Data Article

TH1 and TH2 cytokines dataset in insulin users with diabetes mellitus and newly diagnosed breast cancer

Zachary A.P. Wintroba, Jeffrey P. Hammel, George K. Nimako, Dan P. Gaile, Alan Forrest, Alice C. Ceacareanu

State University of New York at Buffalo, Department of Pharmacy Practice, NYS Center of Excellence in Bioinformatics and Life Sciences, 701 Ellicott Street, Buffalo, NY 14203, USA

Cleveland Clinic, Dept. of Biostatistics and Epidemiology, 9500 Euclid Ave., Cleveland, OH 44195, USA

State University of New York at Buffalo, Department of Biostatistics, 718 Kimball Tower, Buffalo, NY 14214, USA

The UNC Eshelman School of Pharmacy, Division of Pharmacotherapy and Experimental Therapeutics, Campus Box 7569, Chapel Hill, NC 27599, USA

Roswell Park Cancer Institute, Dept. of Pharmacy Services, Elm & Carlton Streets, Buffalo, NY 14263, USA

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A B S T R A C T

Exogenous insulin use may interfere with the T helper cells’ cytokine production. This dataset presents the relationship between pre-existing use of injectable insulin in women diagnosed with breast cancer and type 2 diabetes mellitus, the T-helper 1 and 2 produced cytokine profiles at the time of breast cancer diagnosis, and subsequent cancer outcomes. A Pearson correlation analysis evaluating the relationship between T-helper cytokines stratified by insulin use and controls is also provided.

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### Specifications Table

| Subject area | Clinical and Translational Research |
|--------------|-------------------------------------|
| More specific subject area | Biomarker Research, Cancer Epidemiology |
| Type of data | Tables |
| How data was acquired | Tumor registry query was followed by vital status ascertainment, and medical records review. Luminex®-based quantitation from plasma samples was conducted for the following T-helper 1 and T-helper 2 cytokines: Interleukine-2, soluble interleukine-2 receptor α, interleukine-12 subunit p40, interleukine-12 subunit p70, interferon α 2, interferon γ, chemokine ligand 10 (interferon gamma-induced protein 10), chemokine ligand 9 (monokine-induced by interferon γ), chemokine ligand 8 (interleukine-8) interleukine-5, interleukine-10, and interleukine-13. A Luminex®200TM instrument with Xponent 3.1 software was used to acquire all data. |
| Data format | Analyzed |
| Experimental factors | T-helper 1 and 2 produced cytokines were determined from the corresponding plasma samples collected at the time of breast cancer diagnosis. |
| Experimental features | The dataset included 97 adult females with diabetes mellitus and newly diagnosed breast cancer (cases) and 194 matched controls (breast cancer only). Clinical and treatment history were evaluated in relationship with cancer outcomes and factor-helper 1 and 2 produced cytokine profiles. A biomarker correlation analysis was also performed. |
| Data source location | United States, Buffalo, NY - 42° 53' 50.3592''N; 78° 52' 2.658''W |
| Data accessibility | The data is with this article |

### Value of the data

- This dataset represents the observed relationship between administration of exogenous insulin, circulating T-helper 1 and 2 produced cytokines at breast cancer diagnosis and cancer outcomes.
- The data we present here has the potential to guide future research evaluating the role of insulin in the modulation of type 1 and type 2 immunity.
- Our observations can assist further research exploring the relationship between insulin administration and T-helper-driven signaling in breast cancer occurrence.

### 1. Data

Reported data represents the observed association between pre-existing use of injectable insulin before breast cancer diagnosis and the T-helper 1 and 2 produced cytokine profiles upon cancer diagnosis in women with both breast cancer and diabetes mellitus (Table 1). Data in Table 2 includes the observed correlations between T-helper 1 and 2 cytokines stratified by diabetes mellitus pharmacotherapy and controls.

### 2. Experimental design, materials and methods

Evaluation of the association between profiles of T-helper 1 and 2 produced cytokines, injectable insulin use and BC outcomes was carried out under two protocols approved by both Roswell Park Cancer Institute (EDR154409 and NHR009010) and the State University of New York at Buffalo.
### Table 1

T-helper 1 and 2 produced cytokines' associations with insulin use.

| Biomarker | Biomarker Grouping | Concentration (ng/ml) | Control | No Insulin | Any Insulin | Unadjusted p-value (MVP) |
|-----------|-------------------|----------------------|---------|-----------|------------|-------------------------|
| IL-2 (pg/ml) | (25th–75th) | Median: 1.60 (1.60–3.2) | 1.60 (1.60–3.2) | 1.60 (1.60–3.2) | 0.680 | 0.970 | 0.860 | 0.920 |
|            | OS-Based | 0.10–34.18 | 189 (97.4%) | 72 (94.7%) | 19 (95.0%) | 0.350 | 0.470 | 0.800 | 0.410 |
|            | Optimization | 35.27–516.64 | 5 (2.6%) | 4 (5.3%) | 1 (5.0%) | 0.200 | 0.450 | 0.590 | 0.360 |
|            | DFS-Based | 0.10–1.94 | 131 (67.5%) | 49 (64.5%) | 13 (65.0%) | 0.630 | 0.820 | 0.970 | 0.880 |
|            | Optimization | 1.99–516.64 | 63 (32.5%) | 27 (35.5%) | 7 (35.0%) | 0.560 | 0.640 | 0.880 | 0.700 |
| sIL-2Rα (pg/ml) | (25th–75th) | Median: 3.20 (1.60–47.32) | 7.06 (1.60–60.70) | 49.52 (1.68–117.66) | 0.490 | 0.048 | 0.140 | 0.130 |
|            | Quartiles | 0.00–1.60 | 84 (43.3%) | 30 (39.5%) | 5 (25.0%) | 0.820 | 0.140 | 0.450 | 0.440 |
|            |            | 1.70–7.00 | 16 (8.2%) | 8 (10.5%) | 2 (10.0%) |
|            |            | 7.12–57.42 | 50 (25.8%) | 18 (23.7%) | 4 (20.0%) |
|            |            | 57.68 to ALQ | 20 (26.3%) | 9 (45.0%) |
|            | OS-Based | 0.00–63.34 | 155 (79.9%) | 57 (75.0%) | 11 (55.0%) | 0.380 | 0.021 | 0.090 | 0.044 |
|            | Optimization | 63.37 to ALQ | 39 (20.1%) | 19 (25.0%) | 9 (45.0%) | 0.130 | 0.012 | 0.070 | 0.021 |
|            | DFS-Based | 0.00–62.50 | 153 (78.9%) | 57 (75.0%) | 11 (55.0%) | 0.490 | 0.025 | 0.090 | 0.060 |
|            | Optimization | 62.65 to ALQ | 41 (21.1%) | 19 (25.0%) | 9 (45.0%) | 0.210 | 0.018 | 0.070 | 0.033 |
| IL-12p40 (pg/ml) | (25th–75th) | Median: 8.16 (1.75–30.81) | 12.67 (3.20–30.78) | 11.43 (5.43–24.29) | 0.170 | 0.380 | 0.920 | 0.320 |
|            | Quartiles | 1.25–3.20 | 74 (38.1%) | 20 (26.3%) | 4 (20.0%) | 0.210 | 0.230 | 0.620 | 0.230 |
|            |            | 3.94–9.74 | 29 (14.9%) | 13 (17.1%) | 6 (30.0%) |
|            |            | 9.94–30.67 | 42 (21.6%) | 24 (31.6%) | 5 (25.0%) |
|            | OS-Based | 1.25–3.12 | 53 (27.3%) | 14 (18.4%) | 3 (15.0%) | 0.130 | 0.240 | 1.000 | 0.200 |
|            | Optimization | 3.20–2045.71 | 141 (72.7%) | 62 (81.6%) | 17 (85.0%) | 0.260 | 0.190 | 0.890 | 0.330 |
|            | DFS-Based | 1.25–3.12 | 53 (27.3%) | 14 (18.4%) | 3 (15.0%) | 0.130 | 0.240 | 1.000 | 0.200 |
|            | Optimization | 3.20–2045.71 | 141 (72.7%) | 62 (81.6%) | 17 (85.0%) | 0.260 | 0.190 | 0.890 | 0.330 |
| IL-12p70 (pg/ml) | (25th–75th) | Median: 1.60 (1.60–6.85) | 2.81 (1.60–6.85) | 0.700 | 0.260 | 0.850 | 0.130 |
|            | OS-Based | 0.10–0.59 | 5 (2.6%) | 3 (3.9%) | 3 (15.0%) | 0.690 | 0.029 | 0.100 | 0.041 |
|            | Optimization | 0.70–2510.07 | 189 (97.4%) | 73 (96.1%) | 17 (85.0%) | 0.580 | 0.080 | 0.090 | 0.120 |
|            | DFS-Based | 0.10–2.20 | 120 (61.9%) | 36 (47.4%) | 9 (45.0%) | 0.031 | 0.150 | 0.850 | 0.052 |
|            | Optimization | 2.28–2510.07 | 74 (38.1%) | 40 (52.6%) | 11 (55.0%) | 0.090 | 0.260 | 0.900 | 0.160 |
| IFN-α2 (pg/ml) | (25th–75th) | Median: 7.24 (3.20–13.61) | 6.74 (3.20–17.55) | 12.49 (7.32–18.70) | 0.610 | 0.032 | 0.110 | 0.110 |
|            | Quartiles | 0.61–1.60 | 56 (28.9%) | 24 (31.6%) | 2 (10.0%) | 0.370 | 0.220 | 0.130 | 0.240 |
|            |            | 3.47–7.40 | 42 (21.6%) | 17 (22.4%) | 4 (20.0%) |
|            |            | 7.43–15.15 | 52 (26.8%) | 17 (28.9%) | 7 (35.0%) |
|            | OS-Based | 15.32–1800.18 | 44 (22.7%) | 22 (34.2%) | 3 (15.0%) | 0.780 | 0.120 | 0.110 |
|            | Optimization | 4.18–1880.18 | 131 (67.5%) | 50 (85.8%) | 17 (85.0%) | 0.430 | 0.130 | 0.110 | 0.200 |
|            | DFS-Based | 0.61–2.66 | 29 (14.9%) | 8 (10.5%) | 1 (5.0%) | 0.340 | 0.320 | 0.680 | 0.400 |
|            | Optimization | 2.93–1880.18 | 165 (85.1%) | 68 (89.5%) | 19 (95.0%) | 0.140 | 0.100 | 0.330 | 0.150 |
| IFN-γ (pg/ml) | (25th–75th) | Median: 13.32 (4.70–36.30) | 11.43 (2.55–41.45) | 7.59 (5.21–48.19) | 0.230 | 0.670 | 0.710 | 0.460 |
|            | Quartiles | 0.07–3.86 | 42 (21.6%) | 28 (36.8%) | 3 (15.0%) | 0.026 | 0.030 | 0.008 | 0.004 |
|            |            | 4.03–12.43 | 50 (25.8%) | 12 (15.8%) | 10 (50.0%) |
|            |            | 12.55–37.33 | 56 (28.9%) | 15 (19.7%) | 1 (5.0%) |

