The use of prescriptions for antibiotics and antifungals in Danish blood donors with dry skin

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Conflict of interest

Dr. Henning reports grants from Leo Foundation, Denmark (number LF 18002), during the conduct of the study. Dr. Lindsø Andersen reports grants from Leo Foundation, Denmark (number LF 18002), grants from Naestved, Ringsted and Slagelse Hospitals' Research Fund, during the conduct of the study. Dr. Ibler has nothing to disclose. Dr. Ullum has nothing to disclose. Dr. Erikstrup has nothing to disclose. Dr. Nielsen has nothing to disclose. Dr. Bruun has nothing to disclose. Dr. Rigas has nothing to disclose. Dr. Dinh has nothing to disclose. Dr. Rostgaard has nothing to disclose. Dr. Saunte reports personal fees from AbbVie, personal fees from Janssen, personal fees from Sanofi, personal fees from Leo Pharma, grants and personal fees from Abbvie, personal fees from Leo Pharma, grants from Novartis, personal fees from Jansen, outside the submitted work. Dr. Pedersen has nothing to disclose. Dr. Jemec reports grants and personal fees from Abbvie, personal fees from Coloplast, personal fees from Chemocentryx, personal fees from LEO pharma, grants from LEO Foundation, grants from Afyx, personal fees from Incyte, grants and personal fees from InflaRx, grants from Janssen-Cilag, grants and personal fees from Novartis, grants and personal fees from UCB, grants from CSL Behring, grants from Regeneron, grants from Sanofi, personal fees from Kymera, personal fees from VielaBio, outside the submitted work.

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Statement of contributions

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Conceptualization, Formal analysis, Investigation, Methodology, Project administration, Resources, Software, Validation, Visualization, Writing-original draft

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Formal analysis, Investigation, Methodology, Resources, Software, Supervision, Writing-review & editing

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Title

The use of prescriptions for antibiotics and antifungals in Danish blood donors with dry skin

Running head

Antibiotic and antifungal use in dry skin

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To the Editor,

Dry skin or xerosis is a common ailment occurring both as a separate disease entity and as a symptom of other diseases, e.g. it is a cardinal symptom of atopic dermatitis[1]. Infections have been described in xerosis associated with dermatitis[2]. Whether xerosis without dermatitis is a risk factor for skin infections remains unknown. We therefore tested if individuals with xerosis had a risk of skin infections.

We used data from blood donors born after 1993 included in the Danish Blood Donor Study (DBDS) between June 2018 and March 2019[3]. For xerosis and comparator case definitions, see Figure 1. Bacterial and fungal skin infections were defined using the proxy indicator prescriptions for topical antibiotics and antifungal treatments (Table 1). Medications containing corticosteroids were not included. Data on redeemed prescriptions was collected from the National Prescription Database, which covered the period 1995–2019. Xerosis, sex and smoking were coded as binary variables. Age and body mass index (BMI) were coded as continuous variables. Intensity of prescription-use by xerosis status was assessed in Andersen-Gill models with robust standard errors, adjusted for sex, age, BMI and smoking[4]. Akaike information criterion was used to find the most parsimonious models. Donors were followed-up from birth to 30 June 2018. Missing data observations were excluded. Analyses were conducted in R, version 3.6.3. The assumptions of cox regression were met. The Central Denmark and Zealand Regional Committees on Health Research Ethics and the Danish Data Protection Agency approved the study (M-20090237, SJ-740 and P-2019-99, respectively). Research data are not shared to protect the privacy of study participants.

For a flow diagram of inclusions, see Figure 1. The study consisted of 1,985 blood donors with mild, moderate or severe xerosis and 824 healthy comparators. The results are presented in Table 1.

The data suggests that otherwise healthy children and young adults without concurrent severe disease including dermatoses who develop xerosis have an increased use of topical antibiotics and antifungal treatments. By proxy, the results may therefore indicate an increased risk of clinically meaningful skin infections in individuals with xerosis. This is in accordance with a study of 48,000 adults that also suggested that individuals with xerosis have an increased susceptibility to skin infections[2]. It may therefore be speculated that xerosis is associated with skin barrier disruptions allowing pathogens to enter the skin or some degree of immune-impairment[5].

