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Atopic dermatitis and subsequent suicide: a matched case-control study

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Atopic dermatitis and subsequent suicide: a matched case-control study

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2
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4 performed data analysis, Dr. Drucker drafted the manuscript and all authors contributed to
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7 Drucker attests that all listed authors meet authorship criteria and that no others meeting the
8 criteria have been omitted.
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23 The manuscript is an honest, accurate, and transparent account of the study being reported; that
24 no important aspects of the study have been omitted; and that any discrepancies from the study
25 as planned (and, if relevant, registered) have been explained.
26

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32
33

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38 MOHLTC is intended or should be inferred.”
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40

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Abstract

Objective: To determine the association of atopic dermatitis with a patient's subsequent risk of death from suicide. We hypothesized that persistent atopic dermatitis 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 to 55 years old. We identified cases of suicide from coroners' reports between January 1, 1994 and December 31, 2014 and matched 1:2 with alive controls based on age, sex and socioeconomic status.

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

Main outcome and measure: We used logistic regression to estimate the association between atopic dermatitis and death from suicide.

Results: We identified 18,441 cases of suicide over the twenty-one-year accrual period matched to 36,882 controls. Persistent atopic dermatitis occurred in 174 (0.94%) suicide cases and 285 (0.77%) controls. Persistent atopic dermatitis was associated with a 22% increased risk of suicide (odds ratio = 1.22, 95% confidence interval: 1.01 to 1.48, $p = 0.037$). Two-thirds of atopic dermatitis patients who died from suicide had seen a physician in the month before their death and one-in-eight had a visit for atopic dermatitis in the month before their death. Among patients who died by suicide, jumping and poisoning were relatively more frequent mechanisms among atopic dermatitis patients.

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3 **Conclusions:** Patients with persistent atopic dermatitis have an increased subsequent risk of
4 death from suicide. Physicians caring for these patients have opportunities to intervene for
5 suicide prevention.
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Strengths and limitations of this study

- We conducted a large case-control study adequately powered to detect an association between atopic dermatitis and suicide
- Universal insurance coverage for physician visits allowed us to capture data on physician visits preceding death from suicide
- We conducted numerous sensitivity analyses and analyses with negative controls to test out results
- Our case definition of persistent atopic dermatitis has not been validated; misclassification is a possibility

Introduction

Atopic dermatitis is a common skin disease associated with decreased quality of life comparable to many other chronic conditions.^{1 2} Atopic dermatitis affects approximately one-in-nine children and one-in-fourteen adults, most of whom have mild disease.²⁻⁴ For patients with severe persistent atopic dermatitis, however, the disease can be debilitating with severe itch and impaired quality of life.⁵ Patients with atopic dermatitis can also experience substantial financial hardships due to direct medical costs, missed days from employment and decreased work productivity.^{5 6} Sleep loss related to itch can be especially debilitating;^{2 7} nearly half of US adults who have atopic dermatitis rate their health as poor or fair.²

Past research suggests links between atopic dermatitis and mental illness. In a claims-based study from Taiwan, patients had a seven-fold increased risk of a major depressive disorder and four-fold increased risk of an anxiety disorder.⁸ In two large American cross-sectional studies, atopic dermatitis was associated with twice the risk of depression compared to the general population.⁹ One study from Denmark found a suicide risk twice the population norm for patients with atopic dermatitis.¹⁰ In contrast, a second study also from Denmark found no significant association between atopic dermatitis and subsequent suicide.¹¹ The risk of suicide associated with atopic dermatitis has not been assessed in North America; moreover, other studies have excluded youth despite atopic dermatitis being distinctly common and suicide being a leading cause of death among youth.^{2 4 12}

The objective of this case-control study was to assess the association of atopic dermatitis with a patient's subsequent risk of death from suicide. A secondary aim was to assess the recency of

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2
3 physician visits prior to suicide among atopic dermatitis patients. A randomized controlled trial
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5 was judged impossible because patients cannot be assigned a diagnosis of atopic dermatitis;
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7 therefore, we conducted a large-scale multi-year observational analysis of longitudinal individual
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9 patient data. We hypothesized that persistent atopic dermatitis would increase a patient's risk of
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11 death from suicide and that many suicides would be preceded by a recent physician visit. If true,
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13 this would suggest that preventive efforts targeting vulnerable patients might save lives.
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15

16 17 18 **Methods**

19 20 *Selection of cases and controls*

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22 We conducted a double matched case-control study of patients between the age of 15 and 55
23
24 years in Ontario. The study was approved by the Institute for Clinical Evaluative Sciences
25
26 (ICES) and the Women's College Hospital Research Ethics Board deemed the work exempt
27
28 from supplementary ethics review. Cases of suicide were identified from the Ontario Vital
29
30 Statistics Database from January 1, 1994 to December 31, 2014, representing all available data
31
32 (21 years). We defined deaths from suicide using International Classification of Disease (ICD)
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34 codes (ICD-9 E950–E959, E980–E987; ICD-10 X60–X84, Y10–Y32, Y34).¹³⁻¹⁵ Interrater
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36 agreement among coroners on suicide diagnosis was high and showed 97% concordance with the
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38 vital statistics database.^{16 17} We also extracted data on the mechanism of suicide in categories of
39
40 asphyxiation, jumping, poisoning, violence and miscellaneous mechanisms.
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48 Controls were selected from the general population in Ontario using the Registered Persons
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50 Database that identified all patients insured under the Ontario Health Insurance Plan (OHIP).¹⁸
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52 For each case of suicide, we selected two control patients from the general population matched
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54 on age (within 2 days), socioeconomic status (SES) and sex, using simple random selection when
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3 excess matches were available. All cases and controls were alive and eligible for OHIP coverage
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5 on the index date and one year prior. SES at the index date was estimated from the Statistics
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7 Canada algorithm based on neighborhood income^{19 20} and patients with missing SES were
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9 matched to controls who were also missing SES. As a result, we obtained exact triplets of one
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11 case matched to two controls with no missing matches.
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16 17 *Primary predictor*

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19 We used a five-year look-back interval to assess each individual patient through a consistent
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21 ascertainment interval for cases and controls. The matching date in each triplet of patients was
22
23 defined as the date of death from suicide of the case. Prior medical care for each patient was
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25 evaluated based on physician diagnoses documented as ICD-9 diagnostic codes.¹³ Atopic
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27 dermatitis was defined using diagnosis code 691.¹³ In another population, ICD-9 codes for atopic
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29 dermatitis had a positive predictive value of 50% based on a requirement for two or more ICD-9
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31 codes to identify cases of probable atopic dermatitis.²¹ To increase the specificity and to define
32
33 persistent atopic dermatitis, we required five or more physician visits for the diagnosis, each
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35 separated by at least one week over the look-back interval.
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42 *Additional patient characteristics*

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44 Home location (urban, rural) and SES (quintile) were obtained from the Registered Persons
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46 Database. Specific medical diagnoses (asthma, hayfever or rhinitis, alcoholism, drug
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48 dependence, tobacco abuse, sleep and other disorders, depression, anxiety disorders, psychoses,
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50 personality disorders, malignancy, benign skin tumors, psoriasis) were identified during the five-
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52 year look-back interval using ICD-9 codes in the OHIP database. Measures of overall healthcare
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3 resource utilization were obtained from the OHIP database, the National Ambulatory Care
4 Reporting System and the Discharge Abstract Database (counts of clinic visits, emergency room
5 visits, hospitalizations in the prior year). We collected data on patients' most recent healthcare
6 visit, the specialty of the physician and the associated diagnostic reason. We also collected data
7 on the timing of suicide (season and day of the week, timing relative to the most recent visit with
8 a dermatologist or psychiatrist and relative to the most recent visit for atopic dermatitis).
9

19 *Statistical analysis*

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21 We used logistic regression to calculate odds ratios with 95% confidence intervals for the
22 association of persistent atopic dermatitis with the risk of death from suicide. We checked the
23 robustness of our findings by additionally calculating associations using conditional logistic
24 regression to fully account for matching. To assess for mediation, we conducted stratified
25 analyses by major suicide risk factors (depression, psychoses, personality disorders, sleep and
26 other disorders, drug dependence and alcoholism) within triads of cases and controls. Further, we
27 used logistic regression with suicide as the outcome and major suicide risk factors as covariates
28 to derive an overall suicide predilection score. We then conducted logistic regression stratified
29 by low (at or below the median) or high (above the median) overall suicide predilection score.
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31 To assess for potential mediation or confounding by a major atopic comorbidity, we conducted
32 analyses further stratified by history of asthma.
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49 We plotted Kaplan- Meier curves for patients who died from suicide with and without persistent
50 atopic dermatitis to assess the time interval between the most recent physician visit and ultimate
51 suicide. We compared the two curves using the Log-Rank test. To assess potential differences in
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3 the mechanism of suicide between patients with and without persistent atopic dermatitis, we
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5 calculated descriptive odds ratios with 95% confidence intervals for the different categories of
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7 suicide with no a priori hypotheses.
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12 We conducted several sensitivity analyses as tests of robustness. We used separate analyses to
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14 check results using alternative definitions of atopic dermatitis: (1) spanning between one or more
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16 and ten or more claims associated with diagnostic code 691; (2) requiring an additional comorbid
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18 atopic condition (either asthma or rhinitis); and (3) excluding patients with a history of stasis
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20 ulcers, varicose veins, lymphedema or contact dermatitis. These latter analyses were based on the
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22 rationale that comorbid asthma and rhinitis can improve the positive predictive value of ICD
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24 codes for atopic dermatitis²¹ and because excluding commonly confused conditions can also
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26 decrease false positive cases.
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33 As a test for residual confounding, we conducted analyses with two negative control predictors:
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35 benign skin tumors and psoriasis (another chronic inflammatory skin disease with effective
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37 treatment options for severe cases). We anticipated benign skin tumors and psoriasis might not
38
39 be associated with an increased risk for suicide and thereby validate the distinctive association
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41 with atopic dermatitis. There is no plan to share raw data from this study.
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46 47 *Patient and public involvement*

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49 There was no patient or public involvement in this study.
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52 53 *Data sharing*

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3 There is no plan to share raw data from this study.
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8 **Results**

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10 We identified 18,441 cases of suicide over the twenty-one-year accrual period matched to 36,882
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12 alive controls. The median patient age was 38 years, 74% were male and the average SES was
13
14 below the general population. Mental health disorders were more common among patients who
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16 had died from suicide than among controls, as were malignant neoplasms and asthma (Table 1).
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18 Patients who died from suicide had more clinic visits, emergency department visits and inpatient
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20 admissions in the year prior to the index date than controls.
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26 A history of persistent atopic dermatitis occurred in 174 (0.94%) suicide cases and 285 (0.77%)
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28 controls. In univariate analysis, persistent atopic dermatitis was associated with a 22% increased
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30 risk of suicide. Results were identical for ordinary and conditional logistic regression (odds ratio
31
32 = 1.22, 95% confidence interval: 1.01 to 1.48, $p=0.037$). The net increase was equal to 31 excess
33
34 cases of suicide associated with atopic dermatitis (more than once patient per year).
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40 Stratified analyses showed the association of atopic dermatitis with suicide was accentuated
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42 among older men with a history of addiction (Figure 1). There was no significant differential
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44 association of atopic dermatitis with suicide between strata of patients with and without asthma,
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46 malignancy and other individual suicide risk factors such as depression.
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51 Patients with atopic dermatitis had significantly higher suicide predilection scores compared with
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53 patients without atopic dermatitis (median 0.32 vs. 0.15, $p<0.0001$); Supplementary Figure 1).
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3 Comparisons based on mean scores showed similar imbalance (0.42 vs. 0.33, $p < 0.0001$). The
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5 highest decile of suicide predilection score was nearly twice as common among atopic dermatitis
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7 patients than controls (17% vs. 10%, $P < 0.0001$). Stratified analysis by high and low predilection
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9 scores showed no significant further association of atopic dermatitis with suicide between
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11 patients with high (odds ratio = 0.97, 95% confidence interval: 0.78 to 1.22, $p = 0.81$) and low
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13 (odds ratio = 0.59, 95% confidence interval: 0.34 to 1.03, $p = 0.06$) predilection scores, suggesting
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15 that atopic dermatitis is not an independent contributor to suicide risk beyond its influence on
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17 mental health risk overall.
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24 Nearly all patients with persistent atopic dermatitis who died from suicide had visited a physician
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26 in the year prior to their suicide, 67% within a month and 37% within a week before death.

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28 Among patients who died from suicide, those diagnosed with persistent atopic dermatitis visited
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30 a physician more recently than patients without persistent atopic dermatitis ($P < 0.0001$, Figure 2).

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32 For both patients with and without persistent atopic dermatitis who died from suicide, the most
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34 recent physician visit was most frequently with a family physician (Table 2). Among persistent
35
36 atopic dermatitis patients, one-in-twenty-five had visited a dermatologist last. For one-in-sixteen
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38 persistent atopic dermatitis patients who died from suicide, their last visit was for atopic
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40 dermatitis. There were no meaningful differences in season or day of the week of death from
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42 suicide distinguishing patients with and without persistent atopic dermatitis (Table 3).
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49 Analyses of suicide cases showed diverse mechanisms, of which about 8% were unclassified due
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51 to uncertain, multifactorial or missing details. Asphyxiation was the most common single cause
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53 of suicide and was distinctly less frequent among those who had persistent atopic dermatitis than
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3 controls (odds ratio = 0.55, 95% confidence interval: 0.38 to 0.78, p=0.0008). In contrast,
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5 jumping from a vertical height had the largest relative increase among patients who had
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7 persistent atopic dermatitis (odds ratio = 1.87, 95% confidence interval: 1.21 to 2.89, p=0.0047).
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10 Poisoning was the second largest relative increase among patients who had persistent atopic
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12 dermatitis (odds ratio = 1.41, 95% confidence interval: 1.04 to 1.91, p=0.03). Violent forms of
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14 suicide were infrequent and generally balanced between the two groups (odds ratio = 1.04, 95%
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16 confidence interval: 0.71 to 1.54, p=0.83).
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22 In sensitivity analyses requiring fewer than five visits for atopic dermatitis to define the
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24 predictor, the association with suicide was somewhat attenuated (Supplementary figure 2). When
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26 ten or more visits for atopic dermatitis were required, the confidence intervals widened
27
28 substantially and the association was ambiguous. When a diagnosis of asthma or rhinitis was
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30 required to identify cases of atopic dermatitis, the effect estimate for the risk of suicide was
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32 similar to the primary analysis but not statistically significant (odds ratio = 1.26, 95% confidence
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34 interval: 0.94 to 1.69, p=0.12). When patients who had a diagnosis of stasis ulcers, varicose
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36 veins, lymphedema or contact dermatitis were excluded, the results were similar to the primary
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38 analysis (odds ratio = 1.29, 95% confidence interval: 1.03 to 1.62, p=0.03). Benign skin tumors
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40 were associated with no increase in suicide risk (odds ratio = 0.90, 95% confidence interval: 0.84
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42 to 0.97, p=0.008). Psoriasis was associated with an equivocal increase in suicide risk (odds ratio
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44 = 1.14, 95% confidence interval: 0.99 to 1.31, p=0.06).
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Discussion

In this large longitudinal case-control study, persistent atopic dermatitis was associated with an increased risk of subsequent death from suicide. The patient group at highest risk was older men with a history of addiction. The increased risk of suicide among atopic dermatitis patients was fully explained by mental disorders including depression, anxiety, sleep disorders and substance misuse. Asphyxiation was the most common mechanism of suicide death overall, but poisoning and jumping were relatively increased for patients with persistent atopic dermatitis. Atopic dermatitis patients who died from suicide usually had visited a physician in the month before suicide, suggesting opportunities for intervention.

Our study confirms other literature on the association of atopic dermatitis with adverse mental health. A Norwegian study found that young adults with atopic dermatitis 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 atopic dermatitis. One conducted using administrative data for adults in Denmark found that atopic dermatitis patients had a 71% increased risk of suicide attempts and a 208% increased risk of death from suicide, a more prominent association than in our study.¹⁰ In agreement with our findings, older adults with atopic dermatitis had a further accentuated risk. The only other past study, also from Denmark, found no association between atopic dermatitis and suicide, but had wide confidence intervals and imprecision.¹¹

Our study contains novel findings concerning physician visits among atopic dermatitis patients prior to suicide. Nearly two in five patients with atopic dermatitis who died from suicide saw a physician in the week before their death. The most recent physician visit was most commonly

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3 with a general practitioner, often for reasons related to mental health. In a small number of
4 patients, the most recent physician contact was for their atopic dermatitis. While dermatologists
5 tend to underrecognize depression and anxiety in their patients, all physicians should recognize
6 psychological distress.²² Patients with atopic dermatitis who present with signs of significant
7 mental health distress could be assessed for suicide risk. In particular, standardized tools have
8 been suggested for assessing suicide risk in dermatology clinics, but have not been formally
9 evaluated in that setting.^{23 24}

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21 Asphyxiation is a generally frequent mechanism of suicide yet was relatively uncommon among
22 patients with persistent atopic dermatitis. Instead, atopic dermatitis patients were relatively more
23 prone to die by jumping from tall heights or self-poisoning. The significance of these patterns is
24 unclear. One possibility is that atopic dermatitis patients have high rates of medical and
25 psychiatric comorbidity relative to the general population and are more likely to have access to
26 prescription drugs with the potential to cause death. Another interpretation is that asphyxiation is
27 a more prolonged and painful means of suicide; perhaps atopic dermatitis patients who live in
28 discomfort from their condition choose instantaneous (in the case of jumping) or less painful (in
29 the case of poisoning) means of dying. A greater understanding is needed.

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45 The generalizability of our study is limited to a single large region in a high-income country with
46 universal healthcare access. Specifically, general medical care in our patients may have
47 substantially mitigated some of the suicide risk associated with atopic dermatitis. In addition, we
48 lacked data on atopic dermatitis severity, social isolation, other life stresses or risk factors for
49 suicide completion such as suicidal ideation.²⁵ Our primary outcome examined an extreme
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3 indicator of mental suffering and the overall observed effect size was more modest than those
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5 previously reported for other chronic medical illnesses.²⁶ While only a small minority of atopic
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7 dermatitis patients die by suicide, many more suffer from non-lethal forms of depression and
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9 other mental disorders.^{8 9 11} The population at risk is much larger since each suicide death mirrors
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11 about twenty other patients who attempt suicide.²⁷
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17 Another limitation of our study is how to define persistent atopic dermatitis. A past report
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19 suggested that two or more ICD-9 codes for atopic dermatitis have a 50% positive predictive
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21 value for probable atopic dermatitis.²¹ However, that validation study used stringent clinical
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23 diagnostic criteria unsuitable in a retrospective study to confirm cases. As such, studies using
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25 billing codes to identify patients with atopic dermatitis may underestimate the magnitude of
26
27 associations due to random misclassification bias. Additionally, potential misclassification is
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29 likely to have resulted from less severe skin diseases, such as contact dermatitis, that would bias
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31 our findings towards the null. Our requirement of five diagnostic codes likely improves the
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33 specificity of the atopic dermatitis case definition at a further loss of sensitivity.
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40 Strengths of our study include the large sample of suicide cases, the known validity of suicide
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42 outcomes and our double-matched case-control design. As Ontario has a universal health
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44 insurance program, we were able to comprehensively identify all physician visits prior to death.
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46 Of course, patients who had persistent atopic dermatitis but did not engage with the healthcare
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48 system may have been missed. In summary, patients with persistent atopic dermatitis have an
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50 increased subsequent risk of death from suicide. Physicians may have opportunities to intervene
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52 for suicide prevention in this vulnerable patient population.
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Figure Legends

Figure 1. Relative risk of suicide associated with persistent atopic dermatitis

Forest plot showing relative increase in risk of suicide among patients with persistent atopic dermatitis compared to patients without persistent atopic dermatitis. The x-axis shows odds ratio 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% confidence intervals. Main findings are an increase in risk associated with atopic dermatitis with accentuation of risk among older men, those with mid-to-high socioeconomic status and a history of addiction.

Figure 2. Time from the most recent physician visit to suicide among suicide cases

Kaplan-Meier curve showing the time between the last physician visit and subsequent death from suicide (n=18,441). 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 percent of patients dead from suicide. The red line represent patients with persistent atopic dermatitis. The blue line represents patients without persistent atopic dermatitis. Statistical significance was based on the log-rank test. Main findings show that patients with persistent atopic dermatitis were more likely to see a physician in close proximity to their death.

