ORIGINAL REPORT

Risk of Death, Infections, and Hyperthermia in Ectodermal Dysplasias: A Nationwide Study

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This nationwide population-based study investigated the risk of death, infections, and hyperthermia in Danish patients with ectodermal dysplasia (ED). A validated cohort of ED patients ($n = 396$) and matched population comparators ($n = 3960$) was compared to assess these risks before (case-control analysis) and after ED diagnosis (cohort analysis). Using matched comparators as a reference, the overall hazard ratio (HR) for death was 1.33 (95% confidence interval [CI] 0.70–2.55) in ED patients, and particularly high in males with hypohidrosis (HR 3.77, 95% CI 1.57–9.03) and individuals diagnosed before age 18 (HR 6.53, 95% CI 1.84–23.13). ED was associated with an increased risk of hospital-diagnosed infections before (odds ratio [OR] 2.27, 95% CI 1.81–2.85) and after (HR 2.06, 95% CI 1.74–2.45) diagnosis, varying across subtypes. Sensitivity analyses supported these findings, e.g., using antimicrobial prescriptions to identify infections. An association between hypohidrosis and previous hyperthermia (OR 7.11, 95% CI 3.26–15.51) diminished after diagnosis (HR 1.38, 95% CI 0.54–3.53). This study found an increased mortality risk in males with hypohidrosis and those diagnosed in childhood, and infection and hyperthermia risks depending on ED subtype. These data enhance understanding of ED's clinical course, informing patient management and counselling.

Key words: ectodermal dysplasia; epidemiology; hyperthermia; infectious disease; mortality; prognosis.

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SIGNIFICANCE

Patients with ectodermal dysplasia have been reported to have an increased risk of early death, infections, and critical overheating, although these risks have not been studied extensively. In this Danish study, we used data from nationwide health registries and compared the risks of death, infections, and critical overheating in 396 ectodermal dysplasia patients and a control group. In conclusion, we found an increased risk of death among males with impaired sweating and those diagnosed with ectodermal dysplasia in childhood. Patients with ectodermal dysplasia also face an increased risk of infections and critical overheating, with these risks varying according to the ectodermal dysplasia subtype.

Ectodermal dysplasias (EDs) encompass a heterogeneous group of rare genetic disorders affecting the development and/or homeostasis of tissues from the embryonic ectoderm (1, 2). Cardinal features include hypohidrosis, hypotrichosis, hypodontia, and nail dystrophy (3, 4). However, other symptoms and features may be present, including features involving the ears, eyes, craniofacial dysmorphology, athelia, skeletal defects, and in rare cases immunodeficiency (1, 5–7). The current classification of EDs delineates 49 distinct subtypes/syndromes categorised into 5 molecular-genetic pathways (8). The most common subtype is X-linked hypohidrotic ED (XLHED) caused by pathogenic *EDA* variants (5).

Mucosal gland development can be affected in certain EDs, resulting in impaired or absent mucosal glands in the respiratory and gastrointestinal tracts (1, 9, 10). Furthermore, some patients may present with immunodeficiency or infection susceptibility (11–14). These manifestations may lead to severe complications, e.g., pneumonia, chronic constipation, and chronic diseases affecting the upper respiratory tract system (15–17). The diminished ability to sweat in patients with hypohidrotic ED (HED) may cause severe hyperthermia and death, especially during infancy (16, 18, 19). Cross-sectional studies of HED have reported an infant mortality ranging from 2.1–21.0% (16, 18).

No population-based studies have been published concerning these complications. The universal healthcare system in Denmark with detailed individual-level registrations provides a unique setting to conduct nationwide studies of the clinical course of various diseases (19). Recently, we established a nationwide validated cohort of 396 Danish patients with ED diagnosed in 1995–2021, enabling population-based investigations of ED-relevant clinical courses and outcomes (7). Using this cohort, we aimed to investigate the risk of death, infections, and hyperthermia in patients with ED compared with matched comparators from the general population. Given the paucity of research in this field, such knowledge is important to inform healthcare programmes for patients with ED.

