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Climatic exposures in childhood and the risk of schizophrenia from childhood to early adulthood

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ABSTRACT

Background: Season of birth is a risk factor of schizophrenia, and it is possible that cumulative exposure to climatic factors during childhood affects the risk of schizophrenia. We conducted a cohort study among 365,482 persons born in Finland in 1990–1995 to examine associations of 10-year cumulative exposure to global solar radiation and ambient temperature in childhood with schizophrenia.

Methods: Data on schizophrenia diagnoses and sociodemographic factors from the Finnish population register and health care register were linked to daily meteorological data using residential information. The study population was followed from age 10 until the first schizophrenia diagnosis, death, emigration or December 31, 2017, whichever came first. Hazard ratios (HR) for the risk of schizophrenia were estimated using Cox proportional hazards model.

Results: Compared to the lowest quintile of global solar radiation or ambient temperature, growing up in the second highest quintile (Q4) was associated with greater risk of schizophrenia. These hazard ratios were attenuated after adjustment for parental mental disorder, parental education, parental income, area-level socioeconomic characteristics and urbanicity (HR = 1.29, 95 % CI 1.06–1.58 for radiation; HR = 1.24, 95 % CI, 1.02–1.52 for temperature). Continuous linear terms evaluated in secondary models suggested a greater risk of schizophrenia at greater childhood exposure to global radiation and ambient temperature, but these associations did not remain in fully adjusted models.

Conclusions: We found no consistent evidence that cumulative exposure to sunlight and ambient temperature in childhood is associated with the risk of developing schizophrenia. Studies in other populations residing in different latitudes are needed.

1. Introduction

Season of birth is an established early-life risk factor in schizophrenia, with greater incidence of schizophrenia among people born in winter and early spring (Brown, 2011; Davies et al., 2003; Escott-Price et al., 2019; Hsu et al., 2021; Suvisaari et al., 2001). Studies have also documented seasonality as a proximal risk factor triggering the acute onset or exacerbation of schizophrenia. In the Northern hemisphere, hospital admissions for both first-episode schizophrenia and acute

relapse have been observed to peak in spring and summer (Clarke et al., 1999, 1998; Shiloh et al., 2005; Tian et al., 2006), while studies in the Southern hemisphere suggest a winter peak in first-episode admissions (Davies et al., 2000; Owens and McGorry, 2003). The seasonal patterning suggests that climatic factors may trigger the acute exacerbation of schizophrenia. Several large-scale studies have demonstrated an association between ambient/apparent temperature and hospital admissions for schizophrenia, with mostly high (Lee et al., 2018; Pan et al., 2019; Wang et al., 2018; Yi et al., 2019a), but also cold

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temperatures (Pan et al., 2019; Yi et al., 2019a) associated with more hospitalizations. In addition, greater diurnal temperature variability and temperature change between neighboring days have been associated with a greater risk of psychiatric hospitalization for schizophrenia (Gupta and Murray, 1992; Sung et al., 2011; Yi et al., 2019b; Zhao et al., 2017, 2016). Some evidence exists for a V-shaped association between sunlight and admissions for schizophrenia, with excess admissions occurring during particularly low and high exposure to sunlight (Gu et al., 2019).

Not only may climatic exposures trigger the acute onset or exacerbation of schizophrenia but accumulation of climatic factors may operate on the risk of schizophrenia already at earlier stages of the pathogenesis. In line with the season-of-birth effect, a study in Australian and Dutch mental health registers suggested that long-term perinatal exposure to shorter sunshine duration was associated with higher birth rate of early onset male schizophrenia and earlier age of first schizophrenic episode regardless of sex (McGrath, 2002). Given that numerous postnatal environmental exposures have been implicated in the etiology of schizophrenia (Brown, 2011), it is possible that a cumulative exposure to climatic factors during childhood affects the risk of schizophrenia. However, the association of childhood cumulative climatic exposures and schizophrenia has not been examined.

In the present nationwide register-based study, we combined daily meteorological data with individual-level data from Finnish population-based registers to assess the associations of two climatic exposures in childhood – global solar radiation and ambient temperature – with the onset of schizophrenia from childhood to young adulthood.

