Additional file 1

Recorded skin conditions and later multidimensional chronic pain burden: a response-weighted UK Biobank cohort analysis

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This file contains extended methods, 14 supporting tables, four supporting figures and reproducibility notes. Comparative values are generated from the locked v2 outputs; nested urticaria-only results are retained as sensitivity and continuity analyses.

Supporting Methods

Data integration and person key

All sources were harmonised to one row per participant using n_eid as the person-level key. Baseline data contributed assessment date, demographics, lifestyle, anthropometry, sleep and baseline pain variables. The online pain questionnaire contributed a person-specific completion date and pain-domain responses. Curated first-occurrence data contributed ICD-10 L20, L29, L40 and L50 dates. Inpatient arrays paired Field 41270 diagnosis codes with Field 41280 first-diagnosis dates for the hospital-outcome sensitivity analysis. Source-key uniqueness, join grain and date ranges were tested before modelling (Tables S2, S13 and S14).

Comparative group derivation

For each participant, each recorded condition was set to present only when the first-occurrence date was on or before the participant-specific pain-questionnaire date. The primary factor contained five mutually exclusive levels: none, L20 only, L29 only, L40 only and L50 only. Participants with two or more study conditions were excluded from the primary comparison and retained in a sensitivity analysis. At 0 years, 1,588 participants had multiple recorded study conditions. Raw group counts and model-specific denominators are shown in Table S5.

Pain phenotypes

Chronic pain required pain at one or more sites, or all-over-body pain, lasting at least 3 months. High spatial burden required at least two sites or all-over-body pain. Site count excluded all-over-body responses. Conditional analyses were restricted to chronic-pain cases and used the available site-specific ratings or descriptors. Full definitions appear in Table S1.

Questionnaire-response weighting

A response model was fitted in the baseline cohort with completion of the online pain questionnaire as the outcome and baseline age, sex, assessment centre, body mass index, Townsend deprivation, smoking, alcohol frequency, ethnicity, income, education and pain status as predictors. Respondents received the inverse predicted response probability. Weights were trimmed at the 1st and 99th percentiles and normalised to mean 1. Balance was evaluated by standardised mean differences against the response-model target. After weighting, the largest reported absolute standardised mean difference among response-model variables was below 0.04 (Table S4; Figs S1–S2).

Models, standardisation and multiplicity

Binary outcomes used weighted modified Poisson regression with robust variance; count outcomes used weighted quasi-Poisson models; continuous outcomes used weighted Gaussian models. The five-level group factor and all core covariates were included in each model. A design-based global test assessed the group term. Binary absolute estimates were marginally standardised from corresponding weighted logistic models; count and continuous estimates were standardised from their direct models. The complete standardised estimates, disease-versus-none contrasts and all ten pairwise contrasts per outcome are reported in Tables S6–S8.

Global P values were adjusted within the three population-level outcomes and five chronic-pain-conditional outcomes. Pairwise P values were adjusted within each outcome. Benjamini–Hochberg q values are reported with raw estimates. Non-significant contrasts were not interpreted as equivalence.

Sensitivity and nested urticaria analyses

Comparative chronic-pain models were repeated using 1-, 2- and 5-year lags; in participants without an affirmative baseline chronic-pain proxy; in those explicitly reporting no pain in the previous month at baseline; and with a multiple-condition category added (Table S9). The original L50-versus-condition-free analysis remained locked and was reproduced only as a nested sensitivity. Its sequential adjustment, alternative weight trimming, complete-case and multiple-imputation estimates are shown in Table S10. Prespecified effect-modification results and time-dependent hospital models are shown in Tables S11–S12 and Figures S3–S4.

Hospital-record outcome

Strict hospital-recorded chronic pain used G89.2 or R52.2; a broad sensitivity used any G89 or R52 code. Participants with an outcome on or before baseline were excluded. Follow-up ended at the pain-questionnaire date, and L50 exposure was time varying. Only 3 strict and 7 broad events occurred during exposed person-time in the lag-0 analyses. These estimates are feasibility checks rather than independent confirmation (Table S12; Fig. S4).

Supporting Table Legends

Table S1. Variable definitions and analysis roles.

Table S2. Cohort construction and mutually exclusive condition-group counts.

Table S3. Missingness of core covariates before prespecified missing-data handling.

Table S4. Questionnaire-response weight balance and weight-quality diagnostics.

Table S5. Comparative group counts and chronic-pain events.

Table S6. Marginal standardised estimates across five groups and eight pain outcomes.

Table S7. Adjusted condition-versus-none contrasts across eight pain outcomes.

Table S8. All ten adjusted pairwise contrasts within each of eight pain outcomes.

Table S9. Comparative chronic-pain sensitivity analyses across temporal lags, baseline-pain restrictions and inclusion of multiple recorded conditions.

Table S10. Nested locked urticaria-only analyses: sequential adjustment, response-weight sensitivity, complete-case analysis and multiple imputation.

Table S11. Nested urticaria-only effect-modification tests and stratum-specific estimates.

Table S12. Nested time-dependent hospital-record outcome analyses.

Table S13. First-occurrence date plausibility, source-key and join-grain audits.

Table S14. Independent comparative validation checks.

Supporting Figure Legends

Figure S1. Questionnaire-participation balance before and after response weighting. Points show absolute standardised mean differences for the largest preweighting imbalances. The dashed vertical line is 0.10.

Figure S2. Distribution of trimmed and normalised questionnaire-response weights. The dashed line indicates weight 1.

Figure S3. Stratum-specific nested urticaria associations for sex, obesity, age and insomnia. Estimates are descriptive; formal interaction results are in Table S11.

Figure S4. Time-dependent hospital-record pain sensitivity. Points are weighted hazard ratios and bars are 95% confidence intervals. Wide intervals reflect sparse events during exposed person-time.

Reproducibility and validation

The comparative analysis was separated from the locked original analysis. Automated checks verified participant identifiers, lag-0 group derivation, raw group counts, complete outcome sets, standardised estimates, pairwise contrast keys, finite values, confidence-interval ordering, bounded P and q values and Benjamini–Hochberg calculations. The exact locked L50 model was independently reproduced (n=155,258; L50=3,529; PR=1.080501). All 14 independent comparative checks passed (Table S14).

The first-occurrence source contains records dated after the pain-questionnaire period because it was updated later. Every condition definition therefore applied the participant-specific questionnaire date and any prespecified lag so that post-questionnaire records could not define the exposure.

Table S1. Variable definitions and analysis roles

Domain	Variable	Definition
Recorded condition	Atopic dermatitis	UK Biobank first-occurrence date for ICD-10 L20 on or before the pain-questionnaire date; does not measure activity, severity or persistence.
Recorded condition	Pruritus	UK Biobank first-occurrence date for ICD-10 L29 on or before the pain-questionnaire date; this is a symptom code rather than a single disease entity.
Recorded condition	Psoriasis	UK Biobank first-occurrence date for ICD-10 L40 on or before the pain-questionnaire date; does not measure activity, severity or psoriatic arthritis.
Recorded condition	Urticaria	UK Biobank first-occurrence date for ICD-10 L50 on or before the pain-questionnaire date; does not establish chronic spontaneous urticaria, recurrence or duration beyond 6 weeks.
Grouping	Primary condition group	Mutually exclusive none, L20 only, L29 only, L40 only or L50 only; participants with multiple study conditions were excluded from the primary comparison.
Primary outcome	Chronic pain	Pain reported for at least 3 months at one or more anatomical sites, including all-over-body pain, in the online pain questionnaire.
Population outcome	All-over pain	Participant selected the all-over-body pain option in the online pain questionnaire.
Population outcome	High spatial burden	At least two affected anatomical sites or all-over-body pain.
Conditional outcome	Pain-site count	Number of affected anatomical sites among chronic-pain cases; all-over-body responses were excluded because a finite site count was not defined.
Conditional outcome	Mean pain intensity	Mean of available site-specific pain-intensity ratings on a 0–10 scale among chronic-pain cases.
Conditional outcome	Mean pain interference	Mean of available site-specific pain-interference ratings on a 0–10 scale among chronic-pain cases.
Conditional outcome	Neuropathic-feature count	Number of prespecified neuropathic descriptors among chronic-pain cases with descriptor data.
Conditional outcome	Any neuropathic feature	At least one prespecified neuropathic descriptor among chronic-pain cases with descriptor data.

