
Psoriasis in Australian twins

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Background: Occurrence of psoriasis has been found to be strongly genetically controlled in Northern European and U.S. twin and family studies.

Objective: Our purpose was to assess cumulative incidence and heritability of psoriasis in the Australian population.

Methods: Australian twins reporting psoriasis on a screening questionnaire received from 3808 pairs were mailed a detailed instrument designed to validate the diagnosis, supplemented by telephone interview and examination of medical records.

Results: Only 94 of 160 subjects who screened positive were confirmed to have psoriasis. The cumulative incidence of confirmed psoriasis was 2% in 30- to 60-year-old subjects. The monozygotic twin casewise concordance for confirmed psoriasis was 35% (12 of 34 pairs), and the dizygotic twin concordance 12% (5 of 43 pairs), giving an estimated heritability of 80%, was similar to that found in a genetic reanalysis of three previous twin studies. A case-control analysis of psoriasis-discordant twin pairs found no evidence for influences of alcohol or coffee intake, overweight, birth weight, or personality in the origin of psoriasis.

Conclusion: Occurrence of psoriasis in the Australian population is highly heritable, but identical twins are often discordant; the factor responsible for the onset of disease in one twin and not the other is unclear.

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The prevalence of psoriasis is usually cited as between 1% and 2% in populations of European descent.¹ It is much less common in other races. Several family and twin studies indicate a large genetic component in psoriasis. Although some family studies favor a dominant mode of inheritance^{2,3} larger studies suggest genetic heterogeneity or polygenic inheritance.⁴ Reanalyses^{5,6} of two large Scandinavian population surveys^{7,8} that gave information on the status of relatives concluded that the multifactorial threshold model gave the best fit to the data. Although the HLA system is definitely implicated in predisposition to psoriasis,⁹ twin studies found that it explained only part of the genetic correlation seen between twins.^{10,11}

Twin studies have largely been clinic-based with the usual problems from this design, such as an increased representation of concordant twin pairs. One of the largest series by Farber et al.¹² consisted

of 61 twin pairs of whom one or both were affected. Brandrup et al.^{10,11} reported the only large registry-based study of psoriasis from Denmark, which included a total of 46 monozygous (MZ) pairs and 22 dizygous (DZ) pairs and concordances consistent with a heritability at 90%.

These authors also give information on the accuracy of self-reported diagnosis of psoriasis in the 53 index cases of self-reported psoriasis from the 46 pairs of MZ twins. This diagnosis was found incorrect in 14 patients. Watson et al.⁴ examined eight families of probands with psoriasis and confirmed the diagnosis of psoriasis in 16 of 17 relatives reported to be affected.

The role of environmental factors in the etiology of psoriasis is poorly understood, but does not seem to be significant. The clinical course of the disease is often exacerbated by cold weather, and Australian clinicians have noted that the disease is less frequent and severe in the warmer northern states of Australia. An association has been noted between alcohol excess and psoriasis^{13,14} but is not found in all studies.^{15,16} Coffee drinking was suggested as a possible factor in one study.¹⁶ Brandrup et al.¹¹ found no significant differences in stress, infection, social status, or occupation between psoriasis-discordant MZ twins.

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In the present study we examined concordance for psoriasis in twins from a community-based twin register and estimated the cumulative incidence of psoriasis in this Australian population.

SUBJECTS AND METHODS

In 1980 a questionnaire was sent to adult twins registered with the Australian NH&MRC Twin Registry (ATR). The ATR is a volunteer-based twin registry whose members were recruited by media appeals and by visits to community groups and schools. In 1980 it was estimated to contain 10% of all twins in Australia. The questionnaire included items on several health problems as well as personality measures and disease risk factors such as alcohol and tobacco intake. One item asked "How often have you had any of the following?" and included "psoriasis" as one of the 22 conditions listed. Response was on a 4-point scale: "never," "only as a child," "rarely," "quite often." Zygosity was diagnosed by twins' responses to two items on the questionnaire and supplemented in ambiguous cases by examination of photographs, a method that incorrectly classifies fewer than 5% of twins.¹⁷

The questionnaire was mailed to all 5967 pairs of twins, and replies were received from 3808 complete pairs (64%). The mean age of respondents was 37 years (standard deviation = 14 years; median age 32 years).