Table 1. Patient characteristics

	Suicide cases (n = 18,441)	Matched controls (n = 36,882)
Age (years)		
15 to 24	2,825 (15%)	5,650 (15%)
25 to 34	3,746 (20%)	7,492 (20%)
35 to 44	5,595 (30%)	11,190 (30%)
45 to 55	6,275 (34%)	12,550 (34%)
Sex (male)	13,680 (74%)	27,360 (74%)
Income quintile		
Q5 (highest)	2,839 (15%)	5,678 (15%)
Q4	3,162 (17%)	6,324 (17%)
Q3	3,426 (19%)	6,852 (19%)
Q2	3,814 (21%)	7,628 (21%)
Q1 (lowest)	4,969 (27%)	9,938 (27%)
Unknown/suppressed	231 (1%)	462 (1%)
Home location		
Urban	15,532 (84%)	32,158 (87%)
Rural*	2,893 (15%)	4,462 (12%)
Missing	16 (<1%)	262 (1%)
Comorbidities [^]		
Alcoholism	3,109 (17%)	750 (2%)
Drug dependence/addiction	3,645 (20%)	1,164 (3%)
Psychoses	5,373 (29%)	979 (3%)
Depression	5,753 (31%)	1,788 (5%)
Anxiety disorder	12,807 (69%)	10,690 (29%)
Personality disorder	2,391 (13%)	469 (1%)
Sleep disorders	2,844 (15%)	2,536 (7%)
Malignancy	1,024 (6%)	1,331 (4%)
Asthma	2,291 (12%)	3,247 (9%)
Rhinitis	1,956 (11%)	4,204 (11%)
Health services use in the preceding year		
6 or more clinic visits	11,946 (65%)	12,365 (34%)
1 or more emergency room visits	4,053 (22%)	3,173 (9%)
1 or more inpatient admissions	1,379 (8%)	511 (1%)

* 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).

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

	Persistent atopic dermatitis present (n = 174 patients)	Persistent atopic dermatitis absent (n =18,267 patients)
Physician specialty of most recent visit		
Family practice	121 (48%)	13,320 (55%)
Dermatology	9 (4%)	125 (1%)
Psychiatry	31 (12%)	3,101 (13%)
Pediatrics	π	102 (0%)
Other	91 (36%)	7,516 (31%)
Diagnosis associated with most recent visit		
Atopic dermatitis	16 (6%)	129 (1%)
Mental disorders*	72 (28%)	7,754 (32%)
Other medical diagnosis [^]	166 (65%)	16,281 (67%)
Total number of billing claims [#]	254	24,164

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

π Denotes a cell size below 6

* 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.

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

	Persistent atopic dermatitis present (n = 174 patients)	Persistent atopic dermatitis absent (n =18,267 patients)
Time from last psychiatrist visit		
≤1 month	40 (23%)	3,371 (19%)
>1 month or no visit	134 (77%)	14,896 (82%)
Time from last dermatologist visit		
≤1 month	8 (5%)	98 (<1%)
>1 month or no visit	166 (95%)	18,169 (>99%)
Time from last visit for atopic dermatitis		
≤1 month	14 (8%)	83 (<1%)
>1 month or no visit	160 (92%)	18,184 (>99%)
Season		
Spring	45 (26%)	4,756 (26%)
Summer	50 (29%)	4,812 (26%)
Autumn	36 (21%)	4,515 (25%)
Winter	43 (25%)	4,184 (23%)
Day		
Weekday	125 (72%)	13,242 (73%)
Weekend	49 (28%)	5,025 (28%)
Mechanism of death		
Asphyxiation	40 (23%)	6,460 (35%)
Jumping	24 (14%)	1,439 (8%)
Poisoning	68 (39%)	5,715 (31%)
Violent	31 (18%)	3,144 (17%)
Miscellaneous*	11 (6%)	1,504 (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

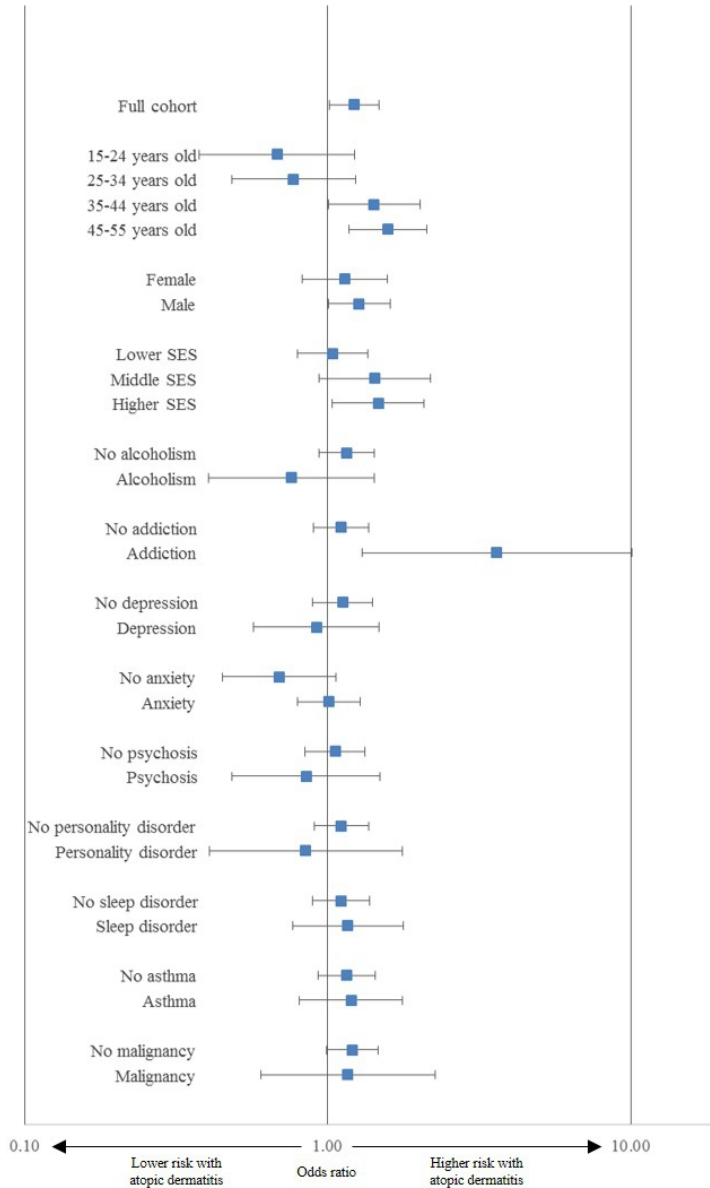


Figure 1. Relative risk of suicide associated with persistent atopic dermatitis

Forest plot showing relative increase in risk of suicide among patients with persistent atopic dermatitis compared to patients without persistent atopic dermatitis. The x-axis shows odds ratio 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% confidence intervals. Main findings are an increase in risk associated with atopic dermatitis with accentuation of risk among older men, those with mid-to-high socioeconomic status and a history of addiction.

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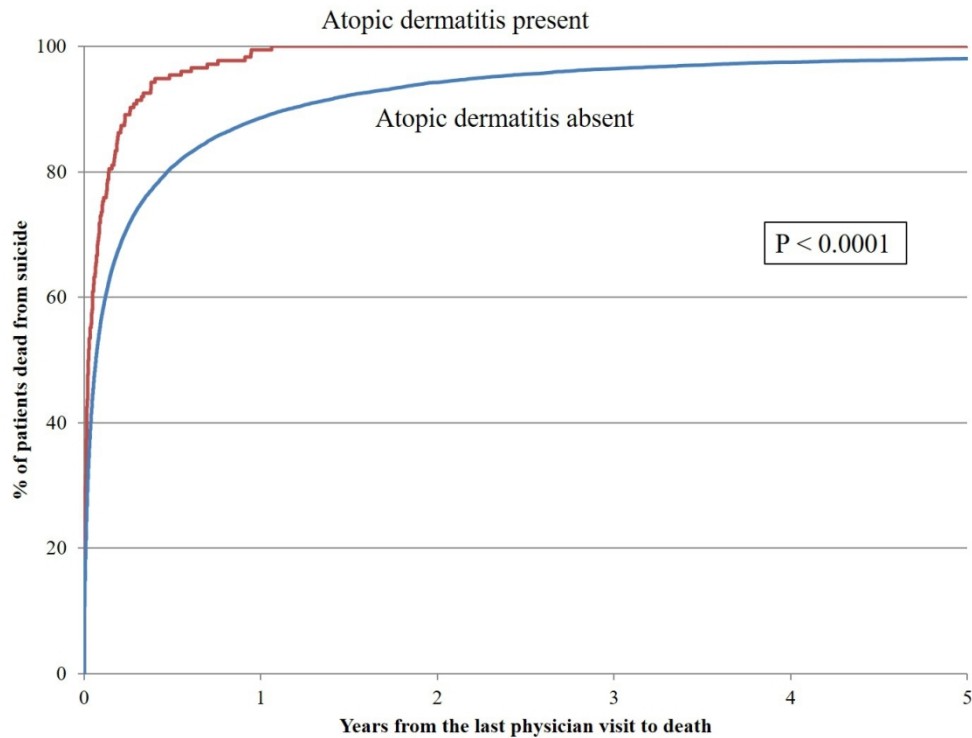
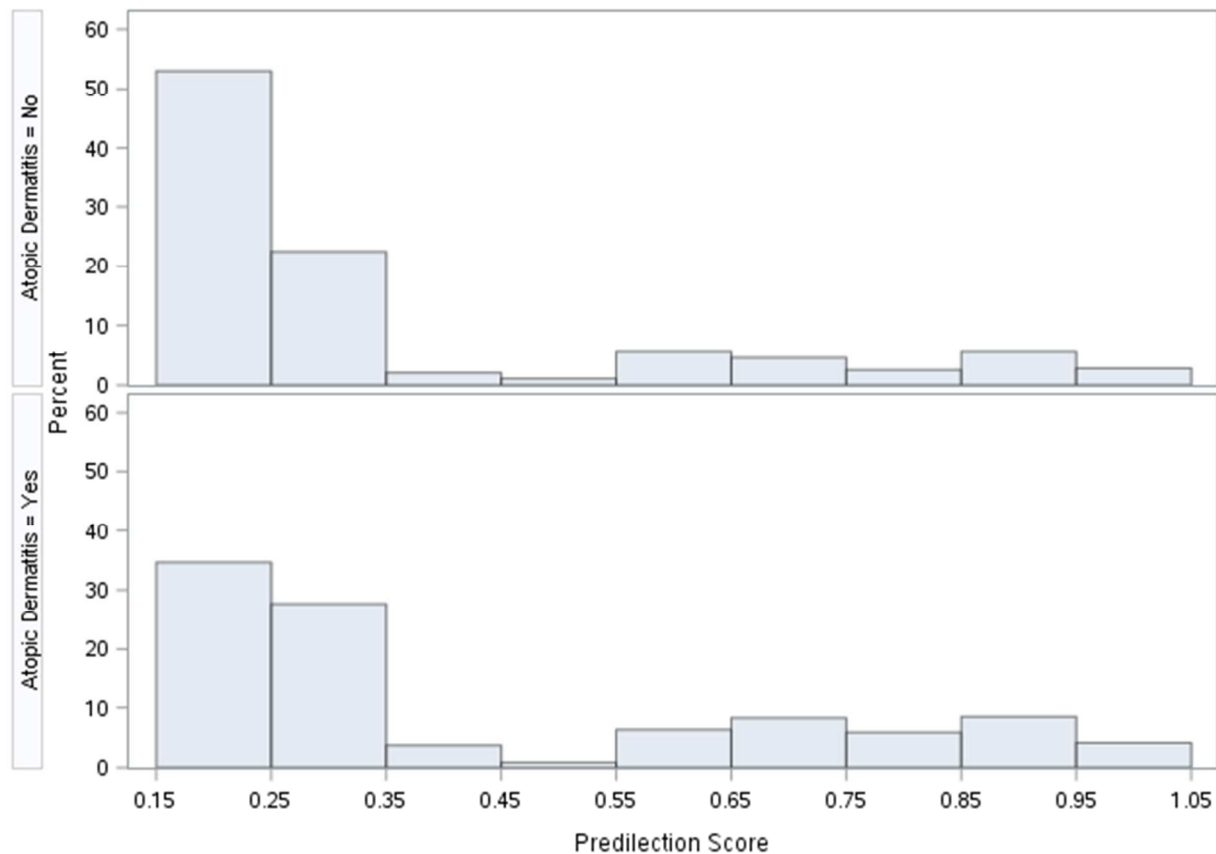


Figure 2. Time from the most recent physician visit to suicide among suicide cases

Kaplan-Meier curve showing the time between the last physician visit and subsequent death from suicide (n=18,441). 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 percent of patients dead from suicide. The red line represent patients with persistent atopic dermatitis. The blue line represents patients without persistent atopic dermatitis. Statistical significance was based on the log-rank test. Main findings show that patients with persistent atopic dermatitis were more likely to see a physician in close proximity to their death.

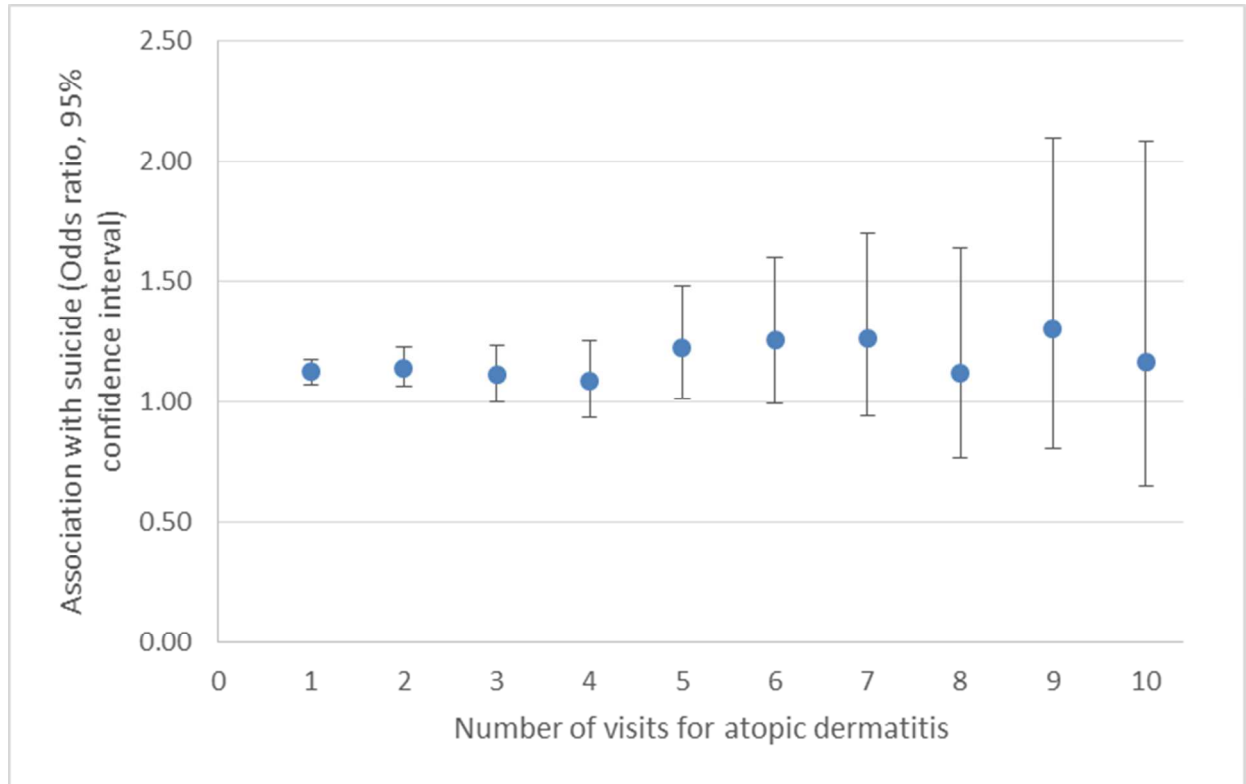
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2 **Supplementary figure 1. Distribution of the derived suicide predilection score according to**
3 **history of atopic dermatitis.**
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Low scores represent a lower risk for suicide based on the patient's history of mental health, sleep and substance disorders and high scores represent a higher risk. Main findings are that patients with persistent atopic dermatitis have generally higher suicide predilection scores than patients without persistent atopic dermatitis.

Supplementary figure 2. Association of atopic dermatitis with suicide when different definitions of atopic dermatitis are applied.



Atopic dermatitis cases are defined by the presence of number of physician visits for diagnostic code 691, including patients with the given number of visits or more. The primary predictor is 5 or more visits for atopic dermatitis. Results are presented as odds ratios (dots) and 95% confidence intervals (lines and bars).

STROBE Statement—Checklist of items that should be included in reports of *case-control studies*

	Item No	Recommendation	
Title and abstract	1	✓ (a) Indicate the study's design with a commonly used term in the title or the abstract	p 1
		✓ (b) Provide in the abstract an informative and balanced summary of what was done and what was found	p 3-4
Introduction			
Background/rationale	2	✓ Explain the scientific background and rationale for the investigation being reported	p6-7
Objectives	3	✓ State specific objectives, including any prespecified hypotheses	p6-7
Methods			
Study design	4	✓ Present key elements of study design early in the paper	p7-10
Setting	5	✓ Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	p7
Participants	6	✓ (a) Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls	p7
		✓ (b) For matched studies, give matching criteria and the number of controls per case	p7-8
Variables	7	✓ Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	p7-9
Data sources/ measurement	8*	✓ For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	p7-9
Bias	9	✓ Describe any efforts to address potential sources of bias	p9-10
Study size	10	✓ Explain how the study size was arrived at	p7
Quantitative variables	11	✓ Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	p9
Statistical methods	12	✓ (a) Describe all statistical methods, including those used to control for confounding	p9-10
		✓ (b) Describe any methods used to examine subgroups and interactions	p9-10
		✓ (c) Explain how missing data were addressed	p7-8
		✓ (d) If applicable, explain how matching of cases and controls was addressed	p7-8
		✓ (e) Describe any sensitivity analyses	p10
Results			
Participants	13*	✓ (a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	p11
		N/A (b) Give reasons for non-participation at each stage	
		N/A (c) Consider use of a flow diagram	
Descriptive data	14*	✓ (a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	p22
		✓ (b) Indicate number of participants with missing data for each variable of interest	p22
Outcome data	15*	✓ Report numbers in each exposure category, or summary measures of exposure	p11
Main results	16	✓ (a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	p11
		N/A (b) Report category boundaries when continuous variables were categorized	
		✓ (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	p11

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Other analyses	17 ✓	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	p13
Discussion			
Key results	18 ✓	Summarise key results with reference to study objectives	p14-16
Limitations	19 ✓	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	p15-16
Interpretation	20 ✓	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	p16
Generalisability	21 ✓	Discuss the generalisability (external validity) of the study results	p15
Other information			
Funding	22 ✓	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	p2

*Give information separately for cases and controls.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at <http://www.strobe-statement.org>.

BMJ Open

Atopic dermatitis and subsequent suicide: a matched case-control study

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Manuscripts

Atopic dermatitis and subsequent suicide: a matched case-control study

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Contributions

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

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The manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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Abstract

Objective: To determine the association of atopic dermatitis with a patient's subsequent risk of death from suicide. We hypothesized that persistent atopic dermatitis 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 to 55 years old. We identified cases of suicide from coroners' reports between January 1, 1994 and December 31, 2014 and matched 1:2 with alive controls based on age, sex and socioeconomic status.

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

Main outcome and measure: Logistic regression to estimate the association between atopic dermatitis and death from suicide.

