Sex Differences in Heritability of BMI: A Comparative Study of Results from Twin Studies in Eight Countries

Karoline Schousboe[1], Gonneke Willemsen[2], Kirsten O. Kyvik[1], Jakob Mortensen[1], Dorret I. Boomsma[2], Belinda K. Cornes[3], Chayna J. Davis[4], Corrado Fagnani[5], Jacob Hjelmborg[1], Jaakko Kaprio[6], Marlies de Lange[7], Michelle Luciano[3], Nicholas G. Martin[3], Nancy Pedersen[4], Kirsi H. Pietiläinen[6,8], Aila Rissanen[8], Suoma Saarni[6], Thorkild I.A. Sørensen[9], G. Caroline M. van Baal[2], and Jennifer R. Harris[10]

[1] *The Danish Twin Registry, Epidemiology, Institute of Public Health, University of Southern Denmark, Denmark*
[2] *Department of Biological Psychology, Vrije Universiteit Amsterdam, The Netherlands*
[3] *Queensland Institute for Medical Research, Brisbane, Australia*
[4] *Karolinska Institute, Stockholm, Sweden*
[5] *Italian National Institute of Health, Laboratory of Epidemiology and Biostatistics, Rome, Italy*
[6] *Department of Public Health, University of Helsinki, Finland*
[7] *Twin Research Unit, St. Thomas' Hospital, London, UK*
[8] *Obesity Research Unit, Biomedicum Research Institute, Helsinki Univ. Central Hospital, Finland*
[9] *Danish Epidemiology Science Centre, Institute of Preventive Medicine, Copenhagen University Hospital, Denmark*
[10] *The Norwegian Insitute of Public Health, Division of Epidemiology, Department of Genes and Environment, Oslo, Norway*

Body mass index (BMI), a simple anthropometric measure, is the most frequently used measure of adiposity and has been instrumental in documenting the worldwide increase in the prevalence of obesity witnessed during the last decades. Although this increase in overweight and obesity is thought to be mainly due to environmental changes, i.e., sedentary lifestyles and high caloric diets, consistent evidence from twin studies demonstrates high heritability and the importance of genetic differences for normal variation in BMI. We analysed self-reported data on BMI from approximately 37,000 complete twin pairs (including opposite sex pairs) aged 20–29 and 30–39 from eight different twin registries participating in the GenomEUtwin project. Quantitative genetic analyses were conducted and sex differences were explored. Variation in BMI was greater for women than for men, and in both sexes was primarily explained by additive genetic variance in all countries. Sex differences in the variance components were consistently significant. Results from analyses of opposite sex pairs also showed evidence of sex-specific genetic effects suggesting there may be some differences between men and women in the genetic factors that influence variation in BMI. These results encourage the continued search for genes of importance to the body composition and the development of obesity. Furthermore, they suggest that strategies to identify predisposing genes may benefit from taking into account potential sex specific effects.

Obesity, a condition of excessive fat accumulation, and its health consequences represent a global epidemic (World Health Organization, 2000) affecting all ages and increasing dramatically in prevalence among children and adolescents (Glaser, 1997). Obesity is associated with numerous health problems, particularly hypertension, dyslipidaemia, Type 2 diabetes, coronary heart disease, stroke, gallbladder disease, osteoarthritis, sleep apnoea and other respiratory problems, and endometrial, breast, prostate, and colon cancers (Eckel, 1997; NHLBI, 1998). Furthermore, increased body weight is associated with increased death rates for all cancers combined and site specific cancers (Calle et al., 2003).

Environmental explanations, such as sedentary lifestyles and high caloric diets (French et al., 2001; Hill & Peters, 1998) are cited as major factors driving the obesity epidemic. The main line of reasoning being that it is unlikely that changes in the gene pool could have occurred during the relatively short time period during which the prevalence of obesity has risen so rapidly. However, large family, adoption and twin studies provide evidence that genetic influences contribute substantially to variation in body mass index (BMI) with an average heritability estimate of around 70% (reviewed by Maes et al., 1997). Collectively, these findings suggest gene–environment interactions whereby obesogenic environments increase the risk of obesity among those who are genetically predisposed to weight gain.

Body mass index is a simple anthropometric measure used most often to quantify adiposity. It is calculated as weight (kg) / height $(m)^2$, two measures which can easily be obtained either by questionnaires or by directly measuring height and weight during a laboratory or home visit. A Danish study found that BMI correlates about 0.9 with body fat as assessed by bioelectrical impedance, indicating that BMI reflects body fat very well (Schousboe, 2003).

Address for correspondence: Jennifer R. Harris, The Norwegian Insitute of Public Health, Division of Epidemiology, Department of Genes and Environment, Post Box 4404 Nydalen, N-0403 Oslo, Norway. Email: jennifer.harris@fhi.no

However, research also reveals that the relationship between BMI and body fat may vary by age, gender and ethnic group (Gallagher et al., 2000).

Generally, estimates of heritability from family studies are smaller (approximately 0.25–0.40) than those derived from twin studies (approximately 0.70). The evidence for weaker genetic effects in family studies and, conversely, greater environmental effects may arise for several reasons. The mathematical basis for such discrepancies have been described (Allison et al., 2003) and reveal that when non-additive effects (gene–gene or gene–environment interaction) are important, which most likely is the case with BMI, then heritability estimates derived from twin studies are more reliable than those derived from family and adoption studies. Age- and sex-dependent effects have also been reported for fat and fat-free mass (Lecomte et al., 1997), and may contribute to the lower heritability estimates for BMI in family studies. Specifically, age-dependent effects could reflect developmental aspects of obesity whereby greater distances in age between relatives in the same family may be characterized by lower levels of familial resemblance for BMI. Furthermore, environmental factors, such as diet advice, availability of fatty foods, and level of physical activity, may change in the generation between parents and offspring and, to a lesser extent, in the smaller age interval between siblings.

Cross-sectional twin studies that explored age effects on genetic and environmental factors for BMI yield varying results, with some reporting decreasing heritability across age (Carmichael & McGue, 1995; Korkeila et al., 1991), while others report increasing values (Herskind et al., 1996). Two longitudinal studies with 28 and 6 years follow-up, respectively, reported stable heritabilities for BMI (Fabsitz et al., 1992; Korkeila et al., 1995). A related question concerns the stability of specific genetic effects, different genes may be active at different ages even if heritability does not change substantially.

Sex-specific effects on the variation of BMI have been examined in a few twin studies that included opposite-sex twin pairs. One study of twins aged 11 did not find evidence for sex-specific effects (Bodurtha et al., 1990), whereas two other studies of twins aged 16–17 (Pietiläinen et al., 1999) and 18–25 (Harris et al., 1995) report some differences in the sets of genes influencing variation in BMI in men and women. Two other twin samples using opposite-sex pairs found that non-additive genetic effects were sex- and age-specific (Neale & Cardon, 1992). These results are congruent with expectations that sex-specific effects may be age dependent and reflect differential genetic influences on weight development during growth and maturation. Understanding sex differences in heritable variation for BMI at different ages may help prevent and ultimately target treatment of excessive body fat accumulation and could be important in designing studies to identify genes for body composition.

