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Childhood exposure to green space – A novel risk-decreasing mechanism for schizophrenia?

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ABSTRACT

Schizophrenia risk has been linked to urbanization, but the underlying mechanism remains unknown. Green space is hypothesized to positively influence mental health and might mediate risk of schizophrenia by mitigating noise and particle pollution exposure, stress relief, or other unknown mechanisms. The objectives for this study were to determine if green space are associated with schizophrenia risk, and if different measures of green space associate differently with risk. We used satellite data from the Landsat program to quantify green space in a new data set for Denmark at 30 × 30 m resolution for the years 1985–2013. The effect of green space at different ages and within different distances from each person's place of residence on schizophrenia risk was estimated using Cox regression on a very large longitudinal population-based sample of the Danish population (943,027 persons). Living at the lowest amount of green space was associated with a 1.52-fold increased risk of developing schizophrenia compared to persons living at the highest level of green space. This association remained after adjusting for known risk factors for schizophrenia: urbanization, age, sex, and socioeconomic status. The strongest protective association was observed during the earliest childhood years and closest to place of residence. This is the first nationwide population-based study to demonstrate a protective association between green space during childhood and schizophrenia risk; suggesting limited green space as a novel environmental risk factor for schizophrenia. This study supports findings from other studies highlighting positive effects of exposure to natural environments for human health.

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1. Introduction

Globally, 450 million people are estimated to suffer from some form of mental illness and the number is expected to increase.(World Health Organization, 2003) Loss of productivity costs national economies billions of dollars, and the economic burden is estimated to 3–4% of GNP for developed countries (World Health Organization, 2003). Increasing rates of mental illnesses have been linked to increasing urbanization and environmental degradation whereas access to green space has been linked to mental health benefits (James et al., 2015; Lee and Maheswaran, 2011; Sandifer et al., 2015; Sugiyama et al., 2008) but the mechanistic link remains unknown.

Since the beginning of the 19th century a number of studies have documented urban rural differences in the occurrence of schizophrenia, generally showing increasing occurrence of schizophrenia in urbanized areas (Faris and Dunham, 1939; Haukka et al., 2001; March et al., 2008; Mortensen et al., 1999; Pedersen and Mortensen, 2001). The underlying mechanism is likely linked to multiple factors, but hypotheses roughly fall within one of two main explanatory categories (DeVerteuil et al., 2007): 1) individuals with schizophrenia migrate into inner-city areas, or 2) disease development is disproportional in inner-cities because of environmental risk factors. Recent studies have shown only partial effects of selective migration, indicating that the urban environment itself is a risk factor (DeVerteuil et al., 2007; Pedersen, 2015; Vassos et al., 2016). A clear difference between urban and rural environments is the amount and types of green space. Green space is known to decrease air and noise pollution (Gidlöf-Gunnarsson and Öhrström, 2007; Nowak et al., 2006) and increase stress restoration (Annerstedt et al., 2013; Beyer et al., 2014; Grahn and Stigsdotter, 2010) – factors that have been linked to mental health and risk of developing schizophrenia

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(Freeman, 1994; Mortensen, 2000). However, with few exceptions, studies investigating which characteristics of green space are important for mental health are lacking (Annerstedt et al., 2012).

Schizophrenia risk could be associated with different measures of green space as well as the spatial distribution of green space – e.g., the quantity or heterogeneity of green space within a given distance from a person's place of residence. We would expect that the quantity is related to availability and density of the surrounding green space, which could be important for e.g. air and noise pollution levels, whereas the heterogeneity is related to variation of the surrounding green space, which could be important for the viewscape and the restorative qualities of the surrounding green space. Expansion of remote sensing programs and increased investments in satellites now provide users with high-resolution earth observation data that can be used to calculate objective measures of green space with broad temporal and spatial coverage (Henke and Petropoulos, 2013; Li and Weng, 2007; Ryznar and Wagner, 2001; Wu et al., 2014). However, satellite data has not been used before in studies of schizophrenia risk.

Assessing the influence of environmental risk factors, such as green space, on schizophrenia requires estimation of incidence rates in representative samples of the general population (Mortensen et al., 1999). Denmark offers a unique opportunity to study the potential association between schizophrenia and green space since place of residence and health of all citizens are recorded longitudinally in national registers. By using data from the Danish national registers we can account for effects of socioeconomic factors and family history allowing more robust estimation of the potential influence of green space on schizophrenia risk.

