

Heritability of Body Mass Index: A Comparison Between The Netherlands and Spain

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A high body mass index (BMI) is commonly used as an index of overweight and obesity. There is persistent evidence of high heritability for variation in BMI, but the effects of common environment appear inconsistent across different European countries. Our objective was to compare genetic and environmental effects on BMI in a sample of twins from two different European countries with distinct population and cultural backgrounds. We analysed data of adult female twins from the Netherlands Twin Register (222 monozygotic [MZ] and 103 dizygotic [DZ] pairs) and the Murcia Twin Register (Spain; 202 MZ and 235 DZ pairs). BMI was based on self-reported weight and height. Dutch women were taller and heavier, but Spanish women had a significantly higher mean BMI. The age related weight increase was significantly stronger in the Spanish sample. Genetic analyses showed that genetic factors are the main contributors to variation in height, weight, and BMI, within both countries. For height and weight, estimates of genetic variances did not differ, but for height, the estimate for the environmental variance was significantly larger in Spanish women. For BMI, both the genetic and the environmental variance components were larger in Spanish than in Dutch women.

A high body mass index (BMI) is commonly used as an index of overweight and obesity. It is calculated as weight divided by height squared, and it constitutes a simple and easy-to-obtain surrogate measure for body fat. A BMI greater than or equal to 25 kg/m² is used as a threshold to classify an individual as overweight, and a BMI greater than or equal to 30 kg/m² is regarded as the threshold for obese. Obesity is a condition of excessive fat accumulation that increases the risk for morbidity and mortality at all ages. It is associated with an increased risk of coronary heart disease, type 2 diabetes, hypertension, stroke, and certain forms of cancer (WHO, 2002). As such, the rapid increase in obesity seen in Westernised societies presents an international cause of alarm (Farooqi &

O'Rahilly, 2007; WHO, 2005). In 2002, 10.4% of men and 11.5% of women were obese in the Netherlands, and in Spain, 15.6% of men and 15.8% of women were obese. In general, Western European countries show a pattern of increasing obesity, although in some southern European countries this increase appears to stabilize (WHO, 2005).

Twin studies have consistently shown heritability for BMI and related traits to be high in both sexes and at all ages. A review by Maes et al. (1997) estimated an average heritability of .7, with a range between .5 and .9, for BMI. For waist to hip ratio, subcutaneous fat, total body fat percentage, total fat mass, and regional fat distribution (trunk or lower body), most heritability estimates were above .7 (Lehtovirta et al., 2000; Maes et al., 1997; Malis et al., 2005). Family studies typically yield lower heritability estimates, probably due to the presence of gene-age interactions. Studies in children suggest that unlike results later in life, height, weight and overweight, in 4-year-olds (Koeppen-Schomerus et al., 2001) and in 5-year-olds (Estourgie-van Burk et al., 2006) are influenced by shared family environment. The contribution of these influences decreases as children grow up (Silventoinen et al., 2007).

The pathways by which genes may affect the risk of being overweight are likely to be multiple, and not limited to metabolic factors. Specific behaviors related to weight increase, like eating habits or physical exercise, may be genetically influenced, and act as mediators between the genes and BMI. For instance, moderate to significant heritability estimates have been documented for reported energy intake, fat intake, meal frequency, pre-meal hunger levels, time of meals, frequency of breakfast consumption, or total energy intake (see review by Faith & Kral, 2006). Some authors have reported heritability estimates (below .3)

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for traits like cognitive dietary restraint, disinhibition or susceptibility to hunger (Provencher et al., 2005).

Although variation in BMI is considerably influenced by genetic differences, the increase in overweight prevalence is likely to be explained by changes in environment and lifestyle (Faith & Krall, 2006; Farooqi & O'Rahilly, 2007; Schousboe et al., 2003). Socioeconomic changes during the last decades have been blamed for the increase in the frequency and intensity of exposure to a 'toxic' environment in terms of risk for obesity (e.g., increased availability and reduced costs of energy-dense food or reduction in physical activity during work and leisure time). The role of genetic factors appears to be crucial in determining how individuals react to such a 'toxic' environment and, hence, who becomes obese (Farooqi & O'Rahilly, 2007; Malis et al., 2005).

