

BMJ Open Cohort profile: the clinical 'Psoriasis in Adolescents' (PIA) cohort in Denmark

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ABSTRACT

Purpose Psoriasis is a chronic inflammatory skin disease that frequently debuts in childhood and adolescence.

We wished to determine environmental and genetic risk factors for the development of psoriasis in children and adolescents, as well as to investigate debut type, trigger factors, course of disease, nature and influence of stress related to both child and family and risk factors for comorbidity. The 'Psoriasis in Adolescents' (PIA) cohort will provide data on the relationship between psoriasis and, respectively, genetic disposition, early-life exposures, quality of life and comorbidity.

Participants The PIA cohort is nested in the large general population Danish National Birth Cohort (DNBC). We invited 390 adolescents with psoriasis and corresponding maternally predisposed and non-predisposed controls. Participants underwent an interview and a clinical examination consisting of a skin inspection and physical measurements including blood sampling and microbiological swabs. Additionally, four self-administered questionnaires on physical and mental health were completed.

Findings to date The final PIA cohort consists of 81 adolescents with psoriasis, 110 parentally predisposed and 124 non-predisposed psoriasis-free adolescents. The validity of the maternally reported psoriasis status from the DNBC was found to be low on clinical examination (47.5%). In contrast, the self-reported psoriasis status of the DNBC mothers was clinically confirmed in 80.8% of the cases.

Future plans The PIA cohort offers the possibility of assessing the clinical characteristics, course of psoriasis and development of comorbidities in adolescents with clinically confirmed disease from a general population. Comparison with predisposed and non-predisposed controls is possible and genetic analyses are scheduled. We plan to invite the participants for a follow-up in 5–10 years. Furthermore, we plan to include newly diagnosed adolescents with psoriasis from the 18-year DNBC follow-up. All information is linkable on the individual level with data from the DNBC and nationwide registries in Denmark.

INTRODUCTION

Psoriasis is a chronic inflammatory skin disease with a complex multifactorial aetiology affecting approximately 3% of the western population.¹ Both genetics and environmental factors influence the onset of disease. In twin studies, it has been shown

Strengths and limitations of this study

- The 'Psoriasis in Adolescents' (PIA) cohort consists of adolescents with psoriasis, as well as genetically predisposed and non-predisposed adolescents without psoriasis, from a large nationwide general population birth cohort in Denmark.
- Collected information includes clinical characteristics of psoriasis, blood samples for cardiovascular/metabolic risk factors and genetic analyses, microbiological swabs and data on physical and mental health.
- A major strength of the PIA cohort is the possibility of linking data to the birth cohort and the national health registries in Denmark.
- The cohort is limited by the relatively small size; however, we have clinically confirmed the psoriasis status.

that up to 70% of the risk of psoriasis can be explained by genetics; furthermore, having one parent with psoriasis yields a 30% risk of the child also having psoriasis, while psoriasis in both parents increases the risk up to 50%–65%.^{2–4} Several genetic risk loci have been identified in genome-wide association studies, including the PSORS1–9 loci. PSORS1 is located in the major histocompatibility complex of chromosome 6p; the HLA-Cw6 allele coded in this region has been shown to be particularly important and it is associated with an early debut of psoriasis.^{5–6} Known environmental risk factors or 'trigger factors' are physical trauma (the Koebner phenomenon), streptococcal throat infection, psychological stress, certain drugs, smoking and obesity.^{7–10} The age of onset is bimodal with peaks around 16–22 and 57–60 years; however, around one-third of patients with psoriasis have had their debut at the age of 16 years.^{6,9} In children and adolescents, the overall prevalence has been shown to be 0.7% with a linear increase from 0.1% at the age of 1 year to 1.2% at 18 years.¹¹ The diagnosis of psoriasis is mostly clinical and based on skin appearance, although a skin biopsy supports the diagnosis. In children and adolescents,