This is the first nationwide population-based study assessing the potential impact of green space on schizophrenia risk. Most studies of health and green space have focussed on quantity (van den Berg et al., 2015), but it is still unclear how green space is linked to mental health. Studies on landscape preference, restorative environments, and usability of green space suggest that the type and characteristics of green space is also important (Bratman et al., 2015; Carrus et al., 2015; Lee and Maheswaran, 2011). We addressed this question by linking the rich Danish population-based register on health and socioeconomic status with two different individual-level exposure during childhood to quantity and heterogeneity of green space from a new high-resolution data set. We used a measure of vegetation greenness, the normalized difference vegetation index (NDVI), calculated from remotely-sensed satellite images at each place of residence for all Danish residents covering the years 1985–2012. It is unclear at what distance green space potentially affects mental health (e.g. Ekkel and de Vries, 2017; Maas et al., 2009; Nutsford et al., 2013), and whether green space surrounding a persons' residence or green space within the neighbourhood is potentially more important. To test this, we examine the effect of green space at different residential proximities. We hypothesize that more green space (higher mean value of NDVI around the residence) reduces the risk of schizophrenia, and that this effect is strongest closest to the residence. Furthermore, as vulnerability to environmental risk factors may vary with age (Pedersen and Mortensen, 2001), we also examine at what age green space exposure is more important for the risk of schizophrenia.

2. Materials and methods

2.1. Study population

Denmark is a small, relatively homogeneous country with a population of 5.8 mill people and a total area of about 43,000 km^2. Distances within the country are small, with most people living within 25 km of a city with >30,000 inhabitants and a psychiatric hospital. The Danish Civil Registration System was established in 1968. For all Danish citizens, it contains a personal identification number and information on gender, date, place of birth, vital status, and parents' personal identification numbers. The personal identification number is used in all national registers, linking each individual to other national registers, e.g., containing information on health, contextual, and socioeconomic information. The study population included all persons born in Denmark 1985–2003 and who were alive and residing in Denmark at their 10th birthday (943,027 persons).

2.2. Assessment of schizophrenia and schizophrenia spectrum disorder

All individuals from the study population and their parents and siblings, were linked up to the Danish Psychiatric Central Research Register (Mors et al., 2011) to obtain information about schizophrenia. The Register contains information on all admissions to Danish psychiatric in-patient facilities since April 1st, 1969 and since 1995 also all contacts to psychiatric outpatient visit or emergency care. There are no private psychiatric in-patient facilities in Denmark. From 1969 to 1993 the diagnostics system used was the Danish modification of ICD-8 (World Health Organization, 1967) and from 1994 the ICD-10 (World Health Organization, 1992). Individuals were classified with schizophrenia and schizophrenia spectrum disorder if they had been admitted to a psychiatric facility, received outpatient care, or visited a psychiatric emergency care unit with a diagnosis of schizophrenia (ICD10: F20 and equivalent ICD-8 codes) and schizophrenia spectrum disorder (ICD10: F20–F29 and equivalent ICD-8 codes) (Pedersen et al., 2014). The date of onset was defined as the first contact diagnosed with the above-defined diagnosis.

2.3. Quantification of green space

We used two measures of green space covering the period of 1985–2013: 1) mean green space, and 2) spatial heterogeneity of green space. Both measures were calculated from the normalized difference vegetation index (NDVI) obtained from 30 m resolution remote sensing images from the Landsat archive (http://earthexplorer.usgs.gov/, accessed 2 February 2016). NDVI is calculated as the difference between absorbed (red) and reflected (near-infrared) light by vegetation following:

$$\mathrm{NDVI} = \frac{\mathrm{NIR} - \mathrm{RED}}{\mathrm{NIR} + \mathrm{RED}}$$

where NIR is the near-infrared and RED is the red band. NDVI is a commonly used and effective measure of green space (Lo, 1997; Rhew et al., 2011). Low values indicate sparse vegetation and high values indicate dense vegetation.

