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SUPPLEMENTARY FIG. S1. Distribution of mean caffeine intake per person during the EDIC study (n = 1,181): (A) raw and (B) square root transformed. The overall mean ± SD caffeine intake per person was 295 ± 214 mg/day.

SUPPLEMENTARY FIG. S2. Distribution of mean caffeine intake per person during the DCCT (n = 1,185): (A) raw and (B) square root transformed. The overall mean ± SD caffeine intake per person was 369 ± 335 mg/day.
**SUPPLEMENTARY FIG. S3.** Scatterplot showing the positive association of mean caffeine intake during the EDIC study with log, transformed SIF$_{1LED\ 375\ nm[0.6, 0.2]}$ ($n = 1,181$). The solid line represents the slope from the unadjusted linear regression analysis.

**SUPPLEMENTARY TABLE S1. Univariate and Multivariable Effects of Covariates on SIF$_{1LED\ 375\ nm[0.6, 0.2]}$ in the DCCT/EDIC Study**

| Covariate                                      | Univariate model | Multivariable model |
|------------------------------------------------|------------------|---------------------|
| Age (years)                                    | 13.6% 0.011 0.00080 1.61E-39 | 0.011 0.00073 2.48E-50 |
| Male versus female                             | 0.0% -0.0023 0.012 0.85 | 0.018 0.010 0.08 |
| Skin tone (arbitrary units)                    | 1.5% 0.00052 0.00012 2.79E-05 | 0.00087 0.00011 2.67E-15 |
| Clinic latitude (>37° North vs. South)         | 1.7% -0.060 0.013 9.05E-06 | -0.056 0.011 5.01E-07 |
| Current versus never smoker                    | 6.9% 0.16 0.017 6.58E-20 | 0.15 0.015 6.32E-22 |
| Current versus former smoker                   | 0.12 0.019 4.13E-09 | 0.11 0.017 2.57E-10 |
| Any eGFR <60 mL/min/1.73 m$^2$ to date (yes vs. no) | 5.6% 0.19 0.023 1.71E-16 | 0.11 0.020 2.27E-08 |
| DCCT eligibility HbA1c (%)                     | 1.6% 0.016 0.0037 9.87E-06 | 0.0064 0.0034 0.057 |
| DCCT mean HbA1c (%)                            | 1.1% 0.016 0.0043 2.28E-04 | 0.0089 0.0041 0.03 |
| EDIC mean HbA1c (%)                            | 6.3% 0.050 0.0056 1.62E-18 | 0.030 0.00534 2.01E-08 |

Data shown are $\beta \pm SE$ values from linear regression analysis for each covariate with ln transformed SIF$_{1LED\ 375\ nm[0.6, 0.2]}$. The $R^2$ shown is the variance explained for each variable in the univariate model. Multivariable models included age, sex, skin tone, clinic latitude, smoking status, any estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m$^2$, DCCT eligibility HbA1c, mean DCCT HbA1c, and mean EDIC HbA1c as covariates.
### Supplementary Table S2. Univariate and Multivariable Effects of Covariates on Mean Caffeine Intake During the EDIC Study

| Covariate                                      | Univariate model | Adjusted model |
|------------------------------------------------|------------------|----------------|
|                                               | R²    | β    | SE    | P value | β    | SE    | P value |
| Age (years)                                    | 4.5%  | 0.20 | 0.027 | 1.89E-13| 0.20 | 0.026 | 3.32E-14|
| Male versus female                             | 1.9%  | 1.81 | 0.38  | 1.94E-06| 1.67 | 0.37  | 7.69E-06|
| Skin tone (arbitrary units)                    | 0.2%  | 0.0060 | 0.0040 | 0.13   | 0.0042 | 0.0039 | 0.29   |
| Clinic latitude (>37º North vs South)          | 0.0%  | 0.22 | 0.43  | 0.60   | 0.10 | 0.40  | 0.80   |
| Current versus never smoker                    | 7.9%  | 4.19 | 0.55  | 8.62E-14| 4.028| 0.55  | 3.43E-13|
| Current versus former smoker                   | 0.66  | 0.62 | 0.29  | 0.62   | 0.60 | 0.30  |        |
| Any eGFR <60 mL/min/1.73 m² to date (yes vs no)| 0.0%  | 0.34 | 0.75  | 0.65   | 0.61 | 0.72  | 0.39   |
| DCCT eligibility HbA1c (%)                     | 0.1%  | 0.11 | 0.12  | 0.38   | 0.060| 0.12  | 0.63   |
| DCCT mean HbA1c (%)                            | 0.0%  | 0.10 | 0.14  | 0.46   | 0.017| 0.15  | 0.91   |
| EDIC mean HbA1c (%)                            | 1.1%  | 0.65 | 0.18  | 3.64E-04| 0.42 | 0.19  | 3.03E-02|

Data shown are β±SE values from linear regression analysis for each covariate with square root transformed mean caffeine intake during the EDIC. The R² shown is the variance explained for each variable in the univariate model. Multivariable models included age, sex, skin tone, clinic latitude, smoking status, any estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m², DCCT eligibility HbA1c, mean DCCT HbA1c, and mean EDIC HbA1c as covariates.