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| Biomarker | Biomarker Grouping | Concentration (ng/ml) | Control | No Insulin | Any Insulin | Unadjusted p-value (MVP) |
|-----------|-------------------|----------------------|---------|------------|-------------|-------------------------|
|           |                   |                      | p1      | p2         | p3          | Global Test             |
| CXCL-10   | Median (IP-10, pg/ml) | 488                  | 463     | 564        |             | 0.610 0.870 0.930 0.880  |
| Quartiles |                   | (347–814)            | (338–688) | (352–733) |             | (0.690 0.260 0.300 0.420) |
| OS-Based  | 376–646.43         | 6 (3.1%)             | 4 (5.3%) | 0 (0%)     |             | (0.370 0.320 0.120 0.310) |
| Optimization |                   | 206.34–646.43        | 4 (3.6%) | 7 (5.0%)   |             | (0.560 0.760 0.770 0.820) |
| CXCL-9    | Median (MIG, pg/ml) | 274                  | 154     | 439        |             | 0.190 0.190 0.070 0.140  |
| Quartiles |                   | (119–504)            | (83–540) | (142–644)  |             | (0.100 0.730 0.270 0.240) |
| OS-Based  | 428.9–3745.0       | 113 (58.2%)          | 43 (56.6%) | 11 (55.0%) |             | (0.730 0.520 0.700 0.810) |
| Optimization |                   | 549.1–3745.0         | 80 (41.2%) | 28 (36.8%) | 11 (55.0%) | (0.350 0.480 0.210 0.410) |
| CXCL-8    | Median (IL-8, pg/ml) | 4.44                 | 6.02    | 5.83       |             | 0.001 0.035 0.880 0.002  |
| Quartiles |                   | (2.5–6.8)            | (4.26–8.72) | (4.57–8.80) |             | (0.060 0.180 0.880 0.120) |
| OS-Based  | 19.66–74.69        | 7 (3.6%)             | 2 (2.6%) | 1 (5.0%)   |             | (0.640 0.570 0.330 0.830) |
| Optimization |                   | 19.66–74.69          | 7 (3.6%) | 2 (2.6%)   | 1 (5.0%)   | (0.640 0.570 0.330 0.830) |
| IL-5 (pg/ml) | Median, ng/ml     | 0.48                 | 0.45    | 0.45       |             | 0.039 0.730 0.570 0.130  |
| Quartiles |                   | (0.35–0.77)          | (0.3–0.77) | (0.3–0.76) |             | (0.390 0.330 0.130 0.270) |
| OS-Based  | 0.45–118.0        | 128 (66.0%)          | 39 (51.3%) | 12 (60.0%) |             | (0.090 0.660 0.630 0.240) |
| Optimization |                   | 0.45–118.0          | 128 (66.0%) | 39 (51.3%) | 12 (60.0%) | (0.090 0.660 0.630 0.240) |
| IL-10 (pg/ml) | Median, ng/ml    | 1.60                 | 1.95    | 3.23       |             | 0.680 0.130 0.330 0.350  |
| Quartiles |                   | (1.60–6.59)          | (1.60–9.31) | (2.67–9.13) |             | (0.500 0.500 0.790 0.610) |
| OS-Based  | 1.61–178         | 3 (1.5%)             | 2 (2.6%) | 0 (0%)     |             | 0.750 0.050 0.130 0.160  |
| Optimization |                   | 1.61–178          | 3 (1.5%) | 2 (2.6%)   | 0 (0%)     | 0.750 0.050 0.130 0.160  |
Demographic and clinical patient information was linked with cancer outcomes and profiles of T-helper 1 and 2 produced cytokines of corresponding plasma specimen harvested at BC diagnosis and banked in the Roswell Park Cancer Institute Data Bank and Bio-Repository.

2.1. Study population
All incident breast cancer cases diagnosed at Roswell Park Cancer Institute (01/01/2003-12/31/2009) were considered for inclusion (n=2194). Medical and pharmacotherapy history were used to determine the baseline presence of diabetes.

2.2. Inclusion and exclusion criteria
All adult women with pre-existing diabetes at breast cancer diagnosis having available banked treatment-naïve plasma specimens (blood collected prior to initiation of any cancer-related therapy - surgery, radiation or pharmacotherapy) in the Institute’s Data Bank and Bio-Repository were included.

Subjects were excluded if they had prior cancer history or unclear date of diagnosis, incomplete clinical records, type 1 or unclear diabetes status. For a specific breakdown of excluded subjects, please see the original research article by Wintrob et al. [1].

A total of 97 female subjects with breast cancer and baseline diabetes mellitus were eligible for inclusion in this analysis.

