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## **(Epi) genetics and twins**

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**Supplement to Chapter 4**

This research was originally published in Journal of Lipid Research. van Dongen J., Willemsen G, Chen WM, de Geus EJ, Boomsma DI. Heritability of metabolic syndrome traits in a large population-based sample. J.Lipid Res. 2013; 54:2914-2923. © the American Society for Biochemistry and Molecular Biology

**Supplemental Methods**

MZ twins are derived from a single fertilized egg cell (zygote) and therefore share (nearly) 100% of their segregating genes. DZ twins (who are derived from two zygotes) and non-twin siblings share on average 50% of their segregating genes. Parents share 50% of their genetic material with their children. Common environmental influences may be shared by siblings (“sibling-shared environmental effects”) or by individuals who share a household (“shared household effects”). In our study, the parents of twins who live together may share household effects, but household effects are not likely to contribute largely to the similarity of siblings and of parents with their offspring because the offspring in our study are adults, thus most live on their own. All family members share 0% of  $V_E$  by definition. Assuming that the variation of a trait is caused by A, D, C (sibling-shared) and E ( $V_P = V_A + V_D + V_C + V_E$ ), the phenotypic covariance of family members can be expressed as a function of  $V_A$ ,  $V_D$ ,  $V_C$  and  $V_E$  (i.e. covariance MZ twins =  $V_A + V_D + V_C$ , covariance DZ twins and sibs =  $1/2 V_A + 1/4 V_D + V_C$ , and covariance parent-offspring =  $1/2 V_A$ ). Correlations, which represent a standardized measure of the shared variance between variables, are also frequently used to summarize the similarity of family members. Following from the equations for the covariances explained above, the phenotypic correlations among relatives can be written as:

$$\text{Phenotypic correlation MZ twins} = h^2 + d^2 + c^2$$

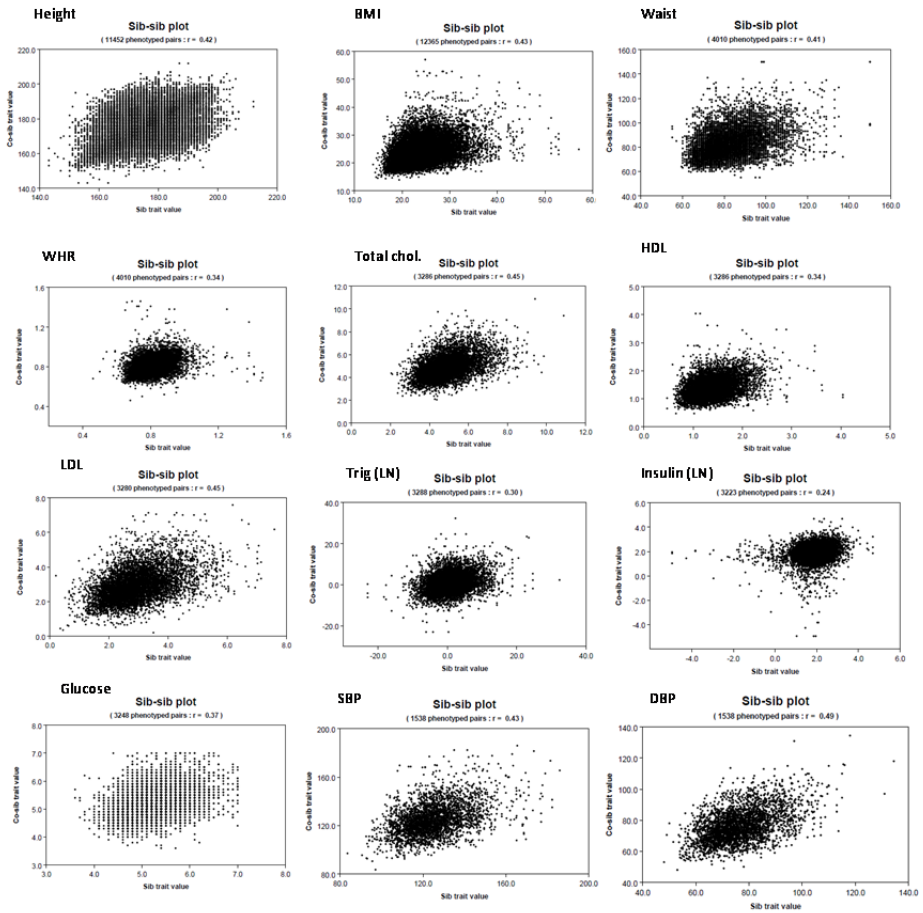
$$\text{Phenotypic correlation Parent-offspring} = \frac{1}{2} h^2$$

$$\text{Phenotypic correlation DZ twin / siblings} = \frac{1}{2} h^2 + \frac{1}{4} d^2 + c^2$$

Where  $h^2$  = proportion of variance due to additive genetic effects ( $V_A / V_P$ ),  $d^2$  = proportion of variance due to non-additive genetic effects ( $V_D / V_P$ ),  $c^2$  = proportion of variance due to sibling shared environment ( $V_C / V_P$ ).

