

Why (an overview of) twin research?

In genetic epidemiology, the crucial first step is the establishment of meaningful genetic contribution to the trait of interest.

Although most of you may engage in molecular genetic approaches, you will nearly always cite twin and family studies in your introduction.

Setting the stage

Journal of Internal Medicine 2002; 252: 247–254

Heritability of death from coronary heart disease: a 36-year follow-up of 20 966 Swedish twins

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Twins born in Sweden between 1886 and 1925

Table 1 Mortality caused by coronary heart disease in the old cohort of the Swedish twin registry, by sex and zygosity

Age at death due to coronary heart disease	Men Monozygotic twins (n = 3280)	Dizygotic twins (n = 5956)	Women* Monozygotic twins (n = 4008)	Dizygotic twins (n = 7722)
36–55 years	20	39		
56–65 years	95	200	(36–65) 48	(36–65) 76
66–75 years	235	561	138	313
76–85 years	324	530	291	546
>85 years	83	121	141	246
Total	757	1451	618	1181

*The age categories of 36–55 and 56–65 years were merged into the age category of 36–65 years for female twins because of the small number of deaths.

4007 CHD-deaths

Heritability of CHD

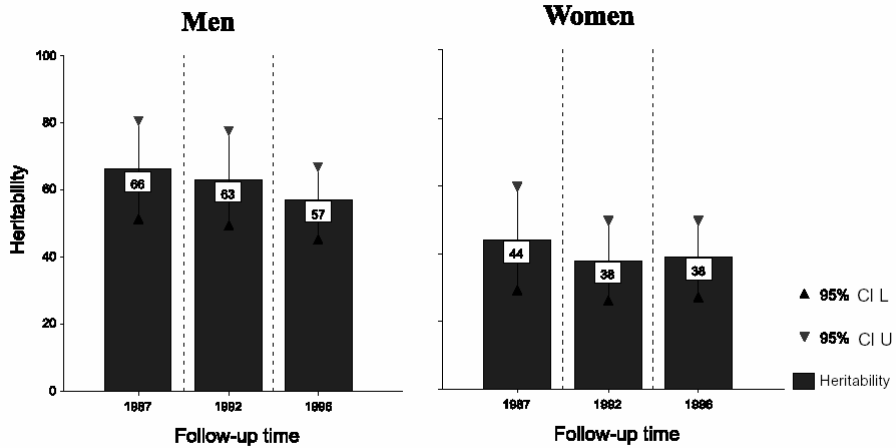
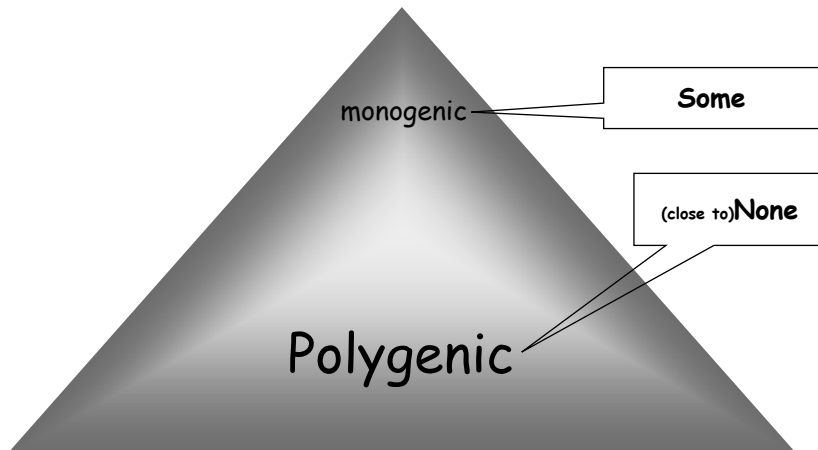
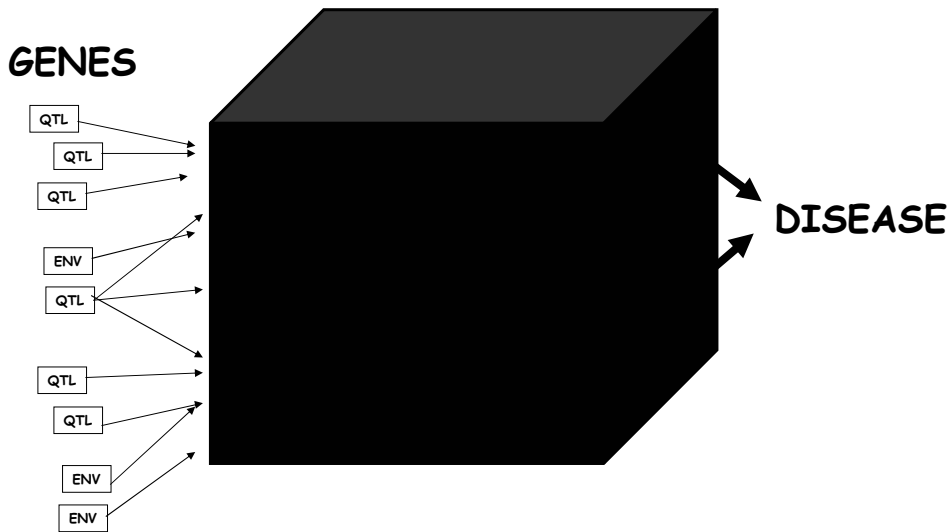