Despite the established consensus that BMI results from multiple genetic and environmental factors that may interact or be correlated with each other, research has advanced independently within each domain. In most cases, genetic research on human obesity has not considered environmental factors, such as macroenvironmental influences, and research on environmental risk factors is commonly performed with nongenetically informative designs (Faith & Kral, 2006). Schousboe et al. (2003), in a comparative study of twins from eight different countries, reported large cross-cultural differences in the prevalence of overweight. The percentage of people, aged 30-39 years, with BMI greater than or equal to 25 ranged from 43.8% in Finland to 4.4% in the Netherlands (males), and from 39.8% in the United Kingdom to 5.1% in the Netherlands (females). Twin correlations confirmed the importance of genetic and nonshared environmental influences on BMI, while the effect of the common environment appeared small and inconsistent across countries. The Schousboe et al. (2003) study showed an interesting pattern of results, as large differences in average BMI were not accompanied by differences in heritabilities. It is possible that environmental factors that fail to cause differences within countries still cause differences across countries, either through direct effects on the phenotype, or through different patterns of interaction with genetic factors. Thus, analyzing BMI data from different countries may help to expand our knowledge about the relative impact of genetic factors under different environments to produce BMI variability (Luke et al., 2001). In this study we analysed data from independent twin samples from two different European countries, the Netherlands and Spain, with distinct population and cultural background differences, to compare the heritability of anthropometric variables.

Participants and Methods

The sample consisted of adult female twins registered with the Netherlands Twin Register (NTR), and the Murcia Twin Register (MTR).

The MRT is a population-based register of twins in the region of Murcia, (southeast of Spain) which is held by the Health and Psychobiology Unit (School of Psychology) of the University of Murcia (Ordoñana et al., 2006; Ordoñana et al., 2007). The MTR reference population comprises all female twin pairs who were born between 1940 and 1965. The twins are located through the computerized databases from the regional health care system. The data used for this study were collected in 2007 through a telephone interview, meant to establish the first contact with the twins and gather initial demographic, health, and lifestyle information. Data for this study were available for 202 monozygotic female (MZF) pairs and 235 dizygotic female (DZF) pairs.

Data for the Dutch twins were obtained from a longitudinal survey study on health, lifestyle, and personality by the NTR (see Boomsma et al., 2002; Boomsma et al., 2006). To match the Spanish and Dutch samples by year of data collection and by age, a subsample of women between 41 and 67 years of age who had provided survey data in 2004 was selected. The NTR sample included 222 MZF and 103 DZF twin pairs.

Zygoty: For 102 pairs from the NTR, zygosity was based on DNA polymorphisms. When information on DNA polymorphisms was not available, zygosity was determined by questionnaire items about physical similarity and frequency of confusion of the twins by family and strangers. This questionnaire-based zygosity corresponds well with zygosity as determined by DNA testing, with an agreement in nearly 97% of cases (Willemsen et al., 2005). The MTR used a translation of the Dutch items to obtain zygosity in the Spanish twins.

Anthropomorphic measures: The data on height and weight were based on self report in both samples. Body Mass Index (BMI) was calculated as:

$$\text{BMI} = \frac{\text{weight (kg)}}{\text{height (meters)}^2}$$

Analyses

The data were analysed using Structural Equation Modelling (SEM), which allows one to test specific theoretical models in a multiple group approach (e.g., Boomsma & Molenaar, 1986). We applied the classical twin design (Plomin et al., 2001; Falconer, 1989) to estimate the contribution of genetic and environmental factors to population variation in height, weight, and BMI. We modeled additive genetic factors (A), common environmental factors that differ across families (C), and environmental factors that are unique to each individual within the family (E). MZ twins share 100% of their segregating genes, and DZ twins share 50%. If MZ twins resemble each other significantly more than DZ twins, that is an indication of genetic effects on individual differences in a given

trait. Similarly, if DZ twins resemble each other by more than half the resemblance of MZ twins, that is an indication of shared environmental effects.

The Mx program (Neale et al., 2003) was used to estimate the means, variances, twin correlations, and the effects of age, on the means in a four group analysis for MZ and DZ twins in the Spanish and Dutch sample. The effects of age on the dependent variables are regressed out, so that the twin correlations (and heritabilities) are estimated on the residuals. This model is called the saturated model. Submodels were fitted to the data to test for mean and variance differences within country (between two members of a twin pair and between MZ and DZ twins) and across countries.

