Familial Resemblance in Fatness and Fat Distribution in Nuclear Families from Biscay (Basque Country)

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INTRODUCTION

Researches on genetic and environmental determinants of body adiposity are getting more and more importance due to the worldwide increase of the overweight and obesity prevalence, which have already reached epidemic proportions in some Western countries (WHO, 1998). This kind of studies, which include different adiposity indicators, are very useful since they take into account the different impact on health of the several types of obesity (adiposity of generalized fatness, excess of subcutaneous fat at trunk-abdominal level, excess of visceral abdominal fatness and excess of gluteo-femoral fatness).

Skinfolds, measured at different sites of the body, are habitually used for the estimations of body fatness. Thus, the sum of several skinfolds, particularly those located at the trunk and extremities, provide an accurate information about the quantity of subcutaneous fatness and its distribution, so it can be considered as a general factor of fat due to their relation with body weight and the total percentage of body fatness. Skinfolds also show a narrow correlation with the results of the quantification of body fatness with other more sophisticated techniques, like computed axial tomography, ultrasounds, and so on, which can be used for the calculation of the body fat percentage and to define the nutritional status of the individuals (Alastrué et al., 1982).

Waist circumference (WC) has also revealed itself as an excellent indicator of body fatness; it is highly correlated with the Body Mass Index (BMI) (Lean et al., 1995), visceral fatness (Lemieux et al., 1996) and total body fat (Lean et al., 1996). WC is independent of height (Han et al., 1997) and is related with the quality of life (Lean et al., 1998) and with cardiovascular risk factors (Ledoux et al., 1997). Regarding the anatomic distribution of the body fat, whose importance on public health is greater than that of obesity *per se* - due to the large number of evidences on the association between fatness at trunk/abdomen with the risk of several cardiovascular and metabolic diseases (Kissebah et al., 1982; Fujimoto et al., 1990; Nunes Faria et al., 2002) – it can be identified through several anthropometric indices, like the waist-to-hip ratio (WHR) or the ratio of several skinfolds, among others. These indices have a notable epidemiological validity in large samples, independently of the accuracy of the measurements (Marcus et al., 1998).

As well as environmental factors, and those related with socio-economic status and nutritional adequacy, the role of the inheritance on human fatness variation seems to be important, on the quantity but above all, on its distribution (Selby et al., 1990). Some studies suggest that a complex genetic architecture exists under the different phenotypes of obesity: genetic pleiotropy (i.e. an only gene affecting several traits) and oligogenetic models (i.e. several genes affecting an only one phenotype) (Gu et al., 1997). The intra-individual resemblance for abdominal or trunk obesity can be due to several factors, including family factors and shared genes, common familial environment and non-familial factors (specific environments) which are not shared by the family members (Li et al., 1996). Even though the studies on genetic and environmental determinants of body fatness are not strictly comparable due to several factors (socio-economic heterogeneity, lack of accuracy of measurements, reduced sample sizes, ethnicity, design of the researches, chosen variables, and so on), it is undoubted that several familial causes underlie the variability of the adiposity, even though it is necessary to define the genetic contribution of obesity by using different indicators and samples from various parts of the world (Katzmarzyk et al., 2000).

The aim of this research is to investigate the degree of familial resemblance for the quantity of body fatness and its distribution, through data obtained from nuclear families that include mates, parents and offspring, and siblings. The study considers 6 skinfolds and their sum (SF6) as fatness indicators and 2 indices of fat distribution (TER and WHR), corrected for adiposity. All skinfolds were introduced in a Principal

Components Analysis (PCA) in order to reduce the size of the problem and make easier its interpretation. The pattern of correlations for the different extracted PCA components, as well as those of the distribution indices, has been used to determine whether the different phenotypes show familial aggregation. Some factors (sex, age) underlying familial aggregation variation will be analysed.

MATERIAL AND METHODS

A sample collected by cross-sectional methodology and composed by 3,023 individuals from 1,330 nuclear families (194 fathers, 461 mothers, 1,180 sons and 1,188 daughters) living in the Biscay province (Basque Country, Spain) was analysed. The age ranged between 22 and 66 years for fathers, from 22 to 62 in mothers, from 4 to 22 years in sons and from 4 to 27 years in daughters. Height (cm), weight (kg), 6 skinfolds (biceps, triceps, subscapular, suprailiac, abdominal and medium calf, mm) and waist and hip circumferences (cm) were measured according to the International Biological Programme protocols (Weiner and Lourie, 1981). The decimal age of each individual was obtained from the difference between the birthday and the sampling day.