2.3. Control-matching approach
Each of the 97 adult female subjects with breast cancer and diabetes mellitus (defined as “cases”) was matched with two other female subjects diagnosed with breast cancer, but without baseline diabetes mellitus (defined as “controls”). The following matching criteria were used: age at diagnosis,
Table 2
T-helper 1 and 2 produced cytokines' correlations by insulin use.

| Compared Biomarkers | Group | Unadjusted Correlation | Adjusted Correlation |
|---------------------|-------|-------------------------|----------------------|
|                     |       | Pearson Correlation     | 95% Confidence Interval | p-value | Pearson Correlation | 95% Confidence Interval | p-value |
| IL-2 sIL-2Ra        | All Subjects (n=291) | 0.268 | 0.158 to 0.371 | < 0.001 | 0.278 | 0.168 to 0.381 | < 0.001 |
|                     | Controls (n=194) | 0.197 | 0.058 to 0.329 | 0.006 | 0.212 | 0.072 to 0.344 | 0.003 |
|                     | No Insulin (n=77) | 0.648 | 0.496 to 0.761 | < 0.001 | 0.649 | 0.494 to 0.764 | < 0.001 |
|                     | Any Insulin (n=20) | 0.001 | −0.442 to 0.443 | 0.996 | −0.075 | −0.537 to 0.421 | 0.771 |
| IL-2 IL-12p40       | All Subjects (n=291) | 0.454 | 0.357 to 0.540 | < 0.001 | 0.454 | 0.357 to 0.541 | < 0.001 |
|                     | Controls (n=194) | 0.711 | 0.634 to 0.775 | < 0.001 | 0.722 | 0.647 to 0.784 | < 0.001 |
|                     | No Insulin (n=77) | 0.406 | 0.200 to 0.577 | < 0.001 | 0.416 | 0.207 to 0.588 | < 0.001 |
|                     | Any Insulin (n=20) | 0.871 | 0.696 to 0.948 | < 0.001 | 0.879 | 0.689 to 0.956 | < 0.001 |
| IL-2 IL-12p70       | All Subjects (n=291) | 0.250 | 0.139 to 0.354 | < 0.001 | 0.253 | 0.142 to 0.358 | < 0.001 |
|                     | Controls (n=194) | 0.461 | 0.342 to 0.565 | < 0.001 | 0.463 | 0.344 to 0.568 | < 0.001 |
|                     | No Insulin (n=77) | 0.224 | 0.000 to 0.427 | 0.048 | 0.233 | 0.004 to 0.438 | 0.044 |
|                     | Any Insulin (n=20) | 0.994 | 0.984 to 0.998 | < 0.001 | 0.995 | 0.986 to 0.998 | < 0.001 |
| IL-2 IFN-α2         | All Subjects (n=291) | 0.339 | 0.233 to 0.437 | < 0.001 | 0.339 | 0.232 to 0.437 | < 0.001 |
|                     | Controls (n=194) | 0.494 | 0.380 to 0.594 | < 0.001 | 0.493 | 0.378 to 0.594 | < 0.001 |
|                     | No Insulin (n=77) | 0.523 | 0.339 to 0.669 | < 0.001 | 0.530 | 0.343 to 0.676 | < 0.001 |
|                     | Any Insulin (n=20) | 0.975 | 0.936 to 0.990 | < 0.001 | 0.983 | 0.951 to 0.994 | < 0.001 |
| IL-2 IFN-γ          | All Subjects (n=291) | 0.379 | 0.276 to 0.473 | < 0.001 | 0.387 | 0.285 to 0.481 | < 0.001 |
|                     | Controls (n=194) | 0.529 | 0.419 to 0.623 | < 0.001 | 0.531 | 0.421 to 0.626 | < 0.001 |
|                     | No Insulin (n=77) | 0.511 | 0.324 to 0.659 | < 0.001 | 0.517 | 0.327 to 0.667 | < 0.001 |
|                     | Any Insulin (n=20) | 0.841 | 0.635 to 0.935 | < 0.001 | 0.871 | 0.671 to 0.953 | < 0.001 |
| IL-2 CXCL-10 (IP-10)| All Subjects (n=291) | −0.027 | −0.142 to 0.088 | 0.641 | −0.031 | −0.146 to 0.085 | 0.603 |
|                     | Controls (n=194) | 0.011 | −0.130 to 0.152 | 0.874 | 0.009 | −0.130–0.151 | 0.898 |
|                     | No Insulin (n=77) | −0.079 | −0.297 to 0.148 | 0.495 | −0.079 | −0.302–0.152 | 0.502 |
|                     | Any Insulin (n=20) | 0.104 | −0.355 to 0.522 | 0.660 | 0.179 | −0.330–0.608 | 0.484 |
# Table 2 (continued)

| Compared Biomarkers | Group          | Unadjusted Correlation | Adjusted Correlation |
|---------------------|----------------|-------------------------|----------------------|
|                     |                | Pearson Correlation     | 95% Confidence Interval | p-value | Pearson Correlation | 95% Confidence Interval | p-value |
| IL-2 CXCL-9 (MIG)   | All Subjects   | 0.192                   | 0.079 to 0.300        | 0.001    | 0.183               | 0.069 to 0.293          | 0.002    |
|                     | (n=291)        | Controls (n=194)        | 0.170                 | 0.030 to 0.303 | 0.018    | 0.160               | 0.018 to 0.295          | 0.027    |
|                     | No Insulin (n=77) | 0.053                 | -0.173 to 0.273       | 0.649    | 0.056               | -0.175 to 0.280         | 0.637    |
|                     | Any Insulin (n=20) | 0.662             | 0.310 to 0.854        | < 0.001  | 0.625               | 0.207 to 0.850          | 0.005    |
| IL-2 CXCL-8 (IL-8)  | All Subjects   | 0.163                   | 0.049 to 0.273        | 0.005    | 0.159               | 0.044 to 0.270          | 0.007    |
|                     | (n=291)        | Controls (n=194)        | 0.379                 | 0.252 to 0.494 | < 0.001  | 0.396               | 0.269 to 0.509          | < 0.001  |
|                     | No Insulin (n=77) | 0.090                 | -0.136 to 0.308       | 0.432    | 0.076               | -0.155 to 0.299         | 0.519    |
|                     | Any Insulin (n=20) | 0.797            | 0.548 to 0.916        | < 0.001  | 0.801               | 0.521 to 0.925          | < 0.001  |
| IL-2 IL-5           | All Subjects   | 0.082                   | -0.034 to 0.195       | 0.164    | 0.080               | -0.036 to 0.193         | 0.177    |
|                     | (n=291)        | Controls (n=194)        | 0.060                 | -0.082 to 0.199 | 0.406    | 0.057               | -0.086 to 0.197         | 0.433    |
|                     | No Insulin (n=77) | 0.147                 | -0.079 to 0.359       | 0.199    | 0.156               | -0.075 to 0.371         | 0.182    |
|                     | Any Insulin (n=20) | 0.554            | 0.148 to 0.801        | 0.008    | 0.517               | 0.048 to 0.799          | 0.028    |
| IL-2 IL-10          | All Subjects   | 0.174                   | 0.060 to 0.283        | 0.003    | 0.180               | 0.066 to 0.289          | 0.002    |
|                     | (n=291)        | Controls (n=194)        | 0.553                 | 0.447 to 0.644 | < 0.001  | 0.565               | 0.460 to 0.654          | < 0.001  |
|                     | No Insulin (n=77) | 0.149                 | -0.078 to 0.361       | 0.194    | 0.155               | -0.077 to 0.370         | 0.186    |
|                     | Any Insulin (n=20) | 0.364            | -0.094 to 0.694       | 0.107    | 0.471               | -0.013 to 0.776         | 0.049    |
| IL-2 IL-13          | All Subjects   | 0.102                   | -0.013 to 0.214       | 0.082    | 0.111               | -0.005 to 0.224         | 0.059    |
|                     | (n=291)        | Controls (n=194)        | 0.235                 | 0.098 to 0.364 | < 0.001  | 0.241               | 0.103 to 0.371          | < 0.001  |
|                     | No Insulin (n=77) | 0.246                 | 0.023 to 0.445        | 0.030    | 0.252               | 0.024 to 0.454          | 0.029    |
|                     | Any Insulin (n=20) | 0.715            | 0.399 to 0.879        | < 0.001  | 0.788               | 0.495 to 0.920          | < 0.001  |
| sIL-2Rx IL-12p40    | All Subjects   | 0.355                   | 0.251 to 0.452        | < 0.001  | 0.357               | 0.252 to 0.454          | < 0.001  |
|                     | (n=291)        | Controls (n=194)        | 0.142                 | 0.001 to 0.277 | 0.048    | 0.145               | 0.003 to 0.281          | 0.044    |
|                     | No Insulin (n=77) | 0.770                 | 0.660 to 0.848        | < 0.001  | 0.775               | 0.664 to 0.853          | < 0.001  |
|                     | Any Insulin (n=20) | 0.301            | -0.163 to 0.656       | 0.188    | 0.273               | -0.239 to 0.666         | 0.279    |
Table 2 (continued)

