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Table S1. Summary of outcomes, exposures, predictors, and related variables according to each study step

| STEP | Study design / purpose | Outcomes (primary / secondary) | Exposures | Predictors / Independent variables | Potential confounders | Effect modifiers / Other relevant variables |
|---|---|---|---|---|---|---|
| **STEP 1** | Cross-sectional comparison between AD patients and healthy controls | Primary: Mechanical alloknesis (MA) score (NRS) - Secondary: Spontaneous itch (NRS), skin dryness (TEWL, SC hydration) | None (single-visit observational study) | Group (AD vs. control), skin site (lesional vs. non-lesional) | Age, sex, ambient conditions (temperature, humidity, sweating rate [not measured]) | None explicitly analyzed |
| **STEP 2** | Cross-sectional sub-analysis in AD patients | Primary: Correlation coefficients between MA and disease-related parameters | None (single-visit blood sampling) | EASI, serum TARC total IgE, eosinophil count | Age, sex, disease severity, duration | None explicitly analyzed |
| **STEP 3** | Prospective cohort study (before–after evaluation of dupilumab treatment) | Primary: Change in MA scores pre- and post-dupilumab - Secondary: Changes in TARC, IgE, eosinophil count | Dupilumab administration (anti-IL-4Rα antibody) | Treatment duration, baseline TARC, baseline severity | Age, sex, concomitant topical therapy | Possible treatment response heterogeneity (baseline biomarker level) |

**Abbreviations**: AD, atopic dermatitis; EASI, Eczema Area and Severity Index; Eos, eosinophil count; IgE, immunoglobulin E; TARC, thymus- and activation-regulated chemokine.

Table S2. Summary of descriptive and inferential statistics for Fig. 2a (spontaneous itch score)

| Variable (Outcome) | Group | Mean (95% CI) | Comparison (post hoc) | P-value | Test |
|---|---|---|---|---|---|
| Spontaneous itch score | Healthy control | 0.00 (0.00–0.00) | HC vs NL | =0.999 | One-way ANOVA (Tukey post hoc) |
| | AD non-lesion | 0.00 (0.00–0.00) | HC vs L | **<0.0001**** | |
| | AD lesion | 2.63 (1.76–3.49) | NL vs L | **<0.0001**** | |

**Abbreviations**: AD, atopic dermatitis; CI, Confidence Interval; HC, healthy control; NL, non-lesional skin; L, lesional skin.

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Table S3: Summary of descriptive and inferential statistics for Fig. 2b (Comparison of MA scores between skin lesion conditions at the same force)

| Force (mN) | Group | Mean (95% CI) | P-value (post hoc: HC vs NL / HC vs L / NL vs L) | Test |
|---|---|---|---|---|
| **5.8** | Healthy control | 0.42 (0.15–0.69) | HC vs NL: =0.999 / HC vs L: **<0.0001**** / NL vs L: **<0.0001**** | One-way ANOVA (Tukey post hoc) |
| | AD non-lesion | 0.17 (0.06–0.28) | | |
| | AD lesion | 2.91 (1.98–3.83) | | |
| **9.8** | Healthy control | 0.90 (0.46–1.34) | HC vs NL: =0.999 / HC vs L: **0.0001**** / NL vs L: **<0.0001**** | 〃 |
| | AD non-lesion | 0.58 (0.27–0.88) | | |
| | AD lesion | 3.17 (2.19–4.14) | | |
| **13.7** | Healthy control | 1.42 (0.81–2.03) | HC vs NL: 0.981 / HC vs L: **0.002**** / NL vs L: **<0.0001**** | 〃 |
| | AD non-lesion | 0.82 (0.37–1.27) | | |
| | AD lesion | 3.42 (2.46–4.38) | | |
| **19.6** | Healthy control | 1.55 (0.91–2.19) | HC vs NL: =0.999 / HC vs L: <**0.0001**** / NL vs L**: <0.0001**** | 〃 |
| | AD non-lesion | 1.31 (0.74–1.88) | | |
| | AD lesion | 3.93 (2.90–4.95) | | |

**Abbreviations:** AD, atopic dermatitis; CI, Confidence Interval; HC, healthy control; NL, non-lesional skin; L, lesional skin.