MATERIALS AND METHODS

Study design and population

We conducted this study using routinely collected data from Danish national health registries linked through a personal identifier number assigned to all residents (20, 21). We used the aforementioned cohort of 396 patients with a validated diagnosis of ED (61% genetically confirmed), previously reported by our research group (7). We risk-set sampled (with replacement) a matched comparison group (10:1) from the general population with the same age (birth month and year), sex, and municipality but without ED on the index date. We defined the index date as the date of ED-defining diagnosis or the corresponding date for matched individuals. Although ED is a genetic condition present at birth, the time of diagnosis can vary largely (7). To capture associated events of infections and hyperthermia before diagnosis without introducing time-related biases due to delayed diagnosis, we applied 2 analyses: (*i*) a case-control analysis to investigate the occurrence of infections and hyperthermia before the index date in patients with ED (cases) vs matched comparators (controls) and (*ii*) a cohort design with a time-to-event analysis of the risk of death, infections, and hyperthermia after the index date in patients with ED (exposed cohort) vs matched comparators (unexposed cohort). **Fig. 1** details the study design, including the identification of study variables using population registries, hospital contacts, and prescription data.

Outcomes

We defined all-cause death using data from the Civil Registration System, which provides vital and migration data for the entire population since 1968 (22). Death causes were obtained from the Danish Register of Causes