Methodological strengths include the use of nationwide data on all redeemed prescriptions and hospital-assigned diagnoses from birth of the study participants to the end-of-study. Additionally, the risk of confounding from concurrent morbidity was low due to the inclusion of blood donors, who are healthy, and exclusion of hospital diagnosed and self-reported dermatoses. Likewise, we adjusted for age, sex, BMI and smoking to eliminate the influence of these possible confounders. However, there might be other confounders that we were unaware of that could have influenced the results. The xerosis case definition may be subjected to reporting bias, however, the results suggests a dose-response relation between severity of xerosis and using prescriptions. This implies that the risk of reporting bias was lower as not only blood donors with the worst degree of xerosis used prescriptions. Additional limitations were selection bias from including blood donors, which could hamper extrapolation of results. To minimize the effect of the uncertainty physicians faced when determining whether skin inflammation was attributed to dermatitis or an infection, topical treatments containing corticosteroids were not included as an outcome.

In conclusion, this study suggests that blood donors with xerosis have an increased risk of using medications against clinically meaningful bacterial and fungal skin infections.

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Legend Table 1

Table 1. Descriptive and analytical statistics

Panel (a) Descriptive statistics

Panel (b) Andersen-Gill models

BMI, Body mass index; Danish Blood Donor Study (DBDS); HR, Hazard ratio; CI, Confidence interval; IQR, Interquartile Range; n, Number;

[a]Difference between xerosis and comparators determined by chi-square or Mann-Whitney U test

[b]Fucidic acid, mupirocin or oxytetracycline defined by the anatomical therapeutic chemical codes D06AX0, D06AX09 or D06AA03, respectively.

[c]Clotrimazole, iconazole, ketoconazole, terbinafine defined by the anatomical therapeutic chemical codes D01AC01, D01AC02, D01AC08, D01AE15, respectively.

[d]Adjusted for age, sex, BMI and smoking

Legend Figure 1

Figure 1. Flowchart of inclusions

[a]Defined by ICD-10[th] diagnoses and by answering 'Yes, moderately' or 'Yes, severely' to the DBDS questionnaire items 'Have you had an itchy rash on your hands?' or 'Have you had eczema?' or by answering 'Yes' to the DBDS questionnaire items 'Have you had hand eczema?' or 'Have you had childhood eczema?';

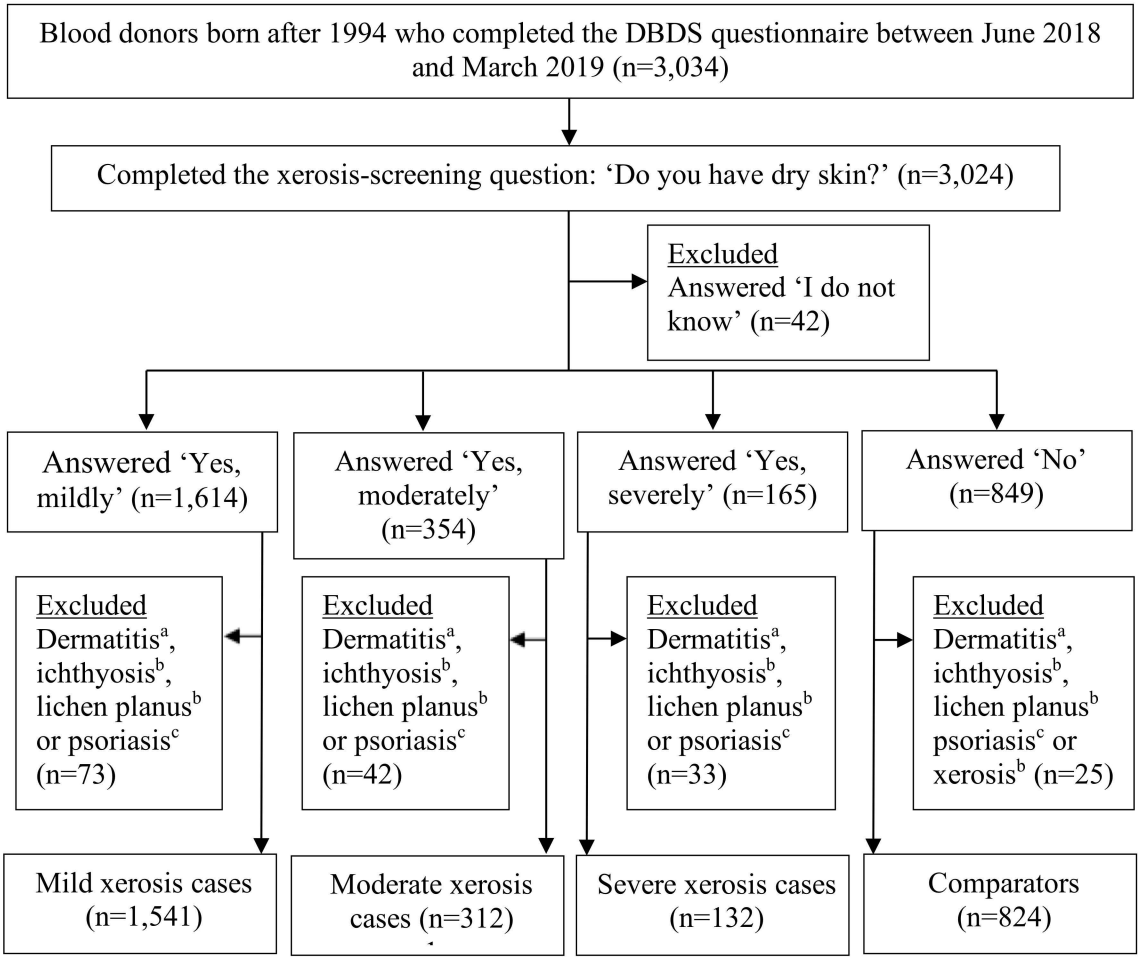
[b]Defined by ICD-10[th] diagnoses;