In 1990 we followed up all 169 pairs in which one or both reported psoriasis and for whom we had a current address (out of 172 possible pairs from 1980). These persons were mailed a detailed questionnaire on psoriasis and then interviewed by telephone. If the diagnosis remained doubtful, the patient's doctor was contacted, and medical records examined. A subset of 72 questionnaires and any related medical notes were reviewed by a dermatologist, who did not know the outcome of the telephone interview.

The questionnaire included items on medical diagnosis of psoriasis, age at onset, medications used, and aggravating and relieving factors such as pregnancy or season; they indicated on a standard figure the pattern of involvement at present and during the worst attack that the patient recalled. Twins were also asked to report their parents' and grandparents' racial origins and whether these and any first-degree relatives had psoriasis.

A diagnosis of psoriasis was made on the basis of the patient's response to key items in order of importance:

1. Report that a dermatologist had diagnosed psoriasis.
2. Report that a medical practitioner had diagnosed psoriasis and appropriate medication prescribed.
3. Description of cutaneous findings that included positive responses to items on the following:
 - a. Red or dull red color
 - b. Presence of scale
 - c. Characterization of the scale as thick or a mixture of thick and thin

- d. Distribution of the eruptions
- e. Presence of nail disease (such as pitting)
- f. Presence of the Koebner phenomenon
- g. Exacerbation with infection such as tonsillitis
- h. Exacerbation by sun exposure, alcohol intake, or stress
- g. Exacerbation during pregnancy, menopause, or the use of oral contraception

Most data analysis has been performed with SAS 6.07.¹⁸ To calculate the cumulative incidence of psoriasis based on the 1990 survey, it is necessary to back-extrapolate to the base population that was screened in 1980. This requires two assumptions. First, loss to follow-up by 1980 must be unrelated to psoriasis; second, the screening instrument must have high sensitivity. Both of these assumptions can be tested to some extent. Data can then be analyzed with "double-sampling" log-linear models that allow for missing data.¹⁹⁻²¹

Concordance of twins for the presence of psoriasis has been measured as the pairwise (or casewise) concordance $a/(a + b)$, where a is the number of twin pairs who both have psoriasis and b is the number of pairs discordant for the diagnosis. The ratio of monozygotic to dizygotic concordances has been analyzed according to Risch.²² The model described by Risch is valid whether one gene or many are believed to be acting and was suggested as a method of determining whether a disease is polygenic in nature, although it cannot always detect this. In the case of a single gene, an additive effect is seen when risk increases linearly as none, one, or two disease alleles are present. In a polygenic trait, interaction between genes can also be additive. Nonadditivity can either be monogenic, because of dominance (either mendelian recessivity or dominance), or epistatic, where interaction between genes is multiplicative (similar to the multifactorial threshold model, [see later]). These different situations give rise to different patterns of ratios between concordance and population prevalence (population risk ratios) (Table I) but can easily be applied directly to the MZ to DZ concordance ratio.

Multifactorial threshold models²³ (MFT) have also been fitted with the program MX,²⁴ which allows analysis of data not including concordant unaffected pairs. The MFT assumes that risk of disease is caused by the effects of many genes, each of small effect. Risk of disease is modeled as a probit function of genetic "dose" (number of disease genes present), which means that each gene acts to multiply risk (by a small amount). Confusingly, these genes are said to be acting "additively" on the probit or *liability* scale. Family environmental factors that might include diet or parental social class can also be modeled as acting in a similar fashion. This *model* has been successfully fitted to data on psoriasis, but this by no means excludes monogenic (with low or intermediate penetrances) or oligogenic mechanisms as the actual cause of disease. The heritability of a binary trait like psoriasis is

Table I. Genetic hypothesis testing for twin studies

Relationship	Interpretation
$PRR_{MZ} > 4 PRR_{DZ}^*$	Epistasis; must be polygenic
$PRR_{MZ-1} > 2 (PRR_{DZ-1})$	Genetic dominance (or epistasis)
$PRR_{MZ-1} = 2 (PRR_{DZ-1})$	Additive genetic effect; either monogenic or polygenic
$PRR_{MZ} = PRR_{DZ} > 1$	No genetic contribution; effects of family environment
$PRR_{MZ} = PRR_{DZ} = 1$	No familial aggregation

DZ, Dizygous; MZ, monozygous; PRR, population risk ratio.

