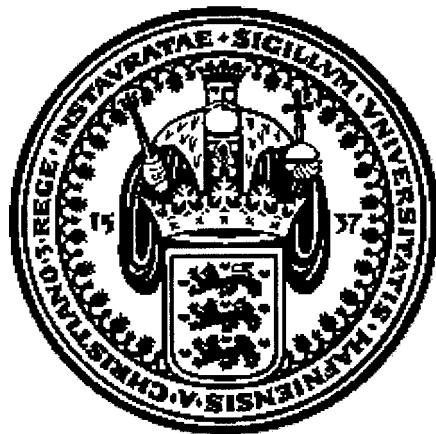


A genetic-epidemiological study of hand eczema in young adult twins

Lars Erik Bryld



Gentofte Hospital

Dept. of Dermatology

University of Copenhagen

Faculty of Health Sciences

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ABBREVIATIONS

ρ :	Correlation in liability
95%CI:	95 % Confidence Interval
ACE:	Additive genetic effect Common environmental effect Environmental (individual specific) effect
AD:	Atopic Dermatitis
C:	Concordant twin pairs
CR:	Concordance Rate
D:	Discordant twin pairs
DZ:	Dizygotic or fraternal (twin pairs)
h^2 :	Heritability
HE:	Hand Eczema
MZ:	Monozygotic or identical (twin pairs)
NPV:	Negative predictive value
OR:	Odds-ratio
PPV:	Positive predictive value

PREFACE

The present study was made possible by a research fellowship grant from the University of Copenhagen. The work was carried out at the Department of Dermatology, Gentofte University Hospital from 1996 to 1999.

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INTRODUCTION

Several community-based surveys have shown that hand eczema is a common disease in the general population. Many people experience occurrences of mild, easily healed, hand eczema on at least a few occasions, but in some cases hand eczema can cause invalidity and even necessitate change of occupation because of chronic, painful skin changes.

General clinical experience suggests that the risk of developing chronic hand eczema increases, when proper treatment is delayed. Contrarily, early intervention may modify or entirely stop severe progression of the disease.

Both constitutional and environmental (e.g. occupational) risk factors can contribute in a case of hand eczema, and they often co-exist. Clinical judgement is used to determine the relative importance of each risk factor. This is important for instituting adequate treatment and preventing relapses, as well as for possible eligibility for worker's compensation, if the disease is considered occupational.

Previous investigations of hand eczema have mainly focused on selected risk factors, and no investigation has, to our knowledge, until now, considered heritability as a separate risk factor in hand eczema.

With a few exceptions, most studies have used patients referred to centralised dermatology units, i.e. selected by severity. The result has been that considerable attention has been paid to allergic, atopic and occupational hand eczemas which tend to be rather more severe than e.g. irritant hand eczema, which is probably more frequent in the general community.

Thus, there are gaps in our current knowledge which this study hopes to investigate.

AIMS OF THE STUDY

To examine the prevalence of self-reported hand eczema in a cohort of twins aged 20–44 years representative of the general population.

To estimate the genetic influence on the propensity to develop hand eczema by estimating probandwise concordance rates and correlations in liability and heritability, using Falconer's threshold model.

To analyse the agreement between self-reported hand eczema and self-reported symptoms of hand eczema and the genetic specificity of the latter.

To further validate the results by a general extension of the Falconer threshold model.

To validate the self-reported hand eczema diagnosis by clinical examination in a subset of the study cohort, and

To present clinical and patch test results from the clinical examination.

BACKGROUND

Definition of hand eczema

Eczema in general

Generally, eczema is considered the same fundamental disease regardless of the afflicted site. Although the skin can be ultrastructurally different at the hands (especially the palms) than at other parts on the body, no previous scientific research results or clinical observations have indicated that hand eczema differs histopathologically or pathogenetically from eczema

presenting elsewhere (with the possible exception of vesicular forms). Therefore, the following generally accepted definition of eczema in general is usually applied to hand eczema:

Eczema is an inflammatory skin reaction characterised histologically by spongiosis with varying degrees of acanthosis, and a superficial lymphohistiocytotic infiltrate. The clinical features of eczema may include itching, redness, scaling, and clustered papulo-vesicles. The condition may be induced by a wide range of external and internal factors acting singly or in combination¹.

The main reason for investigating hand eczema as a separate entity is that a large number of eczema cases predominantly or exclusively involve the hands.

Eczema vs. dermatitis

In this thesis, "eczema" and "dermatitis" will be regarded as synonyms. The term "eczema" will be preferred, except where "dermatitis" has traditionally been used, like in "contact dermatitis" or "atopic dermatitis".

Hand eczema

During a course of hand eczema, the symptoms may concurrently or subsequently appear on the feet or spread locally to the forearms. The disease is still most reasonably considered to be hand eczema. Generalised eczema may involve the hands but is considered hand eczema only if *primarily* originating from the hands, otherwise the term *hand involvement* is preferable². Therefore, not all eczema involving the hands is hand eczema, and not all hand eczema is confined to the hands.

Classification of hand eczema

Traditionally, hand eczema is classified primarily by aetiology, and in particular circumstances by morphology and topography. The most common causes of hand eczema are:

Exogenous:

Contact irritants

Chemical, e.g. soap, detergents, solvents, etc.

Psychical, e.g. friction, minor trauma, cold dry air, etc.

Contact allergens

Delayed (type IV) e.g. chromium, rubber, etc.

Immediate (type I), e.g. latex, food proteins

Ingested allergens, e.g. drugs, possibly nickel, chromium

Infection, e.g. following bacterial infection of hand wounds

Secondary dissemination, e.g. dermatophytide reaction to tinea pedis

Endogenous:

Idiopathic, e.g. discoid, hyperkeratotic palmar dermatitis

Immunological or metabolic defect, e.g. atopic

Psychosomatic. Stress aggravates, but may not be causative

Dyshidrosis. Increased sweating aggravates, but may not be causative

(adapted from¹)

It is generally recognised that hand eczema may be multifactorial, so more than one of the items above may be relevant in a particular case of hand eczema. The list is not exhaustive as other, rare causes of hand eczema exist as well. The classification is, however, a good check list to the clinician when establishing the main cause(s) in the individual case of hand eczema.

Diagnosis

Non-eczematous diseases that can mimic hand dermatitis include *psoriasis*, *scabies* and *fungal infection*. Psoriasis can be diagnosed by family history, specific morphologic features not commonly seen in eczema, and from histologic examination. Scabies can be diagnosed by detection of mites, and fungal infection from microscopic examination or culture of skin samples. Clinically, eczematous skin changes presenting unilaterally on the hands tend to be fungal infections.

Though by definition a separate disease entity, localised *urticaria* with sudden eruptions of itching wheals and flares can sometimes resemble hand eczema as well as exacerbate the development of eczema-specific symptoms such as vesicles, fissures and scaling³.

Epidemiology of hand eczema

The following short review of hand eczema epidemiology is based on the available literature and follows the usual categorisation by major aetiology with some added morphological forms that traditionally are considered mainly constitutional.

Age of onset

Hand eczema can occur at all ages, even in children⁴. An indirect estimate of the predominant age of onset has been established by the age distribution of hand eczema present for 5 years or less⁵. According to this, the vast majority of hand eczemas in women begin in early adulthood (20–35 years). The same is true for men, but to a lesser degree, probably because men have more cases of late-onset hand eczema⁶.

Prevalence

Most studies agree, that hand eczema is very common, though exactly how common depends on the definition of hand eczema, and the observation period used. If “hand eczema ever” (life-time prevalence) is recorded, the prevalence may be as high as 22% in women⁷, but life-time prevalence is critically

dependent of the age distribution in the group examined. Also, lifetime prevalence may be an under-estimation because a few light episodes of hand eczema might have been forgotten by some of the responders. A survey of “current hand eczema” (point prevalence), however, clearly underestimates the true underlying disease distribution, because by definition it excludes all patients with recurrent eczema temporarily in remission. Therefore, most studies have settled for a period prevalence, usually of one year.

A Swedish community study carried out in 1964 from questionnaire answers with clinical validation in a subset estimated the overall population prevalence of *current* hand eczema to be 1.2–2.3% and observed twice as many female as male cases⁸.

A Finnish study carried out in 1975 of a compiled non-patient cohort using clinical examination reported the prevalence of *current* hand eczema to be 2.5% (men) and 5.4% (women)⁹.

A Dutch study carried out in 1979 diagnosing hand eczema *within the last 3 years* by history and clinical examination showed a prevalence of 4.6% (men) and 8% (women)¹⁰.

A Norwegian community study carried out in 1979 using self-reported hand eczema *within the last year* reported the prevalences 4.9% (men) and 13.2% (women)¹¹.

A Swedish community study carried out in 1982 using self-reported hand eczema confirmed by clinical examination had for *current* disease an overall prevalence of 5.4%. The prevalences of self-reported hand eczema *within the last year* were 8.8% (men) and 14.6% (women)¹².

All studies showed a female to male ratio of about 2:1 and had similar prevalences in all age groups. The results are summarised in table 1. Despite the variation in case definitions, the studies viewed together seem to indicate an increasing prevalence of hand eczema during the period 1964–82.

Incidence

Few true follow-up studies of hand eczema have been published. One such with clinical examination of 1,929 persons aged 27–58 in 1979 and again in 1982 showed 45 new cases, and calculated the incidences as 4.7 cases per 1,000 man-years and 11.4 cases per 1,000 woman-years¹³. No studies reporting cumulative incidence or changes in geographic distribution or over time in relation to hand eczema have to date been published.

Prognosis

The prognosis of hand eczema is considered to be dependent on its severity. The longer the eczema has persisted, the greater the likelihood that it will continue to do so. Because hand eczema can take a chronic-intermittent course, it is difficult to

Table 1: Prevalence studies of HE

Study	Participants	HE (men)	HE (women)	Period	Age
Agrup (1969)	107,200	275/*	552/*	actual	10–99
Peltonen (1979)	980	12/478	27/502	actual	10–74
Coenraads (1983)	3,140	76/1,661	119/1,471	3 years	27–70
Kavli (1984)	14,667	364/7,410	961/7,257	1 year	18–55
Meding (1987)	16,584	709/8,014	1,249/8,570	1 year	20–65

*denominator not stated, but sex distribution reported even.

assign a definite cure-date. The prognosis of hand eczema has generally been regarded as unfavorable when the eczema was occupationally caused, especially for men^{14,15}, when allergic¹⁶, or when atopic¹⁷⁻¹⁹. Morphologically the vesicular eruptions with accompanying nickel allergy in particular have been associated with a relatively poor prognosis¹⁶. Irritant contact dermatitis when severe enough to have initiated clinical investigation is also associated with a poor prognosis²⁰. It should be noted that the patients in the above-mentioned follow-up studies in most cases were probably referred to specialised units because of therapy-resistant eczema and thus initially selected for poor prognosis. Follow-up investigations of the milder forms of hand eczema found in the general community¹³ are rare. From patient history in a cross-sectional population study⁵, a mean duration of 11.6 years was calculated. Atopic and allergic hand eczema were characterised by longer duration and higher proportions with continuous symptoms than irritant or other forms of hand eczema. Nevertheless, for irritant hand eczema the mean duration in this study was as high as 10.3 years.

Thus, hand eczema is liable to take a chronic course. By careful observational study design, it is sometimes possible to detect a modest benefit of exposure prevention²¹⁻²³. Possible reasons for a limited effect could be oversight of continuing exposure. The exact exposure mechanisms of ubiquitous allergens (such as nickel or formaldehyde) are not determined completely, and exposure to residual chromate in cement may explain continuing symptoms among workers still occupied in the building industry^{24,25}. Furthermore, the actual extent of allergen/irritant avoidance may be critically dependent on patient compliance. Compliance may in turn be dependent on the patient's understanding of his diagnosis²⁶. Additional pressures from domestic exposure and the possible interaction with inherent propensity to develop eczema (whether manifesting as overt atopic features or not) are other plausible interpretations.

Aetiology of hand eczema

Contact dermatitis

Clinically, many cases of hand eczema are caused by environmental factors. *Contact dermatitis* is the preferred term for eczema caused by direct contact between a substance and the skin. The mechanism of the eczema can be either irritant or allergic in nature. Many common substances in the everyday environment can cause skin problems on the hands. The relative impact of such substances can be dependent on the exposure (intensity, frequency and duration), the particular substance in question, and the condition of the skin prior to exposure

Irritant contact dermatitis

An irritant may be defined as an external substance that upon skin contact produces damage to the skin. Damage is caused by chemical, physical or mechanical properties of the substance, and the resulting reaction to the damage is a non-immunological inflammatory response²⁷. Allergic contact dermatitis to substances present in the patient's environment should be excluded by negative patch tests.