Domain	Variable	Definition
Covariates	Core adjustment set	Age at questionnaire, sex, baseline assessment centre, body mass index and missingness, Townsend deprivation and missingness, smoking, alcohol-use frequency, ethnicity, annual household income and educational qualification.
Selection	Questionnaire-response weight	Inverse predicted probability of completing the online pain questionnaire, trimmed at the 1st and 99th percentiles and normalised to mean 1.
Sensitivity	No affirmative baseline chronic-pain proxy	Excluded participants with any affirmative baseline indicator of pain lasting at least 3 months.
Sensitivity	No pain in previous month at baseline	Required an explicit baseline response indicating no pain in the previous month.

Table S2. Cohort construction and group counts

Stage	n	Exclusion or note
UK Biobank baseline cohort	502226	Source cohort
Pain-questionnaire date available	167125	335101 without a questionnaire date
Linked skin first-occurrence source and valid positive response weight	166980	145 without a linked source or valid weight
Mutually exclusive primary condition groups	165392	1588 with multiple study conditions excluded
Chronic-pain primary model	164983	409 without complete model data after prespecified handling
No recorded study condition	152100	Raw mutually exclusive group count
Atopic dermatitis only	3517	Raw mutually exclusive group count
Pruritus only	2593	Raw mutually exclusive group count
Psoriasis only	4469	Raw mutually exclusive group count
Urticaria only	2713	Raw mutually exclusive group count

Table S3. Covariate missingness before handling

Variable	Missing n	Missing, %
age_baseline	0	0.00
sex	0	0.00
center	0	0.00
bmi	412	0.25
deprivation	213	0.13
smoking	413	0.25
alcohol	132	0.08
ethnicity	597	0.36
income	16765	10.03

Variable	Missing n	Missing, %
education	1637	0.98

Table S4A. Questionnaire-response model balance

Variable	Level	Unweighted SMD	Weighted SMD
education	None_listed	-0.312	-0.032
education	University	0.270	0.013
income	<18k	-0.194	-0.017
income	52-100k	0.162	0.011
income	Missing	-0.160	-0.028
bmi		-0.138	-0.005
deprivation		-0.133	-0.040
ethnicity	White	0.127	0.029
smoking	Current	-0.121	-0.019
income	>100k	0.109	0.006
alcohol	Never	-0.103	-0.026
age_baseline		-0.101	-0.020
income	31-52k	0.096	0.016
ethnicity	Asian_or_Chinese	-0.090	-0.024
education	Missing	-0.085	-0.019
baseline_pain_status	No_pain_last_month	0.085	0.011
ethnicity	Black	-0.081	-0.014
alcohol	Special_only	-0.076	-0.008
alcohol	3-4_week	0.072	0.009
baseline_pain_status	Chronic_pain	-0.072	-0.009
education	Secondary	-0.071	0.010
smoking	Never	0.067	<0.001
alcohol	Daily	0.066	0.009
baseline_pain_status	Unknown	-0.059	-0.021
smoking	Missing	-0.053	-0.014
alcohol	Missing	-0.051	-0.019

Variable	Level	Unweighted SMD	Weighted SMD
sex	Female	0.049	<0.001
sex	Male	-0.049	<0.001
ethnicity	Other	-0.041	-0.012
ethnicity	Missing	-0.029	-0.010

Table S4B. Questionnaire-response weight diagnostics

Respondents	Minimum	Median	Maximum	Effective sample size
167125	0.525	0.835	3.335	132037

Table S5. Comparative group counts and chronic-pain events

Group	Raw n	Weighted n	Non-missing chronic pain	Chronic-pain cases
No recorded condition	152100	151450.7	151729	84774
Pruritus (L29)	2593	2987.4	2585	1678
Psoriasis (L40)	4469	4464.7	4455	2767
Urticaria (L50)	2713	2780.4	2707	1714
Atopic dermatitis (L20)	3517	3531.9	3507	1991

Table S6. Marginal standardised estimates across five groups and eight outcomes

Outcome	Group	Analytic n	Standardised estimate (95% CI)
Chronic pain	L20	3507	0.592 (0.575–0.610)
Chronic pain	L29	2585	0.659 (0.639–0.678)
Chronic pain	L40	4455	0.633 (0.618–0.649)
Chronic pain	L50	2707	0.639 (0.619–0.658)
Chronic pain	None	151729	0.585 (0.583–0.588)
All-over pain	L20	3504	0.077 (0.066–0.088)
All-over pain	L29	2582	0.105 (0.091–0.118)
All-over pain	L40	4446	0.109 (0.098–0.119)
All-over pain	L50	2699	0.094 (0.081–0.106)
All-over pain	None	151548	0.076 (0.074–0.077)
High spatial pain burden	L20	3500	0.527 (0.509–0.545)
High spatial pain burden	L29	2577	0.594 (0.573–0.614)

Outcome	Group	Analytic n	Standardised estimate (95% CI)
High spatial pain burden	L40	4442	0.568 (0.552–0.584)
High spatial pain burden	L50	2696	0.576 (0.556–0.596)
High spatial pain burden	None	151359	0.511 (0.509–0.514)
Number of pain sites	L20	1773	3.912 (3.792–4.032)
Number of pain sites	L29	1424	4.125 (3.991–4.258)
Number of pain sites	L40	2330	4.094 (3.989–4.198)
Number of pain sites	L50	1488	4.064 (3.940–4.189)
Number of pain sites	None	76004	3.863 (3.845–3.881)
Mean pain intensity	L20	1764	3.019 (2.909–3.130)
Mean pain intensity	L29	1408	3.211 (3.082–3.340)
Mean pain intensity	L40	2317	2.990 (2.892–3.087)
Mean pain intensity	L50	1475	3.196 (3.080–3.313)
Mean pain intensity	None	75425	2.942 (2.926–2.959)
Mean pain interference	L20	1756	2.603 (2.480–2.727)
Mean pain interference	L29	1407	2.856 (2.709–3.002)
Mean pain interference	L40	2315	2.657 (2.548–2.766)
Mean pain interference	L50	1478	2.768 (2.631–2.905)
Mean pain interference	None	75334	2.505 (2.487–2.524)
Number of neuropathic features	L20	1621	1.382 (1.296–1.468)
Number of neuropathic features	L29	1281	1.392 (1.295–1.489)
Number of neuropathic features	L40	2128	1.362 (1.291–1.433)
Number of neuropathic features	L50	1359	1.388 (1.300–1.476)
Number of neuropathic features	None	68859	1.333 (1.320–1.346)
Any neuropathic feature	L20	1621	0.623 (0.598–0.649)
Any neuropathic feature	L29	1281	0.636 (0.606–0.665)
Any neuropathic feature	L40	2128	0.625 (0.602–0.647)
Any neuropathic feature	L50	1359	0.632 (0.604–0.660)
Any neuropathic feature	None	68859	0.613 (0.609–0.617)