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

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3 **Conclusions:** Patients with persistent atopic dermatitis have an increased subsequent risk of
4 death from suicide, but this is not independent of overall mental health and the absolute risk is
5 low. Physicians caring for these patients have opportunities to intervene for suicide prevention.
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For peer review only

Strengths and limitations of this study

- We conducted a large case-control study adequately powered to detect an association between atopic dermatitis 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 atopic dermatitis has not been validated somisclassification is a possibility

Introduction

Atopic dermatitis is a common skin disease associated with decreased quality of life comparable to many other chronic medical conditions.^{1 2} Atopic dermatitis affects approximately one-in-nine children and one-in-fourteen adults, most of whom have mild disease.²⁻⁴ For patients with severe persistent atopic dermatitis, however, the disease can be debilitating with severe itch, social embarrassment and impaired quality of life.⁵ Patients with atopic dermatitis 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 be especially debilitating^{2 7} and nearly half of US adults who have atopic dermatitis with fatigue rate their health as poor or fair.²

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

The objective of this case-control study was to assess the association of atopic dermatitis 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 atopic dermatitis patients. A randomized controlled trial

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3 was deemed impossible because patients cannot be assigned a diagnosis of atopic dermatitis;
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5 therefore, we conducted a large-scale multi-year observational analysis of longitudinal individual
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7 patient data. We hypothesized that persistent atopic dermatitis would increase a patient's risk of
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9 death from suicide and that many deaths would be preceded by a recent physician visit. If true,
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11 this would suggest that preventive efforts targeting vulnerable patients might save lives.
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15 16 **Methods**

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18 The study was approved by the Institute for Clinical Evaluative Sciences (ICES) and the
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20 Women's College Hospital Research Ethics Board deemed the work exempt from supplementary
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22 ethics review.
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26 27 *Patient and public involvement*

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29 There was no patient or public involvement in this study.
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43 We conducted a double matched case-control study of patients between the age of 15 and 55
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45 years in Ontario. We included youth 15 and older as atopic dermatitis is a more common
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47 diagnosis and suicide is a common cause of death in youth.^{24 12} We excluded adults older than 55
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49 to avoid misclassification of age-associated xerosis with itch as atopic dermatitis. Cases of
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51 suicide were identified from the Ontario Vital Statistics Database from January 1, 1994 to
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53 December 31, 2014, representing all available data. We defined suicide using International
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3 Classification of Disease (ICD) codes (ICD-9 E950–E959, E980–E987; ICD-10 X60–X84, Y10–
4 Y32, Y34).¹³⁻¹⁵ Interrater agreement among coroners on suicide diagnosis was high and showed
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6 97% concordance with the vital statistics database.^{16 17} We also extracted data on the mechanism
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8 of suicide in categories of asphyxiation, jumping, poisoning, violence and miscellaneous
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10 mechanisms.
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17 Controls were selected from the general population in Ontario using the Registered Persons
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19 Database that identified all patients insured under the Ontario Health Insurance Plan (OHIP).¹⁸
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21 For each case of suicide, we selected two control patients from the general population matched
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23 on age (within 2 days), socioeconomic status (SES) and sex using simple random selection when
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25 excess matches were available. All cases and controls were alive and eligible for OHIP coverage
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27 on the index date and one year prior. SES at the index date was estimated from the Statistics
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29 Canada algorithm based on neighborhood income^{19 20} and patients with missing SES were
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31 matched to controls who were also missing SES. As a result, we obtained exact triplets of one
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33 case matched to two controls with no missing matches.
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38 39 40 *Primary predictor*

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42 We used a five-year look-back interval to assess each individual through a consistent
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44 ascertainment interval for cases and controls. The matching date in each triplet of patients was
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46 defined as the date of suicide death of the case. Prior medical care for each patient was evaluated
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48 based on physician diagnoses documented as ICD-9 diagnostic codes.¹³ In Ontario, physicians
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50 document each encounter with a single ICD-9 code. Atopic dermatitis was defined using
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52 diagnosis code 691.¹³ In another population, ICD-9 codes for atopic dermatitis had a positive
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3 predictive value of 50% based on a requirement for two or more ICD-9 codes to identify cases of
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5 probable atopic dermatitis.²¹ In Denmark, results of a validation study are encouraging with
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7 confirmation of 48 of 50 cases identified by ICD-10 codes.²² To increase the specificity and to
8
9 define persistent atopic dermatitis, we required five or more physician visits for the diagnosis,
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11 each separated by at least one week over the look-back interval.
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16 17 *Additional patient characteristics*

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19 Home location (urban, rural) and SES (quintile) were obtained from the Registered Persons
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21 Database. Specific medical diagnoses (asthma, hayfever or rhinitis, alcoholism, drug
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23 dependence, tobacco abuse, sleep and other disorders, depression, anxiety disorders, psychoses,
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25 personality disorders, malignancy, benign skin tumors, psoriasis) were identified during the five-
26
27 year look-back interval using ICD-9 codes in the OHIP database. Measures of overall healthcare
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29 resource utilization were obtained from the OHIP database, the National Ambulatory Care
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31 Reporting System and the Discharge Abstract Database (counts of clinic visits, emergency room
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33 visits, hospitalizations in the prior year). We collected data on patients' most recent healthcare
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35 visit, the specialty of the physician and the associated diagnosis. We also collected data on the
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37 timing of suicide (season and day of the week, proximity to the most recent visit with a
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39 dermatologist or psychiatrist and recency of a visit for atopic dermatitis).
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47 *Statistical analysis*

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49 We used logistic regression to calculate odds ratios with 95% confidence intervals for the
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51 association of persistent atopic dermatitis with the risk of subsequent death from suicide. We
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53 examined the robustness of our findings by additionally calculating associations using
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3 conditional logistic regression to fully account for matching. To assess for mediation, we
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5 conducted stratified analyses by major suicide risk factors (depression, psychoses, personality
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7 disorders, sleep and other disorders, drug dependence and alcoholism) within triads of cases and
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9 controls. Further, we used logistic regression with suicide as the outcome and major suicide risk
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11 factors as covariates to derive an overall suicide predilection score. We then conducted logistic
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13 regression stratified by low (at or below the median) or high (above the median) overall suicide
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15 predilection score. To assess for potential mediation or confounding by a major atopic
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17 comorbidity, we conducted analyses further stratified by history of asthma.
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24 We plotted Kaplan- Meier curves for patients who died from suicide with and without persistent
25
26 atopic dermatitis to assess the time interval between the most recent physician visit and ultimate
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28 suicide. We compared the two curves using the Log-Rank test. To assess potential differences in
29
30 the mechanism of suicide between patients with and without persistent atopic dermatitis, we
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32 calculated descriptive odds ratios with 95% confidence intervals for the different categories of
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34 suicide with no a priori hypotheses.
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40 We conducted several sensitivity analyses as tests of robustness. We used separate analyses to
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42 check results using three alternative definitions of atopic dermatitis: (1) spanning between one
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44 and ten claims associated with the diagnosis; (2) requiring a comorbid atopic condition (asthma
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46 or rhinitis); and (3) excluding atopic dermatitis patients who had a history of stasis ulcers,
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48 varicose veins, lymphedema, contact dermatitis, seborrheic dermatitis or psoriasis. These latter
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50 two analyses were based on the rationale that comorbid asthma and rhinitis can improve the
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3 positive predictive value of ICD codes for atopic dermatitis²¹ and because excluding commonly
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5 confused conditions can also decrease false positive cases.
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10 As a test for residual confounding, we conducted tracer analyses with two negative control
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12 predictors: benign skin tumors and psoriasis (another chronic skin disease with effective
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14 treatment options). We anticipated benign skin tumors and psoriasis might not be associated with
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16 an increased risk for suicide and thereby validate the distinctive association with atopic
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18 dermatitis. There is no plan to share raw data from this study.
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26 **Results**

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28 We identified 18,441 cases of suicide matched to 36,882 alive controls over the twenty-one-year
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30 accrual period. The median patient age was 38 years, 74% were male and the average SES was
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32 below the population median. Mental health disorders were more common among patients who
33
34 had died from suicide than among controls, as were malignant neoplasms and asthma (Table 1).
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36 Patients who died from suicide had more clinic visits, emergency department visits and inpatient
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38 admissions in the year prior to the index date than controls.
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44 A history of persistent atopic dermatitis occurred in 174 (0.94%) suicide cases and 285 (0.77%)
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46 controls. In univariate analysis, persistent atopic dermatitis was associated with a 22% increased
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48 risk of suicide. Results were identical for ordinary and conditional logistic regression (odds ratio
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50 = 1.22, 95% confidence interval: 1.01 to 1.48, p=0.037). The net increase was equal to 31 excess
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52 cases of suicide associated with atopic dermatitis (more than one patient per year).
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5 Stratified analyses showed the association of atopic dermatitis with suicide was accentuated
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7 among older men with a history of addiction (Figure 1). There was no significant differential
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9 association of atopic dermatitis with suicide between strata of patients with and without asthma,
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11 malignancy and other individual suicide risk factors such as depression.
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17 Patients with atopic dermatitis had significantly higher suicide predilection scores compared with
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19 patients without atopic dermatitis (median 0.32 vs. 0.15, $p<0.0001$); Supplementary Figure 1).
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21 Comparisons based on mean scores showed similar imbalance (0.42 vs. 0.33, $p<0.0001$). The
22
23 highest decile of suicide predilection score was nearly twice as common among atopic dermatitis
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25 patients as controls (17% vs. 10%, $p<0.0001$). Stratified analysis by high or low predilection
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27 scores showed no significant further association of atopic dermatitis with suicide between
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29 patients with high (odds ratio = 0.97, 95% confidence interval: 0.78 to 1.22, $p=0.81$) and low
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31 (odds ratio = 0.59, 95% confidence interval: 0.34 to 1.03, $p=0.06$) predilection scores, suggesting
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33 that atopic dermatitis was not an independent contributor to suicide risk beyond its influence on
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35 mental health risk overall.
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42 Nearly all patients with persistent atopic dermatitis who died from suicide had visited a physician
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44 in the year prior to their death, 67% within a month and 37% within a week. Among patients
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46 who died from suicide, those diagnosed with persistent atopic dermatitis visited a physician more
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48 recently than patients without persistent atopic dermatitis ($P<0.0001$, Figure 2). For both patients
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50 with and without persistent atopic dermatitis who died from suicide, the most recent physician
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52 visit was most frequently with a family physician (Table 2). Among persistent atopic dermatitis
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3 patients, one-in-twenty-five had visited a dermatologist last. For one-in-sixteen persistent atopic
4 dermatitis patients who died from suicide, their last visit was for atopic dermatitis. We found no
5 meaningful differences in season or in day of the week of death distinguishing patients with and
6 without persistent atopic dermatitis (Table 3).
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14 Analyses of suicide cases showed diverse mechanisms, of which about 8% were unclassified due
15 to uncertain, multifactorial or missing details. Asphyxiation was the most common single cause
16 of suicide and was distinctly less frequent among individuals who had persistent atopic
17 dermatitis than controls (odds ratio = 0.55, 95% confidence interval: 0.38 to 0.78, p=0.0008). In
18 contrast, jumping from a vertical height had the largest relative increased risk among patients
19 who had persistent atopic dermatitis (odds ratio = 1.87, 95% confidence interval: 1.21 to 2.89,
20 p=0.0047). Poisoning was the second largest relative increased risk among patients who had
21 persistent atopic dermatitis (odds ratio = 1.41, 95% confidence interval: 1.04 to 1.91, p=0.03).
22 Violent forms of suicide were infrequent and generally balanced between the two groups (odds
23 ratio = 1.04, 95% confidence interval: 0.71 to 1.54, p=0.83).
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40 In sensitivity analyses requiring fewer than five visits for atopic dermatitis to define the
41 predictor, the association with suicide was somewhat attenuated (Supplementary figure 2). When
42 ten or more visits for atopic dermatitis were required, the confidence intervals widened
43 substantially and the association was ambiguous. When a diagnosis of asthma or rhinitis was
44 required to identify cases of atopic dermatitis, the estimated association for the risk of suicide
45 was similar to the primary analysis but not statistically significant (odds ratio = 1.26, 95%
46 confidence interval: 0.94 to 1.69, p=0.12). When patients who had a diagnosis of stasis ulcers,
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3 varicose veins, lymphedema, contact dermatitis, seborrheic dermatitis and psoriasis were
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5 excluded, the results were similar to the primary analysis (odds ratio = 1.26, 95% confidence
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7 interval: 0.99 to 1.61, $p=0.06$), though no longer statistically significant. Benign skin tumors
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9 were associated with no increase in suicide risk (odds ratio = 0.90, 95% confidence interval: 0.84
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11 to 0.97, $p=0.008$). Psoriasis was associated with an equivocal increase in suicide risk (odds ratio
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13 = 1.14, 95% confidence interval: 0.99 to 1.31, $p=0.06$).
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16 17 18 19 Discussion

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21 In this large longitudinal case-control study, persistent atopic dermatitis was associated with an
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23 increased risk of subsequent death from suicide. The association was modest and the absolute
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25 risk low. The patient group at highest risk was older men with a history of addiction. The
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27 increased risk of suicide among atopic dermatitis patients was fully explained by mental
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29 disorders including depression, anxiety, sleep disorders and substance misuse, suggesting that
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31 atopic dermatitis was not an independent contributor to suicide risk beyond its influence on
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33 mental health risk overall. Asphyxiation was the most common mechanism of suicide death
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35 overall, but poisoning and jumping were differentially increased for patients with persistent
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37 atopic dermatitis. Atopic dermatitis patients who died from suicide usually had visited a
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39 physician in the month before death.
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47 Our study confirms other literature on the association of atopic dermatitis with adverse mental
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49 health. A Norwegian study found that young adults with atopic dermatitis and itchy skin had a
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51 24% prevalence of suicidal ideation in the preceding week.⁷ Only two studies have examined the
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53 risk of death from suicide associated with atopic dermatitis, with mixed results. One conducted
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3 using administrative data for adults in Denmark found that atopic dermatitis patients had a 71%
4 increased risk of suicide attempts and double the risk of death from suicide, (a more prominent
5 association than in our study).¹¹ In agreement with our findings, older adults with atopic
6 dermatitis had a further accentuated risk. It is unclear why the association is increased in older
7 populations and one possible explanation could be the cumulative stress of living with a chronic
8 condition for decades. The only other past study, also from Denmark, found no statistically
9 significant association between atopic dermatitis and suicide.¹⁰

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21 Our study contains novel findings concerning physician visits for atopic dermatitis patients prior
22 to suicide. Nearly two in five patients with atopic dermatitis who died from suicide saw a
23 physician in the week before their death. The most recent physician visit was most commonly
24 with a general practitioner, often for reasons related to mental health. In a small number of
25 patients, the most recent physician contact was for their atopic dermatitis. While dermatologists
26 tend to underrecognize depression and anxiety in their patients, all clinicians should recognize
27 psychological distress.²³ Patients with atopic dermatitis who present with signs of significant
28 mental health distress could be assessed for suicide risk. In particular, standardized tools have
29 been suggested for assessing suicide risk in dermatology clinics, but have not been formally
30 evaluated in that setting.^{24 25}

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47 Asphyxiation is a generally frequent mechanism of suicide yet was relatively uncommon among
48 patients with persistent atopic dermatitis. Instead, atopic dermatitis patients were relatively more
49 prone to die by jumping from tall heights or self-poisoning. The significance of these patterns is
50 unclear. One possibility is that atopic dermatitis patients have high rates of medical and
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3 psychiatric comorbidity relative to the general population and are more likely to have access to
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5 prescription drugs with the potential to cause death. Another interpretation is that asphyxiation is
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7 a more prolonged and painful means of suicide so that atopic dermatitis patients who live in
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9 discomfort from their condition choose instantaneous or less painful means of dying. A greater
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11 understanding is needed for future research.
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17 The generalizability of our study is limited to a single large region in a high-income country with
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19 universal healthcare access. Specifically, comprehensive care in our patients may have
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21 substantially mitigated some of the suicide risk associated with atopic dermatitis. In addition, we
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23 lacked data on atopic dermatitis severity, social isolation, other life stresses or risk factors for
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25 suicide completion such as suicidal ideation.²⁶ We also lack data on treatments used for atopic
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27 dermatitis, which can be used to stratify atopic dermatitis cases based on severity and which may
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29 be important given the psychiatric effects of systemic corticosteroids.^{10 27} Our primary outcome
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31 examined an extreme indicator of mental suffering and the overall observed effect size was more
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33 modest than previously reported for other chronic medical illnesses.²⁸ While only a small
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35 minority of atopic dermatitis patients die by suicide, many more suffer from non-lethal forms of
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37 depression and other mental disorders.^{8-10 29}
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45 Another limitation of our study is how to define persistent atopic dermatitis. A past report
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47 suggested that two or more ICD-9 codes for atopic dermatitis have a 50% positive predictive
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49 value for probable atopic dermatitis.²¹ However, that validation study used stringent clinical
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51 diagnostic criteria unsuitable in a retrospective study to confirm cases. A study examining the
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53 validity of ICD-10 codes in Denmark found more encouraging results.²² Misclassification of
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3 atopic dermatitis could bias the results in a number of ways. Random misclassification may
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5 cause underestimates of the magnitude of associations.³⁰ Misclassification of less severe skin
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7 diseases such as contact dermatitis, could also bias our findings towards the null. However,
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9 misclassification of more severe skin diseases such as an exfoliative dermatitis may bias our
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11 results towards an increased risk for suicide. It is unclear whether our requirement of five
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13 occurrences of code 691 increases or decreases the specificity of our atopic dermatitis case
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15 definition and exactly what impact this would have on the results.
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21 Our sensitivity analysis requiring comorbid asthma or rhinitis to define atopic dermatitis was
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23 reassuring in that the effect estimate was largely unchanged (although the result was no longer
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25 significant). Further, we calculated the prevalence of asthma and rhinitis among patients in our
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27 study and found each of these atopic comorbidities to be more than twice as common among
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29 those with persistent atopic dermatitis compared to those without (Supplementary Table 1).
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35 Strengths of our study include the large sample of suicide cases, the known validity of suicide
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37 outcomes and our double-matched case-control design. As Ontario has a universal health
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39 insurance program, we were able to comprehensively identify all physician visits prior to death.
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41 Of course, patients who had persistent atopic dermatitis but did not engage with the healthcare
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43 system may have been missed. In summary, patients with persistent atopic dermatitis have an
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45 increased subsequent risk of death from suicide. Physicians may have opportunities to intervene
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47 for suicide prevention in this vulnerable patient population.
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Figure Legends

Figure 1. Relative risk of suicide associated with persistent atopic dermatitis

Forest plot showing relative increase in risk of suicide among patients with persistent atopic dermatitis compared to patients without persistent atopic dermatitis. The x-axis shows odds ratio 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% confidence intervals. Main findings are an increase in risk associated with atopic dermatitis with accentuation of risk among older men, those with mid-to-high socioeconomic status and a history of addiction.

Figure 2. Time from the most recent physician visit to suicide among suicide cases

Kaplan-Meier curve showing the time between the last physician visit and subsequent death from suicide (n=18,441). 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 percent of patients dead from suicide. The red line represent patients with persistent atopic dermatitis. The blue line represents patients without persistent atopic dermatitis. Statistical significance was based on the log-rank test. Main findings show that patients with persistent atopic dermatitis were more likely to see a physician in close proximity to their death.

Table 1. Patient characteristics

	Suicide cases (n = 18,441)	Matched controls (n = 36,882)
Age (years)		
15 to 24	2,825 (15%)	5,650 (15%)
25 to 34	3,746 (20%)	7,492 (20%)
35 to 44	5,595 (30%)	11,190 (30%)
45 to 55	6,275 (34%)	12,550 (34%)
Sex (male)	13,680 (74%)	27,360 (74%)
Income quintile		
Q5 (highest)	2,839 (15%)	5,678 (15%)
Q4	3,162 (17%)	6,324 (17%)
Q3	3,426 (19%)	6,852 (19%)
Q2	3,814 (21%)	7,628 (21%)
Q1 (lowest)	4,969 (27%)	9,938 (27%)
Unknown/suppressed	231 (1%)	462 (1%)
Home location		
Urban	15,532 (84%)	32,158 (87%)
Rural*	2,893 (15%)	4,462 (12%)
Missing	16 (<1%)	262 (1%)
Comorbidities [^]		
Alcoholism	3,109 (17%)	750 (2%)
Drug dependence/addiction	3,645 (20%)	1,164 (3%)
Psychoses	5,373 (29%)	979 (3%)
Depression	5,753 (31%)	1,788 (5%)
Anxiety disorder	12,807 (69%)	10,690 (29%)
Personality disorder	2,391 (13%)	469 (1%)
Sleep disorders	2,844 (15%)	2,536 (7%)
Malignancy	1,024 (6%)	1,331 (4%)
Asthma	2,291 (12%)	3,247 (9%)
Rhinitis	1,956 (11%)	4,204 (11%)
Health services use in the preceding year		
6 or more clinic visits	11,946 (65%)	12,365 (34%)
1 or more emergency room visits	4,053 (22%)	3,173 (9%)
1 or more inpatient admissions	1,379 (8%)	511 (1%)
OHIP eligible for entire 5-year look-back	17701 (96%)	34447 (93%)

OHIP: Ontario Health Insurance Plan

* Rural includes unknown/suppressed home location

1
2 ^Comorbidities defined by truncated ICD-9 codes: Alcoholism (303), drug dependence/addiction
3 (304), psychoses (291, 292, 295, 296, 298, 299), depression (311), anxiety disorder (300),
4 personality disorder (301), sleep and other disorders (307), malignancy (140-165, 170-175, 179-
5 208), asthma (493), rhinitis (477).
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Table 2. Description of the most recent physician visit among patients who died from suicide.