The sum of 6 skinfolds (SF6) was computed as a fatness indicator and 2 indices of fat distribution: the Waist-to-Hip Ratio (WHR = waist circumference / hip circumference) and the Trunk-Extremities Ratio (TER = Σ trunk skinfolds / Σ extremities skinfolds). Since several authors note fat distribution is not totally independent of body fatness (Malina, 1996), the WHR was corrected for BMI (computed as weight (kg) / height^2 (m^2)), and the TER was corrected for the SF6, through a lineal regression. The descriptive statistics (mean and SD) for age, the raw and derived anthropometric traits of all the studied individuals separated by sex and generation are displayed in Table 1.

Due to the significant group differences in the means, the following fits were conducted separately for each sex-by-generation group: the 8 resulting traits (6 skinfolds, the WHR and TER corrected) were fitted for age and sex by using the LMS method (Cole 1988) and the individual SDS were obtained for each trait. In each generation (parents and offspring), the SDS of the 6 skinfolds were introduced in a PCA in order to reduce the number of variables in the study. In both generations, 2 PCA factors were extracted and considered as summary variables (PC1 and PC2).

Familial resemblance between all kinds of relatives (father-mother or FM, father-son or FS, father-daughter or FD, mother-son or MS, mother-daughter or MD, son-son or SS, son-daughter or

Table 1: Descriptive statistics of the variables studied in the Biscayan sample by sex and generation (M = Mean; SD= Standard Deviation).

	Fathers (n = 194)		*Mothers (n = 461)*		*Sons (n = 1180)*		*Daugthers (n = 1188)*	
Variable	*M*	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*
Age (yr)	41.65	6.62	38.29	6.37	11.86	3.97	12.23	3.93
Height (cm)	171.06	7.05	157.96	6.00	147.94	21.06	146.98	17.50
Weight (kg)	78.71	10.58	62.71	10.66	45.31	17.97	44.62	14.72
Biceps skinfold (mm)	12.16	6.17	16.45	7.31	9.32	5.14	11.56	5.20
Triceps skinfold (mm)	12.14	5.80	21.92	7.05	13.63	5.82	16.90	5.85
Subescapular skinfold (mm)	20.65	7.18	19.99	7.99	10.63	5.95	13.04	6.50
Suprailiac skinfold (mm)	22.50	10.12	22.25	10.77	12.89	9.29	15.10	8.38
Abdominal skinfold (mm)	36.97	12.27	31.92	13.05	16.32	11.45	19.17	11.03
Medial calf skinfold (mm)	21.67	9.33	30.07	9.02	18.48	8.29	21.60	8.00
Waist circumference (cm)	92.43	9.05	76.96	9.39	67.64	10.74	64.45	8.32
Hip circumference(cm)	99.36	6.05	97.28	9.15	79.89	13.27	82.43	12.90
Body Mass Index (BMI)	26.89	3.10	25.11	3.93	19.74	3.40	19.96	3.32
Sum of six skinfolds (SF6) (mm)	125.98	42.39	142.61	47.93	81.30	41.33	97.87	40.92
Waist-to-hip ratio (WHR)	0.92	0.06	0.79	0.05	0.84	0.05	0.79	0.07
Trunk-extremity skinfold ratio (TER)	1.84	0.53	1.08	0.29	0.92	0.37	0.92	0.30
Waist-to-hip ratio adjusted for BMI (WHR_{adj})	0.93	0.03	0.79	0.02	0.85	0.01	0.79	0.02
Trunk-extremity skinfold ratio adjusted for SF6 (TER_{adj})	1.84	0.07	1.08	0.13	0.92	0.18	0.92	0.17

SD, daughter-daughter or DD) was computed though the SEGPATH package (Province and Rao, 1995), for the two factors (PC1 and PC2), as well as for the WHR and TER corrected.

The SEGPATH package allows obtaining univariated correlation by maximum-likelihood between the 8 pairs of relatives indicated above, and simultaneously, it performs a balance of the estimated correlations in function of the quantity of information introduced by the families depending on their different sibships size. For the evaluation of some factors that can influence the familial transmission of the fatness phenotypes studies, a general model of familial transmission, in which 8 different familial correlations were evaluated, was designed. In addition, 9 different reduced models, which were tested against the general model through the likelihood-ratio test, were also designed. This test follows a X^2 distribution with a number of degrees of freedom equal to the difference between the estimated parameters in the general model and each of the reduced models. The reduced models were accepted when their comparison with the general model was non-significant. From the combination of all the reduced models accepted (that is, non-significant) for each variable, a most parsimonious model was designed. In Table 2 can be found all the different tested hypothesis. The 8 types of correlations between relatives were obtained under the general and most parsimonious models, and the maximum heritability of the 4 studied variables was estimated through the Rice et al.'s (1997) formula, which takes into account the resemblance between mates.