Table S7. Adjusted condition-versus-none contrasts across eight outcomes

Outcome	Condition	Estimand	Estimate (95% CI)	Pairwise q	Standardised difference (95% CI)
Chronic pain	L20	Prevalence ratio	1.011 (0.981–1.042)	0.519	0.007 (-0.011–0.025)
Chronic pain	L29	Prevalence ratio	1.119 (1.087–1.151)	<0.001	0.073 (0.053–0.093)
Chronic pain	L40	Prevalence ratio	1.079 (1.053–1.105)	<0.001	0.048 (0.032–0.064)
Chronic pain	L50	Prevalence ratio	1.088 (1.055–1.121)	<0.001	0.053 (0.033–0.073)
All-over pain	L20	Prevalence ratio	1.018 (0.883–1.174)	0.803	0.001 (-0.010–0.012)
All-over pain	L29	Prevalence ratio	1.382 (1.215–1.571)	<0.001	0.029 (0.015–0.042)
All-over pain	L40	Prevalence ratio	1.429 (1.297–1.575)	<0.001	0.033 (0.022–0.044)
All-over pain	L50	Prevalence ratio	1.232 (1.079–1.408)	0.004	0.018 (0.005–0.030)
High spatial pain burden	L20	Prevalence ratio	1.029 (0.994–1.065)	0.130	0.015 (-0.003–0.034)
High spatial pain burden	L29	Prevalence ratio	1.153 (1.115–1.192)	<0.001	0.082 (0.062–0.103)
High spatial pain burden	L40	Prevalence ratio	1.106 (1.076–1.137)	<0.001	0.057 (0.041–0.073)
High spatial pain burden	L50	Prevalence ratio	1.122 (1.084–1.160)	<0.001	0.065 (0.044–0.085)
Number of pain sites	L20	Mean ratio	1.013 (0.982–1.045)	0.613	0.049 (-0.073–0.170)
Number of pain sites	L29	Mean ratio	1.068 (1.033–1.103)	<0.001	0.262 (0.126–0.397)
Number of pain sites	L40	Mean ratio	1.060 (1.032–1.088)	<0.001	0.230 (0.124–0.337)
Number of pain sites	L50	Mean ratio	1.052 (1.020–1.085)	0.005	0.201 (0.075–0.327)
Mean pain intensity	L20	Adjusted mean difference	0.077 (-0.035–0.189)	0.254	0.077 (-0.035–0.189)
Mean pain intensity	L29	Adjusted mean difference	0.268 (0.138–0.399)	<0.001	0.268 (0.138–0.399)
Mean pain intensity	L40	Adjusted mean difference	0.047 (-0.052–0.146)	0.436	0.047 (-0.052–0.146)
Mean pain intensity	L50	Adjusted mean difference	0.254 (0.136–0.372)	<0.001	0.254 (0.136–0.372)
Mean pain interference	L20	Adjusted mean difference	0.098 (-0.027–0.223)	0.177	0.098 (-0.027–0.223)
Mean pain interference	L29	Adjusted mean difference	0.350 (0.203–0.498)	<0.001	0.350 (0.203–0.498)
Mean pain interference	L40	Adjusted mean difference	0.152 (0.041–0.263)	0.024	0.152 (0.041–0.263)
Mean pain interference	L50	Adjusted mean difference	0.263 (0.124–0.401)	<0.001	0.263 (0.124–0.401)
Number of neuropathic features	L20	Mean ratio	1.036 (0.973–1.104)	0.894	0.048 (-0.039–0.136)
Number of neuropathic features	L29	Mean ratio	1.044 (0.973–1.120)	0.894	0.059 (-0.039–0.156)
Number of neuropathic features	L40	Mean ratio	1.021 (0.969–1.077)	0.954	0.029 (-0.044–0.101)
Number of neuropathic features	L50	Mean ratio	1.041 (0.976–1.110)	0.894	0.055 (-0.034–0.144)
Any neuropathic feature	L20	Prevalence ratio	1.016 (0.975–1.059)	0.846	0.010 (-0.016–0.036)
Any neuropathic feature	L29	Prevalence ratio	1.035 (0.989–1.083)	0.807	0.022 (-0.007–0.052)

Outcome	Condition	Estimand	Estimate (95% CI)	Pairwise q	Standardised difference (95% CI)
Any neuropathic feature	L40	Prevalence ratio	1.019 (0.983–1.057)	0.846	0.012 (-0.011–0.035)
Any neuropathic feature	L50	Prevalence ratio	1.032 (0.988–1.077)	0.807	0.019 (-0.009–0.047)

Table S8. All ten pairwise contrasts within each outcome

Outcome	Comparison	Estimand	Direct estimate (95% CI)	Direct q	Standardised difference (95% CI)	Difference q
Chronic pain	L20 vs None	Prevalence ratio	1.011 (0.981–1.042)	0.519	0.007 (-0.011–0.025)	0.486
Chronic pain	L29 vs L20	Prevalence ratio	1.106 (1.062–1.152)	<0.001	0.066 (0.040–0.093)	<0.001
Chronic pain	L29 vs None	Prevalence ratio	1.119 (1.087–1.151)	<0.001	0.073 (0.053–0.093)	<0.001
Chronic pain	L40 vs L20	Prevalence ratio	1.067 (1.027–1.108)	0.001	0.041 (0.017–0.065)	0.001
Chronic pain	L40 vs L29	Prevalence ratio	0.964 (0.929–1.000)	0.076	-0.025 (-0.050–0.000)	0.072
Chronic pain	L40 vs None	Prevalence ratio	1.079 (1.053–1.105)	<0.001	0.048 (0.032–0.064)	<0.001
Chronic pain	L50 vs L20	Prevalence ratio	1.076 (1.032–1.121)	0.001	0.046 (0.020–0.073)	0.001
Chronic pain	L50 vs L29	Prevalence ratio	0.972 (0.933–1.013)	0.224	-0.020 (-0.048–0.008)	0.202
Chronic pain	L50 vs L40	Prevalence ratio	1.008 (0.971–1.047)	0.665	0.005 (-0.020–0.030)	0.688
Chronic pain	L50 vs None	Prevalence ratio	1.088 (1.055–1.121)	<0.001	0.053 (0.033–0.073)	<0.001
All-over pain	L20 vs None	Prevalence ratio	1.018 (0.883–1.174)	0.803	0.001 (-0.010–0.012)	0.844
All-over pain	L29 vs L20	Prevalence ratio	1.357 (1.125–1.637)	0.004	0.028 (0.011–0.045)	0.004
All-over pain	L29 vs None	Prevalence ratio	1.382 (1.215–1.571)	<0.001	0.029 (0.015–0.042)	<0.001
All-over pain	L40 vs L20	Prevalence ratio	1.404 (1.186–1.662)	<0.001	0.032 (0.017–0.047)	<0.001
All-over pain	L40 vs L29	Prevalence ratio	1.034 (0.883–1.211)	0.750	0.004 (-0.013–0.021)	0.692
All-over pain	L40 vs None	Prevalence ratio	1.429 (1.297–1.575)	<0.001	0.033 (0.022–0.044)	<0.001
All-over pain	L50 vs L20	Prevalence ratio	1.210 (1.000–1.465)	0.084	0.017 (0.000–0.033)	0.076
All-over pain	L50 vs L29	Prevalence ratio	0.892 (0.744–1.069)	0.268	-0.011 (-0.029–0.007)	0.296
All-over pain	L50 vs L40	Prevalence ratio	0.862 (0.734–1.013)	0.102	-0.015 (-0.032–0.001)	0.094
All-over pain	L50 vs None	Prevalence ratio	1.232 (1.079–1.408)	0.004	0.018 (0.005–0.030)	0.011
High spatial pain burden	L20 vs None	Prevalence ratio	1.029 (0.994–1.065)	0.130	0.015 (-0.003–0.034)	0.124
High spatial pain burden	L29 vs L20	Prevalence ratio	1.120 (1.069–1.174)	<0.001	0.067 (0.040–0.094)	<0.001
High spatial pain burden	L29 vs None	Prevalence ratio	1.153 (1.115–1.192)	<0.001	0.082 (0.062–0.103)	<0.001
High spatial pain burden	L40 vs L20	Prevalence ratio	1.075 (1.030–1.123)	0.002	0.041 (0.017–0.065)	0.001
High spatial pain burden	L40 vs L29	Prevalence ratio	0.960 (0.920–1.001)	0.082	-0.026 (-0.052–0.000)	0.076
High spatial pain burden	L40 vs None	Prevalence ratio	1.106 (1.076–1.137)	<0.001	0.057 (0.041–0.073)	<0.001
High spatial pain burden	L50 vs L20	Prevalence ratio	1.090 (1.040–1.143)	<0.001	0.049 (0.022–0.076)	<0.001
High spatial pain burden	L50 vs L29	Prevalence ratio	0.973 (0.928–1.019)	0.276	-0.018 (-0.046–0.011)	0.254
High spatial pain burden	L50 vs L40	Prevalence ratio	1.014 (0.971–1.058)	0.533	0.008 (-0.018–0.034)	0.546