Fig. 2 Heritability estimates obtained from the best fitting model, the AE-model with regard to different follow-up times, by sex.

How many genes for cardiovascular disease have we found?



The endophenotype approach



Address: <http://www.genomeutwin.org/>

Complete GENOMEUTWIN twin pairs with resting blood pressure

MISSION STATEMENT RESEARCH

PARTNERS

	MZ	MD	ZM	MZ	DZ	DZ	DOS	age
Sweden	45	73	63	118				43-86 yr
Finland	151	236	122	155				37-76 yr
Denmark	53	146	158	167				18-66 yr
Netherlands	99	78	124	98	84			13-71 yr
Australia	89	40	222	106	106			30-86 yr
UK			498	1078				18-79 yr
								1624 MZ 2485 DZ

STUDIES OF EUROPEAN VOLUNTEER TWINS TO IDENTIFY GENES UNDERLYING COMMON DISEASES

We aim to capitalize special advantages of Europe in population genetics by efficient collaboration of twin researchers, genetic epidemiologists, molecular geneticists and mathematicians. Our goal is to identify clinical genetic and life-style risk factors for common diseases using European strengths in genetics, epidemiology and bioinformatics.

[More information](#)
[Download the genomeutwin logo](#)

MEMBER ENTRANCE

This project is supported by the European Commission under the programme 'Quality of Life and Management of the Living Resources' of 5th Framework Programme (contract number: G1V-CT-01254).



