Heritability of Adult Body Height: A Comparative Study of Twin Cohorts in Eight Countries

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A major component of variation in body height is due to genetic differences, but environmental factors have a substantial contributory effect. In this study we aimed to analyse whether the genetic architecture of body height varies between affluent western societies. We analysed twin data from eight countries comprising 30,111 complete twin pairs by using the univariate genetic model of the Mx statistical package. Body height and zygosity were self-reported in seven populations and measured directly in one population. We found that there was substantial variation in mean body height between countries; body height was least in Italy (177 cm in men and 163 cm in women) and greatest in the Netherlands (184 cm and 171 cm, respectively). In men there was no corresponding variation in heritability of body height, heritability estimates ranging from 0.87 to 0.93 in populations under an additive genes/unique environment (AE) model. Among women the heritability estimates were generally lower than among men with greater variation between countries, ranging from 0.68 to 0.84 when an additive genes/shared environment/unique environment (ACE) model was used. In four populations where an AE model fit equally well or better, heritability ranged from 0.89 to 0.93. This difference between the sexes was mainly due to the effect of the shared environmental component of variance, which appears to be more important among women than among men in our study populations. Our results indicate that, in general, there are only minor differences in the genetic architecture of height between affluent Caucasian populations, especially among men.

Body height is a classic example of a polygenic inherited trait, which is also substantially influenced by environmental factors during fetal life, childhood, and adolescence (Sinclair, 1989). Recently, interest in body height as an indicator of childhood living conditions has increased remarkably in the field of epidemiology. In his seminal work Forsdahl (1977) suggested that poor living conditions in early life could be an important risk factor of cardiovascular disease. Later, Barker (1998) developed this hypothesis further and presented that environmental factors acting during fetal life and early childhood can induce permanent changes in metabolism, which predispose humans to cardiovascular disease. A number of studies confirm an inverse association between body height and cardiovascular disease, and these results are interpreted as offering support for the role of childhood environmental factors in the aetiology of these diseases (Davey Smith et al., 2000; Jousilahti et al., 2000), but the findings are not consistent and this explanation is unproven (Silventoinen et al., 2003a). In light of recent discussion about the possible reasons behind the association between body height and cardiovascular disease, research to improve understanding of factors affecting body height can also yield important insights into the cause of cardiovascular disease.

As well as being a measure of early life material circumstances, body height has also been used as a societal level indicator of the standard of living. The important focus here is on the dramatic increase in body height throughout the world during the 20th century. The increase in body height has been uniform with the possible exceptions of the two world wars, and it seems to be a universal process occurring worldwide in both affluent societies and in the developing world (Silventoinen, 2003). In Europe, mean body height has increased about 1 cm per decade during the 20th century (Cavelaars et al., 2000). This increase is very similar across European countries, and the differences in mean body height have generally remained stable over

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birth cohorts. However, one study (Silventoinen et al., 2001b) has reported that the difference in mean body height between Finland and Sweden has diminished in the cohorts born after the Second World War simultaneously when the Gross National Product in Finland, remarkable lower than in Sweden before the Second World War, started to increase rapidly and eventually reached the level of Sweden. This upward secular trend is probably due to reduction of environmental stress and may reflect a general increase in affluence in the world. This hypothesis is supported by strong aggregate level correlations between the increasing trends in body height and increase in the Gross National Product (Steckel, 1995) as well as reduction in menarcheal age in girls, widely accepted to be due to improved nutrition (Hauspie et al., 1996).

The genetic factors affecting the variation in body height has also been under intensive scrutiny. The earliest estimate for the heritability is available in the data used in the first population genetic study of body height by Karl Pearson and Alice Lee (1903) carried out in British families at the beginning of the last century. Heritability of body height in these data was estimated to be 0.79 by a later study (Crow & Kimura, 1970). A recent review (Silventoinen, 2003) identified 24 twin, 7 adoption, and 22 other family studies which reported familial correlations of body height. Many of those studies are problematic due to data collection issues or small sample sizes, but there are also a few well-conducted studies for which heritability estimates for body height varied from 0.60 (Husén, 1959) to 0.80 (Stunkard et al., 1986) in men.

Previous studies have shown substantial variation in mean body height between European populations. In this study, we examined whether there is corresponding variability in phenotypic variation and in the genetic architecture of body height. We chose to examine twin pairs within the age range of 20 to 40 years, so that growth would have been completed but decreases in body height with aging would not yet have occurred.

Data Sources

This study is based upon existing data in the GenomEUtwin twin cohorts. Where several twin cohorts were available in same country, we selected the latest born to minimize the cohort effect. The participating GenomEUtwin data sets are summarized in Table 1.

Australia

The Australian data were derived from two different studies: the first, conducted during 1980–1982 was of twins enrolled in the Australian Twin Register and born prior to 1964 (Healey et al., 2001); the second was conducted 1989–1990 and was of a younger cohort of twins from the Australian Twin Register born 1964–1971 (Kirk et al., 2000). Both studies were conducted as mailed questionnaires, which included self-reported items on height and weight. Combining twin pairs from both study cohorts gives a total of 3484 twin pairs between the ages of 20 and 40, with self-reported height for both cotwins and known zygosity (which was determined by a combination of traditional diagnostic questions plus blood grouping and genotyping). Between 1993 and 1998, subsets of the older cohort of twins were involved in one or more of a range of studies involving a clinical examination. In this examination height was measured with a stadiometer, resulting in standardised clinical measures of adult height for 2308 individuals from whom the reliability of self-report height

Table 1

Characteristics of the Twin Populations with Data on Height at ages 20–40 years in the GenomEUtwin Study

	Australia	Denmark	Finland	Italy	Netherlands	Norway	Sweden	United Kingdom
Birth cohort	1940–1971	1962–1982	1975–1979	1983	1953–1982	1967–78	1926–1958	1954–1981
Measurement occasions	1980–82, 1988	2002	2000–2002	2003	1991, 1993, 1995, 1997, 2000	1992,1998	1973	1994–2001
Response rate %	75, 78	75	88	enrolment ongoing	69, 44, 60, 57, 53	75 , 63	83	media enrolment
N complete twin pairs within the age group of 20–40 years	3484	4682	2002	697	2118	3637	8747	578
% female twins	63	58	55	59	61	55	53	100
% MZ twins	47	36	33	46	46	37	40	30
N opposite sex pairs	803	1350	674	169	522	1142	none	none
Self reported/ measured	Self	Self	Self	Self	Self	Self	Self	Measured
Measurement unit	cm	cm	cm	cm	cm	cm	cm	cm
Zygosity	Q	Q	Q	Q	Q	Q	Q	genotyping

Note: Q means that zygosity has been diagnosed by a validated questionnaire method.