The Landsat archive contains satellite data of earth acquired by six satellites over >40 years. Over the years, the purpose and spatial focus of the Landsat program has changed, and as a result the availability of the data varies. The Landsat satellites provide images of 4–11 bands at 30–120 m resolution on a 16–18 day revisit cycle. We aimed to obtain images from the growing season in June, July, or August with none to low cloud cover for the entire country each year. The best data coverage comes from the later years, whereas data availability of the earliest years fluctuates. E.g. the satellite images from year 1978–1983 only cover parts of Zealand and the island of Bornholm. Also, due to technical difficulties some years in the time period are only partly covered or not covered at all (see Table S1 for details of each year).

All Landsat images were atmospherically corrected and converted to Top of Atmosphere (TOA) reflectance using ENVI version 5.1 to remove atmospheric effects such as water vapour and the position of the sun. Despite our best efforts to find cloud free images, some images were partly covered by clouds. For images with severe cloud cover (~5–30%), several images were downloaded covering the same area at different dates and merged to obtain a single complete image. Clouds were identified and masked loosely following the approach from Martinuzzi et al., 2007. Clouds on images from Landsat 8 (only for year 2013)

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were identified and masked using the QA band. Manual assessment revealed acceptable match between the cloud masks and clouds on images, although with slight imprecisions with unidentified thin clouds (hazes) and small patches of bare soil wrongly identified as clouds. Lastly, all images were processed with histogram matching using the best (low cloud cover and large land area) image for each year, and large water bodies were masked out before calculating NDVI.

NDVI images were mosaicked into a single image for each year with bilinear interpolation. Missing values were interpolated using simple linear interpolation for cells with a minimum of three measurements across all years. NDVI maps for Denmark can be downloaded from https://bios.au.dk/en/about-bioscience/organisation/ecoinformatics-and-biodiversity/data/. Mean and standard deviation of the NDVI values was then calculated for quadratic areas (exposure zones) of 210 × 210 m, 330 × 330 m, 570 × 570 m, and 930 × 930 m (7, 11, 19, and 31 cells respectively) around each address for the years 1985–2013 as measures of quantity and heterogeneity of green space respectively. For each exposure zone, place of residence was located in the centre of the quadrat. Calculating the mean and standard deviation of the NDVI for this large number of addresses was a challenging computational task. Therefore, we performed these computations using efficient algorithms that can process large amounts of geographic data within a reasonable amount of time (Arge et al., 2012).

2.4. Statistical analyses

Cohort members were followed for the development of schizophrenia from their 10th birthday until onset of schizophrenia, death, emigration from Denmark, or 31st December 2013, whichever came first. Incidence rate ratios of schizophrenia were estimated in a time to event analysis using a Cox regression using age as the underlying timescale with separate baselines for each sex (Andersen and Gill, 1982). Mean and standard deviation of NDVI estimated as described in the above section were linked to each cohort member at age 10 with the addresses. The mean and standard deviation of NDVI were fitted both as numeric and categorical deciles in separate models for all four exposure zone sizes. Degree of urbanization was included to determine to what degree the effect of green space is independent from urbanization in general or just mirrors the urban-rural gradient found in previous studies. Urbanization was fitted as a categorical variable with five levels: capital, capital suburb, provincial city, provincial town, or rural area, as described previously (Pedersen, 2015). Year of birth, sex, and parents' education, income, and employment status for each individual were included to control for individual and socioeconomic confounding factors (Danmarks Statistik, 1991). Calendar year of the end of study for each cohort member was treated as a time-dependent variable to account for different hazard rates over time and categorized as 1995–2000, 2001–2005, 2006–2010, and 2011–2013. All other variables were treated as independent of time. Unless stated otherwise, in the results and discussion section, we present results for the broader diagnosis, schizophrenia spectrum disorder, based on NDVI measured within quadratic exposure zones of 210 × 210 m at place of residence at the 10th birthday.

We performed the following sensitivity analyses on the effect of NDVI by fitting additional Cox regressions: assessing (1) the potential modifying effect of urbanization, (2) the potential modifying effect of socioeconomic status estimated as parents' education, income, and employment status, (3) the potential modifying effect of sex, (4) the effect of different exposure zone sizes, (5) the effect of measuring NDVI at different ages from birth to the 10th birthday, and (6) the effect of measuring green space as mean accumulated NDVI from birth to the 10th birthday for each cohort member with at least 10 observations. P-values were based on likelihood ratio tests and 95% confidence intervals were calculated by Wald's test.