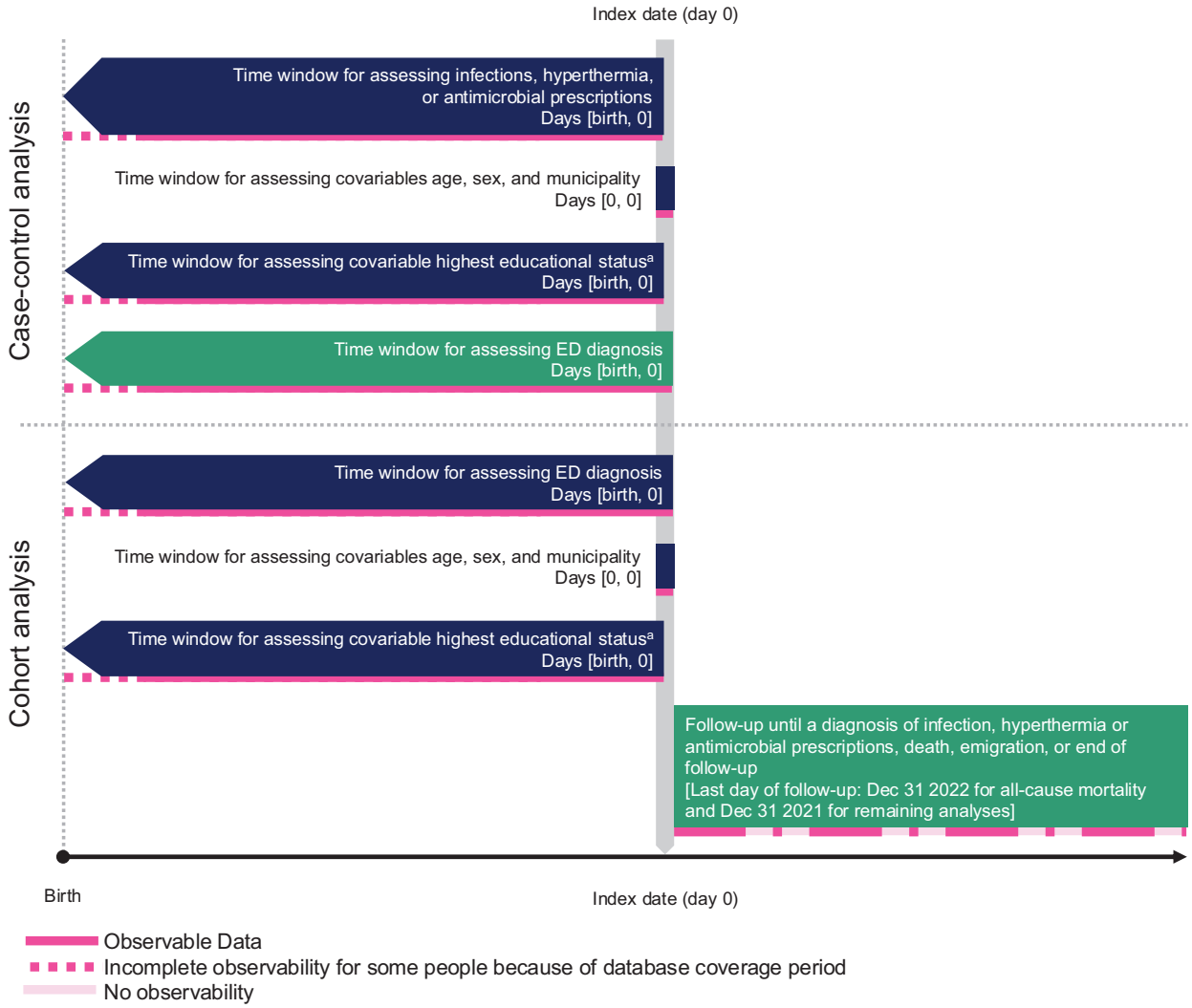

Fig. 1. Diagram of study design. The study design included 2 analyses. A case-control analysis investigating the occurrence of infections and hyperthermia before the date of ectodermal dysplasia (ED) diagnosis or matching date (index date) in patients with ED (cases) vs matched comparators (controls), respectively. Furthermore, a cohort design with a time-to-event analysis of the risk of death, infections, and hyperthermia after the index date in patients with ED (exposed cohort) vs matched comparators (unexposed cohort). [a]Patients' educational status was used for patients ≥ 22 years at index date and parents' educational status was used for patients < 22 years at index date.

of Death (23). We examined the all-cause mortality and cause-specific mortality related to infectious diseases. Due to few observations, a *post hoc* analysis included both infectious and respiratory disease-related deaths (Appendix S1).

Hospital-diagnosed infections, hyperthermia, and febrile convulsions were obtained from the Danish National Patient Registry (DNPR), which includes inpatient contacts since 1977 and outpatient contacts since 1995 (see Appendix S1) (24). Diagnoses in the DNPR are registered by the treating physician using the International Classification of Diseases (ICD, version 8 from 1977 to 1994; version 10 thereafter) (24). We considered both primary (main) and secondary (contributary) diagnoses. Selected subgroups of infections, e.g., pneumonia, septicaemia, and urinary tract infections, were defined as shown in Table SI. A unidirectional mapping of ICD-8 to ICD-10 codes (25) was used for the conversion of codes. Outcomes for the cohort analysis were identified independently of outcome status in the case-control analysis. Thus, the cohort analysis did not exclude those who had records of infection or hyperthermia before the index date.

In a secondary analysis, we supplemented our definition of any infection with prescriptions for systemic antimicrobials as a proxy measure of community-treated infections. Data on prescriptions were obtained from the Danish National Prescription Registry (26) available from 1 January 1995. We also performed analyses according to specific antimicrobials, including systemic antibiotics, antimycotics, and antivirals, as well as ophthalmic and otological formulations (Table SII).

In the cohort analysis, we followed individuals until the outcome of interest, emigration, death, or end of follow-up, whichever came first. Because of data availability, the end of follow-up was 31 December 2022 for all-cause mortality and 31 December 2021 for the remaining outcomes.

Covariables

We included age, sex, calendar time, and municipality at index date as potential confounders, adjusted for by design. We also included educational status as a measure of socioeconomic position, which could influence health-seeking behaviour for both ED and infections/hyperthermia. However, because educational status could also be on the causal pathway if ED affects academic attainment, it was included as a covariable in a sensitivity analysis only. As EDs have a monogenetic cause, we assumed minimal risk of confounding from other variables.

Data on individuals' highest attained education at the index date were obtained from the Population Education Registry through Statistics Denmark (27). For persons below age 22, we used the parent's highest educational status instead, as the final education level may not yet have been attained (see Appendix S1).

Statistical analysis

We characterized patients with ED and matched comparators by descriptive statistics of age, sex, education level, and ED subtype.

In the case-control analysis, we performed conditional logistic regression to calculate odds ratios (ORs) with 95% confidence intervals (CIs) for the association between ED and infection/hyperthermia before the index date. In the cohort analysis, we used stratified Cox proportional hazard regression to compute hazard ratios (HRs) as a measure of the relative risks of death, infection, or hyperthermia after the index date in patients with ED vs. matched comparators. By conditioning/stratifying the regression models on matched sets, the estimates account for age, sex, calendar year of index date, and municipality. We performed all analyses for any ED and selected subtypes (e.g., hypohidrosis, males with XLHED, and incontinentia pigmenti [IP]). The assumption of proportional hazards was confirmed by inspection of log-log plots.

For all-cause death, we computed survival probabilities using the Kaplan–Meier method. To provide an absolute measure of the risk of death in young adults with ED, we examined the survival probability at age 30 among those diagnosed in childhood with delayed entry until age 18.