| Compared Biomarkers | Group                  | Unadjusted Correlation | Adjusted Correlation |
|---------------------|------------------------|-------------------------|----------------------|
|                     |                        | Pearson Correlation     | 95% Confidence Interval | p-value | Pearson Correlation | 95% Confidence Interval | p-value |
| sIL-2Rα IL-12p70    | All Subjects (n=291)   | 0.210                   | 0.097 to 0.317        | < 0.001 | 0.208              | 0.095 to 0.316           | < 0.001 |
|                     | Controls (n=194)       | 0.009                   | −0.132 to 0.150       | 0.896   | 0.012              | −0.130 to 0.154          | 0.868   |
|                     | No Insulin (n=77)      | 0.600                   | 0.434 to 0.726        | < 0.001 | 0.606              | 0.438 to 0.733           | < 0.001 |
|                     | Any Insulin (n=20)     | −0.035                  | −0.470 to 0.414       | 0.884   | −0.122             | −0.569 to 0.381          | 0.636   |
| sIL-2Rα IFN-α2      | All Subjects (n=291)   | 0.164                   | 0.050 to 0.274        | 0.005   | 0.165              | 0.050 to 0.275           | 0.005   |
|                     | Controls (n=194)       | 0.042                   | −0.100 to 0.182       | 0.563   | 0.046              | −0.096 to 0.187          | 0.526   |
|                     | No Insulin (n=77)      | 0.744                   | 0.624 to 0.830        | < 0.001 | 0.750              | 0.629 to 0.835           | < 0.001 |
|                     | Any Insulin (n=20)     | 0.138                   | −0.325 to 0.547       | 0.558   | 0.028              | −0.459 to 0.502          | 0.914   |
| sIL-2Rα IFN-γ       | All Subjects (n=291)   | 0.468                   | 0.373 to 0.553        | < 0.001 | 0.466              | 0.371 to 0.552           | < 0.001 |
|                     | Controls (n=194)       | 0.466                   | 0.348 to 0.569        | < 0.001 | 0.469              | 0.350 to 0.572           | < 0.001 |
|                     | No Insulin (n=77)      | 0.629                   | 0.471 to 0.747        | < 0.001 | 0.635              | 0.476 to 0.754           | < 0.001 |
|                     | Any Insulin (n=20)     | 0.114                   | −0.346 to 0.530       | 0.628   | 0.243              | −0.269 to 0.648          | 0.339   |
| sIL-2Rα CXCL-10 (IP-10) | All Subjects (n=291) | −0.039                  | −0.153 to 0.077       | 0.511   | −0.032             | −0.147 to 0.084          | 0.587   |
|                     | Controls (n=194)       | −0.038                  | −0.178 to 0.104       | 0.599   | −0.027             | −0.168 to 0.115          | 0.709   |
|                     | No Insulin (n=77)      | 0.014                   | −0.211 to 0.237       | 0.905   | 0.011              | −0.218 to 0.239          | 0.923   |
|                     | Any Insulin (n=20)     | −0.213                  | −0.599 to 0.254       | 0.361   | 0.231              | −0.281 to 0.640          | 0.364   |
| sIL-2Rα CXCL-9 (MIG) | All Subjects (n=291)   | 0.119                   | 0.004 to 0.231        | 0.042   | 0.123              | 0.007 to 0.235           | 0.037   |
|                     | Controls (n=194)       | 0.150                   | 0.009 to 0.285        | 0.036   | 0.158              | 0.016 to 0.293           | 0.029   |
|                     | No Insulin (n=77)      | 0.073                   | −0.154 to 0.292       | 0.528   | 0.075              | −0.156 to 0.299          | 0.521   |
|                     | Any Insulin (n=20)     | 0.021                   | −0.426 to 0.459       | 0.931   | −0.145             | −0.585 to 0.360          | 0.572   |
| sIL-2Rα CXCL-8 (IL-8) | All Subjects (n=291)  | 0.146                   | 0.032 to 0.257        | 0.012   | 0.155              | 0.040 to 0.266           | 0.008   |
|                     | Controls (n=194)       | 0.149                   | 0.008 to 0.284        | 0.038   | 0.150              | 0.008 to 0.286           | 0.037   |
|                     | No Insulin (n=77)      | 0.298                   | 0.079 to 0.489        | 0.008   | 0.301              | 0.077 to 0.495           | 0.008   |
|                     | Any Insulin (n=20)     | −0.122                  | −0.536 to 0.339       | 0.604   | −0.283             | −0.672 to 0.229          | 0.262   |
| Compared Biomarkers | Group | Unadjusted Correlation | Adjusted Correlation |
|---------------------|-------|------------------------|----------------------|
|                     |       | Pearson Correlation    | 95% Confidence Interval | p-value | Pearson Correlation | 95% Confidence Interval | p-value |
| sIL-2Rα IL-5        | All Subjects (n=291) | 0.091 | −0.024 to 0.204 | 0.121 | 0.092 | −0.023 to 0.206 | 0.117 |
|                     | Controls (n=194) | −0.023 | −0.163 to 0.118 | 0.752 | −0.020 | −0.161 to 0.123 | 0.788 |
|                     | No Insulin (n=77) | 0.619 | 0.459 to 0.741 | < 0.001 | 0.625 | 0.463 to 0.747 | < 0.001 |
|                     | Any Insulin (n=20) | 0.560 | 0.156 to 0.803 | 0.008 | 0.562 | 0.112 to 0.821 | 0.014 |
| sIL-2Rα IL-10       | All Subjects (n=291) | 0.236 | 0.124 to 0.341 | < 0.001 | 0.234 | 0.122 to 0.340 | < 0.001 |
|                     | Controls (n=194) | 0.054 | −0.088 to 0.193 | 0.456 | 0.053 | −0.090 to 0.193 | 0.470 |
|                     | No Insulin (n=77) | 0.605 | 0.440 to 0.730 | < 0.001 | 0.608 | 0.441 to 0.734 | < 0.001 |
|                     | Any Insulin (n=20) | −0.101 | −0.520 to 0.357 | 0.668 | 0.282 | −0.229 to 0.672 | 0.263 |
| sIL-2Rα IL-13       | All Subjects (n=291) | 0.050 | −0.065 to 0.164 | 0.391 | 0.046 | −0.070 to 0.161 | 0.433 |
|                     | Controls (n=194) | −0.014 | −0.155 to 0.127 | 0.841 | −0.019 | −0.161 to 0.123 | 0.792 |
|                     | No Insulin (n=77) | 0.555 | 0.378 to 0.693 | < 0.001 | 0.558 | 0.377 to 0.697 | < 0.001 |
|                     | Any Insulin (n=20) | −0.169 | −0.568 to 0.297 | 0.473 | −0.061 | −0.526 to 0.432 | 0.814 |
| IL-12p40 IL-12p70   | All Subjects (n=291) | 0.853 | 0.819 to 0.882 | < 0.001 | 0.854 | 0.819 to 0.883 | < 0.001 |
|                     | Controls (n=194) | 0.653 | 0.564 to 0.727 | < 0.001 | 0.655 | 0.565 to 0.729 | < 0.001 |
|                     | No Insulin (n=77) | 0.932 | 0.895 to 0.956 | < 0.001 | 0.931 | 0.893 to 0.956 | < 0.001 |
|                     | Any Insulin (n=20) | 0.825 | 0.602 to 0.928 | < 0.001 | 0.842 | 0.607 to 0.942 | < 0.001 |
| IL-12p40 IFN-α2     | All Subjects (n=291) | 0.591 | 0.510 to 0.661 | < 0.001 | 0.590 | 0.510 to 0.661 | < 0.001 |
|                     | Controls (n=194) | 0.721 | 0.645 to 0.782 | < 0.001 | 0.725 | 0.649 to 0.786 | < 0.001 |
|                     | No Insulin (n=77) | 0.891 | 0.834 to 0.930 | < 0.001 | 0.892 | 0.834 to 0.931 | < 0.001 |
|                     | Any Insulin (n=20) | 0.940 | 0.852 to 0.976 | < 0.001 | 0.935 | 0.825 to 0.977 | < 0.001 |
| IL-12p40 IFN-γ      | All Subjects (n=291) | 0.492 | 0.399 to 0.574 | < 0.001 | 0.493 | 0.400 to 0.575 | < 0.001 |
|                     | Controls (n=194) | 0.473 | 0.356 to 0.576 | < 0.001 | 0.482 | 0.365 to 0.584 | < 0.001 |
|                     | No Insulin (n=77) | 0.662 | 0.515 to 0.772 | < 0.001 | 0.665 | 0.515 to 0.776 | < 0.001 |
|                     | Any Insulin (n=20) | 0.736 | 0.436 to 0.889 | < 0.001 | 0.818 | 0.557 to 0.932 | < 0.001 |
| Compared Biomarkers | Group | Unadjusted Correlation | Adjusted Correlation |
|--------------------|-------|-------------------------|----------------------|