2. Methods

2.1. Participants

Since 1964, all residents in Finland have been issued a unique personal identification code which allows individual-level data to be linked across nationwide administrative registers. We used data from Statistics Finland, which included demographic details, updates on the place of residence and vital status; the Care Register for Health Care, which included data on schizophrenia diagnoses and contact with health care; and the Finnish Meteorological Institute, who provided data on the childhood daily climate exposures. Our study population included all individuals born to two Finnish-born parents in Finland between 1990 and 1995, who were alive and living in Finland until their 10th birthday. Ethical approval for the study was received from the Research Ethics Committee of the Finnish Institute for Health and Welfare (decision #10/2016§751). Permissions for the data were obtained from the Finnish Institute for Health and Welfare and Statistics Finland. Researchers had access to pseudonymized data only.

2.2. Measures

2.2.1. Schizophrenia assessment

A person was defined as having schizophrenia if they received schizophrenia diagnosis (ICD-10 code F20) while being admitted to a psychiatric hospital (data available since 1996), while visiting a psychiatric emergency unit (data available since 1996), while receiving outpatient psychiatric care (data available since 2008), or visiting public primary care (data available since 2011). Date of onset was defined as the first day of first contact with the schizophrenia diagnosis. The diagnostic validity of schizophrenia in the Care Register for Health Care has been reported to be good (Mäkikyrö et al., 1998).

2.2.2. Climatic exposures

Meteorological data on climate exposures were obtained from the Finnish Meteorological Institute.

We used daily recordings of global solar radiation (kJ/m^2) and ambient mean temperature ($^{\circ}\text{C}$) in each residential zip code area in

1990–2005 calculated from $10\text{ km} \times 10\text{ km}$ gridded data (Aalto et al., 2016). We linked each individual's residential zip code on each day from birth to their 10th birthday to the meteorological data and calculated average daily exposure to each climatic factor until the 10th birthday.

2.2.3. Covariates

We controlled for several potential confounders – sex, birth year, birth month, history of parental mental disorders, parental socioeconomic characteristics, area-level socioeconomic characteristics and degree of urbanization – with known or hypothesized relationships to the exposures and outcomes (Fett et al., 2019; Hakulinen et al., 2020; Hsu et al., 2021; Mortensen et al., 2010; Sariaslan et al., 2015). Data on the history of parental mental disorders (1 = diagnosis of any mental disorder; 0 = no diagnosis) before the person's 10th birthday were obtained from the Care Register for Health Care. Parental educational attainment (1 = upper secondary education or higher; 0 = no upper secondary education) and total income in quintiles were extracted from the Statistics Finland registers and they were assessed in the year of the person's birth. Degree of urbanization was assessed in the year of the person's 10th birthday on a three-point scale (2 = urban; 1 = semi-urban; 0 = rural) using the urban-rural classification system of the Finnish Environment Institute (SYKE). Two area-level socioeconomic characteristics – proportion of people without upper secondary education or higher and proportion of people unemployed – were calculated based on data of all residents in each municipality in the year of the person's 10th birthday.

2.3. Analyses

The study population was followed from their 10th birthday until the first diagnosis of schizophrenia, date of death, emigration or December 31, 2017, whichever came first. The maximum length of follow-up was thus up to the 27th birthday (for persons born on 1990). Relative risks of schizophrenia associated with the 10-year exposure to climatic factors in childhood were estimated using Cox proportional hazard models. Schoenfeld's residuals were assessed to verify that the proportional hazards assumption was met. Separate models were conducted for global solar radiation and ambient temperature. Quintiles of the 10-year climatic exposures were selected to the primary analysis to assess potential non-linearity. We first assessed the associations adjusting for sex, birth year, birth month, and time-varying calendar year period. Further adjustments were made for history of parental mental disorder, parental education, parental income, and additionally for area-level socioeconomic characteristics and urbanicity. In secondary analyses, we treated the climatic exposures as continuous linear terms. Analyses were performed with Stata version 16.1.

