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Study of risk factors of psoriasis related to inflammation and immunity in the E3N cohort

*Étude des facteurs de risque de psoriasis liés à l'inflammation et à l'immunité
dans la cohorte E3N*

Thèse de doctorat de l'université Paris-Saclay

École doctorale n° 570 : Santé Publique (EDSP)

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Graduate School : Santé Publique. Référent : Faculté de médecine

Thèse préparée dans l'unité de recherche CESP (Université Paris-Saclay, UVSQ, Inserm), sous la direction de **Gianluca Severi**, HDR, docteur de santé publique, spécialité épidémiologie

Thèse soutenue à Paris-Saclay, le 15 Decembre 2023, par

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Mots clés : cohorte longitudinale ; épidémiologie ; immunité ; inflammation ; psoriasis

Résumé : Le psoriasis est une maladie cutanée à médiation immunitaire qui touche des millions de personnes dans le monde, avec des coûts sociaux et économiques importants.

Le psoriasis reste une maladie incurable en raison d'un manque de compréhension de sa pathogenèse, qui semble impliquer une interaction complexe entre des facteurs génétiques et environnementaux qui provoquent une activation aberrante du système immunitaire.

Des données expérimentales suggèrent que les expositions environnementales contribuent à la pathogenèse du psoriasis en modulant l'immunité et l'inflammation, à la fois en agissant directement sur la maturation des cellules immunitaires innées et adaptatives impliquées et en agissant indirectement sur le microbiome, qui à son tour stimule l'acquisition de la tolérance immunitaire ou, à l'inverse, provoque une activation immunitaire. Cependant, pour de nombreux facteurs environnementaux soupçonnés de jouer un rôle dans la modulation de l'immunité et de l'inflammation et leur relation avec le risque de psoriasis, les études dans la littérature sont rares et peu concluantes.

L'objectif général de ce projet de doctorat était d'étudier le rôle de l'environnement dans le développement du psoriasis. Le concept d'"environnement" adopté dans cette thèse est large et englobe le réseau complexe de facteurs externes et le mode de vie qui peuvent influencer le risque de psoriasis par le biais de réponses immunitaires et inflammatoires.

L'objectif spécifique de la thèse était de tester l'association avec le psoriasis pour trois groupes de facteurs de risque supposés : L'ablation du MALT (tissu lymphoïde associé aux muqueuses - appendicectomie, adénoïdectomie, amygdalectomie), l'environnement de l'enfance (comme le fait de vivre dans un lieu de naissance urbain ou rural, d'avoir des parents agriculteurs et de vivre avec des animaux domestiques) et l'exposition au soleil en milieu résidentiel. Nous avons testé ces associations à l'aide de la cohorte prospective française E3N, établie en 1990 et composée de 98 995 femmes nées entre 1925 et 1950 et affiliées à la Mutuelle Générale de l'Éducation Nationale (MGEN). Nous avons effectué les analyses statistiques à l'aide des modèles de risques proportionnels de Cox et de régression logistique.

Les résultats suggèrent que l'appendicectomie augmente le risque de psoriasis, alors qu'aucune association n'est observée avec l'adénoïdectomie ou l'amygdalectomie. En outre, une association inverse a été observée entre le lieu de naissance rural, le fait d'avoir des parents agriculteurs et le risque de psoriasis. Enfin, une association inverse a été observée entre l'exposition solaire résidentielle et le psoriasis.

Les associations identifiées dans nos analyses, si elles sont reproduites dans d'autres populations, permettront de mieux comprendre la pathogenèse de la maladie psoriasique et pourraient ouvrir des voies prometteuses pour le développement de programmes de prévention ciblant les populations à haut risque de psoriasis.

Title : Study of risk factors of psoriasis related to inflammation and immunity in the E3N cohort

Keywords : longitudinal cohort ; epidemiology ; immunity ; inflammation ; psoriasis

Abstract : Psoriasis is an immune-mediated skin disease that affects millions of people worldwide, with significant social and economic costs.

Psoriasis remains an incurable disease due to a lack of understanding of its pathogenesis, which appears to involve a complex interaction between genetic and environmental factors that cause aberrant activation of the immune system.

Experimental evidence suggests that environmental exposures contribute to the pathogenesis of psoriasis by modulating immunity and inflammation, both by acting directly on the maturation of the innate and adaptive immune cells involved and by acting indirectly on the microbiome, which in turn stimulates the acquisition of immune tolerance or, conversely, causes immune activation. However, for many environmental factors suspected to play a role in modulating immunity and inflammation and their relationship with psoriasis risk, studies in the literature are sparse and inconclusive.

The overall aim of the present PhD project was to investigate the role of the environment in the development of psoriasis. The concept of "environment" used in this thesis is broad, encompassing the complex network of external factors and lifestyle that may influence the risk of psoriasis through immune and inflammatory responses.

The specific aim of the thesis was to test the association with psoriasis for three groups of putative risk factors: MALT (mucosa-associated lymphoid tissue - appendectomy, adenoidectomy, tonsillectomy) removal, childhood environment (such as living in an urban or rural birthplace, having farming parents, and living with pets), and residential sun exposure. We tested these associations using the French prospective E3N cohort, established in 1990 and consisting of 98,995 women born between 1925 and 1950 and affiliated with the Mutuelle Générale de l'Éducation Nationale (MGÉN). We performed statistical analyses using Cox proportional hazards and logistic regression models.

The results suggest that appendectomy increases the risk of psoriasis, while no association is observed with adenoidectomy or tonsillectomy. In addition, an inverse association was observed between rural birthplace, having farming parents and psoriasis risk. Finally, an inverse association was observed between residential sun exposure and psoriasis.

The associations identified in our analyses, if replicated in other populations, will allow a better understanding of the pathogenesis of psoriatic disease and may open promising avenues for the development of prevention programs targeting populations at high risk for psoriasis.

RESUME DE LA THÈSE EN FRANÇAIS

INTRODUCTION

Le psoriasis est une maladie auto-immune de la peau qui englobe de nombreux phénotypes cliniques distincts, tous caractérisés par des plaques cutanées anormales. Ces lésions sont rouges, sèches, prurigineuses et squameuses.

Le psoriasis est aujourd'hui considéré comme une maladie systémique qui détermine un état inflammatoire général dans l'organisme. Les patients atteints de psoriasis ont tendance à souffrir deux fois plus du syndrome métabolique que les sujets sains et à présenter d'autres comorbidités systémiques, comme notamment la maladie de Crohn, la bronchopneumopathie chronique obstructive, la stéatose hépatique et l'uvéïte. Environ 30 % des patients psoriasiques souffrent d'arthrite psoriasique, une affection inflammatoire séronégative qui touche les articulations périphériques, mais aussi les sites enthésaux, les doigts et le squelette axial.

Le psoriasis est également associé à un fardeau psychologique accru pour le patient dû à la stigmatisation sociale, un niveau de stress élevés, des limitations physiques, de la dépression, des problèmes d'emploi et d'autres comorbidités psychosociales.

Le diagnostic du psoriasis repose sur l'examen clinique du médecin, qui utilise des échelles de gravité de la maladie pour classer les cas comme légers, modérés ou sévères.

Le psoriasis léger est traité avec des agents topiques, tandis que le psoriasis modéré à sévère est traité avec des traitements immunosuppresseurs (conventionnels ou biologiques) et/ou de la photothérapie.

Malheureusement, malgré le large éventail de traitements disponibles, le psoriasis reste une maladie incurable dans laquelle les médicaments agissent à différents stades de la cascade inflammatoire pour réduire les symptômes et prévenir ou retarder l'apparition de comorbidités.

Cela est dû en grande partie à un manque de compréhension du réseau immunologique complexe impliqué dans la pathogenèse de la maladie.

On sait que le développement du psoriasis est probablement dû à de multiples sites de susceptibilité génétique, à un dérèglement du système immunitaire, à des facteurs de risque environnementaux et à une dysbiose microbienne qui peuvent agir comme des déclencheurs et qui sont encore aujourd'hui mal compris.

Le psoriasis est une maladie dont la base génétique est importante : la principale association génétique connue avec le psoriasis est représentée par les gènes de la région Human leukocyte antigen-C (HLA-C) du chromosome 6p21.3, désormais appelée région PSORS1. Le rôle des gènes dans PSORS1 n'a pas encore été élucidé, mais HLA-C est probablement capable de réguler la réponse immunitaire innée et adaptative grâce à la présence du complexe majeur d'histocompatibilité de classe I sur les cellules nucléées. D'autres gènes de susceptibilité ont été découverts et les fonctions les plus impliquées de ces gènes sont : la formation de la barrière cutanée ; l'immunité innée, l'immunité adaptative et les gènes de chevauchement entre l'immunité innée et l'immunité adaptative.

La compréhension des mécanismes moléculaires de la maladie des 15 dernières années ont permis d'identifier le rôle central de l'axe IL-17/23.

Le déclenchement initial du psoriasis n'est pas clair, mais les cellules dendritiques de la peau sont certainement impliquées dans la cascade qui amplifie la réponse immunitaire : ces cellules sont capables de recruter des cellules T et des cellules B par le biais de l'IFN-alpha et d'autres interleukines telles que l'IL-6, l'IL-12, le TNF- α et surtout l'IL-23. Ces cytokines conduisent à la différenciation des cellules T en sous-types tels que Th17. Ces cellules Th17 sont impliquées dans le maintien de l'inflammation et assurent le lien entre l'immunité innée et acquise. En effet, les Th17 sécrètent l'IL-17, qui joue un rôle central dans l'activité pro-inflammatoire du psoriasis, induisant l'expression de cytokines pro-inflammatoires par les cellules dendritiques, neutrophiles, cellules T, monocytes/macrophages et cellules épithéliales qui contribuent au maintien de l'inflammation. Les kératinocytes activés sécrètent des peptides antimicrobiens tels que la cathelicidine LL37 qui, en se liant à l'auto-ADN libéré par les cellules des lésions psoriasiques, qui pourraient déclencher une boucle inflammatoire soutenue par les cellules dendritiques.

Le rôle de l'environnement et du style de vie dans la pathogénie du psoriasis est suggéré par la variabilité géographique et temporelle du psoriasis.

En 2019, le nombre de cas prévalents de psoriasis dans le monde a été estimé à environ 40,8 millions (soit 503.6 cas pour 100 000 personnes), tandis que le nombre de nouveaux cas de psoriasis a été estimé à 4,62 millions, avec un taux d'incidence normalisé selon l'âge de 57.8 pour 100 000 personnes.

La prévalence et l'incidence étaient les plus élevées en Europe occidentale, en Australasie et en Amérique du Nord à revenu élevé, tandis qu'elles étaient les plus faibles en Asie du Sud-Est, en Amérique latine centrale et en Afrique subsaharienne orientale.

L'incidence du psoriasis augmente avec l'âge jusqu'à 39 ans, puis commence à diminuer avant d'atteindre un nouveau pic vers 50-59 ans ou 60-69 ans.

Les données ne montrent pas de différence entre les sexes dans l'incidence de la maladie, mais les pics dans la distribution de l'incidence de la maladie par âge semblent être plus précoces chez les femmes (20-29 ans et 50-59 ans) que chez les hommes (30-39 ans et 60-69/70-79 ans).

La littérature fait état d'une augmentation de la prévalence du psoriasis au fil du temps, tandis que l'incidence semble stable ou en légère diminution dans le monde entier. L'augmentation de la prévalence peut être liée à une meilleure connaissance générale de la maladie psoriasique et à une amélioration progressive du traitement, avec pour conséquence une augmentation des diagnostics de psoriasis. La diminution observée de l'incidence du psoriasis pourrait s'expliquer par un effet de cohorte ou un effet de période qu'ont été observés dans la population atteinte de psoriasis et sont liés à des modifications de l'environnement et du mode de vie au fil du temps.

Un large éventail de facteurs liés à l'environnement et au mode de vie a été étudié pour tenter d'améliorer la compréhension du mécanisme sous-jacent à l'activation de la cascade inflammatoire dans le psoriasis.

Parmi ceux-ci, nous pouvons citer les rayons UV, la pollution de l'air, l'alcool, le tabagisme, l'obésité, l'alimentation, le stress psychologique, les médicaments et les infections.

Ces facteurs peuvent agir directement sur la réponse immunitaire mais aussi avoir un effet sur le microbiome, c'est-à-dire l'ensemble des micro-organismes qui colonisent chaque partie du corps humain et dont les changements dans la composition et l'abondance, connus sous le nom de dysbiose, jouent un rôle central dans le dérèglement immunitaire et les maladies à médiation immunitaire, y compris le psoriasis.

Malgré des avancées significatives dans la compréhension des mécanismes moléculaires impliqués dans la maladie et la disponibilité de nouveaux traitements, le psoriasis reste un problème majeur de santé publique en raison de son coût pour la société.

Toutefois, en ce qui concerne les facteurs de risque supposés susceptibles d'affecter les mécanismes immunitaires du psoriasis, les études épidémiologiques disponibles sont rares et présentent souvent des limites telles qu'un petit nombre de participants et la nature rétrospective de la collecte des données sur l'exposition.

L'objectif principal de ce projet de doctorat était d'étudier les associations entre les facteurs environnementaux et de mode de vie liés à l'inflammation et à l'immunité et le risque de psoriasis

dans la cohorte E3N.

MATÉRIEL ET MÉTHODES

La cohorte E3N est une cohorte prospective de 98 995 femmes affiliées à la Mutuelle générale de l'Éducation nationale (MGEN), âgées de 40 à 65 ans (nées entre 1925 et 1950) et vivant en France métropolitaine au moment du recrutement entre 1989 et 1990.

La collecte d'informations sur la santé, la nutrition et le mode de vie a été effectuée au moyen de questionnaires auto-administrés envoyés aux participants tous les deux ou trois ans. Le couplage avec la base de données de la MGEN a permis d'accéder aux données sur le statut vital et l'adresse postale de chaque femme E3N, ainsi qu'aux informations sur les remboursements de médicaments. Les données sur les remboursements de médicaments sont disponibles à partir de 2004 et ne concernent que les médicaments administrés en dehors de l'hôpital.

Ces travaux de thèse sont les premiers à étudier le psoriasis dans la cohorte E3N. La première partie du projet a été consacrée à l'identification des cas par une évaluation et une synthèse des données pertinentes disponibles dans deux sources de la cohorte : les diagnostics de psoriasis autodéclarés à partir des questionnaires et le remboursement des médicaments approuvés pour le traitement du psoriasis à partir de la base de données MGEN sur le remboursement des médicaments.

Une autre source de données a été utilisée pour compléter les deux sources principales : des zones de texte libre, présentes dans tous les questionnaires à partir du deuxième, où les femmes pouvaient signaler la présence de maladies non mentionnées dans d'autres parties du questionnaire ou des hospitalisations survenues depuis le questionnaire précédent.

Dans le 9e, 10e et 12e questionnaires de suivi (envoyés respectivement en 2007, 2011 et 2018), les participants ont été invités à indiquer s'ils avaient déjà eu un diagnostic de psoriasis et à quel moment.

Grâce aux données issues de la MGEN les données de remboursement des médicaments en dehors de l'hôpital pour tous les participants E3N affiliés depuis le 1er janvier 2004 ont été collectées..

Les médicaments actuellement autorisés en France pour le traitement du psoriasis et dont les ordonnances ont été extraites des bases de données de la MGEN sont les suivants : corticostéroïdes topiques, médicaments topiques dérivés des vitamines A et D, psoralènes (PUVA), immunosuppresseurs non biologiques et immunosuppresseurs biologiques.

En combinant les données des trois questionnaires à partir desquels nous avons extrait des

informations sur le psoriasis, nous avons identifié un total de 4 621 cas.

Nous avons ensuite croisé les cas de psoriasis déclarés dans les questionnaires avec les données de remboursement des médicaments et l'analyse a montré que 4 099 cas (88.7 % de la population analysée) avaient fait l'objet d'au moins un remboursement pour un médicament utilisé dans le traitement du psoriasis.

En outre, une analyse des schémas de prescription de médicaments contre le psoriasis réalisée à partir des données MGEN sur l'ensemble de la cohorte a permis d'identifier d'autres cas potentiels de psoriasis qui n'avaient jamais déclaré de psoriasis dans les questionnaires mais qui avaient au moins deux prescriptions de médicaments topiques spécifiques au psoriasis (dérivés de la vitamine A ou de la vitamine D). En utilisant ce critère, nous avons identifié 1 086 cas supplémentaires de psoriasis.

En ajoutant cette population à celle identifiée dans les questionnaires, on obtient une population d'analyse de 5 707 cas de psoriasis. Les cas de psoriasis qui n'étaient présents que dans des zones de texte libre, soit 452 cas, n'ont pas été inclus dans la population de l'analyse principale, mais ont été utilisés pour les analyses de sensibilité. Le nombre total de cas de psoriasis identifiés dans la cohorte s'élève donc à 6 159 cas, soit une prévalence du psoriasis estimée à 6.2 %.

Parmi les cas de psoriasis identifiés, 3 848 (67.4 %) ont déclaré une date de diagnostic valide. Pour les besoins des analyses présentées dans cette thèse, le suivi a commencé au moment où le questionnaire de base de la cohorte a été rempli en 1990. Les cas incidents sont les cas diagnostiqués après le début du suivi, tandis que les cas diagnostiqués avant 1990 sont considérés comme prévalents. Sur la base de cette classification, nous avons identifié 2 567 (44.9 %) cas incidents et 1 281 (22.4 %) cas prévalents.

Pour les 1 859 cas restants (32.7%), la date du diagnostic n'était pas disponible et nous n'avons donc pas pu déterminer s'il s'agissait de cas incidents ou prévalents par rapport au début du suivi. Les 1 086 cas identifiés uniquement par le MGEN ont été inclus dans la catégorie sans date de diagnostic car la date du premier remboursement lié au psoriasis n'a pas été jugée comme un indicateur fiable de la date de diagnostic de la maladie.

Nous avons utilisé les données de remboursement de médicaments de la MGEN pour identifier les cas de psoriasis modérés à sévères, définis comme des cas de psoriasis auto-déclarés avec au moins un remboursement de médicament dans la base de données MGEN pour l'une des classes de médicaments systémiques utilisés dans le psoriasis (c'est-à-dire les psoralènes, les immunosuppresseurs non biologiques, ou les immunosuppresseurs biologiques). En utilisant ce

critère, nous avons trouvé un total de 449 cas de psoriasis modéré à sévère.

La méthode d'identification des cas de psoriasis que nous avons utilisée est similaire à celle utilisée dans d'autres cohortes prospectives telles que NutriNet-Santé, la Nurses' Health Study et l'étude norvégienne HUNT.

Les analyses statistiques de la thèse ont été réalisées à l'aide des modèles de risques proportionnels de Cox. Les modèles univariés ont été ajustés pour la cohorte de naissance, tandis que les modèles multivariés incluaient l'IMC (variable catégorielle : ≤ 24 , 25-30[, et ≥ 30 kg/m²), l'état civil (célibataire, mariée), le statut tabagique (jamais, actuel ou ex-fumeur), le niveau d'éducation (baccalauréat ou moins, maîtrise, doctorat ou plus) et trois variables binaires sur les conditions médicales : le diabète, la dépression ou l'anxiété et l'hypertension. Les effets potentiels des facteurs reproductifs et hormonaux ont été explorés en incluant des facteurs tels que l'âge à la ménarche (≤ 11 ans, 12-14 ans, ≥ 15 ans), le statut ménopausique (préménopause, ménopausée), la parité (nullipare, primipare/multipare) et l'utilisation de la pilule contraceptive orale (non, oui). Certaines variables comme le tabagisme, l'IMC, les comorbidités et le statut ménopausique ont été incluses dans les analyses en tant que variables dépendantes du temps, car leurs valeurs pouvaient changer au cours du suivi.

Compte tenu des différences étiologiques possibles entre les cas de psoriasis léger et les cas de psoriasis modéré à sévère, nous avons effectué, dans chacune des études, des analyses basées sur tous les cas incidents de psoriasis et, séparément, uniquement sur les cas de psoriasis modéré à sévère.

La régression logistique a été utilisée dans les analyses de sensibilité de cette thèse pour évaluer l'association entre les facteurs de risque étudiés et tous les cas potentiels de psoriasis, incluant ceux identifiés dans les encadrés de texte libres.

Toutes les études menées dans le cadre de cette thèse ont utilisé la population E3N décrite ci-dessus. De même, les modèles univariés et multivariés testés ont été ajustés pour les variables énumérées ci-dessus.

MALTECTOMIE ET RISQUE DE PSORIASIS

La première hypothèse était que les tissus lymphoïdes associés aux muqueuses (MALT) jouent un rôle fondamental dans le bon développement du système immunitaire et dans l'homéostasie du microbiome.

Le premier objectif de l'étude était donc de déterminer si l'ablation chirurgicale de trois types de

tissus lymphoïdes (adénoïdectomie, appendicectomie et amygdalectomie) est associée à une réduction du risque de psoriasis à long terme.

Les données sur l'appendicectomie, l'adénoïdectomie et l'amygdalectomie ont été recueillies dans le questionnaire de base de 1990 et, pour l'appendicectomie uniquement, dans les questionnaires de 1992 et 1993.

Au cours de la période de suivi 1990-2018 de 90 119 participants à l'étude 2 433 cas incidents de psoriasis ont été identifiés grâce aux déclarations des patientes, tandis qu'au cours de la période pour laquelle des données sur le remboursement des médicaments étaient disponibles dans la base de données MGEN (2004-2018), 120 cas de psoriasis modéré à sévère ont été recensés.

L'appendicectomie a été associée à un risque accru de psoriasis à la fois dans le modèle univarié [rapports de risque univariés-uHR : 1.17 (intervalle de confiance- IC à 95% : 1.08 -1.27)] et dans le modèle multivariable [rapports de risque multivariés-aHR : 1.14 (IC à 95% : 1.05 -1.24)]. Une association suggestive avec l'appendicectomie a été observée pour le risque de psoriasis modéré à sévère [uHR : 1.40 (IC à 95 % : 0.97-2.02) ; aHR : 1.36 (IC à 95% : 0.94-1.96)]. Aucune association n'a été observée entre l'amygdalectomie et l'adénoïdectomie dans les modèles de psoriasis global et de psoriasis modéré à sévère.

Ce résultat était cohérent avec l'hypothèse selon laquelle des mécanismes immunitaires éloignés de la peau et des interactions entre le système immunitaire et le système digestif pourraient jouer un rôle dans la pathogenèse du psoriasis.

ENVIRONNEMENT RURAL PENDANT L'ENFANCE ET RISQUE DE PSORIASIS

La seconde hypothèse était que l'environnement pendant l'enfance peut déterminer la tolérance immunitaire contre les auto-antigènes et jouer un rôle fondamental dans le développement du profil du microbiome, comme le postule l'hypothèse dite "hygiénique".

Le deuxième objectif de la thèse était d'étudier l'association entre l'environnement pendant l'enfance et le risque de psoriasis.

Cinq variables d'exposition ont été utilisées: quatre individuelles collectées en 2002 à l'aide du questionnaire 7 qui comprenait le fait d'avoir des parents fermiers, de vivre dans une ferme, de vivre avec des animaux de compagnie ou d'autres animaux de ferme pendant l'enfance et une variable écologique de lieu de naissance rural construite à partir du lieu de naissance autodéclaré au moment de l'enquête et du recensement général de l'agriculture de 1970, définissant un lieu de naissance comme rural s'il compte moins de 5 000 habitants.

Au cours du suivi 1990-2018 de 72 154 participants à l'étude, un total de 1 967 cas incidents de psoriasis a été identifié. Au cours du suivi 2004-2018 de 67 917 participants à l'étude, 188 cas de psoriasis modérés à sévères ont été identifiés grâce à des auto-déclarations et à les données provenant de la base de données MGEN.

Des associations négatives avec le risque de psoriasis ont été observées pour le lieu de naissance rural [aHR : 0.87 (IC à 95% : 0.79 -0.96)] et pour le fait d'avoir des parents fermiers [aHR : 0.84 (IC à 95% : 0.72 -0.97)]. Aucune association significative n'a été observée avec le psoriasis modéré à sévère. Ces résultats suggèrent qu'une exposition à un environnement rural pendant l'enfance peut être associée à un risque réduit de psoriasis.

Ces résultats suggèrent que l'enfance est une période critique pour la pathogenèse du psoriasis. Nous émettons l'hypothèse que les associations observées sont liées à l'effet immunomodulateur direct de l'exposition à un environnement rural, qui pourrait également façonner indirectement le microbiome, et qui pourrait être influencé par les parents fermiers à travers l'acquisition de certaines habitudes de vie, telles que les habitudes alimentaires.

EXPOSITION SOLAIRE, TRAITS PIGMENTAIRES ET RISQUE DE PSORIASIS

La troisième hypothèse était que l'exposition résidentielle aux UV est associée à une réduction du risque de psoriasis.

Le troisième objectif de cette thèse était d'évaluer l'association entre l'exposition résidentielle aux UV et le risque de psoriasis et de vérifier si les traits pigmentaires sont associés au risque de psoriasis.

Les traits pigmentaires ont été collectés dans le questionnaire de base, où les participants devaient indiquer leur phototype de peau (albinos, peau claire, blanc, brun clair, brun foncé, noir) et la couleur naturelle de leurs cheveux (albinos, blond, roux, brun clair, brun foncé, noir).

Dans le questionnaire de base, les femmes ont également indiqué leur adresse de résidence actuelle avec le nom de la ville et le code postal qui ont été couplés avec des données sur l'exposition aux UV provenant de la base de données sur le rayonnement solaire (SoDa), y compris les doses d'UV moyennes annuelles, moyennes printemps/été et moyennes automne/hiver exprimées en dose érythémale [kJ/m²].

Au cours de la période de suivi 1990-2018 de 83 896 participants à cet étude 2 078 cas incidents de psoriasis ont été identifiés. Au cours du suivi 2004-2018 de 72 186 participants à l'étude, 108 cas de psoriasis modérés à sévères ont été identifiés grâce à des auto-déclarations et à les données provenant de la base de données MGEN.

Une association inverse a été observée entre l'exposition résidentielle aux UV et le risque de psoriasis [HRs 0.91 (IC à 95% : 0.80-1.01), 0.80 (IC à 95% : 0.70-0.91) et 0.88 (IC à 95% : 0.77-1.00) pour le deuxième, troisième et quatrième quartile respectivement.

La catégorie albinos/très clair était associée à un risque accru de psoriasis par rapport à la catégorie peau blanche (référence) [HRs 1,55 (95%CI : 1,13-2,11)]. À l'inverse, une couleur de peau plus foncée était associée à un risque réduit de psoriasis [HR pour les groupes "brun clair" et "brun foncé-noir" étaient respectivement de 0.87 (IC 95% : 0.80-0.95) et 0.86 (IC à 95 % : 0.59-1.24), tandis qu'aucune association n'a été trouvée entre la couleur naturelle des cheveux et le risque de psoriasis.

L'association entre une couleur de peau plus foncée et un risque plus faible de psoriasis pourrait être due à des facteurs génétiques ou à d'autres facteurs non biologiques non pris en compte, tels que le régime alimentaire ou une perception différente du risque de psoriasis chez les femmes à la peau plus foncée.

CONCLUSION

Cette thèse visait à étudier les associations entre les facteurs de risque liés à la réponse immunitaire et inflammatoire et le risque de psoriasis en utilisant les données de la cohorte prospective E3N.

Les points forts de notre étude sont sa conception prospective, la taille importante de la population étudiée et la longue période de suivi (28 ans).

Les principales limites sont le nombre modeste de cas inclus dans les modèles modérés à sévères, la définition du statut modéré à sévère basée uniquement sur le type de traitement utilisé, la faible variation du statut socio-économique des participants E3N et l'âge tardif des femmes lors de l'inclusion dans la cohorte.

Les variables étudiées dans le présent travail représentent une première approche de l'étude des facteurs environnementaux liés à l'immunité et à l'inflammation dans le psoriasis, et les résultats obtenus montrent une ligne de recherche prometteuse qui élargira nos connaissances sur la pathogenèse de la maladie. Nos résultats doivent être confirmés et étudiés par d'autres groupes de recherche nationaux et internationaux.

Notre étude a montré que certains facteurs liés à la réponse immunitaire peuvent avoir un effet sur l'incidence de la maladie psoriasique.

Sur la base des présents résultats, des programmes de prévention primaire basés sur la prescription d'une ou plusieurs périodes de séjour en zone rurale dans la population d'âge préscolaire et sur une

exposition solaire quotidienne régulière dans la population adulte à haut risque de psoriasis pourrait être développés.

En outre, si le rôle de la dysbiose intestinale dans le psoriasis est confirmé, des signes précoces de modifications du microbiome pourraient être identifiés avant l'apparition des symptômes de la maladie et des mesures prophylactiques telles que la transplantation de microbiome ou l'administration de probiotiques pourraient être envisagées pour interrompre ou retarder le processus pathogène.

De telles mesures préventives devraient être testées dans le cadre d'essais cliniques interventionnels afin de vérifier leur efficacité et nécessiteraient un effort important et la mobilisation de divers acteurs de la santé publique tels que les associations de patients, les instituts de recherche, le système français de santé publique et le ministère de la santé.

SCIENTIFIC VALORISATION

Article accepted for publication in connection with doctoral work :

- Conte M, Varraso R, Fournier A, Rothwell JA, Baglietto L, Fornili M, Sbidian E, Severi G. A prospective study of the association between living in a rural environment during childhood and risk of psoriasis. *Environ Res.* 2023 Sep 1;237(Pt 2):117062. doi: 10.1016/j.envres.2023.117062. Epub ahead of print. PMID: 37660877.

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- Conte M, Faure E, Fournier A, Rothwell JA, Baglietto L, Fornili M, Kvaskoff M, Sbidian E, Severi G. A prospective study of the association between residential sun exposure, pigmentary traits and risk of psoriasis.

Other publications as co-author:

- Giometto S, Baglietto L, **Conte M**, Vannacci A, Tuccori M, Mugelli A, Gini R, Lucenteforte E. Use of antiseizure medications and safety of branded versus generic formulations: A comparative study on Tuscan administrative databases. *Epilepsy Behav.* 2021 Apr;117:107876. doi: 10.1016/j.yebeh.2021.107876. Epub 2021 Mar 11. PMID: 33714929.
- Rothwell JA, Mori N, Artaud F, Fournier A, **Conte M**, Boutron-Ruault MC, Chan SSM, Gunter MJ, Murphy N, Severi G. Colorectal cancer risk following appendectomy: a pooled analysis of three large prospective cohort studies. *Cancer Commun (Lond).* 2022 May;42(5):486-489. doi: 10.1002/cac2.12265. Epub 2022 Feb 7. PMID: 35132829; PMCID: PMC9118062.
- Giometto S, Tillati S, Baglietto L, De Bortoli N, Mosca M, **Conte M**, Tuccori M, Gini R, Lucenteforte E. Use of Biological Drugs for Psoriasis: A Drug-Utilization Study Using Tuscan Administrative Databanks. *Int J Environ Res Public Health.* 2022 Jun 2;19(11):6799. doi: 10.3390/ijerph19116799. PMID: 35682382; PMCID: PMC9180218.

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LIST OF ABBREVIATIONS

AhR : Aryl hydrocarbon receptor
AMP: Antimicrobial peptide
APCs : Antigen presenting cells
Bmi: Body mass index
BSA: Body Surface Area
CCL: Chemokine (C-C motif) ligand
CD: cluster of differentiation
CRH : Corticotropin-releasing hormone
CXC : C-X-C motif
CXCR :C-X-C chemokine receptor type
DAMP: Damage-associated molecular pattern
DC: Dendritic cells
DLQI: Dermatology Quality of Life Index
ER: Endoplasmic reticulum
G-CSF: Granulocyte colony-stimulating factor
HLA: Human leukocyte antigen
IBD: Inflammatory bowel disease
ICAM : InterCellular Adhesion molecule
IFN : interferon gamma
Ig : Immunoglobulin
IL: interleukin

ILC: Innate lymphoid cell

IMIDs: immune-mediated inflammatory diseases

iNOS : Inducible nitric oxide synthetase

JAK-STAT : Janus kinase signal transducers and activators of transcription

LC: Langerhans cell

MALT: Mucosa associated lymphoid tissues

MAPK: Mitogen-activated protein kinase

MSH: Melanocyte-stimulating hormones

NF- κ B: Nuclear factor-kappa B

NK: natural killer

PAHs: Polyaromatic hydrocarbons

PAMPs: pathogen-associated molecular patterns

PASI: Psoriasis Area and Severity Index

pDCs: Plasmacytoid dendritic cells

PGA: Physician's Global Assessment

PRO: patient-reported outcome measure

PSI: Psoriasis Symptom Inventory

RAR: retinoic acid receptor

ROS: Reactive oxygen species

SLE: Systemic lupus erythematosus

SPI: Simplified Psoriasis Index

TGF: Transforming growth factor

Th: T-helper

TLR: Toll-like receptors

Treg: T regulatory

UV: Ultraviolet

VCAM: Vascular cell adhesion molecule

VEGF: Vascular endothelial growth factor

V β : Variable region of the beta chain

$\gamma\delta$: gamma delta

PART I: INTRODUCTION

1. OVERVIEW

Psoriasis is an immune-mediated skin disease that includes many distinct clinical phenotypes, all characterized by abnormal skin patches. Before describing the disease in detail, it is useful to recall the skin structure and functions as well as the main immune-related mechanisms that take place in the skin.

1.1. SKIN STRUCTURE AND FUNCTIONS

Psoriasis is a disease of the skin which is the largest human organ with a surface of 25 m²¹ and a weight that accounts for 15 percent of the total human body².

Skin exerts fundamental roles in human physiology such as absorption, excretion, secretion, regulation, sensory perception and protection. Its morphological structure is composed by three layers: epidermis, dermis and hypodermis.

The outermost layer, the epidermis, is composed by 5 strata: stratum basale (the deepest portion of the epidermis), stratum spinosum, stratum granulosum, stratum lucideum and stratum corneum (the most superficial portion of the epidermis)³. The stratum lucideum is only present in thick skin areas such as palms and soles⁴.

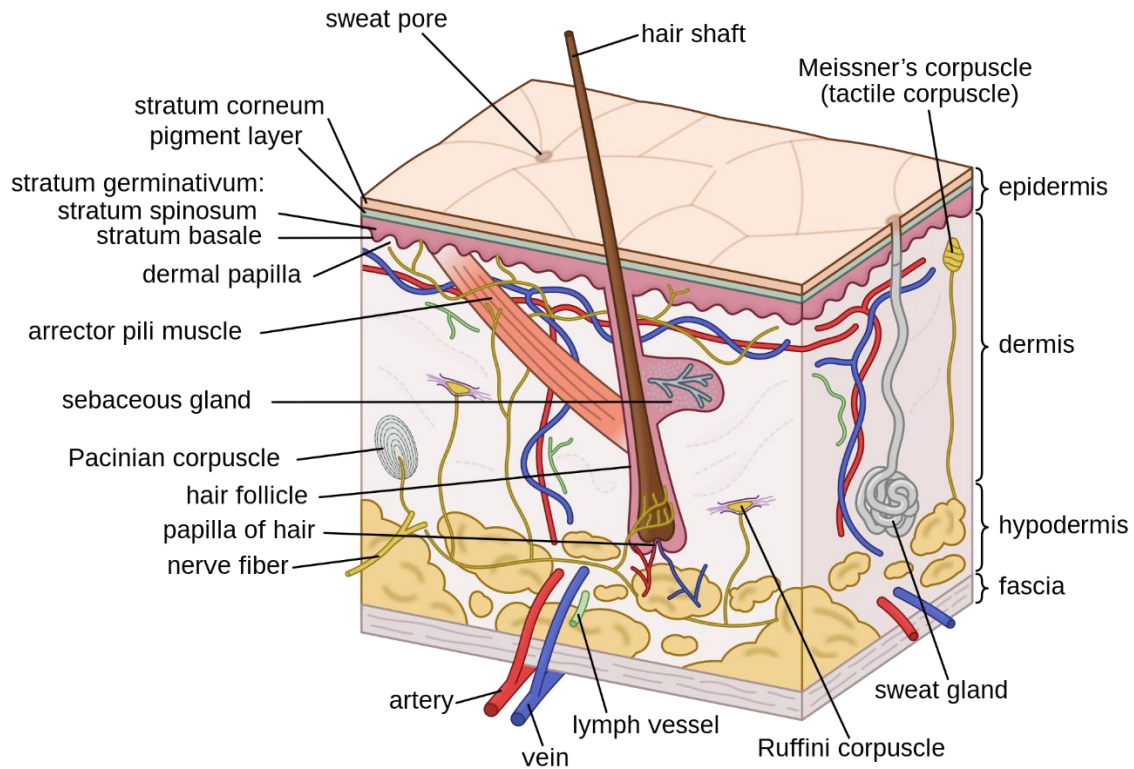


Figure 1: Skin Structure. Source: Tomáš Kebert & umimeto.org (Licence CC BY-SA 4.0)

Epidermis is mainly composed of keratinocytes, whose functions are linked to the protection of inner body from physical (heat, UV radiation) and biological (bacteria, fungi, parasites and viruses) threats. Active replicating keratinocytes form the stratum basale of the epidermis and are connected to dermis by hemidesmosomes on the basal lamina. Keratinocytes derived its name from keratin, a protein whose production is responsible for the barrier function and water loss prevention of epidermis⁴. Another fundamental function of keratinocytes is the production of Vitamin D from 7-dehydrocholesterol precursor through their enzymes (the 25-hydroxylase, and the 1-alpha-hydroxylase) to its active form 1,25 dihydroxyvitamin D (1,25(OH)₂D)⁵.

Other three types of cells are included in epidermis: melanocytes, Langerhans cells and Merkel cells. Melanocytes present in stratum basale contribute to UV protection through melanin production, a pigment derived from the conversion of tyrosine to dihydroxyphenylalanine (DOPA) by the enzyme tyrosinase. Merkel cells are receptor of mechanic movement connected to nerves present in dermis. Langerhans cells are immune cells derived from bone marrow that exert a fundamental role in antigen processing through their expression of major histocompatibility complex (MHC) I and MHC II⁴.

Dermis is composed by two strata: papillary stratum is the uppermost and contiguous to basal lamina of epidermis while the deep reticular stratum is contiguous to hypodermis. Dermis is mainly composed of connective tissue which is thicker in the reticular than in the papillary stratum ⁴.

Dermis is the skin layer where the excretion function takes place thanks to the presence of sudoriparous and sebaceous glands that, through the production of sweat, determine thermoregulation and, through the production of sebum, protect the body from external aggressions ⁶.

Dermis also host blood vessels organized as a superficial plexus, close to epidermis, that nourish epidermal keratinocytes, and a deeper plexus that run between dermis and hypodermis that provides nutrition to sweat glands and piliferous follicles. Both plexuses are controlled by an autonomic nervous system that acts as principal effector of thermoregulation in the skin. Dermis also host three types of nervous system receptors named "corpuscle" that respectively sense deep pressure (Pacini's corpuscle), low-frequency stimulation (Merkel's corpuscle) and skin stretch and pressure (Ruffini corpuscle)⁴.

Hypodermis, the deepest skin layer, is composed mainly of connective and adipose tissues. It contains lymphatic vessels, all major blood vessels from which detach the capillaries that form the dermal blood plexuses and the nerves that receive impulses from the nerve endings. Hypodermis contains piliferous bulbs which are connected to arrector pili muscles, bundles of smooth muscle fibers that are responsible for piloerection and sebaceous glands squeezing. Hypodermis functions include mechanic protection, thermoregulation and energetic metabolism. These functions are granted by the presence of the panniculus adipose which constitutes the principal component of hypodermis together with connective tissue that both separate fat lobules and constitutes fascia that separates hypodermis from muscles ⁴.