RESULTS AND DISCUSSION

The PCA results have been very similar in both generations (Table 3). PC1 presented an eigenvalue similar for parents and for offspring (> 4), with a high percentage of explained variance in both parents and offspring (71.86% in parents and 76.86% in offspring). PC2 explained about 9% in both generations. Even this factor had an eigenvalue < 1, it was considered. In both analysis, the KMO (value of Kaiser-Meyer-Olkin) was close to 0.5 and the Bartlett's test was significant ($p < 0.001$), so this indicate a good adequacy of the sample to the analysis and it allows us to trust on factorial solution as a way to obtain lineal combinations of the variables, respectively. The rotated solution (Varimax) was not used since it did not improve the analysis.

PC1 can be considered as a measure of the total body fat, similarly to the variable SF6, since the weight of the variables on the factor were similar and very high (between 0.77 – 0.90 for parents and 0.78 – 0.92 for offspring). Thus, the individuals with high scores in this factor have a higher level of adiposity than those subjects who displayed low scores. PC2 contrasts the peripheral and the trunk fat, since the limbs skinfolds had positive weights in the factor meanwhile the trunk skinfolds presented negative weights. This way, subjects with a peripheral fat distribution (in extremities) will show high scores for this factor and those individuals with low

Table 3: Principal Components and their eigenvalues.

	Parents		*Offspring*	
Variable (skinfold)	*PC1*	*PC2*	*PC1*	*PC2*
Biceps	0.86	0.19	0.90	0.12
Triceps	0.80	0.43	0.88	0.21
Subescapular	0.87	-0.13	0.88	-0.28
Suprailiac	0.90	-0.32	0.90	-0.31
Abdominal	0.88	-0.35	0.92	-0.20
Medial Calf	0.77	0.26	0.78	0.54
Eigenvalue	4.31	0.53	4.61	0.56
% Variance explained	71.86	8.84	76.86	9.33

Table 2: Summary of hypothesis tested.

Hypothesis	*Parameter reductions*
1. General	All 8 correlations estimated
2. No sex differences in offspring	FS=FD, MS=MD, SD=SS=DD
3. No sex differences in offspring or parents	FS=MS=FD=MD, SD=SS=DD
4. No sex nor generation differences	FS=MS=FD=MD=SD=SS=DD
5. No sibling correlations	SD=SS=DD=0
6. No parent- offspring correlations	FS=MS=FD=MD=0
7. No spouse correlations	FM=0
8. No familial correlations	All 8 correlations are zero
9. Environmental model	All 8 correlations are equal
10. No sibling nor parent- offspring correlations	FS=FD=MS=MD=SD=SS=DD=0
11. Most parsimonious	Combination of all non-rejected hypothesis above

Table 4: Summary of results of the hypothesis tested for fatness and fat distribution variables.

	PC1		*PC2*		TER_{adj}		WHR_{adj}	
Hypothesis	X^2	*p*	X^2	*p*	X^2	*p*	X^2	*p*
General								
No sex differences in offspring	3.79		7.21		7.47		11.49	*
No sex differences in offspring or parents	3.86		9.85		24.88	***	11.63	
No sex nor generation differences	13.44		60.88	***	51.14	***	29.37	***
No sibling correlations	10.96		28.26	***	84.49	***	173.90	***
No parent- offspring correlations	17.81	*	85.45	***	76.03	***	34.89	***
No spouse correlations	23.13	**	99.48	***	76.55	***	204.16	***
No familial correlations	13.58		51.86	***	76.09	***	132.18	***
Environmental model	70.14	***	51.86	***	76.09	***	132.18	***
No sibling nor parent- offspring correlations	70.80	***	51.20	***	81.67	***	128.90	***
Most parsimonious	13.58		9.85		7.47		11.63	

Significance was also indicated when it existed (*pd≤0.05;** pd≤0.01;*** pd≤0.001).

scores will display a more centralized pattern. Even some authors (Li et al., 1996; Katzmarzyk et al., 2000) have found a great similarity (inverse in any way) between the TER and the PC2 (extremities vs. trunk), in our study the correlation between both variables was not statistically significant neither in parents nor in offspring. There are, in consequence, two different variables that can be analysed separately.