The irritancy potential of different substances is very variable, so the initial damage may be strong and produce a correspondingly strong acute inflammatory response, depending on the actual agent. This is the case with many acid or alkaline substances as well as other irritant substances, and the response

often depends on the exposure concentration. Other irritants may produce weak and unnoticeable responses if they are exposed to the skin in concentrations below that necessary to produce acute irritation. Instead, they may through frequent or prolonged exposure more insidiously produce a light or intermittent reaction (not initially considered eczematous²⁸), which may eventually become manifest hand eczema. A pathogenic model of chronic irritant contact dermatitis has been proposed²⁹ and stresses the possible interaction of exposure frequency and sub-clinical irritation.

Irritant hand eczema of the chronic intermittent form is the most common form of hand eczema. Two large population-based studies^{5,8} have estimated that this form constitutes 35–41% of all hand eczemas, and it is also among the most frequently encountered occupational skin diseases⁶. The usual age of onset is early adulthood^{5,8}. The main pathogenesis of irritant hand eczema is typically that of frequent, prolonged exposure to commonly found chemicals of relatively low-irritant potency (often detergents), i.e. substances that do not produce acute reactions with normal exposure intensity. The observed higher prevalence of irritant hand eczema in women compared with men is believed to be caused by additional female exposure to irritants from cleaning and child care³⁰.

Allergic contact dermatitis

Allergic hand eczema is caused by exposure to contact allergens to which the patient has previously been sensitised. Its proportion of all hand eczemas is more difficult to establish and varies in the above mentioned studies^{5,8} from 19% to 35%, probably because the researchers differ about when to consider detected allergens relevant to the pathogenesis of an observed hand eczema. The age of onset is usually reported to be a decade later than its irritant counterpart^{5,8}. The most frequently encountered allergens in a hand eczema patient populations are nickel, cobalt, fragrances, balsam of Peru and colophony³¹ (table 18). The occupational relation can be very clear with relatively rare allergens such as IPPD³² but less so if the occupational allergen is present in the general everyday environment, too. The mechanism of allergic contact dermatitis is usually T-cell mediated, though in some cases IgE-mediated variants can occur, e.g. to latex and food proteins (see below). The risk of primary sensitisation is dependent on the potency of the allergen and the exposure concentration (dosis/area)³³. Whereas a strong allergen can sensitise practically everyone even with a single low-dose exposure³⁴, a substance of low allergenic potency may require high concentration, repeated exposures at the same skin site or concomitantly compromised skin barrier³³. Subsequently, less intensive re-exposures can elicit the skin symptoms once contact allergy has developed³⁵. Allergy reactivity can be semi-quantified as distinct (+), strong (++) or severe (+++)³⁶. The stronger the allergy reactivity is, the less the re-exposure need be. The allergy reactivity seems dependent on the primary intensity of the sensitising exposure (either as high concentration or repeated exposures)³⁷. Whether subsequent re-exposure can enhance reactivity is currently unclear. It has not been clinically demonstrated that re-exposures can boost a present allergy³⁴ but experimentally there are indications supporting that boosting can occur locally³⁸⁻⁴⁰.

Loss of contact allergy

It is a widely held assumption that contact allergy to many (if not most) allergens, once acquired, generally tends to persist throughout life. Theoretically, though, avoidance of the offending allergen might in time lead to disappearance of a previously demonstrated patch test reaction. Follow-up investigations have been performed to test for this possibility with common allergens⁴¹ and with particular allergens of special interest, such as nickel⁴², chromate⁴³, and colophonium⁴⁴. The studies have shown loss of contact allergies in 10–20% with follow-up periods of 2–13 years.

The possibility of misclassification, however, should also be taken into consideration when interpreting such studies. A difference in patch test results on two separate occasions could be ascribed to either false-positive or false-negative readings in either one of the two readings. Also patch test results in individual test-persons have been shown to vary^{45,46}.

Systemic contact dermatitis

A special form of contact dermatitis can be caused by systemic exposure to substances, either by ingestion, intravenously, or topically at a skin area other than the eruption site. The most specific symptoms of systemic contact dermatitis are the Baboon syndrome⁴⁷ on the buttocks and the flare of previous patch test sites, usually on the back, but the reaction is more frequently confined to the hands in the form of eruptive vesicular eczema. Compared with other causes of hand eczema, this type is probably uncommon in a clinical setting (a recent survey⁴⁸ of 250 consecutive hand eczema patients did not encounter a single case). In oral challenge studies several drugs have been shown to be capable of eliciting systemic contact dermatitis, and so have a few allergens such as nickel^{49,50} and balsam of Peru⁵¹.

Protein-contact dermatitis and contact urticaria

Typical eczema eruptions can also be seen following contact with substances to which the patient can be shown to have an allergy mediated through IgE (positive skin prick test, or *Type I allergy*) rather than T-cells (positive patch test, or *Type IV allergy*). Frequently encountered allergens in this respect are proteins from natural rubber (latex)⁵² or from various foods, and the allergies are often found among persons working with food processing^{53,54}.

Besides eczema-specific symptoms, some substances can elicit urticaria reactions on the hands in response to skin contact. This reaction pattern can be concomitant with eczema and exacerbate the severity of the eczema component of the skin problems. In particular, the combination of contact dermatitis and contact urticaria has been described in latex allergy⁵².

Constitutional hand eczema

Hand eczema cases where no environmental cause can be established are called endogenous or constitutional. In such cases neither an exposure history nor patch test gives any help but the family history may disclose earlier cases.

Morphology of hand eczema

Generally, eczema on the hands resemble eczema on other parts of the body and show the usual clinical features of itching, redness, scaling, and clustered papulovesicles. A few special morphological forms of eczema are predominantly or exclusively seen on the hands. These include the *Hyperkeratotic hand eczema*⁵⁵ characterised by a thickening of the horny layer of the skin on the hands (and sometimes feet) with painful fissures. In some cases hyperkeratotic hand eczema may be difficult to separate from mechanically induced hand psoriasis. Another special morphologic form is the *Nummular eczema* which, though as a rule disseminated, is sometimes found exclusively on the hands. Historically nummular eczema has been associated with atopic dermatitis⁵⁶ though this relationship has been challenged^{57,58}. Hyperkeratotic and nummular forms are both quite uncommon (1% and 2% of all eczemas respectively⁵). *Pompholyx* is an eruptive vesicular hand eczema presenting on the sides of the fingers and sometimes in the palm or the dorsal part of the fingertips⁵⁹. Pompholyx usually has little accompanying inflammation and heals with a light scaling but usually without other eczema features, but vesicles can also be just one predominant symptom among numerous other symptoms in a particularly severe attack of hand eczema. Usually the term is reserved for the pure vesicular variant, which – even when not including cases associated with contact allergy or atopic disease – is rather common (5–6% of all eczemas⁵).

Pompholyx when first described was believed to be entirely constitutional⁶⁰, and exogenous causes with this morphology are less frequently found. Nevertheless, pompholyx has in later reviews been associated with several specific exogenous causes such as allergic contact dermatitis⁶¹ systemic contact dermatitis⁴⁹, fungal infection⁶² and atopic dermatitis⁶³.

Susceptibility to hand eczema

The main purpose of the present study is to investigate individual-specific, possibly genetic, susceptibility to hand eczema. Theoretically such a susceptibility could be to hand eczema itself (presenting as a constitutional hand eczema) or to an exogenous risk factor for hand eczema (presenting as a contact dermatitis which is dependent on or aggravated by the predisposing endogenous factor).

Atopic Dermatitis

Atopic dermatitis (AD) is a strongly heritable, generalised dry skin condition that manifests as recurrent eczema eruptions. The usual age of onset is infancy or early childhood. In childhood the eruptions are typically located in the flexures of elbows and knees or in the face and neck, though the first presenting symptoms in infants can be on the hands. In adulthood, the disease, if still present, is often exclusively confined to the hands¹⁷. Thus AD is a marker for a considerable individual-specific predisposition to hand eczema.

Definition of AD

AD, like other forms of eczema, is subject to inherent problems of definition and discrimination from similar skin disorders. For these reasons, a set of symptom-based operational criteria, the Hanifin-Rajka criteria⁶⁴ has been established, where at least 6 confirmed symptoms from the criterion list is diagnostic. One example of these symptoms is the presence of res-

piratory symptoms such as asthma and hay fever in persons with AD or in their near relatives. Since their publication in 1980, the criteria have undergone further refinements⁶⁵.

AD and skin irritants

Persons with previous or present AD experience increased susceptibility to skin irritants and face the risk of developing irritant hand eczema, as shown by numerous experimental and epidemiological studies^{17,19,30,54,66–68}. A recent review¹⁹ estimates that AD at least doubles the effect of irritant exposure.

Even without significant environmental pressures from skin irritants, adults who no longer suffer from AD elsewhere can present isolated hand eczema^{5,17}. This form has been associated with the pompholyx morphology⁶³.

The term *Atopic hand eczema* has rather indiscriminately been used to denote the increased susceptibility to skin irritants as well as the constitutional form seen in persons with previous AD. Its relative proportion of all hand eczemas therefore varies with the broadness of definition (10%–22% of all hand eczemas^{5,8}). The usual age of onset varies but is usually early adulthood (like irritant contact dermatitis, from which it can be difficult to separate).

Present knowledge therefore suggests that atopic hand eczema is a problem complex involving genetic predisposition probably in interaction with environmental pressures, but the relative importance of gene versus environment and the nature of interaction is largely unresolved. Because AD (depending on definition) seems to be affecting an increasing number of the population in Denmark⁶⁹, its impact on hand eczema in a population setting is potentially substantial regardless of whether increased susceptibility, environmental pressures, or a combination hereof is the main cause.

Irritants susceptibility

Individual susceptibility to irritants is highly variable⁷⁰ and not *per se* associated with clinical hand eczema⁷¹. Women generally have hand eczema far more often than men, but it has not been demonstrated that women should be inherently more susceptible to primary irritation than men^{72,73}.

The presence of current localised eczema, even mild, seems to increase general skin reactivity to primary irritants^{71,74}, which provides a possible mechanism for a vicious circle of primary irritation exacerbating the inflammatory response to continued exposure. Especially noteworthy is that the site of preceding eczema need not be in the same region as the site of irritant exposure, though the effect increases proportionally with proximity⁷¹. Pre-eczematous conditions can be monitored by a number of non-invasive bioengineering measuring methods such as transepidermal water loss (TEWL) and corneometry.

Allergy susceptibility

Individual-specific (sometimes genetic) susceptibility to sensitisation has been demonstrated in a number of allergens including nickel^{75–78}. Therefore, allergic contact dermatitis should not be considered a purely environmental disease.

Patients with long-lasting eczema – which often is confined to the hands – sometimes have multiple contact allergies, where not all allergens can be found in the patients' environment. By coincidence, frequently occurring allergens will sometimes be seen simultaneously in the same person, but in a population-based survey the number of people with more than one allergen was higher than should have been expected by chance

alone⁷⁹. When determining the aetiology of allergic contact dermatitis, the exact time of sensitisation often is difficult to establish with certainty at the time of examination. In some cases, the actual eczema seems to be present before sensitisation apparently occurs. In such cases, a possible alternative hypothesis could be that an underlying susceptibility to become sensitised to allergens was associated with a susceptibility to develop eczematous skin reactions – without any direct causal connection between the two⁸⁰. Such a susceptibility could be genetic. Another explanation of multiple concomitant allergies is offered by the hypotheses of “excited skin syndromes” and “angry backs”. Excited skin denotes a stronger reaction of the skin at time of testing because of a generalised eczematous arousal in another part of the skin^{81,82}. Nevertheless, some patients tested in a quiet phase of their disease also demonstrate multiple allergies. The angry back hypothesis offers the explanation that the stronger allergy reactions may have provoked false positive ones. The validity of this hypothesis, however, has recently been challenged^{83,84}.

Methodological issues in population studies

Case definition

By combining any visible skin changes with the patient's history, a dermatologist normally can establish the diagnosis of hand eczema through pattern recognition. As suitable as this approach may be in the clinical setting, it is scientifically unsatisfactory when conducting surveys in larger groups, because the reliability of the diagnosis must be accountable to allow for reproduction and scrutiny. In such cases an operational case definition is called for.

Ideally, an operational definition of hand eczema should clearly distinguish the affliction from other skin diseases occurring on the hands, as well as from normal skin. Nevertheless, significant problems can arise in attempting to define hand eczema operationally, because different skin diseases on the hands can present similar morphological features, and because a clinical distinction between mild dry skin irritation and overt clinical hand eczema is difficult to operationalise.