3. Results

The study population included 365,482 persons who were followed for over 5.5 million person-years. A total of 1353 (0.37 %) persons were diagnosed with schizophrenia during the observation period. Socio-demographic information and incidence rates stratified by the covariates are reported in Table 1. Incidence of schizophrenia was higher among men, among persons who were living in more urban environments in the year of their 10th birthday, and among persons whose parents had a history of mental disorder, low income or no upper secondary education. Geographical variation in global solar radiation and ambient temperature in Finland in the year 2000 is shown in Fig. 1.

Multivariable adjusted hazard ratios for the associations between quintiles of the 10-year exposure to climatic factors (global solar radiation and ambient temperature) and the subsequent risk of schizophrenia are shown in Table 2. When compared to the persons in the lowest quintile of global solar radiation or ambient temperature, growing up in the second highest quintile (Q4) was associated with a greater risk of schizophrenia in models adjusted for sex, birth year, birth month, and time-varying calendar year period. These hazard ratios were

Table 1
Descriptive statistics of the study population ($n = 365,482$) stratified by the covariates.

	Percentage of cases (%)	Incidence rate (per 1,000,000 person years)
	(Total = 1353)	
Sex		
Male	66	0.88
Female	34	0.47
Birth month		
January	9.2	0.74
February	7.7	0.65
March	9	0.65
April	9.3	0.70
May	8.4	0.65
June	9.5	0.75
July	8.6	0.67
August	8.6	0.69
September	7.5	0.62
October	6.9	0.60
November	7.5	0.68
December	8	0.72
Degree of urbanization of residence in the year of 10th birthday		
Urban	56.6	0.76
Semi-urban	17.3	0.62
Rural	24.1	0.56
Paternal educational attainment		
No upper secondary education	24.7	0.78
Upper secondary education	72.7	0.64
Missing information	2.6	0.77
Maternal educational attainment		
No upper secondary education	19.7	0.81
Upper secondary education	77.6	0.64
Missing information	2.7	0.99
Paternal income in quintiles		
Q1	25.2	0.89
Q2	18.4	0.63
Q3	19.1	0.65
Q4	16.9	0.58
Q5	17.8	0.62
Missing information	2.6	0.77
Maternal income in quintiles		
Q1	21.9	0.77
Q2	22.8	0.79
Q3	19.5	0.66
Q4	17.5	0.60
Q5	15.7	0.54
Missing information	2.7	0.97
History of paternal mental disorders		
No history	90.5	0.64
With a history	9.5	1.77
History of maternal mental disorders		
No history	92.9	0.65
With a history	7.1	1.81

somewhat attenuated but remained statistically significant after further adjustment for parental mental disorder, parental education, and parental income, as well as area-level socioeconomic characteristics and urbanicity (fully adjusted HR = 1.29, 95 % CI, 1.06–1.58 for global solar radiation, HR = 1.24, 95 % CI, 1.02–1.52 for ambient temperature,

compared to the lowest quintile (Q1)) (Fig. 2).

In secondary analyses with continuous linear climatic exposures, greater 10-year exposure to global solar radiation and higher ambient temperature in childhood were associated with a greater risk of schizophrenia when adjusting for sex, birth year, birth month, time-varying calendar year period and parental characteristics. In models additionally adjusted for area-level socioeconomic characteristics and urbanicity, these associations had wider confidence intervals and they were no longer statistically significant. (Table 3).

4. Discussion

In this nationwide register-based study of 372,494 Finnish persons, we observed no consistent evidence for associations between 10-year exposure to climatic factors in childhood and the risk of schizophrenia onset from adolescence into adulthood. Although there was some evidence that the risk of schizophrenia was greater among those who were exposed to higher levels of global solar radiation and ambient temperature based on residence during the first 10 years of their life, these associations were non-monotonic and small in magnitude. Compared to those residing in the lowest quintile of global solar radiation or ambient temperature, those residing in the fourth quintile had an elevated risk of schizophrenia, while there was no consistent evidence of an elevated risk of schizophrenia among those residing in the second, third or fifth quintile of global solar radiation or ambient temperature. Continuous linear associations evaluated in the secondary models suggested a greater risk of schizophrenia among those growing up in environments with greater exposure to global solar radiation and higher ambient temperature, but these associations were not robust to adjustment for sex, birth year, birth month, time-varying calendar year period, parental characteristics as well as area-level socioeconomic characteristics and urbanicity.