*PRR equals casewise concordance divided by population prevalence.²²

Table II. Breakdown of twins eligible for 1990 follow-up survey

Status	Individuals	Pairs
Initially lost to follow-up	6	3
Refused/withdrawn ATR	57	45
Diagnosis reached	281 (82%)	114 (66%)
Eligible	344	172

ATR, Australian Twin Registry.

the proportion of the variance of liability caused by the action of genes.

RESULTS

Follow-up

We successfully contacted and reached a diagnosis in 281 persons (including 114 complete pairs) (Table II). The remaining 57 either had withdrawn from the ATR (17), died (10), had moved overseas (1), were uncontactable (8), or failed to return the questionnaire despite repeated telephone reminders (21). Noncontactees did not differ significantly from contactees in prevalence of reported psoriasis (contacted 56%, noncontacted 55%, $p = 0.91$), or sex (contacted men 29%, noncontacted men 39%, $p = 0.16$), but did in age.

Accuracy of screening questionnaire diagnosis

We have successfully followed up 160 of the persons who reported psoriasis in 1980 (83% of this

Table III. Age-specific cumulative incidences of interview-confirmed psoriasis in the entire twin sample (in 1980) adjusted for loss to follow-up (by 1990)

	Birth cohort			
	<1921	1921-1935	1936-1949	>1949
Prevalence (%)	1.6	1.9	2.1	1.3
95% CI	0.4-2.8	1.1-2.7	1.5-2.8	0.9-1.6
No. of twins	510	1088	1972	4046

CI, Confidence interval.

Table IV. Areas affected by disease in twins with interview-confirmed psoriasis (extracted from figure filled in by twin)

Site affected*	In usual episodes (%)	In worst episode (%)
Scalp/eyebrows	76	38
Face	27	10
Arms	49	43
Hands	18	9
Trunk	20	20
Genital region	27	14
Legs	44	36
Soles	12	10

*Twins could indicate more than one area.

group), of whom 66 were deemed to have false-positive results, a positive predictor value (PPV) of 59%. For our two-stage design to have been appropriate, the screening question needs to have perfect or near perfect sensitivity. In fact, of 148 twins who denied psoriasis in 1980, 7 were subsequently found to have psoriasis and to report its onset as before 1982 (the latest date questionnaires were returned), a false-negative rate of 4.7%. We estimated the false-negative rate for the screening questionnaire in those twins not followed up as approximately 0.5%. This was based on the sensitivity and specificity of the screening questionnaire for an individual's diagnosis conditional on the cotwin having screened positive, and taking the prevalence of true psoriasis as 2%.²⁵

Agreement between raters

There was agreement on presence or absence of psoriasis in 63 of 72 cases; an additional four cases could not be decided on by the second rater in the absence of interview data. Therefore definite disagreements were seen in five cases (7%). In one sub-