	Persistent atopic dermatitis present (n = 174 patients)	Persistent atopic dermatitis absent (n =18,267 patients)
Physician specialty of most recent visit		
Family practice	121 (48%)	13,320 (55%)
Dermatology	9 (4%)	125 (1%)
Psychiatry	31 (12%)	3,101 (13%)
Pediatrics	π	102 (0%)
Other	91 (36%)	7,516 (31%)
Diagnosis associated with most recent visit		
Atopic dermatitis	16 (6%)	129 (1%)
Mental disorders*	72 (28%)	7,754 (32%)
Other medical diagnosis [^]	166 (65%)	16,281 (67%)
Total number of billing claims [#]	254	24,164

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

π Denotes a cell size below 6

* 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.

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

	Persistent atopic dermatitis present (n = 174 patients)	Persistent atopic dermatitis absent (n =18,267 patients)
Time from last psychiatrist visit		
≤1 month	40 (23%)	3,371 (19%)
>1 month or no visit	134 (77%)	14,896 (82%)
Time from last dermatologist visit		
≤1 month	8 (5%)	98 (<1%)
>1 month or no visit	166 (95%)	18,169 (>99%)
Time from last visit for atopic dermatitis		
≤1 month	14 (8%)	83 (<1%)
>1 month or no visit	160 (92%)	18,184 (>99%)
Season		
Spring	45 (26%)	4,756 (26%)
Summer	50 (29%)	4,812 (26%)
Autumn	36 (21%)	4,515 (25%)
Winter	43 (25%)	4,184 (23%)
Day		
Weekday	125 (72%)	13,242 (73%)
Weekend	49 (28%)	5,025 (28%)
Mechanism of death		
Asphyxiation	40 (23%)	6,460 (35%)
Jumping	24 (14%)	1,439 (8%)
Poisoning	68 (39%)	5,715 (31%)
Violent	31 (18%)	3,144 (17%)
Miscellaneous*	11 (6%)	1,504 (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

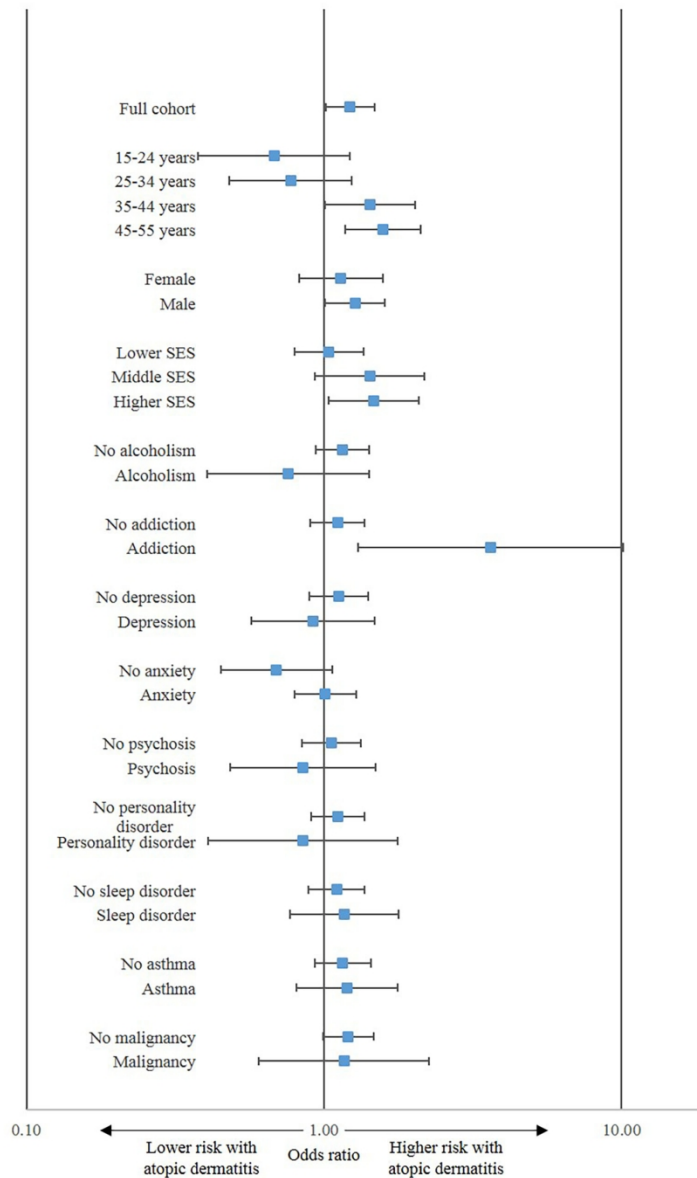


Figure 1. Relative risk of suicide associated with persistent atopic dermatitis

Forest plot showing relative increase in risk of suicide among patients with persistent atopic dermatitis compared to patients without persistent atopic dermatitis. The x-axis shows odds ratio 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% confidence intervals. Main findings are an increase in risk associated with atopic dermatitis with accentuation of risk among older men, those with mid-to-high socioeconomic status and a history of addiction.

140x220mm (300 x 300 DPI)

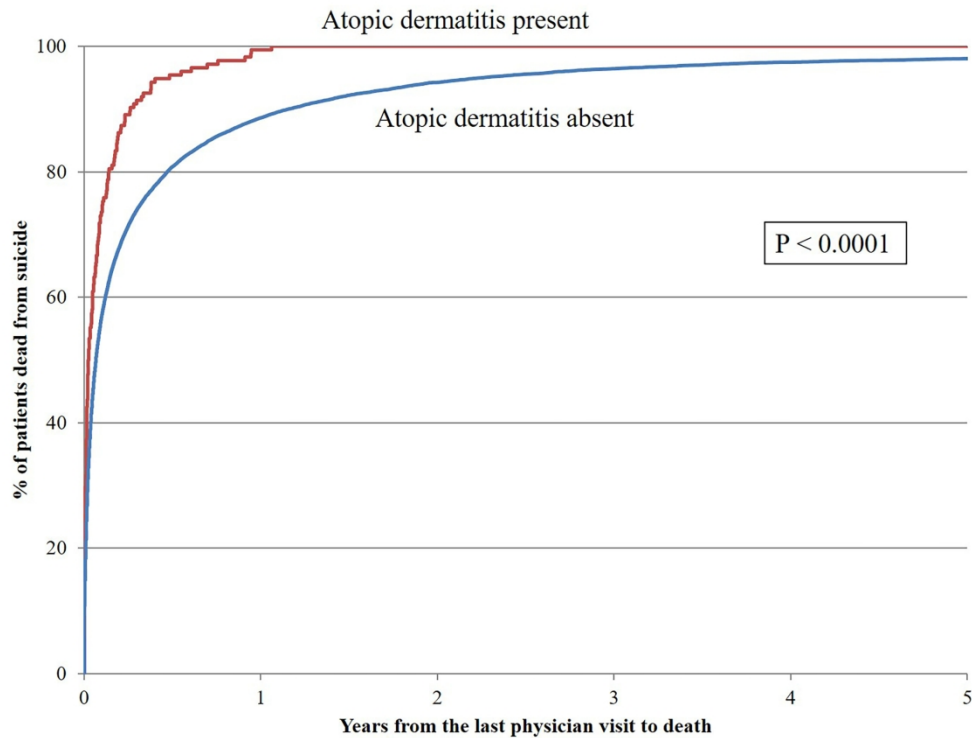


Figure 2. Time from the most recent physician visit to suicide among suicide cases

Kaplan-Meier curve showing the time between the last physician visit and subsequent death from suicide (n=18,441). 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 percent of patients dead from suicide. The red line represent patients with persistent atopic dermatitis. The blue line represents patients without persistent atopic dermatitis. Statistical significance was based on the log-rank test. Main findings show that patients with persistent atopic dermatitis were more likely to see a physician in close proximity to their death.

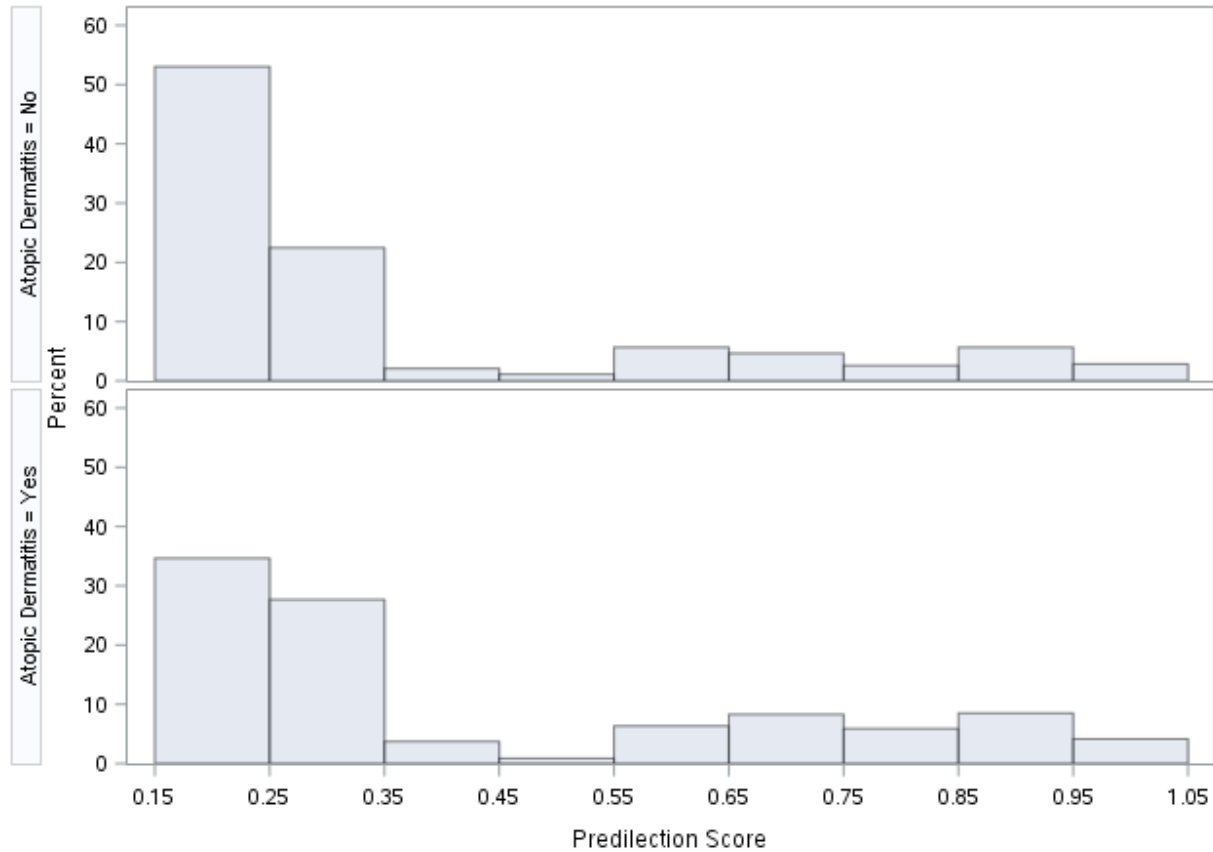
240x182mm (300 x 300 DPI)

Supplementary Table 1. Prevalence of asthma and rhinitis according to history of atopic dermatitis.

Atopic comorbidity	Persistent atopic dermatitis present (n = 459 patients)	Persistent atopic dermatitis absent (n = 54,864 patients)
Asthma	103 (22%)	5,435 (10%)
Rhinitis	132 (29%)	6,028 (11%)

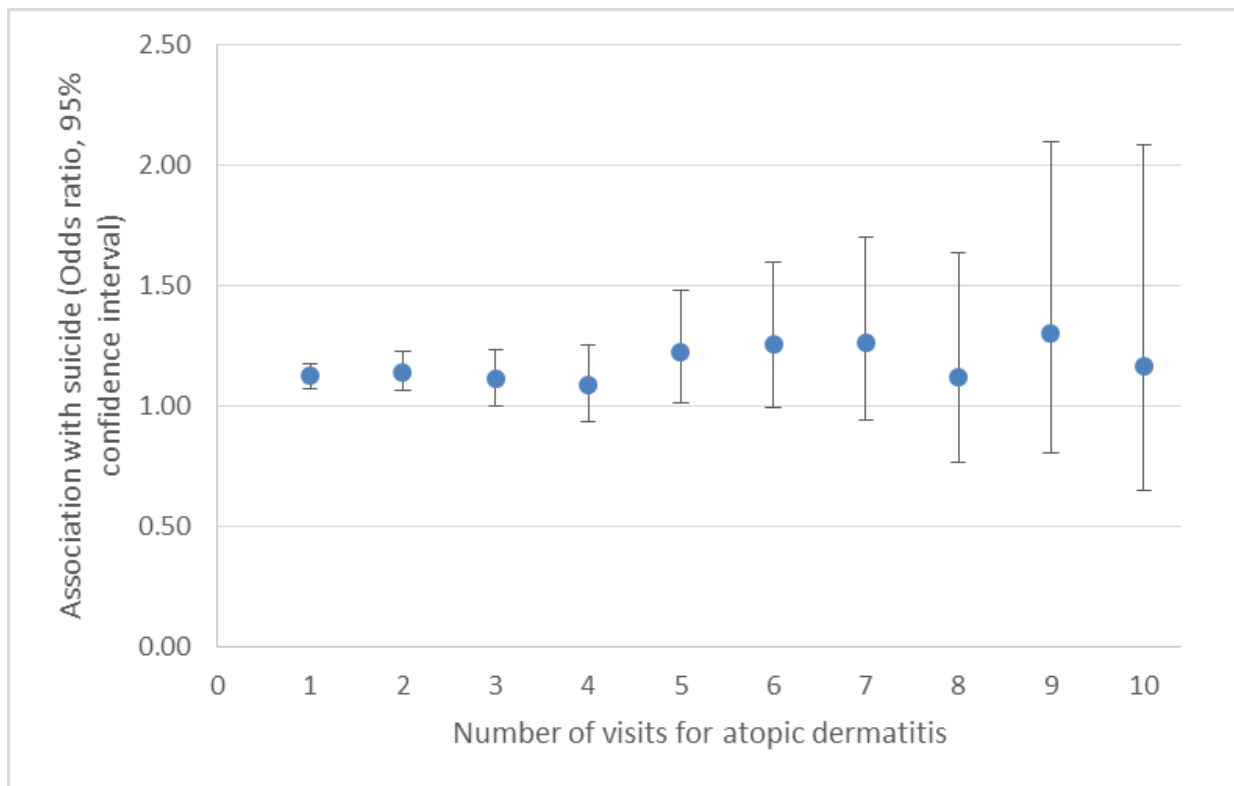
Comorbidities defined by truncated ICD-9 codes: asthma (493), rhinitis (477)

Supplementary figure 1. Distribution of the derived suicide predilection score according to history of atopic dermatitis.



Low scores represent a lower risk for suicide based on the patient's history of mental health, sleep and substance disorders and high scores represent a higher risk. Main findings are that patients with persistent atopic dermatitis have generally higher suicide predilection scores than patients without persistent atopic dermatitis.

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2 **Supplementary figure 2. Association of atopic dermatitis with suicide when different**
3 **definitions of atopic dermatitis are applied.**
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31 Atopic dermatitis cases are defined by the presence of number of physician visits for diagnostic
32 code 691, including patients with the given number of visits or more. The primary predictor is 5
33 or more visits for atopic dermatitis. Results are presented as odds ratios (dots) and 95%
34 confidence intervals (lines and bars).
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60STROBE Statement—Checklist of items that should be included in reports of *case-control studies*

	Item No	Recommendation	
Title and abstract	1	✓ (a) Indicate the study's design with a commonly used term in the title or the abstract	p 1
		✓ (b) Provide in the abstract an informative and balanced summary of what was done and what was found	p 3-4
Introduction			
Background/rationale	2	✓ Explain the scientific background and rationale for the investigation being reported	p6-7
Objectives	3	✓ State specific objectives, including any prespecified hypotheses	p6-7
Methods			
Study design	4	✓ Present key elements of study design early in the paper	p7-10
Setting	5	✓ Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	p7
Participants	6	✓ (a) Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls	p7
		✓ (b) For matched studies, give matching criteria and the number of controls per case	p7-8
Variables	7	✓ Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	p7-9
Data sources/ measurement	8*	✓ For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	p7-9
Bias	9	✓ Describe any efforts to address potential sources of bias	p9-10
Study size	10	✓ Explain how the study size was arrived at	p7
Quantitative variables	11	✓ Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	p9
Statistical methods	12	✓ (a) Describe all statistical methods, including those used to control for confounding	p9-10
		✓ (b) Describe any methods used to examine subgroups and interactions	p9-10
		✓ (c) Explain how missing data were addressed	p7-8
		✓ (d) If applicable, explain how matching of cases and controls was addressed	p7-8
		✓ (e) Describe any sensitivity analyses	p10
Results			
Participants	13*	✓ (a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	p11
		N/A (b) Give reasons for non-participation at each stage	
		N/A (c) Consider use of a flow diagram	
Descriptive data	14*	✓ (a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	p22
		✓ (b) Indicate number of participants with missing data for each variable of interest	p22
Outcome data	15*	✓ Report numbers in each exposure category, or summary measures of exposure	p11
Main results	16	✓ (a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	p11
		N/A (b) Report category boundaries when continuous variables were categorized	
		✓ (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	p11

Other analyses	17 ✓	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	p13
Discussion			
Key results	18 ✓	Summarise key results with reference to study objectives	p14-16
Limitations	19 ✓	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	p15-16
Interpretation	20 ✓	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	p16
Generalisability	21 ✓	Discuss the generalisability (external validity) of the study results	p15
Other information			
Funding	22 ✓	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	p2

*Give information separately for cases and controls.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at <http://www.strobe-statement.org>.

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Atopic dermatitis and subsequent suicide: a matched case-control study

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Manuscripts

Atopic dermatitis and subsequent suicide: a matched case-control study

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Contributions

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

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The manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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Abstract

Objective: To assess the association of atopic dermatitis with a patient's subsequent risk of death from suicide. We hypothesized that persistent atopic dermatitis 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 to 55 years old. We identified cases of suicide from coroners' reports between January 1, 1994 and December 31, 2014 and matched 1:2 with alive controls based on age, sex and socioeconomic status.

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

Main outcome and measure: Logistic regression to estimate the association between atopic dermatitis and death from suicide.