### Supplementary Table S3. Association of Caffeine Intake During the DCCT with SIF

| SIF outcome (excitation wavelength), model | Variance | β±SE        | P value |
|-------------------------------------------|----------|-------------|---------|
| SIF1 (375 nm)                             | 11.8%    | 0.00021±1.67E-05 | 4.2E-34 |
| Unadjusted                                | 2.7%     | 0.00012±1.64E-05 | 2.6E-12 |
| Adjusted                                  |          |             |         |
| SIF14 (456 nm)                             | 8.5%     | 0.00020±1.93E-05 | 9.0E-25 |
| Unadjusted                                | 2.3%     | 0.00012±2.02E-05 | 2.6E-09 |
| Adjusted                                  |          |             |         |

Data shown are β±SE values from linear regression analysis for caffeine intake with SIF1LED 375 nm [0.6, 0.21] and SIF14LED456 nm [0.4, 0.81] (n=1,185). Variance was calculated as a type II squared semipartial correlation. Adjusted models included age, sex, skin tone, clinic latitude, smoking status, any estimated glomerular filtration rate <60 mL/min/1.73 m², DCCT eligibility HbA1c, mean DCCT HbA1c, and mean EDIC HbA1c as covariates.

*aLn transformed.*
## Supplementary Table S5. Proportion of Subjects Reporting Drinking Caffeinated Beverages or Decaffeinated Coffee Consumption at Least Once per Month During EDIC Years 13–15

|                        | Caffeinated coffee \(n = 1,074\) | Decaffeinated coffee \(n = 1,076\) | Regular cola \(n = 1,076\) | Low-calorie cola \(n = 1,074\) | Tea \(n = 1,073\) |
|------------------------|-----------------------------------|------------------------------------|----------------------------|-------------------------------|-----------------|
| Never or less than once per month | 257 (23.93%)                     | 723 (67.2%)                        | 901 (83.7%)                 | 194 (18.1%)                   | 359 (33.5%)     |
| At least once per month | 817 (76.1%)                       | 353 (32.8%)                        | 175 (16.3%)                 | 880 (81.9%)                   | 714 (66.5%)     |

Data shown are \(n\) (%) for the mean intake of each beverage during EDIC Years 13–15.
**Supplementary Table S6. Subject Characteristics of the Pittsburgh EDC Subjects with Caffeine Intake and SIF Measures (n=210) Taken at the Time of SIF Assessment**

| Demographic characteristic                                      | Out of n=210                              |
|-----------------------------------------------------------------|-------------------------------------------|
| Male sex                                                        | 101 (48.1%)                               |
| Age (years)                                                     | 49.3 ± 7.3                                |
| Diabetes duration (years)                                       | 40.6 ± 7.0                                |
| Smoking status*                                                 |                                           |
| Never                                                           | 123 (58.6%)                               |
| Former                                                          | 55 (26.2%)                                |
| Current                                                         | 23 (11.0%)                                |
| Any eGFR <60 ml/min/1.73 m² to date (yes)*                      |                                           |
| Glycemic exposure measured as mean HbA1c (%) (mmol/mol)*        | 8.6 ± 1.0 (70 ± 11)                       |
| Mean caffeine intake (mg/day)                                   | 294 ± 250                                 |
| Time between caffeine intake assessment and SIF1 (years)*       | 18 ± 3.0                                  |
| rs1495741 genotype (AA/AG/GG)*                                  | 101/68/11                                 |
| SIF1LED 375nm, $k_x$=0.6, $k_m$=0.2 (arbitrary units)*          | 3.3 ± 0.24                                |
| SIF14LED 456nm, $k_x$=0.4, $k_m$=0.8 (arbitrary units)*         | 0.43 ± 0.24                               |

Data are n (%) or mean ± SD values as indicated.

*Smoking status was defined by response to the question “Do you smoke cigarettes now?,” with “never smoker” defined as ≤100 cigarettes in a subject’s lifetime.

The estimated glomerular filtration rate (eGFR) was estimated using the Chronic Kidney Disease–Epidemiology Collaboration equation from the 18-year examination.

Mean HbA1c was calculated for each subject using repeated measures collected every 2 years from 1986–1988 to 1996–1998 and again during the 18-year exam (2004–2006).

The minimum lag time between measures of caffeine intake during EDC and measures of SIF was 8 years.

Thirty subjects did not have rs1495741 genotype data available.

Ln transformed.

**Supplementary Table S7. Association of rs1495741 and Caffeine Intake with SIF in the Pittsburgh EDC Study**

| N (AA/AG/GG) | Predictors | $\beta$ ± SE | P value |
|--------------|------------|--------------|---------|
| SIF1 (375 nm)* | rs1495741 | −0.08 ± 0.02 | 0.002 |
|              | Caffeine   | 0.0001 ± 0.00008 | 0.12 |
| SIF14 (456 nm)* | rs1495741 | −0.13 ± 0.03 | 1.7E-05 |
|              | Caffeine   | 0.0002 ± 0.00009 | 0.004 |

Data shown are $\beta$±SE values from linear regression analyses for the effects of rs1495741 and caffeine intake effects when both included in the same model with SIF1LED 375 nm[0.6, 0.2] and SIF14LED 456 nm[0.4, 0.8] after additionally adjusting for age, sex, smoking, and estimated glomerular filtration rate <60 mL/min/1.73 m². SIF14LED 456 nm[0.4, 0.8] was not measured in participants who had SIF measured in 2007–2009; therefore only 140 subjects had genotype, caffeine, and SIF14LED 456 nm[0.4, 0.8] measures available in those analyses.

*Ln transformed.