We repeated the analyses (1) using antimicrobial prescriptions as measures of infection, (2) including only hospitalizations for infection or hyperthermia (as measures of severe disease), (3) adjusting additionally for educational status, and (4) using the Andersen-Gill extension of the Cox model (28) to conduct recurrent event analysis allowing multiple infections during follow-up (Appendix S1).

All statistical analyses were performed in Stata, version 18.0 (StataCorp LLC, College Station, TX, USA). The forest plots were created in R (v4.4.0; R Foundation for Statistical Computing, Vienna, Austria), using the "forestplot" package. We applied the REporting of studies Conducted using Observational Routinely-collected Data (RECORD) reporting guidelines. We do not report results based on <3 observations per regulations by Statistics Denmark.

Ethical approval

The study was approved by the Danish Data Protection Agency (record number: 1-45-70-76-21). Danish legislation does not require ethical review board approval for registry-based studies.

RESULTS

Characteristics

We included 396 patients with ED and 3,960 comparators. The median age at index date was 13 years (interquartile

Table I. Characteristics of the study population

Item	Patients with ED	Matched comparators
Number	396	3,960
Age at index date (years) (median, IQR) [a]	13.0 (4.1–30.4)	13.0 (4.1–30.4)
Age at last follow-up (years) (median, IQR) [a]	26.7 (17.7–45.0)	27.1 (17.9–44.4)
Follow-up time after index date (years), (median, IQR) [a]	12.0 (6.1–18.2)	12.0 (6.1–18.2)
Sex, *n* (%)		
Female	246 (62.1)	2,460 (62.1)
Male	150 (37.9)	1,500 (37.9)
Highest educational level, *n* (%)		
No education	12 (3.0)	214 (5.4)
Lower secondary education	57 (14.4)	425 (10.7)
Upper secondary education	166 (41.9)	1,634 (41.3)
Higher education	161 (40.7)	1,687 (42.6)
Hypohidrosis/anhidrosis, *n* (%)	135 (34.1)	N/A
ED subtypes (%)		
Any ED	396 (100.0)	N/A
Genetically-confirmed subtypes	241 (60.9)	
Incontinentia pigmenti	54 (13.6)	
XLHED, males	50 (12.6)	
XLHED, females	50 (12.6)	
WNT10A-related ED	21 (5.3)	
TRPS	18 (4.5)	
ED 10A + 10B	10 (2.5)	
AEC/EEC/LM/RH syndrome	9 (2.3)	
Clouston syndrome	9 (2.3)	
Goltz syndrome	7 (1.8)	
Other	13 (3.3)	
Non-genetically confirmed ED	155 (39.1)	
Hidrotic ED	55 (13.9)	
Hypohidrotic ED	55 (13.9)	
Incontinentia pigmenti	21 (5.3)	
AEC/EEC/LM/RH syndrome	12 (3.0)	
Other	12 (3.0)	

[a]Quartiles represent means including surrounding observations to obscure individual-level information.
AEC: ankyloblepharon-ectodermal defects: cleft lip/palate; ED: ectodermal dysplasia; EEC: ectrodactyly: ectodermal dysplasia: and cleft lip/palate; IQR: interquartile range; LM: limb-mammary; N/A: not applicable; *n*: number; RH: Rapp–Hodgkin; TRPS: trichorhinophalangeal syndrome; XLHED: X-linked hypohidrotic ectodermal dysplasia.

range (IQR) 4.1–30.4) and 62.1% were females (**Table I**). The median follow-up time after index date was 12.0 years (IQR 6.1–18.2). The highest attained educational level was similar in patients with ED and their comparators. The largest genetically confirmed ED subgroups were IP and XLHED. Hypohidrosis was reported in 135 (34.1%), including 55 patients without a genetic diagnosis.

Mortality

The mortality rate was 220 per 100,000 person-years in the ED cohort and 142 per 100,000 person-years in the comparator group (**Table II**). The median age at death was 48.7 (IQR 17.9–57.7) and 64.0 (IQR 48.3–74.9) years, respectively. Eight deceased cases had a genetic diagnosis, including 4 with an *EDA* variant. The HR of all-cause death was 1.33 (95% CI 0.70–2.55) for any ED vs comparators. Subgroup analyses showed that this increase was explained by increased mortality in males with ED (HR 3.77, 95% CI 1.57–9.03), including those with hypohidrosis (HR 4.39, 95% CI 1.53–12.65), and patients diagnosed with ED during childhood (HR 6.53, 95% CI 1.84–23.13). No increased mortality was seen among females and those diagnosed in adulthood. For patients diagnosed with ED in childhood, the probability of surviving from age 18 to 30 years was 96.4% (95% CI 86.5–99.1), with an absolute mortality risk difference from matched comparators of 3.4% (95% CI: –1.5–8.3%).