Next, Mx was used to estimate parameters in the ACE model (Neale & Cardon, 1992). In the full genetic model all parameters were estimated separately for each country. The fit of the full model to the data was evaluated to that of the saturated model. Submodels constrained parameters to be equal across countries. To be able to use all data from complete and incomplete pairs, Full Information Maximum Likelihood estimation (FIML) with raw data was used. In this method, twice the negative log-likelihood ($-2LL$) of the data for each family is calculated, and parameters are estimated so that the likelihood of the raw data is maximized. Submodels were compared with likelihood ratio tests (LRT), that are obtained by subtracting $-2LL$ for a restricted nested model from that for a less restricted model ($\chi^2 = (-2LL_0) - (-2LL_1)$). The resulting test statistic has a χ^2 -distribution with degrees of freedom (df) equal to the difference of the df between the two models. We tested whether an AE, CE, or E model explained the data as well as an ACE model, and whether estimates could be equated for the Netherlands and Spain.

Results

Table 1 shows the descriptive statistics for age, height, weight, and BMI for the Spanish (S) and Dutch (N) samples. The means across countries suggest that Dutch adult women are taller and heavier than Spanish women, but have a lower BMI. Note that the mean BMI in the Spanish sample is above 25, which means that the Spanish sample on average is overweight. In the table we also include the intercepts,

variances, and age regression coefficients estimated in the best fitting restricted saturated model, in which the dependent variables were corrected for age. Table 1 shows that Spanish women gained more weight and BMI with increasing age than Dutch women.

Estimates of the twin correlations are shown in Table 2. The estimates of the twin correlations suggest a robust presence of genetic effects, and possible effects of shared environment for height in the Dutch sample, but not in the Spanish sample. Twin correlations for the Spanish sample show somewhat lower DZ correlations, which might be consistent with the presence of non-additive genetic effects. Given the low power in the classic twin design to estimate such effects, we restricted our analyses to ACE and AE models.

For height, the age effect on the mean levels is not significantly different across countries, $\chi^2(1) = .732$, $p = .392$. In both countries, height tends to decrease slightly with age. Height variance can be constrained to be equal within — across members of the twin pair — and across zygosity, $\chi^2(6) = 8.012$, $p = .237$, and across countries, $\chi^2(1) = .325$, $p = .569$. Mean height is higher in Dutch than in Spanish women, $\chi^2(1) = 233.957$, $p < .001$.

The first panel in Table 3 shows the fit of the submodels for height. The full ACE model provided a satisfactory fit to the data, with a non-significant χ^2 difference when compared with the saturated model. It was not allowed to constrain the variance components to be equal for both countries (Model 2). Submodels 2.1 to 2.4 show that this decrease in fit is caused by differences between countries in the amount of variance explained by E. The amount of variance explained by A and C can be constrained to be equal without loss of fit. Models 3 and 4 tested the statistical significance of A and C. Constraining A at zero provoked a significant deterioration of the model fit, whereas constraining C at zero had non-significant effects in the model fit. The final model therefore comprised of an AE model, with different contributions of E in each country.

Model fitting results for weight showed significant differences between the Netherlands and Spain in the age effects, $\chi^2(1) = 7.939$, $p < .01$, as well as in the mean levels, $\chi^2(1) = 10.109$, $p < .01$. There were no significant differences in the variance within-across

Table 1

Descriptive Statistics for Height, W weight, BMI and Age by Country

		Uncorrected estimates		Corrected for age		
		Mean	Variance	Intercept	Variance	Age regression
Height	Netherlands	167.16	43.63	175.95	44.45	-.175
	Spain(Murcia)	159.14	47.48	168.17		-.175
Weight	Netherlands	67.40	117.45	62.64	111.88	.095
	Spain(Murcia)	65.61	118.67	44.03		.416
BMI	Netherlands	24.11	13.09	20.57	12.91	.071
	Spain(Murcia)	25.83	20.08	14.45	17.31	.221