[c]Defined by ICD-10[th] diagnoses and the diagnostic algorithm by Dominguez et al., as part of the DBDS questionnaire[6];

DBDS, Danish Blood Donor Study; ICD-10[th], International Classification of Disease-10; n, Study population

Panel (a)							
	Mild xerosis (n=1,541)	p-value[a]	Moderate xerosis (n=312)	p-value[a]	Severe xerosis (n=132)	p-value[a]	Comparators (n=824)
Female, n (%) / male sex, n (%) / missing, n (%)	960 (62.3) / 581 (37.7) / 0 (0)		217 (69.6) / 95 (30.4) / 0 (0)		105 (79.5) / 27 (20.5) / 0 (0)		450 (54.6) / 374 (45.4) / 0 (0)
Age in years, median (IQR) / missing, n (%)	22.0 (20.6–23.0) / 0 (0)	<0.001	22.2 (20.8–23.1) / 0 (0)	<0.001	22.0 (20.6–23.2) / 0 (0)	<0.001	21.8 (20.3–22.9) / 0 (0)
Smoking, n (%) / no smoking, n (%) / missing, n (%)	298 (19.3) / 1,243 (80.7) / 0 (0)	0.80	62 (19.9) /250 (48.1) / 0 (0)	0.75	39 (29.5) / 93 (70.5) / 0 (0)	0.006	155 (18.8) / 669 (81.2) / 0 (0)
BMI, median (IQR) / missing, n (%)	23.4 (21.5–25.7) / 8 (0.5)	0.10	23.1 (21.2–25.5) / 1 (0.3)	<0.001	23.7 (21.4–26.2) / 1 (0.8)	<0.001	23.4 (21.5–25.9) / 3 (0.4)
Topical antibiotic prescriptions[b]		<0.001		<0.001		<0.001	
0, n (%)	742 (48.2)		142 (45.5)		57 (43.2)		404 (49.0)
1 or 2, n (%)	676 (43.9)		137 (43.9)		63 (47.7)		366 (44.4)
3 or more, n (%)	123 (8.0)		33 (10.6)		12 (9.1)		54 (6.6)
Topical antifungal prescriptions[c]		<0.001		0.13		<0.001	
0, n (%)	1,102 (71.5)		205 (65.7)		72 (54.5)		591 (71.7)
1 or 2, n (%)	390 (25.3)		84 (26.9)		46 (34.8)		209 (25.4)
3 or more, n (%)	49 (3.2)		23 (7.4)		14 (10.6)		24 (2.9)
Panel (b)							