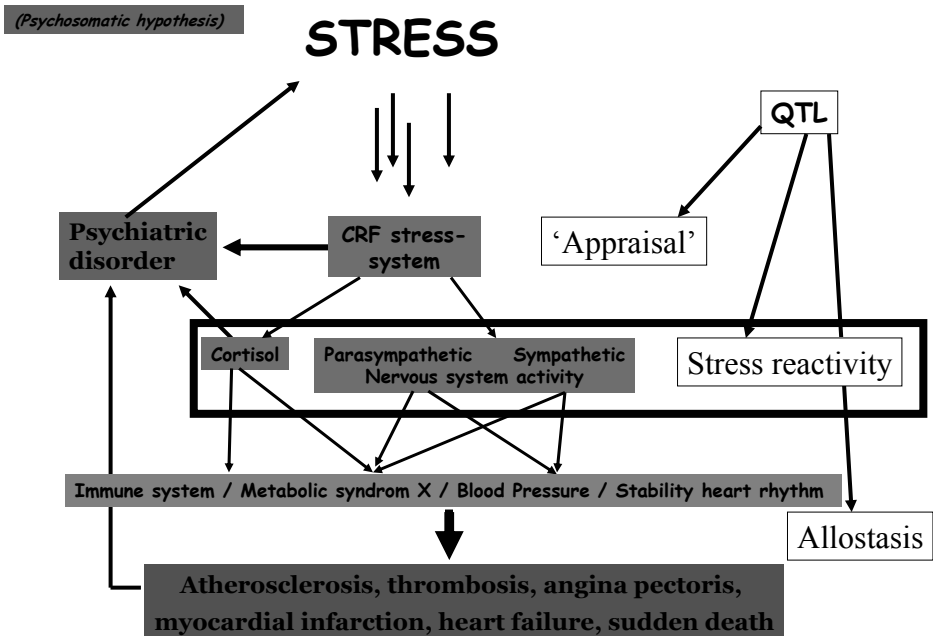
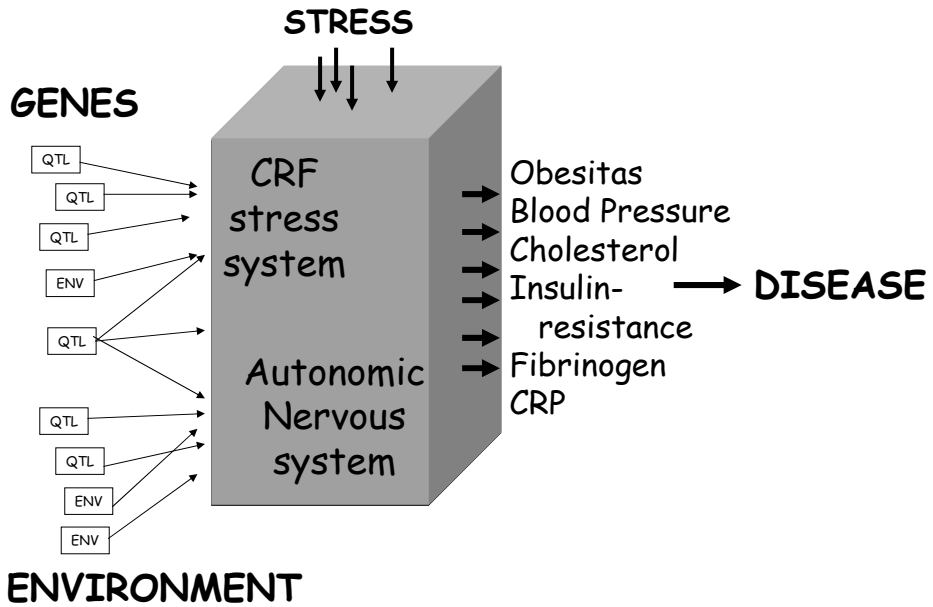
Heritability estimates for Systolic BP

	MZM	DZM	MZF	DZF	DOS	h ²	95% C.I.
Sweden	0.51	0.28	0.51	0.28		0.54	0.41-0.65
Finland	0.45	0.33	0.50	0.43		0.53	0.46-0.60
Denmark	0.60	0.32	0.70	0.46		0.64	0.60-0.71
Netherlands	0.50	0.25	0.47	0.36	0.26	0.54	0.44-0.62
Australia	0.47	0.15	0.55	0.28	0.17	0.52	0.44-0.59
UK			0.56	0.27		0.53	0.48-0.58

Heritability of major cardiovascular risk factors

	h ²	reference
		(review or study with very large samples)
Systolic BP	.52-.66	Evans et al., 2003, <i>Twin Res.</i>
Diastolic BP	.44-.66	Evans et al., 2003, <i>Twin Res.</i>
Obesity (BMI)	.66-.81	Schousboe et al., 2003, <i>Twin Res.</i>
HDL Cholesterol	.62-.75	Beekman et al., 2002, <i>Twin Res.</i>
LDL Cholesterol	.61-.83	Beekman et al., 2002, <i>Twin Res.</i>
Smoking (use)	.52-.59	Li et al., 2003, <i>Addiction</i>
Sports Participation	.59-.80	Stubbe et al., (in prep)
		(best guess so far)
Insulin-resistance	.37-.57	Schousboe e.a., 2003, <i>Diabetologica</i>
Fibrinogen	.32-.54	de Lange et al., 2001, <i>Lancet</i>
CRP	.40-.62	McGregor, 2004, <i>Clin Chem.</i>