The fluctuating nature of eczema introduces special problems. The often used cross-sectional study design normally consists of a single examination, and individuals with recurrent hand eczema will not necessarily have symptoms at the time of examination. Furthermore, the cases observed may not be representative of the true disease pattern in the population, because there would be disproportionately many chronic cases and possibly a distinct subgroup characterised by long-lasting symptoms. To classify hand eczema solely on the basis of the visual findings at the time of examination is therefore less satisfactory. However, a thoroughly sensitive survey involving numerous examinations – or relying on the participants' immediate feedback in case of eruptions – would in all probability quickly find itself facing unacceptably high dropout rates. Because of these problems, any attempt to describe the occurrence of hand eczema in the patient or in a population must include information about the past; i.e. the patients' history must be part of the observation in some way.

The clinical manifestations of hand eczema fluctuate and widely vary in severity over time and between individual cases. Thus, the same clinical entity can present as severely disabling as well as barely noticeable and (more important) can change from one form to the other. This is of special importance when

determining prevalence or attempting classification by morphology or severity.

Generally the morphology of hand eczema seems poorly associated to its aetiology^{18,48,85}. Temporality reasons are probably the culprit here, too. The presentation of symptoms will most likely vary over time – at best, a particular case may be classified from the predominant, most frequently observed presentation over the observation period.

Operational definitions of hand eczema

Hand eczema must fundamentally be defined as what a dermatologist after clinical examination would diagnose as hand eczema. In large epidemiological studies expert disagreement is of minor importance if such difference is non-systematic. Still, clinical examination is time-consuming, and therefore attempts have been made to develop a set of criteria, who could provide the hand eczema diagnosis in a more cost-effective manner for use in large-scale epidemiological studies.

Smit⁸⁶ validated a questionnaire about skin symptoms on the hands as well as self-reported hand eczema against a clinical dermatologist's diagnosis in a group of 109 nurses. The period in question was the preceding year, and the sensitivity and specificity for the symptom questions was 100% and 64% respectively, while the sensitivity and specificity for the self-declared hand eczema was 65% and 93% respectively.

Meding⁵ validated a questionnaire using self-reported hand eczema within the last year in a Swedish population sample of 16,500 persons. In 89% of all who had answered yes, was the diagnosis confirmed by a dermatologist's clinical examination.

Yngveson and Svensson⁸⁷ validated a questionnaire using self-reported actual hand eczema in a group of 2,535 secondary school pupils against a clinical diagnosis made by either a dermatologist or a trained dermatology nurse (the interrater reliability was also checked). They found a sensitivity and specificity of 73% and 99% respectively.

In conclusion validation studies of questionnaires for initial screening show high sensitivity when eczema symptoms are used and high specificity when self-reported hand eczema is used. The general understanding in the Scandinavian populations (where most community-based epidemiological studies have been performed) of what constitutes a case of hand eczema seems reproducible both with respect to sensitivity and specificity. Other countries' languages might give markedly different response patterns because of several synonyms for the disease, and implying more restricted ways of interpreting a given question. In English two interchangeable terms, "eczema" and "dermatitis" exist, which by some respondents might be considered separate diseases. The possibility of false-negative responses if just one out of several similar terms is used should be considered.

An early attempt of recording eczema signs in an objective manner was presented by Rycroft in his thesis on Soluble Oil Dermatitis⁸⁸. He regarded grouped papules, grouped pustules, grouped vesicles or exudation indicative of "skin problems". At least two visible signs of erythema, scaling, oedema, fissuring, or lichenification also qualified. This definition of hand eczema only used actual, visible signs.

In a prevalence study¹⁰, diagnosis was established by agreement of two dermatologists. The working principle behind the diagnoses was a history of the above mentioned signs within the last 3 years⁸⁶. Singular episodes of less than 3 weeks' duration were disregarded. For lack of an official name, these criteria will here be referred to as the Rycroft-Coenraads (or RC) criteria. The criteria are summarised in table 2.

Table 2: The Rycroft-Coenraads criteria for hand eczema

<p>A history or presence of any sign: grouped papules grouped pustules grouped vesicles exudation</p> <p>OR</p> <p>A history or presence of at least 2 signs: erythema scaling oedema fissuring lichenification</p> <p>should have been present for at least 3 weeks</p> <p>OR</p> <p>more than once</p>
--

Application to the present study

In the questionnaire part of this study, self-reported hand eczema in an adaptation of the Smit questionnaire has been used. In the clinical part of this study, detailed histories of past symptoms were taken and current signs were recorded after clinical examination. Clinical diagnoses based on the RC-criteria were subsequently made.

Genetic epidemiology and skin disease

Twin studies

Hand eczema as such has not previously been the subject of family studies. From clinical experience, there are no indications of a simple Mendelian inheritance pattern, and associations between hand eczema and genetic markers have not been reported. From a theoretical point of view, however, genetic factors may be of importance in e.g. atopic or allergic forms of hand eczema, if these are not outweighed by environmental pressures. A twin study can establish the possible existence of a genetic component and quantify its importance in relation to the environmental factors. A prerequisite for generalising the results thus obtained is that twins do not differ from non-twins with respect to the trait investigated. This is not known for hand eczema in particular. Generally twins and others seem very alike in health, as is also reflected in similar mortality rates⁸⁹.

The Falconer threshold model

Because of the obvious problems involved in discriminating between genetic and environmental factors when studying groups of hand eczema cases, a general model embracing all possible risk factors would be preferable. One such model, coincidentally developed to be used in quantitative genetics, is the threshold model, originally proposed by Falconer⁹⁰. This model assumes an underlying compound attribute, the *liability*, which combines all individual-specific risk (e.g. genetic susceptibility) with all external circumstances (e.g. environmental pressures) into one single measurement.

Prerequisites

The variation of liability must be continuous if the model is to be applicable, i.e. the disease must be multifactorial (or oligogenetic with a comparatively large non-genetic variation) rather than determined by a single or a few important major genes. The assumption that this prerequisite is fulfilled in the case of hand eczema is well supported by our current knowledge of the disease.

The liability is transformed so as to yield a normal distribution when applied to a population. This transformation of scale is mathematically possible for all continuous measurements, and the mean liability is measured in standard deviations from the threshold. When comparing two groups, however, the model will also have to assume that the variance of liability remains the same in both groups. It is not possible to test for this assumption; once accepted, the distributions of liability will consequently be different in a population at increased risk of having disease from in the background population (figure 1).

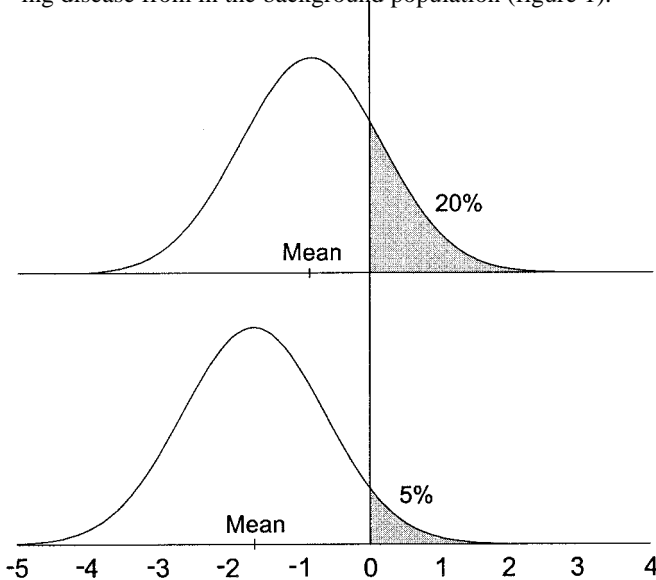


Figure 1. Liability of a risk population compared with the background population

Because the mean liability in a risk population is higher and therefore closer to the disease threshold than in the background population, a larger proportion of the risk population will manifest disease. If genetic factors are of importance in the pathogenesis of the disease, close relatives of affected individuals will constitute such a risk population.

Correlations in liability

With the threshold model, the correlations in liability can be directly calculated from the proportions of affected individuals in the general population and in the populations of relatives to affected twin individuals. The correlations in liability in these two groups must be significantly different in order to accept the presence of genetic factors in the disease.

Furthermore, to exclude the possibility that the difference observed is caused by environmental similarities during adolescence, the correlations in liabilities can be calculated separately for co-twins to disease affected twins. The twin pairs should be divided into identical (monozygotic) MZ pairs and

fraternal (dizygotic) DZ pairs and the correlations for each group should likewise be significantly different.

Heritability

The total phenotypic variation can theoretically be divided into several components.

$$V_{PT} = V_G + V_E \\ = (V_A + V_D + V_I) + (V_C + V_E)$$

V_G represents the total genetic variation and can be further subdivided into an additive component (V_A) from each single gene and two non-additive components (V_D and V_I) from genetic dominance and gene-gene interactions in different loci (Epistasis) respectively. The total environmental variation V_E can be ascribed to common i.e. shared exposure (V_C) that both twins experience(d) and individual-specific environmental exposure (V_E) that is unique for each individual. The proportion of phenotypic variation V_{PT} that can be attributed to additive genetic factors is called the *heritability*.

From the definition follows, that heritability is the proportion:

$$h^2 = \frac{V_A}{V_{PT}}$$

Assuming the non-additive genetic factors to be of minor importance, the heritability can be estimated from the correlations in liability of MZ and DZ twins respectively simply by doubling the difference between them. This simplification of the general model operates solely with Additive genetic factors, Common environmental factors and individual-specific Environmental factors, and for this reason is referred to as the ACE-model. This heritability estimate will, however, overestimate the degree of genetic determination if the non-additive genetic factors are significant, because the correlation difference in fact consists of one-half additive plus three-quarters non-additive variation. Evaluation of the possible amount of non-additive genetic factors requires comparison with heritability estimates of family studies targeting family members other than full sibs⁹⁰. Such studies are at present unavailable for hand eczema.

Concordance rates and recurrence risk

Another and more traditional way of inferring genetic contribution to disease from twin studies is to compare concordance rates of MZ pairs with those of DZ pairs (in principle, concordance rates are proportions, but the rather incorrect term is firmly established). The purpose of using concordance rates is to make an estimate of the recurrence risk, i.e. the conditioned risk of acquiring a disease, given that a near relative is known to have it. Three distinctively different expressions of concordance rates exist and should not be confused.

Pairwise

Traditionally the pairwise concordance rate has been used in many classical twin studies:

$$CR = \frac{C}{C + D}$$

In this formula, C is the number of pairs in the group where

both twins have the disease in question (concordant pairs) and D is the number of pairs in which only one of the twins has the disease (discordant pairs). The interpretation of CR in this respect is the risk of a pair to be concordant for disease. This disease risk of pairs has no clinical interpretation and furthermore is prone to bias if there is not complete ascertainment.

Complete ascertainment implies that all cases of disease have been exhaustively traced and diagnosed within the population examined. This is very rarely the case and the pairwise concordance rate will inevitably be overestimated under incomplete ascertainment⁹¹. However, the calculation of pairwise concordance rates in MZ and DZ twin pairs respectively is easily performed, and testing for significance regarding a difference between the two groups can be done very simply by the chi-square test. The test can be justified because the overestimation will not affect a statistically significant difference (the main object of interest) between the two groups as both are overestimated similarly. It is, however, important that the ascertainment probability does not differ in the two groups⁹².

Casewise

Of still greater interest is the individual disease risk and whether this is increased when the co-twin has the disease compared with the *a priori* risk. This so-called recurrence risk can be estimated by the casewise concordance rate:

$$CR = \frac{2C}{2C + D}$$

In contrast to its pairwise equivalent, this expression gives a particular twins' own risk of acquiring a disease if the co-twin is affected. Like the pairwise CR this too is prone to ascertainment bias in that it tends to overestimate the recurrence risk when ascertainment is incomplete.

Probandwise

The best estimation of the recurrence risk in light of the almost inevitable non-completeness of ascertainment is the probandwise concordance rate:

$$CR = \frac{2C_1 + C_2}{2C_1 + C_2 + D}$$

Here twin pairs are ascertained through probands, who by definition are cases ascertained *independently* of their co-twins. Probands can e.g. be ascertained by clinical examination of people with affirmative answers to a previously submitted screening questionnaire.

It is imperative that probands are independently ascertained; if the co-twin of a proband upon examination turns out to have the same disease without being a proband, he is a so-called secondarily ascertained case. In the formula above, C_1 then means concordant pairs with two probands and C_2 means concordant pairs with one proband and one disease-affected, secondarily ascertained, co-twin. Mathematically it can be shown that the risk estimate obtained using this expression is a very stable and precise estimate of the recurrence risk under different ascertainment probabilities^{92,93}.