Five deaths (45%) in patients with ED were related to infections/respiratory tract diseases with a cause-specific HR of 2.20 (95% CI 0.78–6.17) vs comparators (Table SIII).

Infections

In the case-control analysis, any ED was associated with a higher risk of previous hospital-treated infections (OR 2.27, 95% CI 1.81–2.85) (**Fig. 2**), observed in 46.2% of patients with ED vs 29.4% of comparators (Table SIV). The most prevalent infections in patients with ED were eye and ear, viral, skin, upper respiratory tract infections, and pneumonia, each registered in 9% or more (Table SIV). The ORs varied from 1.27 (95% CI 0.71–2.26) for abscesses to 4.29 (95% CI 1.65–11.15) for septicaemia (Fig. 2). A two-fold increase was observed for most infections examined. Analyses according to ED subtype were limited by low precision but suggested some heterogeneity (Fig. 2). Thus, strong associations with hypohidrosis included septicaemia (OR 10, 95% CI 2.50–39.99) and pneumonia (OR 5.51, 95% CI 3.03–10.02) (Fig. 2B). XLHED in males was also associated with pneumonia (Fig. 2C), whereas effect estimates were generally lower, albeit increased, for XLHED in females and hidrotic ED (Table SIV). IP was associated with various infections before diagnosis, with particularly high OR for skin and subcutaneous infections (Fig. 2D).

Table II. Association between ED and all-cause mortality

	Patients with ED			Matched comparators			HR (95% CI)
Subgroups	Events, *n*/total	Person-years at risk	Mortality rate/100,000 person years	Events, *n*/total	Person-years at risk	Mortality rate/100,000 person years	Unadjusted[a]
Any ED	11/396	4,995	220	71/3,960	50,153	142	1.33 (0.70–2.55)
Males	7/150	2,061	340	19/1,500	20,922	91	3.77 (1.57–9.03)
Females	4/246	2,934	136	52/2,460	29,231	178	0.59 (0.21–1.68)
Hypohidrosis, males	5/78	1,259	397	12/780	12,905	93	4.39 (1.53–12.65)
Hypohidrosis, females	< 3/57	N/A	N/A	16/570	6,998	229	N/A
Age at diagnosis < 18	4/244	3,192	125	7/2,440	32,695	21	6.53 (1.84–23.13)
Age at diagnosis ≥ 18	7/152	1,803	388	64/1,520	17,458	367	0.89 (0.40–1.98)
Males with XLHED	< 3/50	N/A	N/A	7/500	8,338	84	N/A

[a]Adjusted for matching factors (age, sex, and municipality) by design.
CI: confidence interval; ED: ectodermal dysplasia; IP: incontinentia pigmenti; HR: hazard ratio; XLHED: X-linked hypohidrotic ectodermal dysplasia.

