Supplementary Data

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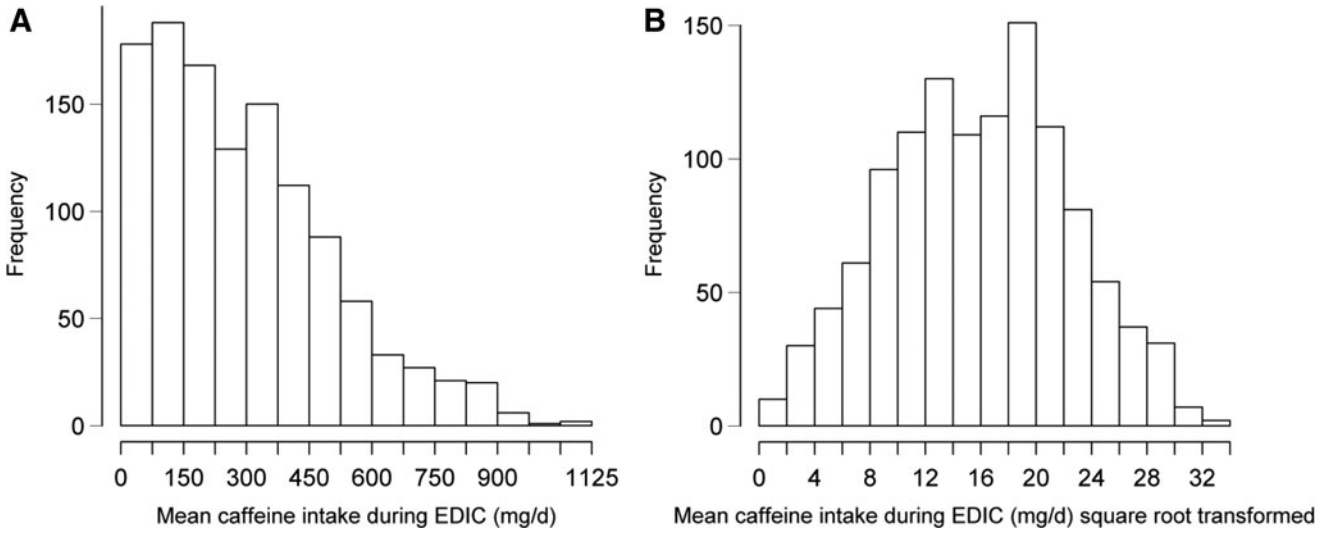
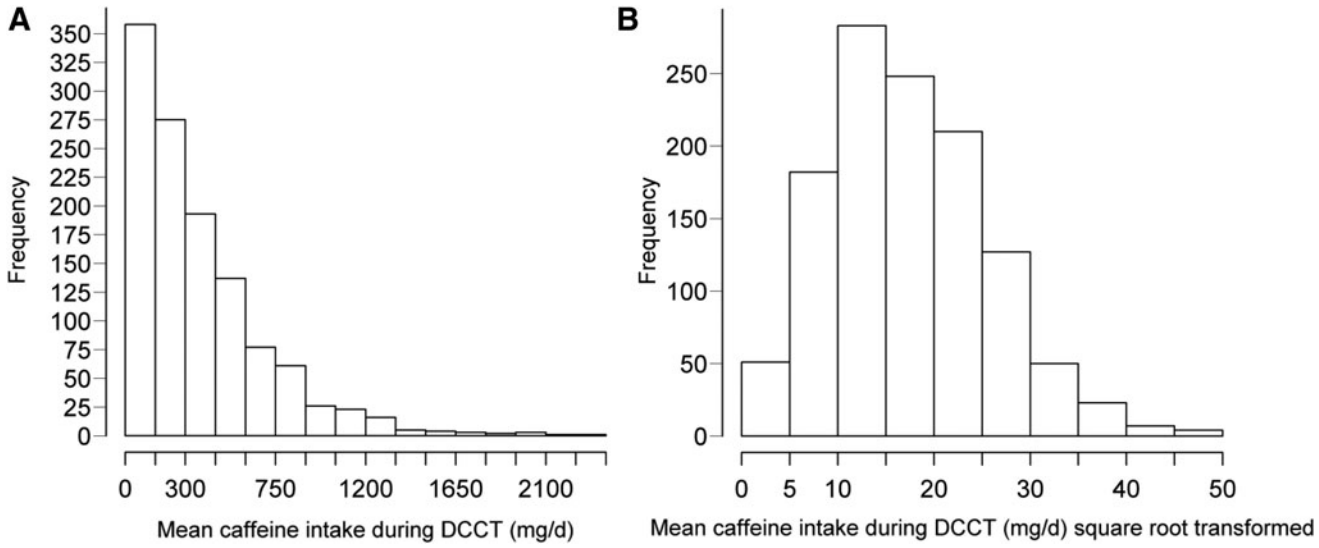
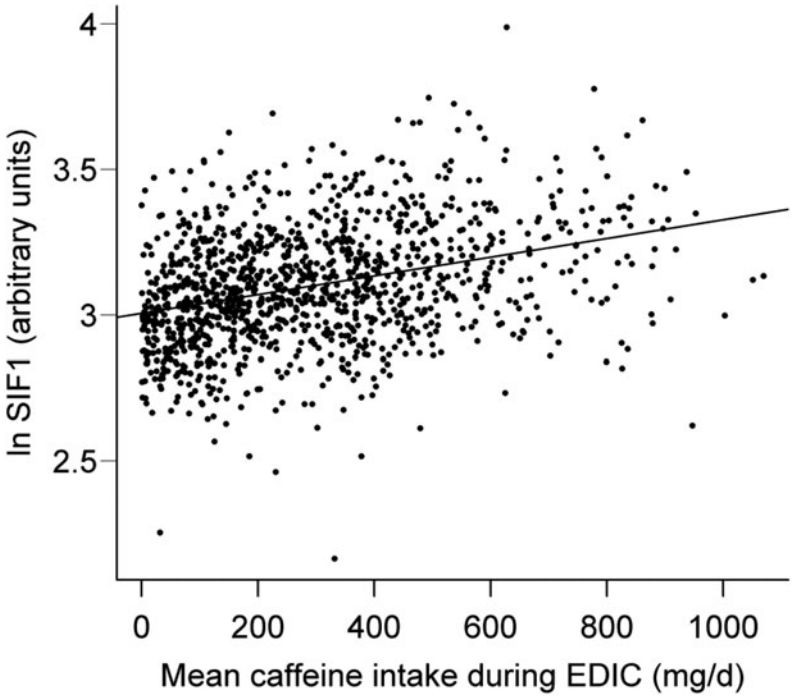