1.2. SKIN IMMUNE SYSTEM

The skin is the most extensive interface between the outside world and the human body. As the body's first barrier, it involves a wide range of cells interconnected by complex signaling networks that allow a high degree of plasticity in the immune response.

The immune factors described here are the main players whose dysregulation underlies the immune-mediated diseases of which psoriasis is one of the best-known examples.

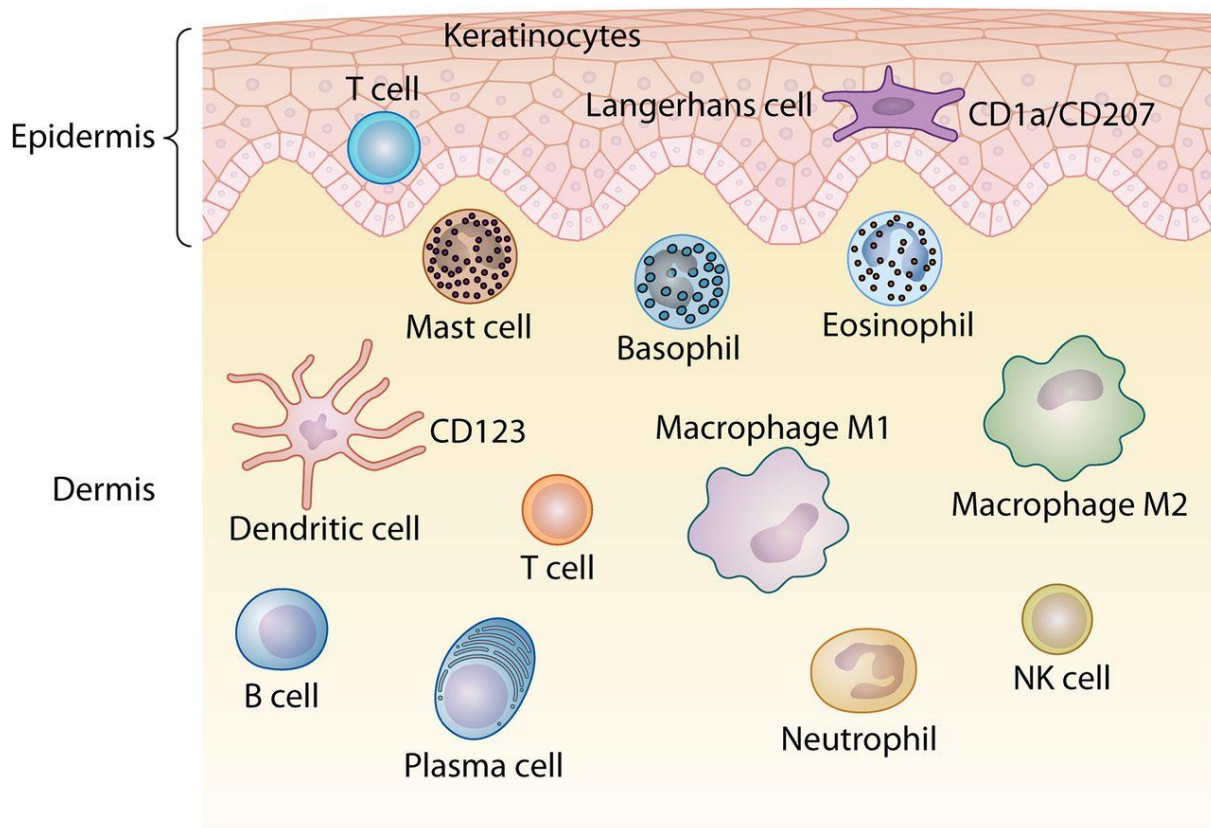


Figure 2: Schematic representation of skin-associated immune cells. Source: Quaresma⁷

A first line of defense is represented by keratinocytes, which, in addition to the mechanical defense of the organism through their joints, produce antimicrobial peptides (AMPs), such as defensins and cathelicidins, which are released when cells are damaged by microbial aggression⁸.

Keratinocytes act as triggers of the immune response: they are able to recognize the host skin microbiome and external antigens through the action of Toll-like receptors (TLRs), which recognize structures known as pathogen-associated molecular patterns (PAMPs), which are highly conserved components of microorganisms⁹.

Once activated by foreign antigens, keratinocytes are capable of producing numerous cytokines, such as interleukin (IL)-1, IL-6, IL-10, IL-17, IL-18, IL-22 and tumor necrosis factor alpha (TNF- α), which activate both the innate and adaptive inflammatory response⁷.

Keratinocytes are involved in the innate immune response through the release of damage-associated molecular patterns (DAMPs). These components of the cellular environment (mitochondria, cytosol, extracellular matrix, endoplasmic reticulum or plasma membrane) are

released upon cellular stress or tissue injury and determine a non-infectious inflammatory response by binding to a pattern recognition receptor on the surface of immune cells (dendritic cells, macrophages, monocytes, neutrophils) and epithelial cells¹⁰.

Other cells involved in the process of antigen recognition and activation of the inflammatory response are dendritic cells (DCs). These myeloid cells are derived from a common progenitor¹¹ and can be further differentiated into Langerhans cells, which are found in the epidermis, and dermal dendritic cells.

DCs act as antigen presenting cells (APCs) and play a key role in the activation of the immune response, which involves three specific steps: capture, processing and presentation of the antigen to T cells.

When DCs internalise antigens in their cytoplasm, they are processed into small amino acid chains and then expressed on the MHC II receptors exposed on the cell surface, together with costimulatory molecules such as C-X-C chemokine receptor type (CXCR) 4, facilitating the migration of DCs to the draining lymph nodes¹². This process occurs continuously, allowing for immune homeostasis and tolerance to self-antigens associated with the skin microbiome.

However, in case of aggression, the exposure of antigens by DCs through MHC II receptors is coupled by co-stimulatory receptors cluster of differentiation (CD) 40 and B7, which interact with T cell receptors (TCR) for the maturation and proliferation of T CD4 cells¹³.

The next order of cells involved in the inflammatory response, lymphoid cells and in particular T-helper (Th) cells, are the main actors in the skin's inflammatory response. There are more than twice as many local lymphocytes in the skin than in the blood system. These cells are found in the epidermis and dermis, where they cluster around capillaries¹⁴. They are classified into at least 9 subtypes based on their interleukin production: Th1, Th2, Th3, Th17, T regulatory (Treg), Th3, Th9, Th22 and Th25.

Th1 are associated with antimicrobial activity and are involved in the pathogenesis of autoimmune and immune-mediated diseases¹⁵. Th2 are involved in allergic reactions¹⁶, while Th3 are Transforming growth factor (TGF)-beta secreting cells and are considered a subpopulation of Treg cells due to their ability to inhibit the proliferation of non-antigen-specific lymphocytes¹⁷. The other type of Treg cells, called Tr1, are mainly involved in the production of IL-10 and are responsible for the inhibition of B cells and natural killer (NK) cells¹⁸.

Th17 contribute to the production and recruitment of neutrophils through the secretion of

Granulocyte colony-stimulating factor (G-CSF) and IL-8 and, synergistically with Th22, are responsible for the activation of keratinocytes through the production of AMPs. Both Th17 and Th22 play a central role in many pathological processes such as psoriasis, lupus erythematosus, lymphoma, allergic and infectious diseases¹⁹.

Other T cell categories, such as Th9, Th25 and gamma delta ($\gamma\delta$) T lymphocytes, have recently been discovered. Their role is not yet clear, but they appear to be involved in Langerhans cell (LC) histiocytosis²⁰, leishmaniasis²¹ and leprosy²².

Following T cell activation, a large number of effector cells are recruited into the skin and have different targets:

- Neutrophils are mainly recruited by Th17 cells and proceed to phagocytise and destroy cells through microbicidal molecules present in phagolysosomes^{23,24}.
- Macrophages are recruited by Th1 and can differentiate into three distinct subpopulations based on the mediators secreted, focusing on pro-inflammatory activity, anti-inflammatory activity and lipid phagocytosis²⁵.
- Eosinophils are recruited by a Th2 response and produce proteins that are toxic to parasites, particularly helminths²⁶. They also produce Immunoglobulin (Ig) E, which binds to the surface of microorganisms and triggers the activation of cationic proteins, peroxidase and neurotoxins.
- B cells are not normally present in the skin, but can act as APCs during inflammatory skin processes²⁷.

Innate immune cells are also present in the skin: NK cells are the innate counterparts of neutrophils. NK cells exert cytotoxic activity against microorganisms and neoplastic cells by producing granzyme, perforin and granulysin²⁸.

Innate lymphoid cells (ILCs) are the innate counterparts of Th cells. Their role is not clear, but in psoriasis they tend to increase with psoriasis severity²⁹. ILCs are classified into three subtypes according to the corresponding adaptive response pathway: Th1 response to intracellular pathogens (ILC1), Th2 response to large parasites (ILC2), and Th17 response to extracellular microbes (ILC3)³⁰.

Melanocytes participate in the innate immune response by expressing TLRs that directly sense environmental stimuli and determine the release of IL-6 and IL-8 for the recruitment of leukocytes involved in the adaptive immune response³¹. They can also act as APCs during

inflammation thanks to their expression of MHC class II by interferon gamma (IFN- γ) stimulation³².

Finally, endothelial cells are responsible for migration and the creation of an inflammatory microenvironment: under the influence of TNF- α and IFN- γ , they produce adhesion molecules such as InterCellular Adhesion Molecule (ICAM)-1, vascular cell adhesion molecule (VCAM)-1 and E-selectin, which determine leukocyte extravasation³³. This process is facilitated by inflammation-induced rearrangements of the endothelial cytoskeleton, allowing extravasation of fluid, chemical mediators and cells³⁴. In addition, the expression of TLRs on the endothelial surface is a strong regulator of the innate and adaptive immune response³⁵.

2. PSORIASIS DESCRIPTION

Psoriasis plaques are histologically characterized by keratinocytes density that is 2-5 times higher than generally observed in the skin³⁶. Keratinocytes show an increased turnover with the obliteration of stratum granulosum and the presence of nuclei in most superficial strata of the epidermis³⁷.

Dermis is infiltrated by immune cells from innate and adaptive immune response such as mature DCs, T cells and neutrophils³⁸.

Finally, a neovascularization process causes the increase in tortuosity, dilatation and permeability of dermal papillary capillaries³⁹.

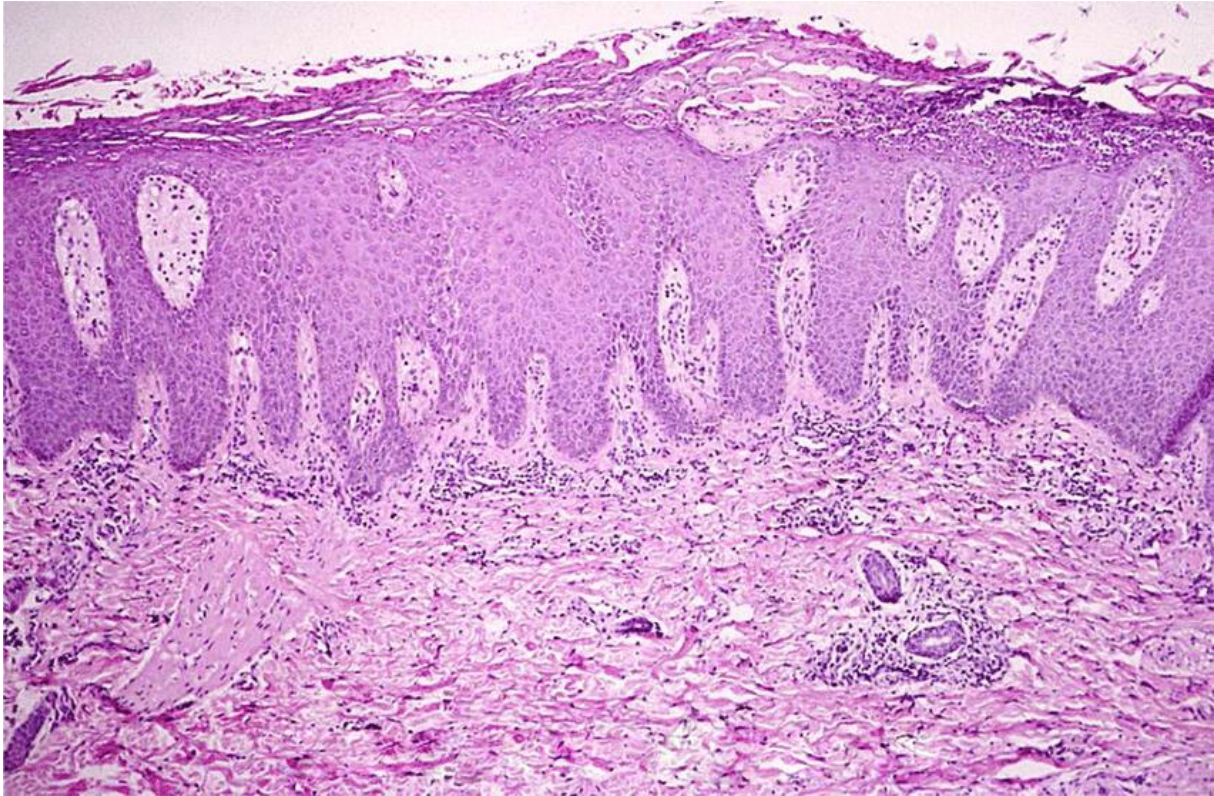


Figure 3: Histopathology of a psoriatic plaque. Source: Pathak S et al.⁴⁰

Psoriasis is now considered a systemic disease that determines a general inflammatory state in the body, as observed by positron emission tomography/computed tomography (FDG PET/CT), which shows subclinical inflammation in the liver, joints and tendons⁴¹. Vascular inflammation in psoriasis causes the atherosclerosis that underlies the increased risk of heart attack and stroke observed in patients with psoriasis^{42,43}.

About 30% of psoriatic patients suffer from psoriatic arthritis, a seronegative inflammatory condition which affects peripheral joints but also enthesal sites, digits and the axial skeleton⁴⁴.

Patients with psoriasis tend to suffer from the metabolic syndrome two times more than healthy subjects⁴⁵ and tend to present with other systemic comorbidities including nephropathy, COPD, fatty liver disease and uveitis^{46,47}.

Psoriasis patients have a three-fold higher risk of developing Chron's disease⁴⁸, an inflammatory bowel disease (IBD) mediated by Th1 interleukins as demonstrated by the presence of IL-23 and IL-17 in the intestinal mucosa of Chron's patients⁴⁹.

Finally, the physical and psychological disease burden, caused by the combined effect of

psoriasis and the abovementioned comorbidities, often trigger a state of depression and anxiety in psoriatic patients⁵⁰ further reducing their life expectancy and quality of life⁵¹.

3. PSORIASIS CLASSIFICATION

Psoriasis is a protean disease that encompasses many different clinical phenotypes, which can be classified according to various parameters such as the region involved (skin folds, scalp, nail), the elementary unit of the lesion (plaques, pustules) or the extent of the lesions (from a single plaque on a covered part of the body to generalized pustular psoriasis or erythrodermic psoriasis).

Plaque psoriasis (or psoriasis vulgaris) is the most common form of the disease. It is characterized by scaly, grey lesions that affect the extensor surfaces of the knees and elbows, the lumbosacral region and the scalp, although any surface of the skin may be affected. It accounts for 90% of all cases of the disease⁵².



Figure 4: Plaque psoriasis. Source: Griffiths and Barker⁵²

Guttate psoriasis is characterized by the presence of papules. It is an acute form that is usually associated with a previous episode of streptococcal pharyngitis. This form has been found to be relatively relieved by tonsillectomy⁵³. These episodes can progress to chronic plaque psoriasis⁵⁴.



Figure 5: Guttate psoriasis. Source: Saleh et al⁵⁵

Erythrodermic psoriasis, in which the entire surface of the skin is erythematous and scaly, is an emergency condition seen in 2-3% of the population with chronic psoriasis. It can lead to hypothermia, electrolyte loss and heart failure⁵⁶.



Figure 6: Erythrodermic psoriasis. Source: Tichy M⁵⁷

Inverse psoriasis has similar characteristics to plaque psoriasis, but mainly involves the axillary, inframammary, inguinal and intergluteal regions and it does not manifest the scaling seen in plaque psoriasis⁵⁸.



Figure 7: Inverse psoriasis. Source: Griffiths and Barker⁵²

The main feature of pustular psoriasis is the presence of sterile pustules and erythema. It is divided into three subtypes: generalised pustular psoriasis (also known as von Zumbusch's disease), palmoplantar pustulosis and Hallopeau's acrodermatitis continua.

Generalized pustular psoriasis is characterized by the sudden appearance of sterile pustules and fever. It can occur after sudden discontinuation of corticosteroid treatment, infection or pregnancy⁵⁹.



Figure 8: Pustular Psoriasis. Source: Sussman M et al.⁶⁰

Palmoplantar pustulosis is common in middle-aged smoking women (aged 30-60 years); it consists of sterile pustules localised on the palms and soles, which eventually develop into a red or brown macula. In 20% of people it is associated with plaque psoriasis.

Finally, in Hallopeau's acrodermatitis continua, the pustules tend to affect the toes and fingers, resulting in the destruction of the unguis plate⁶¹.



Figure 9: Palmoplantar pustolosis. Source: Olazagasti et al⁶²

Other forms of psoriasis may occur in nails with multiple signs such as small pits on one to all nail plates, separation of the nail plate from the nail bed (onycholysis), oil stains (orange-yellow discoloration of the nail bed), hyperkeratosis with elevation of the nail plate (caused by deposition of keratinocytes that have not undergone desquamation), crumbling (dystrophy) of the nail plates, presence of white lines in the nail plates (leukonychia)⁶³.



Figure 10: Onycholysis along with pitting and salmon patches in fingernails. Source:Dogra and Arora⁶³

3.1. PSORIASIS DIAGNOSIS

The diagnosis of psoriasis still relies entirely on the clinician's clinical examination. Skin biopsies are rarely used to differentiate psoriasis from other dermatological conditions such as atopic dermatitis, contact dermatitis, lichen planus, secondary syphilis, mycosis fungoides, tinea corporis and pityriasis rosea⁶⁴.

The medical examination also allows the severity of the disease to be assessed using various outcome tools. Here are some of the most common scales used in clinical assessment of the severity of psoriasis vulgaris:

- Dermatology Quality of Life Index (DLQI): a questionnaire consisting of ten questions designed to measure the impact of a skin condition on the quality of life of a person with the condition⁶⁵
- Psoriasis Area and Severity Index (PASI): combines assessment of lesion severity and area affected into a single score ranging from 0 (no disease) to 72 (maximum disease) ⁶⁶.
- Body Surface Area (BSA): is the measured or calculated surface area of the human body affected by psoriasis⁶⁷
- Physician's Global Assessment (PGA): is used to provide a single estimate of the patient's overall disease severity at a given time. Psoriatic lesions are scored on a 0-5 scale, which is then averaged across all lesions, for induration, erythema and scaling ⁶⁸.
- Psoriasis Symptom Inventory (PSI): Self-administered, patient-reported outcome measure (PRO) to assess symptom severity in chronic plaque psoriasis⁶⁹.
- Simplified Psoriasis Index (SPI): a summary measure of psoriasis with separate components for current severity (SPI-s), psychosocial impact (SPI-p) and history and interventions (SPI-i)⁷⁰.

A case of mild psoriasis is defined as one in which patients have Psoriasis Area Severity Index (PASI), Body Surface Area (BSA) and Dermatology Life Quality Index (DLQI) scores below 10, while those with scores above 10 on any of these scales are considered to have moderate-to-severe psoriasis⁷¹.

One of the limitations of the traditional classification of pathology severity is patients in the mild category. It is not possible to give an unambiguous definition of such patients because

classification based on medical scales such as BSA and PASI fail to correctly capture the severity perceived by patients through questionnaires such as DLQI. Although international scales indicate the use of both medical and subjective scales in assessing the severity of pathology, the aforementioned mild cases are often excluded from clinical trials and thus new treatments.

For this reason, the International Psoriasis Council, a community of physician experts in the psoriasis field⁷², based on a consensus of its members, suggests an alternative classification in which patients destined to receive systemic treatments are those with a BSA>10%, lesions present in specific areas of the body (eg, face, palms, soles, genitalia, scalp) and failure of topical treatment⁷³.

3.2. PSORIASIS TREATMENT

Many factors influence treatment including the disease severity, presence of comorbidities and access to healthcare.

Since the 1950s, thanks in part to advances in synthetic drug production, many molecules have been tested for the treatment of psoriasis and treatment of the disease has evolved.

In particular, over the last 15-20 years, the understanding of the central role of the IL-17/IL-23 pathways, combined with new knowledge in the field of monoclonal antibody production, has enabled the development of therapies capable of achieving increasingly effective control of the disease, even in patients with severe manifestations⁷⁴.

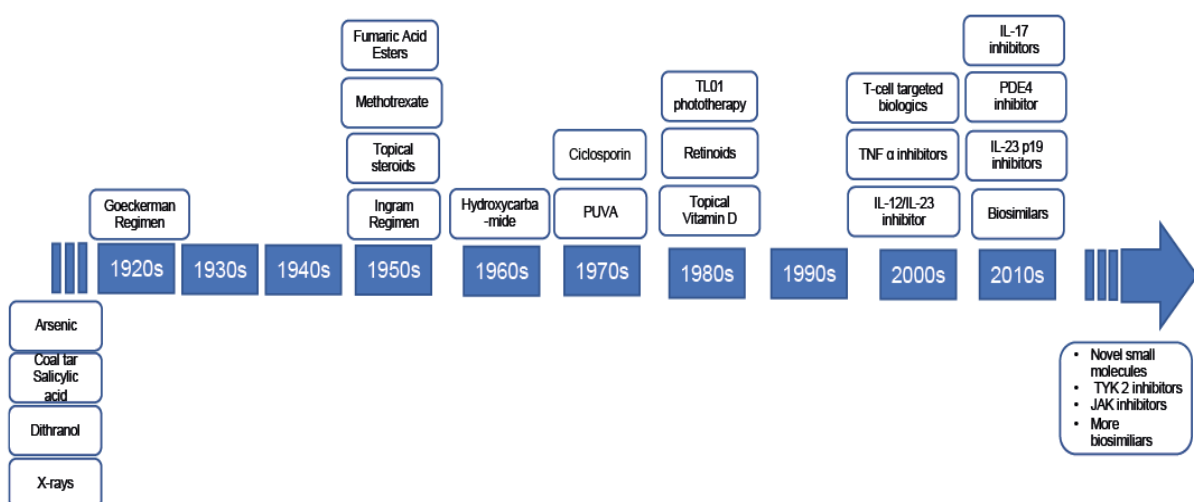


Figure 11: Timeline of the major pharmacological advances in the management of psoriasis occurred

over the past 100 years. Source: Reid and Griffiths⁷⁴

Drugs that are currently approved for the treatment of psoriasis fall into four categories: topicals, non-biologic immunomodulators, biologic immunomodulators and phototherapy.

The assessment of the disease severity is important to assign the adequate treatment according to international guidelines⁷⁵⁻⁷⁹. In particular, mild psoriasis is treated with topical agents, while moderate-to-severe psoriasis is treated with non-biologic immunomodulators, biologic immunomodulators and/or phototherapy.

3.2.1. TOPICALS

Topical preparations are divided into corticosteroids, vitamin D derivatives and vitamin A derivatives:

- Corticosteroids: first introduced in the 1950s, they became useful in the treatment of psoriasis in the 1960s when synthetic corticosteroids were first synthesised. These molecules have anti-inflammatory, immunosuppressive and anti-proliferative effects by blocking gene transcription⁸⁰. Here is a non-exhaustive list of topical corticosteroids used in psoriasis:
 - Betamethasone
 - Clobetasol
 - Desonide
 - Diflucortolone
 - Difluprednate
 - Fluticasone
 - Hydrocortisone Aceponate
- Vitamin D derivatives: first commercialised in the 1980s, they act by inhibiting the proliferation of keratinocytes⁸¹. They may be used in combination with topical steroids to enhance their action. The use of these drugs is exclusively for the treatment of psoriasis:

- Calcipotriol
 - Calcitriol
 - Tacalcitol
- Vitamin A-derived topicals: only one retinoid-derived molecule, tazarotene, was commercialized and introduced in the 1990s. It binds the retinoic acid receptor (RAR) and reduces keratinocyte proliferation, normalizes keratinocyte differentiation and reduces inflammation⁸².

3.2.2. NON-BIOLOGIC IMMUNOMODULATORS

Drugs used to treat moderate-to-severe psoriasis that are taken orally.

- Methotrexate: it was commercialized in the 1950s and it acts through several pathways, including inhibition of pyrimidine production, which reduces keratinocyte proliferation and T-cell activation⁸³.
- Cyclosporine: first introduced in the 1970s, it was discovered by chance as a by-product of solid organ transplant rejection therapy. Its mechanism of action as an inhibitor of T-cell proliferation and migration in psoriasis plaques^{84,85} paved the way for the recognition of psoriasis as a T-cell mediated disease.
- Acitretine: A retinoid-derived drug first commercialized in the 1980s that binds to all three types of retinoic acid receptor (RAR), but its effects are not fully understood but may be based on keratinocyte proliferation and differentiation⁸⁶. It is usually used in combination with corticosteroids and ultraviolet (UV) light therapy.
- Fumaric acid esters: only used in Europe and commercialised in 1994 as a mixture of dimethyl fumarate and monoethyl fumarate (DMF/MEF). DMF was approved as a stand-alone drug in 2017⁸⁷. Its mechanism is based on the inhibition of glutathione, which is involved in the transcriptional activity of the nuclear factor-kappa B (NF-κB) pathway⁸⁸.
- Apremilast: formerly a non-biologic immunomodulators launched in 2014, it belongs to the class of biologic immunomodulators in terms of mechanism of action. It acts as an inhibitor of phosphodiesterase (PDE) 4 on keratinocytes, fibroblasts, endothelial cells and monocytes, reducing the expression of pro-inflammatory mediators such as TNF-α, IFN-γ and IL-12 and increasing the levels of the anti-inflammatory IL-10^{89,90}.

3.2.3. BIOLOGIC IMMUNOMODULATORS

These drugs represent a new era in the treatment of psoriasis, opened at the beginning of the 21st century thanks to a better understanding of the molecular mechanism of psoriatic disease. All these new drugs are monoclonal antibodies that target a specific interleukin pattern. These drugs include:

- Anti TNF- α :
 - Etanercept (FDA approval on April 30, 2004)
 - Infliximab (FDA approval on September 27, 2006)
 - Adalimumab (FDA approval on January 22, 2008)
 - Certolizumab (FDA approval on May 27, 2018)
- Anti IL-12/IL23
 - Ustekinumab (FDA approval on September 25, 2009)
- Anti IL-17
 - Secukinumab (FDA approval on January 21, 2015)
 - Ixekizumab (FDA approval on March 22, 2016)
 - Brodalumab (FDA approval on February 15, 2017)
- Anti IL-23
 - Guselkumab (FDA approval on July 13, 2017)
 - Tildrakizumab (FDA approval on March 21, 2018)
 - Risankizumab (FDA approval on April 23, 2019)

3.2.4. PHOTOTHERAPY

Phototherapy consists of two types of treatment: UVB phototherapy and UVA

photochemotherapy (PUVA).

Developed in the 1960s, UVB phototherapy is based on exposure to lamps that emit two types of radiation: broadband (280 - 320nm) and narrowband (311nm) UVB⁹¹. The latter is the most widely used as it greatly reduces the extent of erythema. The dose is determined by phototype and the number of sessions required to achieve results is generally 3-5 sessions per week for 6-10 weeks of treatment⁹².

PUVA was introduced in 1974 and is currently the most widely used form of phototherapy⁹³. A photosensitising psoralen such as 8-methoxypsoralen (8-MOP, synonym: methoxsalen) or 5-methoxypsoralen (5-MOP) is first administered orally, followed by UVA irradiation after 45-60 minutes. Treatment usually lasts for 6-8 weeks. It is sometimes combined with acitretine to enhance efficacy⁹².

Phototherapy has multiple beneficial effects on psoriatic pathology⁹⁴:

- Proapoptotic effects on epidermal cells.
- Immunomodulatory effects with induction of immunosuppression and regulation of immune cell migration.
- Pro-pigmentation effects with production of proopiomelanocortin and alpha-MSH and reduction of anti-MSH CD8 cells.
- Anti-fibrotic mechanisms with induction of collagen degradation by metalloproteinases.
- Skin microbiome modification by selection of UV-resistant microbial species.

Unfortunately, despite the wide range of treatments available, psoriasis remains an incurable disease in which drugs act at different stages of the inflammatory cascade to reduce symptoms and prevent or delay the onset of co-morbidities.

This is largely due to a lack of understanding of the complex immunological network involved in the pathogenesis of the disease.

4. PSORIASIS PATHOGENESIS

Progress over the last 15 years has led to the identification of the central role of the IL-17/23 axis in the pathogenesis of psoriasis, which is activated by the cascade of events described below.

Insults to keratinocytes cause the release of AMPs such as LL37 from these cells. In addition, in psoriasis, keratinocytes produce large amounts of polyamines that protect DNA from degradation⁹⁵.

These AMPs are potent triggers of plasmacytoid cell activation because they allow the survival of DNA derived from necrotic and apoptotic processes to be internalized by plasmacytoid dendritic cells and promote the activation of TLR-9 (for DNA) and TLR-8 (for RNA)⁹⁶.

Keratinocytes can also directly activate the differentiation of immature T cells into Th17 cells through the interaction of Chemokine (C-C motif) ligand (CCL)-20 RNA complexes with TLR-8^{97,98}.

Plasmacytoid dendritic cells (pDCs) are immunological cells normally found in the bloodstream but not in the skin. After being attracted by the by-products of keratinocytes, they migrate into the dermis and the basal layer of the epidermis⁹⁹. The function of pDCs is to secrete large amounts of interferon alfa (IFN- α)^{8,100,101} and interferon regulatory factor 7 (IRF7)¹⁰² which cause the recruitment of myeloid dendritic cells (mDCs), which are not normally present in the dermis but tend to be attracted during a pathogenic response.

The most important function of mDCs is the production of IL-23, a cytokine responsible for Th17 polarization of T cells, and AMPs such as LL37, which maintains the autoreactive T cell population and perpetuates chronic inflammation^{103,104}.

When activated, mDCs produce TNF- α , the enzyme inducible nitric oxide synthetase (iNOS) and IL-12.

TNF- α induces the maturation of pDCs and limits their IFN- α production¹⁰⁵. It also promotes the conversion of macrophages into dendritic cells¹⁰⁶. TNF- α also inhibits Treg cell function¹⁰⁷.

IL-12 is responsible for polarizing the adaptive immune response through a Th1 pattern¹⁰⁸, while IL-23 is the main mediator of chronic inflammation in Th17 pattern¹⁰⁹. IL-12 and IL-23 share one subunit, p40, whereas IL-12 has a specific p35 and IL-23 a p19 subunit. The increase of the p19 subunit but not of the p40 unit in psoriasis skin samples¹¹⁰ shows that the Th17 pathways play a more important role than the Th1 pathways in psoriasis.

Th17 cells produce large amounts of IL-17, a pro-inflammatory interleukin that has many functions in the inflammatory activation loop:

- Polarization of CD8 T cells that migrate into the epidermis and, through the release of IL-17, IFN- γ , TNF- α , IL-21 and IL-22¹¹¹, cause the activation of keratinocytes. This activation of Th17 cells is characterized by an increase in their proliferation and the release of AMPs (e.g. defensins, cathelicidins) and pro-inflammatory cytokines (e.g. IL-6, IL-8, TNF- α) that act on DCs and T cells, creating a self-amplifying loop¹¹².
- Hyperplasia of keratinocytes due to premature maturation and incomplete cornification driven by an autocrine and paracrine IL-36 loop caused by TNF- α release^{113,114}
- Production of chemokines (C-X-C motif) like CXCL1, CXCL2, CXCL8, CXCL10, CXCR3, CCL2, CCL5. CXCL1, CXCL2, CXCL8 in particular appear to be involved in neutrophil chemoattraction in the epidermis¹¹⁵.
- The production of IL-1 leads to the activation of $\gamma\delta$ T cells and the autocrine activation of other keratinocytes¹¹⁶.
- Production of vascular endothelial growth factor (VEGF), which induces the density, dilation and permeability of dermal capillaries¹¹⁷.
- Production of IL-8, which activates NK cells and basophils¹¹⁸.
- Release of IL-1 α that attract monocytes and neutrophils accumulation in the initial dermal papule. This mediator is also an endothelial activator^{119,120}.
- Release of further AMPs and DNA that further activate mDCs¹²¹.
- IL-36 also act as an activator of mDCs¹²² and induce the production of chemokines such as CXCL1, CXCL2, CXCL8 that enhance neutrophil involvement in the inflammatory mechanism¹²³.

Other skin cells involved in psoriasis include:

- NK cells activated by IL-8 that produce IFN- γ , IL-17, TNF- α and IL-22. Their exact role in the disease is still unknown¹²⁴.
- Basophils activated by IL-9 released from Th17 cells that release large amounts of VEGF. They could also act as APCs due to the presence of MHC II receptors on their surface¹²⁵. This function is also observed when mast cells interact with IFN- γ , which causes mast cells to present antigen to CD4 cells¹²⁶.

- Neutrophil infiltration that is responsible for the pathogenetic sign of Munro micro-abscesses and Kogoj spongiform pustules in early stages of psoriasis¹²⁷. They are responsible for the production of neutrophil extracellular traps (NETs), IL-6, IL-8 and TNF- α . NETs can induce Th17 differentiation through cleaving IL-36¹²⁸ and act as a reservoir for LL37 nucleic acid complexes¹²⁹, which activate various innate immune cells, including neutrophils themselves.
- Monocytes stimulated by LL37 and converted into dendritic cells that secrete IL-23, IL-12 and TNF- α and maintain the inflammatory loop¹³⁰.
- Macrophages activated by LL37 and transformed in dendritic cells under TNF- α stimulus¹⁰⁶ releasing IL-1 α , IL-6, IL-23 and TNF- α ¹³¹. It seems that they infiltrate psoriasis skin lesions later than other leucocytes¹⁰³.
- Keratinocytes that produce IL-23, which further enhances Th17 polarization and causes the loop of sustained inflammation¹³².

5. GENETIC RISK FACTORS

What we know about the genetics of psoriasis contribute, together with the molecular processes described above, to the understanding of the pathology of psoriasis.

Based on the most recent data available in the literature from the most recent meta-analysis of genome-wide association study (GWAS) performed, 109 susceptibility loci have been identified that help explain 59% of the variance in liability to psoriasis¹³³.

The first genetic susceptibility factor to be discovered for psoriasis and the most common one involves genes on the human leukocyte antigen C (HLA-C) region on chromosome 6p21.3 which is now referred to as the PSORS1 region¹³⁴. PSOR1-related genes are involved in antigen presentation to CD8 T cells and interaction with natural killer cells¹³⁵. Among the different HLA-C alleles, the HLA-C*0602 allele has been observed to be associated with psoriasis mainly in patients of European ancestry, while HLA-C*01:02 is more common in Asian patients¹³⁶.

Another interesting point is the prevalence of HLA-C that does not correlate with the incidence of the disease: it is higher in black Africans (15.09%, 95% confidence intervals-CI 5.7-33%) than in Caucasians (9.62%, 95% CI 3.7-18.9%) and similar to that of Australian Aborigines (9.05%, 95% CI 2-16.1%)¹³⁷. Orientals (6.6%, 95% CI 0-16.4%) and Amerindians (6.65%, 95% CI 0-14.6%) have a lower prevalence of HLA-Cw6¹³⁸.

Other non-MHC susceptibility genes have been found^{139–146}. These genes are involved mainly in the formation of the skin barrier but they also have a role in the innate immunity and the adaptive immunity.

Skin barrier functions involved are keratinocyte differentiation, the production of beta-defensin, a class of AMPs involved in the attraction of neutrophils to the skin site during inflammatory processes¹⁴⁷ and in the correct expression of connexin, a group of proteins involved in keratinocyte proliferation¹⁴⁸.

Innate immune genes are involved in the NF- κ B (TNIP1, TNFAIP3, NFKBIA, REL, NOS2, FBXL19, CARD14, CARM1, UBE2L3 and TYK2) and IFN (IFIH1, IFNLR1/IL-28RA, ELMO1, SOCS1, DDX58, RNF114 and TYK2) signaling pathways¹⁴⁹. Among these genes, TNFAIP3 has been shown to be associated with an increased risk of autoimmune diseases such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), systemic sclerosis and celiac disease¹⁵⁰.

Adaptive immune response genes (ERAP1, MBD2, RUNX3, TNFRSF9, IRF4, ETS1, TAGAP, B3GNT2 and HLA-B/C) are involved in antigen presentation and activation of the inflammatory cascade^{141–146,151–154}. In particular, ERAP1 encodes a peptidase in APCs that cleaves antigens at the level of the endoplasmic reticulum (ER) to allow presentation by HLA receptors¹⁵⁵.

Proteins encoded by MBD2, TNFRSF9, B3GNT2, IRF4, TAGAP, RUNX3 and ETS1 are also involved in activating and differentiating CD8 T cells^{149,156}.

Regarding inflammatory activation, the main Th response genes differ according to the type of immune pathway: Th1, Th17 and Th23.

Mutations in genes involved in the Th1 pathway, such as ZC3H12C, STAT5A, STAT5B, ILF3 and TYK2, alter the correct ligation of IL-12 to the IL-12 receptor¹⁵⁷.

On the other hand, one of the most important areas of discovery in recent years has been the Th17 pathway, which underlies the IL-17/IL-23 cascade: TYK2, SOCS2, STAT3, and ETS1 are all involved in downstream Th17 cell differentiation^{158,159}. Another gene, TRAF3IP2, which is involved in the production of a protein that facilitates the activation of IL-17 by the innate immune response¹⁶⁰, also acts through a long-range interacting (LRI) enhancer that regulates IL-17 receptor transcription and NF- κ B cascade activation¹⁶¹.

Psoriasis patients have been shown to have increased copies of the gene for a mediator of the

Th17-related cascade, IL-22¹⁶².

Finally, IL-21 receptor gene variants, in particular the rs6822844 and rs2069778, have been associated with increased psoriasis risk¹⁶³.

However, genetic factors can't explain the whole distribution of psoriasis: a study conducted on 10 725 pair of twins from Danish Twin Registry showed that only 20% of monozygotic twins and 9% of dizygotic twins were both affected by psoriasis. Furthermore, genetic factors could explain 68% (60–75%) of the variation in the susceptibility to psoriasis, whereas the rest of the variation was explained by environmental factors¹⁶⁴.

6. PSORIASIS EPIDEMIOLOGY

Available data on prevalence and incidence worldwide and in France are described in this chapter.

6.1. PREVALENCE

The current estimate of the number of prevalent cases of psoriasis worldwide is approximately 40.8 million (95% CI 39.4-42.1)¹⁶⁵, with an age-standardized prevalence in 2019 of 503.6 (95% CI 486.9-519.2) per 100,000 people¹⁶⁶.