The analysis of familial transmission was performed through the general model, which allows the estimation of 8 familial correlations, and through 9 reduced models which are displayed in Table 4, together with the results of the tests of the hypothesis. For the quantity of fat (PC1) it was accepted that no differences of sex between offspring or between parents-offspring existed, and that no differences of sex or generations were found. It was also accepted that there is no familial resemblance between offspring. However, the hypothesis of no resemblance between parent-offspring ($p < 0.05$), no resemblance between mates ($p < 0.01$), and no resemblance between parent-offspring and siblings ($p < 0.001$) were rejected meanwhile the hypothesis of no familial resemblance was not. On the contrary, the environmental model was also rejected ($p < 0.001$). In this case, the most parsimonious model was that which hypothesised the no familial resemblance for this phenotype.

Regarding the variables of fat distribution (PC2, TER, WHR), a remarkable familial resemblance both between parent-offspring and between siblings, as well as between mates, was accepted: in fact, all the models which hypothesised the absence of resemblance between the different relatives were rejected ($p < 0.001$). The environmental model was also rejected ($p < 0.001$), which indicated a remarkable genetic effect, even though the environmental effects cannot be thrown away. Several models hypothesising the non-influence of the sex were accepted, even not that considering no sex or generation differences ($p < 0.001$). Thus, there were no sex differences in offspring or in parent or offspring on the PC2, there were no sex differences in offspring on TER and nor in parent or offspring on WHR.

Data from nuclear families do not allow separating the familial resemblance in genetic and cultural heritability, since the members of a family share genes as well as familial environment. For this reason, heritability estimated in nuclear families measure the maximum effects of genes (Rice and Borecki, 2001). In this case, the simplest estimator of the maximum or generalized (Multifactorial) heritability is twice the mean correlation between first degree relatives (parent-offspring, siblings), since they have, in mean, half of their genes in common. Table 5 displays the estimated correlations between the 8 pairs of relatives under the general and the most parsimonious models, for the 4 phenotypes of the adiposity.

Except the correlation between FS for PC2, correlations were statistically significant between all pairs of relatives, and for the 4 studied traits. Considering the absolute values, correlations were higher between the same generation pairs (siblings) than between pairs of two different generations (parent-offspring), both under the general model and the most parsimonious model, except in PC1, where correlation estimations were equal. This last agrees with the accepted models, which postulated no sex or generation differences for the amount of fat. Regarding the 3 variables

Table 5: Estimation by maximum likelihood of the familial correlations (r) for the four considered variables, their sample size (n) and the standard errors of the correlations (se).

	PC1			*PC2*			TER_{adj}			WHR_{adj}		
	n	*r*	*se*	*n*	*r*	*se*	*n*	*r*	*se*	*n*	*r*	*se*
General Model												
FM	163	0.26***	0.07	163	0.07**	0.09	163	-0.26***	0.07	168	0.14***	0.08
FS	113	0.23***	0.09	113	0.01	0.10	113	-0.22***	0.09	113	-0.35***	0.08
FD	121	0.15***	0.08	121	0.12***	0.10	121	-0.14***	0.09	122	-0.05*	0.09
MS	245	0.13***	0.06	245	0.18***	0.06	245	0.12***	0.06	248	-0.18***	0.06
MD	277	0.21***	0.06	278	0.23***	0.06	278	0.22***	0.06	287	-0.28***	0.05
SS	160	0.36***	0.06	154	0.57***	0.05	157	0.36***	0.07	146	0.44***	0.06
SD	610	0.27***	0.05	610	0.47***	0.04	604	0.22***	0.05	627	0.30***	0.05
DD	135	0.38***	0.07	143	0.39***	0.06	141	0.39***	0.07	144	0.36***	0.07
Most Parsimonious Model												
FM	163	0.26***	0.07	163	0.07**	0.09	163	-0.26***	0.07	168	0.14***	0.08
FS	1674	0.24***	0.03	686	0.16***	0.02	243	-0.17***	0.06	765	-0.23***	0.03
FD	1674	0.24***	0.03	686	0.16***	0.02	243	-0.17***	0.06	765	-0.23***	0.03
MS	1674	0.24***	0.03	686	0.16***	0.02	555	0.17***	0.04	765	-0.23***	0.03
MD	1674	0.24***	0.03	686	0.16***	0.02	555	0.17***	0.04	765	-0.23***	0.03
SS	1674	0.24***	0.03	771	0.48***	0.02	660	0.29***	0.04	645	0.34***	0.03
SD	1674	0.24***	0.03	771	0.48***	0.02	660	0.29***	0.04	645	0.34***	0.03
DD	1674	0.24***	0.03	771	0.48***	0.02	660	0.29***	0.04	645	0.34***	0.03

Significance was also indicated when it existed (*pd≤0.05;** pd≤0.01;*** pd≤0.001).

which reflect different features of fat distribution (PC2, TER, WHR), it must be noted the high correlations between the different pairs of siblings. The higher resemblance between siblings than between parent-offspring pairs points out the generation effect (age) as well a possible effect of the common familial environment, shared by the siblings.