Many previous studies assessing the associations of climatic factors with schizophrenia have focused on exposure to climatic factors over shorter time intervals triggering the acute exacerbation of schizophrenia. In previous large-scale studies assessing short-term associations between climatic factors and schizophrenia, both high and low temperatures (Lee et al., 2018; Pan et al., 2019; Wang et al., 2018; Yi et al., 2019a), as well as greater diurnal temperature variability and temperature change between neighboring days (Gupta and Murray, 1992; Sung et al., 2011; Yi et al., 2019b; Zhao et al., 2017, 2016) have been associated with more hospital admissions for schizophrenia. There is some evidence for a V-shaped association between sunlight and admissions for schizophrenia, with particularly low and high sunlight exposure associated with more admissions for schizophrenia (Gu et al., 2019). Other studies evaluating the role of proximal effects of season triggering the acute onset of schizophrenia have yielded conflicting findings depending on study location, with both winter and summer seasons associated with the onset of schizophrenia at different latitudes (Clarke et al., 1999, 1998; Davies et al., 2000; Owens and McGorry, 2003; Shiloh et al., 2005; Tian et al., 2006).

Previous studies analyzing the risk of schizophrenia at early stages of the pathogenesis have focused on perinatal seasonal and sunshine exposures. A register-based study in Australia and the Netherlands observed that long-term perinatal exposure to shorter sunshine duration was associated with higher birth rate of early onset male schizophrenia and earlier age of first schizophrenic episode (McGrath, 2002). While several earlier studies have suggested the season of birth effect (Brown, 2011; Davies et al., 2003; Escott-Price et al., 2019; Suvisaari et al., 2001) – higher risk of schizophrenia among people born in winter and early spring – the season-of-birth effect was not as systematically replicated in a later-born Swedish cohort (Karlsson et al., 2019). Also in our study, we did not observe systematic differences in the incidence of schizophrenia according to birth month.

Furthermore, we observed some evidence of a longitudinal non-monotonic association of 10-year childhood exposure to global solar