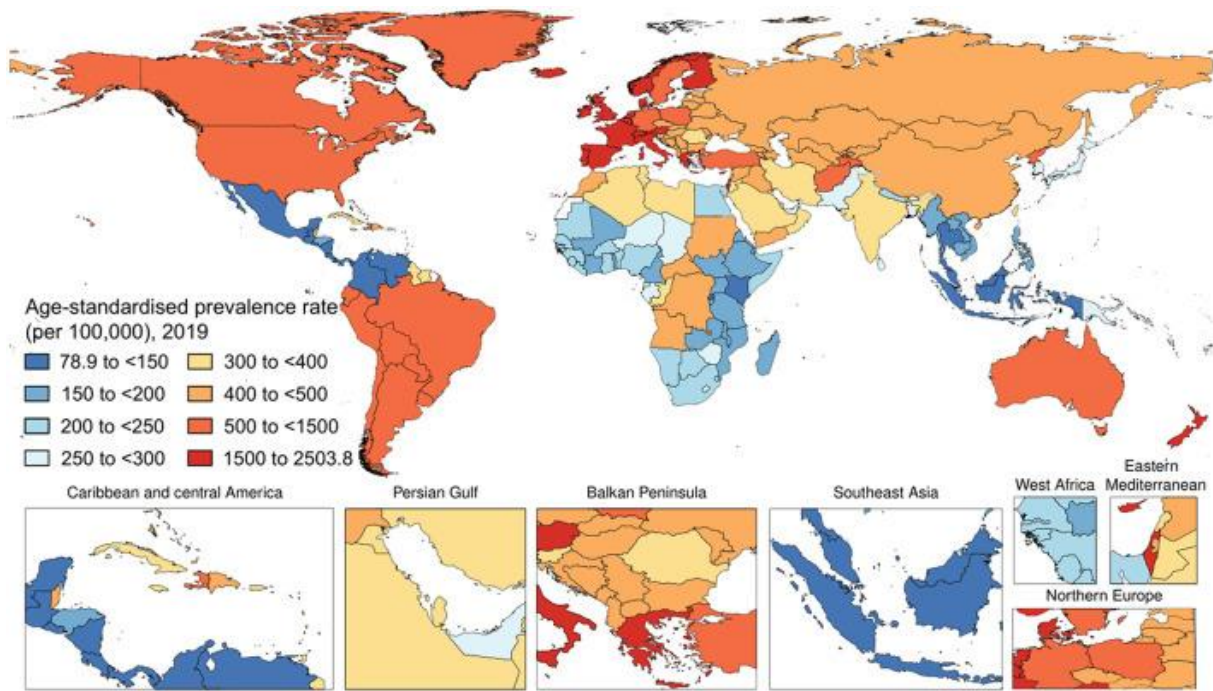


Figure 12: The national age-standardized prevalence rate of psoriasis (per 100,000) in 2019. Source: Damiani et al¹⁶⁶

The age-standardized prevalence rate is highest in Western Europe [1 884 cases per 100 000 people (95% CI 1 817.4-1 948.3)], followed by Australasia [1 506.1 (95% CI 1 448.9-1 560.8)] and high-income North America [1 081.6 (95% CI 1 048.9-1 115.4)], while it is lowest in South-East Asia [128.8 (95% CI 124.5-132.2)], followed by Central Latin America [132.0 (95% CI 127.7-136.5)] and Eastern Sub-Saharan Africa [166.8 (95% CI 160.8-172.9)]¹⁶⁶.

6.2. INCIDENCE

In 2019, the number of new cases of psoriasis was estimated at 4.62 million¹⁶⁵, with an age-standardized incidence rate of 57.8 (95% CI 55.8-59.7) per 100 000 people¹⁶⁶.

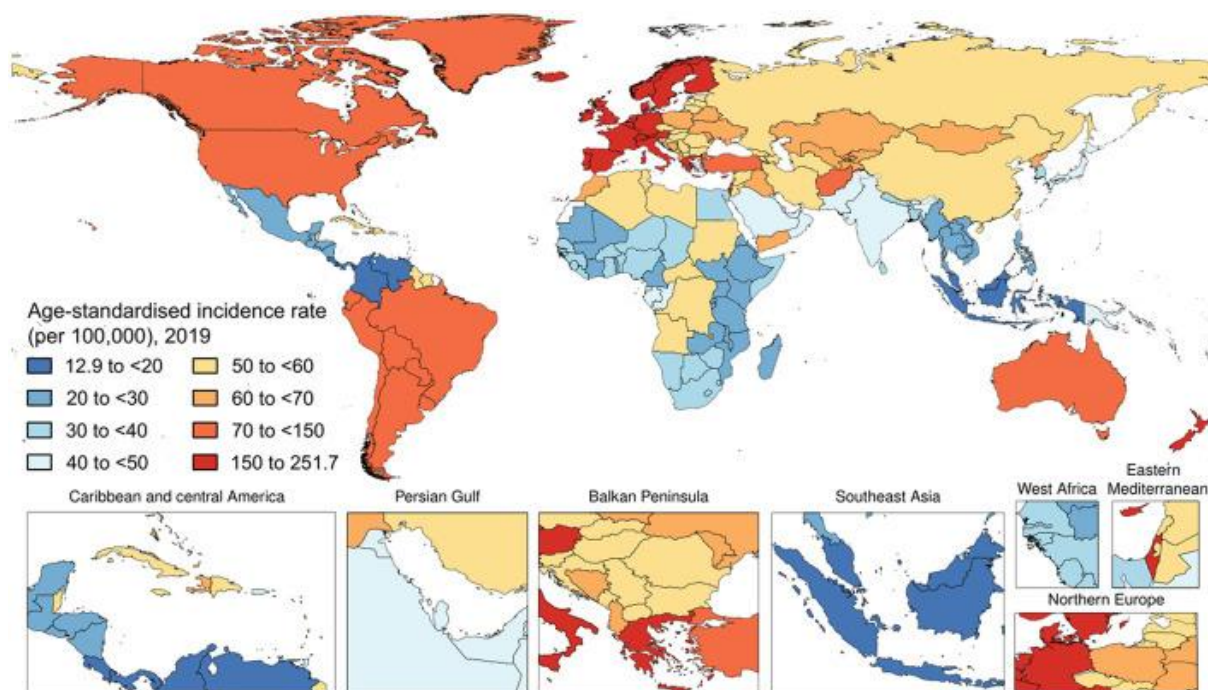


Figure 13: The national age-standardized incidence rate of psoriasis (per 100,000) in 2019. Source: Damiani et al¹⁶⁶

The incidence rate is highest in Western Europe [204.5 cases per 100 000 people (95% CI 197.6-211.4)], followed by Australasia [145.4 (95% CI 139.6-151.4)] and high-income North America [92.7 (95% CI 89.7-95. 5)], while it is lowest in South-east Asia [20.1 (95% CI 19.3-20.8)], followed by Central Latin America [20.7 (95% CI 19.9-21.5)] and Eastern Sub-Saharan Africa [25.1 (95% CI 24.2-26.1)]¹⁶⁶.

Prevalence and incidence data show that there is an inverse association between increasing latitude and the psoriatic disease, which has been attributed to differences in UV exposure ¹⁶⁷⁻¹⁷⁰.

6.3. PSORIASIS IN FRANCE

The exact number of cases of psoriasis in France is difficult to estimate: A study conducted in 2018 using the national health database (SNDS) suggests an incidence of 150 per 100 000 inhabitants and an estimated prevalence of between 1.3 and 2.1%¹⁷¹. However, these data from reimbursed drugs may be underestimated as another case-report study conducted in 2009 estimated a prevalence of 5.2%¹⁷². This suggests that there are between 1 and 3 million prevalent cases in France.

Only one study in Global Burden of Diseases 2019 reports on the incidence of psoriasis in

France, estimating a total of 172 843 (95% CI 166 210-179 240) cases with an age-standardized incidence rate of 251.7 (95% CI 242.5-261.0) per 100 000 people¹⁶⁶.

6.4. AGE AND SEX

The incidence of psoriasis increases with age from 13.5 per 100 000 person-years before the age of 4 years to 53.1 per 100 000 person-years in adolescents aged 14-18 age years¹⁷³. In adulthood, incidence increases up to the age of 39 years and then start to decrease¹⁷⁴ before another peak at around 50-59 years¹⁷⁵ or 60-69 years of age¹⁷⁶.

While some studies report a slightly higher incidence in girls than in boys observed in childhood¹⁷³ and a higher incidence in adult men than in adult women¹⁶⁵, overall no sex difference in the incidence of the disease is observed globally with 2.31 million new cases of psoriasis diagnosed in 2019 in women and 2.32 million in men¹⁷⁷.

Recent data show no sex difference in the incidence of the disease: 2.31 million women and 2.32 million men were diagnosed with psoriasis in 2019¹⁶⁵

The peaks in the age distribution of the disease incidence appear to be earlier in women (at the ages of 20-29 and 50-59 years) than in men (at 30-39 and 60-69/70-79 years)^{175,176,178,179}.

It has been proposed that differences in age at onset and the bimodal distribution of disease incidence may be explained by psychological¹⁸⁰ and environmental¹⁸¹.

6.5. TEMPORAL TRENDS IN INCIDENCE AND PREVALENCE

The literature reports increasing trends over time in psoriasis prevalence. Studies conducted in Canada show a moderate increase in the prevalence of psoriasis from 1.74% to 2.32% between 2000 and 2015^{182,183}. Similar increases in disease prevalence are observed in Taiwan (from 0.18% to 0.28% between 2000 and 2013)¹⁸⁴; in Germany (from 2.2% to 2.3% between 2009 and 2012)¹⁸⁵; in Israel (from 2.5% to 3.8% between 2011 and 2017)¹⁸⁶; in Korea (from 0.47% to 0.61% between 2006 and 2015)¹⁸⁷, in Russia (from 0.21% to 0.23% between 2009 and 2016)¹⁸⁸ and UK (from 2.3% to 2.82% between 1999 and 2013)¹⁸⁹.

Incidence rates of psoriasis appear to be stable or slightly decreasing throughout the world. A

decrease is observed for example in Canada (from 111.1 to 68.7 per 100 000 person-years between 2000 and 2015)^{182,183}, in Italy (from 321.0 to 230.0 per 100 000 person-years between 2001 and 2005)¹⁹⁰, in Taiwan (from 42.0 to 30.3 per 100 000 person-years between 2001 and 2013)¹⁸⁴, in Germany (from 35.3-5.27 in 2009 to 17.1-26.3 per 100 000 person-years between 2009 and 2012 in men; from 46.3-58.1 in 2009 to 19.0-26.3 per 100 000 person-years between 2009 and 2012 in women)¹⁸⁵; in the Netherlands (from 130 to 120 per 100 000 person-years between 1987 and 1995)¹⁹¹; in Israel (from 246 to 243 per 100 000 person-years between 2016 and 2017)¹⁸⁶; in the United Kingdom (from 159 to 129 per 100 000 person-years between 1999 and 2013)¹⁸⁹ and in Russia (from 385.5 to 335.9 per 100 000 person-years between 1999 and 2013)¹⁸⁸.

In Denmark, the incidence of psoriasis has been uneven over time, with a decrease in incidence from 140.1 to 104.0 per 100 000 person-years between 2003 and 2005, followed by an increase to 181.0 per 100 000 person-years in 2010, and then a decrease to 151.2 per 100 000 person-years in 2012¹⁹².

In the USA long-term data limited to Caucasians show an increasing trend in the incidence of psoriasis between 1970 and 1999 (from 40.8 to 62.7 per 100 000 person-years)¹⁷⁸.

The increase in prevalence may be related to a general increase in knowledge about psoriatic disease¹⁹³ and a gradual improvement in treatment⁷⁴, with a consequent increase in psoriasis diagnoses¹⁹⁴. In addition, studies from Israel and the UK suggest that the increase in disease prevalence is also associated with a reduction in premature mortality¹⁷³.

The observed decrease in psoriasis incidence could be explained by a cohort effect or a period effect.

The period effect corresponds to changes in psoriasis incidence rates over a given period for the whole population, within all age groups. The cohort effect reflects changes in disease incidence over successive generations¹⁹⁵. The cohort effect reflects the effect of acquired lifestyles and life experiences common to all individuals born in a given historical period compared to other generations, whereas the period effect may reflect the influence of historical events such as war, labour market conditions, macroeconomic changes, infectious disease outbreaks and medical technology development¹⁹⁶.

The influence of a period effect and a cohort effect on the decreasing trends in psoriasis incidence was demonstrated in a Taiwanese study comparing psoriasis incidence by year of

birth in an age-period-cohort model¹⁹⁷. The period effect consisted of an approximately 25% decrease in the incidence rate ratio for psoriasis from 2002 to 2016, while the cohort effect corresponded to a 43% decrease in the incidence rate ratio between the oldest (1937) and the youngest (2002) cohorts considered.

These results, given the genetic homogeneity of the study population, suggest how lifestyle and environmental exposures may influence the incidence of psoriatic disease.

The data presented in this chapter on the geographical and temporal variability of psoriasis suggest the existence of a link between environmental and lifestyle factors and the pathology of psoriasis.

7. ENVIRONMENTAL AND LIFESTYLE RISK FACTORS

For the reasons described earlier there is general agreement that the interaction of environmental and immunological factors is likely to play a major role in the onset, development and exacerbations of psoriasis.

A wide range of environmental and lifestyle factors have been studied to try to improve the understanding of the mechanism underlying activation of the inflammatory cascade¹⁹⁸⁻²⁰⁰.

Here we present the environmental and lifestyle factors whose association with psoriasis risk has been investigated in epidemiological studies.

The choice of studies included in the thesis was based on a hierarchy of the degree of evidence provided by the articles, favoring clinical studies, meta-analyses and prospective studies when available.

Where not available, we tried to include the most rigorous information available.

Many of the studies presented in the chapter came from journals considered among the most authoritative sources in dermatology such as Journal of the American Academy of Dermatology (JAAD), Journal of the American Medical Association (JAMA) Dermatology and Journal of the European Academy of Dermatology and Venereology (JEADV).

7.1. UV LIGHT AND AIR POLLUTION

As described above, heliotherapy or therapeutic exposure to natural sunlight have been used in the treatment of psoriasis for decades²⁰¹. This relationship is biologically compelling as UVA and UVB radiation has been shown to decrease antigen presentation and alloactivation, resulting in reduced T-cell responses²⁰². UV radiation is also known to induce regulatory T cells with suppressive activities²⁰³.

Several epidemiological studies have found therapeutic sun exposure to be effective to prevent short-term disease manifestations: a study in Israel of 70 patients (40 men, 30 women; age 19-78 years) showed a 75.9% reduction in the PASI score, from a mean of 16.6+/-11.0 before treatment to 4.0+/-4.2 after treatment ($p < 0.001$)²⁰⁴. Similarly, a study of 18 Danish patients treated in Israel who participated in a 4-week treatment programme showed a mean PASI reduction of 13.0 points (88%)²⁰⁵.

The effect of air pollution on the skin is still poorly understood. These effects are likely to be diverse and dependent on the type of pollutant. The human body is continuously exposed to an enormous amount of substances originating from natural and man-made sources (WHO 2005)²⁰⁶ and including gaseous compounds (nitrogen dioxide [NO₂], sulphur dioxide [SO₂], carbon monoxide [CO]), particulate matter (PM), heavy metals, nitrogen oxides which interact with volatile organic compounds (VOCs) under ultraviolet photoactivation to form ground-level ozone, persistent organic compounds (POPs), semi-volatile compounds (SVOCs) and polyaromatic hydrocarbons (PAHs).

Exposure could occur directly on the skin or indirectly through other routes such as ingestion²⁰⁷ or inhalation²⁰⁶. The mechanisms involved could be oxidative damage that triggers transcription factors such as NF- κ B, which could translocate to the nucleus and transcribe pro-inflammatory genes such as IL-1, IL-6, IL-8 and IL-23²⁰⁸. Another targeted mechanism is the activation of the aryl hydrocarbon receptor (AhR) in keratinocytes by airborne particles or benzo(a)pyrene, which has been linked to the induction of pro-inflammatory molecules such as IL-8²⁰⁹ and cyclooxygenase-2²⁰⁹ via the production of reactive oxygen species (ROS) involved in oxidative stress processes. Finally, photo-activation of certain pollutants such as polyaromatic hydrocarbons (PAHs)²¹⁰ or cigarette smoke²¹¹ can lead to skin carcinogenesis through DNA damage with mutational potential on k-ras and p53 transduction pathways.

Studies on exposure to air pollution show an increase in psoriasis flares when there is a sudden increase in particulate matter concentrations. A case-crossover study in Italy involving 957

patients over a 7-year period shows a worsening of psoriatic manifestations (in the form of an absolute increase in PASI) with increasing concentrations of gaseous pollutants such as PM10 [Linear regression model β coefficients=0.052 (P = 0.006)], PM_{2.5} [Linear regression model β coefficients=0.052 (P = 0.006)], NO₂ [Linear regression model β coefficients=0.092 (P-value < 0.001)], NO_x [Linear regression model β coefficients=0.071 (P-value < 0.001)], CO [Linear regression model β coefficients=0.116 (P-value < 0.0001)] and C₆H₆ [Linear regression model β coefficients=0.025 (P-value 0.043)]²¹².

Similarly, another study conducted in China of 13 536 psoriasis outpatient visits in Wuhan over a 4-year period showed that an increase of 10 μ g in NO₂ concentrations was associated with a 0.98% (95% CI 0.01-1.96) increase in the number of outpatient visits ²¹³.

7.2. SMOKING

Smoking is a possible risk factor for psoriasis. A recent meta-analysis based on 34 studies, 23 case-control and 11 cohort studies, showed an increased risk of psoriasis in current [Odds ratio-OR: 1.63 (95% CI: 1.48-1.80)] and former [OR:1.36 (95% CI: 1.13-1.64)] smokers compared with non-smokers²¹⁴.

This association is also observed for passive smoking, but only in relation to childhood-onset psoriasis. A Danish cohort study showed an increased risk for passive smoking during the prenatal period [adjusted odds ratio- aOR relative to non-smoking parents: 1.39 (95% CI: 1.06-1.82)], but not for exposure to passive smoking during infancy [aOR, 1.17 (95% CI: 0.76-1.79)] or childhood [aOR, 1.10; (95% CI: 0.77-1.58)]²¹⁵. However, a study that was able to adjust for other environmental exposure showed that exposure to passive smoking during childhood was associated with increased risk of psoriasis [OR: 2.23 (95% CI : 1.39-3.58)]²¹⁶.

Smoking affects efficacy of treatment with biologics as observed in a metanalysis that compared efficacy of anti-psoriatic drugs after 6 months from the start of the treatment showing that smokers have a reduced disease improvement from biologic agents [pooled OR: 0.80 (95% CI: 0.67–0.95)] compared to non-smokers²¹⁴.

Finally, a recent Mendelian randomization study found a causal relationship with risk of psoriasis for smoking initiation [OR:1.46 (95% CI: 1.32-1.60, P-value = <000.1], number of cigarettes per day (OR 1.38, 95% CI 113-167, P = 0001) and lifetime smoking [OR 1.96 (95% CI 1.41-2.73, P-value = <0.0001)]²¹⁷.

There are many possible biological explanations for this association. Cigarette smoke plays a role in regulating immunity through the production of ROS, which reduce the expression of antioxidant genes, increase the expression of psoriasis-related genes such as HLA-Cw6, HLA-DQA1*0201 and CYP1A1, and induce the activation of signaling pathways such as mitogen-activated protein kinase (MAPK), NF- κ B and Janus kinase signal transducers and activators of transcription (JAK-STAT)²¹⁸. In addition, nicotine interacts with nicotinic acetylcholine receptors (nAChR) present on the surface of various cells involved in the inflammatory cascade: in myeloid DCs, it induces the secretion of IL-12²¹⁹ causing pathological angiogenesis by stimulating endothelial cells²²⁰ which also produce TNF- α and IL-1 causing the migration of macrophages into the dermis²²¹. Finally, it increases mitosis, migration and differentiation of keratinocytes in psoriatic plaques^{222,223}.

7.3. ALCOHOL

There are many levels at which alcohol may act in the pathogenesis of psoriasis: in keratinocytes, alcohol is broken down into acetaldehyde and acetone, each of which has a specific effect on the skin: acetone stimulates the synthesis of mRNA for proliferation genes (alfa-5 integrin, cyclin D1 and keratinocyte growth factor receptor [KGFR]), which alter the permeability of the skin²²⁴.

Acetaldehyde causes the release of reactive oxygen species (ROS), which activate the mitogen-activated protein kinase/activator protein 1 (MAPK/AP1), NF- κ B and Janus kinase (JAK/STAT) signaling pathways, leading to keratinocyte proliferation and secretion of IL-6 and IL-8, which contribute to the recruitment of adaptive immune cells²²⁵.

The other observed effect of alcohol is related to the secretion of TNF- α by circulating monocytes and macrophages and the promotion of the production of elevated levels of plasma soluble TNF receptor 1 (sTNF-R1) by peripheral blood mononuclear cells (PBMCs) in patients with psoriasis²²⁶.

Despite all these mechanisms of action for alcohol being well established in vitro/vivo studies, there is no evidence of an association between alcohol consumption and psoriasis in humans. A meta-analysis of 5 studies (1 cohort and 4 case-control) on alcohol consumption before the disease onset did not allow a conclusion to be drawn on the association between alcohol and incident psoriasis. This is likely to be due to the retrospective nature of the information

collected on alcohol doses in case-control studies that are therefore prone to potential recall or social acceptability bias²²⁷.

A recent Mendelian randomization study using aggregate alcohol consumption data (N=941 280) and psoriasis data from 34 842 individuals (13 299 psoriasis cases and 21,543 controls) from a European psoriasis research consortium found no association between alcohol consumption (estimated from the genetic instrumental variable) and psoriasis risk (p-value=0.37)²¹⁷.

Although the evidence from epidemiological studies is not consistent with an association between alcohol consumption and risk of psoriasis, alcohol appears to alter the efficacy of systemic drugs such as acitretin and methotrexate by interfering with the drugs' mechanisms of action and hepatic metabolism, which may lead to reduced efficacy of these drugs^{228,229}.

7.4. BODY WEIGHT AND OBESITY

Obesity, generally defined as a body mass index (BMI) above 30 kg/m², has long been suspected as a risk factor for psoriasis²³⁰. A meta-analysis of 16 observational studies including 2.1 million subjects (201 831 with psoriasis) showed a pooled OR of 1.46 for the association between obesity and mild psoriasis and an OR of 2.23 for the same association with severe psoriasis²³¹.

Even more robust evidence for obesity as an independent risk factor for psoriasis come from two large prospective cohort studies conducted in the United States: in a study of 78 626 participants in the Nurses' Health Study followed over a 14-year period, multivariate risk ratios (RRs) for psoriasis were 1.40 (95% CI 1.13-1.73) for BMI 25.0-29.9 (overweight); 1.48 (95% CI 1.15-1.91) for BMI 30.0-34.9 (obesity class I) and 2.69 (95% CI, 2.12-3.40) for BMI 35.0 or greater (obesity class II/III)²³². Also, a retrospective study conducted in 2021 on a population of 1.5 million patients followed for 11 years showed a statistically significant increasing risk of developing psoriasis across the different BMI categories: adjusted hazard ratios (aHR) for psoriasis relative to people with a BMI <25.0 were, 1.19 (95% CI, 1.12-1.27) for people who were overweight, 1.43 (95% CI, 1.34-1.53) for class I obese people and 1.83 (CI, 1.71-1.95) for class II/III obese people²³³.

These observations may be explained by the role of adipose tissue in systemic inflammation, and in particular by leptin secreted by adipocytes, which can activate innate immune cells,

leading to the release of proinflammatory mediators (e.g., IL-1, IL-6, TNF- α , and nitric oxide), free radical production, and DC activation²³⁴.

In addition, the hypertrophic state of adipose tissue causes a redistribution of blood flow to adipocytes and consequent adipocyte hypoxia, resulting in the transcription of oxidative stress genes such as NF- κ B, hypoxia-inducible factor 1 α (HIF1 α), and cAMP response element-binding protein (CREB) genes, whose transcripts in turn drive the expression of adipokines, chemokines, metalloproteases, and growth factors that contribute to the state of systemic inflammatory activation²³⁵.

Finally, it should be mentioned that adipose tissue in obese patients is associated with altered pharmacokinetics of drugs commonly used in psoriasis, increasing the risk of serious side effects such as hepatotoxicity with methotrexate²³⁶, nephrotoxicity with cyclosporine²³⁷, hypercholesterolemia with acitretin²³⁸, and weight gain with biologics²³⁹.

7.5. DIET AND NUTRIENTS

Diet may play a role in the pathogenesis of psoriasis through multiple mechanisms. Psoriasis patients have an imbalanced intake of lipids and carbohydrates typical of a Western diet¹⁷⁷. In mouse models appear to increase the number of IL-17-producing cells in the skin and exacerbate psoriasis manifestations²⁴⁰.

There are few nutrients that have been specifically studied for their effects on psoriasis symptoms. Saturated fatty acids (SFAs) and simple sugars have been implicated in promoting the inflammatory cascade and worsening psoriasis manifestations:

- SFAs: SFAs, such as palmitic acid or stearic acid, are found in butter or red meat. A mouse model fed a high-fat diet rich in SFAs has been observed to present exacerbations of psoriasis lesions. In other mouse models, an increase in the expression of CCL20 by keratinocytes and endothelial cells has been observed, which may be related to the increased recruitment of Th17 cells and $\gamma\delta$ T17 cells into the lesions^{241,242}.
- Simple sugars such as sucrose are potent inducers of inflammation. A high-fructose fed rats showed increased serum IL-17F levels compared to control rats²⁴³. This effect is only observed for high-sugar diets, as observed in a study where a high-sugar/low-fat diet caused a worsening of psoriasis manifestations, while a high-fat/low-sugar diet did

not cause these manifestations. However, human studies are inconsistent, as one 2003-2006 National Health and Nutrition Examination Survey data in the US showed lower simple carbohydrate intake in psoriasis patients compared to controls²⁴⁴, while another reported higher simple carbohydrate intake in male psoriasis patients compared to controls²⁴⁵.

On the other hand other nutrients such as vitamin B12, n-3 polyunsaturated fatty acids (PUFAs), dietary fibers, genistein, selenium, short-chain fatty acids (SCFAs) appear to have an anti-inflammatory role by promoting anti-inflammatory and regulatory pathways in the disease:

- Vitamin B12: normally found in fish/shellfish (clams, oysters, mussels, or salmon roe) or liver (beef, pork, or chicken). In vitro studies have shown that vitamin B12 suppresses ROS-induced NF- κ B activation and NF- κ B-dependent production of inflammatory cytokines²⁴⁶. Clinical trials on the topical application of vitamin B12 showed an improvement of disease manifestations after 12 weeks of treatment²⁴⁷. However, intramuscular administration of vitamin B12 gave inconsistent results, as one study of vitamin B12 for 10 days led to clinical improvement of psoriasis²⁴⁸, while a double-blind controlled trial by Baker et al. showed that intramuscular administration of vitamin B12 for 3 weeks offered no benefit to psoriasis patients²⁴⁹.
- PUFAs are made up of two different categories, omega-3 (n-3) and omega-6 (n-6) fatty acids. Omega-3 FAs include α -linolenic acid (ALA), which is mainly found in plants, and eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), which are mainly found in fish and seafood sources¹⁷⁷. Serum n-3 PUFA levels in psoriasis patients are inversely correlated with psoriasis area and severity index (PASI)²⁵⁰. A meta-analysis of randomized clinical trials involving 10 studies and a total of 560 patients found that PUFA led to a reduction in PASI score, erythema, and scaling²⁵¹.
- Selenium: It is widely found in fish/shellfish, eggs, poultry or cereals. In vitro studies show that its role is mainly related to selenium-containing proteins, selenoproteins, such as glutathione peroxidases (GPxs) or thioredoxin reductases (TrxRs), which reduce ROS-induced oxidative stress²⁵². Serum selenium levels are lower in psoriasis patients than in healthy controls²⁵³.
- Dietary fiber: Dietary fiber intake is associated with a reduction in circulating serum levels of C-reactive protein (CRP), IL-6 and TNF- α and with a reduction in body weight²⁵⁴. In

a mouse model, a high-fiber diet is associated with improvement in psoriasis symptoms and secretion of mucin in the ileum and IgA in the cecum²⁵⁵.

- Genistein: It is an isoflavone, a phytoestrogen found in soybeans with potent anti-inflammatory activity. Its activity in vitro reduced the expression of inflammation-related genes such as IL-1 β , IL-6, IL-8, TNF- α , VEGFA (vascular endothelial growth factor A gene), CCL2, and IL-23. In mouse models, genistein induces the reduction of epidermal thickness and the expression of IL-1 β , IL-6, TNF- α , CCL2, IL-17, and IL-23 in skin lesions²⁵⁶.
- SCFAs: are represented by propionate, acetate and butyrate. They are the by-product of the digestion of dietary fiber by intestinal and skin microbes^{257,258}. Murine models showed a downregulation of IL-17 and induction of IL-10 expression²⁵⁹. Likewise, an ex vivo study shows that butyrate can restore the anti-inflammatory activity of inhibited Treg cells isolated from the blood of psoriasis patients. The activity of SCFAs is related to the reduction of pro-inflammatory cytokines, the suppression of the inflammatory function of T cells²⁶⁰ and to the reduction of the overexpression of lipopolysaccharide (LPS), a component of the outer membrane of Gram-negative bacteria, which could induce the production of pro-inflammatory cytokines such as TNF- α , IL-6 and IL-8²⁶¹. They can also induce the differentiation of naive CD4 T cells into peripheral Tregs via histone deacetylase (HDAC) inhibition²⁶².

Diet is not only the sole source of energy intake, but also one of the main gates for antigens from the environment²⁶³. This dual role of food could have an impact on the immunological mechanisms involved in psoriasis, as the observation of a lack of intake of protein-related antigens cause the alteration of the correct intestinal lymphoid tissues and the reduction of T-cell maturation in mouse models²⁶⁴.

While there is no evidence that a specific diet can reduce the risk of psoriatic disease, it is known that diet plays a role in modulating the microbiome that may play a major role in the pathogenetic mechanisms of psoriatic disease²⁶⁵(see section 8.1).

7.6. PSYCHOLOGICAL STRESS

Psychological stress is considered one of the main triggers of psoriasis²⁶⁶, particularly in women, where the impact of the disease on body image and self-esteem is greater²⁶⁷.

The association between psoriasis exacerbations and psychological stress was assessed in two separate reviews conducted by Stewart and Snast in 2018: The first systematic review was based on 12 studies [cross-sectional (n=2), cohort (n=3), and case-control (n=7)] for a total of 19 617 participants and reported that stress was a suggestive risk factor for psoriasis onset, recurrence, and severity²⁶⁸. The second review was based on 39 studies [survey (n=19), cross-sectional (n=7), cohort (n=1) and case-control (n=12)] with a total of 32 537 participants and found that the pooled OR for stressful events prior to psoriasis onset was 3.4 (95% CI 1.8-6.4). However, this association is not considered conclusive by the authors due to heterogeneity in the definition of stressful events, which prevents comparability of data in the literature²⁶⁹.

The manifestations of psoriasis are also a major cause of deterioration in patients' quality of life: fear of social judgment and discrimination at work lead to a decrease in self-confidence, feelings of rejection and shame, with a significant impact on physical and sexual activities, but also on interpersonal relationships²⁶⁶. This is reflected in the association observed in a recent meta-analysis conducted on 17 studies, which shows a pooled risk ratio (RR) of 1.48 (95% CI: 1.16-1.89). between depression and psoriatic disease²⁷⁰.

Mechanisms for the putative effect of stress on psoriasis may involve three pathways: first, the autonomic nervous system (ANS); second, the hypothalamic-pituitary-adrenal (HPA) axis; and finally, peripheral nerve growth.

The ANS is the body's first line of defense and, through the secretion of epinephrine and norepinephrine, can lead to mast cell degranulation and increased vascular permeability in the skin. These two factors can increase the number of inflammatory cells in the psoriatic plaque²⁷¹⁻²⁷³.

The role of the HPA axis is to coordinate the body's ongoing response to stress. Under normal conditions, the HPA axis is tuned by the negative feedback of GC in the blood, but this system appears to be impaired in chronic stress. In psoriasis, there is a decrease in GC secretion²⁷⁴, together with an increased production of catecholamines²⁷⁵, which has repercussions on the HPA axis. Indeed, in recent years, there has been a growing interest in the role of peripheral neurons present in the skin²⁷⁶. Furthermore, there is an embryological link between epidermal and neural cells that share a common ectodermal origin, suggesting the possibility of crosstalk between the two²⁷⁷.

Nerve endings are responsible for the secretion of mediators such as substance P, which is

responsible for increased keratinocyte proliferation, inflammation and lymphocyte activation^{277,278}. CGRP release from nerve endings can stimulate LC migration to lymphocytes, where they can present antigens to T cells and cause their activation²⁷⁹. Finally, corticotropin-releasing hormone (CRH), a neuropeptide produced by both skin and immune cells^{280,281}; in psoriasis, both CRH and its receptor CRH-R1 are increased in psoriatic lesions²⁸²; CRH can increase vascular permeability and mast cell degranulation^{272,273}. Mast cells have also been implicated in nerve-skin reactions, as they are found in close contact with cutaneous nerves²⁸³. However, the exact role of mast cells in the relationship between psychosocial stress and psoriasis is still unclear and requires further research^{284,285}.

7.7. DRUGS

Several drugs are associated with the onset and exacerbation of psoriasis. The exact mechanisms involved are often unknown and this poses problems for clinicians who tend to treat patients with multiple therapies at the same time²⁸⁶. Drug-induced psoriasis is difficult to study because effects can be seen many days or weeks after exposure to the drug²⁸⁷. Patients may experience worsening of existing psoriatic lesions or develop new lesions on previously unaffected skin²⁸⁸.

The drugs that appear to have a strong causal relationship with psoriasis are beta-blockers, lithium, synthetic antimalarials, non-steroidal anti-inflammatory drugs (NSAIDs), tetracyclines, interferons and PD-1 inhibitors. These drugs have been extensively studied and a potential pathological pathway has been described for each of them^{286,289}.

Other drugs, such as anti-TNF- α , anti-IL-17 and anti-IL-23, are commonly used to treat psoriasis and other autoimmune diseases such as rheumatoid arthritis and Crohn's disease, but in some cases could also trigger or cause flares of psoriasis. This appears to be a paradoxical response, but there are still many missing links in the explanation of these responses: TNF- α -induced psoriasis could increase interferon- α production, which in turn activates dendritic cells, which could initiate an inflammatory cascade leading to the production of proinflammatory cytokines¹⁰⁰; IL-17/23 responses are thought to be initiated by drug-induced Th1/Th23 blockade, causing repolarization of the immune response through the Th2 pathway, which is linked to the eczematous reactions observed in these patients²⁹⁰.

7.8. INFECTIONS

Infections have been primarily associated with psoriasis because it was shown 50 years ago that removal of the tonsils in psoriatic patients had a beneficial effect on the disease^{291,292}. *Streptococcus pyogenes* is now thought to be the causative agent of the guttate psoriasis onset, producing T cell-activating superantigens (also produced by *Staphylococcus aureus* and other microorganisms) that bind to the T cell receptor via the variable region of the beta chain ($V\beta$)²⁹³.

T cell antigen priming may occur in the skin-draining lymph nodes and/or tonsils, as suggested by the presence of the same clonal T cell receptor rearrangements in both lesional skin and tonsillar T cells expressing cutaneous lymphocyte antigen in patients with recurrent psoriatic exacerbations induced by streptococcal tonsillitis²⁹⁴. Increased numbers of interferon- γ -producing Th1 cells with specificity for group A streptococcal antigens have been detected in the skin lesions of both guttate and plaque psoriasis, a subset of which recognize streptococcal cell wall antigens²⁹⁵.

Unfortunately, psoriasis tends to return to an active state even after tonsillectomy. Perhaps this is due to streptococcal migration to other lymphoid tissues in the upper airways, or another possible explanation for this prolonged inflammatory state could be that primed streptococcal T cells can be maintained by activation by a skin-specific antigen, in this case without the need for homology to a streptococcal antigen²⁹⁶.

Other infectious agents that might be involved in psoriasis outbreaks and exacerbations are: other bacteria such as *Staphylococcus aureus*, fungi (*Malassezia* and *Candida* species) and viruses such as the human immunodeficiency virus (HIV), hepatitis virus, human papillomavirus (HPV), cytomegalovirus (CMV), Zika virus (ZIKV) and severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2]²¹⁴.

Finally, the impact of vaccinations on psoriasis deserves to be noted. The influenza vaccine, in particular, has been studied in relation to psoriasis because of its relatively widespread use around the world. Although H1N1 and other seasonal vaccines are generally safe and effective, many serious and non-serious vaccine-related adverse events have been reported^{297,298}. The mechanism could be activated by two mechanisms that are antigen specific or antigen non-specific^{299–301}. As the vaccines also contain adjuvants (e.g. aluminium salts, thiomersal, squalene, sorbitol, albumin, neomycin and gentamycin), it is not possible to identify with certainty the agent responsible for the autoimmune phenomena, either the infectious

component of the vaccine or the adjuvant³⁰². Most of the psoriasis exacerbations reported in the literature have been associated with adjuvants influenza vaccines, although only one patient with guttate psoriasis described an exacerbation following the 2009 monovalent H1N1 vaccine infusion without adjuvant³⁰³.

8. THE ROLE OF MICROBIOME

The microbiome is defined as a characteristic microbial community that occupies a reasonably well-defined habitat with distinct physiochemical properties. It consists of a collection of microorganisms belonging to different kingdoms (prokaryotes [bacteria, archaea], eukaryotes [e.g. protozoa, fungi and algae])³⁰⁴.

Each part of the human body has its own resident microbiome with different functions and whose developmental trajectory is linked to factors specific to the individual's lifestyle. Changes in the composition and abundance of the microbiome, known as dysbiosis, have been shown to play a central role in immune dysregulation and immune-mediated diseases, including psoriasis³⁰⁵.

8.1. GUT MICROBIOME IN PSORIASIS

Gut microbiome development starts during fetal life and continues in perinatal period thanks to birth delivery, breastfeeding and contact with external milieu³⁰⁶. Full development is reached at around 36 months of age, when it takes on its final shape, which lasts until adulthood³⁰⁷.

Previous studies of the composition of the gut microbiome in patients with chronic immune-related diseases, including psoriasis, have revealed how complex immune networks may exist between the gut and skin that contribute to the initiation and maintenance of the inflammatory cascade³⁰⁸.

The involvement of the gut microbiota in psoriasis is supported by a number of observations and evidence: both mouse models and human psoriasis patients show alleviation of psoriatic manifestations after antibiotic treatment^{309,310}.

Similarly, modulation of the gut microbiome by probiotic administration³¹¹ or faecal transplantation³¹² has been shown to be an effective treatment for the long-term reduction of

disease manifestations.

Psoriasis-related gut dysbiosis is mainly about the loss of beta-diversity - i.e. the reduction of variability - as communities become dominated by a few dominant species.

These variations are particularly evident at the family level with the relative abundance of Ruminococcaceae, Lachnospiraceae, Clostridiales family XIII, Peptostreptococcaceae, Enterococcaceae, Coriobacteriaceae and Eggerthellaceae appears to increase in psoriasis, whereas the relative abundance of Prevotellaceae, Barnesiellaceae, Tannerellaceae, Rikenellaceae, Porphyromonadaceae, Marinifilaceae, Lactobacillaceae, Streptococcaceae, Pasteurellaceae, Burkholderiaceae, Desulfovibrionaceae, Victivallaceae and Verrucomicrobiaceae appear to decrease³¹³.

The effects of dysbiosis on the pathogenesis of psoriasis is still poorly understood and focus mainly on the reduced metabolism of SCFAs whose mechanism of action in psoriasis was previously described in the 7.5 section.

8.2. SKIN MICROBIOME IN PSORIASIS

The skin microbiome is not a single entity, but a collection of different populations that take on different characteristics based on the structural (such as epidermal thickness, number of sweat and sebaceous glands present) and functional (nutrient accessibility and host immune response) characteristics of the skin area involved³¹⁴.

According to the literature, the most abundant phyla in healthy skin are Actinobacteria, Proteobacteria, Firmicutes and Bacteroidetes³¹⁴. The psoriatic skin shows a reduction in alpha diversity of the skin microbiome. - i.e. a reduction in the number of bacterial species - with Firmicutes being the most abundant phylum, while Actinobacteria were significantly reduced³¹⁵.