Prior exploratory analyses of the twin family data in Mx indicated the absence of sibling-shared environmental effects for the vast majority of traits in our study; these effects were therefore not included in further analyses. Sex or age differences in  $V_A$ ,  $V_D$ ,  $V_C$  or  $V_E$  are indicated by differences in the pattern of phenotypic correlations in male versus female relatives (“quantitative sex difference”) or young versus old relatives (“quantitative age difference”). A smaller correlation in opposite-sex relatives compared to same-sex relatives indicates that different factors (e.g. different genes or different environmental factors) contribute to variation in males and females (“qualitative sex difference”). Similarly, if the phenotypic correlation decreases with increasing age difference between relatives, this is an indication that different factors may play a role at different ages (“qualitative age difference”).

**Supplemental Figure 1: Sib-pair resemblance for metabolic syndrome traits.** The figure shows scatterplots of trait values for all sib-sib relations in the sample (including DZ twins).



**Supplemental Table 1: Numbers and age of twins and family members**

Descriptives total sample			Descriptives of twins by zygosity			
	N	Age Men (SD)	Age women (SD)	N twins	Total N	Age (SD)
<b>BMI</b>						
Twins	12877 (M: 4666, F:8211)	28.79 (11.93)	30.71 (12.84)	MZM 1660	1901	29.83 (12.51)
Sisters	2065 (first: 1759, second: 306)		35.32 (12.87)	DZM 1088	1326	28.04 (11.87)
Brothers	1550 (first: 1333, second: 217)	33.86 (12.88)		MZF 3656	4060	32.60 (13.68)
Parents	10529 (Mo: 6036; Fa:4493)	54.81 (8.37)	52.24 (8.86)	DZF 2020	2345	29.90 (12.09)
Total	27021 (M: 10709, F: 16312 )	40.44 (16.35)	39.26 (15.30)	DOS 2462	3245	27.77 (11.02)
<b>Waist, WHR</b>						
Twins	4305 (M: 1496 , F: 2809)	33.95 (11.62)	35.45 (11.58)	MZM 568	684	35.17 (12.66)
Sisters	869 (first: 725, second: 144)		41.35 (12.88)	DZM 286	395	32.99 (11.20)
Brothers	575 (first: 500, second: 75)	40.03 (13.72)		MZF 1278	1514	36.52 (11.92)
Parents	3216 (Mo: 2052, Fa: 1164)	61.57 (7.34)	55.87 (10.60)	DZF 670	818	34.89 (11.51)
Total	8965 (M: 3235, F: 5730)	44.97 (16.58)	43.66 (14.78)	DOS 630	894	32.94 (10.00)
<b>Glucose and insulin</b>						
Twins	3724(M: 1262 , F: 2462)	33.95 (10.99)	35.84 (11.44)	MZM 398	579	35.07 (11.93)
Sisters	1143 (first: 818, second: 325)		42.12(10.58)	DZM 206	325	33.29(11.05)
Brothers	470 (first: 416 second: 54)	39.69 (13.12)		MZF 1018	1366	36.96 (11.80)
Parents	2226 (Mo: 1263, Fa: 963)	61.88 (7.05)	60.15(7.57)	DZF 526	695	35.12 (11.34)
Total	7563 (M: 2697, F: 4866)	44.94 (16.38)	43.61 (14.47)	DOS 498	759	33.01 (9.40)
<b>Lipids</b>						
Twins	3721 (M: 1273 , F: 2448)	33.92 (11.02)	35.56 (11.16)	MZM 394	583	34.87 (11.89)
Sisters	1185 (first: 842, second: 343)		41.93 (10.47)	DZM 212	329	33.49 (11.32)
Brothers	480 (first: 424, second: 56))	39.46(12.66)		MZF 1004	1352	36.61 (11.57)
Parents	2083 (Mo: 1210, Fa: 873)	61.62 (6.98)	60.26 (7.70)	DZF 526	694	32.91 (11.00)
Total	7469 (M:2628 , F: 4841)	44.15 (16.14)	43.28 (14.39)	DOS 502	763	32.95 (9.23)
<b>Blood pressure</b>						
Twins	2002 (M: 765 , F: 1237)	32.65 (10.46)	32.83 (10.72)	MZM 388	416	32.53 (9.83)
Sisters	243 (first: 213, second: 30)		35.23 (11.81)	DZM 196	213	32.38 (11.42)
Brothers	185 (first: 166, second: 19)	33.85 (12.02)		MZF 704	760	33.24 (10.72)
Parents	362 (Mo: 185, Fa: 177)	47.68 (6.33)	45.28 (5.70)	DZF 284	324	31.88 (10.66)
Total	2792 (M: 1127 , F: 1665)	35.21 (11.54)	34.57 (11.15)	DOS 238	289	33.10 (10.78)