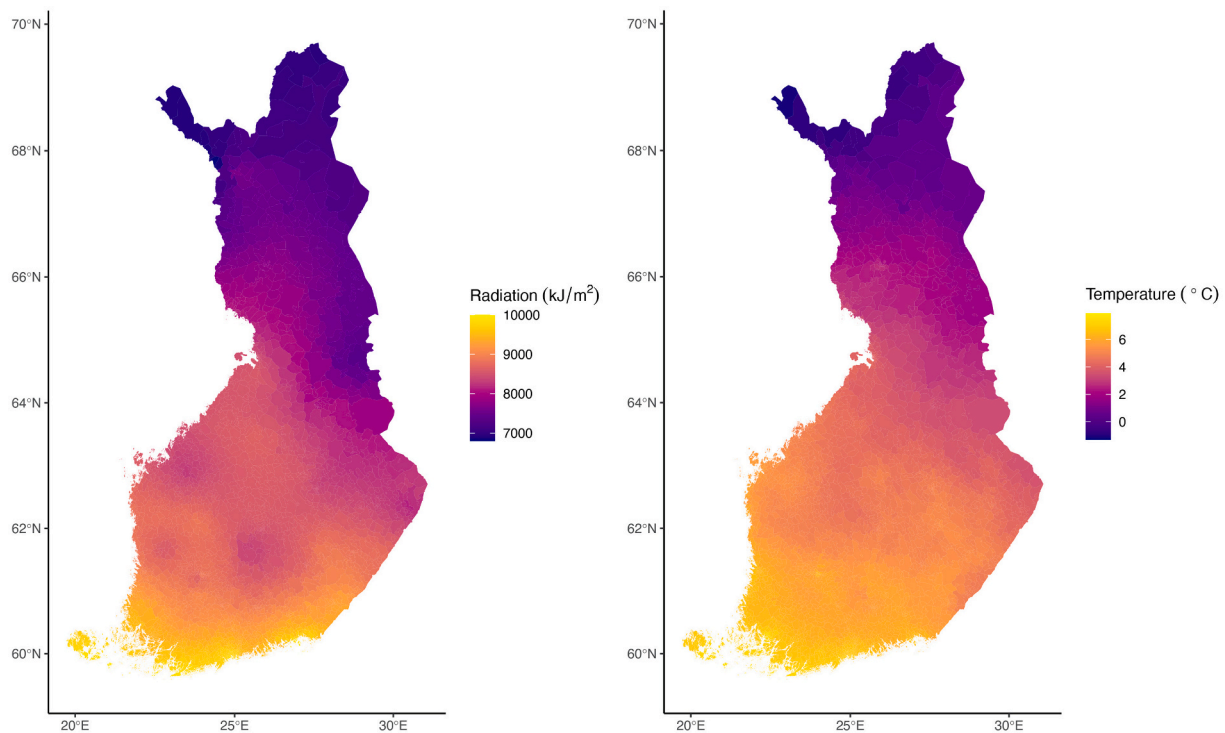


Fig. 1. Geographical variation in global solar radiation and ambient temperature in Finland in the year 2000.

Table 2
Associations of quintiles of global solar radiation and ambient temperature with schizophrenia onset.

	Global solar radiation	Ambient temperature
Model 1		
Q1 (ref)		
Q2	1.13 (0.94–1.35)	1.19 (1.00–1.43)
Q3	1.14 (0.96–1.36)	1.15 (0.96–1.38)
Q4	1.43 (1.22–1.69)	1.40 (1.18–1.66)
Q5	1.23 (1.03–1.47)	1.34 (1.13–1.59)
Model 2		
Q1 (ref)		
Q2	1.13 (0.94–1.35)	1.19 (1.00–1.42)
Q3	1.15 (0.97–1.37)	1.17 (0.97–1.39)
Q4	1.50 (1.27–1.77)	1.45 (1.22–1.72)
Q5	1.27 (1.05–1.52)	1.38 (1.16–1.65)
Model 3		
Q1 (ref)		
Q2	1.08 (0.89–1.3)	1.13 (0.94–1.35)
Q3	1.05 (0.87–1.26)	1.04 (0.86–1.26)
Q4	1.29 (1.06–1.58)	1.24 (1.02–1.52)
Q5	1.06 (0.85–1.32)	1.10 (0.88–1.37)

Values are hazard ratios (and 95 % confidence intervals). Global solar radiation and ambient temperature were used in the analyses as quintiles: Q1 = the lowest quintile, Q5 = the highest quintile.

Model 1: adjusted for sex, year of birth, month of birth and time-varying calendar year period.

Model 2: adjusted for sex, year of birth, month of birth, time-varying calendar year period, parental education, parental income in quintiles and parental history of mental disorders.

Model 3: adjusted for sex, year of birth, month of birth, time-varying calendar year period, parental education, parental income in quintiles, parental history of mental disorders, degree of urbanicity and area-level socioeconomic characteristics.

radiation and ambient temperature with later risk of schizophrenia, so that the risk of schizophrenia was greatest among those exposed to relatively high, although not the highest observed, levels of global solar radiation and ambient temperature based on childhood residence. This finding is somewhat unexpected given that previous literature suggested a greater risk of schizophrenia exacerbation at sunlight or temperature extremes at least over shorter time intervals (Gu et al., 2019; Lee et al., 2018; Pan et al., 2019; Wang et al., 2018; Yi et al., 2019a). Due to the complex relationships among area- and individual-level factors associated with residence and mental health outcomes, assessing the associations of climatic factors with schizophrenia is not straightforward. Although the associations we observed were robust to adjustment for several potential confounders, they did attenuate after adjusting for established risk factors for schizophrenia such as parental mental disorder (Mortensen et al., 2010), family socioeconomic disadvantage (Hakulinen et al., 2020), area-level socioeconomic characteristics (Sariasslan et al., 2015) and urbanicity (Fett et al., 2019). Furthermore, continuous linear terms evaluated in secondary models were similarly attenuated and they were no longer significant after adjusting for these established risk factors. Thus it seems likely that the non-monotonic association we observed may reflect residual or unmeasured confounding rather than a true association.