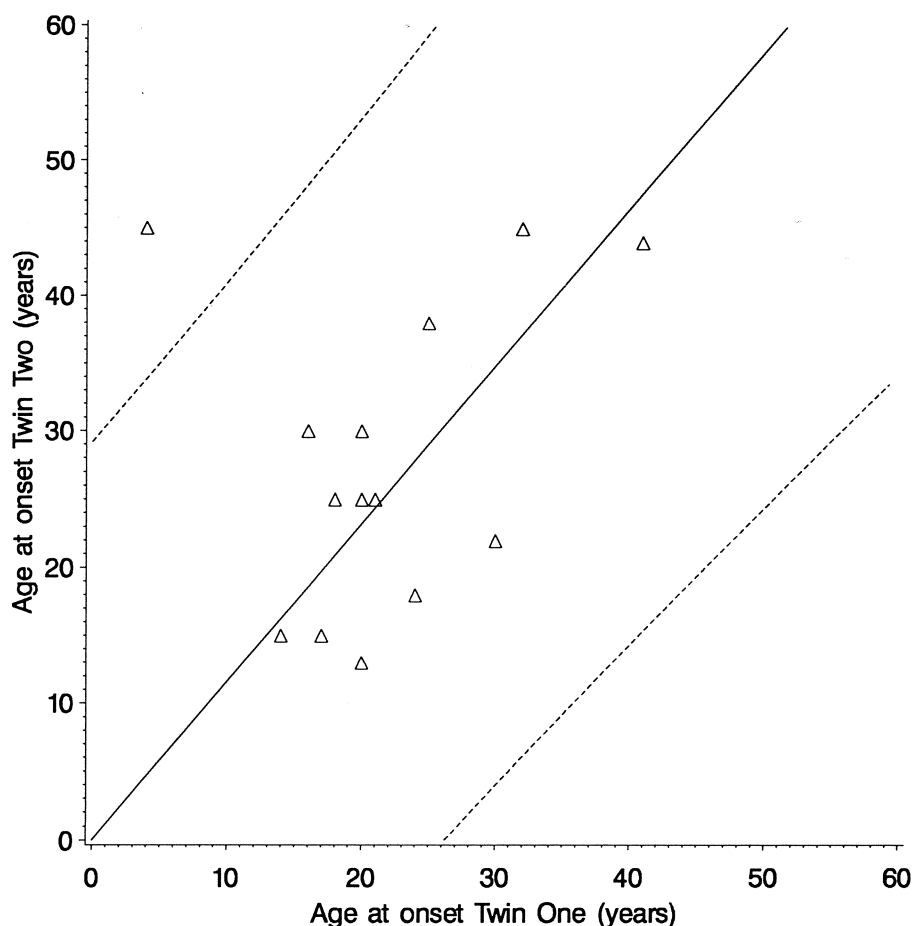


Fig. 1. Age at onset of (confirmed) psoriasis in concordant MZ twins with linear regression line (forced intercept through origin) and 95% confidence limits of predicted values. This plot includes two pairs who became concordant after 1980.

ject, there was no history or findings of skin disease, but an arthroscopically confirmed villous synovitis of the knee developed in 1990, which in view of a strong family history of psoriasis (cotwin and two other siblings) had been diagnosed as psoriatic arthritis. The other four patients had suffered transient skin eruptions and/or eruptions with limited sites about which the telephone interview had given more information than the questionnaire.

Cumulative incidence

In preliminary analyses, we combined the last three categories of the 1980 screening questionnaire to give a lifetime occurrence of *self-reported* psoriasis. The crude lifetime prevalence of psoriasis in this group was 2.5% (females 2.8%, males 2.1%). The mean age of those reporting psoriasis was 40 years.

With the information from the 1990 questionnaire, the crude prevalence of confirmed psoriasis (adjusted for loss to follow-up 1980–1990 and not,

of course, including cases that developed after 1980) in the twins was 1.6% (Table III). The age-specific cumulative incidences peaked at 2.1% in those 30 to 45 years of age (in 1980). The cumulative incidence was higher in southern states (highest in Victoria, lowest in Queensland; corrected for age and sex, Cochran-Mantel-Haenszel test for trend $\chi^2_1 = 9.21$, $p = 0.001$).

The mean age at onset of confirmed psoriasis was 23.1 years (range 1 to 60 years). A physician was reported to have previously diagnosed psoriasis in 81 patients, and 52 had seen a dermatologist about the condition. The area reported by most patients to be affected was the scalp (76%) (Table IV). In addition, 43% reported having involvement of the eyebrows at some time and 60% the genital region. Only 17% reported nail involvement. More than 90% of confirmed patients were of British descent, and only one reported non-European grandparents (Chinese).