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could be estimated (see Healey et al., 2001, for details of zygosity and clinical measures).

Denmark

The height data were collected from the 2002 twin survey of the Danish Twin Registry (Skytthe et al., 2002). A total of 14745 respondents from the birth cohorts 1962–1982 were selected. Respondents with unknown or uncertain zygosity (851 twins) were excluded. Also excluded were 4068 twins with responses from only one twin in a pair, and 231 pairs were excluded due to missing height in one of the twins. The final sample thus includes a total of 4682 twin pairs.

Finland

Height was assessed in the FinnTwin16 fourth wave questionnaire in 2000 to 2002 (Kaprio et al., 2002). At the time of analyses, there were 4657 respondents, of which 269 twins with uncertain zygosity were excluded, as well as 370 with responses from only one twin in the pair. There remained a total of 2009 twin pairs with both twins included and of known zygosity, aged 23–27 years. In seven pairs, height was missing on one or both twins, leaving a final sample size of 2002 pairs.

Italy

In Italy 4827 potential twin pairs born in 1983 (mean age = 19.8 years) residing at the same parental address were contacted by questionnaires mailed in April–May 2003 (Stazi et al., 2002). At the time of the analysis (end of June 2003) 603 letters were not delivered (untraceable addressee). Out of 874 replies, 38 claimed not to be twins, 96 twin pairs refused to enter the study, and 12 replies were from only one twin in a pair. Thirteen were of unknown zygosity, and so 715 pairs were used for the modelling analysis. In 18 pairs, height measure was missing in one twin. Nearly all (~93%) of twin pairs were actually living together.

The Netherlands

As part of a longitudinal study on health and lifestyle, questionnaire booklets were sent in 1991, 1993, 1995, 1997, 2000 to twins, family members, and partners registered with the Netherlands Twin Register (Boomsma et al., 2000; Boomsma et al., 2002). In total, 16,609 participants completed a questionnaire at one or more of these surveys. At each survey participants were asked for their height. For the purpose of this study, we selected all height data reported when participants were aged from 20 to 40 years, being born between 1953 and 1982. If data were available for more than one questionnaire, the latest completed questionnaire data were used, while giving preference to surveys in which both twins participated. The total sample included 5018 twins. In 2118 cases, both twins of a twin pair participated. In 765 cases, only 1 member of the twin pair participated. Zygosity was determined from DNA for 535 twin pairs, in all other cases zygosity was determined from questionnaire data. In 10 cases, 3 complete and 7 incomplete twin pairs zygosity was missing.

Norway

The twins participating in the program of research at the Norwegian Institute of Public Health were born from 1967 through 1979, and were identified through information about plural births contained in the National Medical Birth Registry. The height data were collected from two questionnaire studies conducted in 1992 and 1998 (Harris et al., 2002). The combined first and second questionnaire samples include 9478 twins who responded to at least one of the questionnaires.

Sweden

Data are from the 1973 cohort of the Swedish Twin Registry, which includes the largest sample of twin pairs with height data who were from 20 to 40 years of age at the time of testing (Lichtenstein et al., 2002; Pedersen et al., 2002). The 1973 cohort includes 13197 monozygotic (MZ) and same-sex dizygotic (DZ) twin pairs (26394 individuals) between 15 and 47 years of age. An additional 319 twin pairs with uncertain zygosity were excluded. A final sample size of 8747 MZ and same-sex DZ twin pairs (17494 individuals) between 20–40 years of age were included in the analyses.

United Kingdom

Twins from the St Thomas' UK Adult Twin Registry were ascertained from the general population through national media campaigns in the United Kingdom (Spector & MacGregor, 2002). A large proportion of the twins have visited the Twin Research Unit at St Thomas' Hospital during which a large range of phenotypes was collected for different studies. Height, weight, and other general characteristics were measured. Fasting blood samples were taken for genotyping.

Measurement of Height

In seven countries, adult height measures were based on self-report from questionnaires, while in the UK it was based on measured height using a stadiometer. Information from validation studies of self-reported body height was available from Australia, Finland, and the Netherlands. Among Australian twins, the reported correlation between self-reported and measured height was 0.92 for both females (1525 subjects) and males (783 subjects). In a subsample of the Finnish data set, the correlation between self-reported height and later measured height was 0.97 in men (N = 96) and 0.96 in women (N = 116), with a mean overall difference of 0.28 cm. In the Netherlands, among subjects with self-reported height, who completed the 1997 questionnaire, and who also had their height measured soon afterwards (N = 466 twins) the correlation was 0.93.

Statistical Methods

Genetic modeling was conducted separately by sex, using scripts available on the GenomEUtwin Mx-script library.[1] Standard univariate twin modeling based on linear structural equations is used in this study (Neale and Cardon, 1992). The model assumes that phenotypic variation can be due to variation in additive genetic (A), dominant genetic (D), shared environmental (C), and specific environmental (E) components. The correlations between the environmental components are expected to be the same within all twin pairs regardless of zygosity (1 for shared and 0 for specific environment), but the correlations in the genetic components differ between MZ (1 for the both

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genetic components) and DZ twins (0.5 for additive and 0.25 for dominant genetic component). Our data, which include only twin pairs but not adopted twins or other relatives, do not allow us to estimates simultaneously C and D components. In modeling, we primarily selected the model, which explained the observed covariance matrix best (i.e., provided the best χ^2-value for each study population separately for men and women). In order to provide comparability, we present, however, both ACE and AE models for each population. Age was adjusted for if a significant age effect was present. We did not use opposite-sex pairs in the modeling, because not all centers had data on such pairs.