Table 2

Twin Correlations, Estimated by the Best Fitting Saturated Model

		MZ		DZ	
		N of pairs (complete/incomplete)	Correlation	N of pairs (complete/incomplete)	Correlation
Height	Netherlands	151/71	.885	56/47	.600
	Spain(Murcia)	121/70	.828	143/82	.328
Weight	Netherlands	149/73	.809	56/47	.419
	Spain(Murcia)	138/63	.768	170/64	.313
BMI	Netherlands	146/76	.817	56/47	.366
	Spain(Murcia)	120/71	.734	141/84	.268

members of the twin pair — and across zygosity, $\chi^2(6) = 12.408$, $p = .053$, or across countries, $\chi^2(1) = .714$, $p = .398$. The estimates in Table 2 show that weight has a stronger tendency to increase with age in the Spanish sample, compared with the Dutch sample. Furthermore, once the effects of age are regressed out, the weight differences increase considerably, with the Dutch women being heavier. The twin correlations for weight suggest that family resemblance is exclusively due to additive genetic effects (Table 2).

The second panel of Table 3 shows the model fitting results for weight. All variance components could be constrained to be equal across countries. Constraining additive genetic effects at zero produced a significant decrease in model fit (Model 3). Constraining C at zero did not deteriorate the fit of the model (Model 4). Thus, A and E explain the same amount of variance of weight in the Dutch and Spanish samples.

For BMI, there were significant differences between the countries in age effect, means, and variances, respectively, $\chi^2(1) = 14.098$, $p < .01$; $\chi^2(1) = 8.909$, $p < .01$ and $\chi^2(1) = 9.864$, $p < .01$. There were no significant variance differences across zygosity groups or members of the twin pair within country, $\chi^2(6) = 9.838$, $p = .131$. The increase in BMI with age was stronger in the Spanish sample. It is interesting to see that the age-related increase of BMI is considerably stronger in the Spanish than in the Dutch, leading to an increased BMI in this older Spanish population compared to the Dutch.

Twin correlations for BMI suggest a model with additive genetic effects. The last panel of Table 3 shows the results of the genetic modelling. Model 2, in which all parameters are equated across countries, fitted the data significantly worse than the full model. As the saturated model showed that the variance of BMI in the Spanish sample was significantly larger, this could produce a difference in the absolute amount of variance explained by each component. To test that possibility we fitted Model 3, in which the proportions of variance explained were equated, instead of the absolute values. This is known as a scalar model (Neale et al., 1992). Model 3 fitted the data as well as the full model, and thus the proportion of variance

explained by A, C and E is the same in both samples. The results proved again the significant effects of additive genetic variance (Model 4), and showed non-significant effects of the shared environment (Model 5).

Table 4 provides for both countries the absolute variances and the proportions of variance in height, weight, and BMI which are explained by additive genetic and unique environmental effects. The estimates show that a major proportion of the variance in the three variables is due to additive genetic variation, with the estimates of heritabilities surrounding .80. For height the effects were slightly lower in the Spanish sample. The remaining variance was explained by environmental factors unique to the individual.

Discussion

We have reported a comparison on anthropomorphic measures between two independent samples of middle-aged female twins from two different populations with very different cultural backgrounds. We found significant differences on mean height, weight, and BMI between the two groups. Dutch women were heavier and considerably taller than Spanish women. However, Spanish women had a higher BMI, which accounts for a higher prevalence of overweight and obesity in this sample. This apparent incongruence is explained initially by the large difference in mean stature between the samples (an increase of 5.1% for Dutch women), while differences in weight were much lower (2.3%). This difference in body height is not surprising. Previous studies have reported that population stature is lower in Southern than in Northern European countries, and that Dutch people are the tallest in Europe (Cavelaars et al., 2000; Silventoinen et al., 2003). Although this geographic variation does not have a clear explanation, both environmental and genetic differences between populations have been suggested to account for this effect. Silventoinen et al. (2003) postulates that genetic factors may be the most important when explaining these geographic differences in height. According to these authors, if environmental factors were responsible for those differences, the increasing standards of living after the Second World War in Europe should have had a