|                    |       | Pearson Correlation     | 95% Confidence Interval | p-value | Pearson Correlation | 95% Confidence Interval | p-value |
| IL-12p40 CXCL-10 (IP-10) | All Subjects \((n=291)\) | 0.041 | -0.074 to 0.155 | 0.484 | 0.044 | -0.72 to 0.159 | 0.458 |
|                    | Controls \((n=194)\) | 0.082 | -0.059 to 0.221 | 0.252 | 0.077 | -0.066 to 0.217 | 0.290 |
|                    | No Insulin \((n=77)\) | 0.060 | -0.166 to 0.280 | 0.604 | 0.058 | -0.173 to 0.282 | 0.625 |
|                    | Any Insulin \((n=20)\) | 0.040 | -0.410 to 0.474 | 0.865 | 0.180 | -0.329 to 0.508 | 0.481 |
| IL-12p40 CXCL-9 (MIG) | All Subjects \((n=291)\) | 0.172 | 0.058 to 0.281 | 0.003 | 0.169 | 0.054 to 0.280 | 0.004 |
|                    | Controls \((n=194)\) | 0.248 | 0.111 to 0.376 | <0.001 | 0.249 | 0.111 to 0.378 | <0.001 |
|                    | No Insulin \((n=77)\) | 0.132 | -0.095 to 0.246 | 0.250 | 0.134 | -0.098 to 0.351 | 0.254 |
|                    | Any Insulin \((n=20)\) | 0.543 | 0.132 to 0.794 | 0.010 | 0.433 | -0.060 to 0.756 | 0.074 |
| IL-12p40 CXCL-8 (IL-8) | All Subjects \((n=291)\) | 0.292 | 0.183 to 0.394 | <0.001 | 0.295 | 0.186 to 0.397 | <0.001 |
|                    | Controls \((n=194)\) | 0.571 | 0.467 to 0.659 | <0.001 | 0.572 | 0.468 to 0.660 | <0.001 |
|                    | No Insulin \((n=77)\) | 0.240 | 0.017 to 0.441 | 0.034 | 0.264 | 0.038 to 0.465 | 0.022 |
|                    | Any Insulin \((n=20)\) | 0.650 | 0.291 to 0.848 | 0.001 | 0.551 | 0.096 to 0.816 | 0.017 |
| IL-12p40 IL-5 | All Subjects \((n=291)\) | 0.297 | 0.188 to 0.398 | <0.001 | 0.296 | 0.187 to 0.398 | <0.001 |
|                    | Controls \((n=194)\) | 0.070 | -0.071 to 0.209 | 0.329 | 0.071 | -0.072 to 0.211 | 0.328 |
|                    | No Insulin \((n=77)\) | 0.948 | 0.919 to 0.967 | <0.001 | 0.947 | 0.918 to 0.967 | <0.001 |
|                    | Any Insulin \((n=20)\) | 0.854 | 0.661 to 0.941 | <0.001 | 0.817 | 0.555 to 0.932 | <0.001 |
| IL-12p40 IL-10 | All Subjects \((n=291)\) | 0.909 | 0.886 to 0.927 | <0.001 | 0.910 | 0.888 to 0.928 | <0.001 |
|                    | Controls \((n=194)\) | 0.904 | 0.874 to 0.927 | <0.001 | 0.905 | 0.875 to 0.928 | <0.001 |
|                    | No Insulin \((n=77)\) | 0.943 | 0.911 to 0.963 | <0.001 | 0.942 | 0.909 to 0.963 | <0.001 |
|                    | Any Insulin \((n=20)\) | 0.331 | -0.131 to 0.674 | 0.146 | 0.492 | 0.015 to 0.787 | 0.038 |
| IL-12p40 IL-13 | All Subjects \((n=291)\) | 0.374 | 0.271 to 0.469 | <0.001 | 0.376 | 0.273 to 0.471 | <0.001 |
|                    | Controls \((n=194)\) | 0.444 | 0.323 to 0.550 | <0.001 | 0.449 | 0.327 to 0.555 | <0.001 |
|                    | No Insulin \((n=77)\) | 0.881 | 0.818 to 0.923 | <0.001 | 0.880 | 0.815 to 0.923 | <0.001 |
|                    | Any Insulin \((n=20)\) | 0.563 | 0.161 to 0.805 | 0.007 | 0.685 | 0.304 to 0.877 | 0.001 |
| Compared Biomarkers | Group | Unadjusted Correlation | Adjusted Correlation |
|---------------------|-------|------------------------|----------------------|
|                     |       | Pearson Correlation    | 95% Confidence Interval | p-value | Pearson Correlation    | 95% Confidence Interval | p-value |
| IL-12p70 IFN-α      | All Subjects (n=291) | 0.749 | 0.693 to 0.795 | < 0.001 | 0.749 | 0.693 to 0.796 | < 0.001 |
|                     | Controls (n=194)     | 0.944 | 0.926 to 0.958 | < 0.001 | 0.944 | 0.926 to 0.958 | < 0.001 |
|                     | No Insulin (n=77)    | 0.839 | 0.757 to 0.895 | < 0.001 | 0.836 | 0.751 to 0.894 | < 0.001 |
|                     | Any Insulin (n=20)   | 0.959 | 0.898 to 0.984 | < 0.001 | 0.972 | 0.922 to 0.990 | < 0.001 |
| IL-12p70 IFN-γ      | All Subjects (n=291) | 0.526 | 0.438 to 0.605 | < 0.001 | 0.526 | 0.437 to 0.605 | < 0.001 |
|                     | Controls (n=194)     | 0.506 | 0.393 to 0.604 | < 0.001 | 0.508 | 0.394 to 0.606 | < 0.001 |
|                     | No Insulin (n=77)    | 0.641 | 0.488 to 0.757 | < 0.001 | 0.638 | 0.479 to 0.756 | < 0.001 |
|                     | Any Insulin (n=20)   | 0.831 | 0.615 to 0.931 | < 0.001 | 0.860 | 0.646 to 0.948 | < 0.001 |
| IL-12p70 CXCL-10 (IP-10) | All Subjects (n=291) | 0.047 | -0.069 to 0.161 | 0.426 | 0.053 | -0.063 to 0.168 | 0.367 |
|                     | Controls (n=194)     | 0.059 | -0.082 to 0.199 | 0.411 | 0.063 | -0.080 to 0.203 | 0.386 |
|                     | No Insulin (n=77)    | 0.073 | -0.153 to 0.292 | 0.525 | 0.071 | -0.160 to 0.295 | 0.547 |
|                     | Any Insulin (n=20)   | 0.098 | -0.360 to 0.518 | 0.678 | 0.183 | -0.326 to 0.610 | 0.474 |
| IL-12p70 CXCL-9 (MIG) | All Subjects (n=291) | 0.235 | 0.124 to 0.341 | < 0.001 | 0.235 | 0.123 to 0.342 | < 0.001 |
|                     | Controls (n=194)     | 0.377 | 0.249 to 0.492 | < 0.001 | 0.371 | 0.242 to 0.487 | < 0.001 |
|                     | No Insulin (n=77)    | 0.180 | -0.046 to 0.389 | 0.115 | 0.184 | -0.046 to 0.396 | 0.114 |
|                     | Any Insulin (n=20)   | 0.644 | 0.281 to 0.845 | 0.001 | 0.612 | 0.186 to 0.844 | 0.006 |
| IL-12p70 CXCL-8 (IL-8) | All Subjects (n=291) | 0.182 | 0.069 to 0.291 | 0.002 | 0.188 | 0.074 to 0.297 | < 0.001 |
|                     | Controls (n=194)     | 0.203 | 0.064 to 0.335 | 0.004 | 0.210 | 0.070 to 0.342 | 0.003 |
|                     | No Insulin (n=77)    | 0.249 | 0.026 to 0.448 | 0.028 | 0.278 | 0.052 to 0.476 | 0.016 |
|                     | Any Insulin (n=20)   | 0.812 | 0.576 to 0.923 | < 0.001 | 0.832 | 0.585 to 0.938 | < 0.001 |
| IL-12p70 IL-5       | All Subjects (n=291) | 0.254 | 0.143 to 0.358 | < 0.001 | 0.255 | 0.143 to 0.360 | < 0.001 |
|                     | Controls (n=194)     | 0.030 | -0.111 to 0.171 | 0.674 | 0.033 | -0.109 to 0.174 | 0.649 |
|                     | No Insulin (n=77)    | 0.969 | 0.952 to 0.980 | < 0.001 | 0.969 | 0.951 to 0.980 | < 0.001 |
|                     | Any Insulin (n=20)   | 0.495 | 0.067 to 0.769 | 0.022 | 0.465 | -0.021 to 0.773 | 0.052 |
| Compared Biomarkers | Group | Unadjusted Correlation | Adjusted Correlation |
|---------------------|-------|------------------------|----------------------|
|                     |       | Pearson Correlation | 95% Confidence Interval | p-value | Pearson Correlation | 95% Confidence Interval | p-value |
| IL-12p70 IL-10      | All Subjects (n=291) | 0.897 | 0.872 to 0.917 | < 0.001 | 0.897 | 0.872 to 0.918 | < 0.001 |
|                     | Controls (n=194) | 0.709 | 0.631 to 0.773 | < 0.001 | 0.709 | 0.630 to 0.773 | < 0.001 |
|                     | No Insulin (n=77) | 0.973 | 0.957 to 0.982 | < 0.001 | 0.973 | 0.957 to 0.983 | < 0.001 |
|                     | Any Insulin (n=20) | 0.336 | -0.126 to 0.678 | 0.140 | 0.447 | -0.042 to 0.764 | 0.064 |
| IL-12p70 IL-13      | All Subjects (n=291) | 0.412 | 0.312 to 0.503 | < 0.001 | 0.413 | 0.312 to 0.504 | < 0.001 |
|                     | Controls (n=194) | 0.375 | 0.247 to 0.490 | < 0.001 | 0.380 | 0.252 to 0.495 | < 0.001 |
|                     | No Insulin (n=77) | 0.961 | 0.939 to 0.975 | < 0.001 | 0.960 | 0.938 to 0.975 | < 0.001 |
|                     | Any Insulin (n=20) | 0.724 | 0.415 to 0.884 | < 0.001 | 0.794 | 0.506 to 0.923 | < 0.001 |
| IFN-α2 IFN-γ        | All Subjects (n=291) | 0.620 | 0.544 to 0.686 | < 0.001 | 0.622 | 0.546 to 0.688 | < 0.001 |
|                     | Controls (n=194) | 0.571 | 0.468 to 0.659 | < 0.001 | 0.571 | 0.467 to 0.660 | < 0.001 |
|                     | No Insulin (n=77) | 0.810 | 0.716 to 0.875 | < 0.001 | 0.807 | 0.709 to 0.874 | < 0.001 |