	Topical antibiotics[b]		Topical antifungal treatments[c]	
	Crude HR (95% CI); p-value	Adjusted[d] HR (95% CI); p-value	Crude HR (95% CI); p-value	Adjusted[d] HR (95% CI); p-value
Severe xerosis	1.23 (0.98–1.55); 0.07	1.18 (0.90–1.55); 0.22	2.02 (1.41–2.90); <0.001	2.02 (1.45–2.89); <0.001
Age	1.04 (0.98–1.10); 0.19	1.01 (0.94-1.08); 0.80	0.97 (0.89-1.06); 0.52	0.93 (0.84-1.04); 0.20
Sex	1.04 (0.88–1.23); 0.64	0.95 (0.78-1.17); 0.65	1.02 (0.75-1.38); 0.90	0.92 (0.67-1.25); 0.59
BMI	1.01 (0.99–1.04); 0.39	1.01 (0.99-1.03); 0.47	1.05 (1.00-1.10); 0.06	1.04 (1.00-1.08); 0.06
Smoking	1.04 (0.84–1.28); 0.76	1.01 (0.79-1.30); 0.92	1.37 (0.97-1.95); 0.07	1.26 (0.90-1.76); 0.17
Moderate xerosis	1.16 (0.98–1.38); 0.09	1.16 (0.95–1.41); 0.15	1.43 (1.08–1.88); 0.01	1.45 (1.09–1.94); 0.01
Age	1.04 (0.99–1.09); 0.15	1.00 (0.94–1.07); 0.95	1.05 (0.96–1.15); 0.25	1.03 (0.93–1.13); 0.59
Sex	1.10 (0.94–1.28); 0.23	1.03 (0.86–1.23); 0.77	1.02 (0.77–1.40); 0.90	1.03 (0.77–1.37); 0.87
BMI	1.02 (0.99–1.04); 0.15	1.02 (0.99–1.04); 0.13	1.02 (0.99–1.05); 0.11	1.02 (0.99–1.05); 0.11
Smoking	0.99 (0.81–1.22); 0.93	0.95 (0.75–1.21); 0.69	1.16 (0.85–1.59); 0.35	1.17 (0.83–1.64); 0.38
Mild xerosis	1.02 (0.92–1.14); 0.69	1.02 (0.90–1.17); 0.75	0.93 (0.76–1.13); 0.45	0.93 (0.75–1.14); 0.48
Age	1.00 (0.97–1.04); 0.99	0.98 (0.94–1.02); 0.23	0.99 (0.93–1.06); 0.75	0.97 (0.91–1.04); 0.43
Sex	1.03 (0.92–1.14); 0.63	0.98 (0.86–1.11); 0.74	1.06 (0.88–1.29); 0.52	1.09 (0.89–1.34); 0.39
BMI	1.01 (0.99–1.03); 0.20	1.01 (0.99–1.03); 0.20	1.01 (0.99–1.03); 0.30	1.01 (0.99–1.04); 0.25
Smoking	1.08 (0.95–1.23); 0.26	1.10 (0.95–1.29); 0.21	0.92 (0.76–1.12); 0.41	0.91 (0.73–1.14); 0.40


Blood donors born after 1994 who completed the DBDS questionnaire between June 2018 and March 2019 (n=3,034)
Completed the xerosis-screening question: 'Do you have dry skin?' (n=3,024)
Excluded
Answered 'I do not know' (n=42)
Answered 'Yes, mildly' (n=1,614)
Answered 'Yes, moderately' (n=354)
Answered 'Yes, severely' (n=165)
Answered 'No' (n=849)
Excluded
Dermatitis[a], ichthyosis[b], lichen planus[b] or psoriasis[c] (n=73)
Excluded
Dermatitis[a], ichthyosis[b], lichen planus[b] or psoriasis[c] (n=42)
Excluded
Dermatitis[a], ichthyosis[b], lichen planus[b] or psoriasis[c] (n=33)
Excluded
Dermatitis[a], ichthyosis[b], lichen planus[b] psoriasis[c] or xerosis[b] (n=25)
Mild xerosis cases (n=1,541)
Moderate xerosis cases (n=312)
Severe xerosis cases (n=132)
Comparators (n=824)