Table 3
Model Fitting Results for the Genetic ACE Model Across Countries

Model	-2LL	df	vs	LRT(χ^2)	df	p	AIC
Height							
1 Full ACE model	7627.842	1203	SAT(2)	6.103	6	.412	-2.524
2 Equal ACE across countries	7638.359	1206	1	10.517	3	.015	
2.1 Equal A	7630.627	1204	1	2.756	1	.097	
2.2 Equal C	7630.898	1204	1	3.027	1	.082	
2.3 Equal E	7633.960	1204	1	6.089	1	.014	
2.4 Equal A and C	7630.956	1205	1	3.114	2	.218	
3 A = 0	7725.140	1206	2.4	94.184	1	< .001	
4 C = 0	7630.956	1206	3	0.000	1	1.000	-3.507
			SAT	3.114	2	.211	
Weight							
1 Full ACE model	9308.546	1263	SAT(1)	1.640	6	.950	1.788
2 Equal ACE across countries	9310.993	1266	1	2.447	3	.485	
3 A = 0	9397.323	1267	2	86.330	1	< .001	
4 C = 0	9310.996	1267	2	.000	1	1.000	-3.507
			SAT	4.09	10	.943	
BMI							
1 Full ACE model	6436.975	1194	SAT(1)	11.905	6	.064	-.095
2 Equal ACE across countries	6452.962	1197	1	15.986	3	.001	
3 Equal standardized ACE across countries	6437.493	1197	1	12.423	3	.768	
4 A = 0	6511.144	1199	3	75.651	2	< .001	
5 C = 0	6437.493	1199	3	.000	1	1	-9.57
			SAT	.472	11	.332	

uniform effect. They also found that the geographical differences in mean body height between different European countries were not accompanied by similar differences in the variance of body stature, which is also the case in our study. The high heritability estimates of body height suggest that the environmental conditions are fairly homogeneous within each country, and fail to produce individual differences among individuals of the same nationality. However, it is not necessarily the case that the same factors that explain variability within a given population also explain differences between populations (Rowe & Cleveland, 1996). General environmental conditions, such as lifestyle or dietary habits attached to the culture of each country, as well as historical events, might explain inter-country differences. Furthermore, it should be noted that Spain was relatively isolated from the economic welfare in the rest of Europe until the 1960s. Different studies have shown a relationship between affluence and height (Silventoinen et al., 2001; Steckel, 1995) suggesting that this fact may have collaborated to increase the difference between both samples even further.

Differences in mean weight were less striking. An interesting finding of our study is the stronger age-related weight gain in the Spanish women compared to the Dutch (nonstandardized regression coefficients of .42 vs. .09) and, related, the age effect on BMI was also stronger in the Spanish women (regression coefficients of .22 vs. .07). The result of this stronger weight increase in Spanish women is an increased BMI in Spanish women compared to the Dutch. Age has previously been found

to be an important determining factor for BMI (Cornes et al., 2005; Schousboe et al., 2003), but we have found no previous reports of differences on the age effect between two samples from different European countries.

Height in this age range (41–67 years old) tended to decrease slightly in both the Spanish and Dutch samples. This decrease could present a generational effect. The older women in these samples were born and raised in a postwar milieu, and are likely to have suffered poorer nutritional and health conditions during their developmental years. On the other hand, stature tends to decrease naturally after mid-life, starting at the age of 30 and accelerating with increasing age. Sorkin et al. (1999) found that cumulative height loss from age 30 to 70 averaged about 5 cm for women. They estimated that this height loss would account for an ‘artifactual’ increase in BMI of approximately 1.6 kg/m² for women by the age of 70. However this ‘artifactual’ increase would not explain by itself either the large effect of age on BMI for the Spanish women, or the differential effect of age between the two samples. Therefore, the age related increase on BMI should be interpreted as a larger increase in actual weight across the life span in Spanish women.