Obesity is characterized by etiological heterogeneity whereby several different pathways lead to clinical manifestation. Heritability results from twin studies provide an estimate of all sources of genetic variation in the population being studied regardless of the specific genetic effects. The 2002 version of the annual review of the Human Obesity gene map describes the latest results from the numerous genetic studies conducted to identify genes that may predispose to obesity, and many other monogenic disorders associated with obesity are also known (Chagnon, 2003). Although some research implicates major genes in BMI (Moll et al., 1991), the genes identified to date do not explain variation in most common forms of obesity. Rather, there is ample evidence that these common forms of obesity are multifactorial with a polygenic mode of inheritance (Chagnon et al., 2003). Lack of statistical power due to small sample sizes is a main obstacle in identifying genetic determinants for obesity. Within the GenomEUtwin project the pooling of BMI data from eight countries can become an invaluable source for future molecular genetic studies of obesity.

The aims of the present study were to provide an overview of available data on BMI in the twin registries of the eight different countries participating in the GenomEUtwin project; describe the distribution of BMI in twins aged 20–29 and 30–39; examine the genetic and environmental variance structure of BMI in these age groups in each country; and test for sex differences and sex-specific effects in the genetic and environmental influences on BMI.

Methods

Twin Populations

The eight twin registries participating in the present study have previously been described thoroughly in a special issue of Twin Research (October, 2002). To provide an overview of the BMI data represented in these registers a table was compiled listing the number of pairs with height and weight data by age groupings (Table 1). For the purpose of this paper we narrowed the sample to two age bands (20–29 years and 30–39 years) that represent periods after adolescent growth but before mid-life. The twin registers from which the samples are drawn are described briefly below and characteristics of these samples are presented in Table 2.

Australia. The Australian data were derived from two different studies: the first, conducted during 1980–1982 was of twins enrolled on the Australian Twin register and born prior to 1964 (Healey et al, 2002); the second was conducted 1989–1990 and was of a younger cohort of twins from the ATR born 1964–1971 (Kirk et al, 2000). Both studies were conducted as mailed questionnaires which included self report items on height and weight. Combining twin pairs from both study cohorts gives a total of 3302 twin pairs between the ages of 20 and 40, with self-report height and weight 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 studies involving a clinical examination in which height and weight were measured with a stadiometer and accurate scales respectively, resulting in standardised clinical measures of BMI for 2292 individuals from whom the reliability

Table 1

Number of Twin Pairs by Country and Age Group with Reported and Measured Height and Weight

	Age													
	Birth	2–5	6–11	12–14	15–17	18–19	20–29	30–39	40–49	50–59	60–69	70–79	80–89	90–99
Australia		0	0			560	2495	807	421	349	157	61	5	0
	52,156*			685*	558*		5*	612*	415*	175*	128*	44*	7*	
Denmark	0	0	0	1025	1088	736	5548	5831	2796	2801	958	1050	401	29
						21*	172*	237*	183*	135*	9*			
Finland	4,896§	0	2253	2015	3267	3011	5888	5790	3549	4400	950	177	25	0
							215*	7*	147*	183*	240*	87*		
Italy	0	0	176	149	155	0	410	0	0	0	145	8	3	0
Netherlands				591	1414	1217	1808	261	179	87	39	9	2	0
	21,592*	24,448*	6,869*											
Norway		0	0	0	0	923	3970	525	0	0	0	0	0	0
	4179													
Sweden	0	0	0	0	1392	926	4761	4313	5757	2602	1443	463	0	0
UK	0	0	0	0	0	8	188	338	549	662	435	115	2	0
						32*	210*	376*	644*	797*	448*	48*		

Note: * Measured BMI
§ Reported by parents

of self-report BMI could be estimated (see Healey et al., 2002) for details of zygosity and clinical measures.

Denmark. The population-based Danish Twin Registry (Skytthe et al., 2002) currently comprises 132 birth cohorts of twins from 1870 to 2001, with a total of more than 71,000 pairs included. The cohorts born 1953–1982 participated in a questionnaire survey about various health problems and life style factors in 1994. If data on BMI were not available for both twins in a pair from the 1994 data BMI from a similar questionnaire carried out in 2002 was used in the analyses, if available. Zygosity determination has been based on questions about degree of similarity between co-twins.

Finland. The older part of the Finnish Twin Cohort (Kaprio & Koskenvuo, 2002) consists of all Finnish twin pairs of the same sex born before 1958 and of the opposite sex born 1938–49. The twins were identified through the Central Population Registry of Finland in 1974 and alive in 1975. Twin zygosity was determined by validated questionnaire methods initially in the entire cohort (Sarna et al., 1978). Height and weight were collected from the first questionnaire mailed to all pairs in 1975 and from two follow-up questionnaires in 1981 and 1990. From those questionnaires, pairs aged 30–39 at the time of a questionnaire with BMI data on both twins were identified. In 1986 a new twin panel was established comprising all twin pairs of same and opposite sex born in 1958–86. In the FinnTwin16 study of twins born 1975–1979 (Kaprio et al., 2002) a fourth wave of data collection has yielded 4657 respondents. After excluding 269 twins with uncertain zygosity, 370 with responses from only one twin in the pair, there were 2009 pairs (4018 twins) with both twins included and of known zygosity, aged 23–27yrs. In 21 pairs, height or weight was missing on one or both twins, leaving a final sample size of 1988 pairs.

Italy. A National Twin Registry (Stazi et al., 2002) is currently being established in Italy from a population-based database on "possible twins" identified by a code system with information on all individuals residing in Italy. Questionnaire data on height and weight is currently being collected from twins born in 1983 (aged around 20; mean: 19.8 years). Zygosity is determined by questionnaire.

Netherlands. The Netherlands Twin Registry (Boomsma et al., 2002) comprises a young cohort followed from birth and a cohort of adolescent and young adult twins. In this last cohort, data on height and weight were collected as part of a longitudinal study on health and lifestyle of twins and family members (parents and siblings) (Boomsma et al., 2000; Boomsma et al., 2002). If data were available from more than one questionnaire the most recently completed questionnaire data were used, while giving preference to times that twins completed data at the same time, even if this meant using BMI from an earlier period. When the twins provided data for both age bands, the data were used for analyses of each of the age bands. Zygosity was available from questionnaire data but also from DNA in 535 twins.

Norway. The population-based twin study at the Norwegian Institute of Public Health (NIPH) (Harris et al., 2002) currently includes pairs born from 1967 through 1979. The twins were identified through information about plural births contained in the national Medical Birth Registry. The height and weight data were collected from two questionnaire studies conducted in 1992 and 1998. When longitudinal data were available on a pair the latest value was used if the measurement fell within the same age band, and both measurement occasions were used if they represented the two age bands analysed here. Zygosity classification was determined using questionnaire methodology (Harris et al., 1995).

Sweden. The Swedish Twin Registry (Lichtenstein et al., 2002; Pedersen et al., 2002) has collected data on BMI

from two cohorts. The first birth cohort (1886–1925) was ascertained through all parishes in Sweden, the second cohort (1926–58) was compiled by use of nationalized birth registrations. Descriptive data have been provided for individuals derived from both cohorts and the modeling results are based only on information from the cohort born 1926–1958.