The equilibrium of the skin microbiome is maintained by the continuous interaction of microbial antigens on the skin surface with AMPs normally produced by keratinocytes³¹⁶. External stimuli that induce dysbiosis cause an increase in epidermal apoptosis and the release of DNA, which binds to AMPs and stimulates the production of type I interferons by plasmacytoid dendritic cells pDCs³¹⁷ and the production of TNF- α and iNOS by mDCs³¹⁸.

The increase in keratinocyte replication in the active phase of psoriatic disease amplifies the production of AMPs, which cause the selection of microbial species resistant to these substances, such as *Staphylococcus aureus*, which triggers a strong Th17-type response by inducing T-cell secretion of the cytokines IL-17A, IL-17F and IL-22. IL-22 not only triggers a pro-inflammatory response but also inhibits terminal differentiation of keratinocytes³¹⁹. In addition, as mentioned in the section on infections, superantigens produced by *Staphylococcus* act as a molecular mimic of type I keratin and induce T-cell activation³²⁰.

9. LIMITATIONS OF PREVIOUS EPIDEMIOLOGICAL STUDIES

Despite significant advances in the understanding of the molecular mechanisms involved in the disease and the availability of new treatments, psoriasis remains an incurable disease that represents a major public health problem due to its disease burden¹⁶⁶.

We now know that psoriasis development is likely due to multiple genetic susceptibility loci, immune system dysregulation, microbial dysbiosis, and environmental risk factor that may act as triggers¹⁹⁹ and that are poorly understood³²¹.

A large body of clinical and experimental evidence shows that many environmental factors can affect the immune system and psoriasis directly or indirectly through the microbiome³²².

An observation that is coherent with the direct effect of the environment on the pathology is the immunomodulatory effect that solar exposure has psoriasis: as previously reported, population in Africa, South America and Pacific Islands are almost free of psoriasis indicating that these populations might be less susceptible to the disease but also suggesting a possible link between UV exposure and psoriasis^{169,170}.

On the other hand, the environment and factors linked to lifestyle can affect immune response indirectly, and a potential mediator of this action could be the microbiome: as previously described, psoriasis patients have different pattern of microbiome expression, indicating that dysfunctions in the gut microbiome can impact the immune response in the skin. Many of the factors previously associated with psoriasis, including drugs, lifestyle (smoking, alcohol), diet, stress and infections, have been shown to modulate microbiome composition³²³.

This effect seems related to the existence of the so-called gut-brain axis, i.e. the release of

metabolites and neurotransmitters by the gut microbiome that lead to the activation of immune cells and dysregulation of the skin barrier³²⁴.

However, for putative risk factors that may affect the immune response we had conflicting and inconclusive results for most of the factors studied.

There were several limitations that may explain this result:

- Very often there were studies with few headcount and therefore with low statistical power.
- There were few prospective studies, and the study design is often retrospective or cross-sectional, if not really based on indirect evidence such as in vivo and in vitro studies.
- Studies on the same risk factor used different scales to measure it, as in the case of smoking, alcohol or pollution.
- Studies lacked adjustment for factors such as age weight and other previously studied risk factors.
- In many cases, there were no studies at all.

Given this, there remained many under-researched areas relating to environmental risk factors and psoriasis.

10. OBJECTIVES OF THE THESIS

The main aim of this PhD project was to investigate the associations between inflammatory and immunity-related environmental and lifestyle factors and psoriasis risk in the E3N cohort, a large prospective cohort study of almost 100,000 women followed since 1990.

The main underlying hypotheses to be tested in this project are as follows.

The first hypothesis was that mucosal associated lymphoid tissues (MALT) play a fundamental role in the proper development of the immune system and in the homeostasis of the microbiome.

The first objective of the study was to investigate whether surgical removal of three types of

lymphoid tissue (adenoidectomy, appendectomy and tonsillectomy) is associated with a reduced long-term risk of psoriasis.

The second hypothesis was that the environment during childhood may determine the immune tolerance against self-antigens and play a fundamental role in the development of the microbiome profile, as postulated in the so-called "hygienic hypothesis" .

The second objective of the thesis was to investigate the association between the environment during childhood, in particular an urban versus a rural birthplace, having farming parents, living on a farm and living with pets or other farm animals during childhood and the risk of psoriasis.

The third hypothesis was that residential UV exposure is associated with a reduced risk of psoriasis.

The third objective of this thesis was to evaluate the association between residential UV exposure long-term risk of psoriasis and to test whether pigmentary traits are associated with risk of psoriasis.

Given the possible etiological differences between mild and moderate-to-severe cases of psoriasis, in each of the studies we conducted analyses based on all incident cases of psoriasis and, separately, just on moderate-to-severe cases.

PART II : MATERIALS AND METHODS

1. MATERIALS

The entirety of the analyses conducted in this doctoral project utilized data from the E3N cohort. The purpose of this chapter is to present the E3N cohort, the data collected and to describe the analysis strategies used in the thesis project.

1.1. E3N COHORT

The E3N cohort is a prospective cohort of 98 995 women who were members of the health insurance scheme of the national education system (Mutuelle générale de l'Éducation nationale-MGEN), aged 40 to 65 years (born between 1925 and 1950) and living in metropolitan France at the time of recruitment between 1989 and 1990.

The cohort was established with the aim to study the role of risk factors related to diet and hormonal exposures on cancer incidence in the French context. Over the years, the focus of the research conducted has been expanded to include chronic diseases such as cardiovascular diseases, diabetes, neurodegenerative diseases, psychiatric diseases and immune-mediated diseases.

E3N is managed by the " Exposome and heredity" group of the Centre de Recherche en Épidémiologie et Santé des Populations (CESP, Inserm UMR 1018), based at the Gustave Roussy and Paul Brousse hospitals in Villejuif.

Women included in the cohort gave their consent to the transfer of data on their prescriptions for medical and pharmacological services, changes of residence and vital status from the MGEN database.

At the time of its launch, the E3N cohort was the largest observational prospective study ever conducted in France and today, after more than 30 years of follow-up, it is still one of the largest ongoing studies of women's health.

Since 1993, E3N has been an integral part of the European EPIC cohort, a multicenter prospective cohort of 521 000 men and women from 10 European countries that aims to investigate the links between diet, lifestyle and risk of cancer and other chronic diseases. EPIC

is overseen by the World Health Organization's International Agency for Research on Cancer (IARC-WHO) in Lyon.

1.2 PARTICIPANTS' RECRUITMENT

E3N participants were recruited from January 1989 when a pilot study was conducted among women who were MGEN members from three French departments (Nord, Pas-de-Calais and Tarn-et-Garonne).

Then, 500 000 women between the ages of 40 and 65 (born between 1925 and 1950) were recruited nationwide. They were contacted and invited to participate in the study on a voluntary basis. 98 995 of them responded to the questionnaire. In terms of age and place of residence, the characteristics of the participants were similar to those of the women who did not respond to the survey.

The study was approved by the Commission Nationale Informatique et Liberté (CNIL) and by the Comité consultatif sur le Traitement de l'Information en matière de Recherche dans le domaine de la Santé (CCTIRS). At the time of recruitment to the study, each woman signed an informed consent to participate in the study.

The selection of participants in the MGEN was based on the primary objective of the cohort, which was to study the effect of anthropometric characteristics, lifestyle and diet on cancer risk in women. Specifically, the first objective was to investigate hormone-dependent cancers, such as breast and endometrial cancers, and this determined the choice of a female population aged between 40 and 65 years, as this population made it possible to capture the effect of factors related to puberty, reproductive age and menopause. Later, the cohort objectives were expanded to include other chronic diseases such as diabetes, cardiovascular disease and autoimmune diseases, given the low marginal cost of studying other health outcomes.

The decision to recruit women from the public education system proved to be correct, as this population was able and willing to complete the follow-up questionnaires carefully and regularly, and motivated to participate for a long time, which helped to reduce loss to follow-up. The proportion of participants who completed the thirteen main questionnaires remained remarkably high (i.e. between 77% and 92%)(Table 1)³²⁵.

Table 1: Answer rate for each questionnaire of E3N cohort.

Questionnaire	Year of questionnaire	Number of questionnaires submitted	Number of questionnaires received	Response Rate (%)
Q2	1992	98 990	86 164	87
Q3	1993	93 055	74 529	80
Q4	1995	75 357	69 148	92
Q5	1997	97 860	86 825	89
Q6	2000	96 605	83 196	86
Q7	2002	93 389	81 453	87
Q8	2005	93 121	71 411	77
Q9	2008	92 886	73 705	79
Q10	2011	87 751	70 516	80
Q11	2014	83 612	64 862	78
Q12	2018	82 152	61 033	74
Q13	2021	76 563	On going	On going

In 2011, new funding from the French government enabled the launch of the recruitment of E3N women family members and the creation of the E3N-Generations family cohort, whose recruitment is ongoing.

1.2. COHORT FOLLOW-UP

1.2.1 QUESTIONNAIRES

The cohort baseline questionnaire included questions on sociodemographic factors such as level of education and type of occupation; anthropometric characteristics such as height, weight, silhouette at different ages; reproductive and hormonal factors such as number of pregnancies and births and use of contraceptive methods; health status and previous hospitalizations; participation in screening programs for breast, cervical, and colorectal cancer; tobacco status; physical activity; and family history of cancer.

The first questionnaire was followed by 12 follow-up questionnaires. The second, third and fourth questionnaires were sent only to women who had completed the preceding questionnaire. From the fifth questionnaire onwards, questionnaires were sent to all women still alive who had not withdrawn their participation in the cohort. For each questionnaire, two postal re-bids were made if the questionnaire was not sent back to the study team.

In each of the questionnaires, the health status questions were updated with information from subsequent questionnaires, and a different area of the participants' lifestyle was explored: for example, the 2nd questionnaire (Q2) detailed the woman's reproductive life, while the 4th questionnaire (Q4) included a questionnaire on anthropometric measurements. The third and eighth questionnaires (Q3 and Q8) included a detailed questionnaire on diet (food frequency questionnaire).

The tenth and eleventh questionnaires assessed the women's visual and dental health. These questionnaires also covered mental health and psychological well-being: moods, stress, anxiety.

The 12th questionnaire (Q12) included detailed questions about how families interact and how lifestyles and skills get passed on from one generation to the next. The 13th questionnaire (Q13) included, in addition to the canonical sections on health and lifestyle, new sections on Covid-19 (diagnosis, symptoms, vaccination), on the acoustic and atmospheric environment (sensitivity to noise, characteristics of the place of residence), on independence and quality of life, on sleep and social contacts.

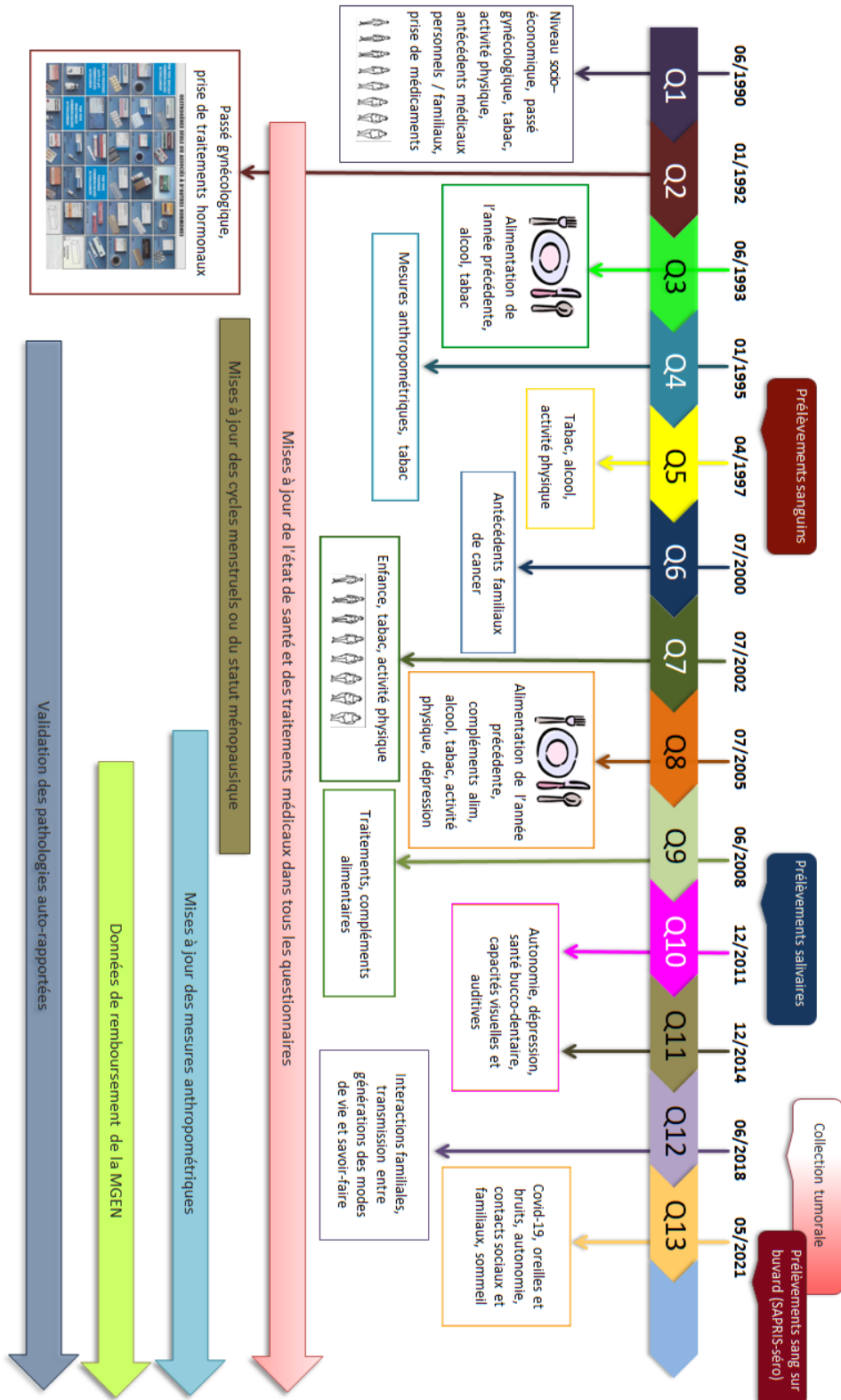


Figure 14: Data collected by self-questionnaires in the E3N cohort. Source: cohort E3N website³²⁶

1.2.2 THE MGEN DATABASE

Every three months, the MGEN provides updated vital status and mailing address for each E3N woman, as well as information on any drug reimbursements. Drug reimbursement data are available from 2004 and include information on out-of-hospital medications only. No information is available on medications delivered during hospitalisations or bought over-the-counter.

The MGEN also provides information on the number of emergency room visits, the number of consultations with general practitioners and other specialists, the number of medical procedures by type of prescriber, and the number of paramedical procedures.

1.2.3 MORTALITY DATA

In addition to the vital status available from the MGEN, information on deaths can also be reported by acquaintances of the deceased participant, often the spouse or the children. For the rare participants who are no longer affiliated with the MGEN health insurance scheme, the MGEN can access the National Death Registry to determine the vital status in the absence of other sources. Causes of death for confirmed deaths are currently available up to 2015 and are provided by the Causes of Death Epidemiology Centre (Cépi-DC) attached to the Institut national de la santé et de la recherche médicale (Inserm).

1.3. BIOLOGICAL DATA

During the life of the cohort, various biological samples were taken for the purpose of expanding and supplementing the information collected through the surveys: between 1994 and 1999, 25 000 women agreed to provide blood samples . The selection was made among the volunteers living in urban areas. Blood samples collected from each participant were divided into 28 aliquots of 500 microliters each consisting of serum, plasma, buffy coat, and erythrocytes. These biological samples were separated in two sets both stored in liquid nitrogen (at -196°C), one set in the EPIC biobank at IARC in Lyon, and the other set in the E3N biobank at the Fondation Jean Dausset-CEPH in Paris. The creation of this Biological Material Bank was approved by a Comité de Protection des Personnes (CPP) Ile-de-France XI.

Between 2009 and 2011, a new collection of saliva samples was established for 44 775 E3N women from those for which a blood sample was not collected. These saliva samples are stored in a freezer at +4°C in the E3N biobank at the Fondation Jean Dausset-CEPH in Paris.

1.3 IDENTIFICATION AND CHARACTERISATION OF PSORIASIS CASES

With this thesis the theme of psoriasis was investigated in E3N for the first time. For this reason, the first part of the project was dedicated to the identification of cases through an evaluation and synthesis of relevant data available in the cohort from the following sources:

- Psoriasis diagnoses self-reported by patients in questionnaires;
- Reimbursement of medicines approved for the treatment of psoriasis in France and identified in MGEN drug reimbursement database.

Another source of data was free text boxes, present in all questionnaires from Q2 onwards, where women could report the presence of diseases not mentioned in other parts of the questionnaire or hospitalizations since the previous questionnaire. We searched the free text to identify women that reported psoriasis and used this information to complement the two main sources mentioned above (Appendix 1).

1.3.1 QUESTIONNAIRES

In the 9th, 10th and 12th follow-up questionnaires (Q9, Q10 and Q12, sent in 2007, 2011 and 2018 respectively), participants were asked to indicate whether they had ever had a diagnosis of psoriasis and when. In Q10 and Q12, women were asked to report a case of psoriasis that had occurred since the previous questionnaire (Figure 15).

If the reported date at diagnosis included only the year, January of that year was considered as the diagnosis date.

Women who self-reported a diagnosis of psoriasis in Q9, Q10 and/or Q12 were distributed as follows:

- 2 608 potential cases of psoriasis reported in questionnaire 9

- 2 363 potential cases of psoriasis reported in questionnaire 10

- 2 080 potential cases of psoriasis reported in questionnaire 12

A graphical representation of the psoriasis cases identified from the questionnaires is given in the Appendix 2.

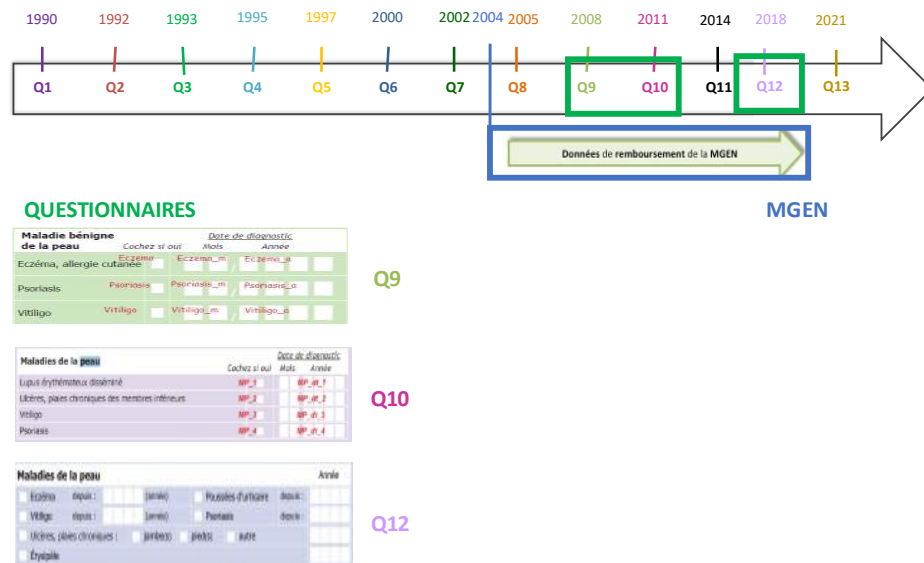


Figure 15: Questionnaires used to identify psoriasis cases in the E3N cohort.

1.3.2 MGEN DATABASE

As described earlier, the MGEN provides the cohort with data on the reimbursement of out-of-hospital medicines for all affiliated E3N participants since 1 January 2004. This information includes the CIP codes (Codes Identifiants de Présentation) and the date of issue of each pack of reimbursed medicines. The CIP codes were used to identify the molecule, dose (usually in mg), route of administration and number of units for each pack.

Listed below are all the drugs currently approved in France for the treatment of psoriasis, whose prescriptions were extracted from the MGEN databases (Table 2).

Table 2: List of drugs that can be indicated for the treatment of psoriasis extracted from MGEN drug reimbursement database.

Drugs category	
Topical drugs derived from vitamin A and D	<ul style="list-style-type: none"> • Calcipotriol • Calcipotriol in association with betamethasone • Calcitriol • Tacalcitol • Tazarotene
Topical steroids	<ul style="list-style-type: none"> • Betamethasone • Clobetasol • Desonide • Diflucortolone • Difluprednate • Fluticasone • Hydrocortisone Aceponate • Hydrocortisone Butyrate
Psoralens (PUVA therapy)	<ul style="list-style-type: none"> • Methoxsalene
Non-biologic immunomodulators	<ul style="list-style-type: none"> • Acitretin • Ciclosporine • Methotrexate
Biologic immunomodulators	<ul style="list-style-type: none"> • Adalimumab • Apremilast • Etanercept • Ixekizumab • Secukinumab • Ustekinumab

Of the drugs considered, only topical vitamin D and vitamin A preparations are used exclusively to treat psoriasis.

1.4 TOTAL PSORIASIS CASES IDENTIFIED

Combining data from all three questionnaires from which we extracted psoriasis information we identified a total of 4 621 cases. Of these, 3 848 cases reported a date of diagnosis.

We then cross-referenced the psoriasis cases reported in the questionnaires with drug reimbursement data and the analysis showed that 4 099 cases (88.7% of the analysis population) had at least one reimbursement for a medicine used to treat psoriasis.

When the data were broken down by type of medication prescribed, 50.8% had prescriptions for topical vitamin A or D derivatives, 97% for topical corticosteroids, 1.1% for biologics, 6.9% for non-biologic immunomodulators and 2.4% for psoralens.

Importantly, women often presented prescriptions for more than one drug category (as example 1 718 women were treated with a combination of topical corticosteroids and topical derived from vitamin A or D).

In addition, a psoriasis medication prescription pattern analysis using MGEN data performed on the entire cohort identified additional potential psoriasis cases who never reported psoriasis in the questionnaires but had at least two psoriasis-specific topical medication prescriptions (vitamin A or D derivatives). Using this criterion, we identified an additional 1 086 cases of psoriasis.

Adding this population to the population identified in the questionnaires gives an analysis population of 5 707 psoriasis cases.

As described above, psoriasis cases that were only present in free text boxes, which amounted to 452 cases, were not included in the principal analysis population but were used for sensitivity analyses.

This led to a total number of psoriasis cases identified in the cohort of 6 159 cases with an estimated psoriasis prevalence of 6.2%.

A breakdown of psoriasis cases identified in the E3N cohort according to their source is reported in the Appendix 3 and 4.

1.5 PSORIASIS DIAGNOSIS DATE

3 848 (67.4%) of the psoriasis cases included in the principal analysis population reported a valid diagnosis date. For the purposes of the analyses presented in this thesis, follow-up began at the time of completion of the cohort baseline questionnaire in 1990. Incident cases are cases diagnosed after the start of follow-up, while cases diagnosed before 1990 are considered prevalent. Based on this classification, we identified 2 567 (44.9%) incident cases and 1 281 (22.4%) prevalent cases.

For the remaining 1 859 cases (32.7%) date of diagnosis was not available and we have therefore not been able to determine whether they were incident or prevalent cases with respective to the beginning of follow-up.

The 1 086 cases identified only through MGEN were included in the no date of diagnosis category because psoriasis is a condition with a significant delay between disease onset and medication use³²⁷, and given that the MGEN database only includes drug reimbursements starting in 2004, the date of the first psoriasis-related reimbursement was not judged to be a reliable proxy for the date of disease diagnosis.

When the self-reported date of disease diagnosis in different questionnaires was discordant (33% of cases with a date of diagnosis), we used the age reported in the first completed questionnaire.

This choice was made considering that the earliest date reported by the woman is the one that is temporally closest to the declared date of diagnosis. Secondly, in previous studies carried out in the E3N cohort, this identical criterion was used for dates reported for diseases such as cancer.

A breakdown of psoriasis cases identified by source of diagnosis date was given in Appendix 5.

1.6 DEFINITION OF MODERATE-TO-SEVERE PSORIASIS

In the absence of clinical data from patients, we used the MGEN drug reimbursement data to identify moderate-to-severe cases of psoriasis.

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

immunomodulators).

Using this criterion, we found a total of 449 cases of moderate-to-severe psoriasis. We defined the start of the manifestation of a moderate-to-severe case as the date of the first drug reimbursement of a systemic medication used for psoriasis.

This approach had a limitation in that the availability of MGEN reimbursement data begins in January 2004, and therefore it cannot be excluded that the first reimbursement of psoriasis-related systemic drugs occurred earlier.

Another limitation was that we could not rule out the use of systemic drugs for conditions other than psoriasis.

1.7 RELIABILITY OF OUR CASE DEFINITION.

As described earlier the identification of cases was mainly based on self-reported information with the integration of data from the MGEN drug reimbursement database available from 2004. A validation phase through the collection of medical records from treating physicians was not possible mainly due to the large number of cases identified in E3N.

While a reliability study based on the collection of information from treating physicians for a small number of cases may be envisaged, there was significant evidence supporting the adequacy of our case definition for the purposes of the epidemiological studies presented in the thesis.

The identification of psoriasis cases in epidemiological studies based on other cohorts such as NutriNet-Santé, HUNT and the Nurses' Health Study II was based on self-reported information and questions that were similar to those used in E3N.

In the NutriNet-Santé cohort, a prospective French general population cohort of 158 361 people³²⁸, a psoriasis self-administered questionnaire consisting of 11 questions about the disease was used. This instrument was validated on a population of 534 outpatients attending consultations in two dermatology departments in the university hospitals of Créteil and Bordeaux. The data provided in the questionnaire were subsequently verified by a dermatological examination. In this study, the case definition based just on self-declarations as in our study (Have you psoriasis? Yes or No) was found to have good sensitivity (82.2%) and very good specificity (98.6%)³²⁹.

Similarly, in the HUNT study, a population-based prospective cohort in the Norwegian county of Nord-Trøndelag consisting of 50 807 people³³⁰, a validation study with dermatological examination of 543 participants (110 with psoriasis and 434 without psoriasis) who answered the question "Have you ever had or do you have psoriasis?" showed a specificity of 99% (95% CI, 98-99%) and a sensitivity of 56% (95% CI, 44-68%) for the self-reported diagnosis of psoriasis³³¹.

Finally, in the US Nurses' Health Study II, an ongoing longitudinal study of 116 608 female registered nurses³³², self-reported diagnoses of psoriasis were confirmed using the Psoriasis Screening Tool (PST). This self-administered questionnaire was validated in a population of 222 consecutive individuals seen in the outpatient dermatology clinics at Brigham and Women's Hospital and validated by a board-certified dermatologist³³³.

The PST included the statements "I have been diagnosed with psoriasis by a dermatologist", "I have been diagnosed with psoriasis by a nurse practitioner or physician assistant", and "I have been diagnosed with psoriasis by a non-dermatologist (rheumatologist, family physician, or other physician)".

All three statements had very good specificity (98%, 99% and 98% respectively), but low sensitivity except for self-reported diagnosis by a dermatologist (93%, 9% and 36% respectively)³³³.

As noted above, self-reported diagnosis of psoriasis is often associated with very good specificity but sensitivity may be moderate or low. This carries the risk that some cases may go undetected and be considered false negatives.

To mitigate the potential limitation of the sensitivity of self-reported diagnosis, we used the MGEN data and identified an additional 1 086 cases not previously identified by questionnaire as explained above.

Our case definition was also supported by the observation that 88% of cases had reimbursement for medications used to treat psoriasis (i.e., vitamin D derivatives, cytokine receptor modulators, immunomodulators, psoralens, and topical steroids).

Furthermore, the drug prescription patterns of women with psoriasis in E3N were similar to those observed in a study in Korea using medical administrative data from the national health system, which showed that among the 316 942 psoriasis cases identified, 86.9% had been treated with topicals, 11.6% with non-biologic immunomodulators and 0.3% with biologics

while 20.2% of cases had no psoriasis-related drug prescription³³⁴.

The observed prevalence of 6.2% in E3N which was slightly higher than the 5.2 % French national estimates based on self-reports¹⁷² may be due to our approach integrating self-reports with drug reimbursement data.

Another possible explanation of the slightly higher prevalence of psoriasis in E3N may be linked to the health awareness of the cohort participants that are more likely to participate in screening programs and being more aware of their health status visit their doctors for check-ups more frequently than in the general population³²⁵.

1.8. COVARIATES

This section describes the covariates included in the multivariable models used in all analyses presented in this thesis.

A description of the specific adjustment variables for each study is provided in the materials chapter of part IV, V and VI.

1.8.1. EDUCATIONAL LEVEL AND MARITAL STATUS

The level of education was collected in the first questionnaire (Q1), where women could choose between the following options: no education, school certificate, vocational certificate, baccalaureate (Bac), up to two years of higher education, three to four years of higher education, five or more years of higher education. We have grouped them into three categories: less than Bac, Bac to Bac +2 years and >Bac +2 years.

Marital status was also collected in the first questionnaire as a binary variable, where women could indicate whether they were married or not.

1.8.2. ANTHROPOMETRIC MEASURES

Weight was collected in each cohort questionnaire, while height was collected in questionnaires Q1, Q4, Q6, Q7 and Q8, from which a single variable for height was created for the entire follow-up. This allowed Body mass index (BMI) to be calculated in each questionnaire by

dividing the weight in kg by the square of the weight in meters. For the purposes of this project we used three BMI categories based on standard WHO cut-offs : $<25 \text{ kg/m}^2$ (underweight and normal weight); $25\text{-}30 \text{ kg/m}^2$ [(overweight) and $\geq 30 \text{ kg/m}^2$ (obese).

1.8.3. SMOKING STATUS

All questionnaires contain questions on smoking that allowed classification of participants in three categories (current smoker, former smoker or never smoker) at each questionnaire. Other information on smoking collected from Q3 onwards includes type of smoking (cigarettes, cigars, pipe), frequency of smoking, smoking initiation and cessation, and finally passive smoking. For the work presented in this thesis, we only looked at the smoking status of women in three categories.

1.8.4. HORMONAL AND REPRODUCTIVE STATUS

Considering the all-female composition of our population and the potential impact of hormonal and reproductive factors on psoriasis, we investigated the effects of reproductive and hormonal factors collected in E3N, including age at menarche as a categorical variable in three categories (12-15 years old, <12 years old, >15 years old), menopausal status (No ,Yes), nulliparous status (No ,Yes) and ever use of oral contraceptives (No ,Yes).

Menopausal status, defined as the absence of menstrual periods for at least 12 months (unless due to hysterectomy), was recorded in all questionnaires except Q7, whereas age at menarche, nulliparous status and ever use of oral contraceptives were reported in the baseline questionnaire.

1.8.5. COMORBIDITIES

In the baseline questionnaire participants were asked about their health history before entering the cohort and in all follow-up questionnaires they were asked to provide any new information about their health since the previous questionnaire. Participants were asked to report any diagnosis of specific health problems (e.g. cancer diagnoses, diagnoses of cardio-metabolic diseases) including the date of diagnosis or their age at diagnosis.

In the models used in all analyses presented in the thesis we included three binary variables related to any diagnosis of three diseases commonly associated with psoriasis: hypertension, diabetes and depression.

Self-reported diagnoses of depression and type 2 diabetes were collected in each questionnaire from baseline to Q12. Data on hypertension were collected in all questionnaires except Q10.

2. METHODS

2.1. DESCRIPTIVE ANALYSES

Descriptive analyses were performed using standard statistical measures: number of observations and frequency (provided as percentage) for categorical variables, mean and standard deviation for continuous variables.

Population characteristics were presented in relation to when women were included in the analyses and by category of the exposure variable of interest and by case/non-case status.

2.2. RISK ANALYSES

We used Cox proportional hazards models to test the association between the exposure variable of interest and risk of psoriasis. We used these models to study associations between three different classes of exposure (MALTectomy, childhood-related environmental risk factors, and skin phenotype and sun exposure) and psoriasis risk. Different variables within each class were generally tested in separate models.

2.2.1. COX MODEL

Cox's semi-parametric proportional hazards model is the most widely used statistical model in prospective studies. It makes it possible to quantify the relationship between a main exposure factor and the occurrence of an event of interest by taking censored events into account³³⁵.

Formally, the model postulates that the instantaneous risk of the occurrence of the event of interest (risk of event per unit of time or hazard) changes over time following a function $h(t)$ that for an individual i at the time t depends on the values of a set of p quantitative or

qualitative explanatory variables $X_i = (X_{i1}, \dots, X_{ip})$. The hazard function can be written as:

$$h(t, X_1, \dots, X_{1p}) = h_0 \cdot e^{(\sum_{k=1}^{k=p} \beta_k \cdot X_k)}$$

In this formula, $h_0(t)$ is the instantaneous risk of disease for a subject for whom all variables X_i are equal to 0, i.e. the 'baseline' instantaneous risk. This model does not allow an absolute risk to be estimated as a function of the values of the various covariates for an individual, since the form of its instantaneous risk function is not specified, but it does allow the risk of individuals to be compared according to their exposure to the factors corresponding to the variables X_i .

2.2.2. HAZARD RATIO

From the instantaneous risk function, we can calculate the ratio between the hazard function of two individuals who differ in terms of the values of an explanatory variables X that assumes value X_1 and X_0 for the two individuals. The ratio of the hazards of two individuals is called hazard ratio (HR(t)) and can be represented as follows:

$$HR(t) = \frac{h(t, X_1)}{h(t, X_0)} = \frac{h_0(t) \cdot e^{\beta \cdot X_1}}{h_0(t) \cdot e^{\beta \cdot X_0}} = e^{\beta \cdot (X_1 - X_0)}$$

The logarithm of the hazard ratio is therefore expressed as a linear term. The estimation of the coefficients β_i of the parameterized part of the hazard function, that correspond to the logarithm of the HRs, and their confidence intervals is the objective of Cox model analyses. This estimation is typically done by maximizing the part of the likelihood of the model that concerns only the coefficients β_i .

An HR significantly greater than 1 (lower bound of the confidence interval greater than 1) indicates a positive association between the variable of interest and the event studied, whereas an HR significantly less than 1 (upper bound of the confidence interval less than 1) indicates an inverse association.

2.2.3. COX MODEL ASSUMPTIONS

There are two main assumptions underlying Cox regression analyses: the proportionality of hazards and the log-linearity between the hazard function and the covariates.

There are many ways to verify the proportionality of hazards. The simplest way is to check that the survival curves of the different groups are parallel to each other.

The method we used is based on the Schoenfeld residuals, which consists in testing, for each event at time t , the difference between the characteristics of the individual who suffered the event and a weighted average of the characteristics of the individuals exposed at time t . This is generally done by visual inspection: if the hypothesis of risk proportionality is met, the fitted curve looks like a horizontal line.

Another way to test for the proportionality of hazards is to perform a test of correlation with time that, if not significant, indicates that the assumption of proportionality of the risks is valid.

The log-linearity hypothesis corresponds to the increase in instantaneous risk as we move from one level of a variable to another.

As continuous variables were not included in the analysis models, the assumption of log-linearity was not tested in the present study.

2.3. AGE AS A TIME SCALE

The Cox model was originally developed to model the delay between the administration of a treatment and the time to relapse or death in clinical trials. The start of the trial, or baseline, is then the time of entry into the trial.

In epidemiological cohort studies, however, the start of exposure and the start of observation are rarely the same, because for many diseases people are at risk of developing the disease from birth, but are only observed from the time of enrolment. In this particular case, it is often preferable to use age as the time scale, i.e. to set the origin at the individual's date of birth (zero age) and the start of observation at the age of enrolment (this is referred to as delayed entry)³³⁶.

Age, much more than the length of follow-up, is a determinant of the incidence of the disease

under study. However, the choice of age as the time scale implies that individuals are not followed from the beginning and that individuals who have already experienced the event ('prevalent' cases at enrolment) are not included in the analysis population.

In E3N, the age at questionnaire response was calculated using the date of birth and the date of response given on the questionnaire, or the date of return of the questionnaire if the date of response was not given.

A further advantage was an easier parameterization of the time-dependent variables included in models.

2.4. BIRTH COHORT EFFECT

A woman's risk of developing psoriasis may depend on her year of birth. For example, as reported in the introduction, it has been reported that a person born in 1936 has a 17-fold higher risk of developing psoriasis than a person born in 1997¹⁹⁷. This phenomenon is known as the 'cohort effect' and needs to be considered when modelling psoriasis risk by attributing different baseline risks to different generations. For this reason, we stratified the Cox models by birth cohort, which was divided into six classes as follows: <1930, 1930-1934, 1935-1939, 1940-1945, 1946-1950 and >1950. This stratification allows for a different baseline risk $h_0(t)$ for each birth cohort. However, it assumes that the associations between the covariates and the risk of the disease under investigation are identical regardless of the birth cohort.

2.5. CENSORING

The Cox model takes into account censored data when quantifying the association between an exposure and the occurrence of an event. Right censoring is the most common form of censoring, where follow-up is completed before the event can occur. Left censoring occurs when the event occurs before the start of follow-up. In this PhD project, we excluded prevalent cases of psoriasis, i.e. those that occurred before the start of follow-up.

2.6. TIME-DEPENDENT VARIABLES

Cox regression analysis allows to include in the models' explanatory variables that change over time. For example, in the case of smoking, a woman may be a smoker at the start of the follow-up period and then become a non-smoker. She will then contribute person-years as a smoker until she reports quitting. If we only consider variables that are fixed over time, a woman who is a smoker at enrolment and becomes a non-smoker during follow-up would be 'misclassified' until the end of her follow-up.

Some covariates that were updated in the E3N follow-up questionnaires (such as smoking status, BMI, comorbidities and menopausal status) were included in the analyses as time-dependent variables, as their values could change during follow-up.

2.7. MISSING DATA

For simple imputation of adjustment variables, if a variable had less than 5% missing data, the missing data was imputed with the value corresponding to the mode for qualitative variables and with the median value for quantitative variables. If a variable had more than 5% missing data, a missing category was created.

2.8. LOGISTIC REGRESSION

Logistic regression is a statistical model used in the sensitivity analyses in this thesis to evaluate the association between the risk factors studied and all potential psoriasis cases, those identified in free text boxes.

Logistic regression models can test association between explanatory variables of various nature (quantitative or qualitative) and a dichotomous outcome variable (event that has occurred – i.e. $E=1$ - or that has not occurred – i.e. $E=0$) without considering the timing of the outcome.

The probability of being affected by the event, knowing the exposure to the different variables (X_i) is then written as:

$$P(E = 1|X_1, \dots, X_p) = \frac{1}{1 + e^{\{-(\alpha + \sum_{i=1}^p \beta_i X_i)\}}}$$

Let α be the intercept and β_i the coefficients associated with the p explanatory variables. The regression coefficients are generally estimated as for the coefficients in a Cox model with methods based on maximum likelihood that is by maximizing the probability of obtaining the distribution of the variable of interest E observed in the sample of the study, given a specific profile of explanatory variables ($X_1 \dots X_p$) of the individuals.

If we note: $\text{Logit } P = \ln \frac{p}{1-p}$, then we can write the logistic model in linear form:

$$\text{Logit } P = \alpha + \sum \beta_i X_i$$

2.8.1. ODDS RATIO

As with Cox regression, the aim of logistic regression is to obtain an estimate of the relative risk that is the ratio of risks for individuals with different values of the explanatory variables. From the coefficients estimated from logistic regression, odds ratios (OR) can be easily estimated.