The main biological hypotheses proposed to explain the early-life origins of schizophrenia involve neonatal vitamin D deficiency and prenatal infections, such as rubella, influenza or toxoplasmosis, all of which have been associated with schizophrenia (Brown, 2006; Brown and Derkits, 2010; Cui et al., 2021). These mechanisms have been implicated in the season-of-birth effect, as both neonatal vitamin D deficiency and prenatal infections are more common during cold seasons with less sunlight, and birth in the winter or spring marks greater exposure to cold. Evidence also suggests that postnatal infections during childhood are associated with greater risk of schizophrenia (Burgdorf et al., 2019; Debost et al., 2019; Khandaker et al., 2012). Although the empirical evidence supporting the vitamin D hypothesis comes from studies with newborns, there is indirect evidence that vitamin D deficiency and infections may also operate on the risk of schizophrenia from

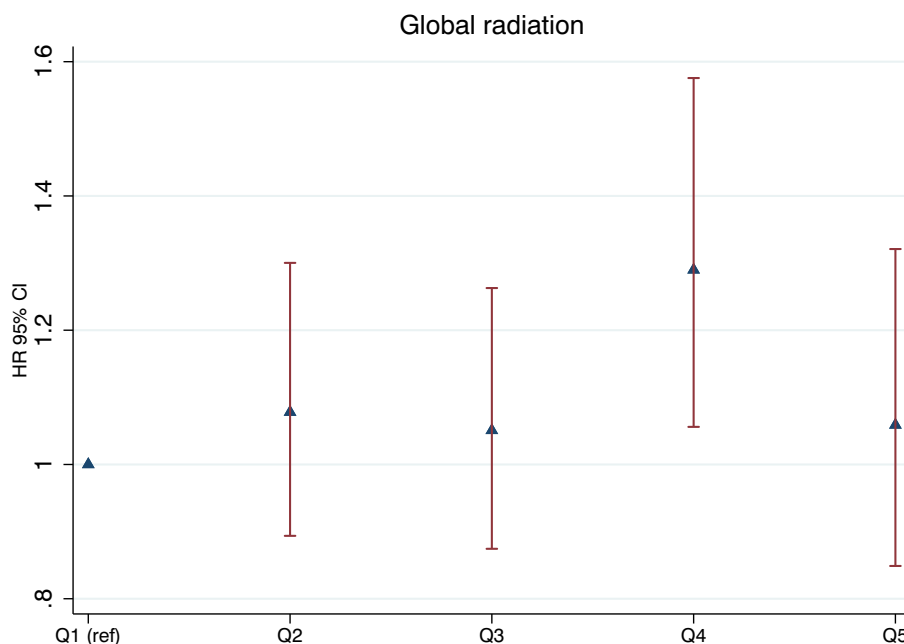


Fig. 2. Adjusted hazard ratios for the association between quintiles of global solar radiation and the onset of schizophrenia.

Table 3

Associations of global solar radiation and ambient temperature with schizophrenia onset.

	Global solar radiation	Ambient temperature
Model 1	1.13 (1.07–1.20)	1.11 (1.05–1.18)
Model 2	1.15 (1.08–1.22)	1.13 (1.06–1.20)
Model 3	1.07 (0.99–1.15)	1.04 (0.97–1.12)

Values are hazard ratios (and 95 % confidence intervals). Global solar radiation and ambient temperature were standardized (mean = 0; standard deviation = 1).

Model 1: adjusted for sex, year of birth, month of birth and time-varying calendar year period.

Model 2: adjusted for sex, year of birth, month of birth, time-varying calendar year period, parental education, parental income in quintiles and parental history of mental disorders.