Table S4: Summary of descriptive and inferential statistics for Figure 2b (Effect of different forces on MA scores under the same lesion conditions)

| Group | Force (mN) | Mean (95% CI) | P-value (vs 5.8 mN) | Test |
|---|---|---|---|---|
| Healthy control | 5.8 | 0.42 (0.15–0.69) | — | One-way ANOVA (Dunnett's multiple comparisons test vs 5.8 mN) |
| | 9.8 | 0.90 (0.46–1.35) | 0.384 | 〃 |
| | 13.7 | 1.42 (0.81–2.03) | **0.015 *** | 〃 |
| | 19.6 | 1.55 (0.91–2.19) | **0.005**** | 〃 |
| AD non-lesion | 5.8 | 0.17 (0.06–0.28) | — | One-way ANOVA (Dunnett's multiple comparisons test vs 5.8 mN) |
| | 9.8 | 0.576 (0.27–0.88) | 0.326 | 〃 |
| | 13.7 | 0.82 (0.37–1.27) | 0.053 | 〃 |
| | 19.6 | 1.31 (0.74–1.88) | **0.0002**** | 〃 |
| AD lesion | 5.8 | 2.91 (1.98–3.83) | — | One-way ANOVA (Dunnett's multiple comparisons test vs 5.8 mN) |
| | 9.8 | 3.17 (2.19–4.14) | 0.962 | 〃 |
| | 13.7 | 3.42 (2.46–4.38) | 0.790 | 〃 |
| | 19.6 | 3.93 (2.90–4.95) | 0.303 | 〃 |

**Abbreviations:** AD, atopic dermatitis. CI, Confidence Interval.

Table S5: Summary of descriptive and inferential statistics for Fig. ~~3a~~2c (TEWL values)

| **Variable (Outcome)** | **Group** | **Mean (95% CI)** | **P-value (post hoc: HC vs NL / HC vs L / NL vs L)** | **Test** |
|---|---|---|---|---|
| TEWL | Healthy control | 30.51 (19.67–41.36) | HC vs NL: 0.380 / HC vs L: 0.472 / NL vs L: **0.032*** | One-way ANOVA (Tukey post hoc) |
| | AD non-lesion | 20.13 (14.46–25.80) | | |
| | AD lesion | 39.70 (24.54–54.86) | | |

**Abbreviations:** AD, atopic dermatitis; CI, Confidence Interval; HC, healthy control; NL, non-lesional skin; L, lesional skin.

Table S6: Summary of descriptive and inferential statistics for Fig. ~~3b~~2d (SC hydration values)

| **Variable (Outcome)** | **Group** | **Mean (95% CI)** | **P-value (post hoc: HC vs NL / HC vs L / NL vs L)** | **Test** |
|---|---|---|---|---|
| SC hydration | Healthy control | 46.49 (38.33 – 54.66) | HC vs NL: **<0.001**** / HC vs L: **<0.0001**** / NL vs L: 0.408 | One-way ANOVA (Tukey post hoc) |
| | AD non-lesion | 28.52 (21.91 – 35.13) | | |
| | AD lesion | 22.48 (16.65– 28.32) | | |

**Abbreviations:** AD, atopic dermatitis; CI, Confidence Interval; HC, healthy control; NL, non-lesional skin; L, lesional skin.

Table S7. Correlation between skin dryness parameters and itch NRS scores in non-lesional and lesional skin of STEP 1 AD patients.

| NRS | Non-lesion | | | | Lesion | | | |
|---|---|---|---|---|---|---|---|---|
| | TEWL | | SC hydration | | TEWL | | SC hydration | |
| | r | P-value | r | P-value | r | P-value | r | P-value |
| Spontaneous itch | | | | | 0.215 | 0.245 | -0.274 | 0.136 |
| 5.8 mN | -0.055 | 0.765 | 0.095 | 0.604 | 0.088 | 0.637 | -0.188 | 0.311 |
| 9.8 mN | 0.013 | 0.944 | 0.151 | 0.382 | 0.071 | 0.706 | -0.161 | 0.386 |
| 13.7 mN | -0.081 | 0.661 | 0.057 | 0.758 | 0.194 | 0.297 | -0.138 | 0.459 |
| 19.6 mN | -0.051 | 0.781 | 0.153 | 0.404 | 0.126 | 0.498 | -0.205 | 0.269 |

Correlation coefficients (r) and p-values are shown for relationships between TEWL or SC hydration and itch NRS scores (spontaneous itch and MA) in non-lesional and lesional skin. Correlation coefficients were calculated using Pearson's correlation test.