|                     | Any Insulin (n=20) | 0.793 | 0.539 to 0.914 | < 0.001 | 0.862 | 0.651 to 0.949 | < 0.001 |
| IFN-α2 CXCL-10 (IP-10) | All Subjects (n=291) | 0.047 | -0.068 to 0.161 | 0.424 | 0.053 | -0.063 to 0.167 | 0.370 |
|                     | Controls (n=194) | 0.056 | -0.086 to 0.195 | 0.440 | 0.0616 | -0.081 to 0.202 | 0.396 |
|                     | No Insulin (n=77) | 0.003 | -0.221 to 0.227 | 0.978 | 0.000 | -0.228 to 0.229 | 0.999 |
|                     | Any Insulin (n=20) | 0.062 | -0.391 to 0.491 | 0.793 | 0.230 | -0.282 to 0.640 | 0.366 |
| IFN-α2 CXCL-9 (MIG) | All Subjects (n=291) | 0.345 | 0.240 to 0.443 | < 0.001 | 0.342 | 0.236 to 0.441 | < 0.001 |
|                     | Controls (n=194) | 0.413 | 0.289 to 0.524 | < 0.001 | 0.406 | 0.280 to 0.518 | < 0.001 |
|                     | No Insulin (n=77) | 0.106 | -0.120 to 0.323 | 0.355 | 0.110 | -0.121 to 0.331 | 0.347 |
|                     | Any Insulin (n=20) | 0.623 | 0.250 to 0.835 | 0.002 | 0.546 | 0.089 to 0.813 | 0.018 |
| IFN-α2 CXCL-8 (IL-8) | All Subjects (n=291) | 0.397 | 0.296 to 0.490 | < 0.001 | 0.403 | 0.302 to 0.496 | < 0.001 |
|                     | Controls (n=194) | 0.396 | 0.270 to 0.508 | < 0.001 | 0.409 | 0.283 to 0.521 | < 0.001 |
|                     | No Insulin (n=77) | 0.315 | 0.097 to 0.503 | 0.005 | 0.331 | 0.111 to 0.520 | 0.004 |
|                     | Any Insulin (n=20) | 0.768 | 0.494 to 0.904 | < 0.001 | 0.735 | 0.394 to 0.898 | < 0.001 |
| Compared Biomarkers     | Group                     | Unadjusted Correlation       | Adjusted Correlation       |
|------------------------|---------------------------|------------------------------|---------------------------|
|                        |                           | Pearson Correlation 95% CI   | p-value Pearson Correlation 95% CI |
| IFN-α2 IL-5            | All Subjects (n=291)      | 0.146 [0.032 to 0.257]      | 0.012                    |
|                        | Controls (n=194)          | 0.043 [−0.099 to 0.182]     | 0.554                    |
|                        | No Insulin (n=77)         | 0.792 [0.690 to 0.863]      | < 0.001                  |
|                        | Any Insulin (n=20)        | 0.703 [0.378 to 0.874]      | < 0.001                  |
| IFN-α2 IL-5            | All Subjects (n=291)      | 0.043 [−0.099 to 0.182]     | 0.554                    |
|                        | Controls (n=194)          | 0.813 [0.758 to 0.855]      | < 0.001                  |
|                        | No Insulin (n=77)         | 0.823 [0.734 to 0.884]      | < 0.001                  |
|                        | Any Insulin (n=20)        | 0.279 [−0.187 to 0.642]     | 0.226                    |
| IFN-α2 IL-5            | All Subjects (n=291)      | 0.556 [0.471 to 0.630]      | < 0.001                  |
|                        | Controls (n=194)          | 0.538 [0.429 to 0.631]      | < 0.001                  |
|                        | No Insulin (n=77)         | 0.807 [0.712 to 0.873]      | < 0.001                  |
|                        | Any Insulin (n=20)        | 0.659 [0.305 to 0.853]      | < 0.001                  |
| IFN-γ CXCL-10 (IP-10)  | All Subjects (n=291)      | 0.062 [−0.054 to 0.175]     | 0.295                    |
|                        | Controls (n=194)          | 0.085 [−0.057 to 0.223]     | 0.239                    |
|                        | No Insulin (n=77)         | 0.807 [0.712 to 0.873]      | < 0.001                  |
|                        | Any Insulin (n=20)        | 0.340 [−0.121 to 0.680]     | 0.134                    |
| IFN-γ CXCL-9 (MIG)     | All Subjects (n=291)      | 0.287 [0.178 to 0.389]      | < 0.001                  |
|                        | Controls (n=194)          | 0.358 [0.228 to 0.475]      | < 0.001                  |
|                        | No Insulin (n=77)         | 0.144 [−0.082 to 0.357]     | 0.208                    |
|                        | Any Insulin (n=20)        | 0.521 [0.102 to 0.783]      | 0.015                    |
| IFN-γ CXCL-8 (IL-8)    | All Subjects (n=291)      | 0.432 [0.334 to 0.521]      | < 0.001                  |
|                        | Controls (n=194)          | 0.485 [0.370 to 0.586]      | < 0.001                  |
|                        | No Insulin (n=77)         | 0.236 [0.013 to 0.437]      | 0.037                    |
|                        | Any Insulin (n=20)        | 0.623 [0.250 to 0.835]      | 0.002                    |
| Compared Biomarkers | Group | Unadjusted Correlation | Adjusted Correlation |
|---------------------|-------|------------------------|---------------------|
|                     |       | Pearson Correlation    | 95% Confidence Interval | p-value | Pearson Correlation | 95% Confidence Interval | p-value |
| IFN-γ IL-5          | All Subjects \(n=291\) | **0.136** | \(0.022\) to \(0.247\) | 0.020 | **0.136** | \(0.021\) to \(0.248\) | 0.021 |
|                     | Controls \(n=194\) | 0.047 | \(-0.094\) to \(0.188\) | 0.514 | 0.049 | \(-0.093\) to \(0.190\) | 0.497 |
|                     | No Insulin \(n=77\) | **0.574** | \(0.401\) to \(0.707\) | \(<0.001\) | **0.570** | \(0.393\) to \(0.707\) | \(<0.001\) |
|                     | Any Insulin \(n=20\) | 0.421 | \(-0.026\) to \(0.728\) | 0.058 | **0.545** | \(0.088\) to \(0.813\) | 0.018 |
| IFN-γ IL-10         | All Subjects \(n=291\) | **0.477** | \(0.383\) to \(0.561\) | \(<0.001\) | **0.476** | \(0.382\) to \(0.561\) | \(<0.001\) |
|                     | Controls \(n=194\) | 0.475 | \(0.358\) to \(0.577\) | \(<0.001\) | 0.480 | \(0.362\) to \(0.582\) | \(<0.001\) |
|                     | No Insulin \(n=77\) | **0.585** | \(0.415\) to \(0.715\) | \(<0.001\) | **0.583** | \(0.409\) to \(0.716\) | \(<0.001\) |
|                     | Any Insulin \(n=20\) | **0.654** | \(0.297\) to \(0.850\) | \(<0.001\) | **0.668** | \(0.276\) to \(0.869\) | \(<0.001\) |
| IFN-γ IL-13         | All Subjects \(n=291\) | **0.492** | \(0.400\) to \(0.575\) | \(<0.001\) | **0.490** | \(0.397\) to \(0.573\) | \(<0.001\) |
|                     | Controls \(n=194\) | **0.503** | \(0.390\) to \(0.601\) | \(<0.001\) | **0.504** | \(0.389\) to \(0.603\) | \(<0.001\) |
|                     | No Insulin \(n=77\) | **0.601** | \(0.436\) to \(0.727\) | \(<0.001\) | **0.591** | \(0.419\) to \(0.722\) | \(<0.001\) |
|                     | Any Insulin \(n=20\) | **0.849** | \(0.650\) to \(0.939\) | \(<0.001\) | **0.852** | \(0.628\) to \(0.945\) | \(<0.001\) |
| CXCL-10 (IP-10) CXCL-9 (MIG) | All Subjects \(n=291\) | 0.093 | \(-0.022\) to \(0.206\) | 0.114 | 0.102 | \(-0.014\) to \(0.215\) | 0.084 |
|                     | Controls \(n=194\) | 0.089 | \(-0.052\) to \(0.227\) | 0.216 | 0.097 | \(-0.046\) to \(0.235\) | 0.183 |
|                     | No Insulin \(n=77\) | **0.258** | \(0.036\) to \(0.456\) | \(0.022\) | **0.261** | \(0.034\) to \(0.462\) | \(0.024\) |
|                     | Any Insulin \(n=20\) | \(-0.090\) | \(-0.512\) to \(0.367\) | 0.703 | 0.061 | \(-0.432\) to \(0.526\) | 0.813 |
| CXCL-10 (IP-10) CXCL-8 (IL-8) | All Subjects \(n=291\) | **0.108** | \(-0.007\) to \(0.220\) | 0.065 | 0.095 | \(-0.021\) to \(0.208\) | 0.108 |
|                     | Controls \(n=194\) | **0.121** | \(-0.020\) to \(0.258\) | 0.092 | 0.110 | \(-0.032\) to \(0.248\) | 0.129 |
|                     | No Insulin \(n=77\) | 0.096 | \(-0.131\) to \(0.313\) | 0.406 | 0.098 | \(-0.134\) to \(0.319\) | 0.406 |
|                     | Any Insulin \(n=20\) | \(-0.040\) | \(-0.474\) to \(0.409\) | 0.864 | 0.059 | \(-0.434\) to \(0.525\) | 0.818 |