In the simple case of a model with a single dichotomous explanatory variable X_1 (for example an exposure to a specific factor), if we call $P_1 = P(E=1|X_1=1)$ the probability of the event occurring among the exposed and $P_0 = P(E=1|X_1=0)$ the probability of the event occurring among the unexposed, the odds ratio is defined as follows:

$$OR = \frac{\frac{P_1}{1-P_1}}{\frac{P_0}{1-P_0}} = e^{\beta(x_1 - x_0)}$$

In the case above of dichotomous explanatory variable (e.g. exposed versus non-exposed) the OR is derived from the estimated coefficient β as follows:

$$OR = \exp(\beta)$$

This formula can be generalized in the case of a multivariate logistic regression model, where

X is a vector of variables and β a vector of the associated coefficients.

An OR significantly greater than 1 (lower bound of the confidence interval greater than 1) indicates a positive association between the explanatory variable and the event studied, while an OR significantly less than 1 (upper bound of the confidence interval less than 1) indicates an inverse association.

All analyses presented in the thesis were performed using SAS version 9.4 (SAS Institute Inc).

PART III: MALTECTOMY AND PSORIASIS RISK

1. INTRODUCTION

The absence or reduced activity of peripheral regulatory T cells, which are responsible for immunologic tolerance by suppressing T helper cells directed against skin self-antigens, is one of the main pathogenetic mechanisms of psoriasis^{337–339}. Regulatory T-cell maturation occurs mainly in the thymus³⁴⁰, but also in peripheral tissues such as mucosa-associated lymphoid tissues (MALT)³⁴¹, lymphoid structures distributed in the digestive and respiratory tract with lymph node-like structure³⁴².

The role of MALT-associated organs, including the adenoids, palatine tonsils, and cecal appendix, was long thought to be limited to a local immune function³⁴³.

Adenoids, tonsils, and appendix harbor extrathymic T cells that express the autoimmune regulator gene (Aire)³⁴⁴ and are involved in T cell selection and in the regulation of peripheral tolerance^{345,346}.

Furthermore, MALT may play a pivotal role in maintaining microbiota homeostasis^{347,348,349}.

Removing MALT tissue, through an adenoidectomy, an appendectomy, or a tonsillectomy, can affect microbiota composition and disrupt peripheral tolerance that may result in autoimmunity³⁵⁰.

In spite of the important role of MALT tissue in systemic immunologic homeostasis, it is not known whether MALTectomy is a risk factor for autoimmunity.

While experimental studies have led to significant advances in the treatment of autoimmune diseases, epidemiologic studies are still essential for a full elucidation of the role of risk factors in the pathogenesis of these diseases.

We therefore investigated the possible associations between MALTectomy and skin autoimmunity and, specifically, the risk of psoriasis. We tested these associations separately for overall and moderate-to-severe psoriasis, using the prospective French E3N cohort, which has been extensively used to study risk factors for autoimmune diseases^{351,352}.

2. MATERIALS AND METHODS

For the present study, were used data from the E3N cohort described previously in section 1.1 of the Materials chapter in the part II.

2.1. MALTECTOMY ASSESSMENT

Data on appendectomy, adenoidectomy, and tonsillectomy were collected in the 1990 baseline questionnaire and, for appendectomy only, in the 1992 and 1993 questionnaires. At baseline, participants were asked to report whether they had had such surgery and their age at the time of surgery from a list of 6-time intervals (age at MALT - adenoidectomy, appendectomy, tonsillectomy: ≤ 10 years; 11-14; 15-19; 20-29; 30-39; ≥ 40) (Figure 16).

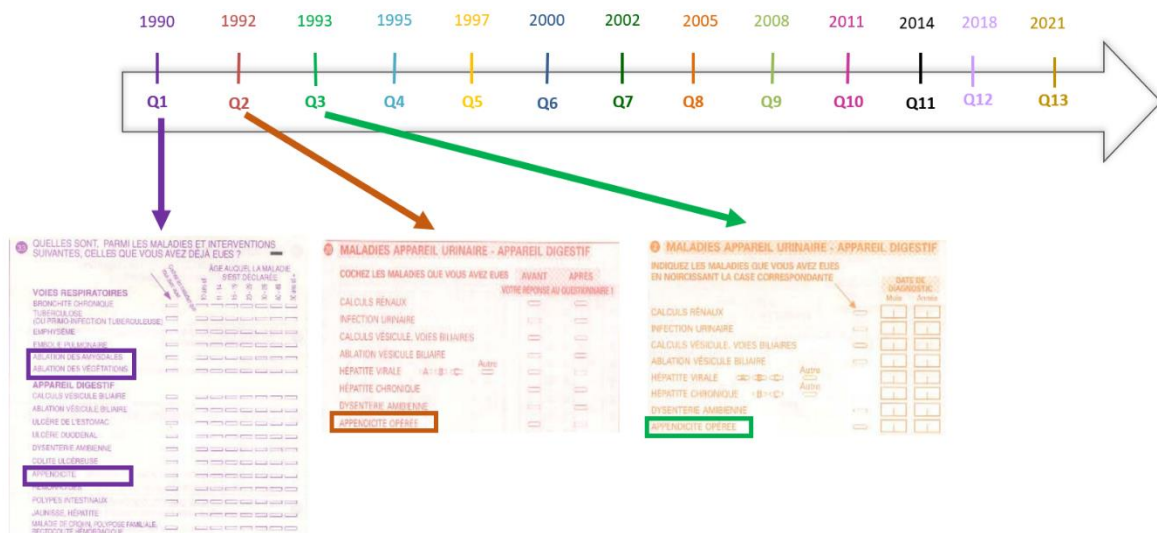


Figure 16: Questionnaires from which information on MALTectomy was collected.

2.2. STUDY POPULATION

The selection procedures for the overall and moderate-to-severe psoriasis cases used in the present study are described in sections 1.3 and 1.6 of the Materials chapter in the part II.

From the population of 98 995 women of E3N we excluded all participants with missing values for appendectomy, tonsillectomy, or adenoidectomy ($n=2\ 493$), all participants who died during follow-up but for whom the MGEN did not provide a valid date of death ($n=44$) and those who reported a date of psoriasis diagnosis after 2004 but for whom no reimbursement

for psoriasis medications was found in the MGEN database (n=124). Depending on whether the outcome of interest was overall psoriasis or moderate-to-severe psoriasis, additional exclusion criteria were applied. Overall psoriasis analyses included 90 119 participants after exclusion of the following groups: i) participants did not respond to any other questionnaire after baseline (n=2 813), ii) all prevalent cases of psoriasis at baseline (n=1 276) and iii) those with missing age at diagnosis (n=2 126)(see Figure 17).

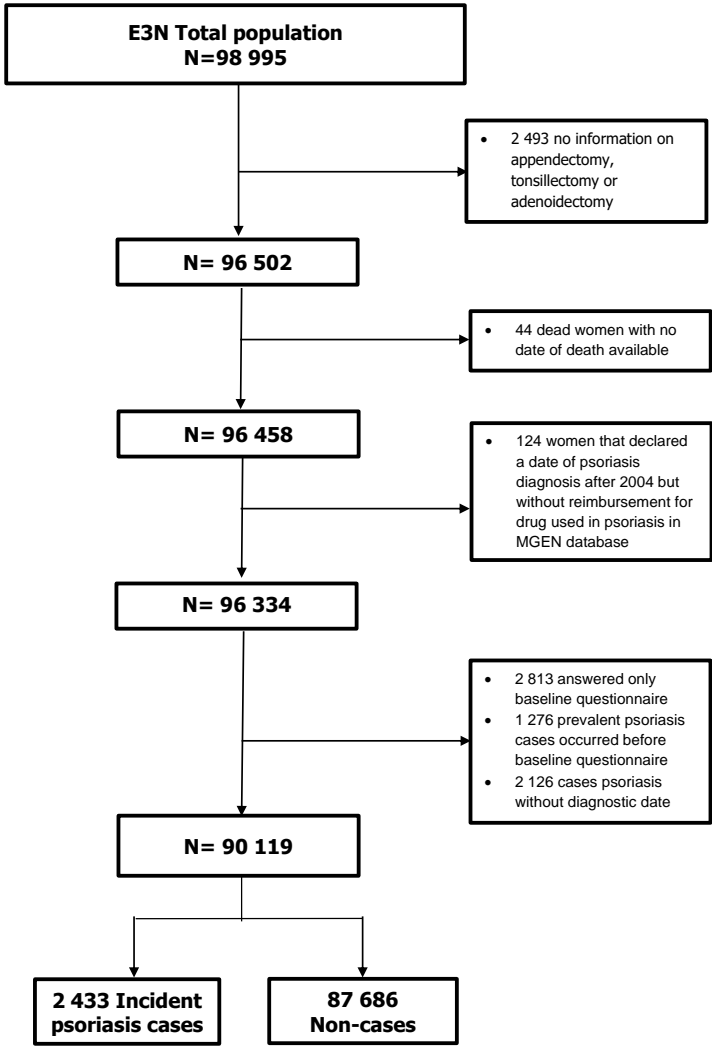


Figure 17: Flow chart of the included participants in overall psoriasis models-MALTEctomy.

The analyses of risk of developing moderate-to-severe psoriasis included 78 269 participants after the exclusion of participants whose follow-up ended before January 1, 2004, died or were lost to follow-up by January 1, 2004, when drug reimbursement data became available for the E3N database (n=16 237) and of psoriasis cases for which the date of diagnosis

could not be determined (n=1 828) (see Figure 18).

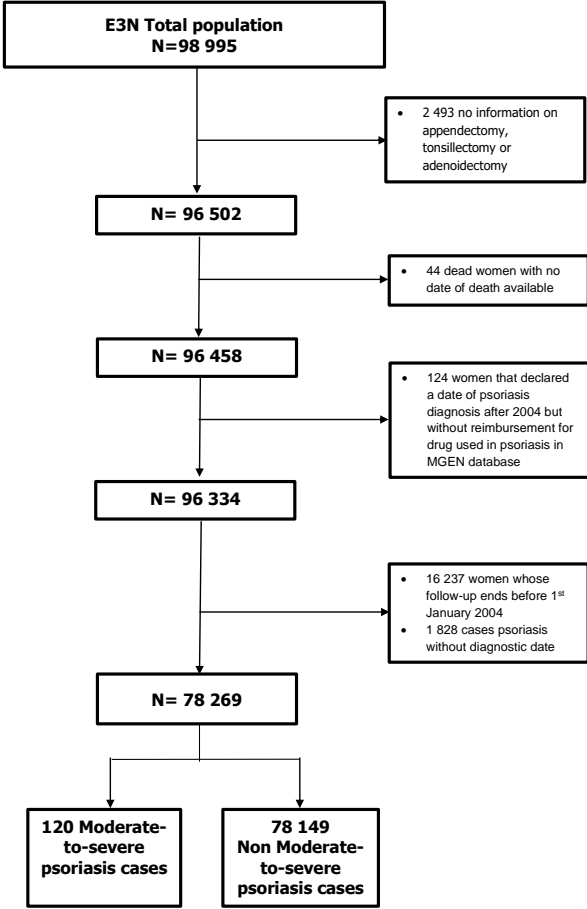


Figure 18: Flow chart of the included participants in moderate-to-severe psoriasis models-MALTectomy.

Appendix 6 shows the comparison between women included and excluded from the overall psoriasis analysis population. The two groups of women (excluded and included in the analysis) did not differ significantly in terms of MALTectomy history. Women who were excluded were more likely to have lower education, higher BMIs, and to be current smokers at the start of the study.

2.3. STATISTICAL ANALYSIS

Women's characteristics at baseline were described as mean (standard deviation) for continuous variables and as number (%) for categorical variables.

Cox proportional hazards regression models were used to estimate hazard ratios (HRs) and 95% confidence intervals (CI) for associations between psoriasis risk and different types of MALTectomy. The age of the participants was used as the time scale. The study observation period began with the return of the baseline survey sent in 1990, and ended with the return of the survey sent in 2018 (the last E3N survey used for this study), the earliest of psoriasis diagnosis, death, the last completed survey, or the return of the survey.

For analyses of moderate-to-severe psoriasis, follow-up began on January 1, 2004, and ended at the earliest date of moderate-to-severe psoriasis status, at death, or on December 31, 2018 (date of most recent available drug reimbursement data), whichever came first. Each type of MALTectomy (adenoidectomy, appendectomy, and tonsillectomy) was modeled as a fixed binary variable at baseline. A graphical representation of the cohort follow-up and data sources is shown in Figure 19.

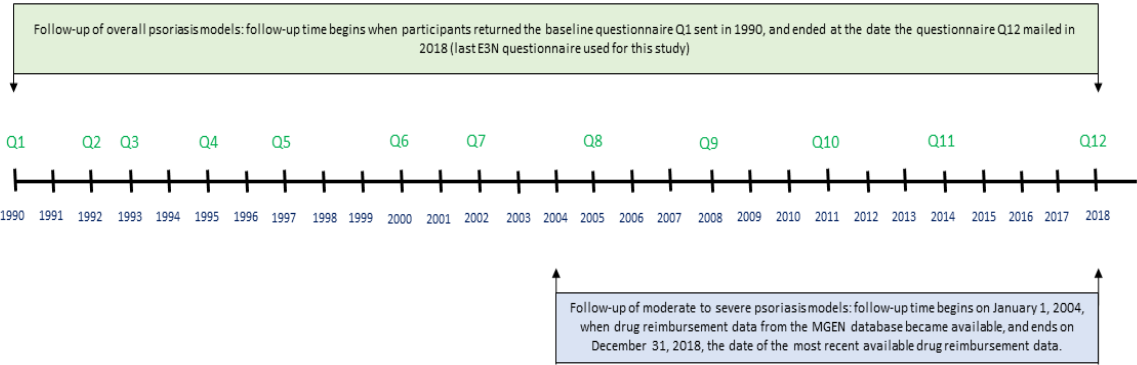


Figure 19: Graphical representation of the cohort follow-up.

Univariate models were adjusted for birth cohort, whereas multivariable models included BMI (categorical variable: ≤ 24 , 25-30[, and ≥ 30 kg/m²), marital status (unmarried, married), smoking status (never, current, or former smoker), educational level (bachelor's degree or less, master's degree, doctorate, or more), and three binary variables about medical conditions: diabetes, depression or anxiety, and hypertension. Both univariate and multivariable models were fitted including only one type of MALTectomy at a time, with absence of specific MALTectomy used as reference category in all models. Potential effects of reproductive and hormonal factors collected in the E3N on the association between MALTectomy and psoriasis were explored, including age at menarche (≤ 11 years, 12-14 years, ≥ 15 years), menopausal status (premenopausal, menopausal), parity (nulliparous, parous),

and ever use of oral contraceptive pills (no, yes).

BMI, smoking status, menopausal status, diabetes, depression and hypertension were modeled as time-varying variables.

Additional models were fitted including age at MALTectomy as a six-categories variable (<10; 11-14; 15-19; 20-29; 30-39; >40 years). Appendectomy was modeled as a time-varying variable in the multivariable model to account for cases that occurred after the start of the study. A further model including alcohol consumption was fitted using 70 350 participants for whom alcohol consumption data were available from the 1993 questionnaire.

Schoenfeld residuals analysis was used to test the proportional hazards assumption. In the case of missing values for a time-varying variable, the last observation carried forward (LOCF) method was used whenever possible. In the case of less than 5% of the missing values for a variable, the mean value or the median value was imputed for quantitative and qualitative variables, respectively.

Finally, a sensitivity analysis was performed using univariate and multivariable logistic regression on all cases regardless of whether they were prevalent, incident or with unknown age at diagnosis. A population of 96 458 and a total of 6 030 psoriasis cases were used for this analysis from which odds ratios (OR) and their 95% confidence intervals (CI) were estimated.

All analyses were performed using SAS version 9.4 (SAS Institute Inc).

3. RESULTS

During a median follow-up of 23.8 years (2 145 448 person-years), 2 433 incident cases of psoriasis were identified or an annual incidence rate of 113 cases per 100 000. Of these, 2 153 (90.4%) were treated with anti-psoriatic drugs. Of those, 1 144 (47.0 %) had at least one prescription for vitamin D-based topical agents, 2 153 (88.5%) for topical steroids, 59 (2.4%) for psoralens, 163 (6.6%) for nonbiologic immunomodulators, and 23 (0.9%) for biologic immunomodulators. Participants were often treated with combinations of the above medications. The mean (standard deviation) follow-up time from baseline was 16.5 (\pm 5.9) years, and the mean age at psoriasis diagnosis was 49.4 (\pm 6.6) years.

Characteristics of the study population at baseline are reported by psoriasis status in Table 3

and by MALT status in appendices 7-9.

Table 3: Characteristics of study participants at baseline according to overall psoriasis status (N=90 119).

Exposure	All (N=90 119)	Psoriasis (n=2 433)	No psoriasis (n=87 686)
Age at baseline	49.4 (±6.6)	48.5 (±6.0)	49.4 (±6.6)
Year of birth			
>1945	30 359 (33.7)	887 (36.4)	29 472 (33.6)
1940-1945	21 780 (24.2)	659 (27.1)	21 121 (24.1)
1935-1940	17 768 (19.7)	482 (19.9)	17 286 (19.7)
1930-1935	12 060 (13.4)	270 (11.1)	11 790 (13.4)
<1930	8 152 (9.0)	135 (5.5)	8 017 (9.1)
BMI at baseline			
BMI<25	73 861 (82.0)	1 944 (79.9)	71 917 (82.0)
25<BMI<30	13 417 (14.9)	385 (15.8)	13 032 (14.9)
BMI>30	2 841 (3.2)	104 (4.3)	2 737 (3.1)
Smoking status at baseline			
Never	48 735 (54.1)	1 187 (48.7)	47 551 (54.2)
Current	13 383 (14.9)	451 (18.6)	12 929 (14.7)
Former	28 001 (31.1)	795 (32.7)	27 206 (31.1)
Marital status at baseline			
Unmarried	15 917 (17.7)	456 (18.7)	15 461 (17.6)
Married	74 202 (82.3)	1 977 (81.3)	72 225 (82.4)
Education level			
Undergraduate or less	3 097 (3.4)	79 (3.2)	3 018 (3.5)
Graduate	12 056 (13.4)	276 (11.3)	11 780 (13.4)
Postgraduate or more	74 966 (83.2)	2 078 (85.5)	72 888 (83.1)
Age at menarche			
12-15 years old	68 244 (75.7)	1 788 (73.4)	66 456 (75.8)
<12 years old	18 337 (20.3)	555 (22.8)	17 782 (20.3)
>15 years old	3 538 (4.0)	90 (3.8)	3 448 (3.9)
Menopause status at baseline			
Premenopausal	46 142 (51.2)	1 369 (56.2)	44 773 (51.1)
Postmenopausal	43 977 (48.8)	1 064 (43.8)	42 913 (48.9)
Nulliparous status			
No	79 568 (88.3)	2 116 (86.9)	77 452 (88.3)
Yes	10 551 (11.7)	317 (13.1)	10 234 (11.7)
Ever use of oral contraceptives at baseline			
No	40 450 (44.9)	1 040 (42.7)	39 410 (44.9)
Yes	49 669 (55.1)	1 393 (57.3)	48 276 (55.1)
Pharmacological classes of drugs prescribed from MGEN database			
Topical drugs derived from vitamin D	2 732 (3.0)	1 144(47.0)	1 588 (1.8)
Biologic immunomodulators	209 (0.2)	23 (0.9)	186 (0.2)
Non-biologic immunomodulators	1 551 (1.7)	163 (6.6)	1 388 (1.5)
Psoralens	165 (0.2)	59 (2.4)	106 (0.1)
Topical steroids	57 817 (64.2)	2 153 (88.5)	55 664 (63.4)
Appendectomy			
No	65 315 (72.5)	1 730 (71.1)	63 585 (72.5)
Yes	24 804 (27.5)	703 (28.9)	24 101 (27.5)
Adenoidectomy			
No	65 315 (72.5)	1 730 (71.1)	63 585 (72.5)
Yes	24 804 (27.5)	703 (28.9)	24 101 (27.5)
Tonsillectomy			
No	61 720 (68.5)	1 653 (67.9)	60 067 (68.5)
Yes	28 399 (31.5)	780 (32.1)	27 619 (31.5)

Cases had a slightly higher body mass index (BMI) and were more likely to have a history of smoking than non-cases.

In the population for the moderate-to-severe psoriasis analyses, 120 participants were classified as having moderate-to-severe psoriasis if they present a reimbursement (at any time) for at least one systemic drugs used in psoriasis (i.e., psoralens, non-biologic immunomodulators, and biologic immunomodulators).

In all models, appendectomy was associated with a modest increase in risk of psoriasis [multivariable model HR: 1.14 (95% CI: 1.05-1.24)], but no association was observed for adenoidectomy and tonsillectomy (Table 4).

Table 4: Hazard Ratios of overall psoriasis risk according to MALTectomy history, (N= 90 119).

Exposure	Psoriasis cases (n=2 433)	Person-years (N=2 145 448)	Hazard Ratio (95% CI)			
			Univariate model ^a	p-value	Multivariable model ^b	p-value
Appendectomy						
No	1417	1 330 923	1.00 [Reference]		1.00 [Reference]	
Yes	1016	814 525	1.17 (1.08-1.27)	<0.001	1.14 (1.05-1.24)	<0.001
Adenoidectomy						
No	1 730	1 553 361	1.00 [Reference]		1.00 [Reference]	
Yes	703	592 087	1.06 (0.97-1.16)	0.15	1.04 (0.95-1.13)	0.33
Tonsillectomy						
No	1 653	1 468 538	1.00 [Reference]		1.00 [Reference]	
Yes	780	676 910	1.02 (0.94-1.11)	0.29	0.99 (0.91-1.08)	0.92

a) Model adjusted for: birth cohort

b) Model adjusted for: birth cohort, BMI, smoking status, education level, marital status at baseline, hypertension, depression, diabetes, age at menarche, menopause status, nulliparous status, ever use of contraceptive pill.

A suggestive association was found with the risk of moderate-to-severe psoriasis for

appendectomy [univariate model HR: 1.40 (95%CI: 0.97 -2.02)] (Table 5).

Table 5: Hazard Ratios of moderate-to-severe psoriasis risk according to MALTectomy history, (N= 78 269).

Exposure	Moderate-to-severe psoriasis cases (n=120)	Person-years (N=1 190 529)	Hazard Ratio (95% CI)			
			Univariate model ^a	p-value	Multivariable model ^b	p-value
Appendectomy						
No	64	737 128	1.00 [Reference]		1.00 [Reference]	
Yes	56	453 401	1.40 (0.97-2.02)	0.06	1.36 (0.94-1.96)	0.10
Adenoidectomy						
No	84	861 948	1.00 [Reference]		1.00 [Reference]	
Yes	36	328 581	1.07 (0.72-1.61)	0.71	1.04 (0.70-1.56)	0.82
Tonsillectomy						
No	83	815 497	1.00 [Reference]		1.00 [Reference]	
Yes	37	375 032	0.89 (0.59-1.33)	0.58	0.86 (0.57-1.29)	0.47

a) Model adjusted for: birth cohort

b) Model adjusted for: birth cohort, BMI, smoking status, education level, marital status at baseline, hypertension, depression, diabetes, age at menarche, menopause status, nulliparous status, ever use of contraceptive pill.

Adenoidectomy or tonsillectomy were not associated with the risk of moderate-to-severe psoriasis. The estimated hazard ratios from the multivariable models were almost the same as those from the univariate models.

The sensitivity analyses based on logistic regression models and including all cases identified in the cohort irrespective of their age at diagnosis, showed results consistent with those from the Cox models. In particular, appendectomy was associated with psoriasis in both univariate [OR: 1.08 (95 % CI: 1.02-1.14)] and multivariable [OR: 1.07 (95 % CI: 1.01-1.13)] models. Tonsillectomy and adenoidectomy were not associated with the risk of developing psoriasis.

The associations between MALTectomy and psoriasis risk were not substantially altered by further adjustment for alcohol consumption or inclusion of appendectomy as a time-varying variable.

No association was observed between psoriasis and age at MALTectomy.

Results are shown in appendices 10-15.

4. DISCUSSION.

The association between MALTectomy and the incidence of psoriasis was observed in a large prospective cohort of women. A modest increase in the risk of psoriasis was associated with appendectomy overall and possibly also with moderate-to-severe psoriasis. The association was nominally slightly stronger for moderate-to-severe psoriasis than for overall psoriasis. No association was found between adenoidectomy, tonsillectomy and risk of psoriasis.

There are only a few studies that have investigated the association between MALTectomy and autoimmune diseases. In patients with both tonsillitis and psoriasis tonsillectomy appears to lead to a reduction in psoriasis manifestations³⁵³. However, it is not clear whether tonsillectomy reduces the risk of developing psoriasis. One study reported a modest positive association between tonsillectomy and risk of psoriasis (SIR-Standardized incidence ratio=1.19, 95% CI 1.08-1.31)³⁵⁴ while a recent study from Taiwan reported an inverse association (HRs = 0.43, 95% CI 0.22-0.87)³⁵⁵. No study has investigated the possible association between appendectomy and the risk of psoriasis but several studies on other diseases, including some meta-analyses, found that appendectomy was positively associated with the risk of Parkinson's disease³⁵⁶ and multiple sclerosis³⁵⁷. Conversely, inverse associations with appendectomy have been observed for ulcerative colitis³⁵⁸ and Crohn's disease [30], whereas no association was found for rheumatoid arthritis^{359,360}.

This study was observational and no conclusions could be drawn about a causal relationship between psoriasis and appendectomy. However, it is possible to formulate some hypotheses about the mechanisms that may be involved.

Based on its evolutionary stability and the relatively rare absence in humans, the appendix plays a fundamental role in immunological homeostasis^{347,348}. Its immunological function is likely to be particularly important during childhood, when the proliferation and activity of the

lymphatic follicles of the appendix are at their peak^{361,362}.

Appendectomy could limit the induction and proliferation of regulatory T cells in the gut, leading to a reduction in the suppression of self-reactive T cells in the skin, which are involved in autoimmunity, as observed in murine models^{363,364}. In allergic skin diseases, although the exact mechanisms are not fully understood, a role for peripheral tolerance induced by gut-immune lymphoid tissue has been suggested^{365–367}. Appendicular lymphoid tissue removal may influence skin autoimmunity by reducing skin tolerance, as has been observed for the spleen in animal models³⁶⁸. The appendix also indirectly influences the intestinal immunological response by acting as a "safe house" for gut microbiome regeneration during infection-induced dysbiosis³⁶⁹ and by producing IgA involved in intestinal biofilm assembly^{348,370}. Appendectomy may interfere with these mechanisms and cause an increase in the number of bacteria associated with intestinal inflammation³⁷¹, resulting in translocation of bacteria into the systemic circulation and induction of skin immunity through the 'gut-skin axis'^{350,372}. Some studies have shown changes in the gut microbiota, specifically an increase in the beta diversity, in psoriatic and arthritic patients compared to healthy controls^{373–375}.

Strengths of our study include its prospective design, large study population size, and long follow-up (28 years). Identification of incident psoriasis cases was based on follow-up questionnaires only, and full validation of cases was not possible. However, the MGEN drug reimbursement database was used to define moderate-to-severe psoriasis diagnoses and to obtain overall indicators of the validity of our case definition.

The observed incidence rate in our study appears in general agreement with estimates from previous studies in European populations, which typically range between 40 and 300 per 100,000 persons per year, depending on the year and country¹⁷⁴.

Some misclassification of cases is still possible, but is likely to be non-differential, i.e., not dependent on MALTectomy status, and would therefore bias the association estimates toward the null. As suggested by the results of the sensitivity analysis based on logistic regression, the exclusion of 2 126 cases with unknown age at diagnosis in the main analyses based on Cox regression is unlikely to affect the results.

The limited number of moderate-to-severe cases and the lack of information on the clinical manifestations of the disease led to some limitations in the analysis of moderate-to-severe psoriasis.

Our definition of moderate-to-severe cases, based on data from the MGEN drug reimbursement database, is based on the observation that international guidelines recommend the use of systemic drugs only for moderate -to-severe psoriasis⁷⁷.

Data on tonsillectomy and adenoidectomy were not available after baseline questionnaire and it was not possible to model them as time-varying variables. Nevertheless, there did not appear to be any significant changes in the magnitude or direction of the associations observed when the variable appendectomy was considered as a time-varying variable. Finally, associations with the risk of developing psoriasis at a younger age, i.e., at the first peak of the disease before the age of 40, could not be assessed in our study.

Our results suggest that appendectomy may play a role in psoriasis development.

Given our findings, appendectomy could be used together with other risk factors to identify high-risk groups who may benefit from regular screening to detect psoriasis at an early stage to put in place a primary prevention program centered on psoriasis that does not currently exist.

Our findings should be subject to validation in other settings, particularly in men and in younger populations. If confirmed, these findings may provide a promising new path for understanding the role of MALT in the pathophysiology of cutaneous autoimmunity and may open new directions for treating psoriasis.

PART IV: RURAL ENVIRONMENT DURING CHILDHOOD AND RISK OF PSORIASIS

1. INTRODUCTION

Psoriasis and other skin inflammatory diseases are currently classified as immune-mediated inflammatory diseases (IMIDs), a term used to collectively describe a group of diseases with a common T-helper ancestor. IMIDs are further classified based on their downstream inflammatory pathways into T-helper 1 (Th1) / T-helper17 (Th17) associated disorders like psoriasis, type 1 diabetes, inflammatory bowel disease, multiple sclerosis, rheumatoid arthritis, and Th2 associated disorders like asthma and atopic dermatitis^{376,377}. Psoriasis, like other IMIDs, is known to have a multifactorial pathogenesis. The interaction between genetic and non-genetic factors is well established^{377,378}.

The recurrent observation of an inverse association between Th2 conditions, such as atopy, and exposure to rural environments during childhood supports the existence of a link between the environment and IMIDs³⁷⁹. In the 1980s, this led to the formulation of the so-called "hygiene hypothesis" that a "cleaner environment" would adversely affect the development of the immune system and could contribute to allergic disease^{380,381}.

The precise mechanisms by which environmental exposures during early life may have an effect on atopy are not fully understood. Observational studies and animal models suggest that the synergistic effects of multiple antigens present in animal housing³⁸² and exposures to microbial and parasite species present in soil and dust may shape the host microbiome^{383–385} and suppress Th2 cytokine production leading to immune-related diseases^{386,387}.

Using data from the prospective E3N cohort, a study was then carried out to examine the association between different environmental factors in childhood and the risk of psoriasis in women.

2. MATERIALS AND METHODS

The E3N cohort, from which the data used in this study are drawn, and the process of identification of psoriasis cases from the cohort have been described previously in part 2 of this thesis.

2.1. ASSESSMENT OF CHILDHOOD EXPOSURES

Five exposure variables were used, four individual and one ecological, all derived from data collected in 2002 with Questionnaire 7 (Q7) which included questions about the childhood environment (Figure 20). The four individual variables were all binary and included factors related to childhood exposure to a rural setting, including living on a farm for 3 consecutive months in childhood, living with livestock for 3 consecutive months in childhood, and having parents who farmed and having pets (dogs or cats) in childhood.

The ecological binary indicator of a rural place of birth was constructed using the self-reported place of birth at baseline and the 1970 General Census of Agriculture, defining a place of birth as rural if it had less than 5 000 inhabitants, as previously done in studies in the E3N cohort on other diseases such as asthma³⁷⁹.

For the purposes of this study childhood is defined as the period from birth to age sixteen years.

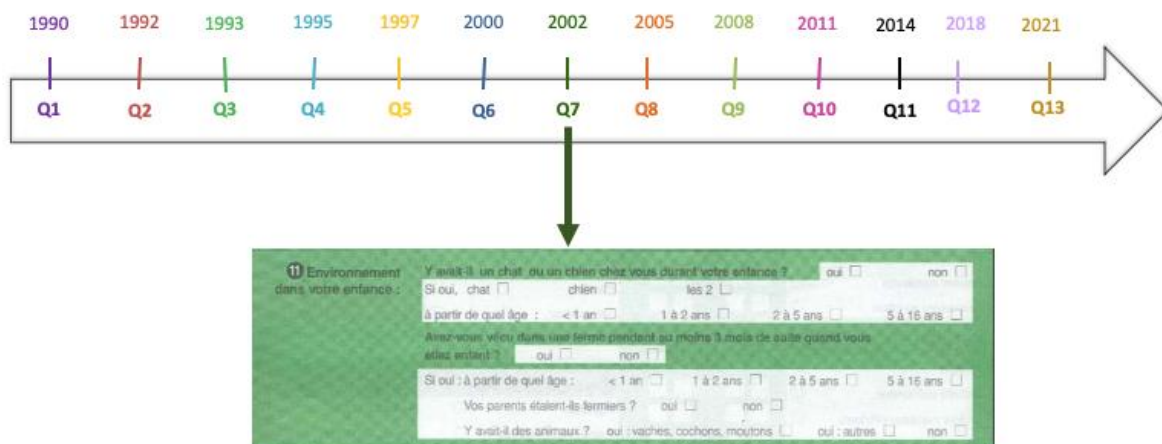


Figure 20: Questionnaires from which information on environmental exposures during childhood was collected.

2.2. STUDY POPULATION

The process of selecting the study population is described in Figure 21. From the initial population of women who completed the baseline questionnaire in 1990 (N = 98 995) were excluded 17 543 participants who did not respond to Q7, 6 232 participants whose place of

birth could not be assigned to the urban or rural category (e.g. birth in a foreign country), and 30 participants who died during follow-up but for whom a valid date of death was not determined. In the overall model were also excluded participants who reported psoriasis in the free text boxes included in each questionnaire (to allow reporting of additional health conditions) but who responded negatively to the specific questions about psoriasis (n=29), and those who reported a date of psoriasis diagnosis after 2004 but for whom no reimbursement for psoriasis medications was found in the MGEN database (n=124).

The study population comprised 72 154 participants after further exclusion of all prevalent cases of psoriasis at baseline (n=1 227) and cases with missing age at diagnosis (n=1 656) (Figure 21).

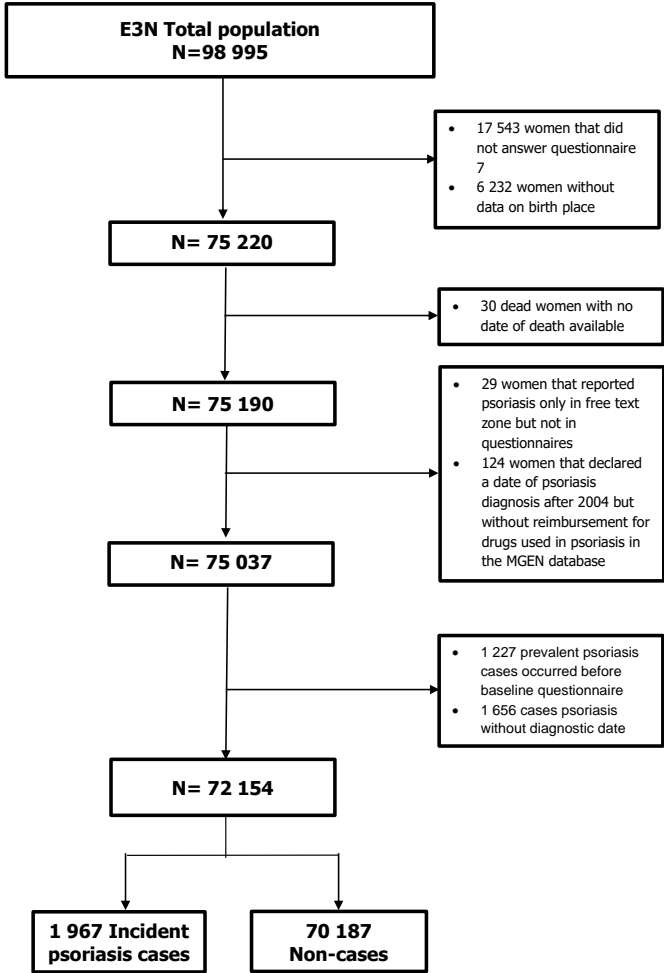


Figure 21: Flow chart of the included participants in overall psoriasis models-Rural childhood environment.

For the moderate-to-severe psoriasis analyses, prevalent cases were not excluded, but 5,914 participants whose follow-up ended before 1 January 2004 were excluded their follow-up ended before 1st January 2004, if they died or were lost to follow-up before 1st January 2004, when the data on drug reimbursement became available. After excluding also psoriasis cases with unknown date of diagnosis (n=1 206) the study population consisted of 67 917 participants(Figure 22).

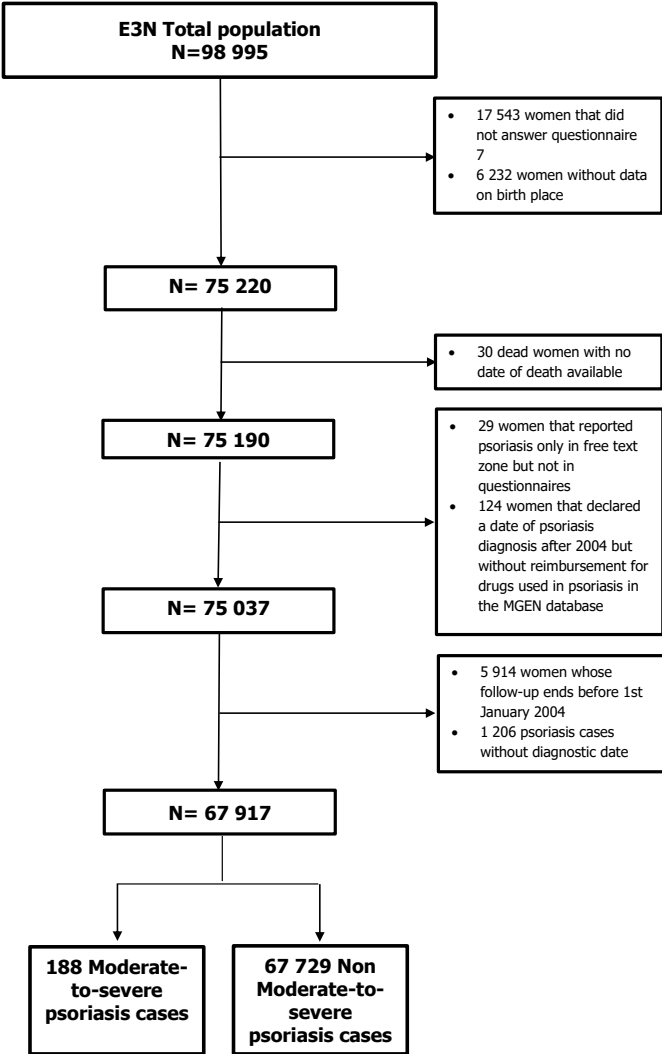


Figure 22: Flow chart of the included participants in the analyses on moderate-to-severe psoriasis-Rural childhood environment.

2.3. STATISTICAL ANALYSIS

The baseline characteristics of the study population were described according to exposure variables and psoriasis status at the baseline. All the explanatory variables were categorical and were described by means of numbers and percentages (%). Cox proportional hazards

regression models were used to estimate hazard ratios (HRs) and 95% confidence intervals (CI) for psoriasis.

Participants were followed from the time they completed the baseline questionnaire to the time they were diagnosed with psoriasis, the time they completed the last questionnaire, death, or the time they completed the Q12 (the last E3N follow-up questionnaire used in this study), whichever came first.

For moderate-to-severe psoriasis analyses, follow-up began January 1, 2004, and ended at the earliest of the following events: occurrence of moderate-to-severe psoriasis (date of first systemic drug claim available from the MGEN database for self-reported psoriasis), date of last completed survey, date of death, or December 31, 2018 (date of the most recent drug claim data available).

Univariate hazard ratios (uHRs) were estimated from models including only one of the five childhood exposures at a time. Multivariable adjusted hazard ratios (aHRs) were then estimated 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), education level (undergraduate or less, graduate, postgraduate, or more; baseline), and three binary variables about medical conditions: history of diabetes, depression, and hypertension (all time-varying variables); hormonal and reproductive variables included 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 oral contraception at baseline (binary variable), along with one of the five exposure variables at a time (binary variables).