**Abbreviations:** TEWL, transepidermal water loss; SC, stratum corneum; NRS, numeric rating scale; MA, mechanical alloknesis; AD, atopic dermatitis.

Table S8: Summary of descriptive and inferential statistics for changes over time associated with dupilumab administration for Fig. 43a (level of spontaneous itch)

| Time point | Mean (95% CI) | P-value (vs. pre) | Test |
|---|---|---|---|
| Pre | 4.46 (3.49–5.44) | — | One-way ANOVA (Dunnett's multiple comparisons test) |
| 1st | 3.31 (1.68–4.93) | 0.624 | 〃 |
| 2nd | 2.86 (0.90–4.81) | 0.443 | 〃 |
| 3rd | 1.82 (0.32–3.32) | **0.011*** | 〃 |
| 4th | 2.86 (0.76–4.95) | 0.443 | 〃 |
| 5th | 1.67 (0.51–2.82) | **0.011 *** | 〃 |
| 6th | 2.50 (1.05–3.95) | 0.271 | 〃 |
| 7th | 2.00 (0.52–3.48) | 0.087 | 〃 |
| 8th | 2.00 (0.67–3.33) | 0.087 | 〃 |
| 9th | 2.17 (0.94–3.39) | 0.131 | 〃 |

**Abbreviation:** CI, Confidence Interval.

Table S9: Summary of descriptive and inferential statistics for changes over time associated with dupilumab administration for Fig. 43b (MA scores at 5.8 mN bending force)

| Time point | Mean (95% CI) | P-value (vs. pre) | Test |
|---|---|---|---|
| Pre | 4.82 (3.55–6.09) | — | One-way ANOVA (Dunnett's multiple comparisons test) |
| 1st | 3.36 (1.64–5.08) | 0.459 | 〃 |
| 2nd | 2.57 (0.63–4.51) | 0.184 | 〃 |
| 3rd | 1.88 (0.51–3.25) | **0.010*** | 〃 |
| 4th | 2.81 (0.61–5.01) | 0.295 | 〃 |
| 5th | 2.22 (0.54–3.91) | **0.049*** | 〃 |
| 6th | 2.28 (0.66–3.90) | 0.128 | 〃 |
| 7th | 2.22 (0.26–4.18) | 0.114 | 〃 |
| 8th | 1.78 (0.56–3.00) | **0.040 *** | 〃 |
| 9th | 2.67 (1.07–4.26) | 0.276 | 〃 |

**Abbreviation:** CI, Confidence Interval.

Table S10: Summary of descriptive and inferential statistics for changes over time associated with dupilumab administration for Fig. 43c (MA scores at 9.8 mN bending force)

| Time point | Mean (95% CI) | P-value (vs. pre) | Test |
|---|---|---|---|
| Pre | 4.82 (3.55 – 6.09) | — | One-way ANOVA (Dunnett's multiple comparisons test) |
| 1st | 3.36 (1.64 – 5.08) | 0.415 | 〃 |
| 2nd | 2.57 (0.63 – 4.51) | 0.154 | 〃 |
| 3rd | 1.88 (0.51 – 3.25) | **0.007**** | 〃 |
| 4th | 2.81 (0.61– 5.01) | 0.256 | 〃 |
| 5th | 1.89 (0.74 – 3.04) | **0.013*** | 〃 |
| 6th | 2.28 (0.66 – 3.90) | 0.105 | 〃 |
| 7th | 2.22 (0.26 – 4.18) | 0.092 | 〃 |
| 8th | 1.78 (0.55 – 3.00) | **0.030*** | 〃 |
| 9th | 2.61 (1.24 – 3.98) | 0.214 | 〃 |

**Abbreviation:** CI, Confidence Interval.

Table S11: Summary of descriptive and inferential statistics for changes over time associated with dupilumab administration for Fig. 43d (MA scores at 13.7 mN bending force)

| Time point | Mean (95% CI) | P-value (vs pre) | Test |
|---|---|---|---|
| Pre | 5.18 (3.70 – 6.66) | — | One-way ANOVA (Dunnett's multiple comparisons test) |
| 1st | 4.21 (2.53 – 5.88) | 0.858 | 〃 |
| 2nd | 2.62 (2.93 – 4.31) | 0.086 | 〃 |
| 3rd | 3.09 (1.59 – 4.60) | 0.129 | 〃 |
| 4th | 3.43 (1.30 – 5.56) | 0.445 | 〃 |
| 5th | 2.48 (1.17 – 3.80) | **0.034*** | 〃 |
| 6th | 3.22 (1.79 – 4.65) | 0.373 | 〃 |
| 7th | 2.56 (0.98 – 4.13) | 0.102 | 〃 |
| 8th | 2.33 (0.75 – 3.91) | 0.060 | 〃 |
| 9th | 2.78 (1.28 – 4.27) | 0.164 | 〃 |

