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A prospective study of the association between living in a rural environment during childhood and risk of psoriasis

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ABSTRACT

Psoriasis is one of the most common immune-mediated inflammatory diseases (IMIDs). Living in a rural environment during childhood is associated with a decreased risk of certain IMIDs, like asthma, in adulthood. However, its role in other IMIDs, such as psoriasis is still unclear. To evaluate the relationships between different factors related to the environment during childhood and the risk of psoriasis in adulthood we conducted a study in E3N, a French prospective cohort composed of 98 995 women.

During the 1990–2018 follow-up of 72 154 study participants, we identified 1 967 incident cases of psoriasis from self-reports in self-administered structured questionnaires. During the 2004–2018 follow-up of 67 917 study participants, 188 moderate-to-severe cases of psoriasis were identified through self-reports and from data from a drug reimbursement database.

We fitted Cox proportional hazards regression models with age as the time scale from which we estimated hazard ratios adjusted for putative confounders (aHRs). We found inverse associations with risk of psoriasis for rural birthplace [aHR: 0.89 (95%CI: 0.79–0.96)] and for having farming parents [aHR: 0.84 (95%CI: 0.72–0.97)]. For moderate-to-severe psoriasis we found a nominally similar inverse association with rural birthplace but not with having farming parents. Our results suggest that an exposure to a rural environment during childhood may be associated with a reduced risk of psoriasis. These findings may help to improve our understanding of the pathogenesis of psoriasis.

1. Introduction

Psoriasis is one of the most common skin inflammatory diseases, affecting around 125 million people globally (Griffiths et al., 2017) for whom it represents a lifelong economic and quality of life burden (Griffiths et al., 2021).

Psoriasis, along other skin inflammatory diseases, is currently classified as an immune-mediated inflammatory disease (IMID), a concept used to collectively describe a group of conditions that share T-helper lineage as common ancestor. IMIDs are further classified on the basis of their downstream inflammatory pathways into T-helper 1 (Th-1)/T-helper 17 (Th-17) related diseases such as psoriasis, type 1 diabetes, inflammatory bowel diseases, multiple sclerosis and rheumatoid arthritis, and Th-2 related diseases, such as asthma and atopic dermatitis (Bunte and Beikler, 2019; Kuek et al., 2007). Like other IMIDs, psoriasis is known to have a multifactorial pathogenesis in which the interaction between genetic and non-genetic factors is well-established (Kuek et al., 2007; Nedoszytko et al., 2020).

The existence of a link between the environment and IMIDs is supported by the recurrent observation of an inverse association between Th-2 conditions, like atopy, and rural environment exposure during childhood (Varraso et al., 2012). In the 1980s, this led to the formulation of the hypothesis that cleaner environments would have a negative impact on the development of the immune system and may contribute to

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allergic diseases, the so-called "hygiene hypothesis" (MichaelSly, 1999; Strachan, 2000).

The exact mechanisms through which childhood environmental exposures may affect atopy are not fully understood. Observational studies and animal models suggest that the synergistic effects of multiple antigens present in animal sheds (von Mutius, 2021) and exposure to microbial and parasitic species present in soil and dust, may shape the host microbiome (Candon et al., 2015; Christoforidou et al., 2018; Rook, 2013) and restrain Th-2 cytokines production responsible for disease manifestations (McCoy et al., 2018; Von Mutius and Vercelli, 2010).

In spite of common features, evidence to support the hypothesis that a rural environment during childhood would impact on Th-1 related IMIDs are still limited and inconsistent (El-Gabalawy et al., 2010; Rahman et al., 2010; Sheikh et al., 2003; Simpson et al., 2002; Wills-Karp et al., 2001). For psoriasis, epidemiological studies on the role of environmental factors, for example air pollution, are limited to short-term effects on flares (Bellinato et al., 2022; Wu et al., 2022) or have limitations such as a cross-sectional design (Lowe et al., 2022).

We carried out a study to test the association between different factors related to the environment during childhood and the risk of psoriasis in women using data from the E3N prospective cohort.

2. Materials and methods

2.1. E3N cohort

The E3N (Étude Épidémiologique auprès de femmes de l'Éducation Nationale) cohort is a French prospective cohort set up to investigate risk factors for major non-communicable diseases in women. It includes 98 995 women affiliated to the Mutuelle Générale de l'Éducation Nationale (MGEN), the French health insurance scheme covering workers in the national education system, mostly teachers, that were aged between 40 and 65 years and residing in metropolitan France at the time of their inclusion in the study in 1990.

The collection of information on health, nutrition and lifestyle was done through self-administered questionnaires sent to participants every two to three years. Linkage to the drug reimbursement database provided by the MGEN allowed access to data on all extra hospital drug reimbursements (i.e., the drug code and the date of purchase) from the year 2004. The cohort characteristics have been already described in detail elsewhere (Clavel-Chapelon, 2015).

The E3N cohort received ethical approval from the French National Commission for Data Protection and Privacy (Commission Nationale de Informatique et des Libertés) and its ClinicalTrials.gov identifier is NCT03285230.

2.2. Identification of psoriasis cases

Psoriasis cases were defined as women that self-reported a diagnosis of psoriasis in at least one of the follow-up questionnaires in which questions about psoriasis were included: questionnaire 9 (Q9) sent in 2008, questionnaire 10 (Q10) sent in 2011, and questionnaire 12 (Q12) sent in 2018. In such questionnaires participants were also asked to report the age at diagnosis.

When the age at diagnosis of the disease self-reported in different questionnaires was discordant (23% of psoriasis cases included in the present study), we retained the age reported in the first completed questionnaire.

We defined moderate-to-severe psoriasis cases as self-reported cases of psoriasis with at least one drug reimbursement in the MGEN database for one of the classes of systemic drugs used to treat psoriasis (i.e. psoralens, non-biologic immunosuppressants or biologic immunosuppressants).

2.3. Assessment of childhood exposures

We used five exposure variables, four individual and one ecological, all derived from data collected in questionnaire 7 (Q7) completed in 2002 and in which questions on the environment during childhood were included. The four individual variables were all binary and included factors related to exposure to a rural environment during childhood like having lived on a farm at least 3 consecutive months during childhood, having lived in contact with farm animals at least 3 consecutive months during childhood and having had farming parents as well as having had pets (dog or cat) during childhood.

The ecological binary indicator of a rural birthplace was created using self-reported birthplace at baseline and the general agricultural census of 1970 and by defining as rural a birthplace with less than 5000 inhabitants as done previously (Varraso et al., 2012).

For the purpose of this study, childhood is the period from birth to sixteen years of age.

