

SUPPLEMENTAL MATERIAL

Correlation Between Absolute Intra-Pair Difference of Adjusted Trait Values and (a) Co-Twin Contact Frequency and (b) Age at Separation From Co-Twin

Phenotype	MZ			DZ		
	r*	p-value	n	r*	p-value	n
(a) Contact frequency						
Cystatin C	-0.046	.09	1348	-0.030	.08	3345
Creatinine	-0.024	.38	1344	-0.018	.31	3348
eGFR(Cys C)	-0.031	.26	1352	-0.028	.11	3370
MDRD(Crea)	-0.024	.38	1344	-0.017	.32	3347
Cdk-epi(Cys C+Crea)	-0.019	.48	1351	-0.030	.09	3364
Cdk-epi(Cys C)	-0.031	.26	1352	-0.029	.10	3369
Cdk-epi(Crea)	-0.013	.64	1350	-0.021	.22	3360
(b) Age at Separation						
Cystatin C	0.016	.55	1352	-0.008	.66	3361
Creatinine	0.018	.50	1348	-0.011	.53	3365
eGFR(Cys C)	0.022	.41	1356	-0.023	.17	3387
MDRD(Crea)	0.018	.50	1348	-0.011	.51	3364
Cdk-epi(Cys C+Crea)	0.018	.52	1355	-0.023	.18	3381
Cdk-epi(Cys C)	0.022	.42	1356	-0.016	.34	3386
Cdk-epi(Crea)	0.014	.60	1354	-0.014	.42	3377

*Spearman correlation coefficient, Note: p-values remained insignificant when stratified by sex

Descriptive Statistics of Phenotypes Raw Values and Values After Log Transformation (where applicable)

Phenotype	Class	N	Mean	SD
Cystatin C				
<i>Unadjusted raw values</i>	MZ	3157	1.0037	0.2297
	DZ	9156	1.0228	0.3032
<i>Adjusted, z-transformed</i>	MZ	3157	-0.0393	0.9268
	DZ	9156	0.0063	0.9747
Creatinine				
<i>Unadjusted raw values</i>	MZ	3157	76.4523	16.2827
	DZ	9156	77.8594	25.6711
<i>Adjusted, z-transformed</i>	MZ	3157	-0.0190	0.9306
	DZ	9156	-0.00087	0.9541
Machine eGFR (Cystatin C)				
<i>Unadjusted raw values</i>	MZ	3157	84.5388	21.4733
	DZ	9156	83.3211	21.9672
<i>Adjusted, z-transformed</i>	MZ	3157	0.0352	0.9808
	DZ	9156	-0.0118	1.0051
MDRD (Creatinine)				
<i>Unadjusted raw values</i>	MZ	3157	83.2342	16.8222
	DZ	9156	83.0576	18.4596
<i>Adjusted, z-transformed</i>	MZ	3157	0.0042	0.9102
	DZ	9156	-0.0083	0.0230
CKD-epi (Creatinine)				
<i>Unadjusted raw values</i>	MZ	3157	81.1792	13.8058
	DZ	9156	80.8516	14.1886
<i>Adjusted, z-transformed</i>	MZ	3157	0.0173	0.9795
	DZ	9156	-0.0054	0.9993
CKD-epi (Cystatin C)				
<i>Unadjusted raw values</i>	MZ	3157	77.0878	19.1120
	DZ	9156	76.1896	19.5713
<i>Adjusted, z-transformed</i>	MZ	3157	0.0343	0.9822
	DZ	9156	-0.0118	1.0058
CKD-epi (Creatinine + Cystain C)				
<i>Unadjusted raw values</i>	MZ	3157	77.9351	15.7393
	DZ	9156	77.1999	16.1028
<i>Adjusted, z-transformed</i>	MZ	3157	0.0341	0.0892
	DZ	9156	-0.0114	1.0042

Adjustment and z-Score Standardization, Stratified by Zygosity

Univariate ACE/ADE estimates for the lowest quintiles for all Clearance equations

Phenotype	Sex	h²	A	C	D	E	Qualitative sex diff	Quantitative sex diff
Cdk-epi(Cys C) [‡]	M	0.77	0.77	0.10		0.13		
	F	0.70	0.70	0.26		0.04		
	Both	0.82	0.82	0.13		0.05	n	N
Cdk-epi(Crea) [‡]	M	0.06	0.06	0.00		0.94		
	F	0.02	0.02	0.00		0.98		
	Both	0.00	0.00	0.00		1.00	n	N
eGFR(Cys C) [*]	M	0.29	0.23		0.06	0.71		
	F	0.92	0.52		0.40	0.07		
	Both	0.73	0.25		0.48	0.27	n	Y
MDRD(Crea) [‡]	M	0.09	0.09	0.18		0.73		
	F	0.18	0.18	0.33		0.49		
	Both	0.30	0.30	0.18		0.52	n	N
Cdk-epi(Cys C+Crea) ^{‡§}	M	0.00	0.00	0.00		1.00		
	F	0.00	0.00	0.00		1.00		
	Both	0.00	0.00	0.00		1.00	n	N

All values adjusted for age and sex. * GFR according to the MDRD formula. † Machine calculated GFR. ° GFR according to the CKD-epi formula. Lowest quintiles as follows: eGFR(Cys C) < 65; MDRD < 70.2; Cdk-epi(Cys C) < 59.6; Cdk-epi(Cys C+Crea) < 64.4; Cdk-epi(Crea) < 69.6. § There were no concordant pairs for this phenotype.