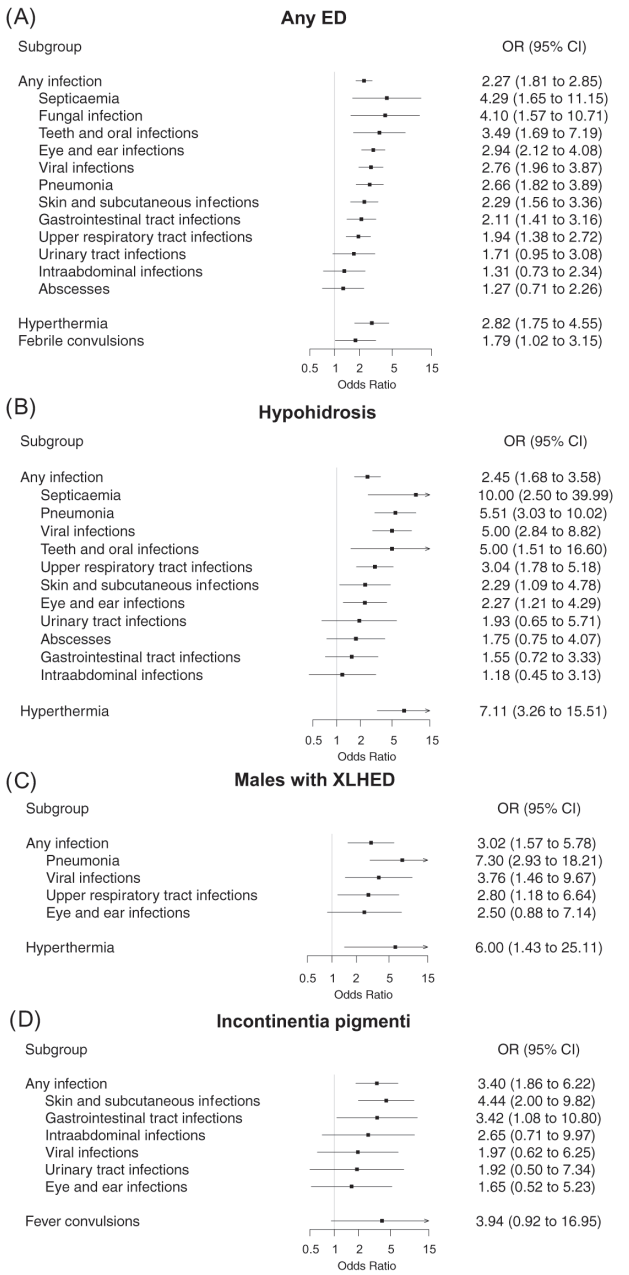

Fig. 2. Unadjusted ORs from case-control analysis of the associations between ectodermal dysplasia (ED) and previous hospital-treated infections, hyperthermia, and febrile convulsions. Results are shown for (A) any ED, (B) hypohidrosis, (V) males with X-linked hypohidrotic ED, and (D) incontinentia pigmenti. Results with < 3 observations are not shown. Detailed results including number of observations, adjusted analyses, and results for additional ED subgroups are provided in Table SIV. CI: confidence interval; OR: odds ratio; XLHED: X-linked hypohidrotic ectodermal dysplasia.