Table V. Concordance for psoriasis in MZ and DZ twins reported in four studies

Study	Zygosity	Concordant	Discordant	Concordance
Pooled reports ¹² (1924–1969) (world)	MZ	23	13	0.64
	DZ	7	20	0.35
Niermann ¹² (1964) (Germany)	MZ	3	0	1.00
	DZ	3	10	0.30
Farber et al. ¹² (1974) (U.S.A.)	MZ	30	11	0.73
	DZ	4	16	0.20
Lynfield ²⁷ (1974) (U.S.A.)	MZ	2	2	0.50
	DZ	2	4	0.33
Brandrup et al. ^{10,11} (1978, 1982) (Denmark)	MZ	18	18	0.56
	DZ	3	19	0.14
Present study (Australia)	MZ	12	22	0.35
	DZ	5	38	0.12

Table VI. Crude concordance for psoriasis in parent-offspring pairs containing an affected twin from the present study

Parent	Affected	Unaffected	Concordance
Father	9	94	0.09
Mother	12	91	0.12

Concordance

The casewise concordance for twins with confirmed psoriasis in our study was 35% for the MZ twins and 12% for the DZ twins. The MZ/DZ concordance ratio was 3.0 (95% confidence limit [CL] = 1.3, 8.6). There was no evidence of increasing concordance with age, although the numbers of subjects 45 years of age and older was small. Concordant MZ pairs were correlated in age at onset (Fig. 1).

Our concordance rates are tabulated along with those from several other twin studies of psoriasis in the literature (Table V), culled especially from the review of Farber et al.¹² The first three studies cited are based on clinical material rather than from a community-based twin register and as such will tend to be biased towards concordant pairs.

Combining studies, the Mantel-Haenszel MZ/DZ concordance ratio was 3.1 (95% CI = 2.2, 4.5). Both Breslow-Day and exact tests for heterogeneity of the risk ratio were not significant (exact test, $p = 0.34$). Under an additive genetic model (in which risk increases linearly with the number of disease alleles carried²²), this ratio is expected to be:

$$\frac{\text{MZ concordance}}{\text{DZ concordance}} = 2 - \frac{\text{Prevalence}}{\text{DZ concordance}}$$

The estimated prevalence of psoriasis in each country differs slightly. The estimate suggested for Denmark was 3.0%,²⁶ whereas that for the United States derived from NHANES is 1.5%.¹ Therefore with an additive model we would expect MZ/DZ concordance ratios that range between 1.8 and 1.95, outside the 95% CLs for the observed concordance ratio.

We have also calculated concordance for all parent-offspring pairs in our study that include a confirmed affected twin (Table VI). A parent was scored as affected if *both* twins reported that the parent had psoriasis. These are similar to the DZ concordance rates, but the number of affected parents was small, and the accuracy of diagnosis is unknown. They can be compared with the results of Watson et al.,⁴ who found that 0.18 of fathers and 0.11 of mothers of affected probands were reported to have psoriasis.

Threshold models

We fitted threshold models to the concordances from the current study using MX. A shared environmental model was rejected ($\chi^2_1 = 6.23$, $p = 0.02$), and an additive genetic model gave a perfect fit. The heritability was estimated as 81%.

Fitting similar models to all six sets of concordances from Table V (Table VII) also confirmed a strong genetic influence on psoriasis.

Case-control study of discordant twins

The 60 pairs (22 MZ, 38 DZ) discordant for the presence of psoriasis were examined for evidence of effects of possible disease risk factors. The putative risk factors were measured on the 1980 screening questionnaire and included body mass index (Quete-

Table VII. Results of threshold models fitted to twin concordances from literature and present study

Model tested*	Proportion of variation from			Test of model goodness-of-fit		
	A	C	E	LR χ^2	df	p Value
ACE	0.30	0.66	0.04	6.62	8	0.58
AE	0.91	—	0.09	6.71	9	0.67
CE	—	0.81	0.19	35.48	9	0.00

*Models contain additive genetic (A), shared (C), and unshared (E) environmental sources of variation. The CE model posits that all familial aggregation of psoriasis is due to environmental factors (so MZ concordance equals DZ concordance) and is rejected. The AE model implies that familial aggregation is entirely due to the additive action of genes (on the liability scale). The ACE model contains both family environmental and genetic factors, but does not significantly improve the model fit compared with the simpler AE model. Different liability thresholds (prevalences) were estimated for clinic-based and registry-based studies.

