

BMJ Open Eczema and subsequent suicide: a matched case-control study

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ABSTRACT

Objective To assess the association of eczema with a patient's subsequent risk of death from suicide. We hypothesised that persistent eczema would be associated with an increased risk for death from suicide.

Design Double matched case-control study.

Setting General population of Ontario, Canada.

Participants Patients 15–55 years old. We identified cases of suicide from coroners' reports between 1 January 1994 and 31 December 2014 and matched 1:2 with alive controls based on age, sex and socioeconomic status.

Exposure The primary predictor was a history of persistent eczema, defined as five or more physician visits for the diagnosis over the preceding 5 years.

Main outcome and measure Logistic regression to estimate the association between eczema and death from suicide.

Results We identified 18 441 cases of suicide matched to 36 882 controls over the 21-year accrual period. Persistent eczema occurred in 174 (0.94%) suicide cases and 285 (0.77%) controls yielding a 22% increased risk of suicide associated with persistent eczema (OR 1.22, 95% CI 1.01 to 1.48, $p=0.037$). In mediation analyses, this association was largely explained through major suicide risk factors. Two-thirds of patients with eczema who died from suicide had visited a physician in the month before their death and one in eight had visited for eczema in the month before their death. Among patients who died by suicide, jumping and poisoning were relatively more frequent mechanisms among patients with eczema.

Conclusions Patients with persistent eczema have a modestly increased subsequent risk of death from suicide, but this is not independent of overall mental health and the absolute risk is low. Physicians caring for these patients have opportunities to intervene for suicide prevention.

INTRODUCTION

Eczema is a common skin disease associated with decreased quality of life comparable to many other chronic medical conditions.^{1 2} Eczema affects approximately 1 in 9 children and 1 in 14 adults, most of whom have mild disease.^{2–4} For patients with severe persistent eczema, however, the disease can be debilitating with severe itch, social embarrassment and impaired quality of life.⁵ Patients with eczema can also experience financial hardships due to direct medical costs, missed days from employment and decreased work productivity.^{5 6} Sleep loss related to itch can

Strengths and limitations of this study

- We conducted a large case-control study adequately powered to detect an association between eczema and suicide.
- Universal insurance coverage for physician visits provide comprehensive data on physician visits preceding death from suicide.
- We conducted several sensitivity analyses and tracer analyses with negative controls to test the robustness of results.
- Our case definition of persistent eczema has not been validated so misclassification is a possibility.

be especially debilitating^{2 7} and nearly half of US adults who have eczema with fatigue rate their health as poor or fair.²

Past research has linked eczema to mental illness. In a claims-based study from Taiwan, patients had a sevenfold increased risk of a major depressive disorder and fourfold increased risk of an anxiety disorder.⁸ In two American cross-sectional studies, eczema was associated with twice the risk of depression compared with the general population.⁹ One study from Denmark found no significant association between eczema and subsequent suicide.¹⁰ Whereas a prior study found a suicide risk twice the population norm for patients with eczema.¹¹ The risk of suicide associated with eczema has not been assessed in North America; moreover, most studies have excluded youth despite eczema being distinctly common and suicide being a leading cause of death in this age group.^{2 4 12}

The objective of this case-control study was to assess the association of eczema with a patient's subsequent risk of death from suicide. A secondary aim was to assess the recency of physician visits prior to suicide among patients with eczema. A randomised controlled trial was deemed impossible because patients cannot be assigned a diagnosis of eczema; therefore, we conducted a large-scale multiyear observational analysis of longitudinal individual patient data. We hypothesised that persistent eczema would increase a patient's risk of death from suicide



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and that many deaths would be preceded by a recent physician visit. If true, this would suggest that preventive efforts targeting vulnerable patients might save lives.

Patient and public involvement

There was no patient or public involvement in this study.