United Kingdom. The St. Thomas' UK Adult Twin Registry (Spector & MacGregor, 2002) was established in 1993 through national media campaigns. It consists of 5000 same sex twin pairs aged 18–80 from all over the UK. A majority of the twins have been seen clinically, but for the present analysis self-reported height and weight from large questionnaires sent out between 1999 and 2002 on health and lifestyle were used to calculate BMI. Zygosity was assigned using questionnaire data, but DNA confirmation was also possible for 50% of these twins.

Measures

In all samples BMI was based on self-reported weight in kg and height in cm. In addition, Australia, Finland, the Netherlands, and the UK also had measured values of BMI in sub samples of the twins. The correlation between self-reported and measured data was calculated from the data in these four countries. The Australian studies had data available on 2292 individuals for whom self-report BMI was obtained in 1988/1989 and measured BMI was obtained as part of a follow up study in 1993–1998. The correlation between self-report and clinically measured BMI was 0.87 for females (1512 subjects) and 0.85 for males (780 subjects). In the Netherlands Twin Registry a sub sample of 462 participants who completed the 1997 questionnaire were measured on height and weight soon thereafter. This correlation between self-reported and measured BMI was 0.83. For Finland, the corresponding correlation was 0.92 for 206 twins in the younger age group (unpublished data) measured on average one year later than the questionnaire; and 0.89 in older twins measured 3–4 years later than the 1990 questionnaire (Korkeila et al., 1998). In the UK sample, just over 2,500 twins who had completed the health questionnaires also visited the Unit within 3 years and had their BMI measured. The correlation between their self-reported and measured BMI was 0.92. This value may be slightly inflated due to experiment bias because the questionnaires were sent during the time period they were measured. However, the correlation was the same using the smaller number of twins (15%) who had responded to the questionnaire prior to visiting the Unit.

Statistical Methods

Quantitative genetic analyses were conducted to identify and quantify genetic and environmental influences on variation in BMI. Sex differences in these variance components were explored through a series of hierarchical procedures. Two questions regarding sex differences were addressed: do the same set of genes influence variation in BMI among males and females, and are there sex differences in the magnitude of the genetic and environmental variance components. These models are widely used and described in detail elsewhere (Neale & Cardon, 1992) and in this special issue by

Table 2
General Characteristics of the Twin Cohorts aged 20–39

	Australia	Denmark	Finland	Italy	Netherlands	Norway	Sweden	UK
Birth Cohorts	1) 1941–1960 2) 1963–1971	1953–1982	1) before 1958 2) 1975–1979	1983	1953–1982	1967–74 1967–1979	1) 1886–1925 2) 1926–1958	1960–1980
Year of Obtained BMI	1980, 1988–1989	1994	1975, 1981, 1990, 2000–2002	2003	1991, 1993, 1995, 1997, 2000	1992, 1998	1963, 1973	1999–2002
Response Rates on Each Occasion (%)	93, 73	86	89, 84, 77, 88	ongoing enrollment	69, 44, 60, 57, 53	75, 63	92, 83	65
Complete Twin Pairs Aged 20–39	3202	9595	7770	410	2139	3637	9067	475
Female Twins (%)	62.6	53.3	54.6	61.6	56.5	55	54.0	100.0
MZ Twins (%)	47.3	31.6	32.9	47.5	32.0	37	37.5	52.0
Opposite Sex Pairs	767	3010	1) 668 2) none	99	523	1142	none	none

Note: MZ = Monozygotic

Posthuma et al. Each model comprises a set of simultaneous linear equations specifying biometric expectations for the degree to which additive genetic (A), dominant genetic (D), shared-environment (C) and non-shared environment (E) contribute to the phenotypic co-variation between twins in the groups defined by zygosity and sex. The significance of specific parameters is assessed using chi-square difference tests and comparing nested models. The natural logarithm of BMI was analyzed and each country fit their model either to raw data or to variance-covariance matrices for the groups defined by zygosity and sex in the separate groups aged 20–29 years and 30–39 years. The model also parameterized age and sex as covariates. Prior to conducting the modeling analyses Pearson correlations were computed to estimate the degree of similarity in BMI between members of the pair. These correlations were stratified by age group, zygosity and sex and used to guide model selection (ACE, ADE) for the biometric analyses.

Results

Data on BMI in men were available in all the samples except for the UK. The mean BMI in men aged 20–29 ranged from 22.20 to 23.87, whereas these values were somewhat higher in the older age group aged 30–39, ranging from 23.41 to 24.69. In both age groups, Sweden exhibited the lowest mean BMI in men while Finland and Australia had the highest BMI in the younger and older age groups, respectively. The mean BMI in women ranged from 20.51–23.12 in the younger group and from 21.57–24.37 in the older group. In both age groups, Sweden exhibited the lowest, whereas UK exhibited the highest mean BMI in women. Although mean levels of BMI were higher among the men, variance in BMI tended to be greater among the women. Means and standard deviations of BMI by country, zygosity and sex are listed in Tables 3a and 3b for the younger and older age groups, respectively.

The percentage of each population, stratified by age group and sex, that met the requirements for obese (BMI $\geq$ 30 kg/m^2), overweight (BMI between 25–29.99 kg/m^2) normal weight (BMI between 18.01–24.99 kg/m^2) and underweight (BMI $\leq$ 18 kg/m^2) is presented in Table 4. Within each country (except Denmark) and age group a larger portion of the male population was overweight than are the females. The general age trend showed decreasing prevalence in the underweight category and an increasing prevalence in overweight and obese categories. An exception to this age trend was seen in the Dutch men and women and the Danish men, for whom the prevalence of underweight, overweight and obesity decreased across age, resulting in a greater percentage (95 % among the Dutch twins) of this age group falling within "normal" for BMI.

Twin correlations for BMI by zygosity, sex and age group (Tables 5a and 5b) show similar patterns across most countries. The magnitude of the difference between MZ and DZ correlations is consistent with a model containing additive genetic and environmental influences. However, for some samples, in particular in Italy and Norway, common environmental effects are also indicated. There is no evidence, based upon these correlations, for genetic dominance.

Next, an ACE model was analyzed that allows for age and sex effects and freely estimates the male-female genetic correlation (r_g).The standardized variance component results from fitting these models to the data from each country are graphed in Figures 1a (age 20–29) and 1b (age 30–39). The figures generally show similar variance structures for across countries and age for genetic and non-shared environmental factors. Most of the variance in BMI is due to the additive genetic component. Estimates of non-shared environment are fairly similar across all groups, but effects of common environment appear inconsistent.

To test the significance of common environment this parameter was excluded from the model and comparative model fitting procedures were conducted. The results are reported in Table 6 as chi-square differences in the model fit between the ACE and AE models. These analyses revealed that C could be excluded from the models without a significant deterioration in fit for all countries and age groups, except for the Norwegian males aged 20–29 yrs where an ACE model provided the best fit for the data (change in $\chi^2 = 14.494_{(1)}$, $p = .001$). The parameter estimates in Table 6 reflect those of the better fitting model for each age group and country. Estimates of heritability were consistently high among both age groups and both sexes; the lowest estimate (0.45) was from the data on the younger Norwegian men, otherwise the other estimates of heritability ranged from 0.64 to 0.84.