All data processing and statistics were performed in R (R Core Team, 2016) using packages data.table, Hmisc, landsat, lubridate, plyr, raster, rgdal, RStoolbox, sp., and survival. The only exception was the TOA conversion, performed using the ENVI software, version 5.1 (Exelis Visual Information Solutions, Boulder, Colorado). Further details of the satellite image processing can be found in Appendix S1.

3. Results

The study population consisted of 943,027 persons all born in Denmark 1985–2003 and living in Denmark at the 10th birthday. Within the study period (from 1985 to 2013) 7609 persons developed schizophrenia spectrum disorder.

NDVI ranged from −0.89 to 0.97 with the lowest values, indicating sparse vegetation, typically in inner city areas and the highest values, indicating dense vegetation (such as forest areas with multiple layers of vegetation), in rural areas, but also in city parks and recreational areas (Fig. 1). Persons residing in the capital lived in areas with lowest green space values and persons residing in rural areas lived with the highest green space values, but with no clear linear correlation with urbanization (Fig. S1). Similarly, persons residing in the capital were exposed to the lowest heterogeneity of green space whereas persons residing in rural areas lived with the highest green space heterogeneity. Together this supports the assumption of less and lower heterogeneity of green space in the inner parts of cities.

The incidence rate ratio (IRR) of schizophrenia spectrum disorder decreased with higher deciles of mean NDVI at age 10 following a dose-response relationship (Fig. 2). Children living in the lowest decile of green space had a 1.52 (95% CI: 1.36, 1.69, $P < 0.000$, Table 1) fold increased risk compared to children living in the highest decile of green space. Likewise, the trend analysis of NDVI fitted numerically showed a 1.42 (95% CI: 1.32–1.52, $P < 0.000$) fold increased risk for children living at the lowest level of green space compared to the highest level of green space. In the following we present trend estimates unless otherwise stated. The effect was lower (IRR: 1.29, 95% CI: 1.20–1.40, $P < 0.000$) when estimates were adjusted for urbanization, but still followed a dose-response relationship. Similarly, the effect was lower when adjusted for socioeconomic factors (IRR: 1.36, 95% CI: 1.26–1.47, $P < 0.000$). The incidence rate ratio of schizophrenia spectrum disorder varied inconsistently with the standard deviation of NDVI, with no indication of a clear relationship between schizophrenia spectrum disorder risk and variability in green space at the place of residence (Fig. 2).

Incidence rate ratio estimates for the four differently sized exposure zones were similar, but with a tendency towards a stronger effect for the smallest zone size (210 m) for NDVI fitted as a trend (Table 2). We observed a stronger association with green space exposure during early childhood for NDVI at modelled separately ages 0 to 10 (Fig. 3). The effect of NDVI interacted weakly with the degree of urbanization, with slightly different risk estimates for each urbanization category (Table S2). However, generally the relationship within each urbanization category was similar to the overall dose-response relationship, with higher green space having a negative association with the incidence rate ratio of schizophrenia spectrum disorder (Fig. S2). Risk estimates were similar for males and females (Table S2). Accumulated NDVI from birth to age 10 was more strongly associated with the incidence rate ratio of schizophrenia spectrum disorder than NDVI at age 10 (IRR: 1.82, 95% CI: 1.67–1.97, $P < 0.000$). Similarly to the results for NDVI at age 10, adjusting for urbanization (IRR: 1.63, 95% CI: 1.50–1.78, $P < 0.000$) and socioeconomic factors (IRR: 1.73, 95% CI: 1.60–1.88, $P < 0.000$) again only slightly decreased the effect of NDVI.