2.4. Assessment of covariates

We used data on putative confounders such as tobacco smoking, height and weight, these latter two used to determine body mass index (BMI), collected in all questionnaires. Education level and marital status were both collected at the baseline questionnaire in 1990.

In our analyses we also included data on diseases that may be associated with psoriasis – i.e. hypertension, depression requiring a pharmacological treatment and type 2 diabetes. Self-reported diagnoses of hypertension and depression were collected in each questionnaire from baseline to Q12 except for hypertension for which no data was collected in Q10. Type 2 diabetes cases and their corresponding date of diagnosis were defined throughout the duration of the follow-up using an algorithm based on self-reported information and drug reimbursement data as described previously (Mancini et al., 2018).

Considering the all-female composition of our population, the potential impact of hormonal and reproductive factors on immunological regulation (Adachi and Honda, 2022) and evidence of psoriasis incidence peaking after menopause (Griffiths et al., 2021), models were also adjusted for menopausal status, defined as absence of menstrual periods for at least 12 months (unless due to hysterectomy) as reported in all questionnaires except for Q7, age at menarche, parity, and ever use of the contraceptive pill reported in the baseline questionnaire.

2.5. Study population

The process of selection of the study population is described in Fig. 1. From the initial population of women that completed the baseline questionnaire in 1990 (N = 98 995), we excluded 17 543 participants that did not answer Q7, 6 232 participants for whom it was not possible to assign the urban-rural category for the birthplace mostly because they were born abroad, and 30 participants who died during follow-up but for whom no valid date of death was retrieved. We further excluded participants who reported psoriasis in free text included in each questionnaire (to allow the report of additional health conditions) but who answered negatively to the specific questions about psoriasis (N = 29) and those who declared a date of psoriasis diagnosis after 2004 but for whom no reimbursement for drugs used in psoriasis was found in the MGEN database (N = 124). These data include reimbursements for five categories of drugs approved for psoriasis treatment (topical drugs derived from vitamin D, topical steroids, psoralens used for phototherapy, non-biologic immunosuppressants, and biologic immunosuppressants; Table S1 in supplementary materials).

After further exclusion of all prevalent cases of psoriasis at baseline (N = 1 227) and cases with missing age at diagnosis (N = 1 656) the study population comprised 72 154 participants (Fig. 1).

For the analyses on moderate-to-severe psoriasis, we did not exclude prevalent cases and those with missing age at diagnosis, but we excluded

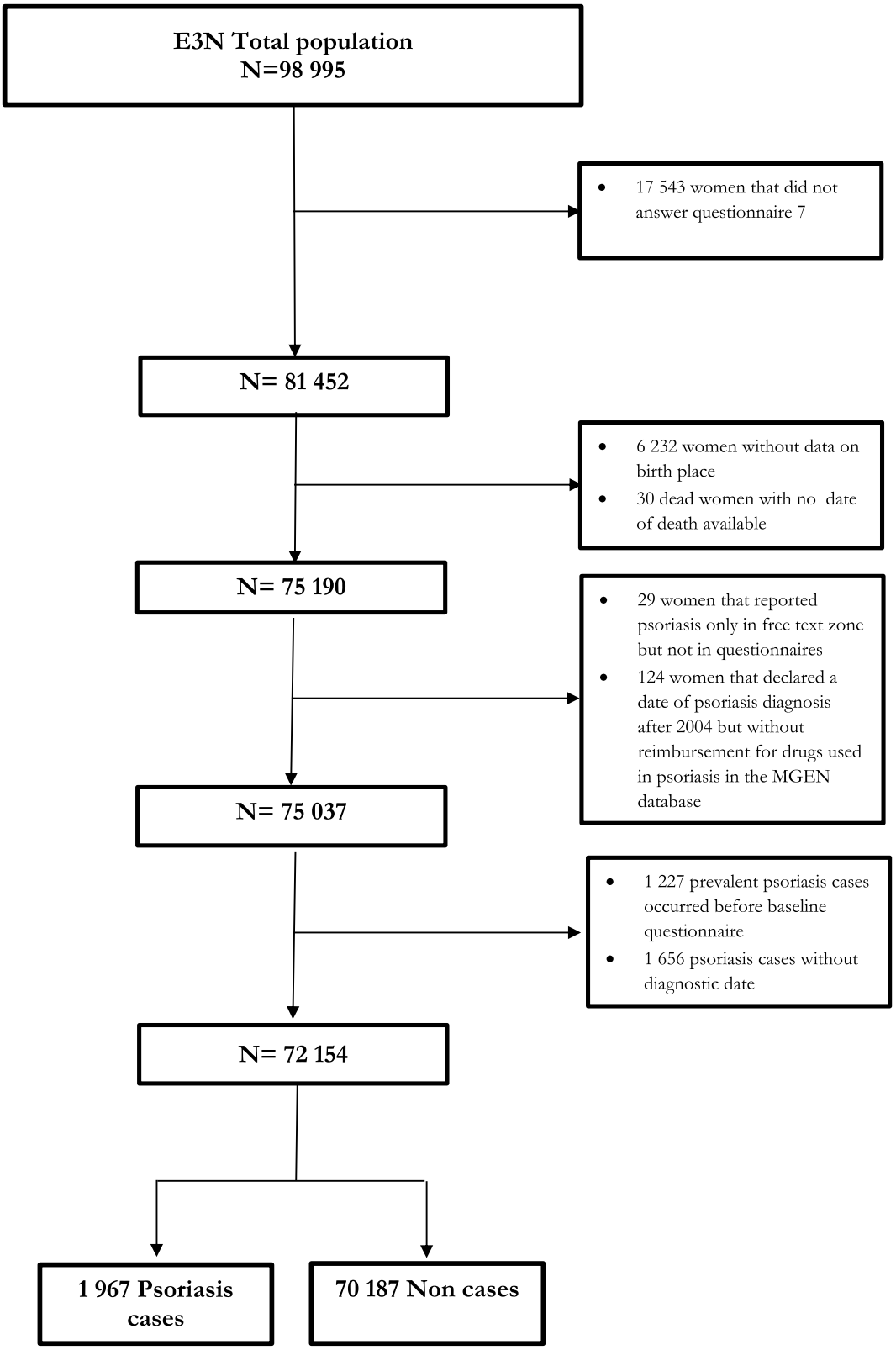

Fig. 1. Flow chart of the included participants in overall psoriasis models. E3N: Étude Épidémiologique auprès des femmes de la Mutuelle générale de l'Education Nationale; MGEN: Mutuelle Générale de l'Education Nationale.

participants that were lost to follow-up (i.e. deceased or no further response to questionnaires) by January 1st, 2004, when drug reimbursement data became available (N = 5 914) and psoriasis cases without a date of diagnosis (N = 1 206) obtaining a study population of 67 917 participants (Fig. 2).