Table 7 presents the results testing for sex differences in variance components, comparing an ACE model in which estimates for men and women are allowed to differ with an ACE model in which the variances for men and women are constrained to be equal and r_g is freed in both models. The results were very consistent; variance components were not equal for men and women in either age group, nor in any of the countries, with the exception of Italy, where the difference in variance components between men and women was not significant.

Data on opposite sex twins were available for 6 countries for age 20–29 yrs and for 4 countries for age 30–39 yrs. Using these data, the assumption that the same genes influenced BMI in men and women was tested by comparing the full ACE model that allowed for variance differences in the parameters for men and women and estimated r_g, with the more restricted model which set r_g to 0.5. As shown in Table 8, results were not consistent across samples and age groups. There was evidence that different genes influence BMI in men and women for data from Australia, Denmark, and Finland in the younger age group, and for the Netherlands and Norway in the older age group. In Italy, slight changes in model parameters largely affected the data, possibly due to limited power and potential influences of C. Therefore, tests of sex-specific limitation in the Italian data were run using the AE model and results indicated that r_g was different from 0.5.

Overall, variation in BMI is largely influenced by additive genetic and unique environmental factors. Sex differences were found in the genetic and environmental variance structure for BMI and there is some evidence that different genes influence variation in BMI for men and women.

Table 3a

Means and Standard Deviations of BMI by Country and Zygosity for Age Group 20–29

	Australia Mean (*SD*)	Denmark Mean (*SD*)	Finland Mean (*SD*)	Italy Mean (*SD*)	Netherlands Mean (*SD*)	Norway Mean (*SD*)	Sweden Mean (*SD*)	UK Mean (*SD*)
MZm	22.75(2.66)	23.34 (2.93)	23.79 (3.26)	22.28 (2.98)	22.26 (2.54)	23.54 (2.74)	22.12 (2.36)	n.a.
DZm	23.44 (2.75)	23.40 (3.12)	23.86 (3.12)	22.52 (2.11)	22.60 (2.91)	23.52 (2.72)	22.25 (2.35)	n.a.
DZOSm	22.82 (2.68)	23.52 (3.01)	23.94 (3.11)	21.64 (4.95)	22.42 (2.75)	23.98 (2.98)	n.a.	n.a.
MZf	21.44(3.08)	21.98 (3.60)	22.11 (3.38)	20.51 (2.64)	21.67 (2.93)	22.16 (3.33)	20.44 (2.28)	22.87 (4.21)
DZf	21.72 (3.12)	22.26 (3.63)	22.48 (3.72)	20.94 (3.41)	22.03 (3.05)	22.48 (3.42)	20.55 (2.29)	23.39 (4.47)
DZOSf	21.63 (3.00)	22.33 (3.67)	22.24 (3.28)	20.31 (4.04)	22.06 (3.33)	22.19 (3.18)	n.a.	n.a.

Table 3b

Means and Standard Deviations of BMI by Country and Zygosity for Age Group 30–39 years

	Australia Mean (*SD*)	Denmark Mean (*SD*)	Finland Mean (*SD*)	Italy Mean (*SD*)	Netherlands Mean (*SD*)	Norway Mean (*SD*)	Sweden Mean (*SD*)	UK Mean (*SD*)
MZm	24.42 (2.97)	24.24 (2.80)	24.35 (2.96)	n.a.	24.56 (2.74)	24.52 (2.80)	23.31 (2.45)	n.a.
DZm	24.87 (3.17)	24.36 (2.84)	24.64 (2.98)	n.a.	23.90 (2.43)	24.62 (2.95)	23.47 (2.61)	n.a.
DZOSm	23.86 (3.39)	24.43 (3.14)	n.a.	n.a.	23.54 (3.63)	24.72 (3.09)	n.a.	n.a.
MZf	23.20 (4.11)	22.47 (4.11)	22.44 (3.24)	n.a.	23.28 (3.48)	22.96 (3.47)	21.39 (2.70)	23.89 (4.49)
DZf	23.12 (3.93)	22.79 (4.21)	22.70 (3.33)	n.a.	23.94 (4.21)	23.00 (3.72)	21.67 (2.77)	24.80 (4.96)
DZOSf	23.14 (4.02)	22.73 (3.88)	n.a.	n.a.	24.41 (3.04)	22.71 (3.12)	n.a.	n.a.

Note: MZ = monozygotic; DZ = dizygotic; DZOS = dizygotic opposite sex; m = males; f = females
n.a. = not assessed

Table 4

Percentages of Males and Females in Each Twin Cohort with BMI values classified as Underweight, Normal Weight, Overweight and Obese

	20–29 years								30–39 years							
BMI	Australia	Denmark	Finland	Italy	Netherlands	Norway	Sweden	UK	Australia	Denmark	Finland	Italy	Netherlands	Norway	Sweden	UK
≤ 18 m	5.2	1.1	0.7	1.9	1.9	0.5	2.0	n.p.	1.5	0.1	0.7	n.p.	0.1	0.0	0.7	n.p.
≤ 18 f	15.8	5.0	4.1	15.3	4.0	0.4	9.7	4.1	8.1	3.8	2.7	n.p.	0.4	2.4	5.2	1.9
> 18 and < 25 m	75.9	73.0	66.5	85.1	85.7	73.4	87.2	n.p	55.4	80.3	55.5	n.p.	95.5	62.7	75.7	n.p
> 18 and < 25 f	73.5	76.2	76.9	76.5	85.4	81.7	86.0	66.2	68.2	71.3	76.4	n.p.	94.2	74.5	84.2	58.4
≥ 25 and < 30 m	17.2	22.7	28.7	11.4	11.5	23.4	10.2	n.p.	37.4	17.5	39.0	n.p.	4.1	32.5	21.8	n.p.
≥ 25 and < 30 f	8.5	15.2	15.2	7.6	8.6	12.3	3.9	17.2	17.3	20.1	17.4	n.p.	4.1	20.0	9.2	23.0
≥ 30 m	1.7	3.2	4.1	1.6	0.9	2.7	0.7	n.p.	5.6	2.1	4.8	n.p.	0.3	4.8	1.8	n.p.
≥ 30 f	2.1	3.6	3.8	0.6	2.0	3.2	0.5	12.6	6.4	4.8	3.5	n.p.	1.0	3.2	1.3	16.8

Note: n.p. = not present; ≤ 18 = underweight, > 18 and < 25 = normal weight, ≥ 25 and < 30 = overweight, ≥ 30 = obese.