In a first sensitivity analysis, using the same cut-off of 5,000 inhabitants as for place of birth, a binary variable for urban-rural residence in adulthood at the time of cohort entry was included in the adjusted models.

A binary variable for women's occupation (teachers or other occupations in the national education system) was further included in the adjusted models.

Because of the role of smoking and BMI in psoriasis physiopathology, a sensitivity analyses was performed by stratifying the Cox models by smoking status into two categories (current or former smoking versus never smoking) and by BMI into two categories (normal weight BMI <25kg/m² versus overweight or obesity BMI >25kg/m²).

When missing values were present and represented less than 5% of the study population, the median or modal category was imputed in the case of fixed adjustment variables, while the Last Observation Carried Forward (LOCF) method was used for time-varying variables.

Finally, all cases, whether prevalent or incident, and all cases with unknown age at diagnosis were included in a sensitivity analysis using logistic regression. For such analyses, based on a population of 75 218 women including 5 004 with psoriasis, univariate and multivariable logistic models were used to estimate odds ratios (ORs) and 95% confidence intervals (CI).

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

Of the 72 154 women in the study population 1 967 reported having been diagnosed with psoriasis during an average follow-up of 25.4 years, which corresponds to an incidence of 107 cases per 100,000 person-years.

The characteristics of the population at baseline are reported according to psoriasis status are reported in Table 6 and according to the explanatory variables in appendix 16. The mean age at the start of the study was 49.3 years (± 6.6 years). The mean age at psoriasis diagnosis was 64.6 years (± 8.4 years), and the mean time from baseline to psoriasis diagnosis was 16.5 years (± 6.3 years).

Table 6: Characteristics of study participants at baseline according to overall psoriasis status (n = 72 154).

Exposure	All (72 154)	Not Psoriasis (n=70 187)	Psoriasis (n=1 967)
Age at baseline (SE)	49.3 (±6.6)	49.3 (±6.6)	48.5 (±6)
Year at birth			
<1930	6 264 (8.7%)	6 157 (8.8%)	107 (5.4%)
1930-1935	9 572 (13.3%)	9 353 (13.3%)	219 (11.1%)
1935-1940	14 424 (20.0%)	14 026 (20.0%)	398 (20.2%)
1940-1945	17 513 (24.3%)	16 974 (24.2%)	539 (27.4%)
>1945	24 381 (33.8%)	23 677 (33.7%)	704 (35.8%)
Body mass index (kg/m²)			
<25	59 911 (83.0%)	58 348 (83.1%)	1 563 (79.5%)
25-30	10 216 (14.2%)	9 899 (14.1%)	317 (16.1%)
>30	2 027 (2.8%)	1 940 (2.8%)	87 (4.4%)
Smoking status			
Never	39 227 (54.4%)	38 283 (54.5%)	944 (48.0%)
Current	9 968 (13.8%)	9 614 (13.7%)	354 (18.0%)
Former	22 959 (31.8%)	22 290 (31.8%)	669 (34.0%)
Marital status			
Not married	12 261 (17.0%)	11 885 (16.9%)	376 (19.1%)
Married	59 893 (83.0%)	58 302 (83.1%)	1 591 (80.9%)
Education level			
Undergraduate or less	2 567 (3.6%)	2 502 (3.6%)	65 (3.3%)
Graduate	8 965 (12.4%)	8 777 (12.5%)	188 (9.6%)
Postgraduate or more	60 622 (84.0%)	58 908 (83.9%)	1 714 (87.1%)
1935-1940	14 424 (20.0%)	14 026 (20.0%)	398 (20.2%)
Hypertension			
No	18 880 (26.2%)	18 305 (26.1%)	575 (29.2%)

Yes	53 274 (73.8%)	51 882 (73.9%)	1 392 (70.8%)
Depression			
No	63 401 (87.9%)	61 759 (88.0%)	1 642 (83.5%)
Yes	8 753 (12.1%)	8 428 (12.0%)	325 (16.5%)
Type 2 diabetes			
No	71 535 (99.1%)	69 580 (99.1%)	1 955 (99.4%)
Yes	619 (0.9%)	607 (0.9%)	12 (0.6%)
Age at menarche			
12-15 years old	55 178 (76.5%)	53 737 (76.6%)	1 441 (73.3%)
<12 years old	14 149 (19.6%)	13 694 (19.5%)	455 (23.1%)
>15 years old	2 827 (3.9%)	2 756 (3.9%)	71 (3.6%)
Menopausal status			
Premenopausal	37 405 (51.8%)	36 296 (51.7%)	1 109 (56.4%)
Postmenopausal	34 749 (48.2%)	33 891 (48.3%)	858 (43.6%)
Nulliparous			
No	63 615 (88.2%)	61 918 (88.2%)	1 697 (86.3%)
Yes	8 539 (11.8%)	8 269 (11.8%)	270 (13.7%)
Ever use of oral contraceptives			
No	32 542 (45.1%)	31 704 (45.2%)	838 (42.6%)
Yes	39 612 (54.9%)	38 483 (54.8%)	1 129 (57.4%)
Life in a farm at least 3 months during childhood			
No	55 886 (77.5%)	54 347 (77.4%)	1 539 (78.2%)
Yes	16 268 (22.5%)	15 840 (22.6%)	428 (21.8%)
Pets during childhood			
No	29 477 (40.9%)	28 679 (40.9%)	798 (40.6%)
Yes	42 677 (59.1%)	41 508 (59.1%)	1 169 (59.4%)
Farming parents			
No	63 289 (87.7%)	61 520 (87.7%)	1 769 (89.9%)
Yes	8 865 (12.3%)	8 667 (12.3%)	198 (10.1%)

Birth town size			
Less than 5000 inhabitants (rural)	24 962 (34.6%)	24 354 (34.7%)	608 (30.9%)
More than 5000 inhabitants (urban)	47 192 (65.4%)	45 833 (65.3%)	1 359 (69.1%)
Living in contact with farm animals at least 3 months during childhood			
No	55 629 (77.1%)	54 091 (77.1%)	1 538 (78.2%)
Yes	16 525 (22.9%)	16 096 (22.9%)	429 (21.8%)

In both univariate [uHR: 0.84 (95%CI: 0.77 -0.93)] and multivariable-adjusted analyses [aHR: 0.87 (95%CI: 0.79 -0.96)], an inverse association was observed between rural birthplace and risk of psoriasis. Similarly, in both univariate [uHR: 0.78 (95%CI: 0.68 -0.91)] and multivariable-adjusted analyses [aHR: 0.84 (95%CI: 0.72 -0.97)], having farming parents was inversely associated with the risk of psoriasis (Table 7).

Table 7: Hazard Ratios of overall psoriasis risk according to rural exposures during childhood (n = 72 154).

Exposure	Psoriasis (n= 1 967)	Person-years (N= 1 863 752)	Hazard Ratios (95% CI)			
			Univariate model ^a	p- value	Multivariable model ^b	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

a) Univariate model was birth cohort adjusted

b) Multivariate model was adjusted for birth cohort, BMI, smoking status, education level, marital status at baseline, hypertension, depression, diabetes, age at menarche, menopause status, nulliparous status, ever use of contraceptive pill.

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 observed for

psoriasis overall, whereas no association was found between having farming parents and risk of moderate-to-severe psoriasis [aHR: 1.04 (95%CI: 0.70 -1.54)] (Table 8).

Table 8: Hazard Ratios of moderate-to-severe psoriasis risk according to rural exposures during childhood (n = 67 917).

Exposure	Psoriasis (n= 188)	Person-years (N= 889 088)	Hazard Ratios (95% CI)			
			Univariate model ^a	p- value	Multivariable model ^b	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

a) Univariate model was birth cohort adjusted

b) Multivariate model was adjusted for birth cohort, BMI, smoking status, education level, marital status at baseline, hypertension, depression, diabetes, age at menarche, menopause status, nulliparous status, ever use of contraceptive pill.

None of the other three exposure variables (Living with pets in childhood, living on a farm for 3 or more consecutive months in childhood, and contact with farm animals for 3 or more consecutive months in childhood) were associated with the risk of overall or moderate-to-severe psoriasis.

The risk of psoriasis was not associated with rural-urban residence at baseline. When both rural-urban residence at birth and at baseline were included in the model, rural residence at birth was inversely associated with risk [aHR: 0.88 (95%CI: 0.80 -0.97)], while rural residence at baseline was not associated with psoriasis [aHR: 0.99 (95%CI: 0.90 -1.10)] (Table 9).

Table 9: Hazard Ratios of overall psoriasis risk according to rural birthplace from models including residence at baseline (n = 72 154).

Exposure	Psoriasis (n= 1 967)	Person-years (N= 1 863 752)	Hazard Ratios (95% CI)	
			Multivariable model ^a	p-value
Residence at baseline				
5000 inhabitants or more (urban)	1385	1 301 698	1.00 (Reference)	
Less than 5000 inhabitants (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 inhabitants (rural)	608	644 896	0.88 (0.80-0.97)	0.02

a) *Multivariate model was adjusted for birth cohort, BMI, smoking status, education level, marital status at baseline, hypertension, depression, diabetes, age at menarche, menopause status, nulliparous status, ever use of contraceptive pill.*

Sensitivity analyses using logistic regression, including prevalent and incident cases as well as cases with unknown age at diagnosis showed an association between rural place of birth and psoriasis [OR: 0.91 (95%CI: 0.85-0.97)], while the association between farming parents and psoriasis was observed in the multivariable model [aOR: 0.91 (95%CI: 0.83 -1.00)] (Appendix 17).

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

Cox models stratified by cigarette smoking showed similar inverse associations between psoriasis and rural birthplace for both smokers and never-smokers, whereas the inverse association with having farming parents appeared to be restricted to never-smokers (Appendix 18).

Cox models stratified by BMI showed inverse associations with rural birthplace and with having farming parents only for women with a normal BMI (Appendix 19).

4. DISCUSSION

In this study it was observed that a rural birthplace and having farming parents were inversely associated with the risk of psoriasis in adulthood. The study also suggested that, as exposure to a rural environment in adulthood (at cohort baseline) was not associated with risk of psoriasis, early exposure to a rural environment is likely to be critical in the pathogenesis of psoriasis.

In spite of the relatively high prevalence of the disease, no previous study had investigated the impact of the environment during childhood on psoriasis. Studies have been limited to other IMIDs such as type 1 diabetes, oligoarticular juvenile idiopathic arthritis, and systemic lupus erythematosus. Such studies have generally had a case-control design, small sample sizes, and have not found significant associations, except for systemic lupus erythematosus. No associations were found between early life exposures such as living in a farm, living in contact with livestock, and remoteness of residence in a population-based case-control study of multiple sclerosis conducted in Tasmania with 136 cases and 272 controls³⁸⁸. Two studies on type 1 diabetes found similar results^{389,390}. Similarly, a case-control study of oligoarticular juvenile idiopathic arthritis risk found no significant associations for regular childhood farm animal contact [adjusted OR: 0.79 (95% CI 0.42-1.47)] or childhood pet contact [adjusted OR: 0.79 (95% CI 0.55-1.14)]³⁸⁹. For the risk of lupus erythematosus, a case-control study conducted in West Virginia among 265 incident cases and 355 controls found an inverse association for individuals who lived in a farm during childhood and were exposed to livestock during both childhood and adulthood [OR: 0.19 (95% CI 0.06, 0.63)]³⁹¹.

Environmental factors are thought to play a role in the immune system's development as they

activate Toll-like receptors on natural killer cells and dendritic cells. This action results in a strong stimulation of T regulatory cells at birth. These cells, further activated by repeated exposure to the same triggers during early childhood, could suppress the Th1 differentiation pathway, a key inflammatory mechanism implicated in psoriasis^{392,393}. Rural residence has been associated with higher blood levels of interleukin-10 (IL-10), which plays a key role in the pathogenesis of psoriasis through stimulation of regulatory T cells and suppression of the Th1 immune response³⁹⁴. The PASTURE birth cohort study of 88 Finnish children, 43 of whom lived in a farming environment, showed that the production of IL-10 was higher in children living on farms³⁹². Similar results showing an increase in IL-10 associated with living conditions more common in a rural environment, such as lack of a home bathroom, exposure to peri-domiciliary animals, and living in a wooden house, were observed in two nested case-control studies of wheezing disorders in 440 children from Ecuador³⁹⁵.

Environmental factors might indirectly influence the risk of psoriasis through their effect on the microbiome, which in turn have an important role on the development of the immune system^{396–398}. The importance of the microbiome in immune regulation is supported by the observation that early colonization by certain soilborne parasitic species, such as helminths, reduces immune responsiveness in the lower gut and promotes the development of peripheral regulatory T cells responsible for tolerance to diet antigens and commensal microbes³⁸⁴. Such microbiome-facilitated tolerogenic effects may echo in other tissues, such as the skin, through immune-networks between the gut and other body systems³⁰⁸.

The influence of the external environment on the microbiome can span multiple generations. One of the key factors associated with the microbiome is diet, which is strongly influenced by parents in childhood through dietary patterns and subsequent food preferences. In the E3N cohort, women with agricultural parents were found to consume more fruits and vegetables compared with women without farming parents³⁷⁹, which may be associated with a reduced risk of psoriasis³⁹⁹. In addition, diets common in rural environments may be different from diets common in urban areas. The former may be characterized not only by a higher consumption of fruits and vegetables, but also by a higher consumption of dairy products and fermented products. Such types of diet may influence the microbiome of the offspring through breast milk, which has been shown to have a higher number of total lactobacilli species in mothers living in rural areas than in mothers living in urban areas^{400,401}. These probiotics have been shown to reduce chronic skin inflammation⁴⁰² and are considered a promising therapy in patients with psoriasis⁴⁰³.

This study has several strengths: the E3N cohort study includes a population of women born between 1925 and 1950, when major lifestyle and urban-rural transitions took place. With the exception of the analyses of moderate-to-severe psoriasis, which remain exploratory, the large size of the study population allowed adequate statistical power to be achieved. With the extensive data collected through the repeated questionnaires it was possible to perform multivariable analyses controlling for several potential confounders including some assessed at different time points. In addition, because of the prospective design of the study, it is unlikely that any potential bias in the reporting of exposures during childhood would differ between cases and non-cases.

A limitation of the study is the number of cases with unknown age at diagnosis that were excluded from the main analyses that is relatively large (n=1 656), but the effect of excluding such cases is likely to be marginal, as suggested by the results of the logistic regression analysis.

The modest number of cases and the disease severity judged only by the type of treatment used are the main limitations of the analyses for moderate-to-severe psoriasis.

The exposure data, which are based on information from only one questionnaire, also have some limitations. For example, it was not possible to determine from the question "Lived in a farm for at least 3 months" how much time a woman spent in a farm. Similarly, although data suggest that occupational mobility in the agricultural sector was limited in France in the first half of the 20th century⁴⁰⁴, it was not possible to determine whether "farming parents" spent their entire working lives in agriculture and animal husbandry.

Compared with other prospective cohorts and the general population, there is less variation in socioeconomic status in the E3N cohort. However, sufficient inter-individual variation was observed for the exposure variables of interest (e.g., 34.6% of the cohort participants were born in a rural environment).

Finally, the E3N cohort includes only women who were between 40 and 65 years of age at the start of the study. Our study was therefore limited to late-onset psoriasis and leaves open the question of whether the observed associations would apply to early-onset psoriasis.

To our knowledge, this is the first study to examine the role of the environment during childhood on psoriasis risk. The study shows that childhood exposure to a rural environment, specifically being born in a rural area or having farming parents, may be associated with a

reduced risk of psoriasis. The results of our study warrant further investigation in other population groups, including men and younger generations. These findings may have implications for our understanding of the pathogenesis of psoriasis.

PART V: SOLAR EXPOSURE, PIGMENTARY TRAITS AND RISK OF PSORIASIS

1. INTRODUCTION

The beneficial effects of sun exposure on some skin diseases, such as vitiligo have been known since the time of the ancient Indians²⁰¹. In the 20th century, Finsen discovered that the therapeutic component of sunlight in psoriasis was UV radiation⁴⁰⁵ and in the 1970s, it was discovered that the beneficial effect of UV radiation could be potentiated by the administration of photosensitizing substances called psoralens. To date, treatment with UV radiation and psoralens is one of the approved treatments for psoriasis⁷⁴.

Despite the established therapeutic role for psoriasis, questions remain about the role of sun exposure on the disease aetiology. It is known that there is an increasing gradient of UV exposure as we move to lower latitude⁴⁰⁶. Studies of geographical distribution of psoriasis that have investigated the hypothesis of an association between higher UV exposure and lower prevalence of psoriatic disease at lower latitudes have produced inconsistent results with some supporting such hypothesis^{167,170} but not others^{168,407}. Limitations of such studies include the cross-sectional or ecological nature, the case definition that generally included only patients actively seeking dermatologic treatment, and the lack of individual information on the skin phenotype and the personal history of sun exposure (e.g. behaviors and history of residence).

Skin sensitivity to solar UV exposure, for example, varies according to the amount and type of melanin present in the skin and may affect risk of psoriasis^{408,409} as suggested by observations of a lower prevalence of psoriasis in non-Caucasian populations⁴¹⁰.

Using the French E3N cohort of women, a prospective study was conducted to examine the association between residential sun exposure, pigmentary characteristics and risk of psoriasis, adjusting for several potential confounders.

2. MATERIALS AND METHODS

2.1. PIGMENTARY TRAITS ASSESTMENT

In the baseline questionnaire participants were asked to report their skin phototype (albino,

fair skin, white, light brown, dark brown, black) and their natural hair color (albino, blond, red, light brown, dark brown, black). Skin color was included as an ordinal variable consisting of four categories from the lightest to the darkest skin tone (albino-very fair; white; light brown; dark brown-black) because albino and black were merged into the very fair and dark categories, respectively, due to low numbers.

Similarly, the variable natural hair color was divided into four categories sorted by hair color from lighter to darker (albino-blonde, red, light brown-dark brown, black) by merging albino-blonde and light brown-dark brown.

2.2. PARTICIPANTS RESIDENCE

In the baseline questionnaire women reported their address of residence with name of the city and postal code that was recoded as an unique code INSEE, a numeric code developed by the Institut national de la statistique et des études économiques (INSEE).

2.3. RESIDENTIAL SUN EXPOSURE ASSESTMENT

The UV exposure data used in the study included mean annual, mean spring/summer, and mean fall/winter UV doses expressed as erythemal dose [kJ/m^2]. The data were obtained from the Internet-based Solar Radiation Data (SoDa) services⁴¹¹.

The data were generated by SoDa using a clear sky model adjusted for several atmospheric factors, including the total column content of ozone and water vapor, the Linke turbidity factor, the Angström coefficient for aerosols and cloud cover, the ground albedo, and the surface elevation above mean sea level. The data cover a period from 1985 to 2005 and have been tested for reliability in a previous paper⁴¹². UV doses were linked to E3N participants' department of residence reported in the baseline questionnaire. UV exposure variables were treated as ordinal variables with four categories defined by quartiles of their distribution : mean annual UV exposure (1st quartile: <1.37 ; 2nd quartile: $[1.37-1.49]$; 3rd quartile: $[1.49-1.66]$; 4th quartile: $>1.66 \text{ kJ}/\text{m}^2$), mean spring/summer UV exposure (1st quartile: <2.35 ; 2nd quartile: $[2.35-2.52]$; 3rd quartile: $[2.52-2.69]$; 4th quartile: $>2.69 \text{ kJ}/\text{m}^2$), and mean fall/winter UV exposure (1st quartile: <0.42 ; 2nd quartile: $[0.42-0.49]$; 3rd quartile: $[0.49-0.62]$; 4th quartile: $>0.62 \text{ kJ}/\text{m}^2$).

Two irradiance-related measures were used in sensitivity analyses of this study: Direct Normal Irradiance (DNI) and Global Horizontal Irradiance (GHI).

GHI represents the solar irradiance captured by a surface horizontal to the Earth's surface⁴¹³, while Direct Normal Irradiance (DNI)⁴¹⁴ represents the irradiance coming directly from the sun and reaching a surface normal to the solar disk. These measurements capture the entire solar spectrum, not just UV radiations, and are measured in W/m². Unlike GHI, DNI doesn't account for scattered irradiance due to ozone and other scattering sources such as dust, pollen, smoke, and water vapor.

Solar irradiance data were collected from 1994 to 2018 and had a spatial resolution of 250x250 meters. Global Horizontal Irradiance (GHI) and Direct Normal Irradiance (DNI) data were obtained from the Global Solar Atlas 2.0, a free web-based application developed and operated by Solargis s.r.o. on behalf of the World Bank Group, using Solargis data and funded by the Energy Sector Management Assistance Program (ESMAP)⁴¹⁵.

The INSEE code allowed us to link each of the 38 725 available French metropolitan municipalities to a set of longitude and latitude coordinates available on data.gouv.fr, the French government's open data platform⁴¹⁶. These coordinates correspond approximately to the geographic center of each municipality.

2.4. STUDY POPULATION

A description of the E3N cohort, which was used for this study, and of the process of the identification of psoriasis cases has been previously described in the Material chapter of the part II.

For the present study participants were excluded for the following reasons: i) sun exposure could not be determined because of missing data on residence at baseline (n=7 872); ii) information on skin pigmentation at baseline was not provided (n=1 077); iii) death during follow-up but date of death was not available (n=44); iv) diagnosis of psoriasis reported only in the free text area but not in the questionnaires (n=418); v) those who reported having been diagnosed with psoriasis after 2004 but were not found in the MGEN database (n=132). Finally, were excluded women that did not answer any questionnaire after baseline (n=2 648), all prevalent cases (n=1 289) and those without a date of diagnosis of psoriasis (n=1 619). After these exclusions the study population for overall model included 83 896 women (Figure

23).

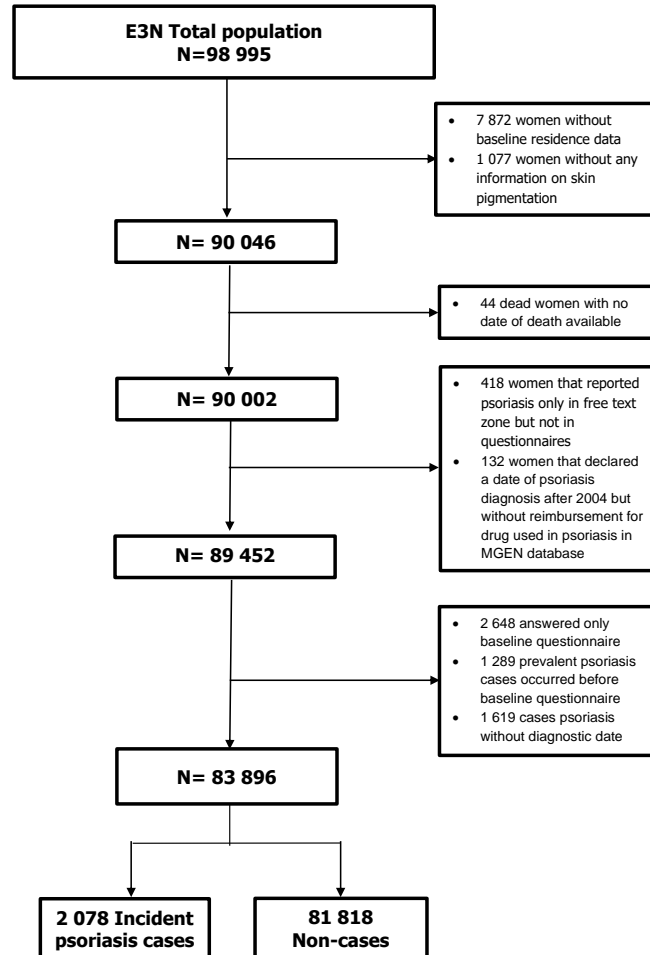


Figure 23: Flow chart of the included participants in overall psoriasis models- Solar exposure and pigmentary traits.

For the analyses on moderate-to-severe were excluded participants for the following reasons : follow-up end before January 1, 2004, died or were lost to follow-up by January 1, 2004 when drug claims data became available (n=14 586) and those with missing diagnostic date (n=2 050) obtaining a study population of 72 816 participants (Figure 24).

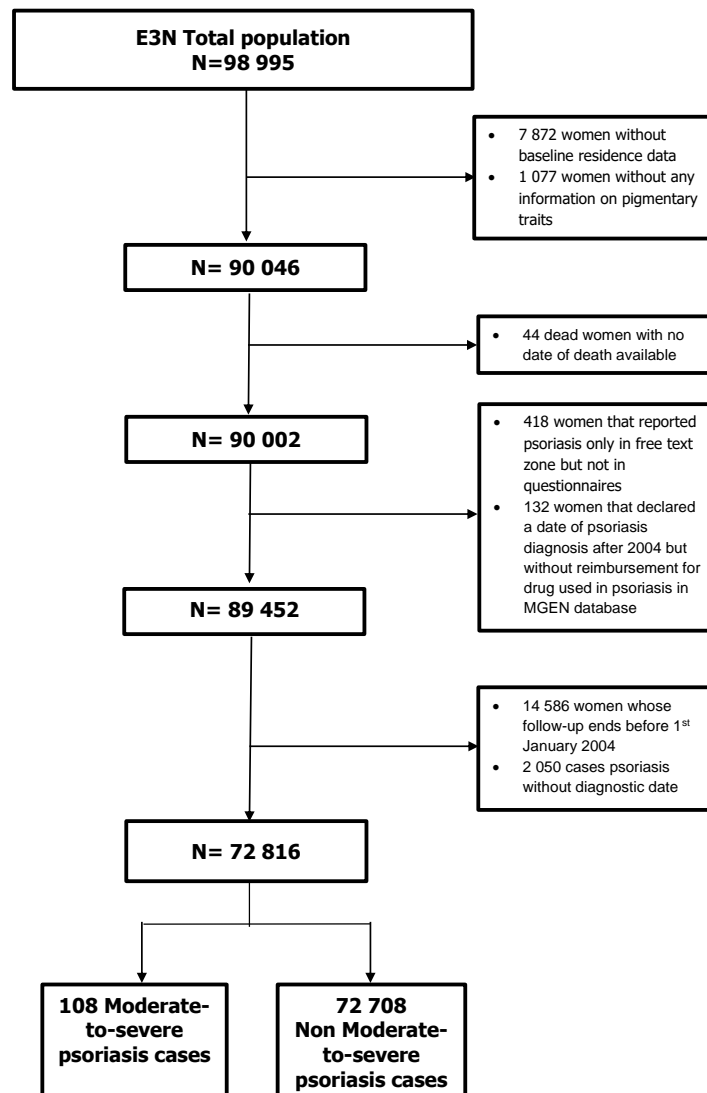


Figure 24: Flow chart of the included participants in the analyses on moderate-to-severe psoriasis- Solar exposure and pigmentary traits.

2.5. STATISTICAL ANALYSIS

Characteristics of the study population were calculated as means and standard deviations for quantitative variables and as numbers and percentages (%) for qualitative variables. Hazard ratios (HRs) for psoriasis and their corresponding 95% confidence intervals (CI) were estimated using Cox proportional hazards regression models. The proportional hazards assumption was tested by analyzing the Schoenfeld residuals.

Follow-up began on the date of completion of the baseline questionnaire and ended on the date of diagnosis of psoriasis, the date of the last completed questionnaire, the date of death, or the date of return of the most recent follow-up questionnaire (Q12), whichever occurred first.

For moderate-to-severe psoriasis, the event was defined as at least one reimbursement of psoriasis-related systemic drug recorded in the MGEN database for a self-reported case of psoriasis. For such analyses follow-up began on January 1, 2004, and ended at the occurrence of a moderate-to-severe psoriasis event (date of the first reimbursement of psoriasis-related systemic drug), at the date of death, or on December 31, 2018 (date of the most recent drug reimbursement data available), whichever occurred first.

Univariate hazard ratios (uHRs) were estimated including only one of the skin pigmentation or sun exposure variables at a time. Multivariable adjusted hazard ratios (aHRs) were estimated including BMI (categorical variable: <25, 25-30[, and ≥ 30 kg/m²), marital status at baseline (never married, married), smoking status (never, current, former smoker), educational level (undergraduate or less, graduate, postgraduate or more; baseline), and history of medical conditions that may be associated with psoriasis (history of diabetes, depression and hypertension as three separate binary variables). Hormonal and reproductive variables were included such as age at menarche (<12 years, 12-15 years, >15 years), menopausal status (premenopausal, postmenopausal), parity (nulliparous, parous) and ever use of oral contraceptive pill at baseline as binary variable. BMI, smoking status, history of medical conditions and menopausal status were included in the models as time-varying variables.

In a sensitivity analysis, the association between sun exposure and psoriasis was tested at the municipality of residence level, including GHI and DNI instead of UV dose.

Finally, all cases, whether prevalent or incident, and all cases with unknown age at diagnosis were included in a sensitivity analysis using logistic regression. In these sensitivity analyses, based on a population of 89 496 women, including 5 051 participants with psoriasis, univariable and multivariable logistic models were fitted to estimate odds ratios (OR) and 95% confidence intervals (CI).

For residential UV exposures, the first quartile of exposure was used as a reference.

In the skin phototype models, the largest category, white was used as a reference. In the analyses on hair colour we used brown color as reference for the same reason.

Descriptive analyses were performed using the PROC FREQ procedure while Cox regression models were fitted using the PHREG procedure in SAS software version 9.4. Copyright © 2013 SAS Institute Inc., Cary, NC, USA.

3. RESULTS

The characteristics of the study population at baseline are described by psoriasis status in Table 10 and by skin pigmentation and sun exposure variables in Appendices 20-24. Mean age at baseline was 49.4 years (± 6.6 years). The mean age at diagnosis of psoriasis was 64.5 years (± 8.4 years), and the mean time from study entry to diagnosis of psoriasis was 16.1 years (± 6.2 years).

Table 10: Characteristics of study participants at baseline according to overall psoriasis status (N = 83 896).

Exposure	All (N=83 896)	Not Psoriasis (n=81 818)	Psoriasis (n=2 078)
Year at birth			
<1930	6 664 (7.9%)	6 559 (8.0%)	105 (5.1%)
1930-1935	10 901 (13.0%)	10 680 (13.1%)	221 (10.6%)
1935-1940	15 923 (19.0%)	15 548 (19.0%)	375 (18.0%)
1940-1945	20 155 (24.0%)	19 585 (23.9%)	570 (27.4%)
>1945	30 253 (36.1%)	29 446 (36.0%)	807 (38.8%)
Body mass index (kg/m²)			
<25	68 765 (82.0%)	67 111 (82.0%)	1 654 (79.6%)
25-30	12 472 (14.9%)	12 139 (14.8%)	333 (16.0%)
>30	2 659 (3.2%)	2 568 (3.1%)	91 (4.4%)
Smoking status			
Never	45 434 (54.2%)	44 439 (54.3%)	995 (47.9%)
Current	12 367 (14.7%)	11 982 (14.6%)	385 (18.5%)
Former	26 095 (31.1%)	25 397 (31.0%)	698 (33.6%)
Marital status			
Not married	14 977 (17.9%)	14 579 (17.8%)	398 (19.2%)

Married	68 919 (82.1%)	67 239 (82.2%)	1 680 (80.8%)
Education level			
Undergraduate or less	2 816 (3.4%)	2 752 (3.4%)	64 (3.1%)
Graduate	11 277 (13.4%)	11 062 (13.5%)	215 (10.3%)
Postgraduate or more	69 803 (83.2%)	68004 (83.1%)	1799 (86.6%)
Hypertension			
No	61 333 (73.1%)	59863 (73.2%)	1470 (70.7%)
Yes	22 563 (26.9%)	21955 (26.8%)	608 (29.3%)
Depression			
No	73 513 (87.6%)	71764 (87.7%)	1749 (84.2%)
Yes	10 383 (12.4%)	10054 (12.3%)	329 (15.8%)
Type 2 diabetes			
No	83 187 (99.2%)	81124 (99.2%)	2063 (99.3%)
Yes	709 (0.8%)	694 (0.8%)	15 (0.7%)
Age at menarche			
12-15 years old	63 529 (75.7%)	61989 (75.8%)	1540 (74.1%)
<12 years old	17 108 (20.4%)	16640 (20.3%)	468 (22.5%)
>15 years old	3 259 (3.9%)	3189 (3.9%)	70 (3.4%)
Menopausal status			
Premenopausal	43 177 (51.5%)	41989 (51.3%)	1188 (57.2%)
Postmenopausal	40 719 (48.5%)	39829 (48.7%)	890 (42.8%)
Nulliparous			
No	74 032 (88.2%)	72231 (88.3%)	1801 (86.7%)
Yes	9 864 (11.8%)	9587 (11.7%)	277 (13.3%)
Ever use of oral contraceptives			
No	37 712 (45.0%)	36834 (45.0%)	878 (42.3%)
Yes	46 184 (55.0%)	44984 (55.0%)	1200 (57.7%)
Skin phototypes			
Albino+very fair	996 (1.2%)	955 (1.2%)	41 (2.0%)

White	48 267 (57.5%)	47013 (57.5%)	1254 (60.3%)
Light brown	33 272 (39.7%)	32518 (39.7%)	754 (36.3%)
Dark Brown+black	1 361 (1.6%)	1332 (1.6%)	29 (1.4%)
Hair color			
Albino+blond	8 436 (10.1%)	8203 (10.0%)	233 (11.2%)
Red	1 452 (1.7%)	1422 (1.7%)	30 (1.4%)
Brown (Light+dark)	69 873 (83.3%)	68162 (83.3%)	1711 (82.3%)
Black	4 135 (4.9%)	4031 (4.9%)	104 (5.0%)
Mean annual daily ambient total UV level (kJ/m²)			
1 st quartile	15 726 (18.7%)	15290 (18.7%)	436 (21.0%)
2 nd quartile	28 640 (34.1%)	27917 (34.1%)	723 (34.8%)
3 rd quartile	18 536 (22.1%)	18124 (22.2%)	412 (19.8%)
4 th quartile	20 994 (25.0%)	20487 (25.0%)	507 (24.4%)
Mean spring/summer daily ambient total UV level (kJ/m²)			
1 st quartile	17 252 (20.6%)	16771 (20.5%)	481 (23.1%)
2 nd quartile	28 727 (34.2%)	27987 (34.2%)	740 (35.6%)
3 rd quartile	16 479 (19.6%)	16125 (19.7%)	354 (17.0%)
4 th quartile	21 438 (25.6%)	20935 (25.6%)	503 (24.2%)
Mean fall/winter daily ambient total UV level (kJ/m²)			
1 st quartile	17 462 (20.8%)	16974 (20.7%)	488 (23.5%)
2 nd quartile	26 532 (31.6%)	25873 (31.6%)	659 (31.7%)
3 rd quartile	19 263 (23.0%)	18840 (23.0%)	423 (20.4%)
4 th quartile	20 639 (24.6%)	20131 (24.6%)	508 (24.4%)

The albino/very light category was associated with an increased risk of psoriasis relative to the white skin category (reference) [aHRs 1.55 (95%CI: 1.13–2.11)]. Conversely, the darker categories were associated with a lower risk of psoriasis, although no conclusions can be drawn for the "dark brown+black" category due to the very small numbers involved.

The aHRs for “light brown” and “dark brown-black” were 0.87 (95%CI: 0.80–0.95) and 0.86 (95%CI: 0.59–1.24) respectively (Table 11).

In contrast, no association was observed between any category of natural hair color and risk of psoriasis.

Table 11: Hazard Ratios of overall psoriasis risk according to pigmentary traits (N= 83 896).

Exposure	Psoriasis cases (n=2 078)	Person-years (n=1 995 453)	Hazard Ratios (95% CI)	
			Univariate Model ^a	Multivariable Model ^b
Skin phototypes				
Albino+very fair	41	22 561	1.66 (1.22-2.27)	1.55 (1.133-2.11)
White	1254	1 168 686	1.00 (Reference)	1.00 (Reference)
Light brown	754	793 041	0.87 (0.79-0.95)	0.87 (0.80-0.95)
Dark Brown+black	29	11 165	0.85 (0.59-1.23)	0.86 (0.59-1.24)
Hair color				
Albino+blond	234	198 988	1.14 (0.99-1.30)	1.13 (0.98-1.29)
Red	30	34 383	0.84 (0.58-1.21)	0.82 (0.57-1.18)
Brown (Light+dark)	1710	1 663 785	1.00 (Reference)	1.00 (Reference)
Black	104	98 297	1.02 (0.84-1.25)	1.02 (0.84-1.25)

a) Model adjusted for: birth cohort

b) Model adjusted for: birth cohort, BMI, smoking status, education level, marital status at baseline, hypertension, depression, diabetes, age at menarche, menopause status, nulliparous status, ever use of contraceptive pill.

No association was observed between any category of skin or hair color and the risk of moderate-to-severe psoriasis (Table 12).

Table 12: Hazard Ratios of moderate-to-severe risk according to pigmentary traits (N = 72 816).

Exposure	Moderate-to-severe psoriasis cases (n=108)	Person-years (n=929 910)	Hazard Ratios (95% CI)	
			Univariate Model ^a	Multivariable Model ^b
Skin phototypes				
Albino+very fair	1	10 324	0.97 (0.13-7.01)	0.86 (0.11-6.22)
White	54	535 624	1.00 (Reference)	1.00 (Reference)
Light brown	53	369 456	1.46 (0.99-2.13)	1.46 (0.99-2.14)
Dark Brown+black	0	14 506	-	-
Hair color				
Albino+blond	10	92 408	0.93 (0.48-1.78)	0.92 (0.48-1.77)
Red	1	15 973	0.54 (0.07-3.87)	0.51 (0.07-3.71)
Brown (Light+dark)	91	775 621	1.00 (Reference)	1.00 (Reference)
Black	6	45 908	1.12 (0.49-2.56)	1.10 (0.48-2.51)

a) Model adjusted for: birth cohort

b) Model adjusted for: birth cohort, BMI, smoking status, education level, marital status at baseline, hypertension, depression, diabetes, age at menarche, menopause status, nulliparous status, ever use of contraceptive pill.

The estimated HRs for residential UV for the three highest quartiles relative to the lowest quartile are shown in Table 13 for the three measures (mean annual exposure, mean spring/summer exposure and mean autumn/winter exposure). In general, the risk of psoriasis appeared to decrease with increasing UV exposure for all three measures. In particular, for mean annual residential UV exposure the aHRs were 0.91 (95%CI: 0.80-1.01), 0.80 (95%CI: 0.70-0.91) and 0.88 (95%CI: 0.77-1.00) for the second, third and fourth quartile respectively.

Table 13: Hazard Ratios of overall psoriasis risk according to residential solar exposure (N = 83 896).

Exposure	Cases (n=2 078)	Person-years (n=1 995 453)	Hazard Ratios (95% CI)	
			Univariate Model ^a	Multivariable Model ^b
Mean annual natural UV exposure (kJ/m²)				
1 st quartile	436	372 873	1.00 (Reference)	1.00 (Reference)
2 nd quartile	723	679 932	0.90 (0.80-1.02)	0.90 (0.80-1.01)
3 rd quartile	412	443 201	0.79 (0.69-0.90)	0.80 (0.70-0.91)
4 th quartile	507	499 447	0.86 (0.76-0.98)	0.88 (0.77-1.00)
Mean spring/summer natural UV exposure (kJ/m²)				
1 st quartile	481	408 701	1.00 (Reference)	1.00 (Reference)
2 nd quartile	740	682 630	0.91 (0.82-1.03)	0.91 (0.81-1.02)
3 rd quartile	354	394 242	0.76 (0.66-0.87)	0.76 (0.66-0.88)
4 th quartile	503	509 880	0.83 (0.74-0.95)	0.85 (0.74-0.96)
Mean fall/winter natural UV exposure (kJ/m²)				

1 st quartile	488	413 868	1.00 (Reference)	1.00 (Reference)
2 nd quartile	659	629 985	0.88 (0.79-0.99)	0.88 (0.78-0.99)
3 rd quartile	423	462 785	0.77 (0.67-0.88)	0.78 (0.68-0.89)
4 th quartile	508	488 815	0.88 (0.78-1.00)	0.90 (0.79-1.02)

a) *Model adjusted for: birth cohort*

b) *Model adjusted for: birth cohort, BMI, smoking status, education level, marital status at baseline, hypertension, depression, diabetes, age at menarche, menopause status, nulliparous status, ever use of contraceptive pill.*

For moderate-to-severe psoriasis, an inverse association was observed only with the third quartile of the mean UV exposure during the spring/summer season [aHR: 0.49 (95%CI: 0.26-0.93)], of the mean UV exposure during the fall/winter season [aHR: 0.47 (95%CI: 0.25-0.86)] and, possibly, of mean annual UV exposure [aHR: 0.53 (95%CI: 0.28-1.01)] (Table 14)

Table 14: Hazard Ratios of moderate-to-severe risk according to residential solar exposure (N= 72 816).