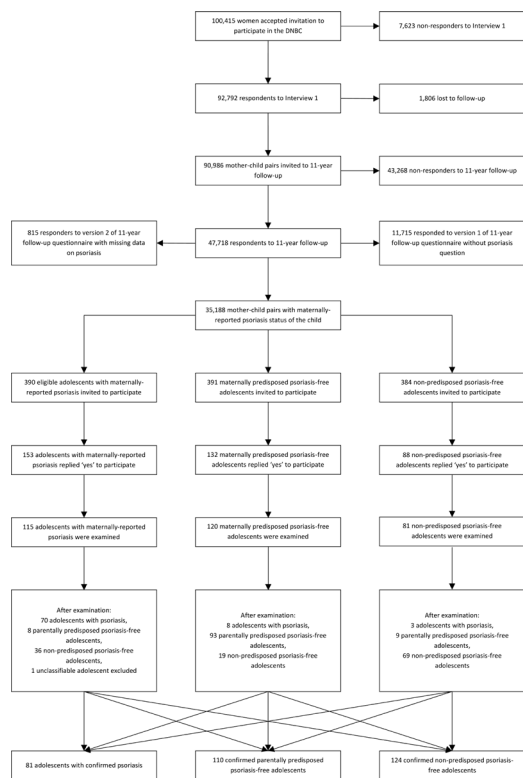


Figure 1 Flowchart showing the recruitment process and classification of the adolescents from the Danish National Birth Cohort in the Psoriasis in Adolescents cohort.

psoriasis can be difficult to diagnose because of mild and overlapping symptoms (eg, atopic and seborrheic dermatitis) and a lack of validated clinical examination-based diagnostic criteria.^{3 12–14} The most common type of psoriasis, plaque psoriasis, manifests itself as well-demarcated red and scaly plaques, with itch and discomfort as common complaints.¹⁵ Psoriasis severely affects quality of life with an impact comparable to other major diseases, not only in adults but also in children and adolescents.^{16 17} In adults, psoriasis has been shown to be associated with a wide range of comorbidities, predominantly cardiovascular and metabolic diseases, and also depression and anxiety and autoimmune disorders including inflammatory bowel disease.^{18–22} Previous studies on children and adolescents with psoriasis have found some of these comorbidities, or risk factors thereof, to be increased.^{11 23–26} Since these studies have mainly been done in highly selected hospital-treated populations, with small sample sizes, or by retrospectively reviewing, for example, patient records, we wished to investigate paediatric psoriasis in a more general population, and also to include psoriasis-free controls for comparison, with the possibility of prospective data collection.^{11 23–49} We therefore established a well-characterised clinical cohort nested in a large, nationwide birth cohort in Denmark in order to investigate the clinical characteristics, trigger factors, comorbidities and related risk factors and genotype of paediatric psoriasis. Our clinical cohort consists of adolescents with psoriasis, as well as predisposed and

non-predisposed psoriasis-free controls: the ‘Psoriasis in Adolescents’ (PIA) cohort.

COHORT DESCRIPTION

Study population

The PIA cohort is a clinical cohort of adolescents (WHO: age 10–19 years) with psoriasis, adolescents with no psoriasis, but with genetic predisposition, and adolescents with no psoriasis nor predisposition. The clinical study population is nested in the large, nationwide birth cohort in Denmark—the Danish National Birth Cohort (DNBC).⁵⁰ The DNBC was established from 1996 to 2002 and consists of the offspring of approximately 100 000 expecting mothers recruited during pregnancy from the general Danish population. The mothers were included at the first antenatal care visit at the general practitioner and candidates were required to speak Danish well enough to participate in telephonic interviews. The mother and child have since been followed up with interviews and online questionnaires at child-age 6 months, 18 months, 7, 11 and 14 years, and an 18-year follow-up is currently undertaken.

We invited adolescent DNBC participants to join the PIA cohort based on three selection criteria: (1) adolescents with maternally reported psoriasis, (2) adolescents with no psoriasis but with maternal predisposition to psoriasis and (3) adolescents with no psoriasis nor maternal predisposition.

The adolescents with psoriasis were identified using version 2 of the 11-year DNBC follow-up questionnaire to the mothers. The majority of the participating mothers received this version. In this, the mothers were asked: “Has your child ever had an outbreak of the disease psoriasis?” This information allowed us to identify adolescents with psoriasis based on their mothers’ self-reported diagnosis. Adolescents with no psoriasis, but with maternal predisposition, were identified using the mother’s first telephonic interview during pregnancy, where she was asked the following series of questions: “Have you ever had any skin disease?” → “Was the skin disease diagnosed by a doctor?” → “What kind of skin disease?” → “Psoriasis”. Accordingly, adolescents with no psoriasis, nor maternal predisposition, were identified.