**Abbreviation:** CI, Confidence Interval.

Table S12: Summary of descriptive and inferential statistics for changes over time associated with dupilumab administration for Fig. 43e (MA scores at 19.6 mN bending force)

| Time point | Mean (95% CI) | P-value (vs pre) | Test |
|---|---|---|---|
| Pre | 5.97 (4.73 – 7.22) | — | One-way ANOVA (Dunnett's multiple comparisons test) |
| 1st | 4.54 (2.81 – 6.27) | 0.454 | 〃 |
| 2nd | 2.91 (1.15 – 4.66) | **0.020*** | 〃 |
| 3rd | 3.46 (1.91 – 5.00) | **0.034*** | 〃 |
| 4th | 4.33 (2.27 – 6.40) | 0.508 | 〃 |
| 5th | 3.07 (1.65 – 4.50) | **0.016*** | 〃 |
| 6th | 3.43 (2.42 – 4.45) | 0.114 | 〃 |
| 7th | 2.72 (1.30 – 4.15) | **0.019*** | 〃 |
| 8th | 2.67 (0.71 – 4.62) | **0.016*** | 〃 |
| 9th | 2.89 (1.33 – 4.45) | **0.030*** | 〃 |

**Abbreviation:** CI, Confidence Interval.

Table S13. Correlation between the number of dupilumab doses and itch NRS scores in STEP 3 AD patients.

| | | From pre-dose to 5th dose | | From 5th to 9th dose | |
|---|---|---|---|---|---|
| | | r | P-value | r | P-value |
| NRS | Spontaneous itch | **-0.388** | **0.006**** | 0.024 | 0.898 |
| | 5.8 mN | **-0.360** | **0.012*** | 0.023 | 0.903 |
| | 9.8 mN | **-0.359** | **0.012*** | -0.141 | 0.441 |
| | 13.7 mN | **-0.299** | **0.042*** | -0.122 | 0.507 |
| | 19.6 mN | **-0.370** | **0.009**** | -0.251 | 0.165 |

Correlation coefficients (r) and p-values are shown for relationships between the cumulative number of dupilumab administrations and itch NRS scores (spontaneous itch and MA) from baseline to the 5th dose and from the 5th to the 9th dose. Correlation coefficients were calculated using Pearson's correlation test. * $p<0.05$, ** $p<0.01$.

**Abbreviations:** NRS, numeric rating scale; AD, atopic dermatitis; MA, mechanical alloknesis.

Table S14: Descriptive and inferential statistics of changes in Eos levels before and after dupilumab treatment (Fig. S3a)

| **Variable (Outcome)** | **Condition** | **Mean (95% CI)** | **P-value** | **Test** |
|---|---|---|---|---|
| Blood eosinophil count (/μL) | Pre | 594.0 (346.8 – 841.2) | — | Paired t-test |
| | Post | 313.0 (190.8 – 435.2) | **0.052** | 〃 |

**Abbreviation:** CI, Confidence Interval.

Table S15: Descriptive and inferential statistics of changes in IgE levels before and after dupilumab treatment (Fig. S3b)

| Variable (Outcome) | Condition | Mean (95% CI) | P-value | Test |
|---|---|---|---|---|
| Serum total IgE (IU/mL) | Pre | 11219.0 (1902.0 – 20536.0) | — | Paired t-test |
| | Post | 2471.0 (453.2 – 4488.0) | **0.026*** | 〃 |

**Abbreviations:** CI, Confidence Interval; IgE, immunoglobulin E.

Table S16: Descriptive and inferential statistics of changes in TARC levels before and after dupilumab treatment (Fig. S3c)

| Variable (Outcome) | Condition | Mean (95% CI) | P-value | Test |
|---|---|---|---|---|
| Serum TARC (pg/mL) | Pre | 4223.0 (1335.0 – 7112.0) | — | Paired t-test |
| | Post | 293.6 (201.2 – 386.0) | **0.013*** | 〃 |

**Abbreviations:** CI, Confidence Interval; TARC, thymus- and activation-regulated chemokine.