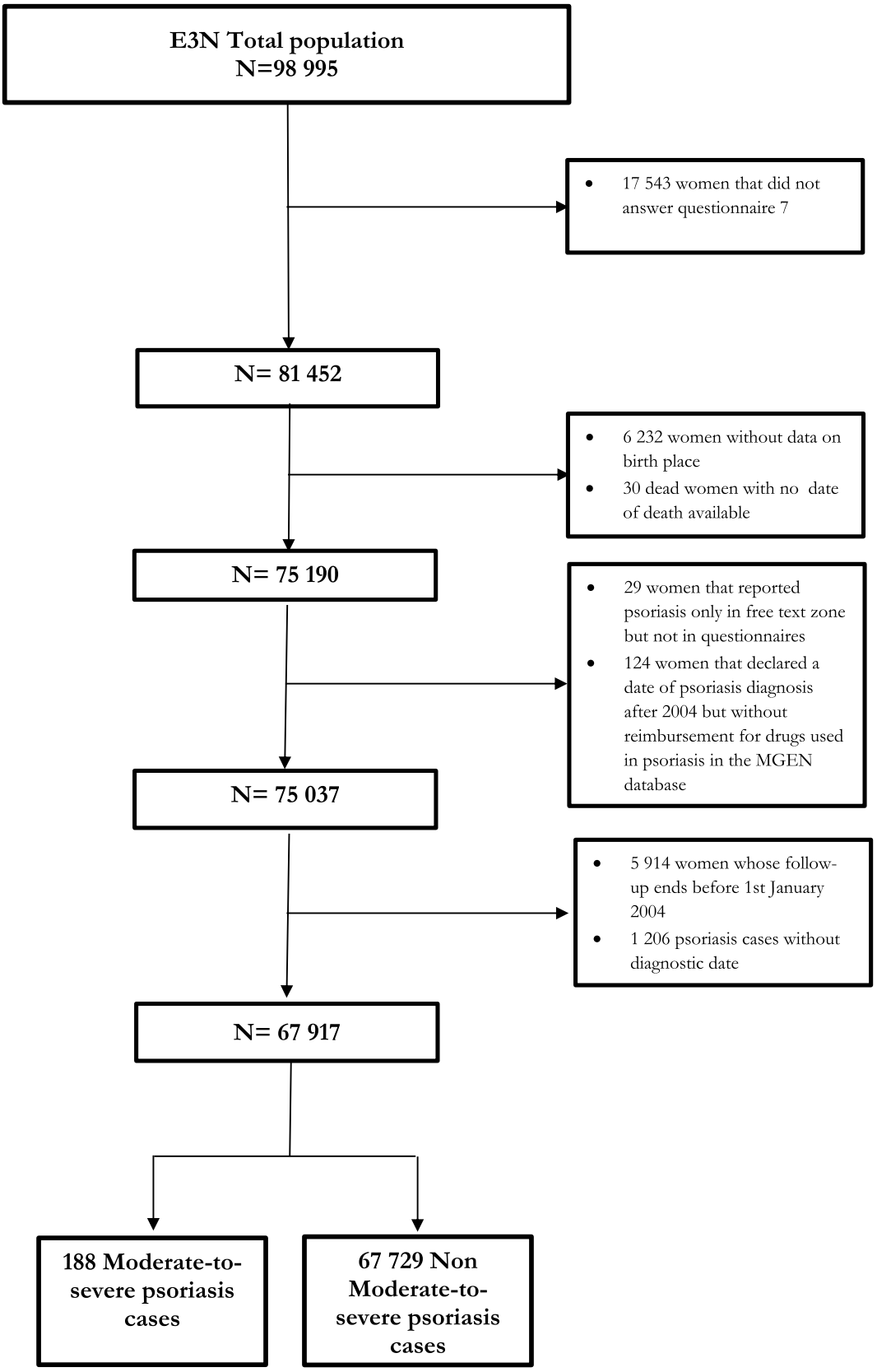

Fig. 2. Flow chart of the included participants in moderate-to-severe psoriasis models. E3N: Étude Épidémiologique auprès des femmes de la Mutuelle générale de l'Education Nationale; MGEN: Mutuelle Générale de l'Education Nationale.

2.6. Statistical analysis

We described the baseline characteristics of the study population according to the exposure variables and to psoriasis status at the end of follow-up. Categorical variables were described with numbers and percentages (%) while numerical variables were described with mean and standard deviation (±). We used Kaplan-Meier curves to appreciate in graphical form differences in incidence of psoriasis according to categories of each exposure variable. We estimated hazard ratios (HRs) and 95% confidence intervals (CI) for psoriasis incidence using Cox proportional hazard regression models.

Follow-up time started at the date of completion of the baseline questionnaire and ended at the date of diagnosis of psoriasis, at the last answered questionnaire, at the date of death or at the date of return of Q12 (the last E3N follow-up questionnaire used for this study), whichever occurred first.

For analyses on moderate-to-severe psoriasis follow-up started on January 1st, 2004, and ended when an event of moderate-to-severe psoriasis occurred (date of first systemic drug reimbursement available from the MGEN database in a self-reported case of psoriasis), at the last answered questionnaire, at the date of death or on December 31st, 2018 (date of the most recent available data on drug reimbursement) whichever occurred first.

We first estimated age-adjusted hazard ratios (uHRs) from models including only one of the five childhood exposure at a time. We then estimated multivariable adjusted hazard ratios (aHRs) from models including BMI (categorical variable: <25, 25–30[, and ≥30 kg/m2; time-varying), marital status (unmarried, married; baseline), smoking status (never, current, former smoker; time-varying), level of education (undergraduate or less, graduate, postgraduate or more; baseline), and three binary variables about medical conditions: history of diabetes, depression, and hypertension (all time-varying); hormonal and reproductive variables included were age at menarche (<12 years, 12–15 years, >15 years; baseline), menopausal status (premenopausal, postmenopausal; time-varying), parity (nulliparous, parous; baseline), and ever use of a contraceptive pill (no, yes; baseline), together with one of the five exposure variable at a time.

In a first sensitivity analysis we included in the adjusted model a binary variable on urban-rural residence at baseline using the same cut-off of 5 000 inhabitants as for the birthplace.

We further added to the adjusted model the working position of the women as a binary variable (teachers or other occupations).