Outcome	Comparison	Estimand	Direct estimate (95% CI)	Direct q	Standardised difference (95% CI)	Difference q
High spatial pain burden	L50 vs None	Prevalence ratio	1.122 (1.084–1.160)	<0.001	0.065 (0.044–0.085)	<0.001
Number of pain sites	L20 vs None	Mean ratio	1.013 (0.982–1.045)	0.613	0.049 (-0.073–0.170)	0.617
Number of pain sites	L29 vs L20	Mean ratio	1.054 (1.009–1.102)	0.049	0.213 (0.034–0.392)	0.049
Number of pain sites	L29 vs None	Mean ratio	1.068 (1.033–1.103)	<0.001	0.262 (0.126–0.397)	<0.001
Number of pain sites	L40 vs L20	Mean ratio	1.046 (1.005–1.089)	0.052	0.182 (0.022–0.341)	0.051
Number of pain sites	L40 vs L29	Mean ratio	0.992 (0.952–1.034)	0.726	-0.031 (-0.201–0.139)	0.725
Number of pain sites	L40 vs None	Mean ratio	1.060 (1.032–1.088)	<0.001	0.230 (0.124–0.337)	<0.001
Number of pain sites	L50 vs L20	Mean ratio	1.039 (0.995–1.085)	0.138	0.153 (-0.020–0.325)	0.139
Number of pain sites	L50 vs L29	Mean ratio	0.985 (0.942–1.030)	0.646	-0.060 (-0.243–0.122)	0.646
Number of pain sites	L50 vs L40	Mean ratio	0.993 (0.954–1.033)	0.726	-0.029 (-0.192–0.134)	0.725
Number of pain sites	L50 vs None	Mean ratio	1.052 (1.020–1.085)	0.005	0.201 (0.075–0.327)	0.006
Mean pain intensity	L20 vs None	Adjusted mean difference	0.077 (-0.035–0.189)	0.254	0.077 (-0.035–0.189)	0.254
Mean pain intensity	L29 vs L20	Adjusted mean difference	0.192 (0.023–0.360)	0.050	0.192 (0.023–0.360)	0.050
Mean pain intensity	L29 vs None	Adjusted mean difference	0.268 (0.138–0.399)	<0.001	0.268 (0.138–0.399)	<0.001
Mean pain intensity	L40 vs L20	Adjusted mean difference	-0.030 (-0.177–0.118)	0.770	-0.030 (-0.177–0.118)	0.770
Mean pain intensity	L40 vs L29	Adjusted mean difference	-0.221 (-0.383–-0.059)	0.019	-0.221 (-0.383–-0.059)	0.019
Mean pain intensity	L40 vs None	Adjusted mean difference	0.047 (-0.052–0.146)	0.436	0.047 (-0.052–0.146)	0.436
Mean pain intensity	L50 vs L20	Adjusted mean difference	0.177 (0.017–0.337)	0.050	0.177 (0.017–0.337)	0.050
Mean pain intensity	L50 vs L29	Adjusted mean difference	-0.014 (-0.188–0.159)	0.872	-0.014 (-0.188–0.159)	0.872
Mean pain intensity	L50 vs L40	Adjusted mean difference	0.207 (0.055–0.359)	0.019	0.207 (0.055–0.359)	0.019
Mean pain intensity	L50 vs None	Adjusted mean difference	0.254 (0.136–0.372)	<0.001	0.254 (0.136–0.372)	<0.001
Mean pain interference	L20 vs None	Adjusted mean difference	0.098 (-0.027–0.223)	0.177	0.098 (-0.027–0.223)	0.177
Mean pain interference	L29 vs L20	Adjusted mean difference	0.252 (0.062–0.443)	0.024	0.252 (0.062–0.443)	0.024
Mean pain interference	L29 vs None	Adjusted mean difference	0.350 (0.203–0.498)	<0.001	0.350 (0.203–0.498)	<0.001
Mean pain interference	L40 vs L20	Adjusted mean difference	0.054 (-0.111–0.219)	0.522	0.054 (-0.111–0.219)	0.522
Mean pain interference	L40 vs L29	Adjusted mean difference	-0.198 (-0.381–-0.016)	0.066	-0.198 (-0.381–-0.016)	0.066
Mean pain interference	L40 vs None	Adjusted mean difference	0.152 (0.041–0.263)	0.024	0.152 (0.041–0.263)	0.024
Mean pain interference	L50 vs L20	Adjusted mean difference	0.165 (-0.019–0.348)	0.132	0.165 (-0.019–0.348)	0.132
Mean pain interference	L50 vs L29	Adjusted mean difference	-0.088 (-0.288–0.112)	0.434	-0.088 (-0.288–0.112)	0.434
Mean pain interference	L50 vs L40	Adjusted mean difference	0.111 (-0.064–0.286)	0.269	0.111 (-0.064–0.286)	0.269
Mean pain interference	L50 vs None	Adjusted mean difference	0.263 (0.124–0.401)	<0.001	0.263 (0.124–0.401)	<0.001
Number of neuropathic features	L20 vs None	Mean ratio	1.036 (0.973–1.104)	0.894	0.048 (-0.039–0.136)	0.921
Number of neuropathic features	L29 vs L20	Mean ratio	1.007 (0.918–1.106)	0.954	0.010 (-0.119–0.139)	0.954

Outcome	Comparison	Estimand	Direct estimate (95% CI)	Direct q	Standardised difference (95% CI)	Difference q
Number of neuropathic features	L29 vs None	Mean ratio	1.044 (0.973–1.120)	0.894	0.059 (-0.039–0.156)	0.921
Number of neuropathic features	L40 vs L20	Mean ratio	0.986 (0.909–1.069)	0.954	-0.020 (-0.132–0.092)	0.954
Number of neuropathic features	L40 vs L29	Mean ratio	0.978 (0.897–1.067)	0.954	-0.030 (-0.150–0.090)	0.954
Number of neuropathic features	L40 vs None	Mean ratio	1.021 (0.969–1.077)	0.954	0.029 (-0.044–0.101)	0.954
Number of neuropathic features	L50 vs L20	Mean ratio	1.005 (0.920–1.098)	0.954	0.006 (-0.116–0.129)	0.954
Number of neuropathic features	L50 vs L29	Mean ratio	0.997 (0.908–1.095)	0.954	-0.004 (-0.134–0.126)	0.954
Number of neuropathic features	L50 vs L40	Mean ratio	1.019 (0.939–1.106)	0.954	0.026 (-0.087–0.139)	0.954
Number of neuropathic features	L50 vs None	Mean ratio	1.041 (0.976–1.110)	0.894	0.055 (-0.034–0.144)	0.921
Any neuropathic feature	L20 vs None	Prevalence ratio	1.016 (0.975–1.059)	0.846	0.010 (-0.016–0.036)	0.865
Any neuropathic feature	L29 vs L20	Prevalence ratio	1.019 (0.959–1.082)	0.846	0.012 (-0.027–0.051)	0.865
Any neuropathic feature	L29 vs None	Prevalence ratio	1.035 (0.989–1.083)	0.807	0.022 (-0.007–0.052)	0.865
Any neuropathic feature	L40 vs L20	Prevalence ratio	1.003 (0.951–1.059)	0.908	0.001 (-0.033–0.036)	0.939
Any neuropathic feature	L40 vs L29	Prevalence ratio	0.985 (0.930–1.043)	0.846	-0.011 (-0.048–0.026)	0.865
Any neuropathic feature	L40 vs None	Prevalence ratio	1.019 (0.983–1.057)	0.846	0.012 (-0.011–0.035)	0.865
Any neuropathic feature	L50 vs L20	Prevalence ratio	1.015 (0.957–1.077)	0.846	0.009 (-0.029–0.046)	0.865
Any neuropathic feature	L50 vs L29	Prevalence ratio	0.996 (0.936–1.060)	0.908	-0.003 (-0.044–0.037)	0.939
Any neuropathic feature	L50 vs L40	Prevalence ratio	1.012 (0.957–1.070)	0.846	0.007 (-0.028–0.043)	0.865
Any neuropathic feature	L50 vs None	Prevalence ratio	1.032 (0.988–1.077)	0.807	0.019 (-0.009–0.047)	0.865