Table 5a

Twin Correlations (R) for BMI and Number of Pairs (N) Assessed by Zygosity and Sex for Twins Aged 20–29 years

	Australia R (*N*)	Denmark R (*N*)	Finland R (*N*)	Italy R (*N*)	Netherlands R (*N*)	Norway R (*N*)	Sweden R (*N*)	UK R (*N*)
MZm	0.67 (390)	0.77 (824)	0.74 (247)	0.83 (66)	0.65 (299)	0.69 (563)	0.77 (887)	n.a.
DZm	0.32 (260)	0.35 (897)	0.32 (304)	0.52 (43)	0.31 (222)	0.41 (479)	0.35 (1346)	n.a.
MZf	0.72 (768)	0.73 (1161)	0.78 (411)	0.83 (129)	0.79 (518)	0.74 (738)	0.73 (1054)	0.74 (89)
DZf	0.33 (486)	0.35 (1046)	0.37 (358)	0.58 (76)	0.41 (336)	0.35 (643)	0.36 (1472)	0.52 (75)
DZOS	0.18 (596)	0.30 (1620)	0.22 (668)	0.12 (96)	0.36 (473)	0.18 (968)	n.a.	n.a.

Table 5b

Twin Correlations (R) for BMI and Number of Pairs (N) Assessed by Zygosity and Sex for Twins Aged 30–39 years

	Australia R (*N*)	Denmark R (*N*)	Finland R (*N*)	Italy R (*N*)	Netherlands R (*N*)	Norway R (*N*)	Sweden R (*N*)	UK R (*N*)
MZm	0.72 (216)	0.62 (490)	0.73 (823)	n.a.	0.79 (33)	0.80 (74)	0.71 (664)	n.a.
DZm	0.43 (124)	0.33 (763)	0.32 (1857)	n.a.	0.19 (13)	0.31 (78)	0.30 (1033)	n.a.
MZf	0.74 (481)	0.73 (552)	0.66 (1070)	n.a.	0.63 (141)	0.75 (120)	0.75 (799)	0.77 (155)
DZf	0.43 (286)	0.34 (852)	0.32 (2032)	n.a.	0.22 (54)	0.40 (117)	0.34 (1154)	0.47 (156)
DZOS	0.33 (309)	0.22 (1390)	n.a.	n.a.	–0.07 (50)	0.05 (185)	n.a.	n.a.

Note: MZ = monozygotic; DZ = dizygotic; DZOS = dizygotic opposite sex; m = males; f = females
n.a. = not assessed

Discussion

GenomEUtwin contains an impressive amount of BMI data spanning childhood through old age. This study focuses on variation in BMI after adolescent development and before mid-life changes. Data were available on 20,608 complete pairs aged 20–29 and 16,930 complete pairs aged 30–39. Similar to previous results (James et al., 2001) mean BMI values are greater among men than among women, whereas the variance is greater among women in all countries. A general increase in mean BMI of about one kg/m^2 was found from the younger to the older age. Because height does not change in the age ranges under study here this increase may be interpreted as an age-related increase in actual weight. Even within each age group the model fitting analyses with age as a covariate revealed small but significant effects, indicating the importance of age in determining BMI.

Although overweight and obesity are increasing worldwide, most European countries do not have the high prevalence of frank obesity that is found, for example, in the USA. We examined differences in percentages of twins who were classified as obese, overweight, within normal weight, or underweight across age groups in the participating countries. In most of our populations the increase in mean BMI across the age groups reveals a distributional shift away from the normal and into the overweight range. However, such age effects should not be confounded with the increase in prevalence rates, which would manifest as younger cohorts being progressively heavier than the preceding cohorts. In our relatively young age group overweight is more pronounced among the men than among the women but more sophisticated measures of body composition would be needed to determine whether this is attributable to sex differences in muscle mass. Some of the inter-country differences in the prevalence of the different adiposity categories within and across age groups may be due to cohort effects as well as to differences in sample sizes and age distributions within the age groups. Future analyses based upon more refined stratification of birth cohorts will help differentiate age, period and cohort effects.

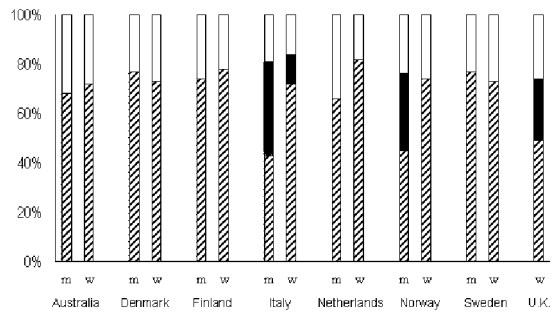

Figure 1a

Phenotypic variance from ACE model partitioned into additive genetic variance (diagonal lines), common environmental variance (black), and individual environmental variance (white) for men (m) and women (w) aged 20–29 years.

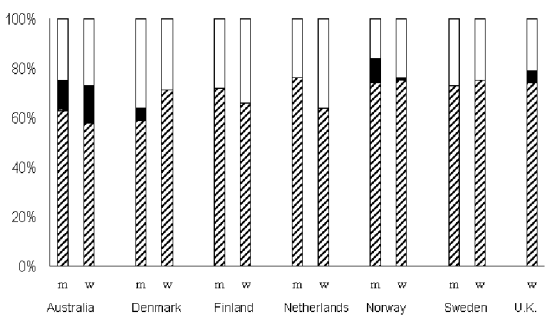

Figure 1b

Phenotypic variance from ACE model partitioned into additive genetic variance (diagonal lines), common environmental variance (black), and individual environmental variance (white) for men (m) and women (w) aged 30–39 years.

Our results confirm those from other twin studies reporting the importance of genetic and non-shared environmental influences. These findings were consistent in all groups with the exception of the data for young Norwegian men, where common environmental factors also were significant. Findings of significant shared environment can be followed-up by testing putative environmental measures in the models. For example, a more refined analysis of shared environmental effects in the Norwegian males would involve testing differences between pairs who are still living together versus those who have moved away from each other and by examining specific environmental measures such as physical activity. Participation in sports is quite common in Norway and physical activity has been shown to moderate genetic responses to weight gain (Heitmann et al, 1997). If the Norwegian male twins are more similar for their participation in sports-related activities than the females this could partly explain the shared environmental effect in the younger age group.

It is particularly important to note that variation in BMI was greater among the women than the men in all countries and in both age groups. The source of this extra variance is most likely related to a multitude of biological explanations (e.g., sex differences in the ability to deposit lean versus fat tissue) and differential environmental exposures (e.g., dieting fads among young women). While we are unable to address why BMI is more variable among women, our findings of sex differences in the genetic and environmental variance components should be interpreted within the context of sex differences in overall phenotypic variation. This is more easily visualized through inspection of the standardized variance components graphed in Figures 1a and 1b which shows highly similar variance structures for the male and female data in most groups. Thus, the finding of sex differences may largely reflect overall differences in phenotypic variation rather than substantially different heritabilities. However, similarity in the variance structures for men and women does not imply that sex-specific effects are not important. To the contrary, our collective data provide strong evidence that the sets of genes contributing to variation in BMI are not identical among men and women. This is not surprising given well-known male-female differences associated with multiple aspects of body composition (e.g.,

Table 6

Variance Component Estimates from an ACE Model and Differences in Fit Between ACE and AE Models