Selection of patients

We conducted a double matched case-control study of patients between the age of 15 and 55 years in Ontario. We included individuals 15 and older as eczema is a common diagnosis and suicide is a common cause of death in youth.^{2 4 12} We excluded adults older than 55 to avoid misclassification of age-associated xerosis with itch as eczema. Cases of suicide were identified from the Ontario Vital Statistics Database from 1 January 1994 to 31 December 2014, representing all available data. We defined suicide using International Classification of Disease (ICD) codes (ICD-9 E950–E959, E980–E987; ICD-10×60–X84, Y10–Y32, Y34).^{13–15} Inter-rater agreement from coroners on suicide diagnosis was high and showed 97% concordance with the vital statistics database.^{16 17} We also extracted data on the mechanism of suicide in five categories as asphyxiation, jumping, poisoning, violence and miscellaneous.

Controls were selected from the general population in Ontario using the Registered Persons Database that identified all patients insured under the Ontario Health Insurance Plan (OHIP).¹⁸ For each case of suicide, we selected two control patients from the general population matched on age (within 2 days), socioeconomic status (SES) quintile and sex using simple random selection when excess matches were available. All cases and controls were alive and eligible for OHIP coverage on the index date and 1 year prior. SES at the index date was estimated from the Statistics Canada algorithm based on neighbourhood income^{19 20} and patients with missing SES were matched to controls who were also missing SES. As a result, we obtained exact triplets of one case matched to two controls with no missing matches. These datasets were linked using unique encoded identifiers and analysed at Institute for Clinical Evaluative Sciences.

Primary predictor

We used a 5-year look-back interval to assess each patient through a consistent ascertainment interval for cases and controls. The matching date in each triplet of patients was defined as the date of suicide death of the case. Prior medical care for each patient was evaluated based on physician diagnoses documented as ICD-9 diagnostic codes.¹³ In Ontario, physicians document each encounter with a single ICD-9 code. Eczema was defined using diagnosis code 691.¹³ In another population, ICD-9 codes for atopic dermatitis, a specific subtype of eczema, had a positive predictive value of 50% based on a requirement for two or more ICD-9 codes to identify cases of probable atopic dermatitis.²¹ To increase the specificity and to define persistent eczema, we required five or more

physician visits for the diagnosis, each separated by at least 1 week over the 5-year look-back interval. Given the uncertain validity of that definition, we refer to our predictor as ‘eczema’ rather than the more specific ‘atopic dermatitis’ throughout the manuscript.

Additional patient characteristics

Specific additional medical diagnoses (asthma, hay fever or rhinitis, alcoholism, drug dependence, tobacco abuse, sleep and other disorders, depression, anxiety disorders, psychoses, personality disorders, malignancy, benign skin tumours, psoriasis) were identified during the 5-year look-back interval using ICD-9 codes in the OHIP database. Measures of overall healthcare resource utilisation were obtained from the OHIP database, the National Ambulatory Care Reporting System and the Discharge Abstract Database (counts of clinic visits, emergency room visits, hospitalisations in the prior year). We collected data on patients’ most recent healthcare visit, the specialty of the physician and the associated diagnosis. We also collected data on the timing of suicide (proximity to the most recent visit with a dermatologist or psychiatrist and recency of a visit for eczema).

Statistical analysis

We used logistic regression to calculate ORs with 95% CIs for the association of persistent eczema with the risk of subsequent death from suicide. We examined the robustness of findings by additionally calculating associations using conditional logistic regression to fully account for matching. To assess for potential mediation, we conducted stratified analyses by major suicide risk factors (depression, psychoses, personality disorders, sleep and other disorders, drug dependence and alcoholism) within triads of cases and controls. Further, we used logistic regression with suicide as the outcome and major suicide risk factors as covariates to derive an overall suicide predilection score. We then conducted logistic regression stratified by low (at or below the median) or high (above the median) overall suicide predilection score. To assess for potential mediation or confounding by a major atopic comorbidity, we conducted analyses further stratified by history of asthma.

We plotted Kaplan-Meier curves for patients who died from suicide with and without persistent eczema to assess the time interval between the most recent physician visit and ultimate suicide. We compared the two curves using the logrank test. To assess potential differences in the mechanism of suicide between patients with and without persistent eczema, we calculated descriptive ORs with 95% CIs for the different categories of suicide with no prespecified hypotheses.