There is a significant correlation between mates in the 4 fatness phenotypes, even though the absolute values were quite low in some cases, like for PC2 (Table 5). This fact agrees with the significance obtained for the 4 variables under the reduced models, which has allowed rejecting the hypothesis of no resemblance between mates. A significant correlation between mates suggests the existence of a common familial environment acting on familial resemblance, if no previous phenotypic homogamy existed, and it must be taken under consideration that it could produce a bias both on the genetic heritability and on the cultural one. A significant resemblance between mates for several anthropometric traits was also observed on a previous research of the parents of the same sample (Salces et al., 2004). Since we cannot know if the resemblance between mates is really due to a phenotypic selection or to the effect of living together, the Rice et al.'s (1987) formula was used to calculate heritability, since it corrects automatically this factor. The obtained results are displayed in Table 6.

Table 6: Maximal heritability estimates.

	PC1	PC2	TER_{adj}	$WAIST_{adj}$
Sibling correlations	0.24	0.48	0.30	0.34
Parent-offspring correlation	0.24	0.16	0.06	0.23
Spouse correlation	0.26	0.07	0.26	0.14
Heritability (h^2)	44%	63%	35%	54%

The highest value of heritability has corresponded to PC2 (63%) followed by the WHR (54%), PC1 (44%) and TER (35%). These values are similar to those of other papers and they point out the greater familial aggregation of fat distribution than of total fatness. Thus, Li et al. (1996) noted that the percentage of variance due to familial aggregation was 46% for a first component (obtained from a PCA based on the same skinfolds that those of the present research), and it express a general measure of adiposity, and 52% for a second component, which contrast the fatness from limbs and trunk. On the other hand, Rice et al. (1997) found a maximum heritability of 34% for the overall level of subcutaneous fat, expressed as the sum of 8 skinfolds. This value is some lower than the estimated for the adiposity factor (PC1) of the present research (44%). On the contrary, some researches based on principal components resulting from skinfolds pointed out higher values of heritability for the first factor (quantity of fat) than for the second (distribution), with values ranging between 62% and 35%, respectively (cited by Li et al., 1996). In addition, the results obtained by Katzmarzyk et al. (2000)

suggest that the heritability of fatness is greater than that for fat distribution (46 - 60% and 29 - 48%, respectively). In any way, the most part of studies suggest that these phenotypes (fatness and fat distribution) are different (Livshits et al., 1998).

Considered in a global way, the obtained results are similar to those of Rice et al. (1997), which showed neither sex nor generation differences on familial correlations for body fatness. In addition, correlations between mates were significant, which agrees with the hypothesis that familial aggregation for body composition, regarding body fat component, reflects both genetic and environmental factors. Also the different values obtained indicate that the relative effects of genes and environment vary depending of which is the adiposity measurement. Regarding this last, it has been noted that the indices based on skinfolds, like TER, measure a different dimension or aspect of fat distribution than the measured by the indices based on circumferences, like WHR. In fact, it seems that skinfolds and circumferences measures are mostly genetically independent, and they represent two different dimensions or aspects of human obesity (Selby et al., 1990, cited by Livshits et al., 1998).

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ABSTRACT Even though the genetic bases of the body fatness quantity and distribution seem broadly accepted, the genetic contributions on obesity are not clearly defined. The aim has been to study the heritability of several indicators of fatness and fat distribution in nuclear families. Material and Methods: A cross-sectional sample of 3,023 individuals from 1,330 nuclear families (194 fathers, 461 mothers, 1,180 sons and 1,188 daughters) living in the Biscay province were analysed. Six skinfolds (and their sum, SF6), height, weight, waist and hip circumferences were measured. The waist-to-hip ratio (corrected for BMI) and the trunk/extremities ratio (TER, corrected for the sum of 6 skinfolds) were calculated. The six skinfolds were introduced in a Principal Components Analysis (PCA) in order to reduce the number of traits. Familial resemblance between all types of relatives was computed through the SEGPATH program for the two first PCA factors and for corrected WHR and TER. Results and Conclusions: Two factors were extracted (PC1, quantity of fat or adiposity, and PC2, distribution of fat trunk vs. extremities). In general, a high and significant heritability for all traits and pairs of relatives was found under the general and most parsimonious models. According to this last, there is not a significant effect of the sex on the offspring.

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