Table S9. Comparative chronic-pain sensitivity analyses

Sensitivity	Comparison	Analytic n	PR (95% CI)	Pairwise q	Global P
Temporal lag 0 years	L20 vs None	164983	1.011 (0.981–1.042)	0.519	<0.001
Temporal lag 0 years	L29 vs None	164983	1.119 (1.087–1.151)	<0.001	<0.001
Temporal lag 0 years	L40 vs None	164983	1.079 (1.053–1.105)	<0.001	<0.001
Temporal lag 0 years	L50 vs None	164983	1.088 (1.055–1.121)	<0.001	<0.001
Temporal lag 0 years	L29 vs L20	164983	1.106 (1.062–1.152)	<0.001	<0.001
Temporal lag 0 years	L40 vs L20	164983	1.067 (1.027–1.108)	0.001	<0.001
Temporal lag 0 years	L50 vs L20	164983	1.076 (1.032–1.121)	0.001	<0.001
Temporal lag 0 years	L40 vs L29	164983	0.964 (0.929–1.000)	0.076	<0.001
Temporal lag 0 years	L50 vs L29	164983	0.972 (0.933–1.013)	0.224	<0.001
Temporal lag 0 years	L50 vs L40	164983	1.008 (0.971–1.047)	0.665	<0.001
Temporal lag 1 years	L20 vs None	164989	1.010 (0.980–1.041)	0.560	<0.001
Temporal lag 1 years	L29 vs None	164989	1.119 (1.087–1.152)	<0.001	<0.001

Sensitivity	Comparison	Analytic n	PR (95% CI)	Pairwise q	Global P
Temporal lag 1 years	L40 vs None	164989	1.077 (1.051–1.103)	<0.001	<0.001
Temporal lag 1 years	L50 vs None	164989	1.086 (1.054–1.119)	<0.001	<0.001
Temporal lag 1 years	L29 vs L20	164989	1.108 (1.063–1.154)	<0.001	<0.001
Temporal lag 1 years	L40 vs L20	164989	1.066 (1.026–1.107)	0.002	<0.001
Temporal lag 1 years	L50 vs L20	164989	1.075 (1.031–1.121)	0.001	<0.001
Temporal lag 1 years	L40 vs L29	164989	0.962 (0.927–0.998)	0.059	<0.001
Temporal lag 1 years	L50 vs L29	164989	0.970 (0.931–1.011)	0.192	<0.001
Temporal lag 1 years	L50 vs L40	164989	1.009 (0.971–1.048)	0.651	<0.001
Temporal lag 2 years	L20 vs None	165012	1.012 (0.982–1.043)	0.489	<0.001
Temporal lag 2 years	L29 vs None	165012	1.118 (1.086–1.151)	<0.001	<0.001
Temporal lag 2 years	L40 vs None	165012	1.075 (1.049–1.102)	<0.001	<0.001
Temporal lag 2 years	L50 vs None	165012	1.088 (1.056–1.121)	<0.001	<0.001
Temporal lag 2 years	L29 vs L20	165012	1.105 (1.060–1.151)	<0.001	<0.001
Temporal lag 2 years	L40 vs L20	165012	1.062 (1.022–1.104)	0.003	<0.001
Temporal lag 2 years	L50 vs L20	165012	1.075 (1.031–1.121)	0.001	<0.001
Temporal lag 2 years	L40 vs L29	165012	0.961 (0.926–0.998)	0.058	<0.001
Temporal lag 2 years	L50 vs L29	165012	0.973 (0.934–1.014)	0.244	<0.001
Temporal lag 2 years	L50 vs L40	165012	1.012 (0.974–1.052)	0.539	<0.001
Temporal lag 5 years	L20 vs None	165255	1.014 (0.984–1.045)	0.409	<0.001
Temporal lag 5 years	L29 vs None	165255	1.115 (1.081–1.150)	<0.001	<0.001
Temporal lag 5 years	L40 vs None	165255	1.073 (1.046–1.101)	<0.001	<0.001
Temporal lag 5 years	L50 vs None	165255	1.080 (1.046–1.115)	<0.001	<0.001
Temporal lag 5 years	L29 vs L20	165255	1.100 (1.054–1.148)	<0.001	<0.001
Temporal lag 5 years	L40 vs L20	165255	1.058 (1.018–1.100)	0.008	<0.001
Temporal lag 5 years	L50 vs L20	165255	1.065 (1.019–1.112)	0.008	<0.001
Temporal lag 5 years	L40 vs L29	165255	0.962 (0.925–1.001)	0.080	<0.001
Temporal lag 5 years	L50 vs L29	165255	0.968 (0.927–1.012)	0.185	<0.001
Temporal lag 5 years	L50 vs L40	165255	1.006 (0.967–1.047)	0.763	<0.001
No affirmative baseline chronic-pain proxy	L20 vs None	99260	0.994 (0.945–1.046)	0.823	<0.001
No affirmative baseline chronic-pain proxy	L29 vs None	99260	1.119 (1.059–1.182)	<0.001	<0.001
No affirmative baseline chronic-pain proxy	L40 vs None	99260	1.077 (1.031–1.124)	0.003	<0.001
No affirmative baseline chronic-pain proxy	L50 vs None	99260	1.100 (1.042–1.162)	0.003	<0.001

Sensitivity	Comparison	Analytic n	PR (95% CI)	Pairwise q	Global P
No affirmative baseline chronic-pain proxy	L29 vs L20	99260	1.125 (1.045–1.211)	0.004	<0.001
No affirmative baseline chronic-pain proxy	L40 vs L20	99260	1.083 (1.015–1.156)	0.028	<0.001
No affirmative baseline chronic-pain proxy	L50 vs L20	99260	1.107 (1.029–1.190)	0.013	<0.001
No affirmative baseline chronic-pain proxy	L40 vs L29	99260	0.963 (0.899–1.031)	0.399	<0.001
No affirmative baseline chronic-pain proxy	L50 vs L29	99260	0.984 (0.912–1.061)	0.746	<0.001
No affirmative baseline chronic-pain proxy	L50 vs L40	99260	1.022 (0.954–1.094)	0.669	<0.001
No pain in the last month at baseline	L20 vs None	71760	0.976 (0.916–1.041)	0.513	<0.001
No pain in the last month at baseline	L29 vs None	71760	1.135 (1.060–1.215)	0.001	<0.001
No pain in the last month at baseline	L40 vs None	71760	1.069 (1.013–1.128)	0.031	<0.001
No pain in the last month at baseline	L50 vs None	71760	1.133 (1.061–1.210)	0.001	<0.001
No pain in the last month at baseline	L29 vs L20	71760	1.162 (1.060–1.274)	0.003	<0.001
No pain in the last month at baseline	L40 vs L20	71760	1.095 (1.008–1.188)	0.052	<0.001
No pain in the last month at baseline	L50 vs L20	71760	1.161 (1.061–1.270)	0.003	<0.001
No pain in the last month at baseline	L40 vs L29	71760	0.942 (0.864–1.026)	0.215	<0.001
No pain in the last month at baseline	L50 vs L29	71760	0.998 (0.909–1.096)	0.974	<0.001
No pain in the last month at baseline	L50 vs L40	71760	1.060 (0.975–1.153)	0.215	<0.001
Including multiple recorded skin conditions	L20 vs None	166570	1.011 (0.981–1.042)	0.520	<0.001
Including multiple recorded skin conditions	L29 vs None	166570	1.119 (1.087–1.151)	<0.001	<0.001
Including multiple recorded skin conditions	L40 vs None	166570	1.079 (1.053–1.105)	<0.001	<0.001
Including multiple recorded skin conditions	L50 vs None	166570	1.088 (1.056–1.121)	<0.001	<0.001
Including multiple recorded skin conditions	L29 vs L20	166570	1.106 (1.062–1.152)	<0.001	<0.001
Including multiple recorded skin conditions	L40 vs L20	166570	1.067 (1.027–1.108)	0.001	<0.001
Including multiple recorded skin conditions	L50 vs L20	166570	1.076 (1.032–1.121)	0.001	<0.001
Including multiple recorded skin conditions	L40 vs L29	166570	0.964 (0.929–1.001)	0.076	<0.001
Including multiple recorded skin conditions	L50 vs L29	166570	0.972 (0.933–1.013)	0.227	<0.001
Including multiple recorded skin conditions	L50 vs L40	166570	1.008 (0.971–1.047)	0.661	<0.001