We conducted several sensitivity analyses as tests of robustness. We replicated separate analyses to check results using alternative definitions of eczema: (1) spanning between 1 and 10 claims associated with the diagnosis; (2) requiring a comorbid atopic condition (asthma or rhinitis) and (3) excluding patients who had a history

of stasis ulcers, varicose veins, lymphoedema, contact dermatitis, seborrheic dermatitis or psoriasis. These latter two analyses were based on the rationale that comorbid asthma and rhinitis can improve the positive predictive value of ICD codes for atopic dermatitis²¹ and because excluding commonly confused conditions can also decrease false positive cases.

As a test for residual confounding, we conducted tracer analyses with two additional control predictors: benign skin tumours and psoriasis (another chronic skin disease with effective treatment options). We anticipated benign skin tumours and psoriasis might not be associated with an increased risk for suicide and thereby validate the distinctive association with eczema.

RESULTS

We identified 18441 cases of suicide matched to 36882 alive controls over the 21-year accrual period. The median patient age was 38 years, 74% were male and the average SES was below the population median. Mental health disorders were more common among patients who had died from suicide than among controls, as were malignant neoplasms and asthma (table 1). Patients who died from suicide had more clinic visits, emergency department visits and inpatient admissions in the year prior to the index date than controls.

A history of persistent eczema occurred in 174 (0.94%) suicide cases and 285 (0.77%) controls. In univariate analysis, persistent eczema was associated with a 22% increased risk of suicide. Results were identical for ordinary and conditional logistic regression (OR 1.22, 95% CI 1.01 to 1.48, $p=0.037$). The net increase was equal to 31 excess cases of suicide associated with eczema (more than one patient per year).

Stratified analyses showed the association of eczema with suicide was accentuated among older men with a history of addiction (figure 1). There was no significant differential association of eczema with suicide between strata of patients with and without asthma, malignancy or other individual suicide risk factors such as depression.

Patients with eczema had significantly higher suicide predilection scores compared with patients without eczema (median 0.32 vs 0.15, $p<0.0001$; online supplementary figure 1). Comparisons based on mean scores showed similar imbalance (0.42 vs 0.33, $p<0.0001$). The highest decile of suicide predilection score was nearly twice as common among patients with eczema as controls (17% vs 10%, $p<0.0001$). Stratified analysis by high or low predilection scores showed no significant further association of eczema with suicide between patients with high predilection scores (OR 0.97, 95% CI 0.78 to 1.22, $p=0.81$) and low predilection scores (OR 0.59, 95% CI 0.34 to 1.03, $p=0.06$), suggesting that eczema was not an independent contributor to suicide risk beyond its influence on mental health risk overall.

Nearly all patients with persistent eczema who died from suicide had visited a physician in the year prior to

Table 1 Patient characteristics

	Suicide cases n=18441, (%)	Matched controls n=36882, (%)
Age (years)		
15–24	2825 (15)	5650 (15)
25–34	3746 (20)	7492 (20)
35–44	5595 (30)	11 190 (30)
45–55	6275 (34)	12 550 (34)
Sex (male)	13 680 (74)	27 360 (74)
Income quintile		
Q5 (highest)	2839 (15)	5678 (15)
Q4	3162 (17)	6324 (17)
Q3	3426 (19)	6852 (19)
Q2	3814 (21)	7628 (21)
Q1 (lowest)	4969 (27)	9938 (27)
Unknown/suppressed	231 (1)	462 (1)
Home location		
Urban	15 532 (84)	32 158 (87)
Rural*	2893 (15)	4462 (12)
Missing	16 (<1)	262 (1)
Comorbidities†		
Alcoholism	3109 (17)	750 (2)
Drug dependence/addiction	3645 (20)	1164 (3)
Psychoses	5373 (29)	979 (3)
Depression	5753 (31)	1788 (5)
Anxiety disorder	12 807 (69)	10 690 (29)
Personality disorder	2391 (13)	469 (1)
Sleep disorders	2844 (15)	2536 (7)
Malignancy	1024 (6)	1331 (4)
Asthma	2291 (12)	3247 (9)
Rhinitis	1956 (11)	4204 (11)
Health services use in the preceding year		
Six or more clinic visits	11 946 (65)	12 365 (34)
One or more emergency room visits	4053 (22)	3173 (9)
One or more inpatient admissions	1379 (8)	511 (1)
OHIP eligible for entire 5-year look-back period	17 701 (96)	34 447 (93)

