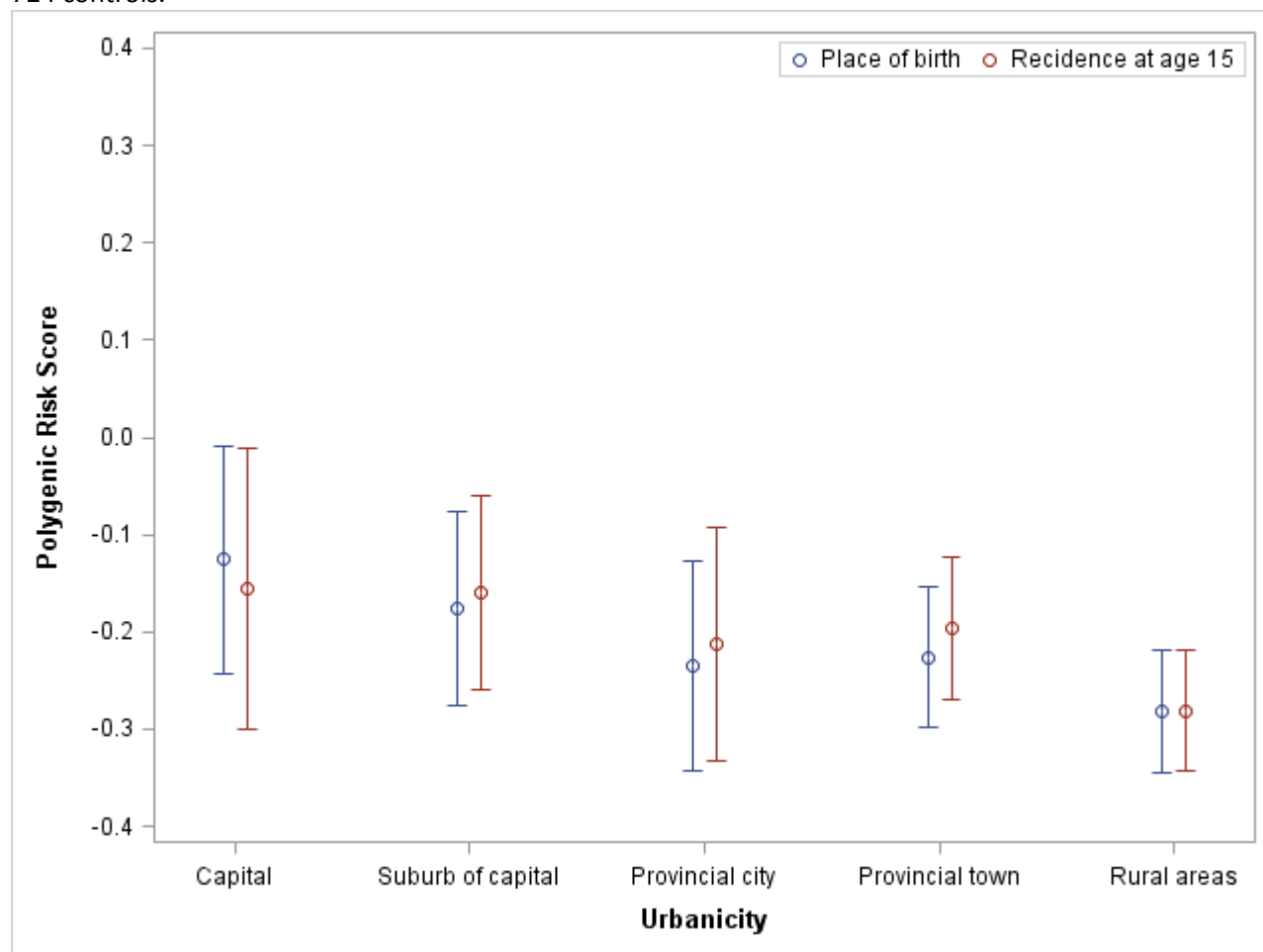
Note: Polygenic risk score adjusted for the first 10 principal components. Only 1 609 controls whose date of matching (case onset) is after the 15th birthday and who lived in Denmark at age 15 are used when considering urbanicity at age 15.

eTable 2: Associations of polygenic risk score for schizophrenia with being born in the capital and living in the capital at age 15, compared to being born or living in rural areas, among controls

	Place of birth				
	Capital (N=181) N (%)	Rural areas[a] (N=621) N (%)	Model 1 OR (95% CI)	Model 2 OR (95% CI)	Model 3 OR (95% CI)
Polygenic risk score[b], *mean (SD)*	-0.05 (0.88)	-0.33 (0.79)	1.29 (1.03,1.61)	1.30 (1.04,1.63)	1.30 (1.04,1.64)
Parental history of mental disorders					
Schizophrenia or bipolar disorder	3 (1.66)	13 (2.09)	0.88 (0.20,2.80)	0.85 (0.19,2.80)	0.99 (0.22,3.30)
Other mental disorders	32 (17.68)	56 (9.02)	2.17 (1.34,3.46)	2.00 (1.19,3.30)	1.93 (1.14,3.22)
No diagnosis of mental disorders	146 (80.66)	552 (88.89)	1.00 Ref	1.00 Ref	1.00 Ref
	Place of residence at age 15*				
	Capital (N=117) N (%)	Rural areas[a] (N=639) N (%)	Model 1 OR (95% CI)	Model 2 OR (95% CI)	Model 3 OR (95% CI)
Polygenic risk score[b], *mean (SD)*	-0.08 (0.86)	-0.33 (0.78)	1.20 (0.92,1.57)	1.20 (0.92,1.57)	1.21 (0.92,1.59)
Parental history of mental disorders					
Mental disorder[c]	21 (17.95)	76 (11.89)	1.58 (0.91,2.65)	1.40 (0.76,2.46)	1.34 (0.72,2.39)
No diagnosis of mental disorders	96 (82.05)	563 (88.11)	1.00 Ref	1.00 Ref	1.00 Ref

*Note: Only controls aged 15 or older at the time of matching are considered for the analysis with place of residence at age 15.

Model 1: Adjusted for sex, age, year of birth, and the first 10 principal components.

Model 2: Model 1 additionally adjusted for parental history of mental disorder.

Model 3: Model 2 additionally adjusted for parental place of birth and paternal age at childbirth.

[a] Municipalities in Denmark where largest town has less than 10 000 inhabitants.

[b] Normalized to the sample

[c] Schizophrenia, bipolar and other psychiatric disorders.