The psychosomatic approach



A PubMed search

- »35393 hits for cortisol
- »10322 hits for plasma cortisol
- »683 hits for salivary cortisol

- »9 hits for cortisol AND (heritability OR MZ twins)

The heritability of basal Cortisol levels

Heritability of cortisol levels: review and simultaneous analysis of twin studies

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Received 5 June 2001; received in revised form 7 December 2001; accepted 11 December 2001

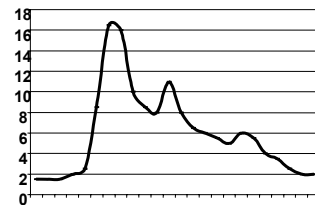
Abstract

Cortisol has a pivotal role in physical and mental health, but relatively few studies have paid attention to individual differences in cortisol levels and the etiology of these differences, in particular their possible genetic basis. In this article we review the existing literature on the heritability of cortisol levels. Most of the studies, which have been carried out in genetically informative samples, lack methodological consistency with regard to frequency and timing of sample collection. The circadian rhythm in cortisol levels was often not taken into account. A power analysis shows that none of these studies used adequate sample sizes to distinguish genetic from shared environmental influences as a cause for familial aggregation. Results of a simultaneous analysis of 5 comparable twin studies suggest a heritability of 62%. Hence, in order to study the contribution of genetic influences to variation in basal cortisol levels, future studies should be designed more rigorously with strict collection and sampling protocols, sufficient sample size and repeated measures across multiple days.

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MZ & DZ Correlations

rMZ: 0.58 rDZ: 0.38
rMZ: 0.57 rDZ: 0.49
rMZ: 0.50 rDZ: 0.27
rMZ: 0.59 rDZ: 0.60
rMZ: 0.50 rDZ: 0.24



Little account of
the diurnal rhythm

Salivary cortisol

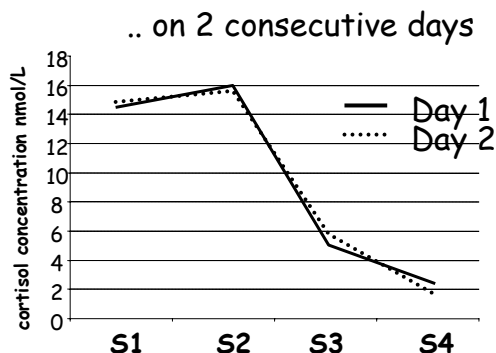
N=180 twin pairs (12 year olds), 4 samples per day:

S1: morning just before getting up (m.t. 07:30 am)

S2: half an hour after getting up (m.t.08:20 am)

S3: before lunch (m.t. 0:30 pm)

S4: in the evening (m.t. 8:30 pm)



Heritability of Daytime Cortisol Levels in Children

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and Dorret I. Boomsma¹

Behav Genet., 33, 2003

Parameter estimates for additive genetic, shared environmental and unique environmental influences with their 95% confidence intervals.

Sample	A	C	E
Day 1 awake	.22 (.09-.35)	-	.78 (.65-.91)
Day 2 awake	.24 (.09-.37)	-	.76 (.63-.91)
Day 1 a+30	.56 (.39-.69)	-	.44 (.31-.61)
Day 2 a+30	.59 (.42-.72)	-	.41 (.28-.58)
Day 1 lunch	.30 (.15-.43)	-	.70 (.57-.85)
Day 2 lunch	.21 (.11-.30)	-	.79 (.70-.89)
Day 1 eve	-	-	1.00 (1.0-1.0)
Day 2 eve	-	-	1.00 (1.0-1.0)



Genetic factors, perceived chronic stress, and the free cortisol response to awakening

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Abstract

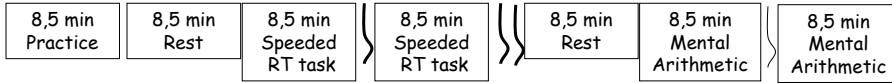
Recent studies have demonstrated that the free cortisol response to awakening can serve as a useful index of hypothalamus–pituitary–adrenal axis (HPA) activity. This endocrine marker is rather consistent, shows good intraindividual stability across time and appears to be able to uncover subtle changes in HPA regulation. The present twin study investigated genetic factors as sources of the intraindividual variation of the postl awakening response. Furthermore,