Results

In men, mean height ranged from 177 cm to nearly 184 cm and in women from 163 cm to nearly 171 cm by country (Table 2). Mean body height was consistently slightly lower in MZ compared to same sex dizygotic (SSDZ) twins in men and women. The only exception was the female population in Norway where both MZ and DZ twins had the same stature. Within countries, there were generally no variance differences between MZ and SSDZ pairs. Standard deviations were very similar between countries and between zygosity groups.

Twin correlations for MZ male pairs were uniformly high in all countries, ranging from 0.87 to 0.94 in male and from 0.84 to 0.94 in female MZ pairs (Table 3). The corresponding DZ correlations were generally slightly more than one-half of the MZ correlations, ranging from 0.42 to 0.60. In six countries, correlations for opposite sex (OS) pairs were available and were generally slightly smaller than the corresponding same-sex pair correlations, with the exception of Italy, where the OS DZ pair correlation was as low as 0.30.

Table 4 gives the results for the genetic modeling for men and women. Among men, an AE model fitted the data best for each country except Sweden. In Sweden, the ACE model provided the best model fit and a significant shared environmental component was observed. The total phenotypic variance varied from 38.9 in Sweden to 48.3 in Italy, but the proportion of variance ascribed to genetic factors was quite similar in all AE models (0.87 to 0.94), but was expectedly lower (0.77) in Sweden under the ACE model.

Among women, the ACE model generally fitted the data better than the AE model, which provided the best fit in Italy, Norway, Sweden and the Netherlands. Total phenotypic variance varied in a similar fashion as in men, but estimates of heritability showed more variation. The lowest heritability was in the UK (0.68) and highest in the Netherlands (0.84) under an ACE model. Heritabilities under the AE models ranged from 0.89 to 0.93.

Discussion

We found substantial geographical variation in mean body height between our study populations; among both men and women the average body height was lowest in Italy and greatest in the Netherlands. A similar geographic pattern has also been found in previous comparative studies, which have shown that mean body height is lowest in Southern Europe and is generally greater in Northern Europe. Similarly, earlier research has also reported that the Dutch people are the tallest people in Europe (Cavelaars et al., 2000; Schmidt et al., 1995). Reasons for this geographic pattern are not fully understood, and both environmental and genetic differences between the populations offer potential explanations. However, since the increasing trends in body height during the last century have generally been very similar in European populations, it is probable that genetic factors are most important when explaining these geographic differences in height. If environmental factors were the main explanation, it is likely that the differences in body height between European countries would have diminished after the Second World War simultaneously with the increasing standard of living in Europe, as occurred in body height differences between Sweden and Finland (Silventoinen et al., 2001b). We also found that unlike the geographic variation in mean body height, there was no corresponding variation in the variance of body height distribution; rather the variances were very similar in the different populations. This is in accordance with previous findings that there is remarkable world wide variation in mean body heights but little variation in phenotypic variance of body height (Eveleth & Tanner, 1990).

An important question is how well twin data represent the general population with respect to body height. Previous literature has shown that twins are shorter at birth and have lower birth weight than singletons, but this difference disappears during childhood (Wilson, 1986). In the UK,

Table 2

Mean (and *SD*) Height by Country and Zygosity Group

	Australia	Denmark	Finland	Italy	Netherlands	Norway	Sweden	UK
MZm	178.4 (6.92)	180.9 (6.62)	179.3 (6.73)	176.5 (7.46)	182.6 (7.21)	180.4 (6.47)	176.9 (6.87)	n.a
DZm	178.9 (6.67)	181.7 (6.65)	179.5 (6.68)	178.0 (7.15)	183.1 (6.89)	181.0 (6.65)	177.2 (6.94)	n.a.
DOSm	179.4 (6.47)	181.8 (6.83)	179.7 (6.31)	177.1 (7.23)	183.6 (7.29)	181.3 (6.61)	n.a.	n.a.
MZf	166.5 (6.83)	167.8 (6.07)	165.3 (5.80)	162.8 (5.99)	169.3 (6.26)	167.3 (6.15)	164.2 (5.59)	164.2 (6.20)
DZf	166.8 (6.92)	168.2 (6.56)	166.3 (5.95)	163.4 (5.31)	170.0 (6.36)	167.3 (6.13)	164.6 (5.67)	163.7 (6.42)
DOSf	166.3 (6.79)	168.5 (6.15)	166.2 (5.49)	164.5 (6.20)	170.9 (6.84)	168.4 (6.00)	n.a.	n.a.

Note: MZm = male monozygotic twins, DZm = male dizygotic twins, DOSm = male dizygotic twins in opposite sex twin pairs, MZf = female monozygotic twins, DZf = female dizygotic twins, DOSf = female dizygotic twins in opposite sex twin pairs
*SD*s for Finland interchanged by sex

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Table 3

Twin Correlations for Height by Country and Zygosity Group

	Australia	Denmark	Finland	Italy	Netherlands	Norway	Sweden	UK
MZm	0.87	0.89	0.92	0.94	0.89	0.87	0.89	n.a.
DZm	0.42	0.47	0.53	0.57	0.47	0.49	0.56	n.a.
MZf	0.84	0.89	0.87	0.94	0.90	0.89	0.89	0.88
DZf	0.49	0.55	0.53	0.49	0.49	0.49	0.49	0.56
DOS	0.46	0.50	0.49	0.30	0.43	0.44	n.a.	n.a.