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

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3 **Conclusions:** Patients with persistent atopic dermatitis have a modestly increased subsequent
4 risk of death from suicide, but this is not independent of overall mental health and the absolute
5 risk is low. Physicians caring for these patients have opportunities to intervene for suicide
6 prevention.
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Strengths and limitations of this study

- We conducted a large case-control study adequately powered to detect an association between atopic dermatitis 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 atopic dermatitis has not been validated so misclassification is a possibility

Introduction

Atopic dermatitis is a common skin disease associated with decreased quality of life comparable to many other chronic medical conditions.^{1 2} Atopic dermatitis affects approximately one-in-nine children and one-in-fourteen adults, most of whom have mild disease.²⁻⁴ For patients with severe persistent atopic dermatitis, however, the disease can be debilitating with severe itch, social embarrassment and impaired quality of life.⁵ Patients with atopic dermatitis 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 be especially debilitating^{2 7} and nearly half of US adults who have atopic dermatitis rate their health as poor or fair.²

Past research has linked atopic dermatitis to mental illness. In a claims-based study from Taiwan, patients had a seven-fold increased risk of a major depressive disorder and four-fold increased risk of an anxiety disorder.⁸ In two American cross-sectional studies, atopic dermatitis was associated with twice the risk of depression compared to the general population.⁹ One study from Denmark found no significant association between atopic dermatitis and subsequent suicide.¹⁰ Whereas a prior study on psoriasis found a suicide risk twice the population norm for patients with atopic dermatitis.¹¹ The risk of suicide associated with atopic dermatitis has not been assessed in North America; moreover, most studies have excluded youth despite atopic dermatitis 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 atopic dermatitis with a patient's subsequent risk of death from suicide. A secondary aim was to assess the recency of

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3 physician visits prior to suicide among atopic dermatitis patients. A randomized controlled trial
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5 was deemed impossible because patients cannot be assigned a diagnosis of atopic dermatitis;
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7 therefore, we conducted a large-scale multi-year observational analysis of longitudinal individual
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9 patient data. We hypothesized that persistent atopic dermatitis would increase a patient's risk of
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11 death from suicide and that many deaths would be preceded by a recent physician visit. If true,
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13 this would suggest that preventive efforts targeting vulnerable patients might save lives.
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16 17 18 **Methods**

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20 The study was approved by the Institute for Clinical Evaluative Sciences (ICES) and the
21
22 Women's College Hospital Research Ethics Board deemed the work exempt from supplementary
23
24 ethics review.
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27 28 29 *Patient and public involvement*

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31 There was no patient or public involvement in this study.
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34 35 36 *Data sharing*

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38 There is no plan to share raw data from this study.
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41 42 43 *Selection of patients*

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45 We conducted a double matched case-control study of patients between the age of 15 and 55
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47 years in Ontario. We included individuals 15 and older as atopic dermatitis is a common
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49 diagnosis and suicide is a common cause of death in youth.^{2 4 12} We excluded adults older than 55
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51 to avoid misclassification of age-associated xerosis with itch as atopic dermatitis. Cases of
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53 suicide were identified from the Ontario Vital Statistics Database from January 1, 1994 to
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3 December 31, 2014, representing all available data. We defined suicide using International
4 Classification of Disease (ICD) codes (ICD-9 E950–E959, E980–E987; ICD-10 X60–X84, Y10–
5 Y32, Y34).¹³⁻¹⁵ Interrater agreement from coroners on suicide diagnosis was high and showed
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8 97% concordance with the vital statistics database.^{16 17} We also extracted data on the mechanism
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12 of suicide in five categories as asphyxiation, jumping, poisoning, violence and miscellaneous.
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17 Controls were selected from the general population in Ontario using the Registered Persons
18 Database that identified all patients insured under the Ontario Health Insurance Plan (OHIP).¹⁸
19 For each case of suicide, we selected two control patients from the general population matched
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22 on age (within 2 days), socioeconomic status (SES) quintile and sex using simple random
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25 selection when excess matches were available. All cases and controls were alive and eligible for
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28 OHIP coverage on the index date and one year prior. SES at the index date was estimated from
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31 the Statistics Canada algorithm based on neighborhood income^{19 20} and patients with missing
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34 SES were matched to controls who were also missing SES. As a result, we obtained exact triplets
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37 of one case matched to two controls with no missing matches.
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40 *Primary predictor*

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42 We used a five-year look-back interval to assess each patient through a consistent ascertainment
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45 interval for cases and controls. The matching date in each triplet of patients was defined as the
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48 date of suicide death of the case. Prior medical care for each patient was evaluated based on
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51 physician diagnoses documented as ICD-9 diagnostic codes.¹³ In Ontario, physicians document
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54 each encounter with a single ICD-9 code. Atopic dermatitis was defined using diagnosis code
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57 691.¹³ In another population, ICD-9 codes for atopic dermatitis had a positive predictive value of
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3 50% based on a requirement for two or more ICD-9 codes to identify cases of probable atopic
4 dermatitis.²¹ To increase the specificity and to define persistent atopic dermatitis, we required
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6 five or more physician visits for the diagnosis, each separated by at least one week over the five-
7
8 year look-back interval.
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11 12 13 14 *Additional patient characteristics*

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16 Specific additional medical diagnoses (asthma, hayfever or rhinitis, alcoholism, drug
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18 dependence, tobacco abuse, sleep and other disorders, depression, anxiety disorders, psychoses,
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20 personality disorders, malignancy, benign skin tumors, psoriasis) were identified during the five-
21
22 year look-back interval using ICD-9 codes in the OHIP database. Measures of overall healthcare
23
24 resource utilization were obtained from the OHIP database, the National Ambulatory Care
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26 Reporting System and the Discharge Abstract Database (counts of clinic visits, emergency room
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28 visits, hospitalizations in the prior year). We collected data on patients' most recent healthcare
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30 visit, the specialty of the physician and the associated diagnosis. We also collected data on the
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32 timing of suicide (proximity to the most recent visit with a dermatologist or psychiatrist and
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34 recency of a visit for atopic dermatitis).
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42 *Statistical analysis*

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44 We used logistic regression to calculate odds ratios with 95% confidence intervals for the
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46 association of persistent atopic dermatitis with the risk of subsequent death from suicide. We
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48 examined the robustness of findings by additionally calculating associations using conditional
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50 logistic regression to fully account for matching. To assess for potential mediation, we
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52 conducted stratified analyses by major suicide risk factors (depression, psychoses, personality
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3 disorders, sleep and other disorders, drug dependence and alcoholism) within triads of cases and
4 controls. Further, we used logistic regression with suicide as the outcome and major suicide risk
5 factors as covariates to derive an overall suicide predilection score. We then conducted logistic
6 regression stratified by low (at or below the median) or high (above the median) overall suicide
7 predilection score. To assess for potential mediation or confounding by a major atopic
8 comorbidity, we conducted analyses further stratified by history of asthma.
9

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11 We plotted Kaplan- Meier curves for patients who died from suicide with and without persistent
12 atopic dermatitis to assess the time interval between the most recent physician visit and ultimate
13 suicide. We compared the two curves using the Log-Rank test. To assess potential differences in
14 the mechanism of suicide between patients with and without persistent atopic dermatitis, we
15 calculated descriptive odds ratios with 95% confidence intervals for the different categories of
16 suicide with no prespecified hypotheses.
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20 We conducted several sensitivity analyses as tests of robustness. We replicated separate analyses
21 to check results using three alternative definitions of atopic dermatitis: (1) spanning between one
22 and ten claims associated with the diagnosis; (2) requiring a comorbid atopic condition (asthma
23 or rhinitis); and (3) excluding patients who had a history of stasis ulcers, varicose veins,
24 lymphedema, contact dermatitis, seborrheic dermatitis or psoriasis. These latter two analyses
25 were based on the rationale that comorbid asthma and rhinitis can improve the positive predictive
26 value of ICD codes for atopic dermatitis²¹ and because excluding commonly confused conditions
27 can also decrease false positive cases.
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3 As a test for residual confounding, we conducted tracer analyses with two additional control
4 predictors: benign skin tumors and psoriasis (another chronic skin disease with effective
5 treatment options). We anticipated benign skin tumors and psoriasis might not be associated with
6 an increased risk for suicide and thereby validate the distinctive association with atopic
7 dermatitis.
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14 15 16 17 18 19 **Results**

20 We identified 18,441 cases of suicide matched to 36,882 alive controls over the twenty-one-year
21 accrual period. The median patient age was 38 years, 74% were male and the average SES was
22 below the population median. Mental health disorders were more common among patients who
23 had died from suicide than among controls, as were malignant neoplasms and asthma (Table 1).
24 Patients who died from suicide had more clinic visits, emergency department visits and inpatient
25 admissions in the year prior to the index date than controls.
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38 A history of persistent atopic dermatitis occurred in 174 (0.94%) suicide cases and 285 (0.77%)
39 controls. In univariate analysis, persistent atopic dermatitis was associated with a 22% increased
40 risk of suicide. Results were identical for ordinary and conditional logistic regression (odds ratio
41 = 1.22, 95% confidence interval: 1.01 to 1.48, $p=0.037$). The net increase was equal to 31 excess
42 cases of suicide associated with atopic dermatitis (more than one patient per year).
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51 Stratified analyses showed the association of atopic dermatitis with suicide was accentuated
52 among older men with a history of addiction (Figure 1). There was no significant differential
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3 association of atopic dermatitis with suicide between strata of patients with and without asthma,
4 malignancy or other individual suicide risk factors such as depression.
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10 Patients with atopic dermatitis had significantly higher suicide predilection scores compared with
11 patients without atopic dermatitis (median 0.32 vs. 0.15, $p<0.0001$); Supplementary Figure 1).

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13 Comparisons based on mean scores showed similar imbalance (0.42 vs. 0.33, $p<0.0001$). The
14 highest decile of suicide predilection score was nearly twice as common among atopic dermatitis
15 patients as controls (17% vs. 10%, $p<0.0001$). Stratified analysis by high or low predilection
16 scores showed no significant further association of atopic dermatitis with suicide between
17 patients with high predilection scores (odds ratio = 0.97, 95% confidence interval: 0.78 to 1.22,
18 $p=0.81$) and low predilection scores (odds ratio = 0.59, 95% confidence interval: 0.34 to 1.03,
19 $p=0.06$), suggesting that atopic dermatitis was not an independent contributor to suicide risk
20 beyond its influence on mental health risk overall.
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35 Nearly all patients with persistent atopic dermatitis who died from suicide had visited a physician
36 in the year prior to their death, 67% within a month and 37% within a week. Among patients
37 who died from suicide, those diagnosed with persistent atopic dermatitis visited a physician more
38 recently than patients without persistent atopic dermatitis ($P<0.0001$, Figure 2). For both patients
39 with and without persistent atopic dermatitis who died from suicide, the most recent physician
40 visit was most frequently with a family physician (Table 2). Among persistent atopic dermatitis
41 patients, one-in-twenty-five had visited a dermatologist last. For one-in-sixteen persistent atopic
42 dermatitis patients who died from suicide, their last visit was for atopic dermatitis. We found no
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3 meaningful differences in season or in day of the week of death distinguishing patients who did
4 and did not have persistent atopic dermatitis (Table 3).
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10 Analyses of suicide cases showed diverse mechanisms, of which about 8% were unclassified due
11 to uncertain, multifactorial or missing details. Asphyxiation was the most common single cause
12 of suicide and was less frequent among individuals who had persistent atopic dermatitis than
13 controls (odds ratio = 0.55, 95% confidence interval: 0.38 to 0.78, $p=0.0008$). In contrast,
14 jumping from a vertical height had the largest relative increased risk among patients who had
15 persistent atopic dermatitis (odds ratio = 1.87, 95% confidence interval: 1.21 to 2.89, $p=0.0047$).
16
17 Poisoning was the second largest relative increased risk among patients who had persistent
18 atopic dermatitis (odds ratio = 1.41, 95% confidence interval: 1.04 to 1.91, $p=0.03$). Violent
19 forms of suicide were infrequent and generally balanced between the two groups (odds ratio =
20 1.04, 95% confidence interval: 0.71 to 1.54, $p=0.83$).
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35 In sensitivity analyses requiring fewer than five visits for atopic dermatitis to define the
36 predictor, the association with suicide was somewhat attenuated (Supplementary figure 2). When
37 ten or more visits for atopic dermatitis were required, the confidence intervals widened
38 substantially and the association was ambiguous. When a diagnosis of asthma or rhinitis was
39 required to identify cases of atopic dermatitis, the estimated association for the risk of suicide
40 was similar to the primary analysis but not statistically significant (odds ratio = 1.26, 95%
41 confidence interval: 0.94 to 1.69, $p=0.12$). When patients who had a diagnosis of stasis ulcers,
42 varicose veins, lymphedema, contact dermatitis, seborrheic dermatitis and psoriasis were
43 excluded, the results were similar to the primary analysis (odds ratio = 1.26, 95% confidence
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3 interval: 0.99 to 1.61, $p=0.06$), although not statistically significant. Benign skin tumors were
4 associated with no increase in suicide risk (odds ratio = 0.90, 95% confidence interval: 0.84 to
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6 0.97, $p=0.008$). Psoriasis was associated with an equivocal increase in suicide risk (odds ratio =
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8 1.14, 95% confidence interval: 0.99 to 1.31, $p=0.06$).
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10 11 12 13 14 15 Discussion

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17 In this large longitudinal case-control study, persistent atopic dermatitis was associated with a
18 modestly increased risk of subsequent death from suicide. The absolute risk was low. The
19 association was fully explained by mental health disorders including depression, anxiety, sleep
20 disorders and substance misuse, suggesting that atopic dermatitis was not an independent
21 contributor to suicide risk beyond its influence on mental health risk overall. . The patient group
22 at highest risk was older men with a history of addiction. . Asphyxiation was the most common
23 mechanism of suicide death overall, but poisoning and jumping were differentially increased for
24 patients with persistent atopic dermatitis. Atopic dermatitis patients who died from suicide
25 usually had visited a physician in the month before death.
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40 Our study is in agreement with other literature on the association of atopic dermatitis with
41 adverse mental health. A Norwegian study found that young adults with atopic dermatitis and
42 itchy skin had a 24% prevalence of suicidal ideation in the preceding week.⁷ Only two studies
43 have examined the risk of death from suicide associated with atopic dermatitis, with mixed
44 results. One conducted using administrative data for adults in Denmark found that atopic
45 dermatitis patients had a 71% increased risk of suicide attempts and double the risk of death from
46 suicide, (a more prominent association than in our study).¹¹ Similar to our findings, older adults
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3 with atopic dermatitis had a further accentuated risk. It is unclear why the association might be
4 increased in older populations and one possible explanation could be the cumulative stress of
5 living with a chronic condition for decades. The only other past study, also from Denmark, found
6 no statistically significant association between atopic dermatitis and suicide.¹⁰
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14 Our study contains novel findings concerning physician visits by atopic dermatitis patients prior
15 to suicide. Nearly two in five patients with atopic dermatitis who died from suicide contacted a
16 physician in the week before their death. The most recent physician visit was most commonly
17 with a general practitioner and often for reasons related to mental health. In a small number of
18 patients, the most recent physician contact was for their atopic dermatitis. While dermatologists
19 tend to underrecognize depression and anxiety in their patients, all clinicians should recognize
20 psychological distress.²² Patients with atopic dermatitis who present with signs of significant
21 mental health distress could be assessed for suicide risk. In particular, standardized tools have
22 been suggested for assessing suicide risk in dermatology clinics, but have not been formally
23 evaluated in that setting.^{23 24}
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40 Asphyxiation is a frequent mechanism of suicide yet was relatively uncommon among patients
41 with persistent atopic dermatitis. Instead, atopic dermatitis patients were comparatively more
42 prone to die by jumping from tall heights or self-poisoning. The significance of these patterns is
43 unclear. One possibility is that atopic dermatitis patients have high rates of medical and
44 psychiatric comorbidity relative to the general population and are more likely to have access to
45 prescription drugs with the potential to cause death. Another interpretation is that asphyxiation is
46 a more prolonged and painful means of suicide so that atopic dermatitis patients who live in
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3 discomfort from their condition choose rapid or less painful means of dying. A greater
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5 understanding is needed for future research.
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10 The generalizability of our study is limited to a single large region in a high-income country with
11 universal healthcare access. Specifically, comprehensive medical care in our patients may have
12 substantially mitigated some of the suicide risk associated with atopic dermatitis. In addition, we
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14 lacked data on atopic dermatitis severity, social isolation, other life stresses or risk factors for
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16 suicide completion such as suicidal ideation.²⁵ We also lack data on treatments used for atopic
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18 dermatitis, which can be used to stratify atopic dermatitis cases based on severity and which may
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20 be important given the psychiatric effects of systemic corticosteroids.^{10 26} Our primary outcome
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22 examined an extreme indicator of mental suffering and the overall observed effect size was more
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24 modest than previously reported for other medical illnesses.²⁷ While only a small minority of
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26 atopic dermatitis patients die by suicide, many more suffer from non-lethal forms of depression
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28 and other mental disorders.^{8-10 28}
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38 The most important limitation of our study related to our definition of persistent atopic
39 dermatitis. A past report suggested that two or more ICD-9 codes for atopic dermatitis have a
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41 50% positive predictive value for probable atopic dermatitis.²¹ The true positive predictive value
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43 may be higher than reported in that study, as it used stringent clinical diagnostic criteria
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45 unsuitable in a retrospective study. Nevertheless, misclassification of persistent atopic dermatitis
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47 cases is a strong possibility and may have impacted our results in a number of ways. Random
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49 misclassification may cause underestimates of the magnitude of associations.²⁹ Misclassification
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51 of less severe skin diseases such as contact dermatitis, could also bias our findings towards the
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3 null. However, misclassification of more severe skin diseases such as an exfoliative dermatitis
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5 may bias our results towards an increased risk for suicide. It is unclear whether our requirement
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7 of five occurrences of code 691 increases or decreases the specificity of our atopic dermatitis
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9 case definition and exactly what impact this would have on the results.
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14 To provide some additional nuances for our case definition, we also calculated the prevalence of
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16 asthma and rhinitis among patients in our study and found each of these atopic comorbidities was
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18 more than twice as common among those with persistent atopic dermatitis compared to those
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20 without (Supplementary Table 1). It is possible that the associations observed between our
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22 primary predictor and these well-known atopic comorbidities are partially confounded by
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24 differential healthcare system access. However, the strong associations seen support our
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26 assertion that our predictor definition represents, to some extent, persistent atopic dermatitis.
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33 Our sensitivity analyses requiring comorbid asthma or rhinitis to define atopic dermatitis and
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35 excluding patients with psoriasis and other skin diseases yielded decreased sample sizes and
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37 showed results that were no longer significant. Nevertheless, we are reassured that the estimates
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39 were largely unchanged and are cautious not to over-interpret statistical significance in post-hoc
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41 secondary analyses.
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47 Strengths of our study include the large sample of suicide deaths, the known validity of suicide
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49 outcomes and our double-matched case-control design. As Ontario has a universal health
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51 insurance program, we were able to comprehensively identify all physician visits prior to death.
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54 Of course, patients who had persistent atopic dermatitis but who did not engage with the
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3 healthcare system may have been missed. In summary, patients with persistent atopic dermatitis
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5 have a modestly increased subsequent risk of death from suicide. Physicians may have
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7 opportunities to intervene for suicide prevention in this vulnerable patient population.
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Figure Legends

Figure 1. Relative risk of suicide associated with persistent atopic dermatitis

Forest plot showing relative increase in risk of suicide among patients with persistent atopic dermatitis compared to patients without persistent atopic dermatitis. The x-axis shows odds ratio 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% confidence intervals. Main findings are an increase in risk associated with atopic dermatitis with accentuation of risk among older men, those with mid-to-high socioeconomic status and a history of addiction.

Figure 2. Time from the most recent physician visit to suicide among suicide cases

Kaplan-Meier curve showing the time between the last physician visit and subsequent death from suicide (n=18,441). 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 percent of patients dead from suicide. The red line represent patients with persistent atopic dermatitis. The blue line represents patients without persistent atopic dermatitis. Statistical significance was based on the log-rank test. Main findings show that patients with persistent atopic dermatitis were more likely to see a physician in close proximity to their death.

Table 1. Patient characteristics

	Suicide cases (n = 18,441)	Matched controls (n = 36,882)
Age (years)		
15 to 24	2,825 (15%)	5,650 (15%)
25 to 34	3,746 (20%)	7,492 (20%)
35 to 44	5,595 (30%)	11,190 (30%)
45 to 55	6,275 (34%)	12,550 (34%)
Sex (male)	13,680 (74%)	27,360 (74%)
Income quintile		
Q5 (highest)	2,839 (15%)	5,678 (15%)
Q4	3,162 (17%)	6,324 (17%)
Q3	3,426 (19%)	6,852 (19%)
Q2	3,814 (21%)	7,628 (21%)
Q1 (lowest)	4,969 (27%)	9,938 (27%)
Unknown/suppressed	231 (1%)	462 (1%)
Home location		
Urban	15,532 (84%)	32,158 (87%)
Rural*	2,893 (15%)	4,462 (12%)
Missing	16 (<1%)	262 (1%)
Comorbidities [^]		
Alcoholism	3,109 (17%)	750 (2%)
Drug dependence/addiction	3,645 (20%)	1,164 (3%)
Psychoses	5,373 (29%)	979 (3%)
Depression	5,753 (31%)	1,788 (5%)
Anxiety disorder	12,807 (69%)	10,690 (29%)
Personality disorder	2,391 (13%)	469 (1%)
Sleep disorders	2,844 (15%)	2,536 (7%)
Malignancy	1,024 (6%)	1,331 (4%)
Asthma	2,291 (12%)	3,247 (9%)
Rhinitis	1,956 (11%)	4,204 (11%)
Health services use in the preceding year		
6 or more clinic visits	11,946 (65%)	12,365 (34%)
1 or more emergency room visits	4,053 (22%)	3,173 (9%)
1 or more inpatient admissions	1,379 (8%)	511 (1%)
OHIP eligible for entire 5-year look-back	17701 (96%)	34447 (93%)

OHIP: Ontario Health Insurance Plan

* Rural includes unknown/suppressed home location

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2 ^Comorbidities defined by truncated ICD-9 codes: Alcoholism (303), drug dependence/addiction
3 (304), psychoses (291, 292, 295, 296, 298, 299), depression (311), anxiety disorder (300),
4 personality disorder (301), sleep and other disorders (307), malignancy (140-165, 170-175, 179-
5 208), asthma (493), rhinitis (477).
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Table 2. Description of the most recent physician visit among patients who died from suicide.

	Persistent atopic dermatitis present (n = 174 patients)	Persistent atopic dermatitis absent (n =18,267 patients)
Physician specialty of most recent visit		
Family practice	121 (48%)	13,320 (55%)
Dermatology	9 (4%)	125 (1%)
Psychiatry	31 (12%)	3,101 (13%)
Pediatrics	π	102 (0%)
Other	91 (36%)	7,516 (31%)
Diagnosis associated with most recent visit		
Atopic dermatitis	16 (6%)	129 (1%)
Mental disorders*	72 (28%)	7,754 (32%)
Other medical diagnosis [^]	166 (65%)	16,281 (67%)
Total number of billing claims [#]	254	24,164

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

π Denotes a cell size below 6

* 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.