Heritability estimates of $h^2=0.40$ for the mean increase and of $h^2=0.48$ for the area under the response curve indicate a significant impact of genetic factors on cortisol levels after awakening. However, no genetic influence on the short day-time profile could be observed. Further-

Another PubMed search

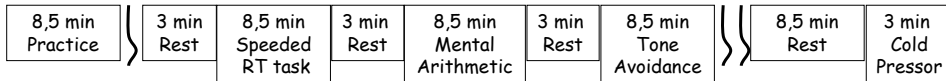
- 151913 hits for blood pressure
- 2749 hits for blood pressure AND (mental stress OR emotional stress OR psychological stress)
- 8 hits for blood pressure AND (mental stress OR emotional stress OR psychological stress) AND (MZ twins OR heritability)

320 Adolescent twins (16.7 yrs ±1.9): '87-'89



REST: average of both 8,5 minute resting periods.
STRESS: average across both 8,5 min Speeded RT periods and both 8,5 min Mental Arithmetic periods.

426 Middle-aged twins (37.2 yrs ±13.2): '93-'94



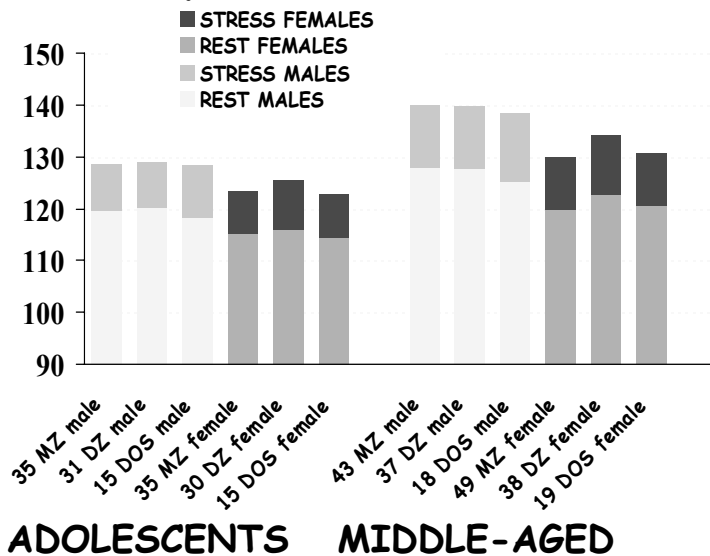
REST: average of first 3 minute and last 8.5 minute resting periods.
STRESS: average across 8,5 min Speeded RT, Mental Arithmetic and Tone Avoidance periods.

Both studies

- Dinamap BP monitor
- Nihon Kohden ICG/ECG/PCG modules
- Identical signal analysis software

} = Pause (no recording)

Systolic Blood Pressure



Heritability BP & HR

	MIDDLE AGED h ²	ADOLESCENTS h ²
SBP rest	.52	.53
SBP stress	.61	.64
DBP rest	.53	.51
DBP stress	.68	.58
HR rest	.64	.65
HR stress	.61	.62

Twin correlations & H²

	MIDDLE AGED			ADOLESCENTS		
	MZ	DZ	h ²	MZ	DZ	h ²
PEP rest	.58	.40	.58	.74	.32	.74
PEP stress	.56	.37	.56	.76	.35	.72
RSA rest	.38	.13	.31	.33	.09	.22
RSA stress	.47	.09	.47	.53	.27	.50

Stress uncovers genetic variance in cardiovascular regulation

The increase in heritability during stress suggests that measuring under stress can uncover genetic variance that remains hidden at rest.

Measurement of cardiovascular parameters in a naturalistic setting may uncover even more genetic factors (with the added advantage that such genes will have high ecological validity).