	Men			Women			Fit Statistics Between ACE and AE Models	
Country	a^2	c^2	e^2	a^2	c^2	e^2	$\chi^2_{(2)}$	AIC
Age 20–29								
Australia	0.67	—	0.33	0.72	—	0.28	0	–4
Denmark	0.77	—	0.23	0.73	—	0.27	0	–4
Italy	0.81	—	0.19	0.85	—	0.15	4.59	0.59
Finland	0.74	—	0.26	0.78	—	0.22	0	–4
Netherlands	0.66	—	0.34	0.81	—	0.19	0	–4
Norway	0.45	.31	0.24	0.74	—	0.26	14.49***	10.49
Sweden	0.77	—	0.23	0.73	—	0.27	0	–4
United Kingdom	na	na	na	0.75	—	0.25	2.02[a]	0.02
Age 30–39								
Australia	0.75	—	0.25	0.73	—	0.27	3.05	–0.948
Denmark	0.65	—	0.35	0.71	—	0.29	0.56	–3.438
Finland	0.72	—	0.28	0.66	—	0.34	0	–4
Italy	na	na	na	na	na	na	na	na
Netherlands	0.76	—	0.24	0.64	—	0.36	0	–4
Norway	0.84	—	0.16	0.76	—	0.24	0.27	–3.734
Sweden	0.73	—	0.27	0.75	—	0.25	0	–4
United Kingdom	na	na	na	0.79	—	0.21	0.13[a]	–1.872

Note: *** $p < .001$
na = not available
[a] on 1 *df*

Table 7

Model Fit Statistics Testing for Sex Differences in Variance Components

	20–20 years		30–39 years	
	$\chi^2_{(3)}$	AIC	$\chi^2_{(3)}$	AIC
Australia	40.40***	34.40	69.12***	63.12
Denmark	234.12***	228.12	321.09***	315.09
Finland	20.12***	14.12	139.47***	133.47
Italy	6.97	0.97	na	n.p.
Netherlands	46.63***	40.63	28.48***	22.48
Norway	62.68***	56.68	15.25**	9.25
Sweden	17.17***	11.17	na	na

Note: ** $p < .01$, *** $p < .001$
na = not available

Table 8

Estimated Correlations between Additive Genetic Deviations in Males and Females (r_g) and Model Fit Statistics Testing that r_g is the Same in Like and Unlike-sexed Pairs

	20–29 years			30–39 years		
	r_g[a]	$\chi^2_{(1)}$	AIC	r_g[a]	$\chi^2_{(1)}$	AIC
Australia	0.26	4.36*	2.36	0.31	0.62	–1.38
Denmark	0.39	5.51*	3.51	0.34	2.79	0.79
Finland	0.31	5.99*	3.99	na	na	na
Italy[b]	0.11	13.44***	11.44	na	na	na
Netherlands	0.44	0.51	–1.49	–0.08	4.02*	2.02
Norway	0.30	1.30	–0.70	–0.12	5.32*	3.22

Note : * $p < .05$, *** $p < .001$ [a]this value should be doubled to obtain the genetic correlation, [b]AE model

fat distribution, deposition and accumulation; metabolism) and with affects related to female reproduction. A UK twin study of females found a substantial heritability of body fat distribution independent of overall BMI which could be an additional factor in women (Samaras 1997). GenomEUtwin provides the opportunity to explore the nature of putative environmental factors, such as pregnancy effects (Korkeila et al., 1991; Korkeila et al., 1995) by incorporating other information available in the data bases. Since childbirth may be an environmental trigger affecting genetic expression an important next step would be to reanalyze these data including information on childbirth into account.

Potential biases in our findings may arise due to assortative mating or non-representativeness of twin samples. Other studies demonstrate positive assortative mating for BMI with values ranging from 0.10 to 0.15 (Allison et al., 1996; Knuiman et al., 1996; Maes et al., 1997; Magnusson & Rasmussen, 2002; Tambs et al., 1992); and it has even been suggested that assortative mating contributes significantly to the recent rise in obesity (Hebebrand et al., 2000). The small, but statistically significant effect of assortative mating could result in a slight overestimate of heritability (Magnusson & Rasmussen, 2002). Research examining partner correlations for relative weight over time (prior to marriage or cohabitation) reports a slight decrease in the correlation (Knuiman et al., 1996) and suggests that people tend to select partners with similar levels of relative weight, rather than the partners becoming more similar as a function of the duration of the relationship. Furthermore, a study of BMI in twins and their spouses (Silventoinen et al., 2003) found that social homogamy effects were stronger than phenotypic assortment effects.

Twins may not represent the general population if special intrauterine experiences or conditions of twinning predispose twins to developmental difficulties or illness. Comparisons of twins versus singletons for growth and BMI do not always yield consistent findings, and may be contingent upon age. For instance, a study of childhood growth in twin children aged 2–12 found that twins tend to overcome growth retardation. A Finnish study compared twins and singletons at 16.5 years old and found that the twin boys, but not the girls were leaner than singletons (Pietiläinen et al., 1999). Another study testing the hypothesis that environmental factors in utero may influence adult BMI analyzed 1,638 MZ pairs (Allison et al., 1995) and did not did not find evidence to suggest that intra-uterine period was critical for development of adult BMI. In other large twin studies (Baird et al., 2001; Johansson & Rasmussen, 2001; Pietiläinen et al., 2002) intra-uterine environment had small, but significant effects on adult BMI, but clearly, fetal time had more pronounced effects on adult stature than on BMI.

Birth weight is another factor that may further complicate comparisons of twins and singletons when studying BMI because birth weight is generally lower among twins (Luke et al., 1991). Body size has consistently been shown to track from birth to adulthood in twins (Pietiläinen et al., 2002) and singletons (Curhan et al., 1996b; Curhan et al., 1996a). Birthweight correlates positively with both height and weight in adulthood, whereas birth length correlates only with adult stature. The joint effects of genes and environments change from birth towards adulthood. In twins, environmental effects are more distinct during fetal time but most of the variance in final body size is explained by genes (Pietiläinen et al., 2002). Furthermore, parental BMI and height modulate the relationship between birth size and young adult body size (Pietiläinen et al., 2001). To examine representativeness of the samples studied here we compared values from the MONICA data sets[1] with the twin values for three of the countries (Denmark, Finland, and Sweden). Mean BMI was generally higher for singletons, whereas there was no consistency in the differences in variances between twins and singletons. This supports data from an age-matched study comparing twins and singletons in the UK found that middle-aged female twins, in particular MZs were slightly lighter than singletons (Andrew 2002). The ideal way to test the difference between singletons and twins would be to compare the BMI of twins with their non-twin siblings. These data are available for the Dutch and Finnish samples and will be analysed in the near future.