Note: MZm = male monozygotic twins, DZm = male dizygotic twins, MZf = female monozygotic twins, DZf = female dizygotic twins, DOS = opposite sex twin pairs

Table 4

Estimates of Variance Components and Heritabilities for Height

	Men							Women						
	Model	Va	Vc	Ve	Vp	h^2	$\Delta\chi^2_1$	Model	Va	Vc	Ve	Vp	h^2	$\Delta\chi^2_1$
Australia	ACE	40.26	0.00	6.30	46.60	0.87	—	ACE	33.80	6.00	7.60	47.40	0.71	—
	AE	40.26		6.30	46.60	0.87	0.00	AE	39.27		7.47	46.74	0.84	4.86*
Denmark	ACE	37.20	1.90	5.00	44.20	0.84	—	ACE	29.50	6.60	4.20	40.30	0.73	—
	AE	38.80		5.00	43.80	0.89	0.55	AE	35.20		4.20	39.40	0.89	13.38***
Finland	ACE	34.28	6.98	3.77	45.03	0.76	—	ACE	24.30	6.10	4.30	34.70	0.70	—
	AE	40.10		3.71	43.81	0.89	3.51	AE	29.61		4.25	33.86	0.87	5.25*
Italy	ACE	37.48	12.90	3.29	53.67	0.70	—	ACE	25.57	4.39	2.31	32.27	0.79	—
	AE	48.31		3.25	51.56	0.94	2.60	AE	29.34		2.30	31.64	0.93	0.99
Netherlands	ACE	38.71	5.49	5.66	49.86	0.78	—	ACE	33.49	2.23	3.94	39.65	0.84	—
	AE	43.66		5.62	49.28	0.89	1.20	AE	35.50		3.92	39.42	0.90	0.58
Norway	ACE	33.32	4.47	5.47	43.26	0.77	—	ACE	30.00	3.34	4.28	37.66	0.79	—
	AE	37.17		5.40	42.57	0.87	2.47	AE	32.95		4.25	37.19	0.89	2.33
Sweden	ACE	29.80	4.10	5.00	38.90	0.77	—	ACE	25.94	1.08	3.48	30.50	0.85	—
	AE	33.32		4.94	38.26	0.87	14.44***	AE	26.90		3.50	30.40	0.89	1.87
UK	ACE							ACE	26.96	8.16	4.56	39.68	0.68	—
	AE							AE	33.89		4.34	38.23	0.89	8.21**

Note: Va = additive genetic variance, Vc = shared environmental variance, Ve = specific environmental variance, Vp = total phenotypic variance, h^2 = heritability estimate, $\Delta\chi^2$ = change in the χ^2-values between AE and ACE models

*$p < .05$, **$p < .01$, ***$p < .001$

comparisons of means and variances for height between twins and singleton women from a population-based study revealed no difference in the means or variances between the MZ and the DZ twins or between the twins and the singletons (Andrew et al., 2001). Furthermore, a previous Finnish study compared mean body height in the twin cohort used in this study when the participants were aged 16–17 years to that of Finnish singletons at the same age and found no differences (Pietiläinen et al., 1999).

Although previous studies suggest that body heights in twins and singletons are comparable, in this study we found some differences between zygosity groups; in most of our study populations DZ twins were slightly taller than MZ twins. A similar difference is reported in a previous study of older Finnish twin cohorts (Silventoinen et al., 2000b). The reasons for this body height difference are not clear. It is possible that the placentation and pregnancy factors special to MZ pairs might be important, and that the shorter MZ twins are those who are monochorionic (Derom et al., 1995). However, even though a lower birth weight has been found among monochorionic MZ twins than among other MZ or DZ twins, and low birth weight predicts lower adult height in twins (Pietiläinen et al., 2001), it has been reported that this difference in body size between monochorionic twins and singletons disappears during childhood (Falkner & Matheny, 1995). The evidence that mothers of DZ twins are, on average, taller than mothers of MZ twins (MacGillivray et al., 1988) offers a further possible explanation.

In spite of the substantial variation in mean body height, especially among men, there was little variation in heritability estimates of body height. The estimates were also quite similar to those from an earlier, large male twin study in the USA; using military register data it was found that the heritability was 0.80 (Stunkard et al., 1986). In Finland, the heritability estimates were slightly lower in older birth cohorts (0.77) compared to this study. We have previously shown that heritability increased in Finland since the beginning of the last century among men, probably indicating a role of environmental factors (Silventoinen et al., 2000b). Among men, the estimates were lowest in Norway and Sweden, partly because ACE models fitted

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Table 5

LOD Scores greater than 2 from Genome Scans of Human Stature.

Chromosomal region	LOD Score	Population	Reference
1p21	2.25	African American	(Wu et al., 2003)
2q11	2.23	Caucasian (Finnish/Botnia)	(Hirschhorn et al., 2001)
3p14	2.31	Caucasian (Finnish)	(Hirschhorn et al., 2001)
3p26	3.17	Caucasian (British/Irish)	(Wiltshire et al., 2002)
3p26	2.06	European American	(Wu et al., 2003)
4q25	2.28	Caucasian (Finnish/Botnia)	(Hirschhorn et al., 2001)
5q31	2.14	Caucasian (North American)	(Deng et al., 2002)
5q31	2.26	European American	(Wu et al., 2003)
6q12	2.66	European American	(Wu et al., 2003)
6q25	3.85	Caucasian (Finnish/Botnia)	(Hirschhorn et al., 2001)
6q25	3.06	Caucasian (Dutch)	(Xu et al., 2002)
7q11-21	2.26	Caucasian (British/Irish)	(Wiltshire et al., 2002)
7q31	2.46	Multiple	(Wu et al., 2003)
7q35	3.40	Caucasian (Swedish)	(Hirschhorn et al., 2001)
7q36	2.91	Caucasian (Finnish)	(Perola et al., 2001)
8q24	2.52	Caucasian (Finnish)	(Hirschhorn et al., 2001)
9p1	2.09	Caucasian (Dutch)	(Xu et al., 2002)
9q21	2.01	Caucasian (Finnish/Botnia)	(Hirschhorn et al., 2001)
9q34	2.61	Caucasian (Finnish)	(Perola et al., 2001)
12p13	2.07	Caucasian (Finnish)	(Hirschhorn et al., 2001)
12q13	3.35	Caucasian (Finnish)	(Hirschhorn et al., 2001)
13q33	3.56	Caucasian (Finnish)	(Hirschhorn et al., 2001)
14q23	3.67	European American	(Wu et al., 2003)
17q21	2.69	Caucasian (Finnish/Botnia)	(Hirschhorn et al., 2001)
20p12	3.00	Pima Indians	(Thompson et al., 1995)
20q13	2.51	Caucasian (Finnish/Botnia)	(Hirschhorn et al., 2001)