Using a very non-discriminating ascertainment criterion (e.g. from the very start to suspect all twins in the cohort of having the disease in question) would make all detected cases probands and by definition negate the existence of any secondary cases thus making the formulas for casewise and probandwise con-

cordance rates identical. For economic and practical reasons, such an approach is only feasible if the disease is relatively common and the examination of possible cases can be performed with a minimum of inconvenience and cost.

Previous twin studies of skin disease

Zwillingsdermatologie

In 1964, Niermann published the results of examining a cohort of twins for a wide variety of skin diseases⁹⁴. For "allergodermien" (which included all cases of contact dermatitis) 1 concordant and 2 discordant MZ twin pairs were observed as opposed to 0 concordant and 13 discordant DZ twin pairs. For "neurodermatitis" (which included atopic dermatitis and pompholyx) 5 concordant and 0 discordant MZ twin pairs were observed as opposed to 3 concordant and 10 discordant DZ twin pairs.

Allergy

Forsbeck examined 51 MZ and 50 DZ twin pairs for reactivity to Tuberculin, DNCB, allergy reactions to common contact allergens and history of atopic features⁷⁶. Only non-significant differences between the concordance rates of MZ versus DZ twins were observed, except for history of atopy.

Edfors-Lubs examined allergy in 7,000 twin pairs aged 42–81 years by questionnaire⁷⁷. Pairwise concordance rates of (atopic) eczema were 15.4% for MZ and 4.5% for DZ twin pairs. For (allergic) contact dermatitis, the corresponding numbers were 9.6% versus 6.1% (n.s.). It was concluded that while hereditary factors were present in the development of allergic disorders, the environmental effects were by far the most important ones. The study concerned primarily the respiratory symptoms of atopy and only incidentally, the atopic skin manifestations.

Nickel allergy

Menné examined nickel allergy by personal interview and patch tests in 86 female twin pairs aged 48–72 years, ascertained by a previous questionnaire screening of 1,546 twin pairs⁷⁸. A recurrence risk of 0.395 in MZ versus 0.204 in DZ pairs for a confirmed history of nickel contact dermatitis and a corresponding heritability estimate of 0.64 was calculated. Patch test results showed a similar though not significant trend. A subsequent analysis focused on concomitant hand eczema in the probands did not reveal any increased recurrence risk for the identical co-twins compared with the overall population risk.

Irritant exposure

Holst⁹⁵ examined 100 twin pairs for skin sensitivity to 3 different cutaneous irritants. For one irritant (potash soap) but not the other 2 substances tested (SLS and benzalkonium chloride), he found significant differences between the MZ, the DZ, and the control group regarding intra-pair reactivity differences. For SLS and benzalkonium chloride there were no non-significant tendencies similar to the differences observed with potash soap. Thus, it would seem that possible genetically determined susceptibility to irritants was specific to each irritant or maybe

to some unknown property that the tested irritants did not have in common.

Atopic dermatitis

Schultz-Larsen⁹⁶ examined atopic dermatitis in 48 twin pairs of children aged 7–21 years who showed a fourfold increased probandwise concordance rate for MZ twins compared with DZ twins, confirming several family studies about (mainly respiratory) atopy. Heritability estimates of 0.96–1.40 were calculated.

Because atopic dermatitis is a well-known risk factor for hand eczema, the impact of this genetic influence in a study focusing on clinical hand eczema would depend on the prevalence of atopic hand eczema (in its constitutional sense) in the general population. The estimate of 22% of all hand eczema cases has previously been made⁵ but since several diagnoses were allowed for each individual, a substantial number also had contact dermatitis diagnoses. If cases with multiple diagnoses are excluded, an adjusted estimate of 10% – presumably consisting of the constitutional forms – can be inferred.

Psoriasis

Brandrup examined psoriasis in 36 twin pairs who showed a fourfold increased recurrence risk for MZ twins compared with DZ twins⁹⁷. Correspondingly, a heritability estimate of 0.90 was calculated. Psoriasis is not a known risk factor for hand eczema although the hyperkeratotic hand eczema is sometimes referred to as a form of psoriasis. This particular type of hand eczema is considered to be relatively rare in the population.

Candidate genes for eczema

Hand Eczema

Hand eczema as an independent disease entity has not been the subject of investigation for specific candidate genes. Because hand eczema is associated with diseases with a verified genetic risk factor such as AD or contact allergy, the ongoing quest for candidate genes for these diseases is of interest for hand eczema also.

Atopic Dermatitis

Given the strong clustering of AD in families, many studies have looked for disease-specific markers. HLA-Bw35 was one of the first promising candidate genes⁹⁸ but subsequent efforts have done little more than emphasize the complexity of the matter, as confirmation has been equivocal and hardly any other associations have been found within the HLA system^{99–102}. Recently promising new candidate genes have been proposed^{103,104}.

Allergic Contact Dermatitis

Similar investigations have taken place for allergic contact dermatitis, mainly for nickel^{105–110}, chromate^{111,112}, and cobalt^{113,114}. Again the evidence has mainly pointed away from demonstrable associations to specific genes, except in selected cases^{108,110,112}.

OWN STUDIES

Subjects and methods

Study cohort

The Danish Twin Register (Young Cohort)

The postal addresses of twins born 1953–1976 were made available from the Young Cohort of the national population-based Danish Twin Register. This part of the register is derived from the national civil registration system. The Danish Twin Register traces and registers all twins in Denmark, and it is currently over 75% complete for the oldest twins included in this study. It is virtually complete for all twins born after computerisation of the civil registration system in 1968. The twins born between 1953 and 1967 were originally traced from an electronically compiled subgroup consisting of all persons with identical addresses born on the same, the previous, or the following day. The sensitivity of this method in identifying likely twin pairs decreased with increasing age as the twins became more likely to have moved apart, and for that reason an arbitrary cut-off at age 14 was used. Two manually compiled twin cohorts supplemented the register.

Upon enrolment in the register in connection with a study in 1994 (response rate 92%), 96% of the participating twins consented to receive invitations to participate in future questionnaire studies¹¹⁵.

The Danish Twin Register also contains younger twins than those included in this study. The decision to omit these twins was partly in order to avoid problems with obtaining informed consent from custodians of legal minors given the expectation of only relatively few cases of hand eczema in these age groups. Because the age of 18–20 years to many also marks the entrance to working life (after finishing secondary school), it was decided to omit these age groups in order to have more participants who were working.

Inclusion criteria

6,666 twin individuals aged 20–44 years were drawn from the Danish Twin Register for the purpose of this study. For inclusion in the study cohort, both members of a same-sex DZ or MZ twin pair had to reside on the island of Sealand or its neighbouring islands. Sealand is the main island of Denmark (figure

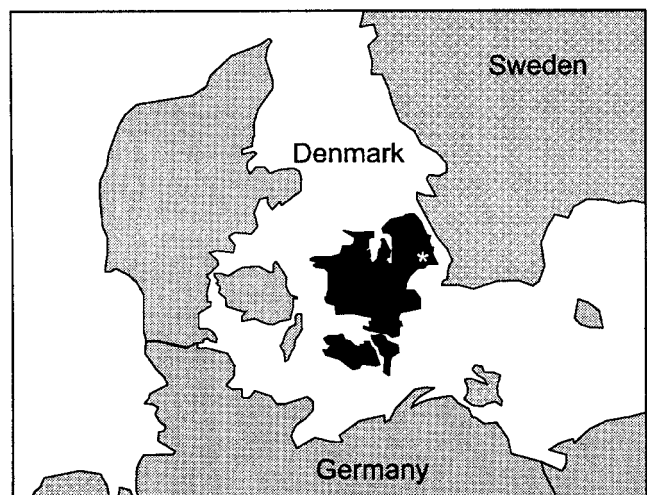


Figure 2. Study area (black): Sealand and the neighbouring islands. *Copenhagen

2) where the capital Copenhagen is situated. The study area covers 9,244 km² and has 2.3 million inhabitants (about half the total population of Denmark). Light industry and office jobs dominate in this area, where there are no larger heavy industry workplaces.

Composition

Altogether there were 3,328 sib pairs in the compiled study cohort, 10 of whom were triplet groups. In the twin analysis, the latter were converted to twin pairs by randomly excluding one person from each triplet group. Zygosity had previously been established by the similarity method¹¹⁶. There were 1,403 MZ twin pairs and 1,774 DZ twin pairs, and 151 pairs were of unknown zygosity. The distribution of pairs by age, sex and zygosity is summarised in table 3.

Table 3: Number of pairs in the study cohort

	MZ	DZ	UZ
W 1953–60	162	291	16
W 1961–68	309	383	26
W 1969–76	263	263	26
M 1953–60	190	273	15
M 1961–68	222	291	32
M 1969–76	257	273	36

Questionnaire study

Procedure

In autumn 1996, a questionnaire with 10 questions regarding hand eczema and eczematous skin symptoms on the hands was mailed to the study cohort together with a stamped self-addressed envelope. The complete questionnaire is shown in table 4. In the accompanying letter, the purpose of the study was described in very general terms where the high frequency and wide variability of hand eczema was stated.

A subsequent reminder with a new questionnaire and envelope was mailed after 4 weeks if the questionnaire had not been returned by then.

Table 4. The mailed questionnaire

<ul style="list-style-type: none"> • Have you ever had a skin disease on your hands? • Did this disease present any of these symptoms: <ul style="list-style-type: none"> • red and swollen hands or fingers • red hands or fingers and cracks • tiny blisters on the hands or between the fingers • scaling hands or fingers with cracks • itching hands or fingers with cracks • Do you have any of these symptoms now? • Have you ever had eczema on your hands? • Do you have eczema on your hands now? • Has a doctor ever told you that you had hand eczema?
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The questions were adapted from a previous investigation by Smit⁸⁶. Here the symptom questions had proved to yield high sensitivity and the self-reported hand eczema high specificity, when compared with a dermatologist’s diagnosis⁸⁶. A confirma-

tory answer to any of the last three questions was considered indicative of previous or present hand eczema.

Proband criteria (questionnaire part)

In order to qualify as a proband in the questionnaire study, a person should:

1. be born 1953–76
2. belong to a twin pair, where both lived within the study area (Sealand and neighbouring islands)
3. belong to a twin pair, where both returned the questionnaire
4. have answered “yes” to at least one of the last 3 questions

Statistics

Comparisons of the study cohort with the background population and of responders with non-responders were performed by likelihood ratio tests.

Concordance rates were calculated by the formula

$$CR = \frac{2C}{2C + D}$$

and 95% confidence intervals were constructed by simulation. The null hypothesis of identical concordance rates in the MZ and DZ group was tested against the hypothesis of greater concordance rate in the MZ than in the DZ group by simulation. With this method, it was unnecessary to calculate any pairwise concordance rates in order to test the hypothesis by chi-square tests, so all concordance rates reported in this thesis reflect the individual recurrence risk.

Correlations in liability were estimated by the maximum-likelihood method described in the statistical appendix, and are given with 95% confidence intervals.

The null hypothesis of no effect of genes (i.e. of identical correlations in liability for MZ and DZ twin pairs) was tested by likelihood ratio test. The model was applied after stratification by sex and age.

Additionally the threshold model was extended in order to perform a joint analysis. In the extended model, hypotheses regarding effects of sex and age were tested and the model was simplified by stepwise omission of non-significant effects. This included a test for no effects of genes on hand eczema.

Clinical follow-up

Procedure

A subset of the respondents was invited to a clinical examination. The procedure used was a letter of invitation. In the accompanying letter, the purpose of the study was again described in very general terms whereas the planned test procedure was described in detail. The invitation was repeated by a telephonic follow-up a week later. If the telephone number was unlisted (as well as unavailable from other sources such as the co-twin) and the person did not respond to the invitation, one reminder with a self-addressed stamped envelope was sent 3 months later.

Inclusion criteria

Those eligible for invitation were the twins, where both persons in the pair lived within 60 km of the centre of Copenha-

gen, where both members in the pair had returned the questionnaire, and where at least one of them had reported any skin symptom or hand eczema, i.e. had answered “yes” to any of the questions. Initially only the respondents with positive answers were invited. Following confirmation of eczema-specific symptoms, the reportedly asymptomatic co-twins were then invited.

A total of 1,327 persons were invited. Because they were selected by positive reports of skin symptoms on the hands, 65% of the invited group were women as expected from the prevalence sex difference of this disease. Of the invited, 1,076 (81%) were eventually examined.

Exclusion criteria

If the respondent was pregnant or nursing, the invitation was withdrawn or postponed until the nursing period was over. The reason for avoiding this group was that application of epicutaneous patch tests was part of the examination. Even though patch tests are not considered harmful to pregnant or nursing women or their children, the aims of the study did not justify any risk, not even a theoretical one.