As smoking and BMI play a role in psoriasis physiopathology, we performed sensitivity analyses by stratifying the Cox models by smoking status in two categories (current or former smokers versus non-smokers) and BMI in two categories (normal weight – i.e. BMI <25 kg/m^2 versus overweight – i.e. BMI >25 kg/m^2).

When missing values were present and accounted for less than 5% of the study population, we imputed the median or the modal category in case of fixed adjustment variables while we used the last observation carried forward (LOCF) method for time-varying variables.

Finally, we performed a sensitivity analysis by using logistic regression to include all cases irrespective of whether they were prevalent or incident as well as all cases with unknown age at diagnosis. In this sensitivity analyses, based on a population of 75 218 women including 5 004 with psoriasis, univariate and multivariable logistic models were fitted from which odds ratios (OR) and 95% confidence intervals (CI) were estimated.

The proportional hazards assumption was verified through the analysis of Schoenfeld residuals. Descriptive analyses were carried using PROC FREQ procedure while Cox regression models were fitted using the PHREG procedure from SAS software version 9.4 Copyright © 2013 SAS Institute Inc., Cary, NC, USA.

3. Results

A total of 1 967 participants declared to have had a diagnosis of psoriasis during follow-up corresponding to an incidence rate of 107 cases per 100 000 person-years.

3.1. Study participant characteristics

The baseline population characteristics are reported according to childhood exposures in Table 1 and according to psoriasis status in Table S2 of supplementary materials. Mean age at baseline was 49.3 (standard deviation 6.6) years. Mean age at diagnosis of psoriasis was 64.6 (standard deviation 8.4) years and mean time from baseline to psoriasis diagnosis was 16.5 (standard deviation 6.3) years.

3.2. Environment during childhood and risk of incident psoriasis

Kaplan Maier curves are presented in the supplementary materials for each of the five exposure variables (Figure S1-S5). We observed an inverse association between rural birthplace and risk of psoriasis both in age-adjusted [uHR: 0.84 (95%CI: 0.77–0.93)] and in multivariable adjusted analyses [aHR: 0.87 (95%CI: 0.79–0.96)]. Similarly, having farming parents was inversely associated with risk of psoriasis both in age-adjusted [uHR: 0.78 (95%CI: 0.68–0.91)] and in multivariable adjusted analyses [aHR: 0.84 (95%CI: 0.72–0.97)] (Table 2).

The estimated association between rural birthplace and risk of moderate-to-severe psoriasis [aHR: 0.82 (95%CI: 0.61–1.08)] was nominally similar to the association with overall psoriasis while we found no association between having farming parents and risk of moderate-to-severe psoriasis [aHR: 1.04 (95%CI: 0.70–1.54)] (Table 3).

We did not observe any associations with risk of overall or moderate-to-severe psoriasis for any of the other three exposure variables (having pets during chilhood, living in a farm at least 3 consecutive months during childhood and living in contact with livestock at least 3 consecutive months during childhood).

Rural-urban residence at baseline was not associated with risk of psoriasis. When both variables were included in the model, rural residence at birthplace was inversely associated with risk [aHR: 0.88 (95% CI: 0.80–0.97)] but not residence at baseline [aHR: 0.99 (95%CI: 0.90–1.10)] (Table 4).

In the sensitivity analysis based on logistic regression and including both prevalent cases (cases diagnosed before the cohort baseline) and cases with unknown age at diagnosis we found an association between rural birthplace and psoriasis in both the univariate [OR: 0.88 (95%CI: 0.83–0.94)] and multivariable models [OR: 0.91 (95%CI: 0.85–0.97)] while the association between farming parents and psoriasis was observed in univariate [OR: 0.87 (95%CI: 0.79–0.95)] but not in the multivariable model [OR: 0.91 (95%CI: 0.83–1.00)] (Table S3 in supplementary materials).

Further adjustment for occupation did not appreciably change the estimated associations (data not shown).

Cox models stratified by cigarette smoking showed similar inverse associations between psoriasis and rural birthplace for both smokers and non-smokers while the inverse association with having farming parents appeared to be limited to non-smokers (Table S4 in supplementary materials).

Cox models stratified by BMI showed inverse associations with rural birthplace and having farming parents only for women with normal BMI (Table S5 in supplementary materials).

4. Discussion

In this study we observed that a rural birthplace and having farming parents were inversely associated with the risk of psoriasis in adulthood. Our study also suggests that early exposure to a rural environment is probably critical in the psoriasis pathogenesis as exposure to a rural

Table 1
Baseline characteristics [n (%) or mean (standard deviation)] of study participants according to childhood exposures.