Finally, considering narrowly-defined schizophrenia as the outcome of interest, 3748 persons developed schizophrenia and we found similar associations to green space as for schizophrenia spectrum disorder (presented in Table 1): Persons residing in the lowest level of NDVI had a 1.38 (95% CI: 1.24–1.53, $P < 0.000$) fold increased risk compared to persons residing at the highest level of NDVI. Again, adjusting for urbanization (IRR: 1.31, 95% CI: 1.17–1.46, $P < 0.000$) and socioeconomic factors (IRR: 1.33, 95% CI: 1.20–1.48, $P < 0.000$) again only slightly decreased

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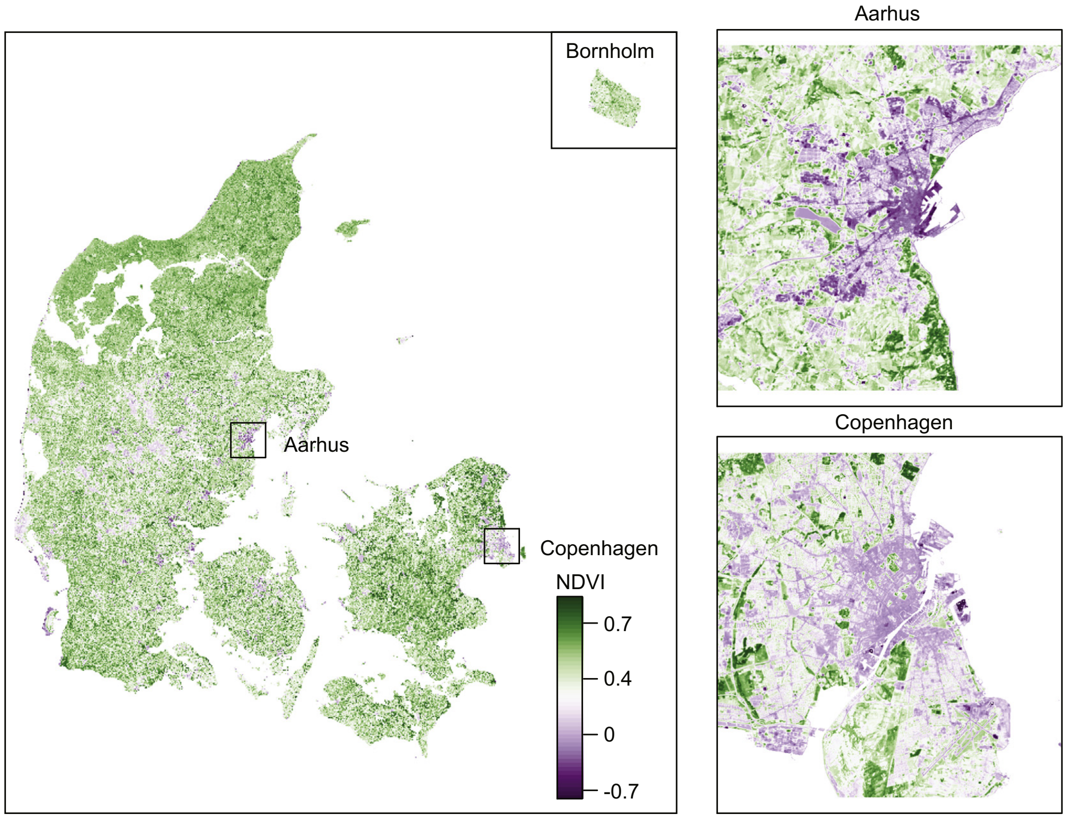

Fig. 1. Mean normalized difference vegetation index (NDVI) for the period 1985–2013 of Denmark and two selected cities. High values of NDVI indicate dense vegetation whereas low values of NDVI indicate sparse vegetation. The zoom-ins show urban differences in NDVI between two cities of the highest (Copenhagen) and medium degree of urbanization (Aarhus).

the effect of NDVI. Finding similar NDVI relations for narrowly defined schizophrenia and schizophrenia spectrum disorder, we refer to them jointly as schizophrenia in the discussion.