*Rural includes unknown/suppressed home location.

†Comorbidities defined by truncated ICD-9 codes: alcoholism (303), drug dependence/addiction (304), psychoses (291, 292, 295, 296, 298, 299), depression (311), anxiety disorder (300), personality disorder (301), sleep and other disorders (307), malignancy (140–165, 170–175, 179–208), asthma (493), rhinitis (477).

ICD-9, International Classification of Disease, Ninth Revision; OHIP, Ontario Health Insurance Plan.

their death, 67% within a month and 37% within a week. Among patients who died from suicide, those diagnosed with persistent eczema visited a physician more recently than patients without persistent eczema ($p<0.0001$, figure 2). For both patients with and without persistent eczema who died from suicide, the most recent physician visit was most frequently with a family physician (table 2).

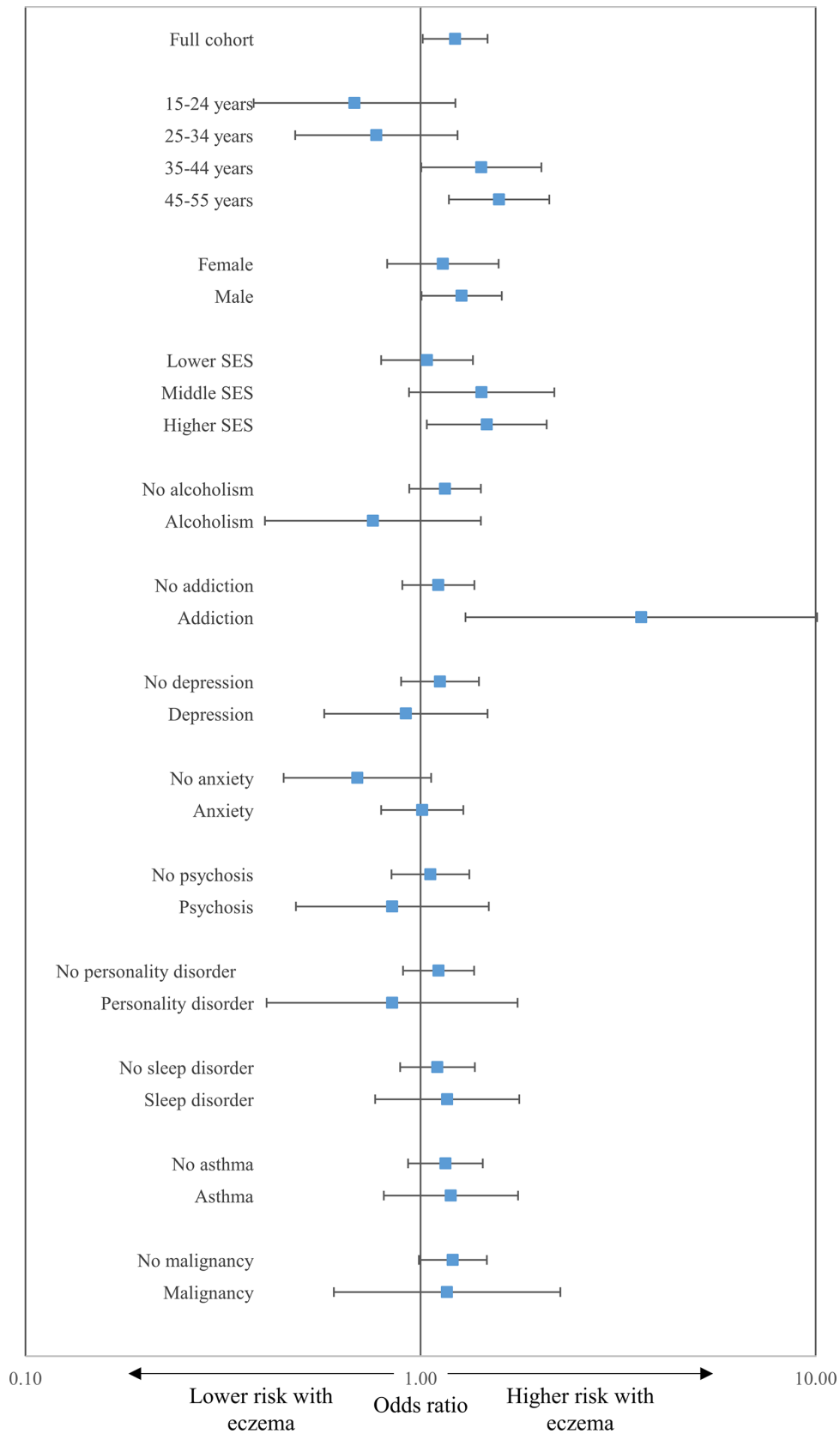


Figure 1 Relative risk of suicide associated with persistent eczema. Forest plot showing relative increase in risk of suicide among patients with persistent eczema compared with patients without persistent eczema. The x-axis shows OR on a logarithmic scale where values more than 1.0 denote increased risk. The y-axis shows specific subgroups of patients with the overall cohort positioned lowest. Squares indicate point estimates and horizontal lines 95% CIs. Main findings are an increase in risk associated with eczema with accentuation of risk among older men, those with mid-to-high socioeconomic status (SES) and a history of addiction.