Heritability estimates for the three anthropometric variables were consistently high for BMI (.77), weight (.79) and height (.88/.83), reflecting the impact of genetic factors on phenotypic variability. Our models confirm the importance of additive genetic and non-shared environmental influences on BMI. As expected, height and weight showed a similar pattern. We found

Table 4

Parameter Estimates of Best Fitting Models

		Unstandardized variance	95% CI	Proportion of variance	95% CI
Height					
A	Netherlands	37.72	33.72–37.72	.882	.851–.906
	Spain(Murcia)			.826	.094–.148
E	Netherlands	5.04	4.06–5.03	.118	.776–.864
	Spain(Murcia)	7.95	6.23–7.95	.174	.136–.224
Weight					
A	Netherlands	88.89	78.86–99.88	.788	.745–.823
	Spain(Murcia)				
E	Netherlands	23.86	20.36–28.21	.212	.177–.254
	Spain(Murcia)				
BMI					
A	Netherlands	9.83	8.38–11.52	.768	.719–.808
	Spain(Murcia)	13.63	12.62–14.15		
E	Netherlands	2.95	2.46–3.59	.231	.229–.281
	Spain(Murcia)	4.10	3.41–4.97		

no evidence of a shared environmental component for BMI in any of the samples. This result is in line with previous studies (Cornes et al., 2005; Maes et al., 1997; Malis et al., 2005) and is similar to what Schousboe et al., (2003) found in most of the countries that participated in their study. In fact, common environmental variance was significant only for young (aged 20–29 years) Norwegian men. Thus, family-wide influences do not seem to help explaining variation in any of the anthropometric measures in our samples. This finding is not surprising, at least for weight and BMI, given the age of these twins, and that most of them have probably not shared the parental environment for the last 30 years or more. However, it should be noted that the DZ twin correlation for height in the Dutch sample is suggestive of the presence of shared environmental effects. The small number of DZ pairs in that sample reduces the power to detect a small effect of the family-wide environment. Moreover, there were few differences in the heritability estimates between the two samples. The variability of BMI was significantly higher in the Spanish sample. The absolute amounts of variance explained by environment and by genes was larger in Spain, but these differences in variances did not translate into significant differences in heritability estimates.

Environmental differences between the countries could help to explain mean and variance differences that appear in this study. Although macro-environmental factors are becoming more similar across European countries, there are still some interesting differences between our two samples. First, most of them were born and raised in the middle years of the 20th century, when Spain and the Netherlands had important cultural differences (e.g., diet composition and cooking habits) and differed greatly in their socioeconomic status (SES), which has shown an inverse relationship with obesity (Faith & Kral, 2006).

Second, these and other environmental factors may still be exerting their differentiating influence in both countries. We do not have comparable data for an in-depth analysis of the effect of inter-country differences in environmental or behavioral variables on BMI, but differences in SES, diet, physical activity, or number of births could be responsible, at least partly, for the higher mean BMI and variance in Spanish women. Differences between both countries have been reported in diet, physical activity, or eating habits (Bamia et al., 2005; Haftenberger et al., 2002; Orfanos et al., 2007; Rütten & Abu-Omar, 2004). Rütten and Abu-Omar (2004), for instance, reported that adult women more frequently practise vigorous (1.61 vs. 0.59 days/week) or moderate (5.37 vs. 1.87 days/week) physical activity in the Netherlands than in Spain.

In summary, our study confirms the relevance of additive genetic and unique environmental factors on the variance of BMI, irrespective of the sample background. We have also shown important inter-country differences on mean height, weight, and BMI, with Spanish women being shorter but *heavier* than Dutch women, and more prone to age related gain in weight. Differences between the Spanish and the Dutch samples may be explained in several ways which are not mutually exclusive, and, in fact, may be complementary: genetic differences between the populations, differences in the level of exposure to a 'toxic environment', and/or differences in the degree of susceptibility to environmental exposure. Although possible, there is no evidence yet of a different frequency of genetic variants that could account for the inter-country difference on BMI. The only common genetic variant clearly related to BMI reported to date, an allele in the FTO (fat mass and obesity associated) gene shows little regional variation in allelic frequency across European areas (Frayling et al., 2007). However,

gene–environment interactions could be responsible for differences in the degree of susceptibility to environmental exposure.

In conclusion, although heritability estimates do not show clear differences on anthropometric measures between two samples from diverse population and cultural backgrounds, divergences on environmental variance, mean, and age effects point to cultural differences. For BMI, there are also differences in the amount of genetic variance. Cross cultural comparisons, including comparable and reliable measures of environmental factors, may be an important resource to better understand the relative impact of genetic and environmental factors on BMI.

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