Table S10A. Nested L50 sequential adjustment

Model	n	L50 n	PR (95% CI)	Risk difference, pp (95% CI)
age_sex	155258	3529	1.11 (1.08–1.14)	6.513 (4.745–8.281)
core	155258	3529	1.08 (1.05–1.11)	5.047 (3.276–6.819)
core_plus_baseline_pain_status	155258	3529	1.05 (1.03–1.08)	3.573 (1.823–5.322)

Table S10B. Nested L50 response-weight sensitivity

Analysis	n	Weight min	Weight max	Effective n	PR (95% CI)
unweighted	155258	1.000	1.000	155258	1.09 (1.06–1.11)
selection_weight_untrimmed	155258	0.468	18.571	115837	1.08 (1.05–1.11)
selection_weight_trim_5_95	155258	0.586	2.179	131991	1.08 (1.05–1.11)
selection_weight_trim_1_99	155258	0.527	3.332	122947	1.08 (1.05–1.11)
stored_primary_weight_trim_1_99	155258	0.525	3.335	122884	1.08 (1.05–1.11)

Table S10C. Nested L50 complete-case analysis

Analysis	n	L50 n	Events	PR (95% CI)
primary_missing_category_plus_indicator	155258	3529	87015	1.08 (1.05–1.11)
complete_case	138491	3137	77024	1.10 (1.07–1.13)

Table S10D. Nested L50 multiple-imputation analysis

Analysis	Imputations	n	L50 n	PR (95% CI)	P
multiple_imputation	10	155258	3529	1.08 (1.05–1.11)	<0.001

Table S11A. Nested L50 formal effect-modification tests

Modifier	Levels	Minimum cell n	Interaction P	FDR q	RERI (95% CI)
sex	Female vs Male	1130	0.698	0.923	-0.023 (-0.082–0.035)
obesity	Not_obese vs Obese	844	0.089	0.355	-0.049 (-0.107–0.009)
age60	<60 vs >=60	887	0.923	0.923	0.004 (-0.063–0.072)
insomnia_binary	No vs Yes	761	0.419	0.839	0.052 (-0.034–0.137)

Table S11B. Nested L50 stratum-specific estimates

Modifier	Level	n	L50 n	PR (95% CI)
sex	Female	88213	2399	1.09 (1.06–1.12)
sex	Male	67045	1130	1.07 (1.01–1.13)
obesity	Not_obese	124804	2685	1.09 (1.06–1.13)
obesity	Obese	30454	844	1.06 (1.01–1.10)
age60	<60	39851	887	1.08 (1.02–1.14)
age60	>=60	115407	2642	1.08 (1.05–1.11)
insomnia_binary	No	40108	761	1.05 (0.97–1.13)

Modifier	Level	n	L50 n	PR (95% CI)
insomnia_binary	Yes	115002	2766	1.08 (1.05–1.11)

Table S12. Nested time-dependent hospital-record pain analyses

Outcome	Lag, years	Adjustment	Events	Exposed-time events	HR (95% CI)	P
strict_G89_2_R52_2	0	age_sex	128	3	1.15 (0.37–3.62)	0.809
strict_G89_2_R52_2	0	parsimonious_selection_weighted	128	3	1.42 (0.38–5.28)	0.603
strict_G89_2_R52_2	1	age_sex	128	3	1.20 (0.38–3.75)	0.760
strict_G89_2_R52_2	1	parsimonious_selection_weighted	128	3	1.47 (0.40–5.48)	0.564
strict_G89_2_R52_2	2	age_sex	128	3	1.25 (0.40–3.92)	0.704
strict_G89_2_R52_2	2	parsimonious_selection_weighted	128	3	1.54 (0.41–5.73)	0.520
broad_G89_R52	0	age_sex	268	7	1.30 (0.62–2.75)	0.490
broad_G89_R52	0	parsimonious_selection_weighted	268	7	1.24 (0.51–3.06)	0.636
broad_G89_R52	1	age_sex	268	6	1.16 (0.52–2.60)	0.723
broad_G89_R52	1	parsimonious_selection_weighted	268	6	1.21 (0.47–3.13)	0.699
broad_G89_R52	2	age_sex	268	6	1.21 (0.54–2.72)	0.642
broad_G89_R52	2	parsimonious_selection_weighted	268	6	1.27 (0.49–3.28)	0.626

Table S13A. First-occurrence date plausibility

Exposure	Raw non-missing	Implausible before birth	Cleaned non-missing
AD_L20	13941	33	13908
pruritus_L29	13041	0	13041
psoriasis_L40	16608	14	16594
urticaria_L50	11339	5	11334

Table S13B. Source-key audit

Source	Rows	Unique IDs	Duplicate IDs
baseline	502226	502226	0
questionnaire	502226	502226	0
skin_dates	501936	501936	0
tdi	502132	502132	0

Table S13C. Join-grain audit

Stage	Rows	Unique IDs
baseline_plus_questionnaire	502226	502226
plus_skin_dates	502226	502226
plus_tdi	502226	502226

Table S14. Independent comparative validation checks

Check	Pass	Detail	Status
Source participant IDs are unique and nonmissing	TRUE	n=167125	PASS
Lag-0 flags have no missing values	TRUE	missing flags=0	PASS
Derived lag-0 group matches stored group	TRUE	mismatches=0	PASS
Primary raw group counts match locked expectations	TRUE	None 152100; L20_only 3517; L29_only 2593; L40_only 4469; L50_only 2713	PASS
All expected outcomes are present exactly once in global tests	TRUE	chronic_pain; all_over_pain_population; high_spatial_burden; site_count; mean_pain_intensity; mean_pain_interference; neuropathic_feature_count; any_neuropathic_feature	PASS
All expected group-by-outcome standardized estimates are present	TRUE	rows=40	PASS
All expected pairwise rows are present and unique	TRUE	rows=80; duplicated keys=0	PASS
All saved numeric estimates are finite	TRUE	Pairwise estimate fields checked	PASS
Confidence intervals are ordered	TRUE	Direct and standardized-difference intervals checked	PASS
All P and q values are within bounds	TRUE	Global and pairwise fields checked	PASS
BH-adjusted P values do not fall below raw P values	TRUE	Global and pairwise fields checked	PASS
Exact locked single-exposure model is reproduced	TRUE	n=155258; L50=3529; PR=1.080500654	PASS
Independent mutually exclusive L50 model matches saved result	TRUE	independent=1.087630740; saved=1.087630741	PASS
Temporal and baseline-restriction sensitivity sets are present	TRUE	baseline_pain_free; include_multiple; lag0; lag1; lag2; lag5; no_baseline_chronic_proxy	PASS