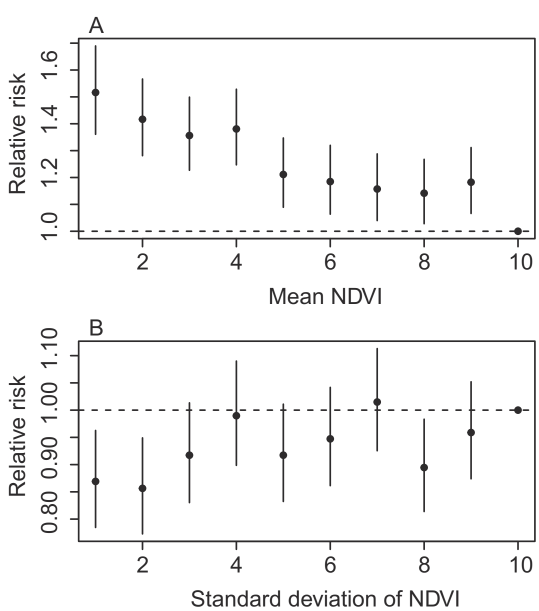

Fig. 2. Incidence rate ratio of schizophrenia spectrum disorder (F20–29) for deciles of A) mean and B) standard deviation of the normalized difference vegetation index (NDVI) at 210 m around place of residence at age 10 for 943,027 persons living in Denmark during the period 1985–2013. Both measures of NDVI were fitted as deciles in classes of ten. Estimates of incidence rate ratio were adjusted for age, year of birth, and sex and plotted with 95% confidence intervals. All estimates are relative to the reference level set to class 10 for both mean and standard deviation of NDVI.

4. Discussion

This is the first nationwide population-based study to investigate the potential effect of green space on schizophrenia risk. We demonstrated a dose-response association between the magnitude of greenspace during childhood and the risk of later developing schizophrenia. This finding was invariant to adjustment for urbanization and sex. Our analysis shows that exposure to more green space during childhood is negatively associated with the risk of schizophrenia, whereas green space heterogeneity, measured as the standard deviation, had no consistent association with the risk of schizophrenia. We found a tendency towards a stronger protective association of green space within the closest distance to a person's residence and results that might indicate that exposure during the earliest years are most strongly associated with the risk of schizophrenia.

We found the effect of green space to be largely independent of urbanization and also robust to controlling for a range of potential confounding factors. This may indicate that green space is a novel environmental risk-reducing factor for schizophrenia development. The potential mechanism behind this association remains unknown, but results from other studies points towards several plausible hypotheses. Air pollution has previously been linked to schizophrenia risk (Attademo et al., 2017; Oudin et al., 2016; Pedersen et al., 2004) and could be moderated by green space. Air pollution is often higher in urban areas, but can be reduced by trees and shrubs (Nowak et al., 2006), which may improve air quality under the right conditions (Escobedo et al., 2011), hence possibly decrease schizophrenia risk. Contact with nature is also thought to enhance immune functioning (Kuo, 2015), which may decrease infections during pregnancy, another proposed risk factor for schizophrenia (Mortensen, 2000). Furthermore, spending time in natural environments has been shown to moderate negative effects on mental health during stressful life events (van den Berg et al., 2010) and decrease chronic stress (Gidlow et al., 2016),

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Table 1
Incidence rate ratio of schizophrenia spectrum disorder (F20–29) according to deciles of green space measured as the normalized difference vegetation index (NDVI).

NDVI	Cases	Unadjusted			Adjusted for urbanization			Adjusted for SES		
		IRR	(95% CI)	P > |z|	IRR	(95% CI)	P > |z|	IRR	(95% CI)	P > |z|
1	674	1.52	(1.36–1.69)	0.000	1.39	(1.25–1.56)	0.000	1.43	(1.28–1.60)	0.000
2	930	1.42	(1.28–1.57)	0.000	1.32	(1.19–1.46)	0.000	1.37	(1.24–1.52)	0.000
3	931	1.36	(1.23–1.50)	0.000	1.31	(1.18–1.44)	0.000	1.33	(1.20–1.47)	0.000
4	824	1.38	(1.25–1.53)	0.000	1.32	(1.19–1.46)	0.000	1.37	(1.23–1.51)	0.000
5	754	1.21	(1.09–1.35)	0.000	1.18	(1.06–1.31)	0.003	1.21	(1.08–1.34)	0.001
6	655	1.18	(1.06–1.32)	0.002	1.18	(1.06–1.31)	0.003	1.18	(1.06–1.31)	0.003
7	665	1.16	(1.04–1.29)	0.007	1.17	(1.05–1.30)	0.004	1.14	(1.03–1.28)	0.014
8	744	1.14	(1.03–1.27)	0.013	1.15	(1.04–1.28)	0.008	1.13	(1.01–1.25)	0.028
9	765	1.18	(1.07–1.31)	0.002	1.17	(1.06–1.30)	0.002	1.17	(1.06–1.30)	0.003
10	668	1	(Ref)	(Ref)	1	(Ref)	(Ref)	1	(Ref)	(Ref)
Summary NDVI Low vs. high		1.42	(1.32–1.52)	0.000	1.29	(1.20–1.40)	0.000	1.36	(1.26–1.47)	0.000