Table 6

Heritabilities for Height in Published Genome Scan Datasets

Reference	Population	Heritability
(Hirschhorn et al., 2001)	Finnish/Botnia	~80%
	Finnish	>95%
	Saguenay-Lac-St.- Jean	~70%
	Swedish	~80%
(Xu et al., 2002)	Dutch	78%
(Deng et al., 2002)	Caucasian (North American)	73%
(Wu et al., 2003)	Multiple	75–98%
(Perola et al., 2001)	Finnish	69%
(Wiltshire et al, 2002)	Caucasian (British/Irish)	89%

better than AE models and may be less comparable. In Sweden this may be because the Swedish data represented older birth cohorts than other data sets; it was also a large data set with more power to detect small effects. A previous study on the Swedish Twin Registry data on middle-aged and older twins has shown that heritability of body height increased over the period from 1963 to 1984 from 0.69 to 0.84 (Harris, 1998), indicating that heritability has increased in the Swedish population as it has in Finland. This is further supported by comparisons to previous literature since in a Swedish study based on a military register data collected in 1948–1958, the heritability estimate was even lower (i.e., 0.60) (Husén, 1959; heritability estimated by Silventoinen, 2003).

The heritability estimates were highest in Italy both among men and women. This may be partly due to ongoing data collection in Italy focused on pairs living at the same address, and both MZ and DZ correlations are probably higher in the current data than they will be after data collection has been completed. However, the Italian data set also includes the youngest individuals of all the cohorts studied. Nevertheless, even if the effect of environmental factors in Italy is slightly underestimated, the high heritability of body height suggests that the smaller average body height in Italy compared to the other countries is not due to environmental factors but rather due to genetic differences between Italian and other European populations. Another, although less likely, explanation is that this difference in mean body height is due to environmental factors with equal effects on the whole population, thus limiting environmental variation. A systematic review of previous twin and family studies on body height showed substantial

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variation in the heritability estimates (Silventoinen, 2003). Our results suggest that this variation between previous studies is more likely to be due to poor data quality and small sample sizes of many previous twin data sets rather than actual substantial differences in the genetic architecture of body height itself.

Variation in the heritability estimates of body height was larger between our study populations in women compared to men. It has previously been suggested that growth in women is more resistant to environmental stress than that in men (Stini, 1969), but our results do not seem to support this hypothesis. A previous Finnish study has shown that the heritability of body height has decreased among women from younger birth cohorts, but a similar trend was not found in men (Silventoinen et al., 2001a). This greater temporal variation among women indicates that there are specific sources of environmental variation among women, which may also change over time. The source of this female-specific environmental variation is not clear but could be associated with the relatively high current prevalence of dieting and eating disorders, which may also explain the geographic variation in female populations in the present study. Other possible relevant factors are changes in maternal health and family size, which may affect women differently than men in the next generation.

Shared environmental factors contributed significantly to variation in body height only in one of the seven male populations, whereas among women it was more important and had an estimable effect in four of the eight female populations. The small effect of common environmental factors on body height in most of our male populations is slightly surprising since previous studies have shown substantial socioeconomic variation in body height both among men and women, which is considered to indicate the effect of childhood material environment on growth and adult body height (Silventoinen et al., 1999). In a previous Finnish twin study we also found that body height differences by educational level were mainly due to the effect of shared environmental factors (Silventoinen et al., 2000a). It is possible that since most of our study populations represent cohorts born in 1970s and 1980s, the standard of living among these cohorts in Europe has been so high that the role of social background is not detectable. The only male population for which we found evidence of shared environmental effects in this study (i.e., Sweden) represented older cohort than other populations, supporting the hypothesis that the genetic architecture may have changed over time.

We also found that the role of shared environment was more important in the female populations, and the stronger effect of environmental factors among women was mainly due to differences in the shared environmental factors. It remains an open question which specific factors related to the environment shared by female twins explain this difference. A previous Finnish study showed that shared environmental factors affecting body height are common not only to co-twins but also to their spouses (Silventoinen et al., 2003b). Thus, these environmental factors need not to be necessarily related only to family background but they may also be part of wider childhood environment.

It is possible that assortative mating may contribute to the results. Previous studies (for a review see Spuhler, 1982) have shown that assortative mating by body height is a universal feature of human behaviour. Assortative mating may inflate the effect of shared environment, since if it is due to the direct effect of the phenotype on spouse selection (i.e., phenotypic assortment) it violates the assumption of random mating presumed in the genetic modelling used in this study. In a previous Finnish study of twins and their spouses, we found that the spousal correlation in body height was partly due to phenotypic assortment, but also to the common background of spouses (social homogamy) contributed to this correlation (Silventoinen et al., 2003b). It is possible that the stronger effect of shared environment among women may be associated with differences in assortative mating between men and women. However, this is not a likely explanation since when we compared male and female twin pairs in this previous study, we did not find any major differences in assortative mating.

It is important to recognise that studies of MZ and DZ twins reared together are incapable of resolving all the components of variance that may be of interest. The negative confounding of dominance and shared environment is the most obvious shortcoming. Since phenotypic assortative mating for a trait of high heritability can substantially increase the additive genetic variance between both MZ and DZ pairs to the same degree, this extra genetic variance will be completely confounded with common environment, and negatively confounded with dominance effects. The only way to resolve all components is in an extended twin design, which includes parents, siblings, spouses and offspring of both MZ and DZ twin pairs. Such an analysis for body height in 30000 subjects from twin families has been carried out in the Virginia Twin Register by Eaves and colleagues (1999). They estimated the following proportions of variance: additive genetic 56% for males, 60% for females; assortment 16%, 17%; dominance 9%, 7%; total genetic 84%, 87%; shared environment 5%, 7%; unique environment including error 15%, 13%; genotype-environment covariance –1%, –8%. These results are from a sample in which malnutrition and major childhood infections have probably not affected growth. It is probable therefore that what in some countries in our study is estimated as common environment is in fact a combination of dominance, assortment, and possibly rather a small amount of genuine shared environment. It would be useful in the future to obtain estimates of the marital correlation for height in each country to estimate the proportion due to assortment.