In order to optimise the composition of the group clinically examined for possible further genetic analysis, participation was discouraged (though not denied) if the co-twin was known to be unavailable for a corresponding examination.

A few were excluded after the telephonic contact because they could definitely ascribe their reported symptoms to a dermatologist-diagnosed non-HE condition, mainly generalised psoriasis. If there was any doubt at all of the diagnosis, they were asked to be formally examined.

Examination

The examination was performed at the hospital (N=809) or in the homes of the participants (N=267). It included a structured interview as well as a clinical assessment of any skin changes on the hands. The main part of the interview was a detailed history taking of previous occurrences of eczema-characteristic symptoms on the hands. These were:

- vesicles (tiny blisters)
- papules (spots)
- scaling
- fissures (cracks)
- redness
- swelling
- exsudation
- lichenification (thick rough skin)

To qualify for hand eczema according to the examination, the appearance (or a history) of vesicles, papules, or exsudation or at least two of the other hand eczema symptoms (scaling, fissures, redness, swelling, or lichenification) should have had been present on at least 2 occasions or for at least 3 weeks. The participants were shown photographs of hand eczema, each with a single predominant morphology, and asked if they could recognise that symptom from their own experience. This case definition was adapted from the RC-criteria originally suggested by Rycroft⁸⁸ and modified by Coenraads⁸⁶. The sign of grouped pustules was not included, as the author considered it too un-specific in relation to hand eczema.

When actual symptoms were visible at the time of the clinical examination, they were recorded in a similar manner by the author.

The RC-definition was not specific in some cases of already diagnosed Psoriasis (N=11), Mb. Darier (N=2), and Porphyria Cutanea Tarda (N=2). These cases were re-classified by the author when encountered and excluded from the analysis.

Patch tests

A patch test (TrueTest®, Alk-Abello) containing the European Standard Series of 24 common skin allergens was mailed to the participants prior to the examination. The test is a plaster containing the substances in a concentration that normally elicits a skin response only in individuals previously sensitised to the allergen. For this study, a commercially available standard test was chosen because it could be applied by the participants themselves before the examination.

The participants placed the test on their backs 3 days before examination and removed it after 2 days (marking the location of the plaster with a pen). Readings of the skin reactions were performed and interpreted in accordance with the ICDRG guidelines³⁶ 72 hours after the application i.e. 24 hours after the removal of the patch test. The severity of a positive allergy reaction was recorded as (+), (++) , or (+++). All readings were done by the author.

Skin prick tests for type-1 allergens were not performed in this study because of the option offered of doing the examination in the home combined with the risk of inducing anaphylaxis by skin prick test. Skin prick test is seldom necessary in the diagnosis of hand eczema, because the most common forms of allergic hand eczema are caused by type IV allergies.

Proband criteria (clinical part)

In order to qualify as a proband in the clinical study, a person should:

1. be born 1953–76
2. belong to a twin pair, where both lived within 60 km from Copenhagen
3. belong to a twin pair, where both returned the questionnaire
4. have answered “yes” to any question in the questionnaire (symptoms or eczema)
5. have hand eczema according to the set criteria

Statistics & validation

Concordance rates were calculated by the formula

$$CR = \frac{2C_1 + C_2}{2C_1 + C_2 + D}$$

and 95% confidence intervals were constructed by simulation. The null hypothesis of identical concordance rates in the MZ and DZ group was tested against the hypothesis of greater concordance rate in the MZ than in the DZ group by simulation.

Finally, the RC-diagnosis of hand eczema (based on the history and presentation of hand eczema symptoms) was compared with the self-reported diagnosis from the originally answered questionnaire.

Results

Study cohort

When the study cohort was compared with the background population, there was an overrepresentation of younger persons ($p < 0.0001$), of women ($p = 0.0005$) and of inhabitants of the counties bordering the greater Copenhagen area (the counties of Frederiksborg and Roskilde, table 5).

Table 5. Distribution by area of the study cohort and background population.

Area	Twin cohort	Population	p
City of Copenhagen	28.17%	31.48%	<0.0001
County of Copenhagen	23.35%	24.17%	0.0976
County of Frederiksborg	15.01%	13.87%	0.0132
County of Roskilde	11.04%	9.36%	0.0002
County of Vestsjælland	12.53%	11.56%	0.0341
County of Storstrøm	9.80%	9.57%	0.3152

Questionnaire study

Representativity

The response rate was 84% after the one reminder. Thus, 5,610

Table 6. Life time prevalence of self-reported hand eczema by sex and age.

	Born	Cases	Population	Prevalence
Women	1953–60	167	823	20.29 %
	1961–68	274	1,339	22.11 %
	1969–76	203	928	21.19 %
Men	1953–60	94	783	12.01 %
	1961–68	117	873	13.40 %
	1969–76	101	864	11.69 %

twin individuals were available for analysis. Non-responders were primarily younger than responders ($p = 0.0006$) and male ($p < 0.0001$). The non-responders did not differ with respect to place of residence ($p = 0.1769$). The frequencies of MZ and DZ pairs were identical in the responder and the non-responder group as well.

Prevalences

A total of 956 (17%) reported a previous or present episode of hand eczema (21% of the women and 12% of the men), while 1,482 (26%) reported one or more symptoms. The most frequent symptoms were “itching with cracks” and vesicles, “tiny blisters” (both 15%). The most frequent single symptom, i.e. not combined with other symptoms, was vesicles (5.3%). The point prevalence of self-reported hand eczema was 4.7%. The proportion of hand eczema was fairly constant in the different age groups of each sex and about 1.8 times more frequent in women than in men (table 6). These observations are tested statistically in the parametric model used for correlations in liability (see table 10).

Concordance rates

The recurrence risk, i.e. the probability of a twin having a disease given the co-twin has it is in a population given by the probandwise concordance rate. In the questionnaire study, the study base consisted of all twin pairs within a well-defined geographic area, irrespective of disease status, and all cases were independently ascertained, i.e. all cases were probands and there were no secondary cases. Therefore, the recurrence risk could be estimated by the formula for casewise concordance.

When stratifying for age, statistical significance was not obtained in all the older age groups, but the ratio between MZ and DZ concordance rates (the rate ratio, RR) was from 1.5 or greater in all groups, except for women born 1953-60 (table 7).

Because all concordance rates but one showed the same trend within age groups, age was subsequently omitted, and the concordance rate for self-reported hand eczema in women was then 49% for MZ pairs versus 32% for DZ pairs. In men, the corresponding values were 31% for MZ pairs and 15% for DZ pairs. Both differences were statistically significant (table 8).

Table 7. Probandwise concordance rates (CR) by sex and age (questionnaire)

	Born	Zyg	C	D	CR	95%CI	RR	p
Women	1953–60	MZ	6	33	26.67%	[9.76% ; 44.0%]	0.85	0.6453
		DZ	15	66	31.25%	[17.98% ; 42.72%]		
	1961–68	MZ	26	62	45.61%	[32.38% ; 56.91%]	1.78	0.0077
		DZ	14	81	25.69%	[13.73% ; 36.21%]		
	1969–76	MZ	27	30	64.29%	[51.95% ; 74.73%]	1.52	0.0093
		DZ	18	49	42.35%	[28.21% ; 54.35%]		
Men	1953–60	MZ	4	24	25.00%	[6.90% ; 44.44%]	1.53	0.2174
		DZ	4	41	16.33%	[4.35% ; 30.19%]		
	1961–68	MZ	6	25	32.43%	[12.12% ; 48.78%]	1.72	0.1226
		DZ	5	43	18.87%	[4.08% ; 31.58%]		
	1969–76	MZ	6	23	34.29%	[12.90% ; 55.0%]	3.34	0.0253
		DZ	2	35	10.26%	[0% ; 23.81%]		

Table 8. Probandwise concordance rates (CR) by sex (questionnaire)

		C	D	CR	95% CI	RR	p
Women	MZ	59	125	48.56%	[40.00% ; 55.69%]	1.50	0.0014
	DZ	47	196	32.41%	[25.18% ; 39.07%]		
Men	MZ	16	72	30.77 %	[18.56% ; 41.44%]	1.97	0.0156
	DZ	11	119	15.60 %	[7.41% ; 23.13%]		

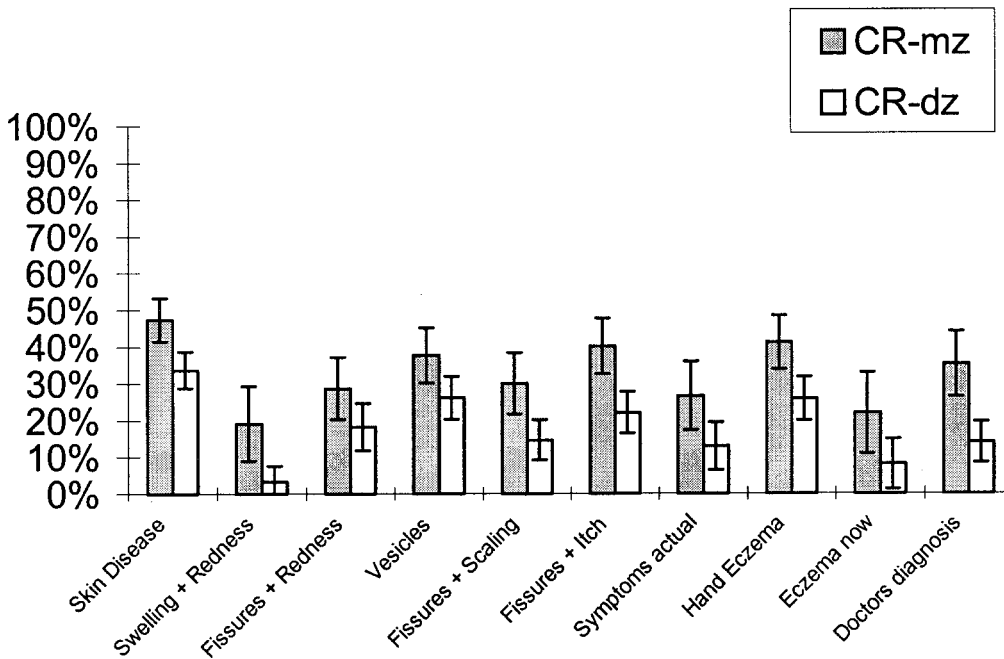


Figure 3. Individual questions, concordance rates with 95% confidence intervals.

Thus the risk of previous or present hand eczema given that the co-twin was affected was at least 1.5 times greater in the groups of MZ twins compared with the groups of DZ twins. This result implies a hereditary component in the pathogenesis of hand eczema.

Individual questions

When each question was examined separately, similar significant differences between the MZ and DZ group were observed. The results of each symptom question were very similar, and they correlated with self-reported hand eczema (figure 3).

As could be expected, each question is also associated with any other question so that a large proportion of persons confirming one question will tend to confirm any of the other questions as well. Table 9 below shows the chance adjusted kappa agreement between each symptom question compared with each other and with self-reported hand eczema.

The best overall association was seen with “Cracks and Itching”, which also showed the closest association with self-reported hand eczema. The least overall and eczema associated symptom was “Swelling and Redness”. Vesicles showed the second best association with self-reported hand eczema but nevertheless a comparatively poor association with any of the other eczema symptoms. The reason for this was the large number of cases with vesicles only.

Table 9. Association between individual questions and self-reported eczema.

S+R	Swelling and Redness				
0.41	C+R	Cracks and Redness			
0.25	0.33	V	Vesicles		
0.30	0.52	0.38	C+S	Cracks and Scaling	
0.34	0.61	0.48	0.53	C+I	Cracks and Itching
0.26	0.36	0.38	0.35	0.42	ECZ Eczema

Liability and heritability

When applying the parametric model and stratifying for age and sex, the genetic contribution was statistically significant in the younger age groups but not in the older subjects, where the total numbers were too small (table 10).

Application of the extended parametric model analysis, however, showed that it was possible to simplify this general model. The tendency towards developing hand eczema (the “distance” between the mean liability and the threshold) was shown to be independent of zygosity (p=0.9304) and age (p=0.6445) but dependent on sex (p<0.0001). The latter observation corresponds to the almost doubled prevalence of hand eczema in women compared with men. In contrast to this, the correlations in liability were found to be independent of sex (p=0.2097) and age (p=0.6378) but dependent on zygosity (p<0.0001), as

Table 10. Correlations in liability (ρ_{MZ}, ρ_{DZ}) and heritability (h^2) estimates.