A major aim of the GenomEUtwin project is to combine the large datasets to find genes affecting BMI. The generally high heritability estimates obtained in the twin studies of BMI has already lead to a substantial interest in the search for obesity genes. The 2002 version of the annual review of the Human Obesity gene map is based on almost 600 references of studies of various phenotypes (e.g., BMI, body-fat mass, skinfolds and plasma leptin levels, in both humans and animal models) (Chagnon et al., 2003). Monogenic forms of obesity includes Mendelian syndromes with both autosomal dominant and recessive as well as X-linked inheritance, (e.g., Prader-Willi, Cohen, Bardet-Biedl syndromes) (Clement et al., 2002). Of 37 syndromes with known map locations there are 23 with well-defined genes or strong candidates (Chagnon et al., 2003). Single-gene mutations mostly fall into two groups: a group in which the mutations cause rare recessive forms of morbid obesity and multiple endocrine dysfunktions; that is, genes coding for leptin (LEP), the leptin receptor (LEPR) and pro-opiomelanocortin (POMC), and a single case of a mutation in the pro-hormone convertase 1 (PC1) which is important in the processing of POMC (Farooqi & O'Rahilly, 2000). The second group is non-syndromic obesity related to numerous mutations in the melanocortin 4 receptor (MC4R) gene, the most common monogenic form of obesity. It has recently been demonstrated that 5.8 % out of 500 probands with severe childhood obesity had mutations in MC4R and that clinical presentation was more severe among individuals homozygous for the mutation (Farooqi et al., 2003; Vaisse et al., 2000).

Association studies have identified 71 candidate genes for obesity related phenotypes. BMI is associated with mutations in 21 candidate genes (Chagnon et al., 2003). Linkage studies, including genome-wide scans have presented evidence for 139, including 68 QTLs, positive candidate genes. Candidate genes identified both by association and linkage studies includes LEP, LEPR, MC4R, Acid phosphatase 1, soluble (ACP1), Adenosine deaminase (ADA), Adrenergic Alpha 2B receptor and Adrenergic Beta 3 receptor (ADBR2 and ADBR3), ATPase Alpha 2 polypeptide (ATP1A2),

Glucocorticoid receptor (GRL), Insulin-like growth factor 1 (IGF1) and Neuropeptide Y (NPY).

Strategies to find genes associated with common forms of obesity may be boosted by findings from quantitative genetics and using data available in GenomEUtwin. For instance, genetic effects for BMI and body fat tend to be stable whereas environmental influences tend to be more temporary or transient (Allison et al., 1995; Fabsitz et al., 1992). Thus, capatilizing upon the longitudinal data in GenomEUtwin and selecting pairs who are stably concordant and discordant for BMI may provide stronger genetic signals while reducing environmental noise due to occasion-specific environmental influences. In contrast, the search for specific environmental effects may be more fruitful by focusing on factors influencing deviation from mean levels of BMI over time.

In conclusion, we confirm previous findings of the importance of genetic and non-shared environment for variation in BMI. There are some consistencies and some differences across countries, age and sex. The most notable inter-country difference concerned evidence for sex-specific sets of genes. In contrast, evidence of sex differences in the variance components is strong and consistent and underscores the need to examine more closely the nature of these differences, how they may vary by age, and whether they can be informative in finding genes influencing BMI.

Endnote

1 Available from http://www.ktl.fi/publications/monica/index.html

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References

Allison, D. B., Neale, M. C., Kezis, M. I., Alfonso, V. C., Heshka, S., & Heymsfield, S. B. (1996). Assortative mating for relative weight: genetic implications. *Behavior Genetics, 26*, 103–111.

Allison, D. B., Paultre, F. , Heymsfield, S. B., & Pi-Sunyer, F. X. (1995). Is the intra-uterine period really a critical period for the development of adiposity? *International Journal of Obesity and Related Metabolic Disorders, 19*, 397–402.

Allison, D. B., Pietrobelli, A., Faith, M. S., Fontaine, K. R., Gropp, E., & Fernández, J. R. (2003). *Genetic influences on obesity.* Obesity (Eckel, R., ed). New York: Elsevier.

Andrew, T., Hart D. J., Snieder H., de Lange M., Spector T. D., & MacGregor A. J. (2001). Are twins and singletons comparable? A study of disease-related and lifestyle characteristics in adult women. *Twin Research*, *4*, 464–477.

Baird, J., Osmond, C., MacGregor, A., Snieder, H., Hales, C. N., & Phillips, D. I. (2001). Testing the fetal origins hypothesis in twins: the Birmingham twin study. *Diabetologia, 44*, 33–39.

Bodurtha, J. N., Mosteller, M., Hewitt, J. K., Nance, W. E., Eaves, L. J., Moskowitz, W. B., et al. (1990). Genetic analysis of anthropometric measures in 11-year-old twins: the Medical College of Virginia Twin Study. *Pediatric Research, 28*, 1–4.

Boomsma, D. I., Beem, A. L., van den, B. M., Dolan, C. V., Koopmans, J. R., Vink, J. M., de Geus, E. J., & Slagboom, P. E. (2000). Netherlands 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., et al. (2002). Netherlands Twin Register: a focus on longitudinal research. *Twin Research, 5*, 401–406.

Busjahn, A. (Ed.)(2002). Twin registers as a global resource for genetic research. *Twin Research {Special Issue} 5,* 317–506.

Calle, E. E., Rodriguez, C., Walker-Thurmond, K., & Thun, M. J. (2003). Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S. adults. *New England Journal of Medicine, 348*, 1625–1638.

Carmichael, C. M., & McGue, M. (1995). A cross-sectional examination of height, weight, and body mass index in adult twins. *Journal of Gerontology Series A: Biological Sciences and Medical Sciences., 50*, B237–B244.

Chagnon, Y. C., Rankinen, T., Snyder, E. E., Weisnagel, S. J., Perusse, L., & Bouchard, C. (2003). The human obesity gene map: The 2002 update. *Obesity Research, 11*, 313–367.

Clement, K., Boutin, P., Froguel, P. (2002). Genetics of obesity. *American Journal of Pharmacogenomics, 2*, 177–187.

Curhan, G. C., Chertow, G. M., Willett, W. C., Spiegelman, D., Colditz, G. A., Manson, J. E., et al. (1996a). Birth weight and adult hypertension and obesity in women. *Circulation*, 1310–1315.

Curhan, G. C., Willett, W. C., Rimm, E. B., Spiegelman, D., Ascherio, A. L., & Stampfer, M. J. (1996b). Birth weight and

adult hypertension, diabetes mellitus, and obesity in US men. *Circulation, 94*, 3246–3250.

Eckel, R. H. (1997). Obesity and heart disease: a statement for healthcare professionals from the Nutrition Committee, American Heart Association. *Circulation, 96*, 3248–3250.

Fabsitz, R. R., Carmelli, D., & Hewitt, J. K. (1992). Evidence for independent genetic influences on obesity in middle age. *International Journal of Obesity and Related Metabolic Disorders, 16*, 657–666.

Farooqi, I. S., Keogh, J. M., Yeo, G. S., Lank, E. J., Cheetham, T., & O'Rahilly, S. (2003). Clinical spectrum of obesity and mutations in the melanocortin 4 receptor gene. *New England Journal of Medicine, 348*, 1085–1095.

Farooqi, I. S., & O'Rahilly, S. (2000). Recent advances in the genetics of severe childhood obesity. *Archives of Disease in Childhood, 83*, 31–34.