We had information about opposite sex twin pairs available in six study populations, and thus were also able to consider the role of sex-specific genetic factors in body height. It is clear that genes on the Y-chromosome increase body height as seen by the sex difference in mean body height as well as the taller stature of XYY men compared to XY men (Ratcliffe et al., 1992), but it is not self evident that these genes affect variation of body height. Sex-specific genetic effects are indicated by lower phenotypic correlation among opposite-sex than same-sex siblings. Our results show only slight differences between correlations of opposite

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sex twins and same sex DZ pairs. This suggests that sex-specific genetic effects only weakly contribute to variation in body height. This confirms our previous results in a Finnish population, where we found no evidence for sex-specific genetic effects (Silventoinen et al., 2001a). The current results suggest that the sex-specific effect has only a small role in the genetic variance of body height, and the genes on the Y-chromosome affect mainly mean body height.

The next step in the study of the genetic architecture of body height is to try to identify the specific genes. In the last two decades success in molecular genetic studies to identify Mendelian disorders has been considerable. A fruitful approach to look for genetic variants for complex traits may be to screen genes known to cause Mendelian syndromes, which have the trait of interest as one of the phenotypes associated with the disorder. For body height, the picture is somewhat more complicated. There are hundreds of Mendelian traits for which abnormal body size characterizes the phenotype (OMIM, 2003). Many Mendelian traits are serious disorders affecting most phases in the development of the individual. Thus, it is plausible to assume that the growth disorder is, in most cases, secondary to the severe systemic effect the inherited disease has on the individual rather than due to a gene also affecting height in the normal population. Therefore, a better strategy would be to exclude such syndromic forms associated with height from the study population as much as possible. In addition, there is the more obvious need to control for other, less genetic syndromes, which affect growth, such as diabetes or malnutrition.

However, certain Mendelian traits do present interesting genes and loci for candidate genes even in general population. Given the trait difference between sexes, an obvious choice would be to study the sex chromosomes. The SHOX gene is associated with Turner's syndrome and idiopathic short stature (Rao et al., 1997). The gene is located in the pseudoautosomal region of the sex chromosomes, which has very high recombination rates and low linkage disequilibrium even for rare SNPs (May et al., 2002). It has also been linked to stature in one of the genome scans listed in Table 5 (Deng et al., 2002). This is also one of the rare genome scan reports, which has included non-autosomal regions in the results. It has been proposed that a RFLP in the non-recombining region of Yq is associated with male stature (Ellis et al., 2001); the deletion of this region also causes syndromic growth disorder (Ogata et al., 1995). Ellis and colleagues (2001) found an association suggesting a possible epistatic effect with biallelic polymorphisms in the aromatase gene (CYP19) and the non-recombining region of the Y-chromosome. Growth hormone 1 in 17q23.3, and the genes in the cascade associated with its actions, have a major effect on growth but mutations in these genes have been regarded as comparatively rare causes of short stature (OMIM, 2003). Only one of the published genome scans has linked 17q to stature (Hirschhorn et al., 2001). Of the genome scans published (Table 5), 7q has been linked to stature in four independent studies (Hirschhorn et al., 2001; Perola et al., 2001; Wiltshire et al., 2002; Xu et al., 2002), which makes this region clearly the most interesting autosomal region for candidate gene selection. Interestingly, this region has been linked to BMI as well (Feitosa et al., 2002), and contains the locus for the leptin gene. The heritabilities for height (Table 6) in the published genome scan data are similar in means to the twin data but show slightly greater variation being derived from sib-pair and family data, and a wider range of populations.

In conclusion, phenotypic variation and the genetic architecture of body height are very similar between populations in spite of the substantial variation in mean body height observed. Heritability of body height is lower among women than among men and there is also greater geographic variation in the heritability estimates among women. This is probably due to unidentified environmental factors specific to women only, which may vary more in time and between populations. Sex-specific genetic factors seem to have only little effect on body height. Specifying the genes generating the genetic variance of body height in general population is an important challenge for future research.

Endnote

1 Available from http://www.psy.vu.nl/mxbib/

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References

Andrew, T., Hart, D. J., Sneider, H., de Lange, M., Spector, T. D., & McGregor, A. J. (2001). Are twins and singletons

https://doi.org/10.1375/twin.6.5.399 Published online by Cambridge University Press

comparable? A study of disease-related and lifestyle characteristics in adult women. *Twin Research, 4*, 454–477.

Barker, D. J. P. (1998). *Mothers, babies and health in later life* (2nd ed.). Edinburgh: Churchill Livingstone.

Boomsma, D. I., Beem, A. L., van den Berg, M., Dolan, C. V., Koopmans, J. R., Vink, J. M., et al. (2000). Netherland's twin family study of anxious depression (NETSAD). *Twin Research*, 3, 323–334.

Boomsma, D. I., Vink, J. M., van Beijsterveldt, T. C., de Geus, E. J., Beem, A. L., Mulder, E. J., Derks, E. M., Riese, H., et al. (2002). Netherlands Twin Register: A focus on longitudinal research. *Twin Research, 5,* 401–406.

Cavelaars, A. E. J. M., Kunst, A. E., Geurts, J. J. M., Crialesi, R., Grötvedt, L., Helmert, U., et al. (2000). Persistent variation in average height between countries and between socio-economic groups: an overview of 10 European countries. *Annals of Human Biology, 27*, 407–421.

Crow, J. F., & Kimura, M. (1970). *An introduction to population genetics theory* New York: Harper and Row.

Davey Smith, G., Hart, C., Upton, M., Hole, D., Gillis, C., Watt, G., & Hawthorne, V. (2000). Height and risk of death among men and women: Aetiological implications of associations with cardiorespiratory disease and cancer mortality. *Journal of Epidemiology and Community Health, 54,* 97–103.