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

	Persistent atopic dermatitis present (n = 174 patients)	Persistent atopic dermatitis absent (n =18,267 patients)
Time from last psychiatrist visit		
≤1 month	40 (23%)	3,371 (19%)
>1 month or no visit	134 (77%)	14,896 (82%)
Time from last dermatologist visit		
≤1 month	8 (5%)	98 (<1%)
>1 month or no visit	166 (95%)	18,169 (>99%)
Time from last visit for atopic dermatitis		
≤1 month	14 (8%)	83 (<1%)
>1 month or no visit	160 (92%)	18,184 (>99%)
Season		
Spring	45 (26%)	4,756 (26%)
Summer	50 (29%)	4,812 (26%)
Autumn	36 (21%)	4,515 (25%)
Winter	43 (25%)	4,184 (23%)
Day		
Weekday	125 (72%)	13,242 (73%)
Weekend	49 (28%)	5,025 (28%)
Mechanism of death		
Asphyxiation	40 (23%)	6,460 (35%)
Jumping	24 (14%)	1,439 (8%)
Poisoning	68 (39%)	5,715 (31%)
Violent	31 (18%)	3,144 (17%)
Miscellaneous*	11 (6%)	1,504 (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

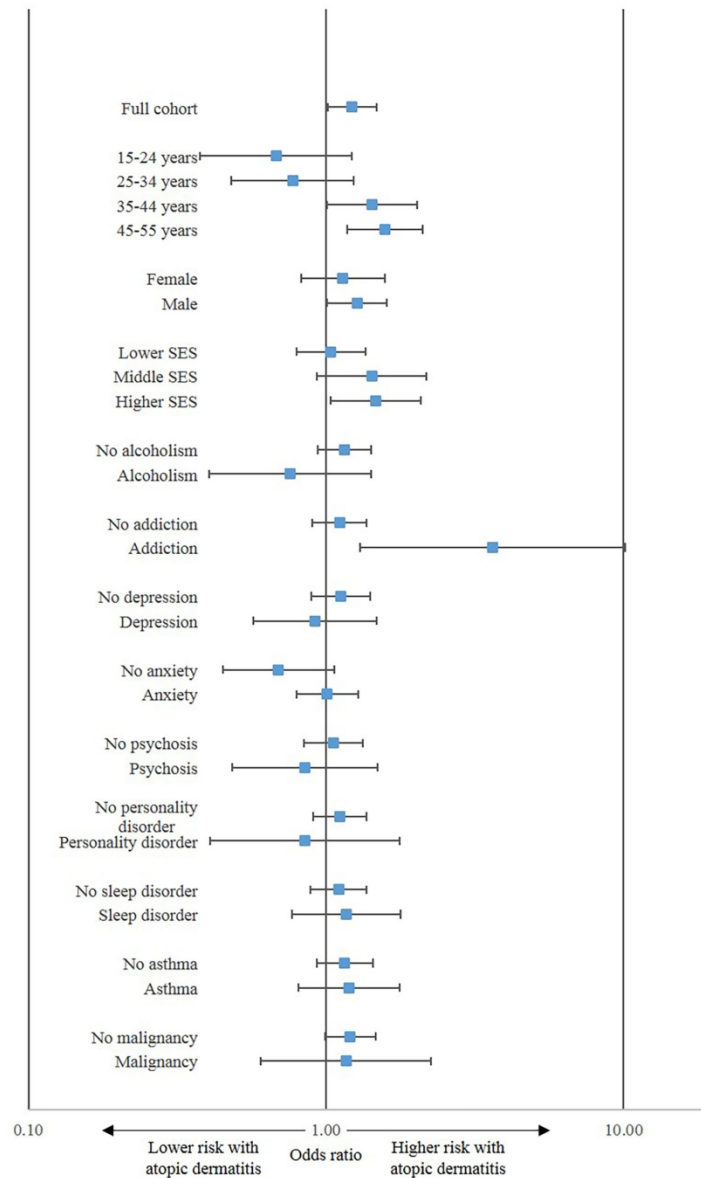


Figure 1. Relative risk of suicide associated with persistent atopic dermatitis

Forest plot showing relative increase in risk of suicide among patients with persistent atopic dermatitis compared to patients without persistent atopic dermatitis. The x-axis shows odds ratio 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% confidence intervals. Main findings are an increase in risk associated with atopic dermatitis with accentuation of risk among older men, those with mid-to-high socioeconomic status and a history of addiction.

140x220mm (300 x 300 DPI)

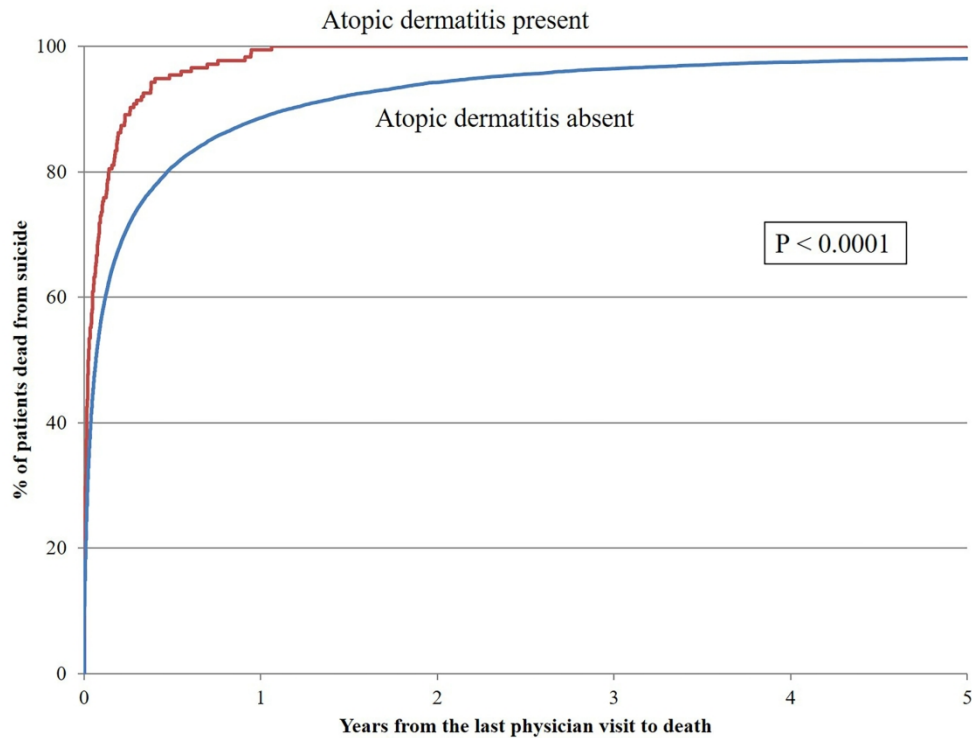


Figure 2. Time from the most recent physician visit to suicide among suicide cases

Kaplan-Meier curve showing the time between the last physician visit and subsequent death from suicide (n=18,441). 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 percent of patients dead from suicide. The red line represent patients with persistent atopic dermatitis. The blue line represents patients without persistent atopic dermatitis. Statistical significance was based on the log-rank test. Main findings show that patients with persistent atopic dermatitis were more likely to see a physician in close proximity to their death.

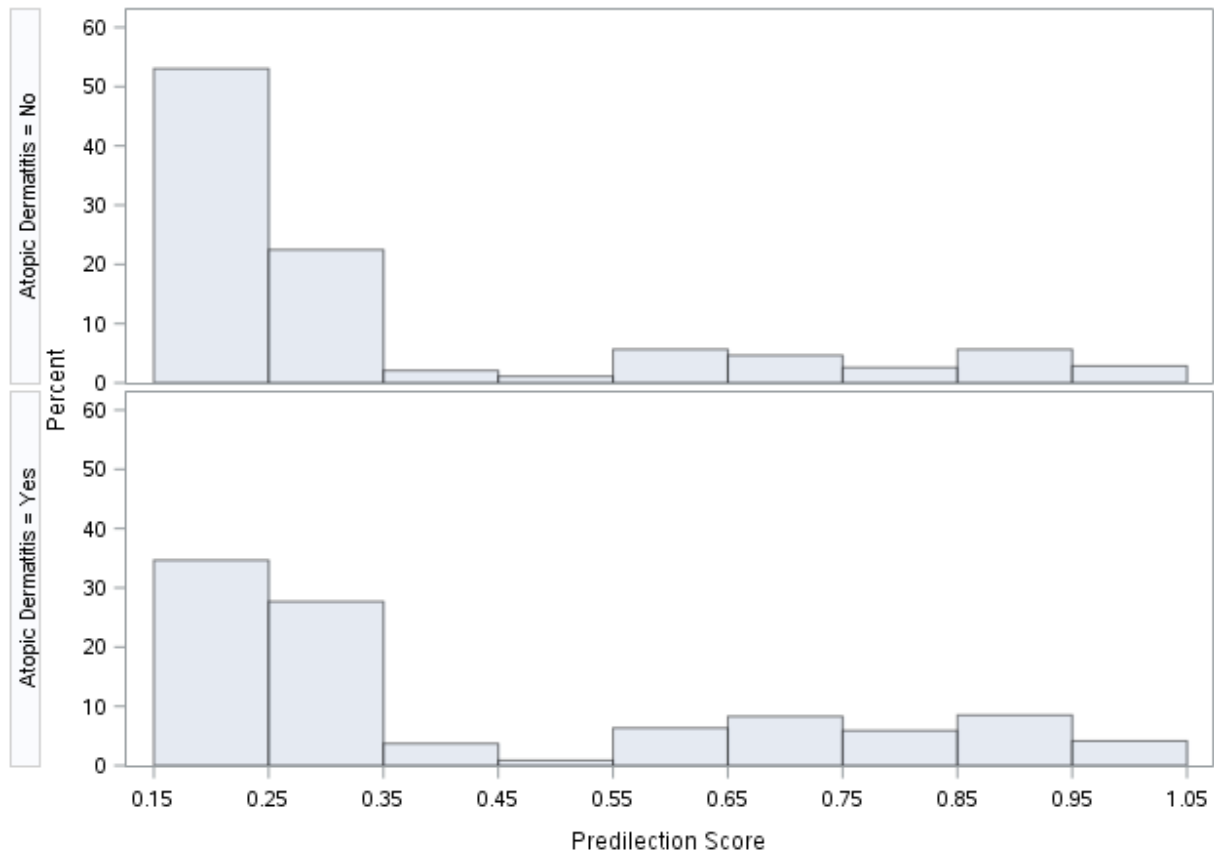
240x182mm (300 x 300 DPI)

Supplementary Table 1. Prevalence of asthma and rhinitis according to history of atopic dermatitis.

Atopic comorbidity	Persistent atopic dermatitis present (n = 459 patients)	Persistent atopic dermatitis absent (n = 54,864 patients)
Asthma	103 (22%)	5,435 (10%)
Rhinitis	132 (29%)	6,028 (11%)

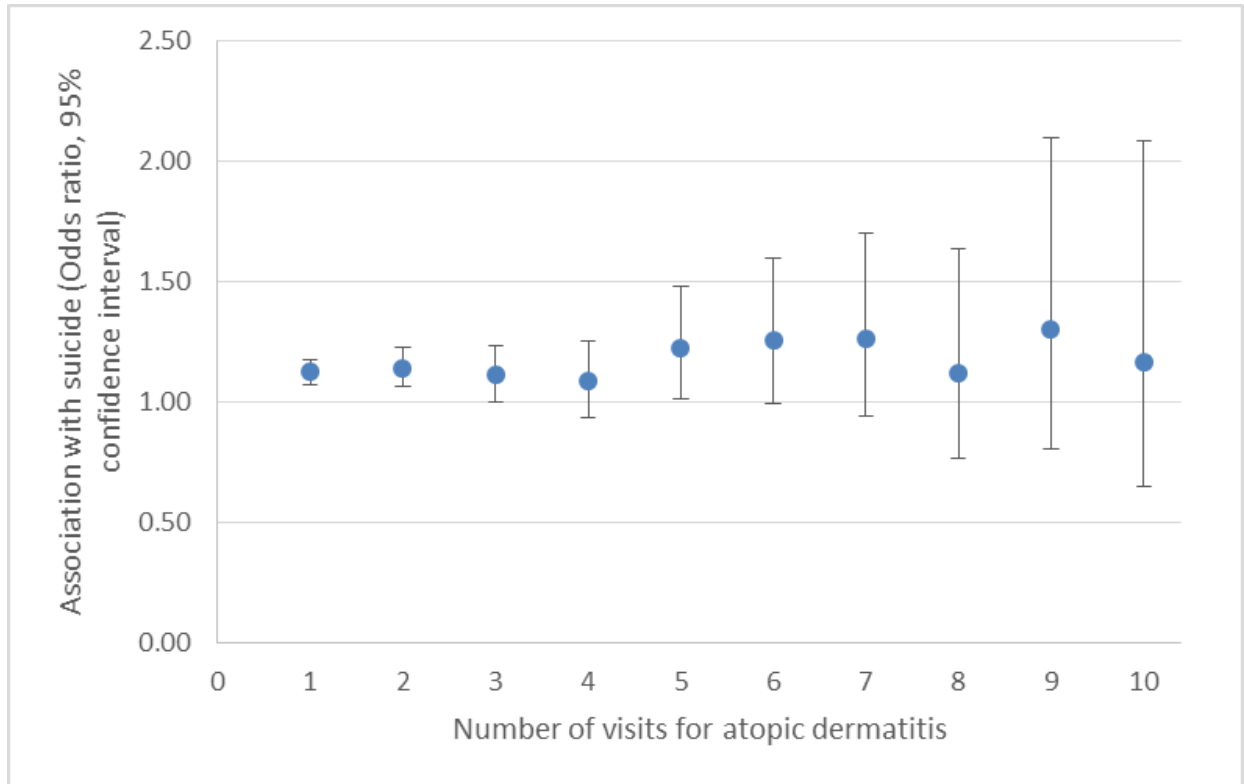
Comorbidities defined by truncated ICD-9 codes: asthma (493), rhinitis (477)

Supplementary figure 1. Distribution of the derived suicide predilection score according to history of atopic dermatitis.



Low scores represent a lower risk for suicide based on the patient’s history of mental health, sleep and substance disorders and high scores represent a higher risk. Main findings are that patients with persistent atopic dermatitis have generally higher suicide predilection scores than patients without persistent atopic dermatitis.

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2 **Supplementary figure 2. Association of atopic dermatitis with suicide when different**
3 **definitions of atopic dermatitis are applied.**
4



31 Atopic dermatitis cases are defined by the presence of number of physician visits for diagnostic
32 code 691, including patients with the given number of visits or more. The primary predictor is 5
33 or more visits for atopic dermatitis. Results are presented as odds ratios (dots) and 95%
34 confidence intervals (lines and bars).
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STROBE Statement—Checklist of items that should be included in reports of *case-control studies*

	Item No	Recommendation	
Title and abstract	1	✓ (a) Indicate the study's design with a commonly used term in the title or the abstract	p 1
		✓ (b) Provide in the abstract an informative and balanced summary of what was done and what was found	p 3-4
Introduction			
Background/rationale	2	✓ Explain the scientific background and rationale for the investigation being reported	p6-7
Objectives	3	✓ State specific objectives, including any prespecified hypotheses	p6-7
Methods			
Study design	4	✓ Present key elements of study design early in the paper	p7-10
Setting	5	✓ Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	p7
Participants	6	✓ (a) Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls	p7
		✓ (b) For matched studies, give matching criteria and the number of controls per case	p7-8
Variables	7	✓ Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	p7-9
Data sources/ measurement	8*	✓ For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	p7-9
Bias	9	✓ Describe any efforts to address potential sources of bias	p9-10
Study size	10	✓ Explain how the study size was arrived at	p7
Quantitative variables	11	✓ Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	p9
Statistical methods	12	✓ (a) Describe all statistical methods, including those used to control for confounding	p9-10
		✓ (b) Describe any methods used to examine subgroups and interactions	p9-10
		✓ (c) Explain how missing data were addressed	p7-8
		✓ (d) If applicable, explain how matching of cases and controls was addressed	p7-8
		✓ (e) Describe any sensitivity analyses	p10
Results			
Participants	13*	✓ (a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	p11
		N/A (b) Give reasons for non-participation at each stage	
		N/A (c) Consider use of a flow diagram	
Descriptive data	14*	✓ (a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	p22
		✓ (b) Indicate number of participants with missing data for each variable of interest	p22
Outcome data	15*	✓ Report numbers in each exposure category, or summary measures of exposure	p11
Main results	16	✓ (a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	p11
		N/A (b) Report category boundaries when continuous variables were categorized	
		✓ (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	p11

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Other analyses	17 ✓	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	p13
Discussion			
Key results	18 ✓	Summarise key results with reference to study objectives	p14-16
Limitations	19 ✓	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	p15-16
Interpretation	20 ✓	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	p16
Generalisability	21 ✓	Discuss the generalisability (external validity) of the study results	p15
Other information			
Funding	22 ✓	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	p2

*Give information separately for cases and controls.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at <http://www.strobe-statement.org>.

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Eczema and subsequent suicide: a matched case-control study

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Manuscripts

Eczema and subsequent suicide: a matched case-control study

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Contributions

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

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The manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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Disclosures

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Associations with commercial entities that could be viewed as having an interest in the general area of the submitted manuscript: Dr. Drucker 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 Inc, Spire Learning, CME Outfitters and Eczema Society of Canada.

Abstract

Objective: To assess the association of eczema with a patient's subsequent risk of death from suicide. We hypothesized 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 to 55 years old. We identified cases of suicide from coroners' reports between January 1, 1994 and December 31, 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 five 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 twenty-one-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 (odds ratio = 1.22, 95% confidence interval: 1.01 to 1.48, $p = 0.037$). In mediation analyses, this association was largely explained through major suicide risk factors. Two-thirds of eczema patients 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 eczema patients.