	Born	ρ_{MZ}	ρ_{DZ}	p	h^2	95% CI
Women	1953–62	0.41	0.26	0.3743	0.29	[0.00 ; 0.85]
	1963–76	0.61	0.25	0.0015	0.73	[0.26 ; 1.00]
Men	1953–62	0.40	0.13	0.2560	0.54	[0.00 ; 1.00]
	1963–76	0.47	0.03	0.0183	0.88	[0.00 ; 1.00]
All		0.52	0.19	<0.0001	0.65	[0.33 ; 0.93]

to be expected for a hereditary disease. The correlation for the MZ group was estimated to be 0.52 [0.40 ; 0.61] and in the DZ group to be 0.19 [0.09 ; 0.31]. The corresponding heritability estimated under the ACE-model was 0.65 [0.33 ; 0.93] and the effect of shared environment was -0.13 [-0.36 ; 0.13].

Clinical examination

Non-participants

1,327 persons were invited for a clinical examination and 1,076 of these attended. Of the 251 who did not, 87 refused participation or failed to appear at the scheduled examination, 83 did not respond to the letters and could not be contacted because of unlisted telephone numbers, 48 were excluded because of pregnancy or nursing, 22 were excluded because their twin sib was already known to be unavailable for the study, 9 did during the telephone conversation substantiate a non-HE diagnosis of their symptoms (mainly generalised psoriasis), and 2 were deceased. The sex ratio was the same in the participating and the non-participating group.

The age distribution of the original study cohort of 6,666 persons and that of the participants was very similar, while the age distribution of the non-participants showed some over-representation in the birth cohorts of 1961–68 (figure 4).

Reported and observed signs

The number of persons who at the examination reported or showed any of the eczema signs used for diagnosing hand eczema by the RC-criteria (pustules excepted) is given in table 11. All signs, that were observed by the author during the examination, were included in the number of reported signs.

Concordance rates

From the clinical examination 244 concordant and 204 discordant twin pairs were obtained, and the results are shown in

Table 11. Number of persons examined who reported or showed hand eczema signs

	Never	Reported	Showed
Papules	828	248	25
Vesicles	488	588	45
Exudation	856	220	5
Erythema	612	464	82
Scaling	626	450	183
Oedema	903	173	2
Fissuring	562	514	50
Lichenification	807	269	106

detail in table 12. The number of concordant pairs comprising 2 probands (C_1) was about the same as the number of concordant pairs comprising secondarily ascertained disease-cases (C_2).

Because of limited statistical power it was not possible to test for effect of age, but assuming that the possible genetic effect was independent of age, as observed in the questionnaire part, the concordance rate for clinically determined hand eczema in women was 70% for MZ pairs versus 71% for DZ pairs. In men, the corresponding values were 59% for MZ pairs and 42% for DZ pairs. The latter difference was statistically significant (table 13).

Because the sampling method of the clinical study involved a two-step selection procedure, the parametric statistical model for correlations in liability was not applicable for these data.

Self-reported vs. RC-diagnosis

Comparison of the self-reported diagnosis with the RC-diagnosis from the interview and examination showed a fair agreement ($\kappa=0.29$) between the two diagnoses. Correspondingly there was a marked association between the two (OR=

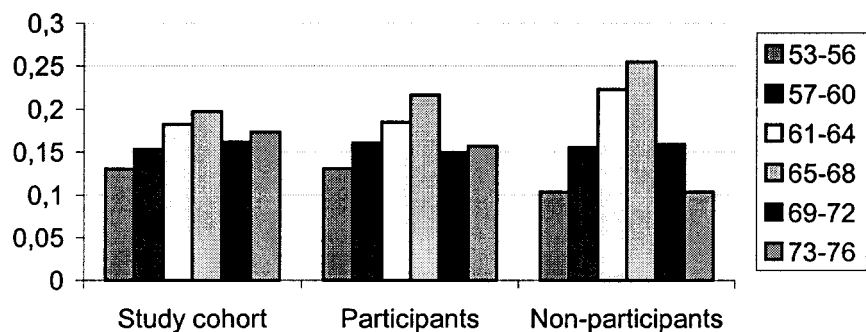


Figure 4. Age distribution.

Table 12. Probandwise concordance rates (CR) by sex and age (clinical)

	Born	Zyg	C ₁	C ₂	D	CR	95%CI	p
Women	1953–65	MZ	25	19	29	70.4%	[60.0% ; 79.6%]	0.6509
		DZ	27	27	30	73.0%	[63.3% ; 81.4%]	
	1966–76	MZ	24	15	28	69.2%	[57.8% ; 79.2%]	
		DZ	24	26	32	69.8%	[59.6% ; 78.6%]	
Men	1953–65	MZ	9	5	11	67.6%	[48.3% ; 83.8%]	0.0423
		DZ	7	10	28	46.2%	[30.0% ; 60.7%]	
	1966–76	MZ	5	8	17	51.4%	[31.3% ; 69.2%]	
		DZ	5	8	29	38.3%	[22.2% ; 54.0%]	

Table 13. Probandwise concordance rates (CR) by sex (clinical)

		C ₁	C ₂	D	CR	95%CI	p
Women	MZ	49	34	57	69.8 %	[62.1% ; 76.8%]	0.6296
	DZ	51	53	62	71.4 %	[64.5% ; 77.6%]	
Men	MZ	14	13	28	59.4 %	[45.3% ; 71.6%]	0.0260
	DZ	12	18	57	42.4 %	[30.8% ; 53.4%]	

Table 14. Agreement between self-reported and RC-defined HE

Self-reported HE	RC-HE yes	RC-HE no		Sensitivity	53%	
	407	42	449	Specificity	86%	
HE not reported	368	259	627	PPV	91%	
	775	301	1,076	NPV	41%	
				OR	6.82	[4.78 ; 9.73]
				Kappa	0.29	[0.24 ; 0.34]

6.82). These results and the sensitivity, specificity and predictive values of the self-report are given in table 14.

The main reason for disagreement was the large group of persons fulfilling the RC-criteria for hand eczema but who themselves perceived their symptoms as “ordinary skin-dryness”. The 42 persons who reported HE but did not fulfil the RC-criteria most often had undiagnosed psoriasis or had answered yes to eczema in the sense of “psoriasis-eczema”.

Further subdivision of the questionnaire answer pattern (table 15) showed that over one third of persons, who considered themselves to have always been completely free of hand eczema symptoms, still fulfilled the RC-criteria for previous or present hand eczema.

Table 15. Agreement between reported HE symptoms and RC-defined HE

	RC-HE yes	RC-HE no	
Self-reported HE	407	42	449
Self-reported symptoms	240	58	298
Symptoms not reported	128	201	329
	775	301	1,076

Current signs

A total of 151 persons (14%) had visible, current hand eczema at the time of investigation according to the RC-definition (another 6 presented with the relevant symptoms but had only had them for less than 3 weeks and never before). Of the 151 with current hand eczema according to the RC-criteria, 78 had in the questionnaire reported that it was confirmed by a physician, another 16 had declared self-reported hand eczema without medical confirmation. 49 had reported the symptoms, but not interpreted them as hand eczema, while 8 had denied having symptoms altogether. The most commonly observed signs were scaling and lichenification (table 11), and the distribution of reported symptoms in persons with current hand eczema was similar to the total group examined. 16 pairs were concordant for current hand eczema (8 MZ and 8 DZ, 11 female and 5 male).

Atopic dermatitis

Of the persons examined, 118 fulfilled the operational criteria for AD, that was established by the UK working party as an adaptation of the Hanifin-Rajka criteria^{64,65}. Of these, 106 had hand eczema according to the RC-criteria and 91 had self-reported hand eczema according to the questionnaire. Of the 958 persons who did not have AD, 669 had hand eczema according

to the RC-criteria and 358 had self-reported hand eczema. The resulting odds-ratio for association between AD and RC-defined HE was 3.82 [2.07 ; 7.04]. For AD and self-reported HE the OR was 5.65 [3.61 ; 8.85].

Persons with AD as a group were a little younger (median age 30.5 years) than persons without AD (median age 32 years). The distribution was fairly similar otherwise (figure 5).

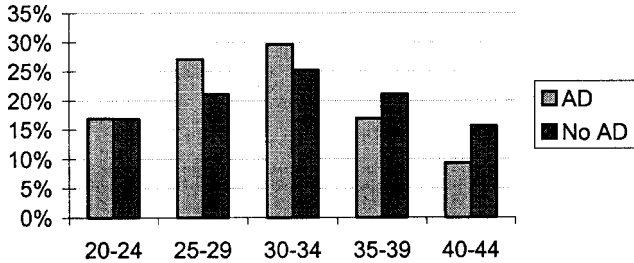


Figure 5: Age distribution of persons with and without AD

If atopic hand eczema (AHE) is defined as cases with HE according to the RC-criteria and with AD, 15 pairs were concordant for AHE, 12 female and 3 male. All female pairs were primarily ascertained, whereas 2 out of the 3 male pairs were secondarily ascertained. Concordance rates for each sex and zygosity showed a rate ratio of 1.9 in both sexes, suggesting genetic influence in women as well as in men.

Table 16. Number of allergic skin reactions by allergen, sex and self-reported HE

	Women		Men		Allergies
	HE	÷	HE	÷	
1 Nickel	89	75	3	3	170
2 Wool alcohols	0	0	0	0	0
3 Neomycin	1	1	1	0	3
4 Chromate	4	0	1	2	7
5 Caine mix	0	0	0	0	0
6 Fragrance mix	8	5	1	3	17
7 Colophony	6	7	4	1	18
8 Epoxy resin	4	3	0	0	7
9 Quinoline mix	0	0	0	0	0
10 Balsam of Peru	0	1	0	0	1
11 Ethylenediamine	4	0	0	0	4
12 Cobalt	8	4	0	0	12
13 p-t-BFR	4	6	2	1	13
14 Paraben mix	0	1	0	1	2
15 Carba mix	3	0	0	0	3
16 Black rubber mix	1	1	0	0	2
17 Kathon CG	4	0	1	1	6
18 Quaternium-15	2	1	0	0	3
19 Mercapto benzotriazole	0	0	0	0	0
20 p-phenylene diamine	0	0	0	0	0
21 Formaldehyde	2	0	1	0	3
22 Mercapto mix	0	1	0	0	1
23 Thiomersal	9	8	1	6	24
24 Thiuram mix	5	1	0	0	6
All tested	306	391	143	236	302 1,076

Patch tests

A total of 302 allergies in 244 persons were observed. The results are presented in table 16 below stratified for sex (W/M) and self-reported HE (+/-) because of the known deviations in the study group from the background population with respect to these parameters and because of their possible association with contact allergy. It should be remembered that the following results were obtained in a group of persons selected either for skin symptoms on their hands, or for close family relationships with people with symptoms. Therefore, the results must be cautiously interpreted in terms of external validity.

In all, 215 out of 697 (31%) women and 15 out of 379 (4.0%) men showed contact allergy to at least one substance. The sex difference is largely explained by the many nickel allergies seen in women.

Nickel skin reactions

In order to examine the possible association between allergy and hand eczema, all nickel skin reactions were stratified by sex and self-reported HE (table 17).

Table 17. Number of nickel skin reactions by severity, sex and self-reported HE.

	Women		Men	
	HE	÷	HE	÷
All	306	391	143	236
any visible reaction	113	99	5	16
	37%	25%	3.5%	6.8%
follicular or positive reactions	107	95	3	10
	35%	24%	2.1%	4.2%
any positive allergy reaction	89	75	3	3
	29%	19%	2.1%	1.3%
strongly positive (++,+++)	75	51	2	2
	25%	13%	1.4%	0.8%
very strongly positive (+++)	22	13	1	1
	7.2%	3.3%	0.7%	0.4%

Out of 306 women reporting hand eczema, 113 had a visible skin reaction to the nickel patch test, and of these 89 had a nickel allergy (defined as a +, a ++, or a +++ reaction). Similarly, out of 391 female self-reported hand eczema non-cases, 99 showed a visible reaction to the patch tests, including 75 with nickel allergy.

The proportion of nickel allergy positive individuals seemed generally larger in the groups with hand eczema in both sexes than in the groups without hand eczema, and this difference increased with increasing severity of the reaction. The difference seemed apparent even for the sub-clinical follicular and doubtful reactions in women, though the pattern was reversed in the male group.

Of the 536 persons aged 20–31 years, 77 had a nickel allergy (14%), while 93 of the 540 persons aged 32–44 years had a nickel allergy (17%). Thus no association between age and nickel allergy was seen (p=0.1811).

For other allergens than nickel the numbers were too small to show convincing differences.

If nickel hand eczema (NHE) is defined as cases with HE according to the RC-criteria and with nickel allergy, 21 pairs

were concordant for NHE; all were female. The concordance rates were similar in the MZ and DZ group.