Deng, H. W., Xu, F. H., Liu, Y. Z., Shen, H., Deng, H., Huang, Q. Y., et al. (2002). A whole-genome linkage scan suggests several genomic regions potentially containing QTLs underlying the variation of stature. *American Journal of Medical Genetics*, *113,* 29–39.

Derom, R., Derom, C., & Vlietinck, R. (1995). Placentation. In L. Keith et al. (Eds.), *Multiple pregnancy: Epidemiology, gestation & perinatal outcome*. London: The Parthenon Publishing Group.

Eaves, L. J., Heath, A. C., Martin, N. G., Neale, M. C., Meyer, J. M., Silberg, J. L., et al. (1999). Biological and cultural inheritance of stature and attitudes. In C. R. Cloninger (Ed.), *Personality and psychopathology* (pp. 269–308). Washington, DC: American Psychopathological Association.

Ellis, J. A., Stebbing, M., & Harrap, S. B. (2001). Significant population variation in adult male height associated with the Y chromosome and the aromatase gene. *Journal of Clinical Endocrinology and Metabolism, 86*, 4147–4150.

Eveleth, P., & Tanner, J. M. (1990). *Worldvide variation in human growth* (2nd ed.). Cambridge: Cambridge University Press.

Falkner, F., & Matheny, A. (1995). "The long-term development of twins: Anthropometric factors and cognition. In L. Keith et al. (Eds.), *Multiple pregnancy: Epidemiology, gestation & perinatal outcome.* London: The Parthenon Publishing Group.

Feitosa, M. F., Borecki, I. B., Rich, S. S., Arnett, D. K., Sholinsky, P., Myers, R. H., et al. (2002). Quantitative-trait loci influencing body-mass index reside on chromosomes 7 and 13: The National Heart, Lung, and Blood Institute Family Heart Study. *American Journal of Human Genetics, 70*, 72–82.

Forsdahl A. (1977). Are poor living conditions in childhood and adolescence an important risk factor for arteriosclerotic disease? *British Journal of Preventive and Social Medicine, 31*, 91–95.

Harris, J. R. (1998). *The etiology of indivudual differences in health and anthropometric measures: A developmental study of adult twins.* The Pennsylvania State University.

Harris, J. R., Magnus, P., & Tambs, K. (2002). The Norwegian Institute of Public Health Twin Panel: A description of the sample and program of research. *Twin Research*, *5,* 415–423.

Hauspie, R. C., Vercauteren, M., & Susanne, C. (1996). Secular changes in growth. *Hormony Research*, *41*(Suppl. 2), 8–17.

Healey, S. C., Kirk, K. M., Hyland, V. J., Munns, C. F., Henders, A. K., Batch, J. A., et al. (2001). Height discordance in monozygotic females is not attributable to discordant inactivation if X-linked stature determining genes, *Twin Research*, 4, 19–24.

Hirschhorn, J. N., Lindgren, C. M., Daly, M. J., Kirby, A., Schaffner, S. F., Burtt, N. P., et al. (2001). Genomewide linkage analysis of stature in multiple populations reveals several regions with evidence of linkage to adult height. *American Journal of Human Genetics, 69*, 106–116.

Husén, T. (1959). *Psychological twin research.* Uppsala: Almqwist and Wiksells.

Jousilahti, P., Tuomilehto, J., Vartiainen, E., Eriksson, J., & Puska, P. (2000). Relation of adult height to cause-specific and total mortality: A prospective follow-up study of 31,199 middle-aged men and women in Finland. *American Journal of Epidemiology, 151,* 1112–1120.

Kaprio, J., Pulkkinen, L., & Rose, R. J. (2002). Genetic and environmental factors in health-related behaviors: Studies on Finnish twins and twin families. *Twin Research, 5,* 366–371.

Kirk, K. M., Bailey, J. M., Dunne, M. P., & Martin, N. G. (2000). Measurement models for sexual orientation in a community twin sample. *Behavior Genetics*, *30*, 345–356.

Lichtenstein, P., de Faire, U., Floderus, B., Svartengren, M., Svedberg, P., & Pedersen, N. L. (2002). The Swedish Twin Registry: A unique resource for clinical, epidemiological and genetic studies. *Journal of Internal Medicine*, *252,* 184–205.

MacGillivray, I., Samphier, M., & Little, J. (1988). Factors affecting twinning. In I. MacGillivray, D. M. Campbell, & B. Thompson (Eds.), *Twinning and twins.* Chichester: John Wiley & Sons.

May, C. A., Shone, A. C., Kalaydjieva, L., Sajantila, A., & Jeffreys, A. J. (2002). Crossover clustering and rapid decay of linkage disequilibrium in the Xp/Yp pseudoautosomal gene SHOX. *Nature Genetics*, *31,* 272–275.

Neale, M. C., Cardon, L. R. (1992). Methodology for genetic studies of twins and families. Dordrecht: Kluwer Academic Publisher.

OMIM (TM) Online Mendelian Inheritance in Man. McKusic-Nathans Institute for Genetic Medicine, John Hopkins University (Baltimore, MD) and National Center for Biotechnology Information, National Library of Medicine (Bethesda, MD; 2003). Retrieved from http://www.ncbi.nlm.nih.gov/omim/

Ogata, T., Yoshizawa, A., Muroya, K., Matsuo, N., Fukushima, Y., Rappold, G., & Yokoya, S. (1995). Short stature in a girl with partial monosomy of the pseudoautosomal region distal to DXYS15: Further evidence for the assignment of the critical region for a pseudoautosomal growth gene(s). *Journal of Medical Genetics*, *32,* 831–834.

Pearson, K., & Lee, A. (1903). On the laws on inheritance in man. *Biometrika*, 2, 356–462.

Pedersen, N. L., Lichtenstein, P., & Svedberg, P. (2002). The Swedish Twin Registry in the third millennium. *Twin Research, 5,* 427–432.

https://doi.org/10.1375/twin.6.5.399 Published online by Cambridge University Press

Perola, M., Ohman, M., Hiekkalinna, T., Leppavuori, J., Pajukanta, P., Wessman, M., et al. (2001). Quantitative-trait-locus analysis of body-mass index and of stature, by combined analysis of genome scans of five Finnish study groups. *American Journal of Human Genetics*, *69,* 117–123.