Table VIII. Intrapair differences (psoriatic twin value minus nonpsoriatic twin value) in level of possible risk factors within psoriasis-discordant twinships

Variable	No. of pairs	Difference	SEM	t Value	p Value
Body mass index	59	+0.58 kg/m ²	0.38 kg/m ²	1.52	0.13
Coffee consumption	60	−0.22 cups/day	0.48 cups/day	0.45	0.65
Birth weight	52	+26.5 gm	22.1 gm	1.2	0.23
Weekly alcohol intake	60	−2.61 drinks*	2.4 drinks*	1.08	0.28

*Estimated number of standard drinks (10 gm of ethanol).

let's index, measured in kilograms per square meter), birthweight; tea, coffee (daily intake in cups), and alcohol use (estimated weekly intake based on a retrospective 1-week diary); and state of residence. No effects of any significance were noted (Table VIII). There were also no differences in score (data not shown) on the three scales of the Eysenck Personality Questionnaire²⁸ or those of the DSSI/SAD (a psychiatric symptoms questionnaire²⁹).

DISCUSSION

We have confirmed that the occurrence of psoriasis is under genetic control. The heritability of psoriasis from the pooled studies is high, but only slightly higher than that seen in the Australian population. Although there is no significant heterogeneity detected in heritability between studies (mainly because of low power to detect such), there are significant differences in MZ (but not DZ) concordances. The MZ concordance in Australian twins is much lower than that of the Northern Hemisphere studies (Table V). An alternative explanation is that the Australian and Danish data, which are registry based, will be lower than the clinic-based studies, which are prone to collect concordant pairs at the expense of the DZ pairs. This latter hypothesis, in fact, fits the data better (with a lower Akaike Information Criterion, 7.2, than that for the North-South dichotomization of the studies, 9.5).

Concordance might be expected to increase with age, but this is, in fact, a complex process because new discordant pairs may also appear. Because the MZ and DZ groups in the present study did not differ in age, the concordance ratio on which genetic hypothesis testing depended should remain constant.

An interesting difference is seen between the conclusions reached by the approach of Risch²² and the more usual MFT. These are not as inconsistent as they might seem. The MZ/DZ nonadditivity found with the former approach may be caused by epistasis; an important point is that additivity on the MFT probit liability scale is a multiplicative effect on the risk scale. If epistasis is present, it requires psoriasis to be polygenic in nature.

The low predictive value of the screening items for psoriasis should also be noted. Prevalence estimates based on a self-reported diagnosis of psoriasis would tend to be too high. In the present study, the lifetime prevalence of confirmed psoriasis is close to that reported in surveys of other populations of European descent.¹ Because we have only confirmed the absence of psoriasis in screen-negative persons whose cotwin has screened positive, we cannot say exactly by how much our prevalence value is an underestimate, but as noted earlier, this might be by as much as 0.5%. To measure accurately the specificity of our instrument would have required following up several hundred screen-negative twins to obtain a sufficient

number of false-negatives. We believe that the few disagreements in the repeat diagnosis of the subset of patients used for validation were caused by the additional interview information available.

The negative findings of the case-control analysis of discordant pairs reflect the lack of knowledge about environmental causes of psoriasis and the nature of the data collected in the 1980 screening questionnaire, which, although extensive, concentrated on lifestyle and personality. The MZ concordance of only 35% in the Australian twins, as well as the well-known variability in disease expression over time, suggests that nongenetic factors must play a role in psoriasis. The influence of climate, or mean temperature, was suggested by the lower incidence of psoriasis in hotter states. There were too few twins discordant for state of residence to examine this factor by the discordant matched-pair analysis.

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