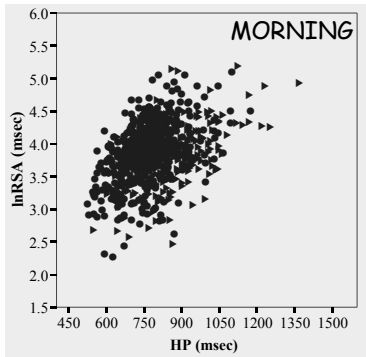
Netherlands twin family Study of Ambulatory monitoring

803 twins and siblings from 341 families

- Heart rate (HR) *VU-AMS*
- Blood pressure (DBP, SBP) *Spacelabs*
- Respiration rate (RR) *VU-AMS*
- Sympathetic cardiac drive (PEP) *VU-AMS*
- Parasympathetic cardiac drive (RSA) *VU-AMS*
- Daily Activity (diary prompting
each 30 min) *VU-AMS*
- Body Movement (vertical
accelerometer) *VU-AMS*

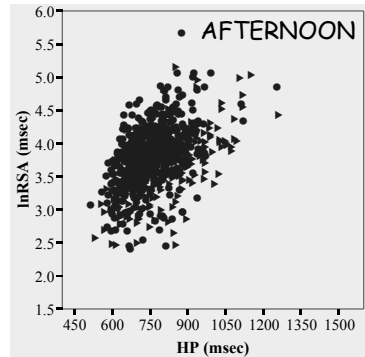
- Salivary Cortisol
(9, 11, 15, 20, 22:30,
awake, awake+30)





▶ Men

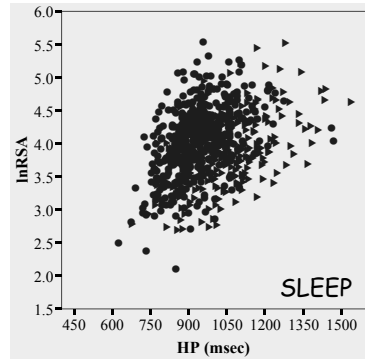
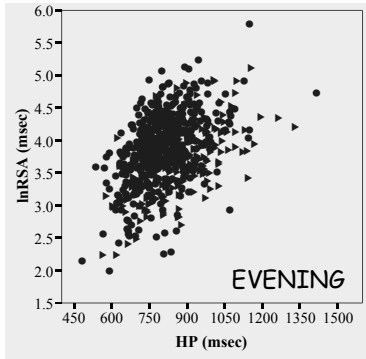
HP 846.8 (126.4)
 HP 810.1 (121.3)
 HP 858.7 (123.7)
 HP 1058.0 (139.5)
 lnRSA 3.8 (0.40)
 lnRSA 3.7 (0.51)
 lnRSA 3.9 (0.57)



(Sitting only)

● Women

HP 764.0 (101.5)
 HP 751.7 (94.2)
 HP 799.7 (106.7)
 HP 938.2 (109.4)
 lnRSA 3.9 (0.51)
 lnRSA 3.8 (0.50)
 lnRSA 3.7 (0.49)
 lnRSA 4.0 (0.54)



RSA

Heritability estimates
and their 95% CI's

Morning	.40	(.26 - .52)
Afternoon	.46	(.32 - .59)
Evening	.50	(.36 - .62)
Night	.54	(.41 - .65)

Heart Period

Heritability estimates
and their 95% CI's

Morning	.42	(.30 - .53)
Afternoon	.47	(.35 - .58)
Evening	.43	(.30 - .55)
Night	.50	(.38 - .60)

Reasons to be cheerful

- Often employed measures in this field (BP, HR, PEP, RSA level, cortisol awakening peak) have moderate heritability or better.
- The effects of some genes may be uncovered only under stress.
- The effects of some genes may be uncovered only during night time ambulatory recording.
- Psychosomatic endophenotypes provide added value in the search for genetic variation influencing cardiovascular disease risk.

The Netherlands Twin Registry, cardiovascular/hormonal crew:

**Nina Kupper
Mireille van den Berg
Meike Bartels**

**Danielle Posthuma
Gonneke Willemsen
Dorret Boomsma
Eco de Geus**



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