Exposure	All (N = 72 154)	Not living in a farm at least 3 months during childhood (n = 55 886)	Living in a farm at least 3 months during childhood (n = 16 268)	No pets at home during childhood (n = 29 477)	Pets at home during childhood (n = 42 677)	Not farming parents (n = 63 289)	Farming parents (n = 8865)	Rural birthplace (n = 24 962)	Urban birthplace (n = 47 192)	Not Living in contact with farm animals at least 3 months during childhood (N = 55 629)	Living in contact with farm animals at least 3 months during childhood (N = 16 525)
Age at baseline (SE)	49.3 (±6.6)	49.2 (±6.6)	49.7 (±6.3)	49.4 (±6.7)	49.2 (±6.5)	49.3 (±6.6)	49.2 (±6.4)	49.8 (±6.6)	49.0 (±6.5)	49.2 (±6.6)	49.8 (±6.3)
Psoriasis status											
No	70 187 (97.3%)	54 347 (97.2%)	15 840 (97.4%)	28 679 (97.3%)	41 508 (97.3%)	61 520 (97.2%)	8667 (97.8%)	24 354 (97.6%)	45 833 (97.1%)	54 091 (97.2%)	16 096 (97.4%)
Yes	1 967 (2.7%)	1 539 (2.8%)	428 (2.6%)	798 (2.7%)	1 169 (2.7%)	1 769 (2.8%)	198 (2.2%)	608 (2.4%)	1 359 (2.9%)	1 538 (2.8%)	429 (2.6%)
Age of psoriasis diagnosis	64.6 (±8.4)	64.4 (±8.5)	65.2 (±8)	64.6 (±8.6)	64.6 (±8.3)	64.4 (±8.5)	65.7 (±7.3)	64.4 (±8.5)	65 (±8.2)	64.3 (±8.6)	65.6 (±7.8)
Time between baseline and psoriasis diagnosis	16.5 (±6.3)	16.1 (±6.3)	15.8 (±6.1)	16.1 (±6.4)	16.0 (±6.2)	16 (±6.4)	16.7 (±6)	16.0 (±6)	16.1 (±6.4)	16 (±6.3)	16.2 (±6)
Year at birth											
<1930	6 264 (8.7%)	5 007 (9.0%)	1 257 (7.7%)	2 743 (9.3%)	3 521 (8.3%)	5 567 (8.8%)	697 (7.9%)	2 473 (9.9%)	3 791 (8.0%)	4 988 (9.0%)	1 276 (7.7%)
1930–1935	9 572 (13.3%)	7 202 (12.9%)	2 370 (14.6%)	3 984 (13.5%)	5 588 (13.1%)	8 422 (13.3%)	1 150 (13.0%)	3 610 (14.5%)	5 962 (12.6%)	7 111 (12.8%)	2 461 (14.9%)
1935–1940	14 424 (20.0%)	10 597 (19.0%)	3 827 (23.5%)	5 984 (20.3%)	8 440 (19.8%)	12 628 (20.0%)	1 796 (20.3%)	4 978 (19.9%)	9 446 (20.0%)	10 546 (19.0%)	3 878 (23.5%)
1940–1945	17 513 (24.3%)	13 376 (23.9%)	4 137 (25.4%)	6 662 (22.6%)	10 851 (25.4%)	15 253 (24.1%)	2 260 (25.5%)	6 377 (25.5%)	11 136 (23.6%)	13 273 (23.9%)	4 240 (25.7%)
>1945	24 381 (33.8%)	19 704 (35.3%)	4 677 (28.7%)	10 104 (34.3%)	14 277 (33.5%)	21 419 (33.8%)	2 962 (33.4%)	7 524 (30.1%)	16 857 (35.7%)	19 711 (35.4%)	4 670 (28.3%)
Body mass index (kg/m2)											
<25	59 911 (83.0%)	46 638 (83.5%)	13 273 (81.6%)	24 658 (83.7%)	35 253 (82.6%)	52 645 (83.2%)	7 266 (82.0%)	20 604 (82.5%)	39 307 (83.3%)	46 480 (83.6%)	13 431 (81.3%)
25–30	10 216 (14.2%)	7 710 (13.8%)	2 506 (15.4%)	4 061 (13.8%)	6 155 (14.4%)	8 850 (14.0%)	1 366 (15.4%)	3 653 (14.6%)	6 563 (13.9%)	7 643 (13.7%)	2 573 (15.6%)
>30	2 027 (2.8%)	1 538 (2.8%)	489 (3.0%)	758 (2.6%)	1 269 (3.0%)	1 794 (2.8%)	233 (2.6%)	705 (2.8%)	1 322 (2.8%)	1 506 (2.7%)	521 (3.2%)
Smoking status											
Never	39 227 (54.4%)	29 630 (53.0%)	9 597 (59.0%)	15 780 (53.5%)	23 447 (54.9%)	33 549 (53.0%)	5 678 (64.0%)	14 562 (58.3%)	24 665 (52.3%)	29 444 (52.9%)	9 783 (59.2%)
Current	9 968 (13.8%)	8 136 (14.6%)	1 832 (11.3%)	4 343 (14.7%)	5 625 (13.2%)	9 196 (14.5%)	772 (8.7%)	2 862 (11.5%)	7 106 (15.1%)	8 157 (14.7%)	1 811 (11.0%)
Former	22 959 (31.8%)	18 120 (32.4%)	4 839 (29.7%)	9 354 (31.7%)	13 605 (31.9%)	20 544 (32.5%)	2 415 (27.2%)	7 538 (30.2%)	15 421 (32.7%)	18 028 (32.4%)	4 931 (29.8%)
Marital status											
Not married	12 261 (17.0%)	9 698 (17.4%)	2 563 (15.8%)	5 305 (18.0%)	6 956 (16.3%)	11 049 (17.5%)	1 212 (13.7%)	3 736 (15.0%)	8 525 (18.1%)	9 674 (17.4%)	2 587 (15.7%)
Married	59 893 (83.0%)	46 188 (82.6%)	13 705 (84.2%)	24 172 (82.0%)	35 721 (83.7%)	52 240 (82.5%)	7 653 (86.3%)	21 226 (85.0%)	38 667 (81.9%)	45 955 (82.6%)	13 938 (84.3%)
Education level											
Undergraduate or less	2 567 (3.6%)	1 934 (3.5%)	633 (3.9%)	1 019 (3.5%)	1 548 (3.6%)	2 211 (3.5%)	356 (4.0%)	937 (3.8%)	1 630 (3.5%)	1 923 (3.5%)	644 (3.9%)
Graduate	8 965 (12.4%)	6 373 (11.4%)	2 592 (15.9%)	3 124 (10.6%)	5 841 (13.7%)	7 399 (11.7%)	1 566 (17.7%)	3 645 (14.6%)	5 320 (11.3%)	6 305 (11.3%)	2 660 (16.1%)
Postgraduate or more	60 622 (84.0%)	47 579 (85.1%)	13 043 (80.2%)	25 334 (85.9%)	35 288 (82.7%)	53 679 (84.8%)	6 943 (78.3%)	20 380 (81.6%)	40 242 (85.3%)	47 401 (85.2%)	13 221 (80.0%)
Hypertension											
No	53 274 (73.8%)	41 418 (74.1%)	11 856 (72.9%)	21 930 (74.4%)	31 344 (73.4%)	46 792 (73.9%)	6 482 (73.1%)	18 133 (72.6%)	35 141 (74.5%)	41 304 (74.2%)	11 970 (72.4%)
Yes	18 880 (26.2%)	14 468 (25.9%)	4 412 (27.1%)	7 547 (25.6%)	11 333 (26.6%)	16 497 (26.1%)	2 383 (26.9%)	6 829 (27.4%)	12 051 (25.5%)	14 325 (25.8%)	4 555 (27.6%)
Depression											
No	63 401 (87.9%)	49 129 (87.9%)	14 272 (87.7%)	26 007 (88.2%)	37 394 (87.6%)	55 497 (87.7%)	7 904 (89.2%)	21 940 (87.9%)	41 461 (87.9%)	48 950 (88.0%)	14 451 (87.4%)
Yes	8 753 (12.1%)	6 757 (12.1%)	1 996 (12.3%)	3 470 (11.8%)	5 283 (12.4%)	7 792 (12.3%)	961 (10.8%)	3 022 (12.1%)	5 731 (12.1%)	6 679 (12.0%)	2 074 (12.6%)
Type 2 diabetes											
No	71 535 (99.1%)	55 394 (99.1%)	16 141 (99.2%)	29 232 (99.2%)	42 303 (99.1%)	62 727 (99.1%)	8 808 (99.4%)	24 781 (99.3%)	46 754 (99.1%)	55 127 (99.1%)	16 408 (99.3%)
Yes	619 (0.9%)	492 (0.9%)	127 (0.8%)	245 (0.8%)	374 (0.9%)	562 (0.9%)	57 (0.6%)	181 (0.7%)	438 (0.9%)	502 (0.9%)	117 (0.7%)