Supporting Figures

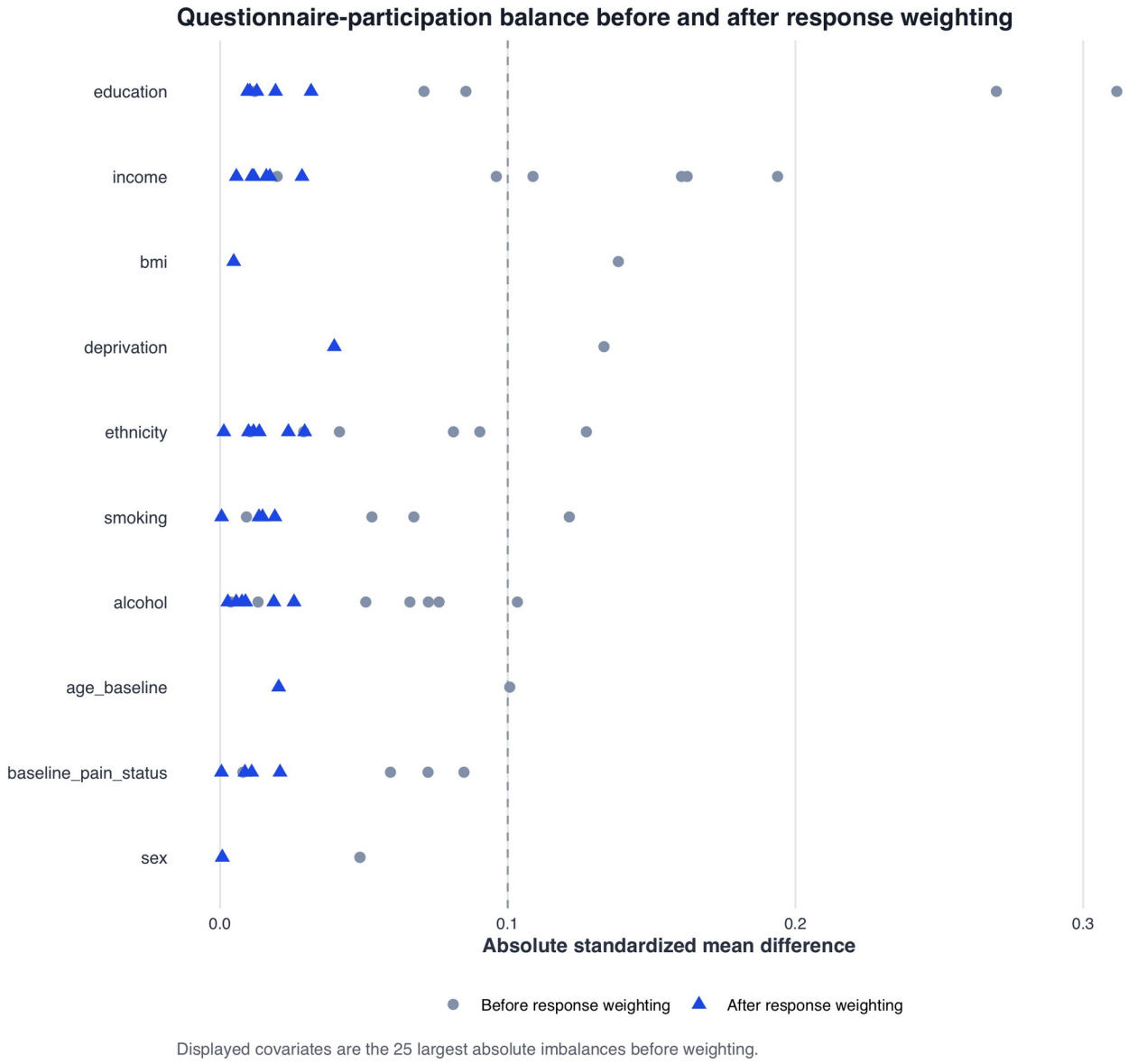

Figure S1. Questionnaire-participation balance before and after response weighting.

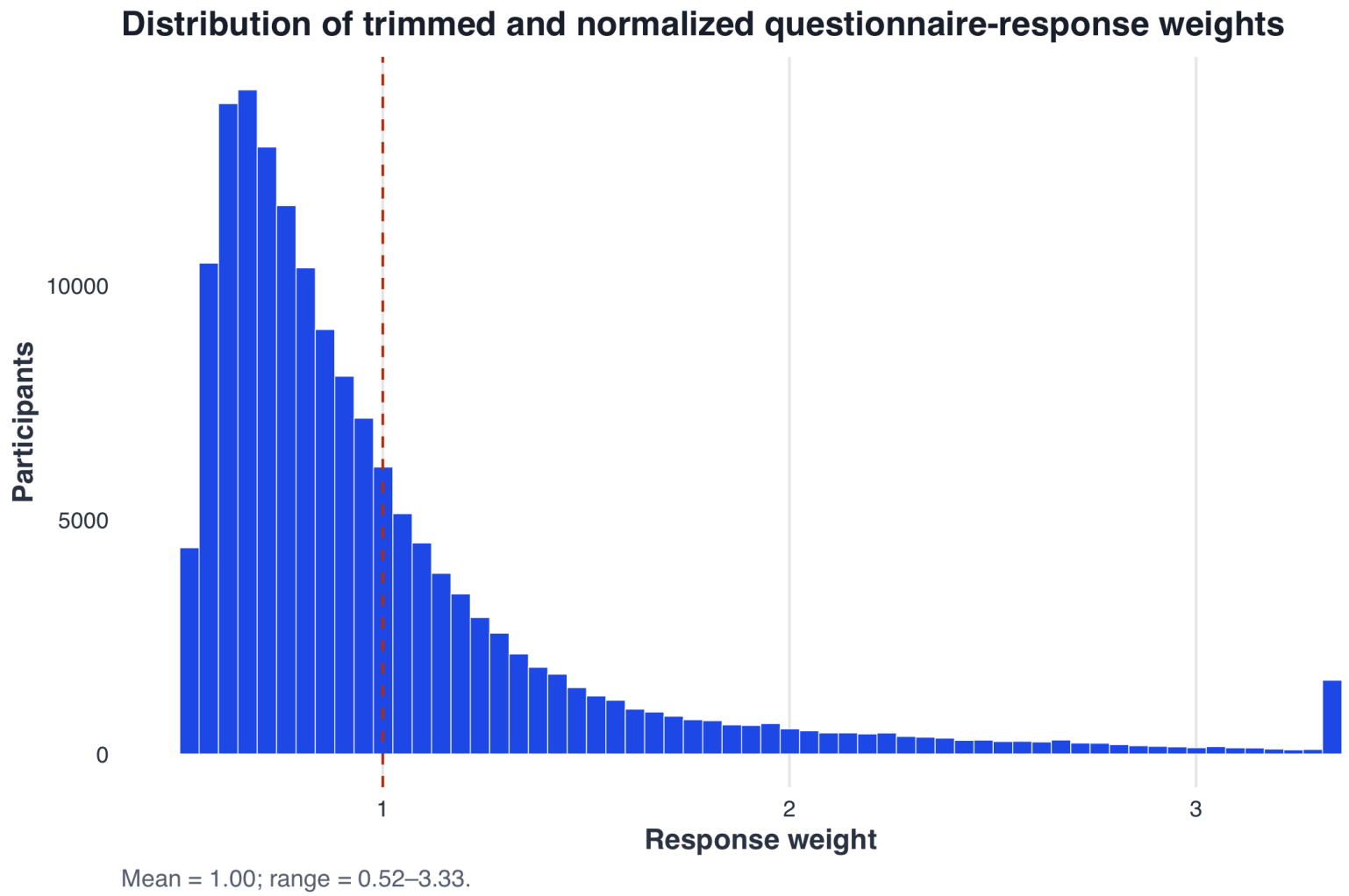

Figure S2. Distribution of trimmed and normalised questionnaire-response weights.