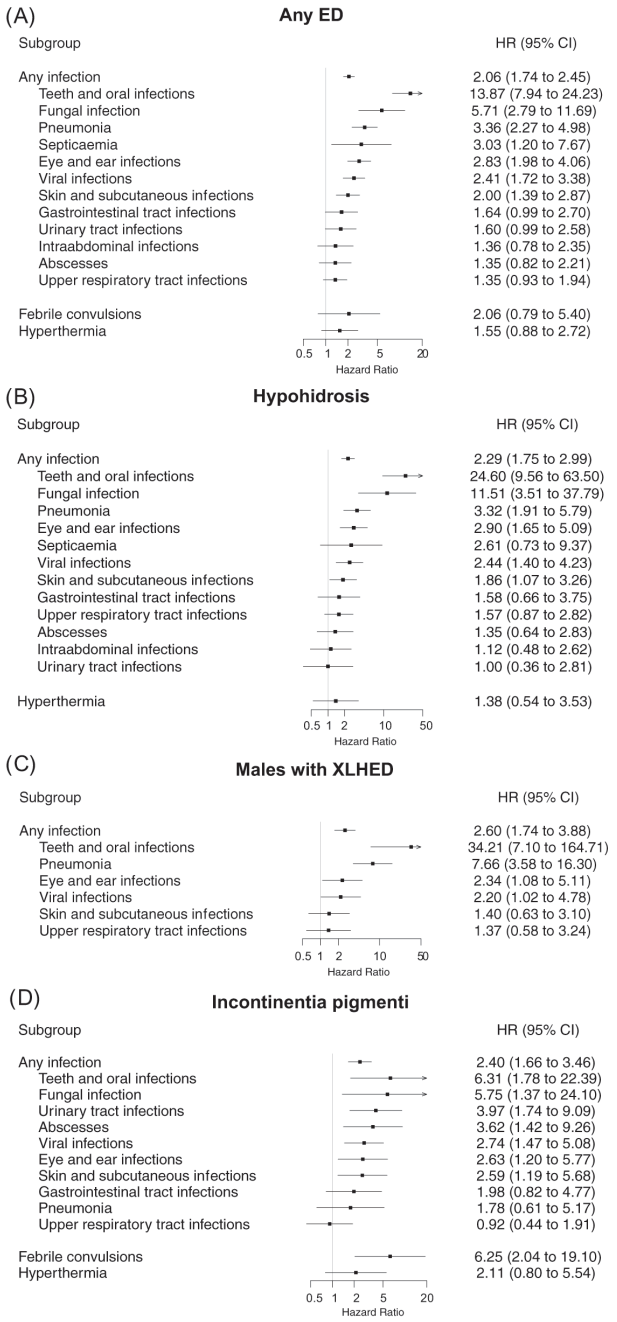

Fig. 3. Unadjusted hazard ratios from cohort analysis of the associations between ectodermal dysplasia (ED) diagnosis and subsequent first-time hospital-treated infections, hyperthermia, and febrile convulsions. Results are shown for (A) any ED, (B) hypohidrosis, (C) males with X-linked hypohidrotic ED, and (D) incontinentia pigmenti. Results with < 3 observations are not shown. Detailed results including number of events, person-time at risk, incidence rates, adjusted analyses, and results for additional ED subgroups are provided in Table SV. CI: confidence interval; HR: hazard ratio; XLHED: X-linked hypohidrotic ectodermal dysplasia.

In the cohort analysis, ED was also associated with an increased relative risk of any hospital-treated infection following the ED diagnosis (HR 2.06, 95% CI 1.74–2.45, **Fig. 3**). The incidence rate was 5,619 per 100,000 person-years in patients with ED (Table SV). As in the case-control analysis, viral, eye and ear, skin, upper respiratory tract infections, and pneumonia occurred most frequently (Table SV). The HRs for the specific types of infections were generally close to corresponding ORs from the case-control analysis, except for a much higher point estimate for teeth and oral infections in the cohort analysis (HR 13.87, 95% CI 7.94–24.23). The increased relative risk of any infection was also confirmed for hypohidrosis (HR 2.29, 95% CI 1.75–2.99), males with XLHED (HR

2.60), IP (HR 2.40), females with XLHED (HR 1.58), and hypohidrosis without genetic diagnosis (HR 2.24), although HRs were numerically slightly lower. The associations with viral infections, pneumonia, eye and ear, and teeth and oral infections were also quite consistent across these subtypes. The modest association with hidrotic ED with no genetic diagnosis in the case-control analysis (OR 1.64, 95% CI 0.94–2.89) was not observed (HR 1.09, 95% CI 0.61–1.95).

Hyperthermia and febrile convulsions

In the case-control analysis, ED was associated with hyperthermia (OR 2.82, 95% CI 1.75–4.55) and febrile convulsions (1.79, 95% CI 1.02–3.15) before the index date (Fig. 2, Table SIV). As expected, the highest ORs for hyperthermia were associated with hypohidrosis (7.11, 95% CI 3.26–15.51, Fig. 2B) and XLHED in males (6.00, 95% CI 1.43–25.11, Fig. 2C). The associations waned in the cohort analysis considering events after ED diagnosis (Fig. 3, Table SV), although an association between IP and febrile convulsions was observed (HR 6.25, 95% CI 2.04–19.10) (Fig. 3).

Additional analyses

ED was associated with any infection defined from hospital contacts and prescriptions, before (OR 3.74, 95% CI 2.46–5.69, Table SVI) and after (HR 1.43, 95% CI 1.26–1.62, Table SVII) ED diagnosis. The increased risk of infections was also observed for antimicrobial prescriptions only (Tables SVIII–SIX) and hospitalizations only (Tables SX–SXI). However, the precision decreased substantially when restricted to hospitalizations for certain infections (e.g., teeth and oral and fungal infections). The recurrent event analyses of hospital contacts and prescriptions generally produced higher HR estimates than the first-event analyses (Tables SXII–XIII). Overall, adjustment for educational status had little impact on the results (Tables SIII–SXIII).

DISCUSSION

In this nationwide study, we found that ED males with hypohidrosis and patients diagnosed in childhood have increased mortality. Moreover, we observed associations with increased relative risks of various infections and hyperthermia, depending on the ED subgroup.

To improve healthcare and outcomes for patients with ED, more knowledge regarding the natural and clinical course is needed. We confirm previous findings of increased mortality in patients with ED, particularly HED (16, 18, 19). While previous studies focused on infant mortality, our results add to the current evidence on increased mortality beyond infancy. Direct comparisons with previous reports of 2–21% (16, 18) infant mortality are challenged by different methodologies; however, we consider the mortality rate of ED in our study to be low based on only 11 deaths among 396 patients with ED. We speculate whether improved general medical care and diagnostics may have improved the prognosis compared with the reports from 1987 (18) and 2010 (16).