| CXCL-10 (IP-10) IL-5 | All Subjects \(n=291\) | **0.000** | \(-0.115\) to \(0.115\) | 0.996 | \(-0.002\) | \(-0.117\) to \(0.114\) | 0.975 |
|                     | Controls \(n=194\) | \(-0.007\) | \(-0.148\) to \(0.134\) | 0.918 | \(-0.013\) | \(-0.155\) to \(0.129\) | 0.857 |
|                     | No Insulin \(n=77\) | 0.073 | \(-0.153\) to \(0.292\) | 0.527 | 0.070 | \(-0.161\) to \(0.293\) | 0.554 |
| Compared Biomarkers | Group | Unadjusted Correlation | Adjusted Correlation |
|---------------------|-------|------------------------|----------------------|
|                     |       | Pearson Correlation | 95% Confidence Interval | p-value | Pearson Correlation | 95% Confidence Interval | p-value |
| Any Insulin (n=20)  |       | – 0.157               | – 0.560 to 0.307       | 0.503    | 0.129               | – 0.375 to 0.574       | 0.616   |
| CXCL-10 (IP-10)     | All Subjects (n=291) | 0.058               | – 0.057 to 0.172       | 0.324    | 0.061               | – 0.055 to 0.175       | 0.302   |
|                     | Controls (n=194)     | 0.067               | – 0.075 to 0.206       | 0.353    | 0.070               | – 0.073 to 0.209       | 0.338   |
|                     | No Insulin (n=77)    | 0.087               | – 0.140 to 0.305       | 0.451    | 0.085               | – 0.146 to 0.308       | 0.470   |
|                     | Any Insulin (n=20)   | **0.477**           | **0.044 to 0.759**     | **0.028**| 0.114               | – 0.388 to 0.564       | **0.659**|
| CXCL-10 (IP-10)     | All Subjects (n=291) | **0.140**           | **0.026 to 0.251**     | **0.016**| **0.144**           | **0.029 to 0.255**     | **0.014**|
|                     | Controls (n=194)     | 0.140               | **0.001 to 0.275**     | 0.051    | **0.149**           | **0.008 to 0.285**     | **0.038**|
|                     | No Insulin (n=77)    | 0.119               | – 0.108 to 0.334       | 0.302    | 0.116               | – 0.115 to 0.336       | 0.322   |
|                     | Any Insulin (n=20)   | 0.307               | – 0.156 to 0.660       | 0.179    | 0.205               | – 0.305 to 0.624       | 0.421   |
| CXCL-9 (MIG) IL-8   | All Subjects (n=291) | **0.118**           | **0.003 to 0.230**     | **0.043**| **0.122**           | **0.007 to 0.234**     | **0.038**|
|                     | Controls (n=194)     | 0.107               | – 0.035 to 0.244       | 0.137    | 0.119               | – 0.023 to 0.257       | 0.100   |
|                     | No Insulin (n=77)    | – 0.022             | – 0.245 to 0.203       | 0.849    | – 0.017             | – 0.244 to 0.212       | 0.888   |
|                     | Any Insulin (n=20)   | **0.518**           | **0.098 to 0.781**     | **0.015**| 0.426               | – 0.069 to 0.753       | 0.079   |
| CXCL-9 (MIG) IL-5   | All Subjects (n=291) | 0.038               | – 0.077 to 0.153       | 0.515    | 0.037               | – 0.079 to 0.152       | 0.527   |
|                     | Controls (n=194)     | – 0.025             | – 0.165 to 0.117       | 0.734    | – 0.023             | – 0.164 to 0.119       | 0.752   |
|                     | No Insulin (n=77)    | 0.162               | – 0.064 to 0.372       | 0.157    | 0.166               | – 0.065 to 0.380       | 0.156   |
|                     | Any Insulin (n=20)   | 0.404               | – 0.046 to 0.718       | 0.070    | 0.192               | – 0.318 to 0.616       | 0.453   |
| CXCL-9 (MIG) IL-10  | All Subjects (n=291) | **0.149**           | **0.035 to 0.260**     | **0.011**| **0.153**           | **0.038 to 0.264**     | **0.009**|
|                     | Controls (n=194)     | **0.274**           | **0.139 to 0.400**     | < **0.001**| **0.274**           | **0.137 to 0.400**     | < **0.001**|
|                     | No Insulin (n=77)    | 0.132               | – 0.095 to 0.346       | 0.250    | 0.134               | – 0.098 to 0.352       | 0.253   |
|                     | Any Insulin (n=20)   | 0.075               | – 0.380 to 0.501       | 0.752    | 0.196               | – 0.314 to 0.619       | 0.443   |
| CXCL-9 (MIG) IL-13  | All Subjects (n=291) | **0.159**           | **0.045 to 0.269**     | **0.006**| **0.166**           | **0.052 to 0.277**     | **0.004**|
|                     | Controls (n=194)     | **0.186**           | **0.047 to 0.319**     | **0.009**| **0.191**           | **0.051 to 0.324**     | **0.008**|
| Compared Biomarkers | Group | Unadjusted Correlation | Adjusted Correlation |  |
|---------------------|-------|------------------------|----------------------|---|
|                     |       | Pearson Correlation    | 95% Confidence Interval | p-value | Pearson Correlation | 95% Confidence Interval | p-value |
| CXCL-8 (IL-8)       | No Insulin (n=77) | 0.211  | -0.013 to 0.416 | 0.063 | 0.217  | -0.012 to 0.425 | 0.061 |
|                     | Any insulin (n=20) | 0.414  | -0.035 to 0.724 | 0.063 | 0.489  | 0.011 to 0.785 | 0.039 |
|                     | CXCL-8 (IL-8) | All Subjects (n=291) | 0.125  | 0.010 to 0.237 | 0.033 | 0.125  | 0.010 to 0.237 | 0.033 |
|                     | Controls (n=194) | 0.107  | -0.034 to 0.245 | 0.135 | 0.107  | -0.036 to 0.245 | 0.141 |
|                     | No Insulin (n=77) | 0.215  | -0.009 to 0.419 | 0.058 | 0.245  | 0.017 to 0.448 | 0.034 |
|                     | Any insulin (n=20) | 0.424  | -0.022 to 0.730 | 0.056 | 0.189  | -0.321 to 0.614 | 0.460 |
| CXCL-8 (IL-8)       | IL-5 IL-10 | All Subjects (n=291) | 0.402  | 0.301 to 0.494 | <0.001 | 0.408  | 0.307 to 0.500 | <0.001 |
|                     | Controls (n=194) | 0.672  | 0.586 to 0.742 | <0.001 | 0.677  | 0.592 to 0.747 | <0.001 |
|                     | No Insulin (n=77) | 0.293  | 0.073 to 0.485 | 0.009 | 0.318  | 0.096 to 0.509 | 0.005 |
|                     | Any insulin (n=20) | 0.260  | -0.207 to 0.630 | 0.261 | 0.377  | -0.127 to 0.726 | 0.127 |
| CXCL-8 (IL-8)       | IL-13 IL-10 | All Subjects (n=291) | 0.640  | 0.567 to 0.703 | <0.001 | 0.651  | 0.579 to 0.713 | <0.001 |
|                     | Controls (n=194) | 0.687  | 0.605 to 0.755 | <0.001 | 0.695  | 0.613 to 0.761 | <0.001 |
|                     | No Insulin (n=77) | 0.306  | 0.088 to 0.496 | 0.006 | 0.330  | 0.110 to 0.519 | 0.004 |
|                     | Any insulin (n=20) | 0.527  | 0.110 to 0.786 | 0.013 | 0.596  | 0.162 to 0.837 | 0.008 |
| IL-5 IL-10 All Subjects (n=291) | 0.308  | 0.200 to 0.408 | <0.001 | 0.309  | 0.200 to 0.410 | <0.001 |
|                     | Controls (n=194) | 0.134  | -0.007 to 0.270 | 0.270 | 0.138  | -0.004 to 0.275 | 0.056 |
|                     | No Insulin (n=77) | 0.981  | 0.970 to 0.988 | <0.001 | 0.981  | 0.970 to 0.988 | <0.001 |
|                     | Any insulin (n=20) | 0.033  | -0.416 to 0.468 | 0.890 | 0.248  | -0.264 to 0.651 | 0.327 |
| IL-5 IL-13 All Subjects (n=291) | 0.134  | 0.020 to 0.245 | 0.022 | 0.134  | 0.018 to 0.246 | 0.023 |
|                     | Controls (n=194) | 0.065  | -0.076 to 0.204 | 0.364 | 0.066  | -0.077 to 0.206 | 0.363 |
|                     | No Insulin (n=77) | 0.915  | 0.869 to 0.945 | <0.001 | 0.914  | 0.866 to 0.945 | <0.001 |
|                     | Any insulin (n=20) | 0.233  | -0.233 to 0.613 | 0.314 | 0.379  | -0.125 to 0.727 | 0.124 |
| IL-10 IL-13 All Subjects (n=291) | 0.513  | 0.423 to 0.593 | <0.001 | 0.512  | 0.422 to 0.593 | <0.001 |
|                     | Controls (n=194) | 0.596  | 0.497 to 0.680 | <0.001 | 0.601  | 0.501 to 0.684 | <0.001 |
2.4. Demographic and clinical data collection