M= Male, F=Female, Mo=Mother, Fa=Father, N=Number of subjects

**Supplemental Table 2: Twin correlations for metabolic syndrome traits stratified by age and sex.**

	Height	BMI	Waist	WHR	TC	HDL	LDL	Trig	Insulin	Glucose	SBP	DBP
<b>Young twins</b>												
<b>MZ twins</b>												
MZ males	0.91	0.73	0.65	0.48	0.78	0.79	0.74	0.72	0.40	0.54	0.59	0.63
MZ females	0.90	0.72	0.66	0.41	0.70	0.70	0.74	0.57	0.39	0.53	0.57	0.54
<b>DZ twins</b>												
DZ males	0.55	0.58	0.47	0.50	0.43	0.36	0.43	0.32	0.26	0.42	0.48	0.25
DZ females	0.54	0.33	0.20	0.26	0.41	0.38	0.43	0.12	0.09	0.35	0.56	0.49
DZ opposite	0.39	0.39	0.40	0.24	0.07	0.14	0.07	0.26	0.34	0.39	0.41	0.40
<b>Older twins</b>												
<b>MZ twins</b>												
MZ males	0.89	0.75	0.76	0.57	0.67	0.58	0.64	0.69	0.56	0.43	0.67	0.69
MZ females	0.88	0.70	0.68	0.51	0.71	0.58	0.71	0.57	0.44	0.50	0.64	0.68
<b>DZ twins</b>												
DZ males	0.42	0.38	0.40	0.36	0.17	0.44	0.11	0.25	0.15	0.20	0.10	0.17
DZ females	0.55	0.32	0.42	0.38	0.47	0.34	0.40	0.30	0.22	0.35	0.50	0.48
DZ opposite	0.57	0.19	0.27	0.34	0.47	0.34	0.41	0.2	0.25	0.25	0.22	0.26

Age categories were defined based on the median age of twins (young twins=twins with an age below the median and older twins=twins with an age above the median). The median age of twins was 32 years for all metabolic syndrome variables. For height only, birth year (median=1973) instead of age was used to define categories. TC= Total cholesterol. Trig= Triglycerides.

**Supplemental Table 3:** Age-specific heritability estimates of metabolic syndrome traits and height.

	Height	BMI	Waist	WHR	TC	HDL	LDL	Trig	Insulin	Glucose	SBP	DBP
<b>Young</b>												
$V_P$	42.4	11.92	104.68	0.004	0.81	0.12	0.65	20.5	0.51	0.25	132.6	92.72
$a^2$	0.84	0.33	0.37	0.29	0.39	0.36	0.42	0.25	0.23	0.58	0.61	0.62
$d^2$	0.07	0.47	0.38	0.16	0.28	0.27	0.27	0.32	0.25	0.00	0.00	0.00
$H^2$	0.91	0.79	0.75	0.45	0.67	0.63	0.69	0.57	0.48	0.58	0.61	0.62
SE	0.03	0.04	0.06	0.10	0.06	0.08	0.06	0.06	0.06	0.06	0.13	0.12
<b>Old</b>												
$V_P$	43.4	16.15	135.02	0.01	1.07	0.15	0.90	22.0	0.50	0.33	211.2	120.7
$a^2$	0.83	0.34	0.41	0.43	0.40	0.53	0.41	0.34	0.23	0.48	0.61	0.64
$d^2$	0.07	0.34	0.30	0.13	0.21	0.21	0.19	0.30	0.26	0.00	0.00	0.00
$H^2$	0.90	0.68	0.70	0.56	0.61	0.74	0.60	0.63	0.49	0.48	0.61	0.64
SE	0.03	0.03	0.05	0.10	0.06	0.07	0.05	0.06	0.07	0.05	0.08	0.10
$r_A$ Young-Old	0.96	1.00	1.00	0.85	1.00	0.90	1.00	1.00	1.00	0.64	0.24	0.56

The estimates were obtained from a model in which  $V_P$ ,  $V_A$  and  $V_E$  were allowed to differ between young and old subjects, whereas  $V_D$  was constant. Age categories were defined based on the median age of subjects (young=subjects with an age below the median and old=subjects with an age above the median). The median age was 35 years for SBP and DBP, 39 years for BMI, 40 years for HDL, LDL, total cholesterol and triglycerides, and 41 for insulin, glucose, waist and WHR. For height only, birth year (median=1966) instead of age was used to define categories. TC= Total cholesterol. Trig= Triglycerides. SE=Robust standard error of the broad heritability estimate from poly.  $r_A$  Young-Old=Correlation between additive genetic effects in young and old subjects.