Exposure	Moderate-to-severe psoriasis cases (n=108)	Person-years (n=929 910)	Univariate Model ^a	Multivariable Model ^b
Mean annual natural UV level (kJ/m²)				
1 st quartile	24	172 207	1.00 (Reference)	1.00 (Reference)
2 nd quartile	41	317 635	0.91 (0.54-1.50)	0.88 (0.53-1.46)
3 rd quartile	15	207 277	0.52 (0.27-0.99)	0.53 (0.28-1.01)
4 th quartile	28	232 791	0.87 (0.50-1.51)	0.88 (0.51-1.52)
Mean spring/summer natural UV level (kJ/m²)				
1 st quartile	30	188 721	1.00 (Reference)	1.00 (Reference)
2 nd quartile	38	319 124	0.73 (0.45-1.18)	0.72 (0.44-1.16)
3 rd quartile	14	184 537	0.48 (0.25-0.90)	0.49 (0.26-0.93)
4 th quartile	26	237 529	0.69 (0.41-1.18)	0.70 (0.41-1.20)
Mean fall/winter natural UV level (kJ/m²)				
1 st quartile	31	191 459	1.00 (Reference)	1.00 (Reference)
2 nd quartile	34	294 102	0.70 (0.42-1.14)	0.68 (0.42-1.12)
3 rd quartile	16	217 316	0.45 (0.25-0.83)	0.47 (0.25-0.86)

4 th quartile	27	227 033	0.74 (0.44-1.25)	0.76 (0.45-1.27)
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a) *Model adjusted for: birth cohort.*

b) *Model adjusted for: birth cohort BMI, smoking status, education level, marital status at baseline, hypertension, depression, diabetes, age at menarche, menopause status, nulliparous status, ever use of contraceptive pill.*

When DNI and GHI were used in the models it was observed an associations with psoriasis similar to those observed for average annual UV exposure (Appendix 25).

In the logistic regression models including all cases of psoriasis including prevalent and incident cases as well as cases with unknown age at diagnosis it was observed an associations between skin color and psoriasis risk similar to those obtained from the Cox regression models (Appendices 26-27).

For hair color, an inverse association was observed between psoriasis risk and red hair color [aOR_{RED}: 0.72 (95%CI: 0.55-0.92)] and brown hair color [aOR_{BROWN}: 0.90 (95%CI: 0.82-0.98)] relative to albino-very fair category.

For UV exposure, the associations with psoriasis risk estimated from logistic regression were slightly weaker than those from the Cox regression models.

4. DISCUSSION

In this study based on the E3N prospective cohort, we found that risk of psoriasis was lower in women with higher levels of ambient UV exposure. Relative to women with a white skin color, a darker skin color was associated with a reduced risk of psoriasis while women with a very fair/albino skin color had a higher risk of psoriasis. Hair colour was not associated with risk of psoriasis

These results were the first to look at residential UV exposure and pigmentation factors in relation to the risk of developing psoriasis. The inverse associations observed for psoriasis are consistent with those observed for other immune-related diseases such as Crohn's disease⁴¹⁷, rheumatoid arthritis⁴¹⁸ and juvenile idiopathic arthritis⁴¹⁹.

In a retrospective study on the effect of sun exposure on psoriatic disease flares in a population of 2 270 psoriasis patients occupations associated with higher sun exposure were associated with a decreased risk of seasonal exacerbations in late-onset psoriasis⁴²⁰.

The associations may be explained by several mechanisms. The effects of vitamin D on the main pathogenetic mechanisms of psoriasis are manifold. It shifts the immune response from a Th17 phenotype towards the production of regulatory cells⁴²¹, leading to a reduction in the levels of pro-inflammatory cytokines (IL-17, IL-21) and an increase in the levels of the anti-inflammatory cytokine IL-10⁴²². It also inhibits the differentiation and maturation of DCs, maintaining an immature phenotype as evidenced by reduced expression of MHC class II molecules²⁰².

Vitamin D indirectly influences the immune response by acting on the composition of the microbiome and the permeability of the intestinal barrier.

An increase in bacteria belonging to the phyla Bacteroidetes, which stimulate the production of anti-inflammatory IL-10 and tight junction proteins responsible for intestinal barrier integrity, was associated with serum vitamin D levels⁴²³. These bacterial species are normally depleted in psoriasis patients^{424,425}.

Finally, levels of vitamin D are related to physical and functional gut barrier integrity⁴²⁶. Reduced levels of vitamin D could disrupt these mechanisms, causing increasing permeability of the gut barrier and bacterial translocation in the systemic circulation, triggering immunity activation^{414,415}.

Other potential immunomodulatory effects of sun exposure independent of vitamin D production include the immunosuppressive effect induced by other UVB-sensitive chromophores such as trans-urocanic acid (UCA), tryptophan, and lipids resulting in the release of prostaglandin E2 (PGE2), IL-10 and IL-22 by keratinocytes and APCs⁴²⁹; and the UV-induced DNA damage resulting in the depletion of nicotinamide adenine dinucleotide (NAD) levels in keratinocytes and thus the metabolic energy of these cells⁴³⁰.

The association between skin color and psoriasis could be interpreted as being influenced by lifestyle factors other than those studied, such as diet, and possibly certain diets rich in fruits and vegetables containing furanocoumarins, which have been shown to have a potential photosensitizing effect⁴³¹.

Another possible explanation was related to possible differences in the clinical presentation of the disease and less recourse to dermatological treatment in dark-skinned individuals, as observed in other studies conducted in the United States and Canada^{410,432,433}. The contribution of ethnic genetic factors involved in skin barrier and immune activation mechanisms to the

observed results could not be excluded⁴³².

One of the main limitations of this study is that residential UV exposure was estimated at the broader level of department and not at the municipal level. However, this limitation was partly compensated by the use of the DNI and GNI indices in the sensitivity analyses from which results were similar to those obtained in the main analyses based on the UV exposure.

Another limitation was the lack of information on sun exposure related to leisure activities, individual behaviour related to sun exposure and time spent in places other than the place of residence.

Skin pigmentation relied on self-reported information skin and hair color that may be prone to social desirability bias in reported skin color. However, it is unlikely that such possible bias would differ between cases and non-cases of psoriasis.

This study had many strengths, including high statistical power, a large amount of information about the women's lifestyle, and a prospective design that makes reverse causation bias unlikely.

In conclusion, this was the first study to test the association between residential UV exposure, skin color and the risk of psoriasis. Further studies are needed to confirm these findings particularly in studies in men and in younger generations. Future studies should also focus on trying to determine whether a critical time window exists in which the inverse association between residential UV exposure and psoriasis is strongest. Such findings could allow to devise preventive measures to reduce the risk of disease occurrence in at-risk populations.

PART VI: GENERAL DISCUSSION

1. OVERVIEW

This thesis aimed to study the associations between risk factors related to immune and inflammatory response and the risk of psoriasis using data from the E3N prospective cohort. In this work we intended the environment in broad sense as different external factors that might influence the pathogenesis of psoriasis through immune and inflammation-related mechanisms. This section summarizes the results obtained and the future perspectives related to this thesis work.

2. SUMMARY OF MAIN RESULTS

Our first study focusing on removal of MALT (appendix, adenoids and tonsils) and psoriasis risk showed that appendix removal is associated with a moderate increase in risk of psoriasis. This result is consistent with the hypothesis that immune mechanisms distant from the skin and interactions between the immune and digestive systems may play a role in psoriasis pathogenesis.

The second article focusing on the association of lifestyle factors and the environment during childhood, showed that a rural birthplace and having farmers parents were associated with a lower risk of psoriasis while residence in a rural area in adulthood was not associated with risk of psoriasis. While it is well known that childhood is a critical time for the development of the immune system⁴³⁴, our findings suggest that childhood is a critical time also for the pathogenesis of psoriasis. We hypothesize that the observed associations are related to the direct immunomodulatory effect of exposure to a rural environment, which could also indirectly shape the microbiome, and may be further influenced by farmers parents through the acquisition of certain lifestyle habits, such as dietary habits.

Finally, in the third article, we observed that a higher residential sun exposure decreases the risk of psoriasis. We also observed that a lighter skin color was associated with an augmented risk of psoriasis while a darker skin color was associated with a lower risk of psoriasis. This could be due to genetic or other non-biological factors not taken into account, such as diet or a different perception of psoriasis risk in women with darker skin.

3. STRENGTHS AND LIMITATIONS OF THE STUDY

3.1. STRENGTHS

This study has several strengths: first, it is a study with an important sample size, which allowed us to have robust statistical power.

The long and detailed Follow-up of the cohort was an important pre-requisite for reliable outcome assessment especially for chronic diseases such as psoriasis where exposure to an event is often long-term, and its impact on health can appear many years after first occurrence.

The prospective design of the study allowed us to calculate rates of disease in exposed and unexposed individuals over time (e.g. incidence, relative risk) less prone to bias.

The response rate was very high from the beginning, and the number of women lost to follow-up accounted for only about 3% of cases for each questionnaire.

Availability of extensive data on health and lifestyle of participants reduced levels of uncontrolled confounding.

Data on extra-hospital medical prescriptions (from 2004) helped us in the definition of moderate to severe cases and in the further confirmation of the reliability of self-reported diagnoses in questionnaires.

3.2. LIMITATIONS

There were limitations to this study, including that the ascertainment of incident psoriasis cases was mainly based on the follow-up questionnaires, as we did not have access to the patients' medical records. However, several features of the study allow these data to be considered reliable.

First, the observed incidence rate of psoriasis in our study, 120 cases of psoriasis per 100,000 persons/year, appears to be broadly in line with estimates from previous studies in the European population, which vary widely, typically between 40 and 300 cases per 100,000 persons/year, depending on the year and country.

Drug reimbursement data, available for 88% of our self-reported cases, were another element.

The higher level of education of the women in the cohort and the use of the drug reimbursement database to supplement self-reported information likely increased the reliability of our classification of psoriasis cases.

The reliability of self-reported diagnoses in questionnaires compared with other prospective studies is discussed in the Materials chapter.

The main limitations of the analyses of moderate-to-severe psoriasis were the modest number of cases and the fact that severity was assessed only by the type of treatment used. In addition, the availability of drug reimbursement data only from 2004 onwards left uncertainties about the true date of onset of moderate-to-severe symptoms. For this reason, these analyses should be considered exploratory.

Prevalent cases and cases without a date of diagnosis were excluded because it was not possible to determine a follow-up period. In addition, the date of diagnosis of prevalent cases could be subject to recall bias of greater magnitude than for incident cases, as prevalent cases occurred much earlier. However, their exclusion did not seem to have a major impact on the results obtained, as the logistic analyses essentially reflected the results observed in the Cox models.

Finally, our study was not adequate to investigate associations with psoriasis occurring before the age of 40. This was related to the design of the E3N cohort, which included women aged between 40 and 65 years at the time of recruitment.

Finally, compared with the general population and other prospective cohorts, in E3N there was less variation in socioeconomic status as women were predominantly teachers with medium to high levels of education. Despite (e.g. the percentage of E3N women that were born in a rural area was 34.6%) our results should be confirmed in other populations and in more socially diverse populations.

4. RESEARCH PERSPECTIVES

The variables studied in the present work represent a first approach to the study of environmental factors related to immunity and inflammation in psoriasis, and the results obtained show a promising line of research that will broaden our knowledge of the disease pathogenesis. Our results need to be confirmed and studied by other national and international research groups, a selection of which we report here with reasons why they are suitable to continue our research work.

4.1. FRANCE

4.1.1. E3N COHORT

The role of diet in the development of psoriasis is poorly understood and would therefore represent an interesting research focus, particularly as diet may be modified. The E3N is one of the few cohorts that benefits from the repeated collection of detailed dietary data. To understand the complex interactions between diet, lifestyle and the development of psoriasis, it would be interesting to use the wealth of data available from the E3N study to test the association between intake of various foods, micronutrients, macronutrients and dietary patterns and risk of psoriasis.

Another potential factor that could elucidate the effect of the microbiome on disease would be to study associations between gut transit and association with psoriasis. If an association is observed, one could then consider using the microbiome samples in the cohort to understand if there is a specific microbiome profile that correlates with certain lifestyle characteristics.

The studies conducted in psoriasis could be replicated in other immune-mediated diseases, such as rheumatoid arthritis, which was the subject of a thesis discussed in 2021 by Yann Nguyen. Given the protean nature of autoimmunity and inflammation, it could be interesting to find out if there are points of contact between the associations identified in the present work and those in other immune-mediated diseases.

Similarly, the relationship between psoriasis and environmental pollutants such as endocrine disruptors, which is available in our cohort thanks to data from the Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail (ANSES), should be investigated.

4.1.2. E3N-GENERATIONS COHORT

The E3N-Generations cohort is an extension of E3N including the husbands, children, and grandchildren of the E3N women. The advantage of this cohort is that it is a heterogeneous population in terms of age and sex. This cohort will collect data on the exposures studied by us in E3N and allow us to understand whether the influence of the factors studied may have trans-generational characteristics. In particular, it will be important to understand whether the risk of psoriasis is influenced by the changes in lifestyle that have been observed over the last 50 years. For example, many of the families now live in an urban environment, so it will be interesting to understand whether the reduction in psoriasis risk observed in women who grew up in a rural environment has been passed on to younger generations through the inheritance of lifestyle habits from rural life, or whether conversely the aspect related to physical exposure to the rural environment is more important.

In addition, E3N-Generations will allow a more accurate solar exposure profile than is currently available in E3N, based on prospective data that will be collected over the next decades.

4.2. INTERNATIONAL STUDIES

4.2.1. EPIC

The E3N cohort is the French component of the European Prospective Investigation into Cancer and Nutrition (EPIC)⁴³⁵. This consortium of cohorts consists of 521 000 participants from 10 European countries recruited between 1992 and 1999. A study based on the EPIC cohorts with information on psoriasis would allow to achieve a large sample size to investigate the association between lifestyle (diet in particular) and risk of psoriasis in different European populations.

4.2.2. NURSES' HEALTH STUDY

The Nurses' Health Study (NHS), established by the Harvard Medical School, Harvard School of Public Health, and several Harvard-affiliated hospitals, is a prospective cohort of 121 700 female nurses aged 30 to 55 years at the time of recruitment in 1976.

The study was enriched through two subsequent recruitment campaigns of 116 430 female

nurses aged 25 to 42 years in 1989 (Nurses' Health Study II – NHS II) and around 100 000 male and female nurses in 2010 (Nurses' Health Study III – NHS III).

The NHS has also has a biobank of biological specimens (blood, saliva, urine), to which a collection of stool from more than 20,000 women within the NHS II is being added for studies on the gut microbiome⁴³⁶.

Currently, 1 611 cases of psoriasis have been identified in NHSI, 1 593 in NHS II, and 1 263 in NHS III⁴³⁷. NHS data have been used to study the association of obesity⁴³⁸, smoking⁴³⁹, alcohol consumption⁴⁴⁰ and physical inactivity⁴⁴¹ with psoriasis risk. The advantages of the NHS are numerous: this study is composed of women with a similar level of education as the E3N, and this, combined with the wide range of data available on sun exposure, medical and lifestyle history, and the microbiome biobank, would allow us to confirm and further strengthen the results observed in our analyses.

4.2.3. NORWEGIAN AND DANISH STUDIES

The HUNT study (Nord-Trøndelag Health Study)³³⁰ consists of large population-based cohorts initiated in the 1980s with 125 000 Norwegian participants; HUNT1 was recruited between 1984 and 1986, HUNT2 between 1995 and 1997, and HUNT3 between 2006 and 2008. The HUNT3 study included a psoriasis-specific sub-study in which 2 094 participants reported a diagnosis of psoriasis³³¹. HUNT has the advantage of being a large prospective cohort in the general population aged 20-100 years with a follow-up of 27 years. With detailed data on childhood behavior, work and family life, HUNT may provide the opportunity for additional studies on the relationship between environmental factors and psoriasis.

Finally, the Danish cohort 'Psoriasis in Adolescents' (PIA)⁴⁴², consisting of 81 adolescents with psoriasis, 110 with parental predisposition and 124 non-predisposed, psoriasis-free adolescents recruited, is suited for the study of lifestyle and microbiological factors within a population of early-onset psoriasis cases, to unravel whether environmental and lifestyle factors may influence the course of the disease, even in this adolescent population where genetics is thought to have a predominant effect on the onset and the manifestations of the disease.

5. PUBLIC HEALTH IMPLICATIONS

Although the incidence of psoriasis has increased by 26.5% in the last 30 years⁴⁴³, causing a significant social and health-related economic burden⁴⁴⁴, there is currently no known preventive option for psoriasis.

Our study showed that some environmental factors related to the immune response may have an effect on the incidence of psoriatic disease.

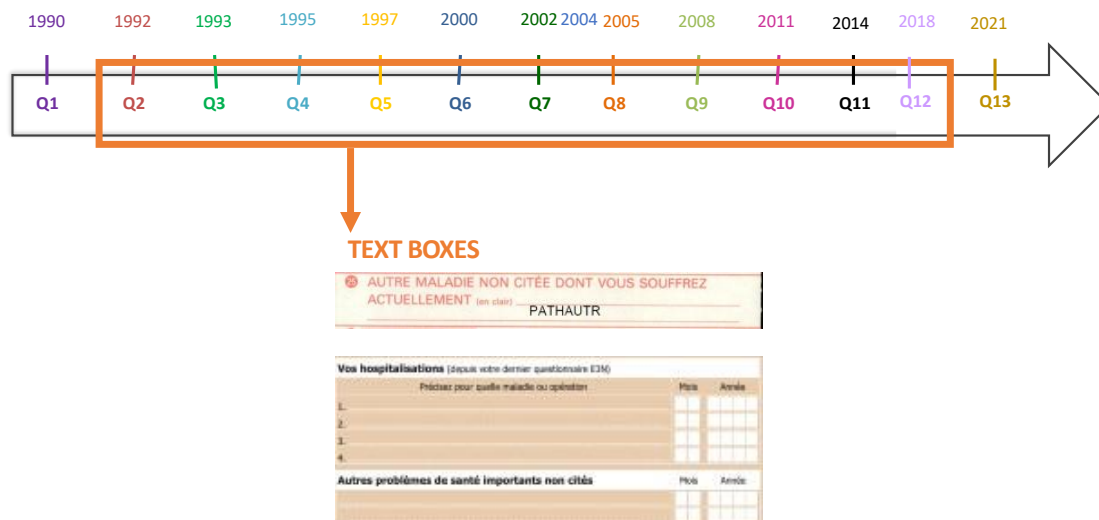
On the basis of the present results, an attempt could be made to implement a primary prevention program based on the prescription of one or more periods of vacation in rural areas in preschool age population and on regular daily sun exposure on the adult population at high risk of psoriasis.

In addition, if a role of intestinal dysbiosis in psoriasis is confirmed, early signs of microbiome changes could be identified before the occurrence of symptoms of the disease and prophylactic measures such as microbiome transplantation or probiotic administration could be envisaged to interrupt or delay the pathogenic process.

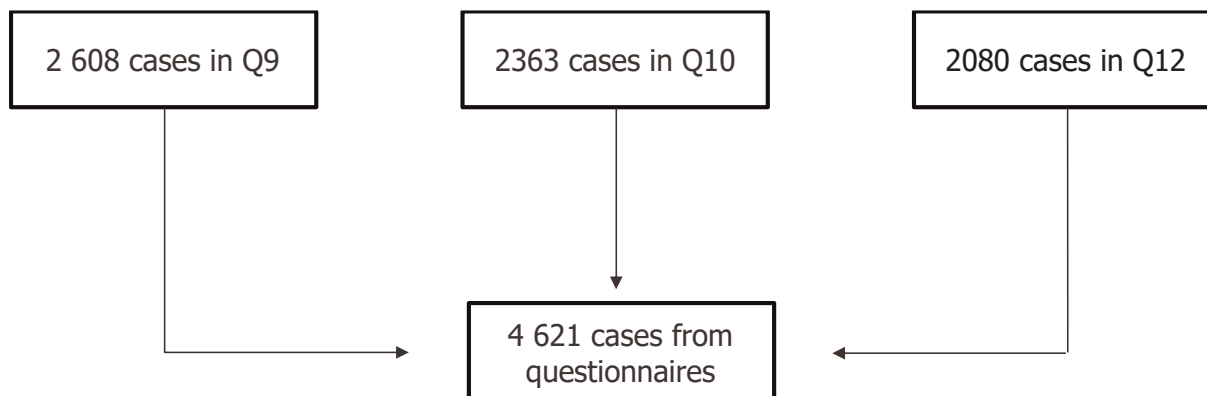
Such preventive measures would need to be tested in interventional clinical trials to test their effectiveness and would require a major effort and mobilization of various public health actors such as patient associations, research institutes, the French public health system and the Ministry of Health.

APPENDIX

Appendix 1: Free text boxes used to identify psoriasis cases in the E3N cohort.



Appendix 2: Characteristics of psoriasis cases identified by questionnaire where psoriasis was reported.



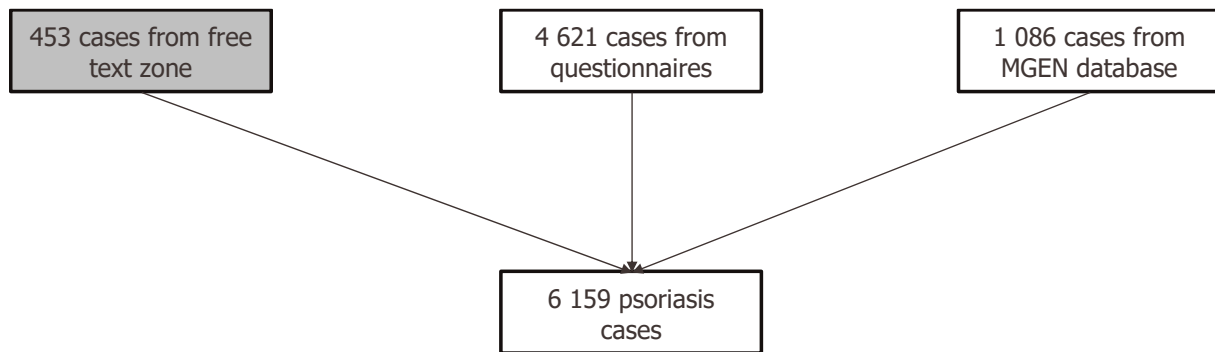
Appendix 3: Breakdown of psoriasis cases identified in the E3N cohort according to their source.

Cases of psoriasis reported in Q9	Cases of psoriasis reported in Q10	Cases of psoriasis reported in Q12	Cases of psoriasis reported in free text boxes	Cases of psoriasis presenting reimbursement for psoriasis drugs in MGEN database	Total
0	0	0	0	1	1086

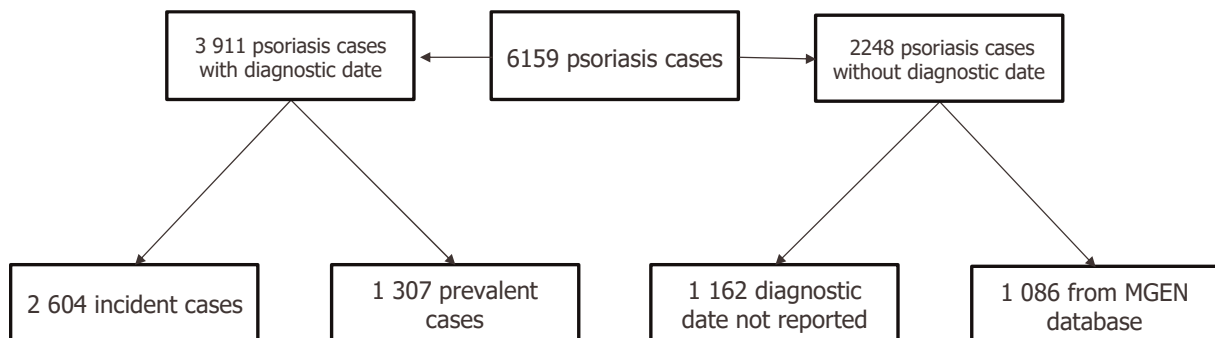
0	0	0	1	0	115
0	0	0	1	1	337
0	0	1	0	0	83
0	0	1	0	1	721
0	0	1	1	0	6
0	0	1	1	1	69
0	1	0	0	0	93
0	1	0	0	1	594
0	1	0	1	0	7
0	1	0	1	1	73
0	1	1	0	0	25
0	1	1	0	1	244
0	1	1	1	0	10
0	1	1	1	1	88
1	0	0	0	0	149
1	0	0	0	1	867
1	0	0	1	0	20
1	0	0	1	0	130
1	0	1	0	0	16
1	0	1	0	1	136
1	0	1	1	0	5
1	0	1	1	1	57
1	1	0	0	0	53
1	1	0	0	1	373
1	1	0	1	0	22
1	1	0	1	1	160
1	1	1	0	0	19
1	1	1	0	1	311
1	1	1	1	0	14

1	1	1	1	1	276
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Appendix 4: Characteristics of psoriasis cases identified in sources other than questionnaires.



Appendix 5: Classification of psoriasis cases identified according to date of diagnosis.



Appendix 6: Characteristics of study participants according to exclusion status in the overall psoriasis population compared to the entire E3N population (N = 98 995).

	Exclusion status	
	Excluded population (n= 8 876)	Included population (n= 90 119)
Psoriasis		
No	5 150 (58.0%)	87 686 (97.3%)
Yes	3 726 (42.0%)	2 433 (2.7%)

Appendectomy		
No	3 896 (43.9%)	55 731 (61.8%)
Yes	2 726 (30.7%)	34 388 (38.2%)
Missing	2 254 (25.4%)	0 (0%)
Adenoidectomy		
No	4 875 (54.9%)	65 315 (72.5%)
Yes	1 970 (22.5%)	24 804 (27.5%)
Missing	2 031 (22.9)	0 (0%)
Tonsillectomy		
No	4 568 (51.5%)	61 720 (68.5%)
Yes	2 294 (25.8%)	28 399 (31.5%)
Missing	2 014 (22.7%)	0 (0%)
Year of birth		
>1945	3 179 (35.8%)	30 359 (33.7%)
1940-1945	2 146 (24.2%)	21 780 (24.2%)
1935-1940	1 668 (18.8%)	17 768 (19.7%)
1930-1935	1 137 (12.8%)	12 060 (13.4%)
<1930	746 (8.4%)	8 152 (9.0%)
BMI at baseline		
BMI<25	6 935 (78.1%)	73 861 (82.0%)
25<BMI<30	1 515 (17.1%)	13 417 (14.9%)
BMI>30	426 (4.8%)	2 841 (3.2%)
Smoking status at baseline		
Never	4 911 (55.3%)	48 735 (54.1%)
Current	1 497 (16.9%)	13 383 (14.9%)
Former	2 468 (27.8%)	28 001 (31.1%)
Marital status at baseline		
Unmarried	1688 (19.0%)	15 917 (17.7%)
Married	7 188 (81.0%)	74 202 (82.3%)

Education level		
Undergraduate or less	633 (7.1%)	3 097 (3.4%)
Graduate	1 377 (15.5%)	12 056 (13.4%)
Postgraduate or more	6 866 (77.4%)	74 966 (83.2%)
Age at menarche		
12-15 years old	6 802 (76.6)	68 244 (75.7%)
<12 years old	1 721 (19.4%)	18 337 (20.3%)
>15 years old	353 (4.0%)	3 538 (3.9%)
Menopause status at baseline		
Premenopausal	4 858 (54.7%)	46 142 (51.2%)
Postmenopausal	4 018 (45.3%)	43 977 (48.8%)
Nulliparous status		
No	7 350 (82.9%)	79 568 (88.3%)
Yes	1 516 (17.1%)	10 551 (11.7%)
Ever use of oral contraceptives at baseline		
No	4 360 (49.1%)	40 450 (44.9%)
Yes	4 516 (50.9%)	49 669 (55.1%)

Appendix 7: Characteristics of study participants at baseline according to appendectomy status (n = 90 119).

	Appendectomy status	
	Appendectomy (n= 34 388)	No Appendectomy (n= 55 731)
Psoriasis		
No	33 372 (97.0%)	54 314 (97.5%)
Yes	1 016 (3.0%)	1 417 (2.5%)
Adenoidectomy		
No	23 433 (68.1%)	41 882 (75.2%)
Yes	10 955 (31.9%)	13 849 (24.8%)
Tonsillectomy		
No	21 746 (63.2%)	39 974 (71.7%)
Yes	12 642 (36.8%)	15 757 (28.3%)
Year of birth		
>1945	11 184 (32.5%)	19 175 (34.4%)
1940-1945	8 572 (24.9%)	13 208 (23.7%)
1935-1940	7 069 (20.6%)	10 699 (19.2%)
1930-1935	4 563 (13.3%)	7 497 (13.5%)
<1930	3 000 (8.7%)	5 152 (9.2%)
BMI at baseline		
BMI<25	27 588 (80.2%)	46 273 (83.0%)
25<BMI<30	5 538 (16.1%)	7 879 (14.1%)
BMI>30	1 262 (3.7%)	1 579 (2.8%)
Smoking status at baseline		
Never	18 032 (52.4%)	30 703 (55.1%)
Current	5 297 (15.4%)	8 086 (14.5%)
Former	11 059 (32.2%)	16 942 (30.4%)

Marital status at baseline		
Unmarried	6 038 (17.6%)	9 879 (17.7%)
Married	28 350 (82.4%)	45 852 (82.3%)
Education level		
Undergraduate or less	1 160 (3.4%)	1 937 (3.5%)
Graduate	5 287 (15.4%)	6 769 (12.1%)
Postgraduate or more	27 941 (81.3%)	47 025 (84.4%)
Age at menarche		
12-15 years old	25 674 (74.7%)	42 570 (76.4%)
<12 years old	7 374 (21.4%)	10 963 (19.7%)
>15 years old	1 340 (3.9%)	2 198 (3.9%)
Menopause status at baseline		
Premenopausal	17 107 (49.7%)	29 035 (52.1%)
Postmenopausal	17 281 (50.3%)	26 696 (47.9%)
Nulliparous status		
No	30 610 (89.0%)	48 958 (87.8%)
Yes	3 778 (11.0%)	6 773 (12.2%)
Ever use of oral contraceptives at baseline		
No	15 485 (45.0%)	24 965 (44.8%)
Yes	18 903 (55.0%)	30 766 (55.2%)

Appendix 8: Characteristics of study participants at baseline according to adenoidectomy status (N = 90 119)

	Adenoidectomy status	
	Adenoidectomy (n= 28 399)	No Adenoidectomy (n= 61 720)
Psoriasis		
No	24 101 (97.2%)	63 585 (97.4%)
Yes	703 (2.8%)	1 730 (2.6%)
Appendectomy		
No	10 955 (44.2%)	23 433 (35.9%)
Yes	13 849 (55.8%)	41 882 (64.1%)
Tonsillectomy		
No	6 319 (25.5%)	55 401 (84.8%)
Yes	18 485 (74.5%)	9 914 (15.2%)
Year of birth		
>1945	8 845 (35.7%)	21 514 (32.9%)
1940-1945	6 061 (24.4%)	15 719 (24.1%)
1935-1940	4 974 (20.1%)	12 794 (19.6%)
1930-1935	2 972 (12.0%)	9 088 (13.9%)
<1930	1 952 (7.9%)	6 200 (9.5%)
BMI at baseline		
BMI<25	20 338 (82.0%)	53 523 (81.9%)
25<BMI<30	3 661 (14.8%)	9 756 (14.9%)
BMI>30	805 (3.2%)	2 036 (3.1%)
Smoking status at baseline		
Never	12 848 (51.8%)	35 887 (54.9%)
Current	3 754 (15.1%)	9 629 (14.7%)
Former	8 202 (33.1%)	19 799 (30.3%)

Marital status at baseline		
Unmarried	4 584 (18.5%)	11 333 (17.4%)
Married	20 220 (81.5%)	53 982 (82.6%)
Education level		
Undergraduate or less	805 (3.2%)	2 292 (3.5%)
Graduate	2 621 (10.6%)	9 435 (14.4%)
Postgraduate or more	21 378 (86.2%)	53 588 (82.0%)
Age at menarche		
12-15 years old	18 509 (74.6%)	49 735 (76.1%)
<12 years old	5 425 (21.9%)	12 912 (19.8%)
>15 years old	870 (3.5%)	2 668 (4.1%)
Menopause status at baseline		
Premenopausal	13 213 (53.3%)	32 929 (50.4%)
Postmenopausal	11 591 (46.7%)	32 386 (49.6%)
Nulliparous status		
No	21 727 (87.6%)	57 841 (88.6%)
Yes	3 077 (12.4%)	7 474 (11.4%)
Ever use of oral contraceptives at baseline		
No	10 614 (42.8%)	29 836 (45.7%)
Yes	14 190 (57.2%)	35 479 (54.3%)

Appendix 9: Characteristics of study participants at baseline according to tonsillectomy status (N = 90 119).

	Tonsillectomy status	
	Tonsillectomy (n= 28 399)	No Tonsillectomy (n= 61 720)
Psoriasis		
No	27 619 (97.3%)	60 067 (97.3%)
Yes	780 (2.7%)	1 653 (2.7%)
Appendectomy		
No	12 642 (44.5%)	21 746 (35.2%)
Yes	15 757 (55.5%)	39 974 (64.8%)
Adenoidectomy		
No	18 485 (65.1%)	6 319 (10.2%)
Yes	9 914 (34.9%)	55 401 (89.8%)
Year of birth		
>1945	10 118 (35.6%)	20 241 (32.8%)
1940-1945	7 081 (24.9%)	14 699 (23.8%)
1935-1940	5 598 (19.7%)	12 170 (19.7%)
1930-1935	3 376 (11.9%)	8 684 (14.1%)
<1930	2 226 (7.8%)	5 926 (9.6%)
BMI at baseline		
BMI<25	23 024 (81.1%)	50 837 (82.4%)
25<BMI<30	4 388 (15.5%)	9 029 (14.6%)
BMI>30	987 (3.5%)	1 854 (3.0%)
Smoking status at baseline		
Never	14 792 (52.1%)	33 943 (55.0%)
Current	4 333 (15.3%)	9 050 (14.7%)
Former	9 274 (32.7%)	18 727 (30.3%)
Marital status at baseline		
Unmarried	5 201 (18.3%)	10 716 (17.4%)

Married	23 198 (81.7%)	51 004 (82.6%)
Education level		
Undergraduate or less	960 (3.4%)	2 137 (3.5%)
Graduate	3 540 (12.5%)	8 516 (13.8%)
Postgraduate or more	23 899 (84.2%)	51 067 (82.7%)
Age at menarche		
12-15 years old	21 304 (75.0%)	46 940 (76.1%)
<12 years old	6 072 (21.4%)	12 265 (19.9%)
>15 years old	1 023 (3.6%)	2 515 (4.1%)
Menopause status at baseline		
Premenopausal	15 126 (53.3%)	31 016 (50.3%)
Postmenopausal	13 273 (46.7%)	30 704 (49.7%)
Nulliparous status		
No	25 010 (88.1%)	54 558 (88.4%)
Yes	3 389 (11.9%)	7 162 (11.6%)
Ever use of oral contraceptives at baseline		
No	12 223 (43.0%)	28 227 (45.7%)
Yes	16 176 (57.0%)	33 493 (54.3%)

Appendix 10: Hazard ratios for the associations between age at appendectomy and psoriasis risk (N = 90 119).

Appendectomy Time-intervals (years)	No psoriasis cases (n=87 686)	Psoriasis cases (n=2 433)	Hazard Ratios (95% CI)	
			Univariate model ^a	p-value
No appendectomy	54 314	1 417	1.00 (Reference)	
<10	5 583	200	1.33 (0.92-1.94)	0.12
11-14	5 320	174	1.23 (0.84-1.80)	0.27
15-19	7 327	211	1.11 (0.77-1.61)	0.56
20-29	8 918	269	1.18 (0.83-1.27)	0.36
30-39	3 582	94	1.05 (0.70-1.57)	0.78
>40	1 377	36	1.12 (0.69-1.80)	0.63
Appendectomy cases without diagnostic date	1 265	32	Not computable	Not computable

a) Model adjusted for: birth cohort

Appendix 11: Hazard ratios for the associations between age at adenoidectomy and psoriasis risk (N = 90 119).

Adenoidectomy Time-intervals (years)	No psoriasis cases (n=87 686)	Psoriasis cases (n=2 433)	Hazard Ratios (95% CI)	
			Univariate model^a	p-value
No adenoidectomy	65 520	1 784	1.00 (Reference)	
<10	19 790	587	1.02 (0.77-1.35)	0.85
11-14	1 823	51	1.01 (0.69-1.48)	0.93
15-19	329	6	0.65 (0.28-1.53)	0.33
20-29	151	3	0.75 (0.23-2.42)	0.64
30-39	40	1	0.95 (0.13-6.91)	0.96
>40	9	0	Not computable	Not computable
Adenoidectomy cases without diagnostic date	24	1	1.57 (0.21-11.37)	0.65

a) Model adjusted for: birth cohort

Appendix 12: Hazard ratios for the associations between age at tonsillectomy and psoriasis risk (n = 90 119).

Tonsillectomy Time-intervals (years)	No psoriasis cases (n=87 686)	Psoriasis cases (n=2 433)	Hazard Ratios (95% CI)	
			Univariate model ^a	p-value
No tonsillectomy	61 523	1 689	1.00 (Reference)	
<10	18 718	542	1.09 (0.78-1.53)	0.60
11-14	2 349	65	1.08 (0.71-1.62)	0.70
15-19	1 312	40	1.18 (0.75-1.85)	0.46
20-29	2 753	76	1.07 (0.72-1.59)	0.71
30-39	822	18	0.87 (0.49-1.53)	0.63
>40	168	3	0.76 (0.23-2.47)	0.65
Tonsillectomy cases without diagnostic date	41	0	Not computable	Not computable

a) Model adjusted for: birth cohort

b) Model adjusted for: birth cohort, BMI, smoking status, education level, marital status at baseline, hypertension, depression, diabetes, age at menarche, menopause status, nulliparous status, ever use of contraceptive pill.

Appendix 13: Hazard ratio for the associations between appendectomy as time-varying variable and psoriasis risk (N = 90 119).

Exposure	No psoriasis cases (n=87 686)	Psoriasis cases (n=2 433)	Hazard Ratios (95% CI)			
			Univariate model ^a	p-value	Multivariable model ^b	p-value
Appendectomy						
No	54 352	1410	1.00 [Reference]		1.00 [Reference]	
Yes	33 334	1023	1.16 (1.07-1.26)	0.002	1.13 (1.04-1.23)	0.002

a) Model adjusted for: birth cohort

b) Model adjusted for: birth cohort, BMI, smoking status, education level, marital status at baseline, hypertension, depression, diabetes, age at menarche, menopause status, nulliparous status, ever use of contraceptive pill.