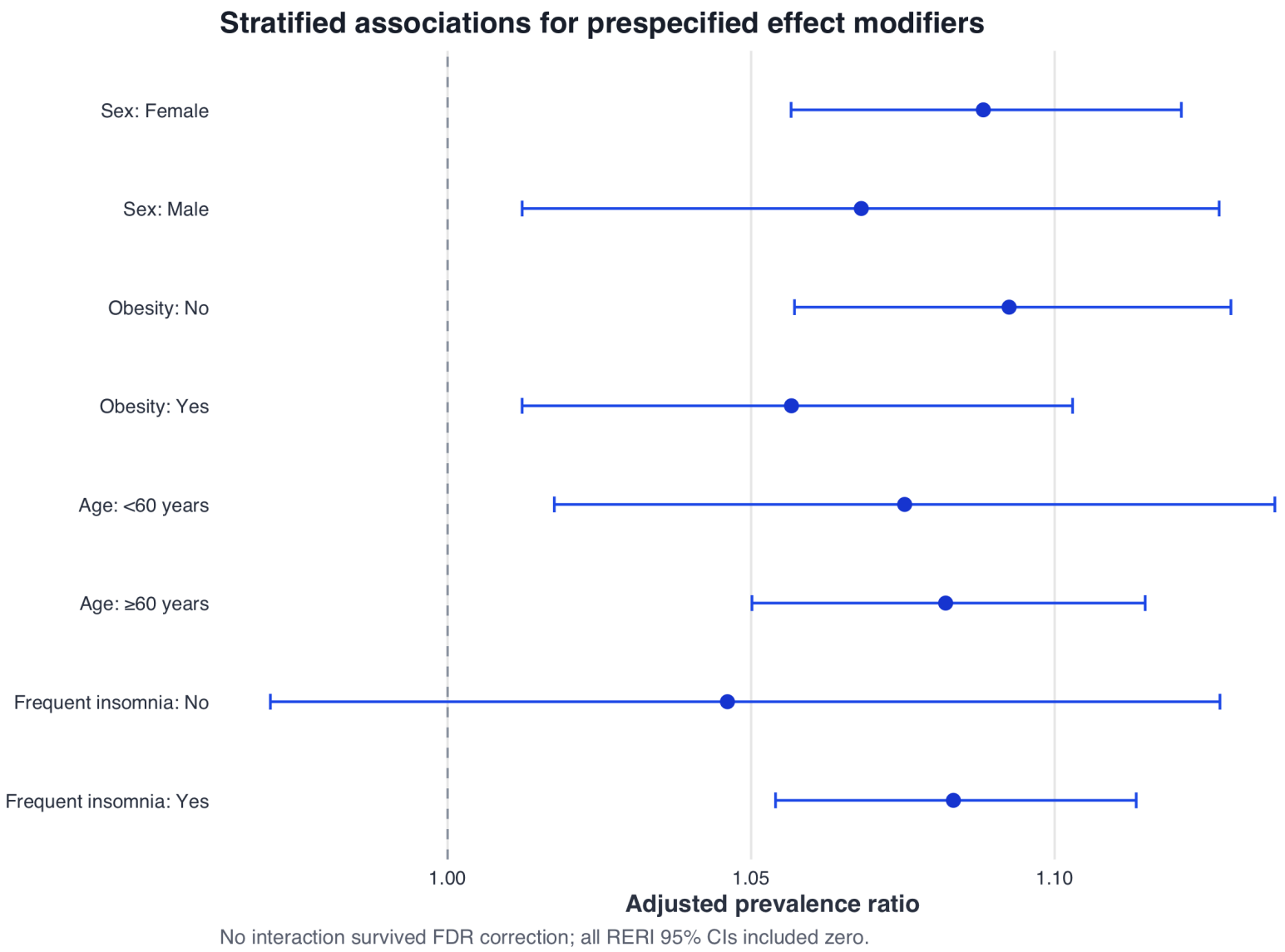

Figure S3. Nested urticaria stratum-specific associations.

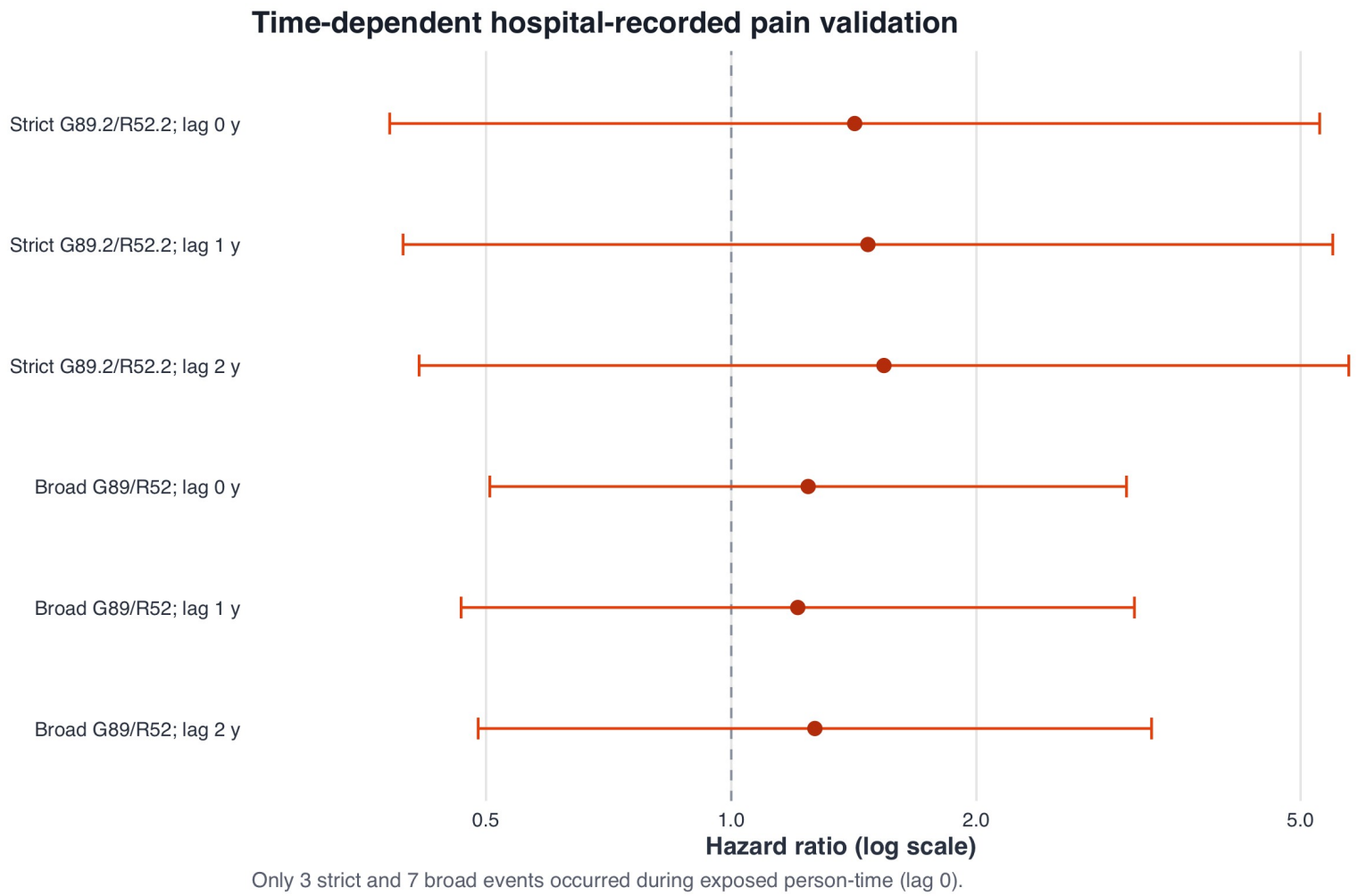

Figure S4. Nested time-dependent hospital-record pain sensitivity.