Discussion

Study cohort representativity

Comparison of the study cohort with the background population showed an over-representation of younger persons and of women. As previously mentioned, the method used when establishing the Twin Register was dependent on the twins having been registered at the same address by the civil registration system in 1968 and thus older twins were more likely to be missed. Since then, the Danish Twin Register has continually traced older twin pairs and the former observation reflects its level of completeness at the start of the study. The female predominance might be explained by non-disease-dependent volunteer bias favouring participation of women. Also disease-dependent but not disease-specific volunteer bias might have been present, because women as a group more often report disease than men¹¹⁷ but the possible effect of this seems of little importance when analysing same-sex intrapair correlations.

Questionnaire study

Representativity

Comparison of the responders with the study cohort also showed overrepresentation of women but under-representation of younger persons. Because hand eczema is more likely to occur in women, a possible effect of disease specific volunteer bias cannot entirely be ruled out; but such bias can hardly explain the difference in age profiles observed nor the original difference of the study cohort from the background population. In the large Gothenburg hand eczema study³¹ sex was significant in the dropout analysis (favouring female participation) but no effects of age or disease status were found. The assumption that younger men are generally more likely to refuse to participate than women may account for the major part of the differences observed; this is supported by a previous allergy study in an unselected Danish population⁷⁹ and the dropout analysis of a national general health survey performed in Denmark¹¹⁸.

Prevalences

The point prevalence of self-reported hand eczema is similar to the results of other population studies using questionnaire screening and subsequent clinical follow-up^{12,119} even though the age groups differ in each study. Furthermore, the present study had fairly similar prevalence rates in the different age groups (table 6). In accordance with previous studies, this study confirms that hand eczema is almost twice as common in women as in men¹.

Two possible explanations for the difference in sex-specific prevalence are different susceptibilities to allergens/irritants and increased environmental pressures. Increased susceptibility in women has been rejected in several studies^{72,73,120}, so increased environmental pressures has been the preferred hypothesis (hence the clinical expression "Housewives' dermatitis"¹²¹⁻¹²⁴), and in consequence some focus has been put on the combination of manual labour and added domestic duties commonly occurring in women. Added domestic exposure is difficult to quantify, but proxy-variables such as absence of washing or dish-washing machines, and presence of small children in the

household are recognised risk-factors for developing hand eczema^{30,122,125}.

Concordance rates

Because concordance rates for a given trait depend on the underlying risk, they must necessarily be different for each sex as a consequence of the sex-specific prevalences, but the differences between the MZ and DZ groups remain of a similar and significant magnitude after stratification for sex.

The women in the oldest birth cohorts of 1953–60, did not show the same differences in concordance rates between the MZ and DZ groups as the other subjects. In this subgroup, the 95% confidence intervals were very wide ([9.76% ; 44.00%] and [17.98% ; 42.72%] in the MZ and DZ groups respectively), and a true difference in the concordance rates might well have been missed due to lack of statistical power.

Individual questions

The differences in CR between the MZ and DZ groups were also significant for each of the symptom questions as well as for present symptoms or present hand eczema (figure 3). The last two findings suggest that chronic forms are hereditary, because we would expect a subgroup reporting current symptoms to represent an over-sample of the more chronic forms of hand eczema. The reason for this assumption is that diseases of relatively long duration have a better chance of being currently present at the time of investigation than diseases of shorter duration. With the exception of the symptom question "redness with swelling", self-reported hand eczema seemed to be equally strongly associated with all of the specific symptom questions. This is in accordance with the discouraging results of previous attempts to connect specific morphology with aetiology in hand eczema^{18,85,126}. Swelling is a feature of the relatively infrequent acute severe eczema and this may explain the lower association with the other symptoms. In a patient's history, swelling and redness can also be symptoms of a urticarial reaction.

Age dependency

A stronger effect of genetic contribution seemed to be present in the younger age groups of either sex compared with the older ones, although the number of participants was too small to confirm it statistically. Quite the opposite result could theoretically be expected because of the possibility that discordant pairs in time could be concordant because of late-onset hand eczema. However, previous investigations have shown that onset of hand eczema usually occurs early in life^{5,119} so this effect should not be considerable.

Assuming that the results observed in this study are indicative of a real age dependency, a possible explanation could be that the demonstrated inherited liability to hand eczema in fact depends on additional excessive environmental pressures on the hands, predominantly experienced in the younger years where occupational as well as domestic exposure, for example to soapy water, could be higher³⁰. The reporting of hand eczema in the older age groups might then be affected by recall bias favouring persisting chronic hand eczema, while forgetting transient hand eczema episodes of younger years.

Liability and heritability

Likewise, the extended parametric model analysis showed that whereas the tendency towards developing eczema was dependent on sex only, the correlations in liability were dependent on zygosity but not on either sex or age. That the tendency to develop hand eczema does not depend on age or zygosity additionally strengthens the validity of the conclusions inferred from a classical twin analysis.

Analysis of the extended parametric model confirmed the female sex affinity with hand eczema. The common heritability calculated under the classic ACE-model (0.65) was highly significant, and this suggests that the observed correlations in liability and the marked difference in these between the MZ and DZ group are the result of genetic contribution rather than the effect of previous or present common environmental pressures to the hands. That the effect of shared environment turned out negative, although not significantly so, challenges the suitability of the ACE-model for hand eczema. Prerequisites for the heritability estimate are that there are no genetic heterogeneity in the disorder and that no major gene contributes to the causation¹²⁷ Furthermore, the model assumes that there is no variance due to non-additive genetic effects, i.e. effects due to gene-gene interaction. At this point it is not possible to determine whether hand eczema is a disorder that fulfils these criteria. The correlations in liability as such, however, are not dependent of the prerequisites for the ACE-model estimate and are significantly different in the MZ and DZ groups. Thus, the observation of hereditary risk factors for hand eczema remains valid.

Common environmental exposure

The questionnaire does not attempt to assess the level of exposure of the hands to environmental factors. Instead, the variability of environmental exposure was assumed to be distributed in a zygosity independent way, i.e. MZ twins were not believed to expose their hands more similarly within pairs than DZ twins. Furthermore, because the study area generally contained jobs in light industry and administration as opposed to large workplaces of heavy industry, no considerable subset of the study population was to our knowledge exposed to environmental pressures in any extreme amount.

Gene-environment interaction

When observing an inherited liability towards developing hand eczema, the question arises of whether this liability requires any additional or initiating environmental exposure in order to manifest as hand eczema, or whether it is truly constitutional. Because this study is population-based i.e. not selected for any extreme or homogenous exposure, the results observed support the conclusion that the inherited liability effectively does not require environmental pressure. Even so, the true underlying mechanism might still essentially be dependent on some low level of unavoidable everyday environmental exposure as that could produce the same observation.

Zygosity

The presented analyses assume that the zygosity diagnoses are correct in all twin pairs. This is, of course, unlikely, as the similarity method used¹¹⁶ has a misclassification rate of 2–4%¹²⁸. The obvious solution in smaller scale studies would be to test

the zygosity by serological markers in all participants, but that approach was clearly impracticable in this study.

Clinical validation

Representativity

The participation rate in the clinical follow-up was very satisfactory (81%). Non-participation was mainly because of pregnancy or nursing, though some were recovered by postponing the examination past the nursing period.

While 87 refused or failed to attend, 83 never responded to the letters. As they couldn't be contacted by telephone either, it is unresolved if they ever actually received the letter. Formally the post-office may not deliver letters to an invalid address, but we noticed this in some cases, where the participants were instead traced through their sibs.

No overt association between participation willingness and self-reported eczema or sex was seen. The over-representation of the mid age group among the non-participants may be explained by the current usual age of childbearing in Denmark (late 20s to mid 30s). Among the explanations given for refusal, a recurrent one was attempted pregnancy.

In summary, the participation was high and not obviously dependent on disease status. This is possibly best explained by the well-known generally high motivation of twins compared with similar groups, and perhaps the fact that a non-invasive free allergy test was a declared part of the examination. Currently there is a considerable awareness of and interest in allergic diseases in the general population and the request for participation might well have been received as an offer of a free allergy check-up.

Concordance rates

The twin analysis of the clinical study did not confirm the marked differences in concordance rates between MZ and DZ twins seen in the questionnaire study. The expected genetic influence was only significantly demonstrated for the male group. During the planning of the clinical part of this study, the results from the questionnaire study encouraged our assumption that genetic contribution to HE was so distinct, that a clinical study with more detailed criteria would produce even more marked results. Still, even if 1076 persons examined seems high for a clinical study, the necessary sample sizes for twin studies on non-continuous traits (here: presence/absence of disease) can often be very high. Subdividing a threshold trait (e.g. in "no disease", "possible disease", "little disease", and "much disease") can help a little in recovering power¹²⁹, but would not have improved the results obtained for the women, as no trend was seen. A separate explanation of the discrepant results is the difference in case definitions discussed below.

Self-reported cases vs. RC-cases

Diagnosis by self-report of diseases with a gliding transition to non-disease may increase sensitivity in families with another affected member because of increased awareness of the disease. The effect on specificity is unclear and over-reporting is a possibility. There is, however, no reason to suspect that this hypothesised awareness effect should be zygosity-dependent. Thus even if self-report may over-sample concordant pairs, this effect would probably be the same in the groups of MZ and DZ

twins and of minor consequence to the conclusions inferred from a classical twin study.

Several studies^{12,86,87} have demonstrated good accordance between self-reported and medically diagnosed hand eczema, though self-reported diagnosis results in an under-estimation of the true prevalence. Consequently, some individuals with hand eczema, reporting symptoms but not hand eczema, have inevitably been missed and were not included in the present analyses, i.e. the sensitivity could have been higher. For the purpose of a study of this kind, however, specificity had to take precedence.

The accordance between the self-reported diagnosis and the RC-diagnosis was unexpectedly lower than in previous validity studies. There are several possible explanations for this. The study by Smit et al.⁸⁶ concerned recent (within 1 year) manifestations, and the participants (being hospital nurses) might have been especially symptom-aware. The study by Yngvesson et al.⁸⁷ considered only currently occurring hand eczema, which bypasses the problems of how to interpret the history of past symptoms.

The main problem with the RC-diagnosis as used here lies in the temporality. Formally the mandatory (usually 2) symptoms should always appear simultaneously during the required 3 weeks or at repeated intervals. In practice, it proved impossible for the participants from memory to account for simultaneity in such detail. When the RC-diagnosis was more certain, as with the 151 cases with current hand eczema, the sensitivity of self-reported hand eczema increased from 53% to 62%.

In conclusion, the self-declared diagnosis seemed to make a better job of separating RC-diagnosed cases from non-cases than did the RC-criteria in separating self-reported cases from non-cases. Therefore, the main part of the presented analyses has relied on the self-reported diagnosis from the questionnaire rather than the RC-criteria.

Atopic dermatitis

In all, 118 persons (11%) had AD according to the Hanifin-Rajka criteria in the UK working party's formulation. This number is somewhat lower than theoretically might have been expected in a subgroup selected for hand eczema, but a marked association between hand eczema and AD was observed. This association was seen both with the self-reported diagnosis and with the RC-diagnosis but was more pronounced with the former.

When calculating concordance rates in the subgroup of cases with both HE and AD, marked differences between the MZ and DZ groups could be seen. This was to be expected given the strong heredity known in AD and the known association between AD and HE. It does, however, not explain all of the observations suggesting genetic influence in the entire study, as AD was only present in 22 male and 66 female pairs with HE. In contrast, the genetic influence was also seen in the entire group of clinically examined men (table 12) comprising 142 pairs. As the number of person in the clinical study cohort with AD is relatively small, AD does not appear to be the main explanation of the genetic influence observed, though it was a contributing factor.

Patch tests

The distribution of positive patch test reactions were similar to that encountered from a previous population-based study⁷⁹ with a marked frequency of nickel allergies (16%) followed by Thiomersal (2.2%), Colophony (1.7%) and Fragrances (1.6%).

Table 18: Most frequently encountered allergens in the current study (C) compared with a previous study of hand eczema patients, (M)³¹ and a previous study in unselected individuals, (N)⁷⁹.

	Women			Men		
	M	N	C	M	N	C
Nickel	22%	11%	24%	0.3%	2.2%	1.6%
Thiomersal		3.1%	2.4%		3.6%	1.8%
Colophony	3.4%	1.0%	1.9%	2.5%	0.4%	1.3%
Fragrance	5.7%	1.0%	1.9%	6.2%	1.1%	1.1%
Cobalt	9.4%	1.4%	1.7%	1.1%	0.7%	0
p-t-BFR		1.0%	1.4%		1.1%	0.8%

Because the participants in the present study were selected by hand skin symptoms, an over-sample of allergies causing (or associated with) such symptoms might theoretically have occurred. This may well be the case, as the frequencies observed in the examined group lie somewhere between those of the previous studies on a randomly selected sub-population and a hand eczema affected group (table 18).