Recruitment process

In the DNBC, 390 adolescents with maternally reported psoriasis were eligible for invitation to participate in our clinical study and all of these adolescents were invited. We also identified approximately 2500 mothers with psoriasis, and out of these mother–child pairs and the entire remaining DNBC population, we correspondingly invited a similar number of maternally predisposed (391) and non-predisposed psoriasis-free adolescents (384) by random selection (figure 1).

From 2016 to 2017, we sent out invitational letters to the mother–child pairs. Adolescents of legal age (≥ 18 years) were addressed directly. The invitational letter

contained a self-addressed stamped envelope for preliminary declaration of interest to participate. To maximise the response rate, we invited all adolescents with maternally reported psoriasis twice, and participants were compensated for mileage expenses and the adolescents were offered a gift card (250 DKK). Interested mothers and adolescents were contacted by telephone and a date for interview and clinical examination at one of three locations in Denmark were scheduled. These locations were the Department of Dermatology and Allergy at Herlev and Gentofte Hospital, the Department of Dermatology at Aarhus University Hospital and dermatological private practice NORD in Aalborg. Interviews and clinical examinations were undertaken from January 2016 to June 2017.

For adolescents under the legal age, it was mandatory to be accompanied by a minimum of one parent/guardian and consent from both parents/guardians was required; however, a letter of attorney from the absent parent/guardian was accepted. Participants were included only after oral and written consent.

Out of the 1165 invited adolescents from the DNBC, the overall positive response rate was 32.0%, and we managed to include 27.1% of the total invited adolescents. Specified by invitational group, we included 115 (29.5%) of the adolescents with maternally reported psoriasis, 120 (30.7%) of the adolescents with no psoriasis but with maternal predisposition and 81 (21.1%) of the adolescents with no psoriasis nor predisposition.

Interview

During an interview on the scheduled day of visit, the investigator completed a questionnaire by asking the adolescent a predefined series of questions. In order to minimise recall bias, the accompanying parent/guardian was allowed to help. The questionnaire consisted of psoriasis-specific questions and more general health-related questions. Regarding psoriasis, the adolescents were asked about their own psoriasis history and possible symptoms of psoriasis, family history of psoriasis and psoriatic arthritis, possible trigger factors for psoriasis (eg, stress, medication or throat infections) and, if relevant, present and ever psoriasis-specific treatment. Adolescents with psoriasis were asked about age and sites of psoriasis at debut, and the primary clinical phenotype was characterised. The general part of the questionnaire covered comorbidities, particularly cardiovascular and metabolic disease, atopic diseases and inflammatory bowel disease, as well as history of diaper rash in infancy. Additionally, information on smoking, alcohol use and psychosocial areas was included. Finally, general medication use was recorded. In addition to the research questionnaire completed by the investigator, the adolescents completed four self-administered questionnaires. These questionnaires concerned depression (Major Depression Inventory),⁵¹ general anxiety (The Generalized Anxiety Disorder 7-Item Scale),⁵² activity in daily life (ad hoc questionnaire) and skin-related quality of

life (The Children's Dermatology Life Quality Index).⁵³ A subgroup of the adolescents also participated as members of a focus group in the construction and validation of a paediatric psoriasis-specific quality of life assessment tool.

Clinical examination

Regardless of psoriasis status in the DNBC, the clinical examination of the adolescents included a thorough inspection of the skin and nails for signs of psoriasis and other skin diseases, and we also recorded the Tanner stage.^{54,55} The clinical examination decided the final psoriasis status of the adolescents irrespective of the status in the DNBC. Among adolescents with clinically confirmed psoriasis, the disease severity was assessed and scored using both Psoriasis Area and Severity Index (PASI) and body surface area (BSA). PASI assesses redness, scaling, infiltration and area of the involved skin, whereas BSA includes only the area.⁵⁶ The distribution of psoriasis was noted and marked on a diagram and the present psoriasis phenotype was recorded. The clinical diagnosis of psoriasis in the adolescents was supported by a history of physician-diagnosed psoriasis and a predefined set of criteria on paediatric psoriasis from a Delphi consensus by the International Psoriasis Council.¹⁴ These criteria consist of either one major criterion or three minor criteria and we used them to support our psoriasis diagnosis based on present examination or medical history. Adolescents fulfilling these requirements are termed 'clinically confirmed'. Psoriasis in the family was confirmed based on a history of physician-diagnosed psoriasis and clinical appearance where possible. The adolescents were categorised as predisposed if either mother or father had psoriasis.