Appendix 14: Hazard Ratios of psoriasis risk according to MALTectomy history further adjusted for alcohol consumption, (N = 70 350).

Exposure	No psoriasis cases (n=68 340)	Psoriasis cases (n=2 010)	Hazard Ratios (95% CI)	
			Multivariable model ^a	p-value
Appendectomy				
No	42 771	1 177	1.00 [Reference]	
Yes	25 569	833	1.16 (1.06-1.27)	<0.001
Adenoidectomy				
No	49 397	1 413	1.00 [Reference]	
Yes	18 943	597	1.07 (0.97-1.18)	0.15
Tonsillectomy				
No	46 754	1 354	1.00 [Reference]	
Yes	21 586	656	1.01 (0.92-1.11)	0.71

a) Model adjusted for: birth cohort, BMI, smoking status, education level, marital status at baseline, hypertension, depression, diabetes, age at menarche, menopause status, nulliparous status, ever use of contraceptive pill.

Appendix 15: Logistic analyses of overall psoriasis risk according to MALTectomy (N = 96 458).

Exposure	Non- cases of psoriasis (n=90 428)	Psoriasis cases (n=6 030)	Odds Ratios (95% CI)			
			Univariate model ^a	p-value	Multivariable model ^b	p-value
Appendectomy						
No	55 984	3 615	1.00 [Reference]		1.00 [Reference]	
Yes	34 444	2 415	1.08 (1.02-1.14)	<0.01	1.07 (1.01-1.13)	0.01
Adenoidectomy						
No	65 601	4 343	1.00 [Reference]		1.00 [Reference]	
Yes	24 827	1 687	1.01 (0.96-1.08)	0.51	1.00 (0.94-1.06)	0.91
Tonsillectomy						
No	61 938	4 117	1.00 [Reference]		1.00 [Reference]	
Yes	28 490	1 913	1.00 (0.94-1.06)	0.93	0.98 (0.93-1.04)	0.68

a) Model adjusted for: birth cohort

b) Model adjusted for: birth cohort, BMI, smoking status, education level, marital status at baseline, hypertension, depression, diabetes, age at menarche, menopause status, nulliparous status, ever use of contraceptive pill.

Appendix 16: Characteristics of study participants at baseline according to according to childhood exposures (n = 72 154).

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=8 865)	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%)	8 667 (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	46 638	13 273	24 658	35 253	52 645	7 266	20 604	39 307	46 480	13 431

	(83.0%)		(83.5%)	(81.6%)		(83.7%)	(82.6%)		(83.2%)	(82.0%)		(82.5%)	(83.3%)		(83.6%)	(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%)
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%)

Appendix 17: Logistic analyses of overall psoriasis risk according to rural environment during childhood factors, (n = 75 218).

Exposure	Non-cases (%)	Psoriasis (%)	Odds Ratios (95% CI)			
			Univariate model ^a	p-value	Multivariable model ^b	p-value
Life in a farm at least 3 months during childhood						
No	54 367 (77.5)	3 892 (77.7)	1.00 (Reference)		1.00 (Reference)	
Yes	15 847 (22.5)	1 112 (22.3)	0.98 (0.91-1.05)	0.55	0.99 (0.93-1.07)	0.96
Pets during childhood						
No	28 690 (40.9)	2 050 (40.9)	1.00 (Reference)		1.00 (Reference)	
Yes	41 524 (59.1)	2 954 (59.1)	0.99 (0.93-1.05)	0.80	0.99 (0.94-1.05)	0.93
Farming parents						
No	61 547 (87.6)	4 455 (89.0)	1.00 (Reference)		1.00 (Reference)	
Yes	8 667 (12.4)	549 (11.0)	0.87 (0.79-0.95)	0.003	0.91 (0.83-1.00)	0.06
Birth town size						
5000 inhabitants or more (urban)	45 851 (65.3)	3 407 (68.0)	1.00 (Reference)		1.00 (Reference)	
Less than 5000 inhabitants (rural)	24 363 (34.7)	1 597 (32.0)	0.88 (0.83-0.94)	<0.001	0.91 (0.85-0.97)	0.005
Living in contact with farm animals at least 3 months during childhood						
No	54 112 (77.0)	3 876 (77.4)	1.00 (Reference)		1.00 (Reference)	
Yes	16 102	1 128	0.97	0.52	1.00	0.90

	(23.0)	(22.6)	(0.91-1.04)		(0.93-1.01)	
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a) Model adjusted for: birth cohort

b) Model adjusted for: birth cohort, BMI, smoking status, education level, marital status at baseline, hypertension, depression, diabetes, age at menarche, menopause status, nulliparous status, ever use of contraceptive pill.

Appendix 18: Associations between psoriasis risk and rural environment during childhood factors stratified on smoking status (N = 72 154).

NON SMOKERS (n=39 227; Psoriasis cases = 944)						
Exposure	Psoriasis cases (%)	Person/years (n= 993 572)	Hazard Ratios (95% CI)			
			Univariate model ^a	p-value	Multivariable model ^b	p-value
Life in a farm at least 3 months during childhood						
No	739 (78.2)	750 413	1.00 (Reference)		1.00 (Reference)	
Yes	205 (21.8)	243 159	0.85 (0.72-0.99)	0.04	0.86 (0.74-1.01)	0.07
Pets during childhood						
No	371 (39.3)	399 113	1.00 (Reference)		1.00 (Reference)	
Yes	573 (60.7)	594 459	1.03 (0.90-1.17)	0.65	1.04 (0.91-1.18)	0.54
Farming parents						
No	837 (88.6)	849 096	1.00 (Reference)		1.00 (Reference)	
Yes	107 (11.4)	144 476	0.74 (0.61-0.91)	0.004	0.77 (0.63-0.95)	0.01
Birth town size						
5000 inhabitants or more (urban)	628 (66.5)	625 592	1.00 (Reference)		1.00 (Reference)	
Less than 5000 inhabitants (rural)	316 (33.5)	367 980	0.85 (0.74-0.97)	0.02	0.88 (0.77-1.01)	0.07
Living in contact with farm animals at least 3 months during childhood						
No	737 (78.1)	745 247	1.00 (Reference)		1.00 (Reference)	
Yes	207 (21.9)	248 325	0.83 (0.71-0.97)	0.02	0.85 (0.72-0.99)	0.04
CURRENT AND FORMER SMOKERS (n=32 927; Psoriasis cases = 1 023)						
Exposure	Psoriasis cases (%)	Person/years (n=838 681)	Univariate model ^a	p-value	Multivariable model ^b	p-value
Life in a farm at least 3 months during childhood						
No	800 (78.2)	668 718	1.00 (Reference)		1.00 (Reference)	

Yes	223 (21.8)	169 963	1.09 (0.94-1.26)	0.25	1.09 (0.94-1.27)	0.23
Pets during childhood						
No	427 (41.7)	348 278	1.00 (Reference)		1.00 (Reference)	
Yes	596 (58.2)	490 403	0.98 (0.87-1.11)	0.81	0.98 (0.86-1.11)	0.06
Farming parents						
No	932 (91.1)	756 558	1.00 (Reference)		1.00 (Reference)	
Yes	91 (8.9)	82 123	0.88 (0.71-1.09)	0.27	0.90 (0.72-1.12)	0.35
Birth town size						
5000 inhabitants or more (urban)	731 (71.4)	573 137	1.00 (Reference)		1.00 (Reference)	
Less than 5000 inhabitants (rural)	292 (28.6)	265 544	0.86 (0.75-0.98)	0.03	0.87 (0.76-0.99)	0.04
Living in contact with farm animals at least 3 months during childhood						
No	801 (78.2)	666 748	1.00 (Reference)		1.00 (Reference)	
Yes	222 (21.8)	171 933	1.06 (0.92-1.24)	0.77	1.07 (0.92-1.24)	0.37

a) Model adjusted for: birth cohort

b) Model adjusted for: birth cohort, BMI, smoking status, education level, marital status at baseline, hypertension, depression, diabetes, age at menarche, menopause status, nulliparous status, ever use of contraceptive pill.

Appendix 19: Associations between psoriasis risk and rural environment during childhood factors stratified on BMI (N = 72 154).

NORMAL WEIGHT-BMI<25 kg/m² (n=59 911; Psoriasis cases = 1 563)						
Exposure	Psoriasis	Person/years (n= 1 533 741)	Hazard Ratios (95% CI)			
			Univariate model^a	p-value	Multivariable model^b	p-value
Life in a farm at least 3 months during childhood						
No	1 229 (78.6)	1 193 582	1.00 (Reference)		1.00 (Reference)	
Yes	334 (21.4)	340 159	1.02 (0.92-1.13)	0.68	0.97 (0.86-1.09)	0.21
Pets during childhood						
No	632 (40.4)	630 119	1.00 (Reference)		1.00 (Reference)	
Yes	931 (59.6)	903 622	0.94 (0.84-1.07)	0.75	1.03 (0.93-1.14)	0.50

Farming parents						
No	1 409 (90.1)	1 346 338	1.00 (Reference)		1.00 (Reference)	
Yes	154 (9.9)	187 403	0.77 (0.65-0.92)	0.003	0.82 (0.69-0.97)	0.02
Birth town size						
5000 inhabitants or more (urban)	1 091 (69.8)	1 006 139	1.00 (Reference)		1.00 (Reference)	
Less than 5000 in habitants (rural)	472 (30.2)	527 602	0.82 (0.74-0.92)	0.0006	0.85 (0.76-0.94)	0.003
Living in contact with farm animals at least 3 months during childhood						
No	1 232 (78.8)	1 189 036	1.00 (Reference)		1.00 (Reference)	
Yes	331 (21.2)	344 705	0.92 (0.81-1.04)	0.18	0.94 (0.83-1.06)	0.36
OVERWEIGHT-BMI>25 kg/m² (n=12 243; Psoriasis cases = 404)						
Exposure	Psoriasis	Person/years (n= 298 512)	Univariate model^a	p-value	Multivariable model^b	p-value
Life in a farm at least 3 months during childhood						
No	310 (76.7)	225 550	1.00 (Reference)		1.00 (Reference)	
Yes	94 (23.3)	72 962	0.95 (0.75-1.20)	0.69	0.99 (0.78-1.25)	0.95
Pets during childhood						
No	166 (41.1)	117 273	1.00 (Reference)		1.00 (Reference)	
Yes	238 (58.9)	181 239	0.91 (0.75-1.11)	0.39	0.92 (0.76-1.13)	0.46
Farming parents						
No	360 (89.1)	259 318	1.00 (Reference)		1.00 (Reference)	
Yes	44 (10.9)	39 194	0.81 (0.59-1.10)	0.18	0.87 (0.63-1.20)	0.40
Birth town size						
5000 inhabitants or more (urban)	268 (66.3)	192 590	1.00 (Reference)		1.00 (Reference)	
Less than 5000 in habitants (rural)	136 (33.7)	105 922	0.93 (0.76-1.15)	0.53	0.98 (0.79-1.21)	0.86
Living in contact with farm animals at least 3 months during childhood						
No	306 (75.7)	222 959	1.00 (Reference)		1.00 (Reference)	
Yes	98 (24.3)	75 553	0.96 (0.76-1.20)	0.74	1.00 (0.80-1.26)	0.96

a) Model adjusted for: birth cohort

b) Model adjusted for: birth cohort, BMI, smoking status, education level, marital status at baseline, hypertension, depression, diabetes, age at menarche, menopause status, nulliparous status, ever use of contraceptive pill.

Appendix 20: Characteristics of study participants at baseline according to skin phototypes (n = 83 896).

Exposure	ALL (N=83 896)	ALBINO/WHITE (n=996)	MEDIUM (n=48 267)	BROWN (n=33 272)	BLACK (n=1 361)
Year at birth					
<1930	6 664 (7.9%)	51 (5.1%)	3 651 (7.6%)	2 812 (8.5%)	150 (11.0%)
1930-1935	10 901 (13.0%)	87 (8.7%)	6 048 (12.5%)	4 577 (13.8%)	189 (13.9%)
1935-1940	15 923 (19.0%)	163 (16.4%)	8 968 (18.6%)	6 513 (19.6%)	279 (20.5%)
1940-1945	20 155 (24.0%)	268 (26.9%)	11 588 (24.0%)	7 964 (23.9%)	335 (24.6%)
>1945	30 253 (36.1%)	427 (42.9%)	18 012 (37.3%)	11 406 (34.3%)	408 (30.0%)
Body mass index (kg/m²)					
<25	13 639 (78.1%)	68 765 (82.0%)	748 (75.1%)	39 259 (81.3%)	27 657 (83.1%)
25-30	3 069 (17.6%)	188 (18.9%)	7 426 (15.4%)	4 651 (14.0%)	207 (15.2%)
>30	754 (4.3%)	60 (6.0%)	1 582 (3.3%)	964 (2.9%)	53 (3.9%)
Smoking status					
Never	10 027 (57.4%)	487 (48.9%)	26 315 (54.5%)	17 851 (53.7%)	781 (57.4%)
Current	2 247 (12.9%)	341 (34.2%)	15 205 (31.5%)	10 180 (30.6%)	369 (27.1%)
Former	5 188 (29.7%)	168 (16.9%)	6 747 (14.0%)	5 241 (15.8%)	211 (15.5%)
Marital status					
Not married	2 926 (16.8%)	214 (21.5%)	8 504 (17.6%)	6 007 (18.1%)	252 (18.5%)
Married	14 536 (83.2%)	782 (78.5%)	39 763 (82.4%)	27 265 (81.9%)	1 109 (81.5%)
Education level					
Undergraduate or less	595 (3.4%)	2 816 (3.4%)	35 (3.5%)	1 590 (3.3%)	1 150 (3.5%)
Graduate	2 732 (15.6%)	123 (12.3%)	6 488 (13.4%)	4 415 (13.3%)	251 (18.4%)
Postgraduate or more	14 135 (80.9%)	838 (84.1%)	40 189 (83.3%)	27 707 (83.3%)	1 069 (78.5%)
Hypertension					
No	5 342 (30.6%)	697 (70.0%)	35 165 (72.9%)	24 471 (73.5%)	1 000 (73.5%)
Yes	12 120 (69.4%)	299 (30.0%)	13 102 (27.1%)	8 801 (26.5%)	361 (26.5%)
Depression					

No	15 391 (88.1%)	839 (84.2%)	42 101 (87.2%)	29 371 (88.3%)	1 202 (88.3%)
Yes	2 071 (11.9%)	157 (15.8%)	6 166 (12.8%)	3 901 (11.7%)	159 (11.7%)
Type 2 diabetes					
No	17 305 (99.1%)	983 (98.7%)	47 867 (99.2%)	32 997 (99.2%)	1 340 (98.5%)
Yes	157 (0.9%)	13 (1.3%)	400 (0.8%)	275 (0.8%)	21 (1.5%)
Age at menarche					
12-15 years old	63529 (75.7%)	715 (71.8%)	1013 (74.4%)	25095 (75.4%)	36706 (76.0%)
<12 years old	17108 (20.4%)	234 (23.5%)	291 (21.4%)	6861 (20.6%)	9722 (20.1%)
>15 years old	3259 (3.9%)	47 (4.7%)	57 (4.2%)	1316 (4.0%)	1839 (3.8%)
Menopausal status					
Premenopausal	9579 (54.9%)	591 (59.3%)	25558 (53.0%)	16405 (49.3%)	623 (45.8%)
Postmenopausal	7883 (45.1%)	405 (40.7%)	22709 (47.0%)	16867 (50.7%)	738 (54.2%)
Nulliparous					
No	74032 (88.2%)	848 (85.1%)	1219 (89.6%)	29509 (88.7%)	42456 (88.0%)
Yes	9864 (11.8%)	148 (14.9%)	142 (10.4%)	3763 (11.3%)	5811 (12.0%)
Ever use of oral contraceptives					
No	8 436 (48.3%)	441 (44.3%)	21 439 (44.4%)	15 167 (45.6%)	665 (48.9%)
Yes	9 026 (51.7%)	555 (55.7%)	26 828 (55.6%)	18 105 (54.4%)	696 (51.1%)

Appendix 21: Characteristics of study participants at baseline according to hair color (n = 83 896).

Exposure	ALL (N=83896)	ALBINO/BLO ND (n=8436)	RED (n=1452)	BROWN (n=69873)	BLACK (n=4135)
Year at birth					

<1930	6 664 (7.9%)	1 079 (12.8%)	192 (13.2%)	9 126 (13.1%)	504 (12.2%)
1930-1935	10 901 (13.0%)	1 079 (12.8%)	192 (13.2%)	9 126 (13.1%)	504 (12.2%)
1935-1940	15 923 (19.0%)	1 542 (18.3%)	261 (18.0%)	13 367 (19.1%)	753 (18.2%)
1940-1945	20 155 (24.0%)	2 034 (24.1%)	377 (26.0%)	16 753 (24.0%)	991 (24.0%)
>1945	30 253 (36.1%)	3 086 (36.6%)	536 (36.9%)	25 059 (35.9%)	1 572 (38.0%)
Body mass index (kg/m²)					
<25	13 639 (78.1%)	6 918 (82.0%)	1 175 (80.9%)	57 302 (82.0%)	3 370 (81.5%)
25-30	3 069 (17.6%)	1 232 (14.6%)	220 (15.2%)	10 397 (14.9%)	623 (15.1%)
>30	754 (4.3%)	286 (3.4%)	57 (3.9%)	2 174 (3.1%)	142 (3.4%)
Smoking status					
Never	10 027 (57.4%)	4 414 (52.3%)	738 (50.8%)	38 008 (54.4%)	2 274 (55.0%)
Current	2 247 (12.9%)	1 365 (16.2%)	244 (16.8%)	10 135 (14.5%)	623 (15.1%)
Former	5 188 (29.7%)	2 657 (31.5%)	470 (32.4%)	21 730 (31.1%)	1 238 (29.9%)
Marital status					
Not married	2 926 (16.8%)	1 587 (18.8%)	292 (20.1%)	12 397 (17.7%)	701 (17.0%)
Married	14 536 (83.2%)	6 849 (81.2%)	1 160 (79.9%)	57 476 (82.3%)	3 434 (83.0%)
Education level					
Undergraduate or less	595 (3.4%)	284 (3.4%)	48 (3.3%)	2 356 (3.4%)	128 (3.1%)
Graduate	2 732 (15.6%)	1 082 (12.8%)	166 (11.4%)	9 389 (13.4%)	640 (15.5%)
Postgraduate or more	14 135 (80.9%)	7 070 (83.8%)	1 238 (85.3%)	58 128 (83.2%)	3 367 (81.4%)
Hypertension					
No	5 342 (30.6%)	6 163 (73.1%)	1 053 (72.5%)	51 078 (73.1%)	3 039 (73.5%)
Yes	12 120 (69.4%)	2 273 (26.9%)	399 (27.5%)	18 795 (26.9%)	1 096 (26.5%)
Depression					
No	15 391 (88.1%)	7 353 (87.2%)	1 273 (87.7%)	61 209 (87.6%)	3 678 (88.9%)
Yes	2 071 (11.9%)	1 083 (12.8%)	179 (12.3%)	8 664 (12.4%)	457 (11.1%)
Type 2 diabetes					
No	17 305 (99.1%)	8 360 (99.1%)	1 438 (99.0%)	69 304 (99.2%)	4 085 (98.8%)
Yes	157 (0.9%)	76 (0.9%)	14 (1.0%)	569 (0.8%)	50 (1.2%)

Age at menarche					
12-15 years old	63 529 (75.7%)	6 493 (77.0%)	3 080 (74.5%)	52 863 (75.7%)	1 093 (75.3%)
<12 years old	17 108 (20.4%)	1 588 (18.8%)	925 (22.4%)	14 291 (20.5%)	304 (20.9%)
>15 years old	3 259 (3.9%)	355 (4.2%)	130 (3.1%)	2 719 (3.9%)	55 (3.8%)
Menopausal status					
Premenopausal	9 579 (54.9%)	4 367 (51.8%)	747 (51.4%)	35 885 (51.4%)	2 178 (52.7%)
Postmenopausal	7 883 (45.1%)	4 069 (48.2%)	705 (48.6%)	33 988 (48.6%)	1 957 (47.3%)
Nulliparous					
No	74032 (88.2%)	7443 (88.2%)	3662 (88.6%)	61693 (88.3%)	1234 (85.0%)
Yes	9864 (11.8%)	993 (11.8%)	473 (11.4%)	8180 (11.7%)	218 (15.0%)
Ever use of oral contraceptives					
No	8 436 (48.3%)	3 672 (43.5%)	631 (43.5%)	31 494 (45.1%)	1 915 (46.3%)
Yes	9 026 (51.7%)	4 764 (56.5%)	821 (56.5%)	38 379 (54.9%)	2 220 (53.7%)

Appendix 22: Characteristics of study participants at baseline according to mean annual daily ambient total UV level (kJ/m²) (n = 83 896).

Exposure	All (N=83 896)	1st QUARTILE (n=8 436)	2nd QUARTILE (n=1 452)	3rd QUARTILE (n=69 873)	4th QUARTILE (n=4 135)
Year at birth					
<1930	6 664 (7.9%)	6 664 (7.9%)	1 129 (7.2%)	2 225 (7.8%)	1 520 (8.2%)
1930-1935	10 901 (13.0%)	10 901 (13.0%)	1 811 (11.5%)	3 631 (12.7%)	2 451 (13.2%)
1935-1940	15 923 (19.0%)	15 923 (19.0%)	2 864 (18.2%)	5 389 (18.8%)	3 450 (18.6%)
1940-1945	20 155 (24.0%)	20 155 (24.0%)	3 663 (23.3%)	6 785 (23.7%)	4 449 (24.0%)
>1945	30 253 (36.1%)	30 253 (36.1%)	6 259 (39.8%)	10 610 (37.0%)	6 666 (36.0%)
Body mass index (kg/m²)					
<25	68 765 (82.0%)	12 342 (78.5%)	23 583 (82.3%)	15 355 (82.8%)	17 485 (83.3%)
25-30	12 472 (14.9%)	2 739 (17.4%)	4 137 (14.4%)	2 655 (14.3%)	2 941 (14.0%)
>30	2 659 (3.2%)	645 (4.1%)	920 (3.2%)	526 (2.8%)	568 (2.7%)

Smoking status					
Never	45 434 (54.2%)	9 138 (58.1%)	14 513 (50.7%)	10 306 (55.6%)	11 477 (54.7%)
Current	12 367 (14.7%)	1 939 (12.3%)	4 751 (16.6%)	2 504 (13.5%)	3 173 (15.1%)
Former	26 095 (31.1%)	4 649 (29.6%)	9 376 (32.7%)	5 726 (30.9%)	6 344 (30.2%)
Marital status					
Not married	14 977 (17.9%)	2552 (16.2%)	5658 (19.8%)	3085 (16.6%)	3682 (17.5%)
Married	68 919 (82.1%)	13174 (83.8%)	22982 (80.2%)	15451 (83.4%)	17312 (82.5%)
Education level					
Undergraduate or less	2 816 (3.4%)	530 (3.4%)	950 (3.3%)	574 (3.1%)	762 (3.6%)
Graduate	11 277 (13.4%)	2 446 (15.6%)	3 486 (12.2%)	2 600 (14.0%)	2 745 (13.1%)
Postgraduate or more	69 803 (83.2%)	12 750 (81.1%)	24 204 (84.5%)	15 362 (82.9%)	17 487 (83.3%)
Hypertension					
No	61 333 (73.1%)	10 901 (69.3%)	21 071 (73.6%)	13 515 (72.9%)	15 846 (75.5%)
Yes	22 563 (26.9%)	4 825 (30.7%)	7 569 (26.4%)	5 021 (27.1%)	5 148 (24.5%)
Depression					
No	73 513 (87.6%)	13 855 (88.1%)	25 092 (87.6%)	16 119 (87.0%)	18 447 (87.9%)
Yes	10 383 (12.4%)	1 871 (11.9%)	3 548 (12.4%)	2 417 (13.0%)	2 547 (12.1%)
Type 2 diabetes					
No	83 187 (99.2%)	15 590 (99.1%)	28 388 (99.1%)	18 380 (99.2%)	20 829 (99.2%)
Yes	709 (0.8%)	136 (0.9%)	252 (0.9%)	156 (0.8%)	165 (0.8%)
Age at menarche					
12-15 years old	63 529 (75.7%)	11 957 (76.0%)	21 708 (75.8%)	14 176 (76.5%)	15 688 (74.7%)
<12 years old	17 108 (20.4%)	3 079 (19.6%)	5 809 (20.3%)	3 708 (20.0%)	4 512 (21.5%)
>15 years old	3 259 (3.9%)	690 (4.4%)	1 123 (3.9%)	652 (3.5%)	794 (3.8%)
Menopausal status					
Premenopausal	43 177 (51.5%)	8 575 (54.5%)	14 995 (52.4%)	9 550 (51.5%)	10 057 (47.9%)
Postmenopausal	40 719 (48.5%)	7 151 (45.5%)	13 645 (47.6%)	8 986 (48.5%)	10 937 (52.1%)
Nulliparous					
No	74 032 (88.2%)	14 052 (89.4%)	24 843 (86.7%)	16 490 (89.0%)	18 647 (88.8%)

Yes	9 864 (11.8%)	1 674 (10.6%)	3 797 (13.3%)	2 046 (11.0%)	2 347 (11.2%)
Ever use of oral contraceptives					
No	37 712 (45.0%)	7 652 (48.7%)	12 006 (41.9%)	8 209 (44.3%)	9 845 (46.9%)
Yes	46 184 (55.0%)	8 074 (51.3%)	16 634 (58.1%)	10 327 (55.7%)	11 149 (53.1%)

Appendix 23: Characteristics of study participants at baseline according to mean fall/winter daily ambient total UV level (kJ/m²) (N = 83 896).

Exposure	ALL (N=83 896)	1st QUARTILE (n=17 462)	2nd QUARTILE (n=26 532)	3rd QUARTILE (n=19 263)	4th QUARTILE (n=20 639)
Year at birth					
<1930	10 901 (13.0%)	3 471 (13.1%)	2 454 (12.7%)	3 044 (14.7%)	3 471 (13.1%)
1930-1935	15 923 (19.0%)	4 948 (18.6%)	3 606 (18.7%)	4 158 (20.1%)	4 948 (18.6%)
1935-1940	20 155 (24.0%)	6 239 (23.5%)	4 601 (23.9%)	5 185 (25.1%)	6 239 (23.5%)
1940-1945	30 253 (36.1%)	6 987 (40.0%)	9 735 (36.7%)	7 092 (36.8%)	6 439 (31.2%)
>1945	10 901 (13.0%)	3 471 (13.1%)	2 454 (12.7%)	3 044 (14.7%)	3 471 (13.1%)
Body mass index (kg/m²)					
<25	68 765 (82.0%)	13 639 (78.1%)	21 982 (82.9%)	15 972 (82.9%)	17 172 (83.2%)
25-30	12 472 (14.9%)	3 069 (17.6%)	3 755 (14.2%)	2 746 (14.3%)	2 902 (14.1%)
>30	2 659 (3.2%)	754 (4.3%)	795 (3.0%)	545 (2.8%)	565 (2.7%)
Smoking status					
Never	45 434 (54.2%)	10 027 (57.4%)	13 432 (50.6%)	10 724 (55.7%)	11 251 (54.5%)
Current	12 367 (14.7%)	2 247 (12.9%)	4 399 (16.6%)	2 570 (13.3%)	3 151 (15.3%)
Former	26 095 (31.1%)	5 188 (29.7%)	8 701 (32.8%)	5 969 (31.0%)	6 237 (30.2%)
Marital status					

Not married	14 977 (17.9%)	2 926 (16.8%)	5 226 (19.7%)	3 194 (16.6%)	3 631 (17.6%)
Married	68 919 (82.1%)	14 536 (83.2%)	21 306 (80.3%)	16 069 (83.4%)	17 008 (82.4%)
Education level					
Undergraduate or less	2 816 (3.4%)	595 (3.4%)	868 (3.3%)	604 (3.1%)	749 (3.6%)
Graduate	11 277 (13.4%)	2 732 (15.6%)	3 130 (11.8%)	2 647 (13.7%)	2 768 (13.4%)
Postgraduate or more	69 803 (83.2%)	14 135 (80.9%)	22 534 (84.9%)	16 012 (83.1%)	17 122 (83.0%)
Hypertension					
No	61 333 (73.1%)	5 342 (30.6%)	6 978 (26.3%)	5 204 (27.0%)	5 039 (24.4%)
Yes	22 563 (26.9%)	12 120 (69.4%)	19 554 (73.7%)	14 059 (73.0%)	15 600 (75.6%)
Depression					
No	73 513 (87.6%)	15 391 (88.1%)	23 230 (87.6%)	16 799 (87.2%)	18 093 (87.7%)
Yes	10 383 (12.4%)	2 071 (11.9%)	3 302 (12.4%)	2 464 (12.8%)	2 546 (12.3%)
Type 2 diabetes					
No	83 187 (99.2%)	17 305 (99.1%)	26 302 (99.1%)	19 113 (99.2%)	20 467 (99.2%)
Yes	709 (0.8%)	157 (0.9%)	230 (0.9%)	150 (0.8%)	172 (0.8%)
Age at menarche					
12-15 years old	63 529 (75.7%)	13 200 (75.6%)	20 190 (76.1%)	14 771 (76.7%)	15 368 (74.5%)
<12 years old	17 108 (20.4%)	3 551 (20.3%)	5 249 (19.8%)	3 787 (19.7%)	4 521 (21.9%)
>15 years old	3 259 (3.9%)	711 (4.1%)	1 093 (4.1%)	705 (3.7%)	750 (3.6%)
Menopausal status					
Premenopausal	43 177 (51.5%)	9 579 (54.9%)	13 765 (51.9%)	10 112 (52.5%)	9 721 (47.1%)
Postmenopausal	40 719 (48.5%)	7 883 (45.1%)	12 767 (48.1%)	9 151 (47.5%)	10 918 (52.9%)
Nulliparous					
No	74 032 (88.2%)	15 519 (88.9%)	23 036 (86.8%)	17 125 (88.9%)	18 352 (88.9%)
Yes	9 864 (11.8%)	1 943 (11.1%)	3 496 (13.2%)	2 138 (11.1%)	2 287 (11.1%)
Ever use of oral contraceptives					
No	37 712 (45.0%)	8 436 (48.3%)	11 101 (41.8%)	8 446 (43.8%)	9 729 (47.1%)
Yes	46 184 (55.0%)	9 026 (51.7%)	15 431 (58.2%)	10 817 (56.2%)	10 910 (52.9%)

Appendix 24: Characteristics of study participants at baseline according to mean spring/summer daily ambient total UV level (kJ/m²) (N= 83 896).

Exposure	ALL (N=83896)	1st QUARTILE (n=17252)	2nd QUARTILE (n=1452)	3rd QUARTILE (n=28727)	4th QUARTILE (n=21 438)
Year at birth					
<1930	6 664 (7.9%)	1 271 (7.4%)	2 208 (7.7%)	1 371 (8.3%)	1 814 (8.5%)
1930-1935	10 901(13.0%)	2 038 (11.8%)	3 565 (12.4%)	2 245 (13.6%)	3 053 (14.2%)
1935-1940	15 923 (19.0%)	3 150 (18.3%)	5 361 (18.7%)	3 100 (18.8%)	4 312 (20.1%)
1940-1945	20 155 (24.0%)	4 013 (23.3%)	6 845 (23.8%)	3 934 (23.9%)	5 363 (25.0%)
>1945	30 253 (36.1%)	6 780 (39.3%)	10 748 (37.4%)	5 829 (35.4%)	6 896 (32.2%)
Body mass index (kg/m²)					
<25	13 639 (78.1%)	13 658 (79.2%)	23 632 (82.3%)	13 636 (82.7%)	17 839 (83.2%)
25-30	3 069 (17.6%)	2 920 (16.9%)	4 164 (14.5%)	2 371 (14.4%)	3 017 (14.1%)
>30	754 (4.3%)	674 (3.9%)	931 (3.2%)	472 (2.9%)	582 (2.7%)
Smoking status					
Never	10 027 (57.4%)	9 937 (57.6%)	14 530 (50.6%)	9 190 (55.8%)	11 777 (54.9%)
Current	2 247 (12.9%)	2 199 (12.7%)	4 747 (16.5%)	2 199 (13.3%)	3 222 (15.0%)
Former	5 188 (29.7%)	5 116 (29.7%)	9 450 (32.9%)	5 090 (30.9%)	6 439 (30.0%)
Marital status					
Not married	2 926 (16.8%)	2 864 (16.6%)	5 633 (19.6%)	2 760 (16.7%)	3 720 (17.4%)
Married	14 536 (83.2%)	14 388 (83.4%)	23 094 (80.4%)	13 719 (83.3%)	17 718 (82.6%)
Education level					
Undergraduate or less	595 (3.4%)	604 (3.5%)	943 (3.3%)	500 (3.0%)	769 (3.6%)
Graduate	2 732 (15.6%)	2 633 (15.3%)	3 561 (12.4%)	2 252 (13.7%)	2 831 (13.2%)
Postgraduate or more	14 135 (80.9%)	14 015 (81.2%)	24 223 (84.3%)	13 727 (83.3%)	17 838 (83.2%)
Hypertension					
No	5 342 (30.6%)	12 006 (69.6%)	21 205 (73.8%)	11 975 (72.7%)	16 147 (75.3%)
Yes	12 120 (69.4%)	5 246 (30.4%)	7 522 (26.2%)	4 504 (27.3%)	5 291 (24.7%)
Depression					

No	15 391 (88.1%)	15 186 (88.0%)	25 190 (87.7%)	14 316 (86.9%)	18 821 (87.8%)
Yes	2 071 (11.9%)	2 066 (12.0%)	3 537 (12.3%)	2 163 (13.1%)	2 617 (12.2%)
Type 2 diabetes					
No	17 305 (99.1%)	17 097 (99.1%)	28 483 (99.2%)	16 337 (99.1%)	21 270 (99.2%)
Yes	157 (0.9%)	155 (0.9%)	244 (0.8%)	142 (0.9%)	168 (0.8%)
Age at menarche					
12-15 years old	63 529 (75.7%)	13 073 (75.8%)	12 573 (76.3%)	16 043 (74.8%)	12 573 (76.3%)
<12 years old	17 108 (20.4%)	3 435 (19.9%)	3 328 (20.2%)	4 593 (21.4%)	3 328 (20.2%)
>15 years old	3 259 (3.9%)	744 (4.3%)	578 (3.5%)	802 (3.7%)	578 (3.5%)
Menopausal status					
Premenopausal	9 579 (54.9%)	9 325 (54.1%)	15 146 (52.7%)	8 421 (51.1%)	10 285 (48.0%)
Postmenopausal	7 883 (45.1%)	7 927 (45.9%)	13 581 (47.3%)	8 058 (48.9%)	11 153 (52.0%)
Nulliparous					
No	74 032 (88.2%)	15 432 (89.5%)	24 908 (86.7%)	14 629 (88.8%)	19 063 (88.9%)
Yes	9 864 (11.8%)	1 820 (10.5%)	3 819 (13.3%)	1 850 (11.2%)	2 375 (11.1%)
Ever use of oral contraceptives					
No	8 436 (48.3%)	8 192 (47.5%)	12 091 (42.1%)	7 390 (44.8%)	10 039 (46.8%)
Yes	9 026 (51.7%)	9 060 (52.5%)	16 636 (57.9%)	9 089 (55.2%)	11 399 (53.2%)

Appendix 25: Associations between other solar exposure measures and overall psoriasis risk (n = 83 896).

Exposure	Cases (N= 2 078)	Hazard Ratios (95% CI)	
		Univariate Model ^a	Multivariable Model ^b
Direct Normal Irradiance (DNI)			
1 st quartile	739	1.00 (Reference)	1.00 (Reference)
2 nd quartile	453	0.93 (0.83-1.05)	0.95 (0.85-1.07)
3 rd quartile	337	0.83 (0.73-0.95)	0.85 (0.75-0.97)
4 th quartile	549	0.86 (0.77-0.96)	0.88 (0.79-0.98)
Global Horizontal Irradiance (GHI)			
1 st quartile	695	1.00 (Reference)	1.00 (Reference)
2 nd quartile	466	0.90 (0.80-1.01)	0.92 (0.82-1.03)
3 rd quartile	342	0.82 (0.72-0.94)	0.85 (0.74-0.97)
4 th quartile	575	0.86 (0.77-0.96)	0.88 (0.79-0.99)

a) Model adjusted for: birth cohort

b) Model adjusted for: birth cohort, BMI, smoking status, education level, marital status at baseline, hypertension, depression, diabetes, age at menarche, menopause status, nulliparous status, ever use of contraceptive pill.

Appendix 26: Logistic analyses of overall psoriasis risk according to pigmentary traits, (N = 89 496).

Exposure	Non cases (n= 84 445)	Cases (n=5 051)	Odds Ratios (95% CI)	
			Univariate Model ^a	Multivariable Model ^b
Skin phototypes				
Albino+very fair	1 014	87	1.34 (1.07-1.67)	1.24 (0.99-1.57)
White	48 487	3060	1.00 (Reference)	1.00 (Reference)
Light brown	33 566	1837	0.87 (0.82-0.92)	0.87 (0.82-0.92)
Brown+black	1 378	67	0.78 (0.61-1.00)	0.80 (0.62-1.02)
Hair color				
Albino+blond	8 476	561	1.11 (1.02-1.22)	1.11 (1.01-1.22)
Red	1 477	74	0.84 (0.66-1.06)	0.79 (0.62-1.01)
Brown (Light+dark)	70 297	4156	1.00 (Reference)	1.00 (Reference)
Black	4 195	260	1.04 (0.91-1.19)	1.06 (0.93-1.21)

a) Model adjusted for: birth cohort

b) Model adjusted for: birth cohort, BMI, smoking status, education level, marital status at baseline, hypertension, depression, diabetes, age at menarche, menopause status, nulliparous status, ever use of contraceptive pill.

Appendix 27: Logistic analyses of overall psoriasis risk according to solar exposure, (n = 89 496).

Exposure	Non cases (n= 84 445)	Cases (n=5 051)	Odds Ratios (95% CI)	
			Univariate Model ^a	Multivariable Model ^b
Mean annual daily ambient total UV level (kJ/m2)				
1 st quartile	15 762	990	1.00 (Reference)	1.00 (Reference)
2 nd quartile	28 852	1726	0.95 (0.88-1.03)	0.93 (0.86-1.01)
3 rd quartile	18 648	1004	0.86 (0.78-0.94)	0.86 (0.78-0.94)
4 th quartile	21 183	1331	1.01 (0.92-1.10)	1.02 (0.93-1.11)
Mean spring/summer daily ambient total UV level (kJ/m2)				
1 st quartile	17 314	1 089	1.00 (Reference)	1.00 (Reference)
2 nd quartile	28 895	1 745	0.96 (0.89-1.04)	0.94 (0.87-1.02)
3 rd quartile	16 595	880	0.84 (0.77-0.92)	0.83 (0.76-0.92)
4 th quartile	21 641	1 337	0.99 (0.91-1.07)	1.00 (0.92-1.09)
Mean fall/winter daily ambient total UV level (kJ/m2)				
1 st quartile	17 526	1116	1.00 (Reference)	1.00 (Reference)
2 nd quartile	26 708	1580	0.93 (0.86-1.01)	0.92 (0.85-1.01)
3 rd quartile	19 397	1028	0.83 (0.76-0.91)	0.83 (0.76-0.91)

4 th quartile	20 814	1327	1.01 (0.93-1.10)	1.02 (0.94-1.11)
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- a) *Model adjusted for: birth cohort*
- b) *Model adjusted for: birth cohort, BMI, smoking status, education level, marital status at baseline, hypertension, depression, diabetes, age at menarche, menopause status, nulliparous status, ever use of contraceptive pill.*

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