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Table 1 (*continued*)

Exposure	All (N = 72 154)	Not living in a farm at least 3 months during childhood (n = 55 886)	Living in a farm at least 3 months during childhood (n = 16 268)	No pets at home during childhood (n = 29 477)	Pets at home during childhood (n = 42 677)	Not farming parents (n = 63 289)	Farming parents (n = 8865)	Rural birthplace (n = 24 962)	Urban birthplace (n = 47 192)	Not Living in contact with farm animals at least 3 months during childhood (N = 55 629)	Living in contact with farm animals at least 3 months during childhood (N = 16 525)
Age at menarche											
12–15 years old	55 178 (76.5%)	42 436 (75.9%)	12 742 (78.3%)	22 373 (75.9%)	32 805 (76.9%)	48 061 (75.9%)	7 117 (80.3%)	19 562 (78.4%)	35 616 (75.5%)	42 208 (75.9%)	12 970 (78.5%)
<12 years old	14 149 (19.6%)	11 401 (20.4%)	2 748 (16.9%)	6 027 (20.4%)	8 122 (19.0%)	12 871 (20.3%)	1 278 (14.4%)	4 272 (17.1%)	9 877 (20.9%)	11 386 (20.5%)	2 763 (16.7%)
>15 years old	2 827 (3.9%)	2 049 (3.7%)	778 (4.8%)	1 077 (3.7%)	1 750 (4.1%)	2 357 (3.7%)	470 (5.3%)	1 128 (4.5%)	1 699 (3.6%)	2 035 (3.7%)	792 (4.8%)
Menopausal status											
Premenopausal	37 405 (51.8%)	29 492 (52.8%)	7 913 (48.6%)	15 111 (51.3%)	22 294 (52.2%)	32 682 (51.6%)	4 723 (53.3%)	12 397 (49.7%)	25 008 (53.0%)	29 421 (52.9%)	7 984 (48.3%)
Postmenopausal	34 749 (48.2%)	26 394 (47.2%)	8 355 (51.4%)	14 366 (48.7%)	20 383 (47.8%)	30 607 (48.4%)	4 142 (46.7%)	12 565 (50.3%)	22 184 (47.0%)	26 208 (47.1%)	8 541 (51.7%)
Nulliparous											
No	63 615 (88.2%)	49 017 (87.7%)	14 598 (89.7%)	25 743 (87.3%)	37 872 (88.7%)	55 582 (87.8%)	8 033 (90.6%)	22 382 (89.7%)	41 233 (87.4%)	48 791 (87.7%)	14 824 (89.7%)
Yes	8 539 (11.8%)	6 869 (12.3%)	1 670 (10.3%)	3 734 (12.7%)	4 805 (11.3%)	7 707 (12.2%)	832 (9.4%)	2 580 (10.3%)	5 959 (12.6%)	6 838 (12.3%)	1 701 (10.3%)
Ever use of oral contraceptives											
No	32 542 (45.1%)	24 732 (44.3%)	7 810 (48.0%)	13 261 (45.0%)	19 281 (45.2%)	28 222 (44.6%)	4 320 (48.7%)	12 034 (48.2%)	20 508 (43.5%)	24 590 (44.2%)	7 952 (48.1%)
Yes	39 612 (54.9%)	31 154 (55.7%)	8 458 (52.0%)	16 216 (55.0%)	23 396 (54.8%)	35 067 (55.4%)	4 545 (51.3%)	12 928 (51.8%)	26 684 (56.5%)	31 039 (55.8%)	8 573 (51.9%)
Life in a farm at least 3 months during childhood											
No	55 886 (77.5%)			26 196 (88.9%)	29 690 (69.6%)	55 757 (88.1%)	129 (1.5%)	15 587 (62.4%)	40 299 (85.4%)	54 171 (97.4%)	1 715 (10.4%)
Yes	16 268 (22.5%)			3 281 (11.1%)	12 987 (30.4%)	7 532 (11.9%)	8 736 (98.5%)	9 375 (37.6%)	6 893 (14.6%)	1 458 (2.6%)	14 810 (89.6%)
Pets during childhood											
No	29 477 (40.9%)	26 196 (46.9%)	3 281 (20.2%)			28 667 (45.3%)	810 (9.1%)	6 797 (27.2%)	22 680 (48.1%)	26 312 (47.3%)	3 165 (19.2%)
Yes	42 677 (59.1%)	29 690 (53.1%)	12 987 (79.8%)			34 622 (54.7%)	8 055 (90.9%)	18 165 (72.8%)	24 512 (51.9%)	29 317 (52.7%)	13 360 (80.8%)
Farming parents											
No	63 289 (87.7%)	55 757 (99.8%)	7 532 (46.3%)	28 667 (97.3%)	34 622 (81.1%)			18 135 (72.7%)	45 154 (95.7%)	55 287 (99.4%)	8 002 (48.4%)
Yes	8 865 (12.3%)	129 (0.2%)	8 736 (53.7%)	810 (2.7%)	8 055 (18.9%)			6 827 (27.3%)	2 038 (4.3%)	342 (0.6%)	8 523 (51.6%)
Birth town size											
More than 5000 inhabitants (urban)	47 192 (65.4%)	40 299 (72.1%)	6 893 (42.4%)	22 680 (76.9%)	24 512 (57.4%)	45 154 (71.3%)	2 038 (23.0%)			40 383 (72.6%)	6 809 (41.2%)
Less than 5000 inhabitants (rural)	24 962 (34.6%)	15 587 (27.9%)	9 375 (57.6%)	6 797 (23.1%)	18 165 (42.6%)	18 135 (28.7%)	6 827 (77.0%)			15 246 (27.4%)	9 716 (58.8%)
Living in contact with farm animals at least 3 months during childhood											
No	55 629 (77.1%)	54 171 (96.9%)	1 458 (9.0%)	26 312 (89.3%)	29 317 (68.7%)	55 287 (87.4%)	342 (3.9%)	15 246 (61.1%)	40 383 (85.6%)		
Yes	16 525 (22.9%)	1 715 (3.1%)	14 810 (91.0%)	3 165 (10.7%)	13 360 (31.3%)	8 002 (12.6%)	8 523 (96.1%)	9 716 (38.9%)	6 809 (14.4%)		

environment in adulthood (at the cohort baseline) was not associated with risk of psoriasis.