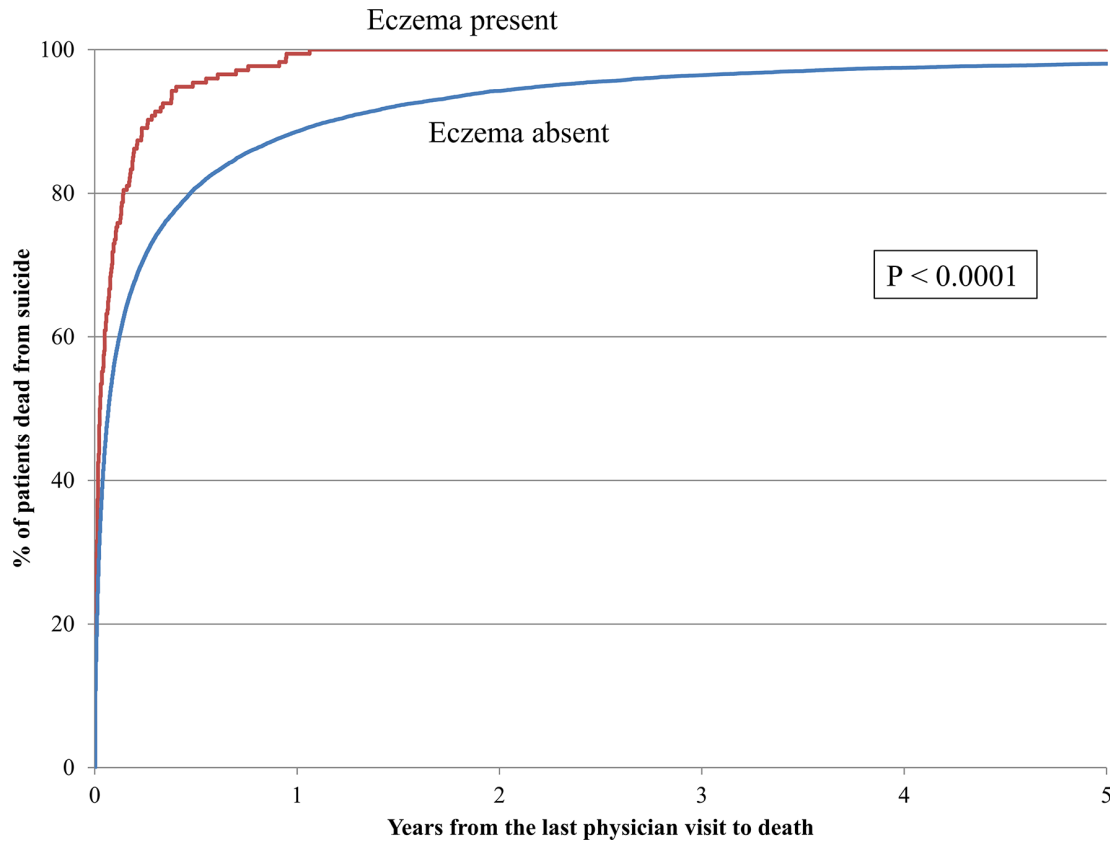


Figure 2 Time from the most recent physician visit to suicide. Kaplan-Meier curve shows the time between the last physician visit and subsequent death from suicide (n=18441). The x-axis shows the time in years lapsed between the most recent physician visit and the date of death. The y-axis shows the per cent of patients dead from suicide. The red line represents patients with persistent eczema. The blue line represents patients without persistent eczema. Statistical significance was based on the logrank test. Main findings show that patients with persistent eczema were more likely to see a physician in close proximity to their death.

Among patients with persistent eczema, 1 in 25 had visited a dermatologist last. For 1 in 16 patients with persistent eczema who died from suicide, their last visit was for eczema. We found no meaningful differences in season or in day of the week of death distinguishing patients who did and did not have persistent eczema (table 3).

Analyses of suicide cases showed diverse mechanisms, of which about 8% were unclassified due to uncertain, multifactorial or missing details. Asphyxiation was the most common single cause of suicide and was less frequent among individuals who had persistent eczema than controls (OR 0.55, 95% CI 0.38 to 0.78, p=0.0008). In contrast, jumping from a vertical height had the largest