NDVI: normalized difference vegetation index. NDVI was calculated as the mean for a 210 × 210 m quadrat around each individuals' place of residence.
IRR: Incidence rate ratio (IRR). Estimates of IRRs was based on all persons born in Denmark 1985–2003 who lived in Denmark at the 10th birthday (N = 943,027) who was followed for the development of schizophrenia spectrum disorder from 1985 to 2013, during which 7609 developed schizophrenia spectrum disorder. SES: Socioeconomic factors included parents' education, income, and relation to the work market. All estimates of incidence rate ratio were adjusted for age, year of birth, and sex.

which might trigger expression of schizophrenia or affect prenatal health (Corcoran et al., 2002). However, studies are needed to elucidate the potential mechanisms underlying the association between green space and schizophrenia.

Identifying the qualities that link green space and mental health can help identify the drivers responsible for this association. Different land cover types have been shown to influence mental health differently (Alcock et al., 2015) and different aspects of urban green space has been linked to stress restoration (Grahn and Stigsdotter, 2010). Although we found the quantity of green space to be associated with schizophrenia risk in a clear dose-response relationship, the effect of heterogeneity of green space was not similarly clear (Fig. 2). Using the standard deviation as a measure of heterogeneity means that low values simply indicate homogeneous areas of either urban or green space, whereas high values indicate areas with both urban and green space. One might expect higher variation to be linked to improved mental health, as this indicates an environment containing benefits from both urban and green space and a more interesting viewscape and variable environment. However, this was not supported by our results. Other measures, such as land cover or vegetation types, might be more appropriate for evaluating green space variability in relation to mental health. For countries, such as Denmark, with many people residing near the coast, the aquatic environment (blue space) could provide similar mental health benefits as green space (White et al., 2013). Large waterbodies were excluded in our study, but smaller water bodies, which generate negative NDVI values, were included and could to some degree average out positive NDVI values of green areas (Ekkel and de Vries, 2017) and confuse the association with schizophrenia risk. Further work is needed to identify which qualitative aspects of green and blue space provide mental health benefits.

The effect of green space is not only determined by quantity, but could also be distance dependent. Depending on the mechanism, green space could be important at place of residence or as a neighbourhood characteristic. Identifying the distance at which green space has the strongest effect could guide city planning towards healthier city environments. We found a weak tendency for the strongest effect of NDVI at the smallest exposure zone size (Table 2), indicating that green space closer to the place of residence has a stronger association with schizophrenia risk. Aggregated green space indicators that consider percentages or averages of all green space within a given distance have shown consistent and positive associations with health indicators (Ekkel and de Vries, 2017). In contrast to our findings, Nutsford et al., 2013, found stronger effects of green space on mental health at 3 km than 300 m distance, but is consistent with view of vegetation decreasing annoyance from traffic noise at peoples home (Van Renterghem and Botteldooren, 2016). Distance to green space may interact with qualitative characteristics of green space, providing different functions in relation to mental health. The interaction between distance and green space qualities is another issue that deserves further attention. Accumulated green space from birth to age 10 also showed a stronger association with schizophrenia risk than green space exposure at any given age, showing that an accumulated green space measure should be considered if the data is available.

Table 2
Incidence rate ratio of schizophrenia spectrum disorder (F20–29) in relation to green space within different quadrat sizes around place of residence.