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

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

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 one-in-nine children and one-in-fourteen 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 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 seven-fold increased risk of a major depressive disorder and four-fold increased risk of an anxiety disorder.⁸ In two American cross-sectional studies, eczema was associated with twice the risk of depression compared to the general population.⁹ One study from Denmark found no significant association between eczema and subsequent suicide.¹⁰ Whereas a prior study on psoriasis 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 eczema patients. A randomized controlled trial was deemed

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3 impossible because patients cannot be assigned a diagnosis of eczema; therefore, we conducted a
4
5 large-scale multi-year observational analysis of longitudinal individual patient data. We
6
7 hypothesized that persistent eczema would increase a patient's risk of death from suicide and that
8
9 many deaths would be preceded by a recent physician visit. If true, this would suggest that
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11 preventive efforts targeting vulnerable patients might save lives.
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15 16 **Methods**

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18 The study was approved by the Institute for Clinical Evaluative Sciences (ICES) and the
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20 Women's College Hospital Research Ethics Board deemed the work exempt from supplementary
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22 ethics review.
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25 26 27 *Patient and public involvement*

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29 There was no patient or public involvement in this study.
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32 33 34 *Data sharing*

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36 There is no plan to share raw data from this study.
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39 40 41 *Selection of patients*

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43 We conducted a double matched case-control study of patients between the age of 15 and 55
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45 years in Ontario. We included individuals 15 and older as eczema is a common diagnosis and
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47 suicide is a common cause of death in youth.^{2 4 12} We excluded adults older than 55 to avoid
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49 misclassification of age-associated xerosis with itch as eczema. Cases of suicide were identified
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51 from the Ontario Vital Statistics Database from January 1, 1994 to December 31, 2014,
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53 representing all available data. We defined suicide using International Classification of Disease
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3 (ICD) codes (ICD-9 E950–E959, E980–E987; ICD-10 X60–X84, Y10–Y32, Y34).¹³⁻¹⁵ Interrater
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5 agreement from coroners on suicide diagnosis was high and showed 97% concordance with the
6
7 vital statistics database.^{16 17} We also extracted data on the mechanism of suicide in five
8
9 categories as asphyxiation, jumping, poisoning, violence and miscellaneous.
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14 Controls were selected from the general population in Ontario using the Registered Persons
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16 Database that identified all patients insured under the Ontario Health Insurance Plan (OHIP).¹⁸
17
18 For each case of suicide, we selected two control patients from the general population matched
19
20 on age (within 2 days), socioeconomic status (SES) quintile and sex using simple random
21
22 selection when excess matches were available. All cases and controls were alive and eligible for
23
24 OHIP coverage on the index date and one year prior. SES at the index date was estimated from
25
26 the Statistics Canada algorithm based on neighborhood income^{19 20} and patients with missing
27
28 SES were matched to controls who were also missing SES. As a result, we obtained exact triplets
29
30 of one case matched to two controls with no missing matches. These datasets were linked using
31
32 unique encoded identifiers and analyzed at ICES.
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40 *Primary predictor*

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42 We used a five-year look-back interval to assess each patient through a consistent ascertainment
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44 interval for cases and controls. The matching date in each triplet of patients was defined as the
45
46 date of suicide death of the case. Prior medical care for each patient was evaluated based on
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48 physician diagnoses documented as ICD-9 diagnostic codes.¹³ In Ontario, physicians document
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50 each encounter with a single ICD-9 code. Eczema was defined using diagnosis code 691.¹³ In
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52 another population, ICD-9 codes for atopic dermatitis, a specific subtype of eczema, had a
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3 positive predictive value of 50% based on a requirement for two or more ICD-9 codes to identify
4 cases of probable atopic dermatitis.²¹ To increase the specificity and to define persistent eczema,
5 we required five or more physician visits for the diagnosis, each separated by at least one week
6 over the five-year look-back interval. Given the uncertain validity of that definition, we refer to
7 our predictor as “eczema” rather than the more specific “atopic dermatitis” throughout the
8 manuscript.
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16 17 18 19 *Additional patient characteristics*

20 Specific additional medical diagnoses (asthma, hayfever or rhinitis, alcoholism, drug
21 dependence, tobacco abuse, sleep and other disorders, depression, anxiety disorders, psychoses,
22 personality disorders, malignancy, benign skin tumors, psoriasis) were identified during the five-
23 year look-back interval using ICD-9 codes in the OHIP database. Measures of overall healthcare
24 resource utilization were obtained from the OHIP database, the National Ambulatory Care
25 Reporting System and the Discharge Abstract Database (counts of clinic visits, emergency room
26 visits, hospitalizations in the prior year). We collected data on patients’ most recent healthcare
27 visit, the specialty of the physician and the associated diagnosis. We also collected data on the
28 timing of suicide (proximity to the most recent visit with a dermatologist or psychiatrist and
29 recency of a visit for eczema).
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47 *Statistical analysis*

48 We used logistic regression to calculate odds ratios with 95% confidence intervals for the
49 association of persistent eczema with the risk of subsequent death from suicide. We examined
50 the robustness of findings by additionally calculating associations using conditional logistic
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3 regression to fully account for matching. To assess for potential mediation, we conducted
4 stratified analyses by major suicide risk factors (depression, psychoses, personality disorders,
5 sleep and other disorders, drug dependence and alcoholism) within triads of cases and controls.
6
7 Further, we used logistic regression with suicide as the outcome and major suicide risk factors as
8 covariates to derive an overall suicide predilection score. We then conducted logistic regression
9 stratified by low (at or below the median) or high (above the median) overall suicide predilection
10 score. To assess for potential mediation or confounding by a major atopic comorbidity, we
11 conducted analyses further stratified by history of asthma.
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24 We plotted Kaplan- Meier curves for patients who died from suicide with and without persistent
25 eczema to assess the time interval between the most recent physician visit and ultimate suicide.
26 We compared the two curves using the Log-Rank test. To assess potential differences in the
27 mechanism of suicide between patients with and without persistent eczema, we calculated
28 descriptive odds ratios with 95% confidence intervals for the different categories of suicide with
29 no prespecified hypotheses.
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40 We conducted several sensitivity analyses as tests of robustness. We replicated separate analyses
41 to check results using three alternative definitions of eczema: (1) spanning between one and ten
42 claims associated with the diagnosis; (2) requiring a comorbid atopic condition (asthma or
43 rhinitis); and (3) excluding patients who had a history of stasis ulcers, varicose veins,
44 lymphedema, contact dermatitis, seborrheic dermatitis or psoriasis. These latter two analyses
45 were based on the rationale that comorbid asthma and rhinitis can improve the positive predictive
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3 value of ICD codes for *atopic* dermatitis²¹ and because excluding commonly confused conditions
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5 can also decrease false positive cases.
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10 As a test for residual confounding, we conducted tracer analyses with two additional control
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12 predictors: benign skin tumors and psoriasis (another chronic skin disease with effective
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14 treatment options). We anticipated benign skin tumors and psoriasis might not be associated with
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16 an increased risk for suicide and thereby validate the distinctive association with eczema.
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23 **Results**

24
25 We identified 18,441 cases of suicide matched to 36,882 alive controls over the twenty-one-year
26
27 accrual period. The median patient age was 38 years, 74% were male and the average SES was
28
29 below the population median. Mental health disorders were more common among patients who
30
31 had died from suicide than among controls, as were malignant neoplasms and asthma (Table 1).
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33 Patients who died from suicide had more clinic visits, emergency department visits and inpatient
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35 admissions in the year prior to the index date than controls.
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42 A history of persistent eczema occurred in 174 (0.94%) suicide cases and 285 (0.77%) controls.
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44 In univariate analysis, persistent eczema was associated with a 22% increased risk of suicide.
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46 Results were identical for ordinary and conditional logistic regression (odds ratio = 1.22, 95%
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48 confidence interval: 1.01 to 1.48, p=0.037). The net increase was equal to 31 excess cases of
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50 suicide associated with eczema (more than one patient per year).
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3 Stratified analyses showed the association of eczema with suicide was accentuated among older
4 men with a history of addiction (Figure 1). There was no significant differential association of
5 eczema with suicide between strata of patients with and without asthma, malignancy or other
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7 individual suicide risk factors such as depression.
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14 Patients with eczema had significantly higher suicide predilection scores compared with patients
15 without eczema (median 0.32 vs. 0.15, $p<0.0001$); Supplementary Figure 1). Comparisons based
16 on mean scores showed similar imbalance (0.42 vs. 0.33, $p<0.0001$). The highest decile of
17 suicide predilection score was nearly twice as common among eczema patients as controls (17%
18 vs. 10%, $p<0.0001$). Stratified analysis by high or low predilection scores showed no significant
19 further association of eczema with suicide between patients with high predilection scores (odds
20 ratio = 0.97, 95% confidence interval: 0.78 to 1.22, $p=0.81$) and low predilection scores (odds
21 ratio = 0.59, 95% confidence interval: 0.34 to 1.03, $p=0.06$), suggesting that eczema was not an
22 independent contributor to suicide risk beyond its influence on mental health risk overall.
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38 Nearly all patients with persistent eczema who died from suicide had visited a physician in the
39 year prior to their death, 67% within a month and 37% within a week. Among patients who died
40 from suicide, those diagnosed with persistent eczema visited a physician more recently than
41 patients without persistent eczema ($P<0.0001$, Figure 2). For both patients with and without
42 persistent eczema who died from suicide, the most recent physician visit was most frequently
43 with a family physician (Table 2). Among persistent eczema patients, one-in-twenty-five had
44 visited a dermatologist last. For one-in-sixteen persistent eczema patients who died from suicide,
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3 their last visit was for eczema. We found no meaningful differences in season or in day of the
4 week of death distinguishing patients who did and did not have persistent eczema (Table 3).
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10 Analyses of suicide cases showed diverse mechanisms, of which about 8% were unclassified due
11 to uncertain, multifactorial or missing details. Asphyxiation was the most common single cause
12 of suicide and was less frequent among individuals who had persistent eczema than controls
13 (odds ratio = 0.55, 95% confidence interval: 0.38 to 0.78, $p=0.0008$). In contrast, jumping from a
14 vertical height had the largest relative increased risk among patients who had persistent eczema
15 (odds ratio = 1.87, 95% confidence interval: 1.21 to 2.89, $p=0.0047$). Poisoning was the second
16 largest relative increased risk among patients who had persistent eczema (odds ratio = 1.41, 95%
17 confidence interval: 1.04 to 1.91, $p=0.03$). Violent forms of suicide were infrequent and
18 generally balanced between the two groups (odds ratio = 1.04, 95% confidence interval: 0.71 to
19 1.54, $p=0.83$).
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35 In sensitivity analyses requiring fewer than five visits for eczema to define the predictor, the
36 association with suicide was somewhat attenuated (Supplementary figure 2). When ten or more
37 visits for eczema were required, the confidence intervals widened substantially and the
38 association was ambiguous. When a diagnosis of asthma or rhinitis was required to identify cases
39 of eczema, the estimated association for the risk of suicide was similar to the primary analysis
40 but not statistically significant (odds ratio = 1.26, 95% confidence interval: 0.94 to 1.69, $p=0.12$).
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49 When patients who had a diagnosis of stasis ulcers, varicose veins, lymphedema, contact
50 dermatitis, seborrheic dermatitis and psoriasis were excluded, the results were similar to the
51 primary analysis (odds ratio = 1.26, 95% confidence interval: 0.99 to 1.61, $p=0.06$), although not
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3 statistically significant. Benign skin tumors were associated with no increase in suicide risk
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5 (odds ratio = 0.90, 95% confidence interval: 0.84 to 0.97, p=0.008). Psoriasis was associated
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7 with an equivocal increase in suicide risk (odds ratio = 1.14, 95% confidence interval: 0.99 to
8
9 1.31, p=0.06).

14 Discussion

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17 In this large longitudinal case-control study, persistent eczema was associated with a modestly
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19 increased risk of subsequent death from suicide. The absolute risk was low. The association was
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21 fully explained by mental health disorders including depression, anxiety, sleep disorders and
22
23 substance misuse, suggesting that eczema was not an independent contributor to suicide risk
24
25 beyond its influence on mental health risk overall. . The patient group at highest risk was older
26
27 men with a history of addiction. . Asphyxiation was the most common mechanism of suicide
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29 death overall, but poisoning and jumping were differentially increased for patients with
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31 persistent eczema. Eczema patients who died from suicide usually had visited a physician in the
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33 month before death.

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40 Our study is in agreement with other literature on the association of eczema with adverse mental
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42 health. A Norwegian study found that young adults with eczema and itchy skin had a 24%
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44 prevalence of suicidal ideation in the preceding week.⁷ Only two studies have examined the risk
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46 of death from suicide associated with eczema, with mixed results. One conducted using
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48 administrative data for adults in Denmark found that eczema patients had a 71% increased risk of
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50 suicide attempts and double the risk of death from suicide, (a more prominent association than in
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52 our study).¹¹ Similar to our findings, older adults with eczema had a further accentuated risk. It is
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3 unclear why the association might be increased in older populations and one possible explanation
4 could be the cumulative stress of living with a chronic condition for decades. The only other past
5 study, also from Denmark, found no statistically significant association between eczema and
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10 suicide.¹⁰
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15 Our study contains novel findings concerning physician visits by atopic dermatitis patients prior
16 to suicide. Nearly two in five patients with eczema who died from suicide contacted a physician
17 in the week before their death. The most recent physician visit was most commonly with a
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Our study contains novel findings concerning physician visits by atopic dermatitis patients 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 recent physician contact was for their eczema. While dermatologists tend to underrecognize depression and anxiety in their patients, all clinicians should recognize psychological distress.²² Patients with eczema who present with signs of significant mental health distress could be assessed for suicide risk. In particular, standardized 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, eczema patients 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 eczema patients 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 eczema patients who live in discomfort from their condition

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3 choose rapid or less painful means of dying. A greater understanding is needed for future
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5 research.
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10 The generalizability of our study is limited to a single large region in a high-income country with
11 universal healthcare access. Specifically, comprehensive medical care in our patients may have
12 substantially mitigated some of the suicide risk associated with eczema. In addition, we lacked
13 data on eczema severity, social isolation, other life stresses or risk factors for suicide completion
14 such as suicidal ideation.²⁵ We also lack data on treatments used for eczema, which can be used
15 to stratify eczema cases based on severity and which may be important given the psychiatric
16 effects of systemic corticosteroids.^{10 26} Our primary outcome examined an extreme indicator of
17 mental suffering and the overall observed effect size was more modest than previously reported
18 for other medical illnesses.²⁷ While only a small minority of eczema patients die by suicide,
19 many more suffer from non-lethal forms of depression and other mental disorders.^{8-10 28}
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35 The most important limitation of our study related to our definition of persistent eczema. A past
36 report suggested that two or more ICD-9 codes for atopic dermatitis have a 50% positive
37 predictive value for probable atopic dermatitis.²¹ The true positive predictive value may be
38 higher than reported in that study, as it used stringent clinical diagnostic criteria unsuitable in a
39 retrospective study. Nevertheless, misclassification of persistent eczema cases is a strong
40 possibility and may have impacted our results in a number of ways. Random misclassification
41 may cause underestimates of the magnitude of associations.²⁹ Misclassification of less severe
42 skin diseases such as contact dermatitis, could also bias our findings towards the null. However,
43 misclassification of more severe skin diseases such as an exfoliative dermatitis may bias our
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3 results towards an increased risk for suicide. It is unclear whether our requirement of five
4 occurrences of code 691 increases or decreases the accuracy of our case definition for identifying
5 cases of *atopic* dermatitis and exactly what impact this had on the results.
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12 To provide some additional nuances for our case definition, we calculated the prevalence of
13 asthma and rhinitis among patients in our study and found each of these atopic comorbidities was
14 more than twice as common among those with persistent eczema compared to those without
15 (Supplementary Table 1). It is possible that the associations observed between our primary
16 predictor and these well-known atopic comorbidities are partially confounded by differential
17 healthcare system access. However, the strong associations seen support the notion that our
18 predictor definition represents, to some extent, persistent *atopic* dermatitis. Our sensitivity
19 analyses requiring comorbid asthma or rhinitis to define eczema and excluding patients with
20 psoriasis and other skin diseases yielded decreased sample sizes and showed results that were no
21 longer significant. We are reassured that the estimates were largely unchanged and are cautious
22 not to over-interpret statistical significance in post-hoc secondary analyses. Nevertheless, due to
23 the uncertain validity of our primary predictor, we use the non-specific term “eczema”
24 throughout the manuscript.
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47 Strengths of our study include the large sample of suicide deaths, the known validity of suicide
48 outcomes and our double-matched case-control design. As Ontario has a universal health
49 insurance program, we were able to comprehensively identify all physician visits prior to death.
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54 Of course, patients who had persistent eczema but who did not engage with the healthcare
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3 system may have been missed. In summary, patients with persistent eczema have a modestly
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5 increased subsequent risk of death from suicide. Physicians may have opportunities to intervene
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7 for suicide prevention in this vulnerable patient population.
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Figure Legends

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 to patients without persistent eczema. The x-axis shows odds ratio 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% confidence intervals. Main findings are an increase in risk associated with eczema with accentuation of risk among older men, those with mid-to-high socioeconomic status and a history of addiction.

Figure 2. Time from the most recent physician visit to suicide among suicide cases

Kaplan-Meier curve showing the time between the last physician visit and subsequent death from suicide (n=18,441). 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 percent of patients dead from suicide. The red line represent patients with persistent eczema. The blue line represents patients without persistent eczema. Statistical significance was based on the log-rank test. Main findings show that patients with persistent eczema were more likely to see a physician in close proximity to their death.

Table 1. Patient characteristics

	Suicide cases (n = 18,441)	Matched controls (n = 36,882)
Age (years)		
15 to 24	2,825 (15%)	5,650 (15%)
25 to 34	3,746 (20%)	7,492 (20%)
35 to 44	5,595 (30%)	11,190 (30%)
45 to 55	6,275 (34%)	12,550 (34%)
Sex (male)	13,680 (74%)	27,360 (74%)
Income quintile		
Q5 (highest)	2,839 (15%)	5,678 (15%)
Q4	3,162 (17%)	6,324 (17%)
Q3	3,426 (19%)	6,852 (19%)
Q2	3,814 (21%)	7,628 (21%)
Q1 (lowest)	4,969 (27%)	9,938 (27%)
Unknown/suppressed	231 (1%)	462 (1%)
Home location		
Urban	15,532 (84%)	32,158 (87%)
Rural*	2,893 (15%)	4,462 (12%)
Missing	16 (<1%)	262 (1%)
Comorbidities [^]		
Alcoholism	3,109 (17%)	750 (2%)
Drug dependence/addiction	3,645 (20%)	1,164 (3%)
Psychoses	5,373 (29%)	979 (3%)
Depression	5,753 (31%)	1,788 (5%)
Anxiety disorder	12,807 (69%)	10,690 (29%)
Personality disorder	2,391 (13%)	469 (1%)
Sleep disorders	2,844 (15%)	2,536 (7%)
Malignancy	1,024 (6%)	1,331 (4%)
Asthma	2,291 (12%)	3,247 (9%)
Rhinitis	1,956 (11%)	4,204 (11%)
Health services use in the preceding year		
6 or more clinic visits	11,946 (65%)	12,365 (34%)
1 or more emergency room visits	4,053 (22%)	3,173 (9%)
1 or more inpatient admissions	1,379 (8%)	511 (1%)
OHIP eligible for entire 5-year look-back	17701 (96%)	34447 (93%)

OHIP: Ontario Health Insurance Plan

* Rural includes unknown/suppressed home location

1
2 ^Comorbidities defined by truncated ICD-9 codes: Alcoholism (303), drug dependence/addiction
3 (304), psychoses (291, 292, 295, 296, 298, 299), depression (311), anxiety disorder (300),
4 personality disorder (301), sleep and other disorders (307), malignancy (140-165, 170-175, 179-
5 208), asthma (493), rhinitis (477).
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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 =18,267 patients)
Physician specialty of most recent visit		
Family practice	121 (48%)	13,320 (55%)
Dermatology	9 (4%)	125 (1%)
Psychiatry	31 (12%)	3,101 (13%)
Other ^π	93 (37%)	7,618 (32%)
Diagnosis associated with most recent visit		
Eczema	16 (6%)	129 (1%)
Mental disorders*	72 (28%)	7,754 (32%)
Other medical diagnosis [^]	166 (65%)	16,281 (67%)
Total number of billing claims [#]	254	24,164

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

^π Includes pediatrician 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.

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 =18,267 patients)
Time from last psychiatrist visit		
≤1 month	40 (23%)	3,371 (19%)
>1 month or no visit	134 (77%)	14,896 (82%)
Time from last dermatologist visit		
≤1 month	8 (5%)	98 (<1%)
>1 month or no visit	166 (95%)	18,169 (>99%)
Time from last visit for eczema		
≤1 month	14 (8%)	83 (<1%)
>1 month or no visit	160 (92%)	18,184 (>99%)
Season		
Spring	45 (26%)	4,756 (26%)
Summer	50 (29%)	4,812 (26%)
Autumn	36 (21%)	4,515 (25%)
Winter	43 (25%)	4,184 (23%)
Day		
Weekday	125 (72%)	13,242 (73%)
Weekend	49 (28%)	5,025 (28%)
Mechanism of death		
Asphyxiation	40 (23%)	6,460 (35%)
Jumping	24 (14%)	1,439 (8%)
Poisoning	68 (39%)	5,715 (31%)
Violent	31 (18%)	3,144 (17%)
Miscellaneous*	11 (6%)	1,504 (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

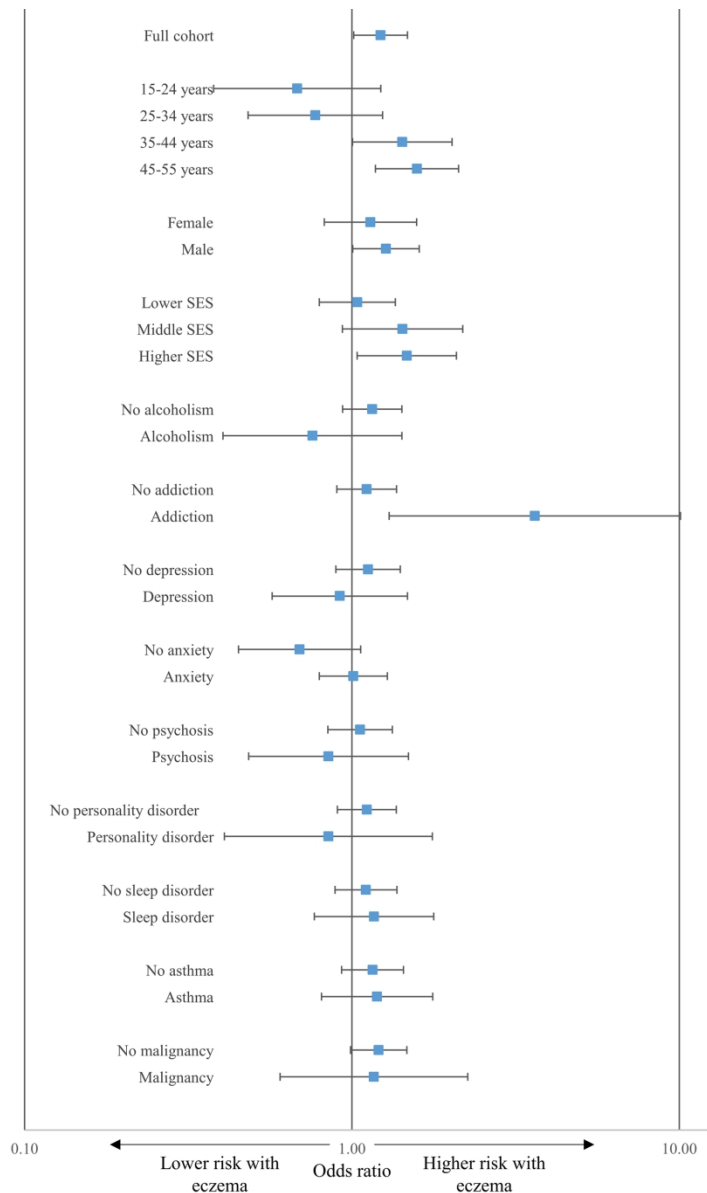


Figure 1. Relative risk of suicide associated with persistent eczema

Forest plot showing relative increase in risk of suicide among patients with persistent eczema compared to patients without persistent eczema. The x-axis shows odds ratio 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% confidence intervals. Main findings are an increase in risk associated with eczema with accentuation of risk among older men, those with mid-to-high socioeconomic status and a history of addiction.