relative increased risk among patients who had persistent eczema (OR 1.87, 95% CI 1.21 to 2.89, p=0.0047). Poisoning was the second largest relative increased risk among patients who had persistent eczema (OR 1.41, 95% CI 1.04 to 1.91, p=0.03). Violent forms of suicide were infrequent and generally balanced between the two groups (OR 1.04, 95% CI 0.71 to 1.54, p=0.83).

In sensitivity analyses requiring fewer than five visits for eczema to define the predictor, the association with suicide was somewhat attenuated (online supplementary figure 2). When 10 or more visits for eczema were required, the CIs widened substantially and the

association was ambiguous. When a diagnosis of asthma or rhinitis was required to identify cases of eczema, the estimated association for the risk of suicide was similar to the primary analysis but not statistically significant (OR 1.26, 95% CI 0.94 to 1.69, p=0.12). When patients who had a diagnosis of stasis ulcers, varicose veins, lymphoedema, contact dermatitis, seborrheic dermatitis and psoriasis were excluded, the results were similar to the primary analysis (OR 1.26, 95% CI 0.99 to 1.61, p=0.06), although not statistically significant. Benign skin tumours were associated with no increase in suicide risk (OR 0.90, 95% CI 0.84 to 0.97, p=0.008). Psoriasis was associated with an equivocal increase in suicide risk (OR 1.14, 95% CI 0.99 to 1.31, p=0.06).