Physical measurements, blood samples and microbiological swabs

For all the clinically examined adolescents, we measured blood pressure and pulse using a *MicroLife BP A3 Plus* automatic blood pressure monitor. Height, weight and hip and waist circumferences were also recorded. The majority of the adolescents performed spirometry testing with an *EasyOne Volksspirometer* spirometer. Blood samples were collected to measure haemoglobin A1c (2 mL blood), high-sensitivity C-reactive protein, cholesterol (high-density lipoprotein (HDL), low-density lipoprotein (LDL), very-low-density lipoprotein (VLDL) and total) and triglycerides (3 mL blood). All analyses were done per standard protocol at Department of Clinical Biochemistry, Herlev and Gentofte Hospital. Blood was also collected for subsequent DNA (6 mL blood) and RNA (3 mL blood) analyses, in addition to serum (4 mL blood) that was stored in a biobank for potential later analyses. Furthermore, microbiological swabs (*COPAN eSwab*) were taken from the throat and perineum, and the samples were analysed by standard methods at the Department of Clinical Microbiology, Herlev and Gentofte Hospital.

Power calculation and data management

Prior to study start, a power calculation was performed. We used a hypothetical case–control study, assessing whether overweight (exposure 10%) is associated with psoriasis in the adolescents, as a model.⁵⁷ Cases were adolescents with psoriasis and the controls were adolescents without psoriasis. To detect an OR of 2.5 with 80% power and an α -level of 5%, it was necessary to estimate a minimum sample size of 302 (151 cases and 151 controls).

All data from the clinical examination, the general research questionnaire, the four self-administered questionnaires and the laboratory results were entered in a secure REDCap database.⁵⁸ To ensure data consistency, all information was entered twice by two separate individuals.

Patient and public involvement statement

Patients were first involved at the time of receiving the invitational letter, but the invited families were active in the DNBC since inclusion during pregnancy. Our participants were not directly involved in the design of the PIA cohort. On completion of the study, all participants will receive a concluding letter with study findings and information on future perspectives of the research.

FINDINGS TO DATE

Final cohort and validity of the DNBC psoriasis status

The final psoriasis grouping of the adolescents included in the PIA cohort was determined by the clinical examination and medical history, irrespective of the a priori designations recorded in the DNBC: (1) adolescents with clinically confirmed psoriasis, (2) adolescents with no psoriasis but with parental predisposition to psoriasis and (3) adolescents with no psoriasis nor parental predisposition (figure 1).

After interview and clinical examination, the included adolescents were classified as follows: 81 adolescents with clinically confirmed psoriasis, 110 adolescents with no psoriasis but with parental predisposition to psoriasis and 124 adolescents with no psoriasis nor parental predisposition. As shown in the flowchart (figure 1), we reclassified a substantial number of the included adolescents, as we found some misclassification in the DNBC psoriasis status of both the adolescents and the mothers.

The majority of the adolescents were of Scandinavian descent. The median (range) age in the three groups were 16.0 (13.5–18.5), 15.3 (13.5–18.0) and 15.6 (13.8–18.4) years, respectively, for the adolescents with psoriasis, the non-predisposed and the predisposed psoriasis-free adolescents. The sex ratio was roughly even, with a slight male predominance in the psoriasis group (53.1% vs 44.6% vs 44.4%). The adolescents with psoriasis were found to have mild disease on examination with a median PASI of 1.2 (range 0.1–11.4) and a median BSA of 1.0% (range 0.1–12%). This was reflected in the used treatments with topical corticosteroids of moderate-to-high potency being the most commonly used.