GCTA analysis lowest quintiles for all Clearance equations

Phenotype	Source	Variance	SE	P-value
eGFR(Cys C) *	V genotypic (g)	0.042	0.011	3.992E ⁻⁰⁵
	V environmental (e)	0.121	0.011	
	V phenotypic (p)	0.163	0.003	
	V (g) / V (p) §	0.257	0.067	
MDRD(Crea) †	V genotypic (g)	0.000	0.010	0.500
	V environmental (e)	0.161	0.010	
	V phenotypic (p)	0.161	0.003	
	V (g) / V (p)	0.000001	0.059	
Cdk-epi(Cys C+Crea) ‡	V genotypic (g)	0.024	0.010	0.006
	V environmental (e)	0.140	0.011	
	V phenotypic (p)	0.164	0.003	
	V (g) / V (p)	0.145	0.063	
Cdk-epi(Cys C) ‡	V genotypic (g)	0.017	0.010	0.038
	V environmental (e)	0.144	0.010	
	V phenotypic (p)	0.161	0.003	
	V (g) / V (p)	0.103	0.063	
Cdk-epi(Crea) ‡	V genotypic (g)	0.002	0.009	0.418
	V environmental (e)	0.159	0.010	
	V phenotypic (p)	0.161	0.003	
	V (g) / V (p)	0.011	0.057	

All values adjusted for age, sex and correlated principal components. SE= Standard error, V=variance. * Glomerular filtration rate (GFR) according to the modification of diet in renal disease (MDRD)-formula. † Machine calculated GFR. ‡ GFR according to the CKD-epi formula (Lowest quintiles as follows: eGFR(Cys C) < 65; MDRD < 70.2; Cdk-epi(Cys C) < 59.6; Cdk-epi(Cys C+Crea) < 64.4; Cdk-epi(Crea) < 69.6). § V(g)/V(p) = h²(heritability).

Bivariate heritability analysis Cystatin C & Creatinine vs Stroke & CAD

	Males	Females	Combined
Bivariate Correlations		Cystatin C vs STROKE	
Genetic (r_a)	0.26	0.36	0.29
Shared environmental (r_c)	0.59	-0.46	0.15
Non-shared environmental (r_e)	0.09	-0.07	0.02
Phenotypic correlation	0.16	0.16	0.16
mediated by:			
Bivariate heritability (biv h^2)	0.61	1.22	0.94
Bivariate shared environment (biv c^2)	0.10	0.00	0.00
Bivariate non-shared environment (biv e^2)	0.29	-0.22	0.06
Bivariate Correlations		Creatinine vs STROKE	
Genetic (r_a)	0.40	0.36	0.23
Shared environmental (r_c)	-0.56	-0.24	0.94
Non-shared environmental (r_e)	-0.04	-0.21	-0.08
Phenotypic correlation	0.07	0.09	0.08
mediated by:			
Bivariate heritability (biv h^2)	1.69	2.06	1.56
Bivariate shared environment (biv c^2)	-0.37	-0.04	0.00
Bivariate non-shared environment (biv e^2)	-0.32	-1.03	-0.56
Bivariate Correlations		Cystatin C vs CAD	
Genetic (r_a)	0.28	-0.20	0.20
Shared environmental (r_c)	-0.99	0.99	0.99
Non-shared environmental (r_e)	0.04	0.16	0.11
Phenotypic correlation	0.15	0.16	0.15
mediated by:			
Bivariate heritability (biv h^2)	0.90	-0.03	0.69
Bivariate shared environment (biv c^2)	0.00	0.58	0.01
Bivariate non-shared environment (biv e^2)	0.10	0.45	0.30
Bivariate Correlations		Creatinine vs CAD	
Genetic (r_a)	0.25	-0.20	0.11
Shared environmental (r_c)	0.11	1.32	-0.99
Non-shared environmental (r_e)	-0.12	0.18	0.03
Phenotypic correlation	0.09	0.04	0.07
mediated by:			
Bivariate heritability (biv h^2)	1.49	-1.74	0.85
Bivariate shared environment (biv c^2)	0.01	0.66	-0.04
Bivariate non-shared environment (biv e^2)	-0.50	2.08	0.19