Clinical and treatment history was documented as previously described [1]. Briefly, users of any insulin were defined as patients receiving a form of injectable insulin – alone or in combination – at the time of breast cancer diagnosis. Vital status was obtained from the Institute’s Tumor Registry, a database updated biannually with data obtained from the National Comprehensive Cancer Networks’ Oncology Outcomes Database. Outcomes of interest were breast cancer recurrence and/or death. Details regarding patient demographics and clinical characteristics have been previously published [1].

2.5. Plasma specimen storage and retrieval

All the plasma specimens retrieved from long-term storage were individually aliquoted in color coded vials labeled with unique, subject specific barcodes. Overall duration of freezing time was accounted for all matched controls ensuring that the case and matched control specimens had similar overall storage conditions. Only two instances of freeze-thaw were allowed between biobank retrieval and biomarker analyses: aliquoting procedure step and actual assay.

2.6. Luminex® assays

A total of 12 biomarkers - interleukine-2, soluble interleukine-2 receptor α, interleukine-12 subunit p40, interleukine-12 subunit p70, interferon α 2, interferon γ, chemokine ligand 10, CXCL-10 (interferon gamma-induced protein 10, IP-10); chemokine ligand 9, CXCL-9 (monokine-induced by interferon γ, MIG); chemokine ligand 8, CXCL-8 (interleukine-8, IL-8); interleukine-5, IL-5; interleukine-10, IL-10; interleukine-13, IL-13.

2.7. Biomarker-pharmacotherapy association analysis

Biomarker cut-point optimization was performed for each analyzed biomarker. Biomarker levels constituted the continuous independent variable that was subdivided into two groups that optimized the log rank test among all possible cut-point selections yielding a minimum of 10 patients in any resulting group. Quartiles were also constructed. The resultant biomarker categories were then tested for association with type 2 diabetes mellitus therapy and controls by Fisher’s exact test. The continuous biomarker levels were also tested for association with diabetes therapy and controls across groups by the Kruskal-Wallis test and pairwise by the Wilcoxon rank sum. Multivariate adjustments

Table 2 (continued)

| Compared Biomarkers | Group | Unadjusted Correlation | | | Adjusted Correlation | | |
|--------------------|-------|------------------------|---|------------------|---|------------------|---|
|                    |       | Pearson Correlation    | 95% Confidence Interval | p-value | Pearson Correlation | 95% Confidence Interval | p-value |
| No Insulin (n=77)  | 0.943 | 0.912 to 0.964         | < 0.001                  | 0.943 | 0.911 to 0.964 | < 0.001 |
| Any Insulin (n=20) | 0.508 | 0.084 to 0.776         | 0.018                    | 0.460 | −0.027 to 0.770 | 0.056 |

Significant correlations are displayed in bolded text. The differences that are only significant in either adjusted or unadjusted correlations are further denoted by an outline. Interleukine-2, IL-2; soluble interleukine-2 receptor α, sIL-2Rα interleukine-12 subunit p40, IL-12p40; interleukine-12 subunit p70, IL-12p70; interferon α 2, IFN-α2; interferon γ, IFN-γ chemokine ligand 10, CXCL-10 (interferon gamma-induced protein 10, IP-10); chemokine ligand 9, CXCL-9 (monokine-induced by interferon γ, MIG); chemokine ligand 8, CXCL-8 (interleukine-8, IL-8); interleukine-5, IL-5; interleukine-10, IL-10; interleukine-13, IL-13.

body mass index category, ethnicity, menopausal status and tumor stage (as per the American Joint Committee on Cancer). Some matching limitations applied [1].
were performed accounting for age, tumor stage, body mass index, estrogen receptor status, and cumulative comorbidity. The biomarker analysis was performed using R Version 2.15.3. Please see the original article for an illustration of the analysis workflow [1].

Correlations between biomarkers stratified by type 2 diabetes mellitus pharmacotherapy and controls were assessed by the Pearson method. Correlation models were constructed both with and without adjustment for age, body mass index, and the combined comorbidity index. Correlation analyses were performed using SAS Version 9.4.

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Transparency document. Supporting information

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.dib.2017.02.028.

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