Despite the prevalence of the disease, no previous study had investigated the impact of the environment during childhood on psoriasis. Studies were limited to other IMIDs, like type 1 diabetes, oligoarticular juvenile idiopathic arthritis and erythematosus lupus, and had generally a case-control design, small sample size and did not find significant associations except for erythematosus lupus. A population-based case-control study on multiple sclerosis, conducted in Tasmania on 136 cases and 272 controls, did not find associations between early-life exposures to farming, livestock, specific farm animals and remoteness of residence (Siejka et al., 2016). Similar results were obtained in two studies on type 1 diabetes (Radon et al., 2005; Wernroth et al., 2017). Also, a case-control study conducted on oligoarticular juvenile idiopathic arthritis risk did not find any significant association between the disease and regular farm animal contact during childhood [adjusted odds ratio: 0.79 (95% CI 0.42–1.47)] or pet contact during childhood [adjusted odds ratio: 0.79 (95% CI 0.55–1.14)] (Radon et al., 2010). For lupus erythematosus risk, a case-control study conducted in West Virginia on 265 incident cases and 355 controls found an inverse association for individuals who lived in a farm during childhood and were exposed to livestock both during childhood and adulthood [odds ratio = 0.19 (95% CI 0.06, 0.63)] (Parks et al., 2008).

Environmental factors may influence the development of psoriasis through a direct effect on the development of the immune system through the activation of Toll-like receptors of natural killer cells and dendritic cells by environmental antigens (fungi, bacteria, parasites). This action brings to the vigorous stimulation of T regulatory cells at

Table 2
Associations between overall psoriasis risk and rural environment during childhood factors (N = 72 154), 1990–2018 (Hazard ratios and 95% confidence intervals).

Exposure	Psoriasis (N = 1 967)	Person-years (N = 1 863 752)	Model 1	p-value	Model 2	p-value
Life in a farm at least 3 months during childhood						
No	1 539 (78.2)	1 443 488	1.00 (Reference)		1.00 (Reference)	
Yes	428 (21.8)	420 264	0.95 (0.85–1.06)	0.37	0.97 (0.87–1.09)	0.66
Pets during childhood						
No	798 (40.5)	761 044	1.00 (Reference)		1.00 (Reference)	
Yes	1 169 (59.5)	1 1027 708	1.00 (0.91–1.09)	0.95	1.02 (0.93–1.11)	0.78
Farming parents						
No	1 769 (89.9)	1 633 327	1.00 (Reference)		1.00 (Reference)	
Yes	198 (10.1)	230 425	0.78 (0.68–0.91)	0.001	0.84 (0.72–0.97)	0.01
Birth town size						
5000 inhabitants or more (urban)	1 359 (69.0)	1 218 856	1.00 (Reference)		1.00 (Reference)	
Less than 5000 in habitants (rural)	608 (31.0)	644 896	0.84 (0.77–0.93)	0.0008	0.87 (0.79–0.96)	0.008
Living in contact with farm animals at least 3 months during childhood						
No	1 538 (78.2)	1 436 216	1.00 (Reference)		1.00 (Reference)	
Yes	429 (21.8)	427 536	0.93 (0.83–1.04)	0.21	0.95 (0.86–1.06)	0.43

Model 1: Adjusted for age (as the time scale). Model 2: M1 and adjusted for year of birth, body mass index, smoking status, education level, marital status at baseline, hypertension, depression, diabetes, age at menarche, menopausal status, parity at baseline, ever use of contraceptive pill at baseline.

Table 3
Associations between moderate-to-severe psoriasis risk and rural environment during childhood factors (N = 67 917), 2004–2018 (Hazard ratios and 95% confidence intervals).

Exposure	Psoriasis (N = 188)	Person-years (N = 889 088)	Model 1	p-value	Model 2	p-value
Life in a farm at least 3 months during childhood						
No	145 (77.1)	688 373	1.00 (Reference)		1.00 (Reference)	
Yes	43 (22.9)	200 715	1.00 (0.74–1.36)	0.95	1.03 (0.76–1.40)	0.81
Pets during childhood						
No	77 (40.9)	362 789	1.00 (Reference)		1.00 (Reference)	
Yes	111 (59.1)	526 299	0.93 (0.71–1.20)	0.57	0.93 (0.72–1.21)	0.62
Farming parents						
No	167 (88.8)	778 462	1.00 (Reference)		1.00 (Reference)	
Yes	21 (11.2)	110 626	0.97 (0.65–1.43)	0.88	1.04 (0.70–1.54)	0.83
Birth town size						
5000 inhabitants or more (urban)	134 (71.2)	581 838	1.00 (Reference)		1.00 (Reference)	
Less than 5000 in habitants (rural)	54 (28.8)	307 250	0.78 (0.59–1.03)	0.08	0.82 (0.61–1.08)	0.16
Living in contact with farm animals at least 3 months during childhood						
No	150 (79.7)	684 727	1.00 (Reference)		1.00 (Reference)	
Yes	38 (20.3)	204 361	0.91 (0.67–1.25)	0.58	0.94 (0.69–1.29)	0.72

Model 1: Adjusted for age (as the time scale). Model 2: Model 1 and adjusted for year of birth, body mass index, smoking status, education level, marital status at baseline, hypertension, depression, diabetes, age at menarche, menopausal status, parity at baseline, ever use of contraceptive pill at baseline.

Table 4
Associations between overall psoriasis risk and rural-urban birthplace when including adjustment for rural-urban baseline residency in the overall psoriasis model (N = 72 154), 1990–2018 (Hazard ratios and 95% confidence intervals).

Exposure	Psoriasis (N = 1967)	Person-years (N = 1 863 752)	Model 2	p-value
Residence at baseline				
5000 inhabitants or more (urban)	1 385	1 301 698	1.00 (Reference)	
Less than 5000 in habitants (rural)	582	562 054	0.99 (0.90–1.10)	0.70
Birth town size				
5000 inhabitants or more (urban)	1 359	1 218 856	1.00 (Reference)	
Less than 5000 in habitants (rural)	608	644 896	0.88 (0.80–0.97)	0.02

Model 2 adjusted for year of birth, body mass index, smoking status, education level, marital status at baseline, hypertension, depression, diabetes, age at menarche, menopausal status, parity at baseline, ever use of contraceptive pill at baseline.

birth that, further activated by repeated exposures to the same triggers during early childhood, could curb Th-1 differentiation pathway, a key inflammatory mechanism implicated in psoriasis (Kääriö et al., 2016; Schröder et al., 2017). Living in a rural environment has been associated with increased blood concentrations of interleukin-10 (IL-10), who plays a key role in psoriasis pathogenesis through the stimulation of regulatory T and suppression of Th-1 immune response (Hu et al., 2021). The PASTURE birth cohort study on 88 Finnish children, including 43 living in a farming environment, showed a higher production of IL-10 in children living in farms (Kääriö et al., 2016). Similar results were observed in two nested case-controls studies on wheezing disorders on 440 children from Ecuador showing an increase in IL-10 associated with living conditions more common in a rural environment such as the lack of household bathroom, exposure to peri-domiciliary animals, and living in a wood house (Cooper et al., 2015).