ED was associated with infections before and after the ED diagnosis depending on the ED subgroup. One consistent association was between XLHED in males (and hypohidrosis overall) and pneumonia. This documents the susceptibility of respiratory tract infections in XLHED, which is thought to be explained by the lack of mucous glands (9). This susceptibility could also be mediated by asthma, which is commonly reported in patients with XLHED (5, 12). Considering the high prevalence of pneumonia in males with XLHED, it may be a relevant outcome in clinical trials of XLHED therapies.

For other associations of interest, we observed a couple of dynamic changes comparing the results from before and after the ED diagnosis. The association with hyperthermia present before the date of ED diagnosis waned in the cohort analysis. It is possible that the risk of hyperthermia declines with age or that receiving the ED diagnosis leads to more preventive behaviour to avoid pyrexia episodes. The risk of tooth and oral/odontogenic infections was markedly higher in the cohort analysis, which could represent infectious complications related to maxillofacial procedures and implants in the dental care of patients with ED. Also, routine examinations at specialized hospital dental clinics following the diagnosis of ED could lead to an increased chance of having such infections detected and recorded in the hospital registry. Although such ascertainment bias may also impact the observed risk of other infections, our findings were confirmed in analyses restricted to hospitalizations and prescriptions, which we presume are less prone to such differential bias.

IP has previously been associated with infection susceptibility (29, 30), and we could confirm this at the population level. However, the associated types of infections differed from the other EDs. IP is caused by pathogenic variants in *IKBKG*, which encodes a protein involved in NF-κB signalling important for immune function (14). Although skewed X-inactivation is thought to provide protection, some patients have recurrent infections and signs of immune dysfunction, as previously reported (14, 31). Interestingly, IP has recently been associated with thymic dysplasia, type I IFN-neutralizing autoantibodies, and viral disease susceptibility (32). IP was also associated with viral infections in our cohort analysis. The observed association with skin infections preceding the IP diagnosis could, however, represent initial misdiagnosing of IP as neonatal skin infections (e.g., bullous impetigo).

This study is the first to investigate the association between ED, mortality, and risks of infections and

hyperthermia in a nationwide and population-based setting. Key strengths include the use of a large validated nationwide ED cohort with matched comparators from the general population and outcome data from a setting with universal healthcare. Moreover, our results were confirmed in several sensitivity analyses, including the incorporation of prescription data. However, considering the high prevalence of antimicrobial prescriptions (~70–80% of patients), the validity of this definition to identify infections should be considered.

Although the present study examined a relatively large nationwide cohort of patients with ED, the heterogeneity of EDs challenges the interpretation of analyses from the entire cohort. It is important also to investigate these associations in more homogeneous, preferably genetically defined, subgroups. While we provide results for some subgroups, we considered others, e.g., *TP63*-associated EDs, too rare for statistically meaningful analyses in our data (see Table I). Another possible limitation is the incompleteness of the Danish ED cohort identified from health registries (7). Selection bias due to missing critically ill patients who died before being registered with an ED diagnosis in our data cannot be excluded (7) and may have led to underestimates of the (infant) mortality and risk of severe infections or hyperthermia in ED. We adjusted for matching factors by design and for educational status in a sensitivity analysis, which did not markedly alter our results. Finally, many of our results were based on relatively small numbers, e.g., 11 deaths among patients with ED, which limited the interpretation of the results, including subgroup analyses. Although our data are most compatible with an increased relative risk of most events of interest, the confidence intervals for some infections were compatible with a wide range of estimates, including decreased and increased risks.

In conclusion, we found increased mortality in male ED patients with hypohidrosis and those diagnosed with ED in childhood. EDs were also associated with hyperthermia and infections. These findings contribute valuable insights into the prognosis of ED, both generally and across subtypes. Furthermore, they underscore the importance of heightened vigilance for infections and hyperthermia in patients with ED and highlight the need for preventive strategies and early interventions to avoid critical disease.

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IRB approval status: The study was approved by the Danish Data Protection Agency (record number: 1-45-70-76-21). Danish legislation does not require ethical review board approval for registry-based studies.

Conflict of interest disclosures: Sigrún A.J. Schmidt has received speaker honoraria from GSK Pharma for lectures unrelated to the present study. Mette Sommerlund received honoraria from Leo-Pharma and Sanofi for lectures unrelated to the present study. Laura Krogh Herlin and Trine H. Mogensen have no conflicts of interest to disclose.

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