SUPPLEMENTARY FIG. S1. Distribution of mean caffeine intake per person during the EDIC study ($n = 1{,}181$): **(A)** raw and **(B)** square root transformed. The overall mean ± SD caffeine intake per person was 295 ± 214 mg/day.



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 $\log_e$ transformed $SIF1_{LED\ 375\ nm[0.6,\ 0.2]}$ ($n = 1{,}181$). The solid line represents the slope from the unadjusted linear regression analysis.

SUPPLEMENTARY TABLE S1. UNIVARIATE AND MULTIVARIABLE EFFECTS OF COVARIATES ON $SIF1_{LED\ 375\ nm[0.6,\ 0.2]}$ IN THE DCCT/EDIC STUDY

	Univariate model				*Multivariable model*		
	R^2	β	*SE*	P *value*	β	*SE*	P *value*
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 $SIF1_{LED\ 375\ nm[0.6,\ 0.2]}$. 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

	Univariate model				*Adjusted model*		
	R^2	*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 (>37° 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 m^2 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 $\beta \pm$ SE values from linear regression analysis for each covariate with square root transformed mean caffeine intake during the EDIC. 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 S3. Association of Caffeine Intake During the DCCT with SIF

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

Data shown are $\beta \pm$ SE values from linear regression analysis for caffeine intake with $SIF1_{LED\ 375\,nm[0.6,\ 0.2]}$ and $SIF14_{LED456\,nm[0.4,\ 0.8]}$ (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 m^2, DCCT eligibility HbA1c, mean DCCT HbA1c, and mean EDIC HbA1c as covariates.