Environmental factors may affect risk of psoriasis indirectly through their action on the microbiome that in turn may modulate immunological development (Haahtela et al., 2013; Lisa et al., 2021; Von Hertzen et al., 2015). The importance of the microbiome on the regulation of the immune system is supported by the observation that early colonization by certain species of parasites present in soil, like helminths, decreases responsiveness of the immune system within the lower intestinal tract and promote the development of peripheral regulatory T cells responsible for tolerance against dietary antigens and commensal microorganisms (Christoforidou et al., 2018; Cosovanu and Neumann, 2020; Pandiyan et al., 2019; Sorci et al., 2013; White et al., 2020). These tolerogenic effects promoted by the microbiome could reverberate in other tissues, such as the skin, thanks to immunological networks that exist between the gut and other body systems (Pessemier

et al., 2021).

The influence of the external environment on the microbiome may encompass multiple generations. One of the key factors that are associated with the microbiome is diet that, in childhood, is strongly shaped by parents through dietary behavior and subsequent food preferences. In the E3N cohort it was observed that, relative to women without farming parents, women with farming parents tend to consume more fruit and vegetables (Varraso et al., 2012), that might be associated with a reduced risk of psoriasis (Musumeci et al., 2022). Furthermore, in rural areas diet may be distinct and characterized not only by a higher consumption of fruit and vegetables but also a higher consumption of dairy products as well as fermented products than in urban areas. Such distinct diets may influence the offspring microbiome through breast milk that has been shown to presents a higher count of total Lactobacilli species in mothers living in rural areas than in mothers living in urban areas (Safaei et al., 2015; Sinkiewicz and Ljunggren, 2008). These probiotics have been shown to reduce chronic skin inflammation (Un-Nisa et al., 2023) and are considered a promising therapy in psoriatic patients (Moludi et al., 2021).

This study has several strengths: the E3N cohort study includes a population of women born between 1925 and 1950 when major lifestyle and rural-urban shifts occurred. The large size of the study population allowed to achieve adequate statistical power, except for the analyses on moderate-to-severe psoriasis that remain exploratory. The wealth of data collected in the E3N cohort, often at different points in time, permitted us to control for several potential confounding factors in multivariable analyses. Also, with the prospective design of the study potential bias in the reporting of exposures in childhood is unlikely to be differential between cases and non-cases.

A limitation of the study is that case identification was based mainly through self-reported information. However, also previous studies on psoriasis in large prospective cohorts used self-reported diagnosis that has been shown to be reliable in comparison with dermatologist assessment (Phan et al., 2018; Setty et al., 2007). While full validation of self-reported diagnoses through the acquisition of medical reports or specific questionnaires to collect clinical information was not possible, we complemented self-reported data with data from the MGEN drug reimbursement database. In particular, our case definition was supported by the observation that 97% of cases had reimbursements of drugs used to treat psoriasis (i.e., derivatives of vitamin D, cytokine receptor modulators, immunosuppressants, psoralens, and topical steroids). In general, the positive predictive value of self-reported diagnosis of psoriasis may be sub-optimal in a general population setting (Modalsli et al., 2016), but the higher level of education of the women in the cohort and the use of the drug reimbursement database to complement self-reported information for moderate-to-severe cases in our study have likely increased the reliability of our classification of cases and non-cases. Another observation supporting our case definition is that the incidence rate of psoriasis observed in our study is in general agreement with incidence rates reported in other studies in Europe that ranged between 40 and 300 per 100 000 persons per year (Parisi et al., 2020).

The number of cases with unknown age at diagnosis that we excluded from our main analyses is relatively large (N = 1 656) but the impact of the exclusion of such cases is likely to be marginal as suggested by the results of the sensitivity analysis based on logistic regression where all cases identified have been included.

The main limitations of the analyses on moderate-to-severe psoriasis are the modest number of cases, and the degree of severity judged only by the type of treatment used. In addition, the availability of drug reimbursement data only from 2004 onward leaves uncertainties about the true date of the first onset of moderate-to-severe symptoms.

Some limitations also concern the exposure data based only on information available from one questionnaire. For example, from the question "Living in a farm at least 3 months" it was not possible to determine the time a woman spent in a farm. Similarly, we could not determine whether "farming parents" spent their entire working life in agriculture and animal breeding despite data suggest that occupational mobility in the agricultural sector in the first half of the 20th century in France was limited (Molinier, 1977).

With respect to other prospective cohorts and to the general population, in the E3N cohort there is less variation in socio-economic status but we observed sufficient interindividual variation for the exposure variables of interest (e.g., 34.6% of the cohorts' participants were born in a rural environment).

Finally, the E3N cohort includes only women that were aged between 40 and 65 years at baseline. Our study was therefore limited to late-onset psoriasis and leaves the question open as to whether the same associations we observed would apply to early-onset psoriasis or whether they would apply also to men.

5. Conclusions

To our knowledge this is the first study exploring the role of the environment during childhood on psoriasis risk. The study shows that exposure to a rural environment in childhood, and specifically rural birthplace or having farming parents, might be associated with a reduction in risk of psoriasis. Our results warrant further investigations in other populations, including men and younger generations. These findings may help to improve our understanding of the pathogenesis of psoriasis.

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Institutional review board statement

Approval was obtained from the French National Commission for Data Protection and Individual Freedom (327346-V14) and the French Advisory Committee on Information Processing in Material Research in the Field of Health (13.794).

Informed consent statement

All participants signed an informed consent form at the study entry.

Credit author statement

Marco Conte: Conceptualization, Data curation, Methodology, Formal analysis, Writing – original draft, Raphaëlle Varraso: Conceptualization, Writing – review & editing, Agnes Fournier: Writing – review & editing, Joseph A. Rothwell: Writing – review & editing, Laura Baglietto: Writing – review & editing, Marco Fornili: Writing – review & editing, Emilie Sbidian: Conceptualization, Writing – review & editing, Gianluca Severi: Supervision.

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.

Data availability

Data will be made available on request.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envres.2023.117062.

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