DISCUSSION

In this large longitudinal case-control study, persistent eczema was associated with a modestly increased risk of subsequent death from suicide. The absolute risk was low. The association was fully explained by mental health disorders including depression, anxiety, sleep disorders and substance misuse, suggesting that eczema was not an independent contributor to suicide risk beyond its influence on mental health risk overall. The patient group at

Table 2 Description of the most recent physician visit among patients who died from suicide

	Persistent eczema present n=174 patients, (%)	Persistent eczema absent n=18267 patients, (%)
Physician speciality of most recent visit		
Family practice	121 (48)	13320 (55)
Dermatology	9 (4)	125 (1)
Psychiatry	31 (12)	3101 (13)
Other*	93 (37)	7618 (32)
Diagnosis associated with most recent visit		
Eczema	16 (6)	129 (1)
Mental disorders†	72 (28)	7754 (32)
Other medical diagnosis‡	166 (65)	16281 (67)
Total no of billing claims§	254	24164

Results are presented as the number of billing claims (%).

*Includes paediatrician visits.

†Includes disorders of substance use.

‡Includes cases for which no diagnosis is listed.

§For some patients, more than one billing claim is included if they occurred on the same day.

highest risk was older men with a history of addiction. Asphyxiation was the most common mechanism of suicide death overall, but poisoning and jumping were differentially increased for patients with persistent eczema. Patients with eczema who died from suicide usually had visited a physician in the month before death.

Our study is in agreement with other literature on the association of eczema with adverse mental health. A Norwegian study found that young adults with eczema and itchy skin had a 24% prevalence of suicidal ideation in the preceding week.⁷ Only two studies have examined the risk of death from suicide associated with eczema, with mixed results. One conducted using administrative data for adults in Denmark found that patients with eczema had a 71% increased risk of suicide attempts and double the risk of death from suicide, (a more prominent association than in our study).¹¹ Similar to our findings, older adults with eczema had a further accentuated risk. It is unclear why the association might be increased in older populations and one possible explanation could be the cumulative stress of living with a chronic condition for decades. The only other past study, also from Denmark, found no statistically significant association between eczema and suicide.¹⁰

Our study contains novel findings concerning physician visits by patients with atopic dermatitis prior to suicide. Nearly two in five patients with eczema who died from suicide contacted a physician in the week before their death. The most recent physician visit was most commonly with a general practitioner and often for reasons related to mental health. In a small number of patients, the most

Table 3 Timing and mechanism of death from suicide among patients with and without a history of persistent eczema

	Persistent eczema present n=174 patients, (%)	Persistent eczema absent n=18267 patients, (%)
Time from last psychiatrist visit		
≤1 month	40 (23)	3371 (19)
>1 month or no visit	134 (77)	14896 (82)
Time from last dermatologist visit		
≤1 month	8 (5)	98 (<1)
>1 month or no visit	166 (95)	18169 (>99)
Time from last visit for eczema		
≤1 month	14 (8)	83 (<1)
>1 month or no visit	160 (92)	18184 (>99)
Season		
Spring	45 (26)	4756 (26)
Summer	50 (29)	4812 (26)
Autumn	36 (21)	4515 (25)
Winter	43 (25)	4184 (23)
Day		
Weekday	125 (72)	13242 (73)
Weekend	49 (28)	5025 (28)
Mechanism of death		
Asphyxiation	40 (23)	6460 (35)
Jumping	24 (14)	1439 (8)
Poisoning	68 (39)	5715 (31)
Violent	31 (18)	3144 (17)
Miscellaneous*	11 (6)	1504 (8)

Poisoning deaths include deaths caused by prescription and non-prescription and illicit and legal substances. Violent deaths include those caused by firearms or other weapons.

*Includes mechanisms listed as uncertain.

recent physician contact was for their eczema. While dermatologists tend to under-recognise depression and anxiety in their patients, all clinicians should recognise psychological distress.²² Patients with eczema who present with signs of significant mental health distress could be assessed for suicide risk. In particular, standardised tools have been suggested for assessing suicide risk in dermatology clinics, but have not been formally evaluated in that setting.^{23 24}

Asphyxiation is a frequent mechanism of suicide yet was relatively uncommon among patients with persistent eczema. Instead, patients with eczema were comparatively more prone to die by jumping from tall heights or self-poisoning. The significance of these patterns is unclear. One possibility is that patients with eczema have high rates of medical and psychiatric comorbidity relative

to the general population and are more likely to have access to prescription drugs with the potential to cause death. Another interpretation is that asphyxiation is a more prolonged and painful means of suicide so that patients with eczema who live in discomfort from their condition choose rapid or less painful means of dying. A greater understanding is needed for future research.