On basis of the clinical examination, secondarily we had the opportunity to perform a validation of the DNBC information on psoriasis status of both the mothers and the adolescents. For practical reasons, we screened the adolescents with maternally reported psoriasis living in the western part of Denmark for likelihood of actual psoriasis on the first telephonic contact. However, all adolescents with maternally reported psoriasis included at Herlev and Gentofte Hospital were unscreened and therefore totally unselected. Unexpectedly, in this latter unselected group of adolescents, we could only confirm the diagnosis of psoriasis with a debut before the 11-year follow-up in 28 out of 59 adolescents (47.5%). In most cases, the adolescents had atopic dermatitis or unspecified eczema instead. The telephonic screening explains why the validity of the maternally reported psoriasis status appears to be higher in the flowchart, with 70 confirmed psoriasis cases out of 114 examined adolescents (61.4%, 1 adolescent was excluded), since this number also includes the actively selected group from the western part of Denmark. Regarding the mothers, out of the total 120 mothers with self-reported psoriasis at time of inclusion during pregnancy, we could confirm the diagnosis with a debut before inclusion in the DNBC in 97 of them (80.8%).

Strengths and limitations

Our PIA cohort offers the opportunity to assess the course and clinical phenotype of adolescent psoriasis in a general population. The diagnosis of psoriasis has been confirmed clinically, and even though no recognised clinical examination-based criteria on paediatric psoriasis exist we supported our diagnosis by a predefined set of criteria.¹² We have data on possible trigger factors for psoriasis and medical history regarding a range of other diseases and known comorbidities. The cohort includes genetically predisposed controls and controls with no predisposition to compare with, and we plan to collect data prospectively in future follow-ups. Furthermore, the clinical characteristics are complemented by laboratory data on cardiovascular and metabolic risk factors and microbiological carrier status. Additionally, genetic analyses, including gene–environment analysis, will be carried out to further clarify the complex aetiology of psoriasis, its phenotypes and trigger factors. Finally, we seek to investigate the impact of an early debut of psoriasis on quality of life and to develop a paediatric psoriasis-specific assessment tool. A great advantage of the PIA cohort is the possibility of linking data from every follow-up of the DNBC and also linkage to routinely collected health data in national registries. The DNBC contains data on a large variety of subjects relating to the child's environment and development rarely found in the national registries, including information on home environment, diet, sleep, allergy, exercise, mental health and parental predispositions. All inhabitants in Denmark are assigned a unique 10-digit personal identification number in the Danish Civil Registration System that allows linkage on

the individual level with the DNBC and other national registries, for example, the Danish National Patient Registry and the Danish National Prescription Registry, respectively, containing information on all hospital diagnoses and prescribed medication in Denmark.^{50 59–61}

Our cohort is limited by relatively small size; however, we validated the self-reported psoriasis status of the DNBC for both the adolescents and the mothers. The small sample size could make some associations and differences more difficult to show, and furthermore, even though the adolescents are from an unbiased general population cohort the risk of selection bias should still be kept in mind when generalising any findings from the PIA cohort. The data from our cohort show that the self-reported psoriasis status of the mothers in the DNBC has a high validity comparable to what has previously been shown in Norway.⁶² This is in contrast with the low validity of the maternally reported psoriasis in their offspring. The main reasons for this discrepancy are probably that only the mothers were asked specifically about physician-diagnosed psoriasis and that psoriasis in childhood can be difficult to diagnose due to mild and overlapping symptoms.¹³ This emphasises the importance of asking as specific and unambiguous questions as possible when collecting self-reported data. Importantly, we plan to invite and add newly diagnosed adolescents with psoriasis to the PIA cohort using the ongoing 18-year follow-up of the DNBC. Here, the adolescents are asked specifically about physician-diagnosed psoriasis, which expectedly will increase the validity of this information.

COLLABORATION

We are interested in collaborations with other research groups having data related to psoriasis in children and adolescents. Please find data sharing statement below.

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Contributors LS and A-MNA were the instigators and designers of the study and took care of funding and all required approvals. CB was the lead investigator and drafted the manuscript. LS and CZ provided consultant advice on clinical matters. LS, A-MNA, JG and CZ gave expert advice on, and were integral parts of, the writing process. All authors have read and approved the final manuscript.

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Competing interests None declared.

Patient consent for publication Not required.

Ethics approval As required by the law, the project was approved by The National Committee on Health Research Ethics (protocol no. H-15004238) and the Danish Data Protection Agency (journal no: GEH-2015-071, I-Suite no: 03641).

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request.

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