143x240mm (300 x 300 DPI)

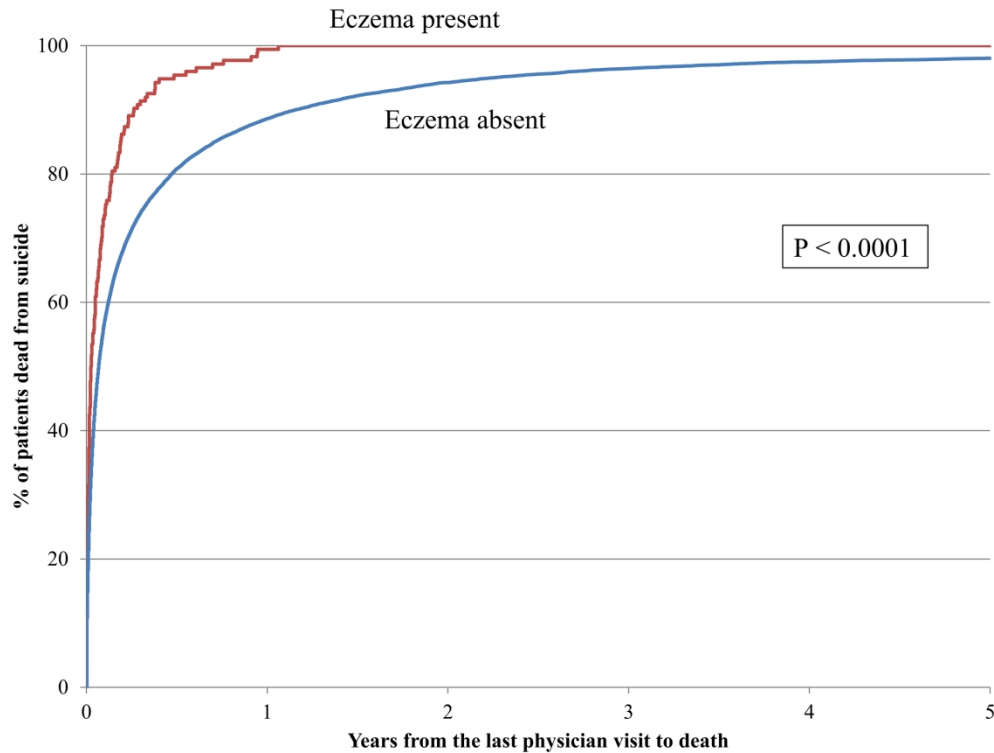


Figure 2. Time from the most recent physician visit to suicide among suicide cases

Kaplan-Meier curve showing the time between the last physician visit and subsequent death from suicide (n=18,441). 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 percent of patients dead from suicide. The red line represent patients with persistent eczema. The blue line represents patients without persistent eczema. Statistical significance was based on the log-rank test. Main findings show that patients with persistent eczema were more likely to see a physician in close proximity to their death.

234x176mm (300 x 300 DPI)

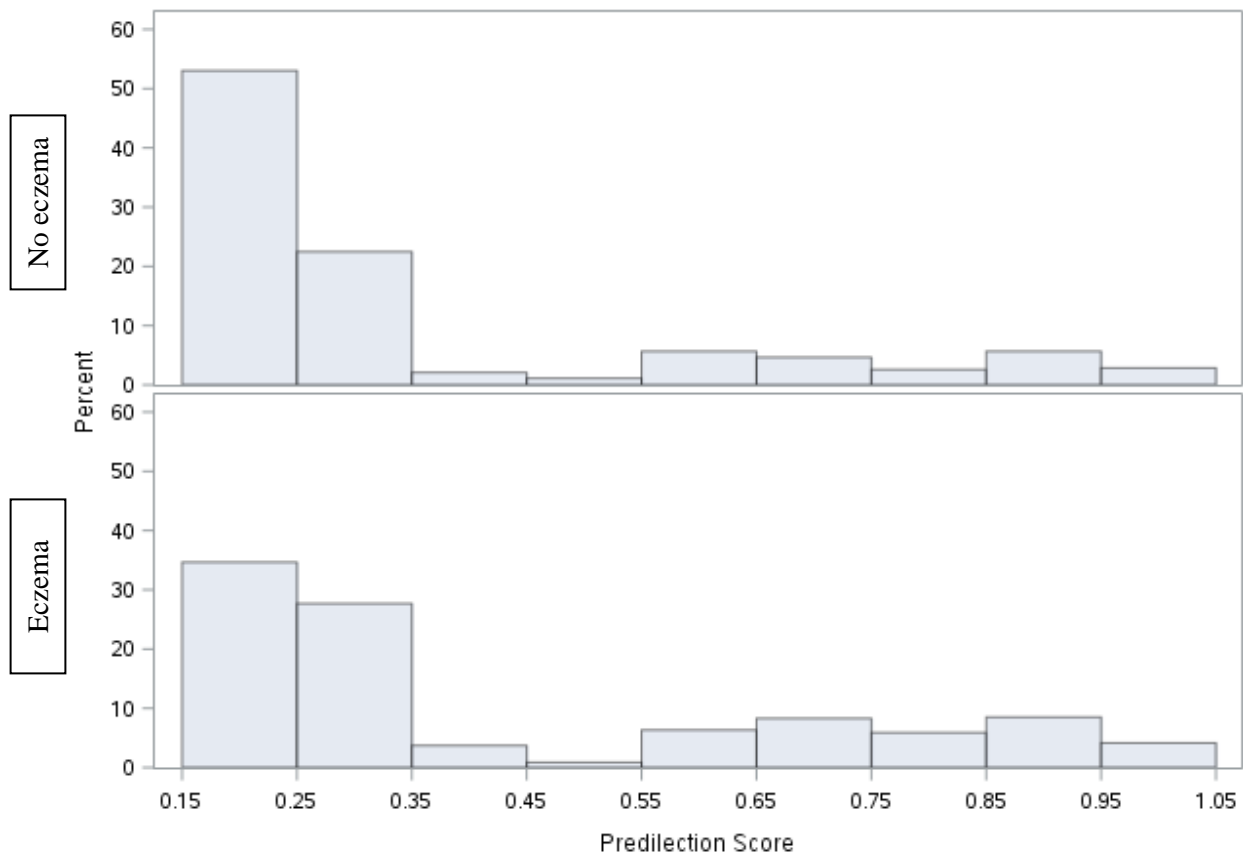
Supplementary Table 1. Prevalence of asthma and rhinitis according to history of eczema.

Atopic comorbidity	Persistent eczema present (n = 459 patients)	Persistent eczema absent (n = 54,864 patients)
Asthma	103 (22%)	5,435 (10%)
Rhinitis	132 (29%)	6,028 (11%)

Comorbidities defined by truncated ICD-9 codes: asthma (493), rhinitis (477)

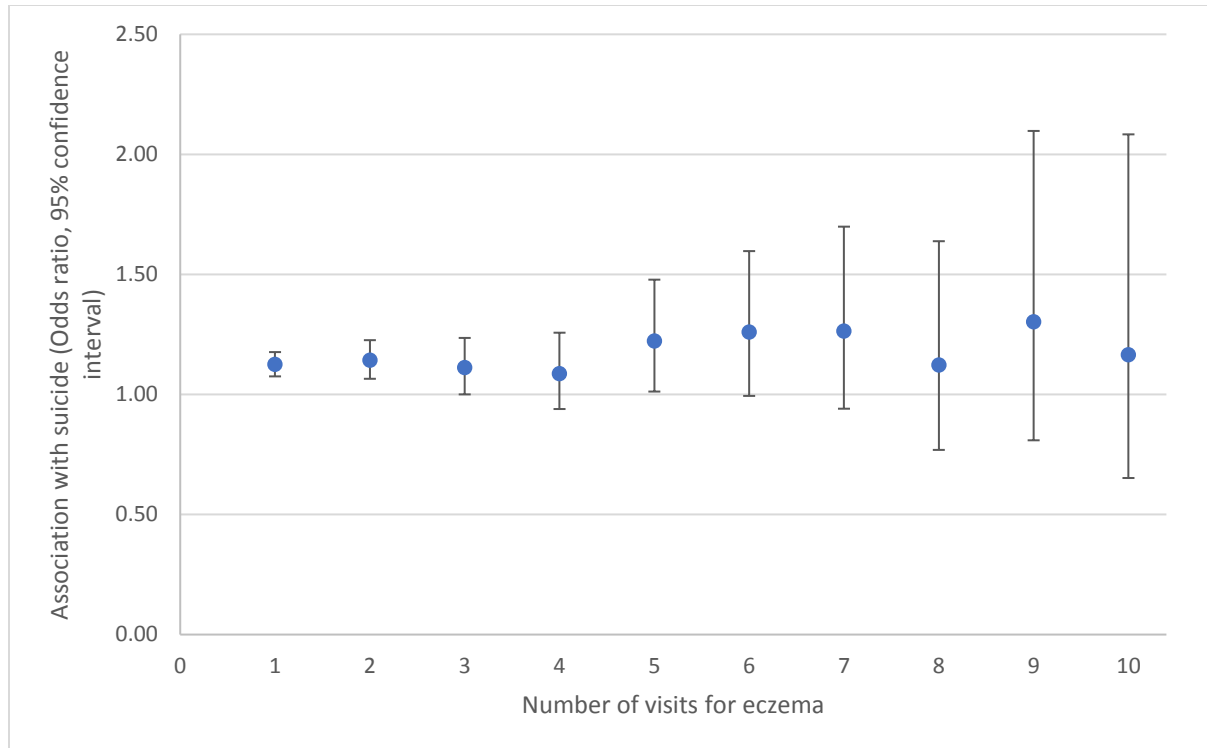
For peer review only

1
2 **Supplementary figure 1. Distribution of the derived suicide predilection score according to**
3 **history of eczema.**
4



33
34 Low scores represent a lower risk for suicide based on the patient's history of mental health,
35 sleep and substance disorders and high scores represent a higher risk. Main findings are that
36 patients with persistent eczema have generally higher suicide predilection scores than patients
37 without persistent eczema.
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2 **Supplementary figure 2. Association of eczema with suicide when different definitions of**
3 **eczema are applied.**
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29
30 Eczema cases are defined by the presence of number of physician visits for diagnostic code 691,
31 including patients with the given number of visits or more. The primary predictor is 5 or more
32 visits for eczema. Results are presented as odds ratios (dots) and 95% confidence intervals (lines
33 and bars).
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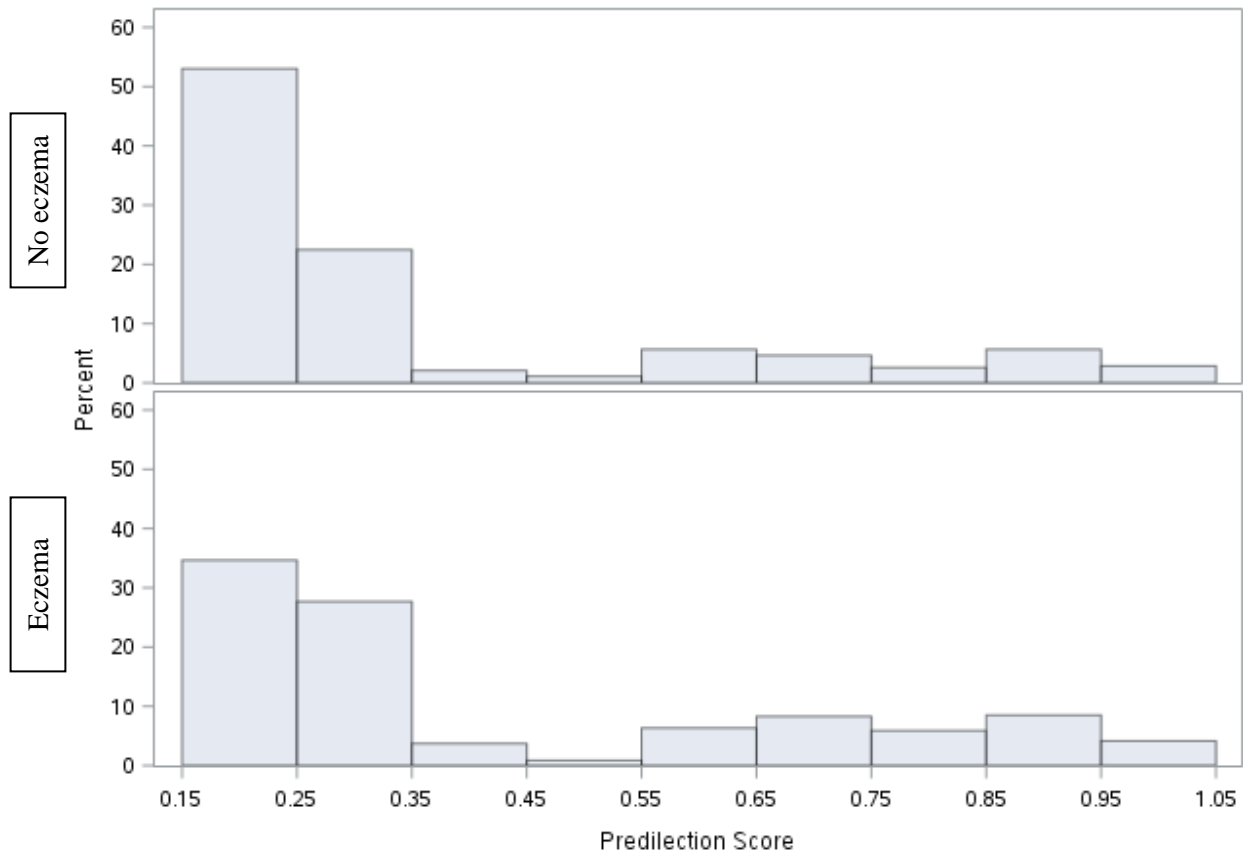
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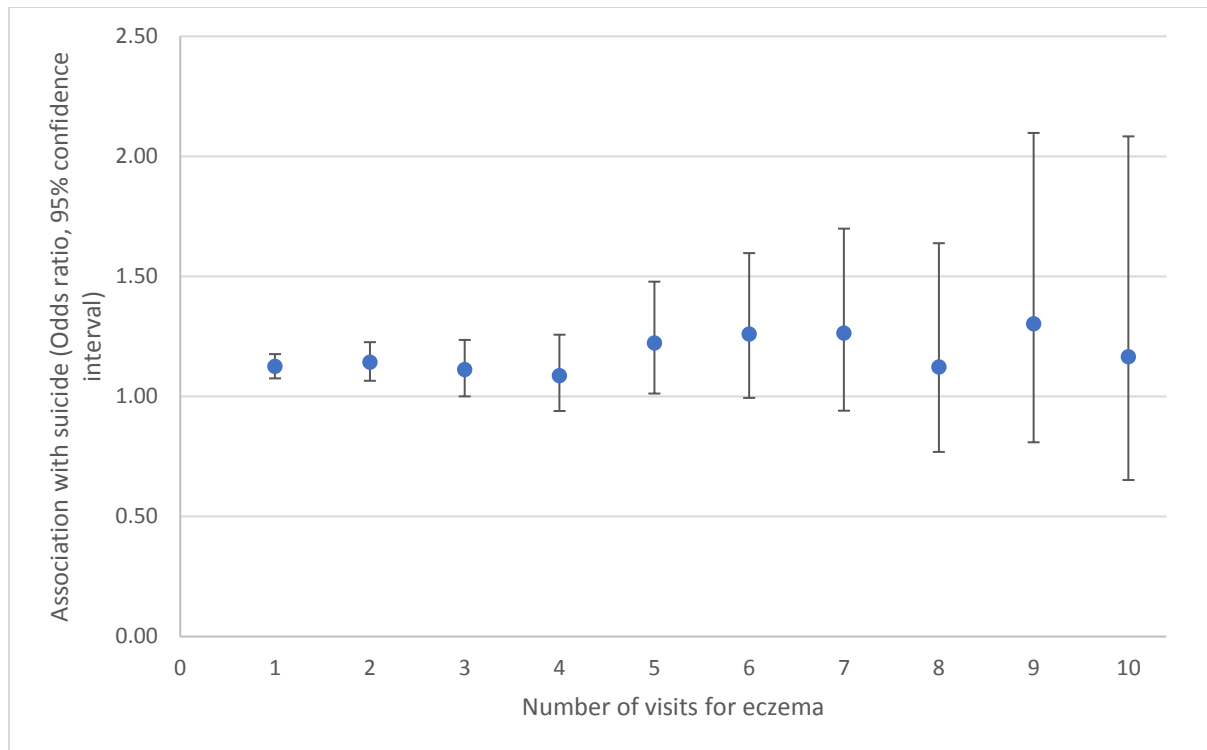
10 Comorbidities defined by truncated ICD-9 codes: asthma (493), rhinitis (477)
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Supplementary figure 1. Distribution of the derived suicide predilection score according to history of eczema.



Low scores represent a lower risk for suicide based on the patient's history of mental health, sleep and substance disorders and high scores represent a higher risk. Main findings are that patients with persistent eczema have generally higher suicide predilection scores than patients without persistent eczema.

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60STROBE Statement—Checklist of items that should be included in reports of *case-control studies*

	Item No	Recommendation	
Title and abstract	1	✓ (a) Indicate the study's design with a commonly used term in the title or the abstract	p 1
		✓ (b) Provide in the abstract an informative and balanced summary of what was done and what was found	p 3-4
Introduction			
Background/rationale	2	✓ Explain the scientific background and rationale for the investigation being reported	p6-7
Objectives	3	✓ State specific objectives, including any prespecified hypotheses	p6-7
Methods			
Study design	4	✓ Present key elements of study design early in the paper	p7-10
Setting	5	✓ Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	p7
Participants	6	✓ (a) Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls	p7
		✓ (b) For matched studies, give matching criteria and the number of controls per case	p7-8
Variables	7	✓ Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	p7-9
Data sources/ measurement	8*	✓ For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	p7-9
Bias	9	✓ Describe any efforts to address potential sources of bias	p9-10
Study size	10	✓ Explain how the study size was arrived at	p7
Quantitative variables	11	✓ Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	p9
Statistical methods	12	✓ (a) Describe all statistical methods, including those used to control for confounding	p9-10
		✓ (b) Describe any methods used to examine subgroups and interactions	p9-10
		✓ (c) Explain how missing data were addressed	p7-8
		✓ (d) If applicable, explain how matching of cases and controls was addressed	p7-8
		✓ (e) Describe any sensitivity analyses	p10
Results			
Participants	13*	✓ (a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	p11
		N/A (b) Give reasons for non-participation at each stage	
		N/A (c) Consider use of a flow diagram	
Descriptive data	14*	✓ (a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	p22
		✓ (b) Indicate number of participants with missing data for each variable of interest	p22
Outcome data	15*	✓ Report numbers in each exposure category, or summary measures of exposure	p11
Main results	16	✓ (a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	p11
		N/A (b) Report category boundaries when continuous variables were categorized	
		✓ (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	p11

Other analyses	17 ✓	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	p13
Discussion			
Key results	18 ✓	Summarise key results with reference to study objectives	p14-16
Limitations	19 ✓	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	p15-16
Interpretation	20 ✓	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	p16
Generalisability	21 ✓	Discuss the generalisability (external validity) of the study results	p15
Other information			
Funding	22 ✓	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	p2

*Give information separately for cases and controls.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at <http://www.strobe-statement.org>.