French, S. A., Story, M., & Jeffery, R. W. (2001). Environmental influences on eating and physical activity. *Annual Review of Public Health, 22*, 309–335.

Gallagher, D., Heymsfield, S. B., Heo, M., Jeb, S. A., Murgatroyd, P. R. & Sakamoto, Y. (2000). Healthy percentage body fat ranges: an approach for developing guidelines based on body mass index. *American Journal of Clinical Nutrition,* 72, 694–701.

Glaser, N. S. (1997). Non-insulin-dependent diabetes mellitus in childhood and adolescence. *Pediatric Clinics of North America, 44*, 307–337.

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.

Harris, J. R., Tambs, K., & Magnus, P. (1995). Sex-specific effects for body mass index in the new Norwegian twin panel. *Genetic Epidemiology, 12*, 251–265.

Healey, S. C., Kirk, K. M., Hyland, V. J., Munns, C. F., Henders, A. K., Batch, J. A., et al. (2002). Height discordance in monozygotic females is not attributable to discordant inactivation if X-linked stature determining genes. *Twin Research*, vol. 4, pp. 19–24.

Hebebrand, J., Wulftange, H., Goerg, T., Ziegler, A., Hinney, A., Barth, N., et al. (2000). Epidemic obesity: are genetic factors involved via increased rates of assortative mating? *24*, *International Journal of Obesity and Related Metabolic Disorders, 24.* 345–353.

Heitmann, B. L., Kaprio, J., Harris, J. R., Rissanen, A., Korkeila M., & Koskenvuo, M. (1997). Are genetic determinants of weight gain modified by leisure-time physical activity? A prospective study of Finnish twins. *American Journal of Clinical Nutrition, 66,* 672–678.

Herskind, A. M., McGue, M., Sørensen, T. I., & Harvald, B. (1996). Sex and age specific assessment of genetic and environmental influences on body mass index in twins. *International Journal of Obesity and Related Metabolic Disorders, 20*, 106–113.

Hill, J. O., Peters, J. C. (1998). Environmental contributions to the obesity epidemic. *Science, 280*, 1371–1374.

Hopper, J. L. (2002). The Australian Twin Registry. *Twin Research, 5*, 329–336.

James, P. T., Leach, R., Kalamara, E., & Shayeghi, M. (2001). The worldwide obesity epidemic. *Obesity Research, 9 Supplement 5*, S228–S233.

Johansson, M., Rasmussen, F. (2001). Birthweight and body mass index in young adulthood: The Swedish young male twins study. *Twin Research, 4*, 400–405.

Kaprio, J., & Koskenvuo, M. (2002). Genetic and environmental factors in complex diseases: the older Finnish Twin Cohort. *Twin Research, 5,* 358–365.

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, 2000.

Knuiman, M. W., Divitini, M. L., Welborn, T. A., Bartholomew, H. C. (1996). Familial correlations, cohabitation effects, and heritability for cardiovascular risk factors. *Annals of Epidemiology, 6*, 188–194.

Korkeila, M., Kaprio, J., Rissanen, A., Koshenvuo, M., Sørensen, T.I. (1998). Predictors of major weight gain in adult Finns: Stress, life satisfaction and personality traits. *International Journal of Obesity and Related Metabolic Disorders, 22*, 949–957.

Korkeila, M., Kaprio, J., Rissanen, A., & Koskenvuo, M. (1991). Effects of gender and age on the heritability of body mass index. *International Journal of Obesity and Related Metabolic Disorders, 15*, 647–654.

Korkeila, M., Kaprio, J., Rissanen, A., & Koskenvuo, M. (1995). Consistency and change of body mass index and weight. A study on 5967 adult Finnish twin pairs. *International Journal of Obesity and Related Metabolic Disorders, 19*, 310–317.

Lecomte, E., Herbeth, B., Nicaud, V., Rakotovao, R., Artur, Y., & Tiret, L. (1997). Segregation analysis of fat mass and fat-free mass with age- and sex-dependent effects: The Stanislas Family Study. *Genetic Epidemiology, 14*, 51–62.

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.

Luke, B., Witter, F. R., Abbey, H., Feng, T., Namnoum, A. B., Paige, D. M., & Johnson, T. R. (1991). Gestational age-specific birthweights of twins versus singletons. *Acta Geneticae Medicae et Gemellologiae, 40*, 69–76.

Maes, H. H., Neale, M. C., & Eaves, L. J. (1997). Genetic and environmental factors in relative body weight and human adiposity. *Behavior Genetics, 27*, 325–351.

Magnusson, P. K., & Rasmussen, F. (2002). Familial resemblance of body mass index and familial risk of high and low body mass index. A study of young men in Sweden. *International Journal of Obesity and Related Metabolic Disorders, 26*, 1225–1231.

Moll, P. P., Burns, T. L., & Lauer, R. M. (1991). The genetic and environmental sources of body mass index variability: The Muscatine Ponderosity Family Study. *American Journal Human Genetics, 49*, 1243–1255.

Neale, M. C., & Cardon, L. R. (1992). *Methodology for genetic studies of twins and families.* Dordrecht, the Netherlands: Kluwer Academic Publishers.

NHLBI (1998). National Heart, Lung, and Blood Institute, in cooperation with the National Institute of Diabetes and Digestive and Kidney Diseases. *Clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults: The evidence report.* Bethesda, Maryland: National Institutes of Health Publication No. 98–4083, September.

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

Pietiläinen, K.H., Kaprio, J., Rasanen, M., Rissanen, A., & Rose, R.J. (2002). Genetic and environmental influences on the tracking of body size from birth to early adulthood. *Obesity Research, 10*, 875–884.

Pietiläinen, K.H., Kaprio, J., Rasanen, 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.

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

Samaras K., Spector T. D., Nguyen T. V., Baan K., Campbell L. V., & Kelly P. .J. (1997). Independent Genetic Factors Determine the Amount and Distribution of Fat in Women after the Menopause. *Journal of Clinical Endocrinology and Metabolism, 82*, 781–785

Sarna, S., Kaprio, J., Sistonen, P., & Koskenvuo, M. (1978). Diagnosis of twin zygosity by mailed questionnaire. *Human Heredity, 28*, 241–254.

Schousboe, K. (2003). *Body Composition and Glucose Homeostasis: Genes and Environment.* Unpublished doctoral dissertation, Faculty of Health Sciences, University of Southern Denmark.

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

Skytthe, A., Kyvik, K. O., 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.

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.

Tambs, K., Moum, T., Eaves, L. J., Neale, M.C., Midthjell, K., Lund-Larsen, P. G., & Naess, S. (1992). Genetic and environmental contributions to the variance of body height in a sample of first and second degree relatives. *American Journal of Physical Anthropology, 88*, 285–294.

Vaisse, C., Clement, K., Durand, E., Hercberg, S., Guy-Grand, B., & Froguel, P. (2000). Melanocortin-4 receptor mutations are a frequent and heterogeneous cause of morbid obesity. *Journal of Clinical Investigation, 106*, 253–262.

World Health Organization. (2000). *Obesity: preventing and managing the global epidemic.* WHO Obesity Technical Report Series 894. Geneva, Switzerland: Author.