Pietiläinen, K. H., Kaprio, J., Rissanen, A., Winter, T., Rimpelä, A., Viken, R. J., et al. (1999). Distribution and heritability of BMI in Finnish adolescents aged 16 y and 17 y: A study of 4884 twins and 2509 singletons. *International Journal of Obesity and Related Metabolic Disorders, 23,* 107–115.

Pietiläinen, K. H., Kaprio, J., Räsänen, M., Winter, T., Rissanen, A., & Rose, R. J. (2001). Tracking of body size from birth to late adolescence: Contributions of birth length, birth weight, duration of gestation, parents' body size, and twinship. *American Journal of Epidemiology, 154,* 21–29.

Rao, E., Weiss, B., Fukami, M., Rump, A., Niesler, B., Mertz, A., et al. (1997). Pseudoautosomal deletions encompassing a novel homeobox gene cause growth failure in idiopathic short stature and Turner syndrome. *Nature Genetics, 16*, 54–63.

Ratcliffe, S. G., Pan, H., & McKie, M. (1992). Growth during puberty in the XYY boy. *Annals of Human Biology, 19*, 579–587.

Schmidt, I. M., Jorgensen, M. H., & Michaelsen, K. F. (1995). Height of conscripts in Europe: Is postneonatal mortality a predictor?" *Annals of Human Biology*, *22,* 57–67.

Silventoinen, K. (2003). Determinants of variation in adult body-height. *Journal of Biosocial Science, 35*, 263–285.

Silventoinen, K., Kaprio, J., Koskenvuo, M., & Lahelma, E. (2003a). The association between body height and coronary heart disease among Finnish twins and singletons. *International Journal of Epidemiology, 32*, 78–82.

Silventoinen, K., Kaprio, J., & Lahelma, E. (2000a). Genetic and environmental contributions to the association between body height and educational attainment: A study of adult Finnish twins. *Behavior Genetics, 30*, 477–485.

Silventoinen, K., Kaprio, J., Lahelma, E., & Koskenvuo, M. (2000b). "Relative effect of genetic and environmental factors on body-height: Differences across birth cohorts among Finnish men and women. *American Journal of Public Health, 90*, 627–630.

Silventoinen, K., Kaprio, J., Lahelma, E., Viken, R. J., & Rose, R. J. (2001a). Sex differences in genetics and environmental factors contributing to body-height. *Twin Research, 4,* 25–29.

Silventoinen, K., Kaprio, J., Lahelma, E., Viken, R. J., & Rose, R. J. (2003b). Assortative mating by body height and BMI: Finnish twins and their spouses. *American Journal of Human Biology* (in press).

Silventoinen, K., Lahelma, E., Lundberg, O., & Rahkonen, O. (2001b). Body-height, birth cohort and social background in Finland and Sweden. *European Journal of Public Health*, *11,* 124–129.

Silventoinen, K., Lahelma, E., & Rahkonen, O. (1999). Social background, adult body-height and health. *International Journal of Epidemiology, 28*, 911–918.

Sinclair, D. (1989). *Human growth after birth* (5th ed.). London: Oxford University Press.

Skytthe, A., Kyvik, K., Holm, N. V., Vaupel, J. W., & Christensen, K. (2002). The Danish Twin Registry: 127 birth cohorts of twins. *Twin Research, 5*, 352–357.

Spector, T. D., & MacGregor, A. J. (2002). The St Thomas' UK Adult Twin Registry. *Twin Research*, *5*, 440–443.

Spuhler, J. N. (1982). Assortative mating with respect to physical characteristics. *Social Biology, 29*, 53–66.

Stazi, M. A., Cotichini, R., Patriarca, V., Brescianini, S., Fagnani, C., D'Ippolito, C., et al. (2002). The Italian Twin Project: From the personal identification number to a national twin registry. *Twin Research, 5*, 382–386.

Steckel, R. H. (1995). Stature and the standard of living. *Journal of Economic Literature, 33,* 1903–1940.

Stini, W. A. (1969). Nutritional stress and growth: Sex difference in adaptive response. *American Journal of Physical Anthropology, 31*, 417–426.

Stunkard, A. J., Foch, T. T., & Hrubec, Z. (1986). A twin study of human obesity. *JAMA, 256*, 51–54.

Thompson, D. B., Ossowski, V., Janssen, R. C., Knowler, W. C., & Bogardus, C. (1995). Linkage between stature and a region on chromosome 20 and analysis of a candidate gene, bone morphogenetic protein 2. *American Journal of Medical Genetics*, *59*, 495–500.

Wilson, R. S. (1986). Growth and development of human twins. In F. Falkner, & J. M. Tanner (Eds.), *Human growth: Ecological, genetic, and nutritional effects on growth* (Vol. 3; pp. 197–211). London: Plenum Press.

Wiltshire, S., Frayling, T. M., Hattersley, A. T., Hitman, G. A., Walker, M., Levy, J. C., et al. (2002). Evidence for linkage of stature to chromosome 3p26 in a large U.K. Family data set ascertained for type 2 diabetes. *American Journal of Human Genetics, 70*, 543–546.

Wu, X., Cooper, R. S., Boerwinkle, E., Turner, S. T., Hunt, S., Myers, R., et al. (2003). Combined analysis of genomewide scans for adult height: Results from the NHLBI Family Blood Pressure Program. *European Journal of Human Genetics, 11,* 271–274.

Xu, J., Bleecker, E. R., Jongepier, H., Howard, T. D., Koppelman, G. H., Postma, D. S., & Meyers, D. A. (2002). Major recessive gene(s) with considerable residual polygenic effect regulating adult height: Confirmation of genomewide scan results for chromosomes 6, 9, and 12. *American Journal of Human Genetics.*

https://doi.org/10.1375/twin.6.5.399 Published online by Cambridge University Press