The generalisability of our study is limited to a single large region in a high-income country with universal healthcare access. Specifically, comprehensive medical care in our patients may have substantially mitigated some of the suicide risk associated with eczema. In addition, we lacked data on eczema severity, social isolation, other life stresses or risk factors for suicide completion such as suicidal ideation.²⁵ We also lack data on treatments used for eczema, which can be used to stratify eczema cases based on severity and which may be important given the psychiatric effects of systemic corticosteroids.^{10 26} Our primary outcome examined an extreme indicator of mental suffering and the overall observed effect size was more modest than previously reported for other medical illnesses.²⁷ While only a small minority of patients with eczema die by suicide, many more suffer from non-lethal forms of depression and other mental disorders.^{8–10 28}

The most important limitation of our study relates to our definition of persistent eczema. A past report suggested that two or more ICD-9 codes for atopic dermatitis have a 50% positive predictive value for probable atopic dermatitis.²¹ The true positive predictive value may be higher than reported in that study, as it used stringent clinical diagnostic criteria unsuitable in a retrospective study. Nevertheless, misclassification of persistent eczema cases is a strong possibility and may have impacted our results in a number of ways. Random misclassification may cause underestimates of the magnitude of associations.²⁹ Misclassification of less severe skin diseases such as contact dermatitis could also bias our findings towards the null. However, misclassification of more severe skin diseases such as an exfoliative dermatitis may bias our results towards an increased risk for suicide. It is unclear whether our requirement of five occurrences of code 691 increases or decreases the accuracy of our case definition for identifying cases of atopic dermatitis and exactly what impact this had on the results.

To provide some additional nuances for our case definition, we calculated the prevalence of asthma and rhinitis among patients in our study and found each of these atopic comorbidities was more than twice as common among those with persistent eczema compared with those without (online supplementary table 1). It is possible that the associations observed between our primary predictor and these well-known atopic comorbidities are partially confounded by differential healthcare system access. However, the strong associations seen support the notion that our predictor definition represents, to some extent, persistent atopic dermatitis. Our sensitivity analyses requiring comorbid asthma or rhinitis to define eczema and excluding patients with psoriasis and

other skin diseases yielded decreased sample sizes and showed results that were no longer significant. We are reassured that the estimates were largely unchanged and are cautious not to overinterpret statistical significance in post hoc secondary analyses. Nevertheless, due to the uncertain validity of our primary predictor, we use the non-specific term ‘eczema’ throughout the manuscript.

Strengths of our study include the large sample of suicide deaths, the known validity of suicide outcomes and our double-matched case–control design. As Ontario has a universal health insurance programme, we were able to comprehensively identify all physician visits prior to death. Of course, patients who had persistent eczema but who did not engage with the healthcare system may have been missed. In summary, patients with persistent eczema have a modestly increased subsequent risk of death from suicide. Physicians may have opportunities to intervene for suicide prevention in this vulnerable patient population.

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Contributors AMD and DAR designed and obtained funding for the study. DT performed data analysis. AMD drafted the manuscript and all authors contributed to critical revision of the manuscript. DAR accepts full responsibility for the work, the conduct of the study, had access to the data, and the decision to publish. AMD attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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Competing interests AMD served as an investigator and has received research funding from Sanofi and Regeneron and has been a consultant for Sanofi, RTI Health Solutions, Eczema Society of Canada and the Canadian Agency for Drugs and Technologies in Health. He has received honoraria from Astellas Canada, Prime, Spire Learning, CME Outfitters and Eczema Society of Canada.

Patient consent Not required.

Ethics approval The study was approved by the Institute for Clinical Evaluative Sciences (ICES) and the Women’s College Hospital Research Ethics Board deemed the work exempt from supplementary ethics review.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement There is no plan to share raw data from this study.

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