A suspicion that nickel allergy may be associated with hand eczema was further strengthened by the higher prevalences found in the eczema reporting groups than the reportedly non-eczematous groups (table 14). A history of hand eczema following direct exposure to nickel was only obtained in a few cases. Nevertheless the association seems to be there, although it should be investigated in a more representative group of persons than the current group. A previous study⁷ has demonstrated a similar association.

Some differences in the test methods need further consideration. In the study by Nielsen, reading of patch tests took place 2 days after application as opposed to the 3rd day reading used here and in the other study of hand eczema patients by Meding. As a result, the results obtained from the 2nd day readings may well have missed a number of true allergies emerging after the reading, as about 10% of all true allergic reactions are missed when using a 2nd day patch reading alone.

Another explanation of the relatively high proportion of nickel reacting persons could be different age distributions in the studies. The two previous studies included persons from 15 to 69 years of age and in the randomly selected group demonstrated a large clustering of nickel allergy among the youngest. The present study group is homogenous with respect to allergy distribution over age and it consists entirely of people born in the same years as the youngest group in the Nielsen study. The increased prevalence of nickel allergy observed could then result from the increasing popularity of skin piercing in this particular age group.

A recent study¹³⁰ indicate that the nickel sensitisation rate may have begun to decrease again. Possible reasons for this may be that skin piercing may no longer be in fashion, or perhaps that increased awareness of nickel allergy has resulted in improved piercing techniques including nickel-free instruments and jewellery.

The concordance rates for persons with both nickel allergy and HE did not suggest that the genetic propensity to nickel allergy seen in a previous study⁷⁸ was a major contributing factor to the genetic influence in hand eczema.

Concluding remarks

Assuming the genetic influence observed in the questionnaire study to be valid, the conflicting results of the clinical study must be ascribed to the different case definition (the RC-criteria) which unexpectedly appeared less specific than self-reported hand eczema. The marked genetic influence on hand eczema recorded from the questionnaire study was, however, confirmed in men as opposed to women. The RC-criteria as used here might have recorded irritant pre-eczematous symptoms which more frequently could occur in a female group because of added domestic irritant exposure.

Atopy played a part in the overall genetic influence, but did not appear to be the main contributor. Especially did atopic dermatitis not seem over-represented in the clinically examined group. A demonstrable effect from genetically determined propensity to contact allergies was not seen.

Future studies should further explore the genetic influence on the development of hand eczema, with a certain emphasis on the part that could not be ascribed to atopy or allergy. A long-term follow-up on relatives to probands with diagnosed hand eczema would be interesting. A family study with additional non-sib relatives in order to establish the possible degree of genetic dominance would also be desirable. Lastly, the sub-clinical and pre-eczematous skin changes in relatives of probands with (hand) eczema as investigated by non-invasive clinical measuring methods are of interest to further investigation of genetic propensity to eczema.

SUMMARY

Hand eczema in a population-based twin cohort of 6,666 persons aged 20–44 years was investigated by means of a questionnaire study with a subsequent clinical examination in a subset comprising 1,076 persons. Results from the questionnaire survey and the clinical examination are presented.

Life time prevalence of self reported hand eczema was 21% in women and 12% in men, while overall point prevalence was 4.7%. The results are in accordance with previous epidemiological studies of hand eczema.

A statistical parametric model was developed to perform a joint analysis, by extension of the Falconer threshold model used in quantitative genetics. Correlations in liability were able to depend on sex and age and non-significant effects were subsequently omitted.

Hereditary factors were found to be of significance for the development of hand eczema, as demonstrated by the proband-wise concordance rates as well as by the parametric model analysis. The recurrence risk was almost twice as high for MZ as for DZ twins in both sexes. In consequence a common heritability estimate of 0.65 (95% CI: [0.33 ; 0.93]) could be calculated. A tendency towards stronger hereditary influence in men and in younger individuals was present but was not statistically significant.

Self reported hand eczema symptoms were present in 26% of the respondents and were associated with each other. No individual symptom patterns presented as specifically hereditary or environmental.

Hereditary factors for hand eczema were observed despite a presumably substantial individual-specific environmental variation. It seems likely that hereditary risk factors may play a significant part in the development of hand eczema in the gen-

eral population when no extreme environmental exposure exists.

The twin analysis of the subsample clinically examined could not convincingly confirm the results from the questionnaire study, except in men. A possible explanation for this was the difference in case definitions.

The comparison of self-reported diagnosis with symptom-based diagnosis revealed a distinct (but unexpectedly weak) agreement between self-reported and symptom-defined hand eczema cases. Recollection errors about the simultaneity regarding previous symptoms might have made the chosen diagnosis criteria sensitive at the expense of specificity.

Patch test results from the clinical study are presented. The frequencies and distribution of demonstrated allergies were similar to previous studies on population-based and hand eczema specific cohorts despite the special selection of persons tested in this study. A quantitative association between nickel patch score and hand eczema is suggested, but should ideally be investigated in a more specific study.

SUMMARY IN DANISH

Håndeksem blev undersøgt i en populationsbaseret tvillingkohorte med et spørgeskema og en efterfølgende klinisk validering. Udgangskohorten bestod af 6.666 tvillingindivider i alderen 20–44 år, hvoraf 1.076 deltog i en efterfølgende klinisk undersøgelse. Resultater fra spørgeskemaundersøgelsen og den kliniske undersøgelse præsenteres.

Livstidsprævalensen af selvrapporeret håndeksem var 21% for kvinder og 12% for mænd, mens punktprævalensen i hele gruppen var 4,7%. Resultaterne er i overensstemmelse med tidligere epidemiologiske undersøgelser af håndeksem.

En statistisk parametrisk model til analyse af data baseret på en udvidelse af Falconers tærskelmodel for kvantitativ genetik blev udviklet. Korrelationer i liability kunne i denne model afhænge af alder og køn, hvorefter ikke-signifikante parametre trinvist blev fjernet fra modellen.

Arvelige faktorer fandtes signifikant at influere på udviklingen af håndeksem vist ved probandvise konkordansrater og i den parametriske modelanalyse. Tilbagefaldsrisikoen var næsten dobbelt så høj i gruppen af enæggede tvillinger som i gruppen af tvæggede. Tilsvarende kunne et generelt heritabilitets-estimat for hele gruppen på 0,65 (95% CI: [0,33 ; 0,93]) udregnes. Der observeredes ikke-signifikante tendenser til kraftigere genetisk indflydelse i de yngre aldersgrupper og hos mænd.

Selvrapporerede håndeksemsymptomer var tilstede hos 26% af dem som besvarede spørgeskemaet, og disse symptomer korrelerede med hinanden. Ingen symptomkonstellation udviklede en særligt stærk eller svag tendens til arvelighed.

Den genetiske effekt kunne påvises på trods af en formentlig udtalt individuel variation i miljøet. Det forekommer derfor sandsynligt, at arvelige forhold kan spille en betydelig rolle i udviklingen af håndeksem i befolkningen, når der ikke forekommer ekstreme miljøpåvirkninger.

Tvillinganalyse af den klinisk undersøgte kohorte kunne ikke overbevisende bekræfte resultaterne fra spørgeskemaundersøgelsen, bortset fra hos mænd. En mulig forklaring er forskellen i sygdomsdefinition i de to studier.

Sammenligningen af spørgeskemadiagnosen med den kliniske diagnose viste en tydelig (men overraskende svag) overensstemmelse mellem selvrapporeret og symptom-defineret håndeksem. Fejlagtig erindring vedrørende overståede symp-

tomers samtidighed kan have gjort den valgte symptombaserede diagnose sensitiv på bekostning af specificiteten.

Resultater fra allergitests (lappeprøver) præsenteres. Prævalensen og fordelingen af de fundne positive allergiprøver svarer nogenlunde til tidligere studier på befolkningsbaserede og håndeksemspecifikke populationer til trods for den særlige udvælgelse af personerne, som blev testet i denne undersøgelse. En kvantitativ sammenhæng mellem positiv nikkellappeprøvens styrke og håndeksem syntes at være til stede, men fundet bør efterprøves i en undersøgelse som er målrettet mod at teste denne hypotese.

STATISTICAL APPENDIX

The threshold model

The threshold model originally proposed by Falconer⁹⁰ in the parametrisation described by Neale and Cardon¹³¹ was used to analyse the data. For each twin we have recorded whether or not hand eczema was present. Let

$$Y_{ji} = \begin{cases} 0, & \text{if the } j\text{'th twin in the } i\text{'th twin pair has no hand} \\ & \text{eczema} \\ 1, & \text{if the } j\text{'th twin in the } i\text{'th twin pair has hand} \\ & \text{eczema} \end{cases}$$

be the indicator of hand eczema for the j 'th twin in the i 'th twin pair. It is assumed that these binary phenotypes reflect an underlying, unobservable, normally distributed liability to hand eczema. If Y_{ji}^* denotes the liability for the j 'th twin in the i 'th twin pair, it is assumed that

$$Y_{ji}^* = \begin{cases} 0, & \text{if } Y_{ji}^* < \tau \\ 1, & \text{if } Y_{ji}^* \geq \tau \end{cases}$$

where the latent variables (Y_{sj}^* , Y_{ji}^*) are normally distributed with

$$\begin{bmatrix} Y_{1i}^* \\ Y_{2i}^* \end{bmatrix} \sim N \left(\begin{bmatrix} 0 \\ 0 \end{bmatrix}, \begin{bmatrix} 1 & \rho_{z_i} \\ \rho_{z_i} & 1 \end{bmatrix} \right)$$

where z_i is the zygosity for the i 'th twin pair.

The parameter τ is the so-called threshold and describes the tendency towards hand eczema. A twin has hand eczema if the individual liability exceeds the threshold. The higher the threshold, the smaller the risk of hand eczema. The parameters ρ_{MZ} and ρ_{DZ} are the correlations between the unobservable liabilities, and are called correlations in liability. A higher correlation in liability for MZ twin pairs than DZ twin pairs is interpreted as an effect of genes under the assumption that MZ and DZ twins are subject to the same degree of common environment.

There is no effect of genes, if the correlations in liability are identical in the two groups ($\rho_{MZ} = \rho_{DZ}$). Provided there is no effect of genes, neither is there any effect of common environment, if the common correlation in liability $\rho = 0$.

The parameters (τ , ρ_{MZ} , ρ_{DZ}) were estimated by the maximum-likelihood method¹³². The hypotheses of no effect of genes, subsequently of no effect of common environment, were tested by likelihood ratio tests.

It is assumed that the threshold τ is the same for all twin pairs (especially independent of zygosity), whereas the corre-

lation between twins depends on zygosity. The first assumption was examined by letting the threshold depend on zygosity and then testing the hypothesis that the threshold was independent of zygosity. The above model was applied after stratification for sex and age.

The analyses were performed using the statistical software package SAS and the procedural language IML.

The extended threshold model

In order to perform a joint analysis, the threshold model was extended by allowing the threshold value and the correlations in liability to depend on sex and age. The extended model is based on the following assumptions where Y_{ji} still denotes the indicator of hand eczema for the j 'th twin in the i 'th twin pair. We assume that:

$$Y_{ji} = \begin{cases} 0, & \text{if } Y_{ji}^* < \tau_{a_i, s_i} \\ 1, & \text{if } Y_{ji}^* \geq \tau_{a_i, s_i} \end{cases}$$

and that the unobservable liabilities are normally distributed

$$\begin{bmatrix} Y_{1i}^* \\ Y_{2i}^* \end{bmatrix} \sim N \left(\begin{bmatrix} 0 \\ 0 \end{bmatrix}, \begin{bmatrix} 1 & \rho_{a_i, s_i, z_i} \\ \rho_{a_i, s_i, z_i} & 1 \end{bmatrix} \right)$$

where a_i is the age group and s_i the sex of the i 'th twin pair. The model contains 4 threshold parameters (one for each combination of sex and age group) and 8 correlations in liability (for MZ and for DZ in each of the previously mentioned groups). Again, the parameters were estimated by the maximum-likelihood method¹³².

The model was simplified by likelihood ratio test by stepwise omission of non-significant effects, including a test for no effect of genes (i.e. that the correlations in liability were independent of zygosity).

As a test for goodness-of-fit, the model was further extended by letting the thresholds depend on zygosity as well. The hypothesis of no dependence on zygosity was, again, tested by likelihood ratio test.

The analyses were performed using the statistical software package SAS and the procedural language IML.

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