[a]Ln transformed.

Supplementary Table S4. Association of Mean Caffeine Intake During the DCCT and EDIC Jointly with SIF

SIF outcome (excitation wavelength), model, predictor	*Model* R^2	$\beta \pm SE$	P *value*
SIF1 (375 nm)[a]			
M1			
DCCT mean caffeine	13.4%	0.000128 ± 2.34E-05	5.34E-08
EDIC mean caffeine		0.00018 ± 3.67E-05	1.14E-06
M2			
DCCT mean caffeine	37.0%	4.74E-05 ± 2.13E-05	2.62E-02
EDIC mean caffeine		0.000157 ± 3.18E-05	9.16E-07
SIF14 (456 nm)[a]			
M1			
DCCT mean caffeine	11.4%	8.25E-05 ± 2.69E-05	2.18E-03
EDIC mean caffeine		0.000265 ± 4.21E-05	4.58E-10
M2			
DCCT mean caffeine	26.0%	2.58E-05 ± 2.62E-05	3.25E-01
EDIC mean caffeine		0.000219 ± 3.91E-05	2.85E-08

Data shown are $\beta \pm$ SE values from linear regression analyses for both mean caffeine intake during DCCT and EDIC with $SIF1_{LED\ 375\,nm[0.6,\ 0.2]}$ and $SIF14_{LED\ 456\,nm[0.4,\ 0.8]}$ ($n = 1{,}181$). M1 includes only DCCT and EDIC caffeine intake as predictors in the model. M2 is additionally adjusted for age, sex, skin tone, clinic latitude, smoking status, any estimated glomerular filtration rate <60 mL/min/1.73 m^2, DCCT eligibility HbA1c, mean DCCT HbA1c, and mean EDIC HbA1c as covariates.
[a]Ln 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

	Out of n = *210*
Demographic characteristic	
Male sex	101 (48.1%)
Age (years)	49.3 ± 7.3
Diabetes duration (years)	40.6 ± 7.0
Smoking status[a]	
Never	123 (58.6%)
Former	55 (26.2%)
Current	23 (11.0%)
Any eGFR < 60 ml/min/1.73 m^2 to date (yes)[b]	60 (28.6%)
Glycemic exposure measured as mean HbA1c (%) (mmol/mol)[c]	8.6 ± 1.0 (70 ± 11)
Mean caffeine intake (mg/day)	294 ± 250
Time between caffeine intake assessment and SIF1 (years)[d]	18 ± 3.0
rs1495741 genotype (AA/AG/GG)[e]	101/68/11
$SIF1_{LED\ 375nm,\ kx=0.6,\ km=0.2}$ (arbitrary units)[f]	3.3 ± 0.24
$SIF14_{LED\ 456nm,\ kx=0.4,\ km=0.8}$ (arbitrary units)[f]	0.43 ± 0.24

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

[a]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.

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

[c]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).

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

[e]Thirty subjects did not have rs1495741 genotype data available.

[f]Ln transformed.

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

	N (AA/AG/GG)	*Predictors*	$\beta \pm SE$	P *value*
SIF1 (375 nm)[a]	180 (101/68/11)	rs1495741	−0.08 ± 0.02	0.002
		Caffeine	0.0001 ± 0.00008	0.12
SIF14 (456 nm)[a]	140 (77/56/7)	rs1495741	−0.13 ± 0.03	1.7E-05
		Caffeine	0.0002 ± 0.00009	0.004

Data shown are $\beta \pm$ SE values from linear regression analyses for the effects of rs1495741and caffeine intake effects when both included in the same model with $SIF1_{LED\ 375\,nm[0.6,\ 0.2]}$ and $SIF14_{LED\ 456\,nm[0.4,\ 0.8]}$ after additionally adjusting for age, sex, smoking, and estimated glomerular filtration rate <60 mL/min/1.73 m^2. $SIF14_{LED\ 456\,nm[0.4,\ 0.8]}$ was not measured in participants who had SIF measured in 2007–2009; therefore only 140 subjects had genotype, caffeine, and $SIF14_{LED\ 456\,nm[0.4,\ 0.8]}$ measures available in those analyses.

[a]Ln transformed.