Model 3: adjusted for sex, year of birth, month of birth, time-varying calendar year period, parental education, parental income in quintiles, parental history of mental disorders, degree of urbanicity and area-level socioeconomic characteristics.

early childhood until puberty (Cui et al., 2021). Nevertheless, we observed a greater risk of schizophrenia among those with greater rather than smaller exposure to sunlight and higher temperature during childhood, and thus our data do not seem very compatible with either of these explanations. It is of note, also, that at least vitamin D may play a lesser role in our sample given that vitamin D deficiency is a common public health issue in northern latitudes, including Finland, throughout the year (Kull et al., 2009).

Some limitations should be noted. First, although the incidence rates of schizophrenia for both men and women are known to peak before the age of 25, a notable proportion of cases are diagnosed after the age of 25, especially in women (Gureje, 1991). In our study, the maximum age of follow-up was 27 years, and it is likely that not all schizophrenia cases were diagnosed during our follow-up time interval. The proportion of individuals diagnosed with schizophrenia in our sample was relatively small (0.4 %) compared to the established life-time prevalence of schizophrenia (0.9 %) in the general population in Finland (Perälä et al., 2007), and the small number of cases might have affected our findings. Second, our assessment of climatic exposures was based on

meteorological data linked to individuals based on residential zip codes. Residential exposure to climatic factors does yet only approximate the actual exposure which is influenced by various behavioral factors (e.g. time spent outdoors) or living circumstances (e.g. variations in climatic factors are less relevant in indoor settings with appropriate lighting, heating or air conditioning). In addition, we had nationwide data on global solar radiation only and thus we could not assess exposure to any specific wavelength of solar radiation. For instance, exposure to ultraviolet (UV) radiation, UVB in particular, is a key factor in vitamin D synthesis (Holick, 2007), and it is possible that specific wavelengths play distinct roles in the pathogenesis of schizophrenia, and further studies are needed to assess such possibilities in more detail. The population density is greater in the lower half of Finland. Although participants exposed to greater levels of global solar radiation and ambient temperature were generally living in a more densely populated geographical area, the zip code areas vary considerably in population size also in the southern parts of Finland. To account for confounding due to population density and other area-level factors associated with the risk of schizophrenia, we controlled for urbanicity and area-level socioeconomic characteristics in the analyses. However, we cannot rule out the possibility of unmeasured confounding by other geographically distributed factors that could differ across different parts of Finland. Finally, our data is from a single country, and our results do not generalize to other geographical locations, especially given that variations in climatic factors are massively dependent on latitude.

The main strength of our study is the use of interlinked Finnish national registers, which provided high statistical power and allowed us to link accurate residential address information to daily information of climatic factors from birth to the 10th birthday. The schizophrenia cases were acquired from the Care Register for Health Care, which has been reported to have good diagnostic validity of schizophrenia (Mäkikyrö et al., 1998). Finally, the present study is representative of the nonimmigrant Finnish population.

In conclusion, we observed no consistent evidence of an association of 10-year childhood exposure to global solar radiation and ambient temperature with later risk of schizophrenia. Although the risk of schizophrenia was greatest among those exposed to relatively higher levels of global solar radiation and ambient temperature based on childhood residence, the associations were small in magnitude and not clearly interpretable. Nevertheless, our study contributes to the growing

literature on early-life environmental exposures and adult mental health (Antonsen et al., 2020; Engemann et al., 2019). No previous studies have evaluated the longitudinal associations between climatic factors in childhood and schizophrenia incidence in adulthood. Further studies are needed to replicate these findings in other populations residing in different latitudes, as well as assess the relevance of early-life climatic factors to other psychiatric and physiological outcomes over the life-course.

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CRediT authorship contribution statement

K. Komulainen and C. Hakulinen had full access to the data and take responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: K. Komulainen, C. Hakulinen, M. Elovainio.

Acquisition, analysis, or interpretation of data: All authors.

Drafting of the article: K. Komulainen, C. Hakulinen.

Critical revision of the article for important intellectual content: All authors.

All authors have given final approval of the version of the article to be published.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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