NDVI trend quadrat size	IRR	(95% CI)	P > |z|
210 × 210 m (7 × 7 cells)	1.42	(1.32–1.52)	0.000
330 × 330 m (11 × 11 cells)	1.41	(1.31–1.52)	0.000
570 × 570 m (19 × 19 cells)	1.41	(1.31–1.52)	0.000
930 × 930 m (31 × 31 cells)	1.40	(1.30–1.50)	0.000

NDVI, normalized difference vegetation index; IRR, incidence rate ratio; 95% CI, 95% confidence interval. Quadrat size indicates the exposure zones of green space in 30 × 30 m cells centred around place of residence. IRR was estimated with Cox regression for NDVI as numeric deciles. All estimates of incidence rate ratio were adjusted for age, year of birth, and sex.

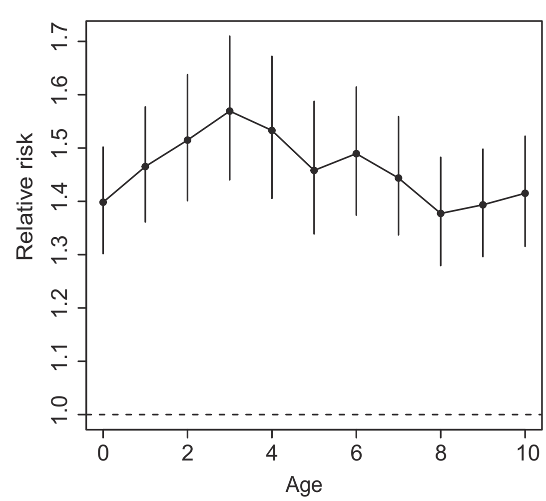

Fig. 3. Age-specific incidence rate ratio of schizophrenia spectrum disorder (F20–29) for ages 0–10 in relation to the mean of the normalized difference vegetation index (NDVI) at 210 m around place of residence for 943,027 persons living in Denmark from 1985 to 2013. Separate cox regressions were fitted for each age with NDVI fitted as deciles. Estimates of incidence rate ratio were adjusted for age, year of birth, and sex and plotted with 95% confidence intervals.

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The risk estimates presented here may be influenced by the study design. The major strengths of this register-based longitudinal study are the nationwide coverage of the Danish population and prospective design with no attrition. Also, reliance on diagnosis of schizophrenia provides are highly reliable in this data set, as it was assessed by professional clinicians (Jakobsen et al., 2005) compared to e.g. self-reported mental health in many survey studies. The latter however might include untreated persons who would be undiagnosed in our data set (Regier et al., 1998). Consequently, the register-based approach should be considered complimentary to survey studies (Pedersen et al., 2014). Treatment of mental illnesses is provided through the government healthcare system in Denmark, and financial factors are less likely to influence the results presented here. Drug use, crime rates, and exposure to infections are also possible confounders that could influence risk estimates (Marcelis et al., 1998; Vassos et al., 2016) but were beyond the scope of this paper. Similar to any other observational study of human health we cannot provide conclusive evidence of causality, whatever the confounders included or however these are modelled (Gray-Donald and Kramer, 1988; Rothman et al., 1998).

A general green space effect should lead to a similar estimated association of green space with schizophrenia spectrum for all urbanization levels, while a variable effect would suggest interaction with other factors linked to urbanicity. The risk estimates differed slightly between urbanization classes (Table S2), but were always close to the overall dose-response relationship, meaning that the effect of green space is largely independent from the effect of urbanicity (Fig. S2). These weak differences could result from selection effects caused by healthier persons choosing to move to greener areas or persons with schizophrenia moving to urban areas (Freeman, 1994; Pedersen, 2015), but other explanations are also possible. Potential selection effects could also be explored further in relation to green space and schizophrenia.

This is the first study to identify an association between green space and schizophrenia. By taking advantage of the large Danish National Registers, satellite imagery, and a novel computational approach we found that being surrounded by more green space at place of residence was associated with decreased schizophrenia risk at a national scale, also after controlling for a broad range of potentially confounding factors such as age, sex, and socioeconomic status. These results point to important new research questions exploring the mechanisms underlying this positive effect of green space in relation to schizophrenia spectrum disorder and schizophrenia risk. Furthermore, our research framework could be expanded to other aspects of mental health or different measures of green space to determine the generality and mechanistic nature of green space effects on mental health. Overall, this research could be used to guide city planning towards green space infrastructure designs to optimally benefit psychological health (Hartig and Kahn, 2016).

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