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Changes in genetic and environmental influences on disordered eating between pre-menarche and post-menarche girls. A twin study

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Background. Eating disorders´ incidence and heritability significantly increase during puberty. The goal of this research is to evaluate changes during puberty which could have genetic and environmental influences on a broad spectrum of disordered eating attitudes and behaviors.

Methods. Participants were 158 pairs of adolescent female twins, categorized in two groups according to menarche stage (pre or post). ED measures: Disordered eating attitudes and behaviors were assessed by means of the Children's Eating Attitudes Test and four sub-scales of the Eating Disorders Inventory: Drive for thinness, Body dissatisfaction, Ineffectiveness, and Perfectionism. Intra-class correlations in monozygotic (MZ) and dizygotic (DZ) twins were calculated separately in premenarche and premenarche group for each ED subscale

Results. 48 premenarche twins (30 MZ twins and 18 DZ twins) and 110 premenarche twins (66 MZ and 44 DZ twins) were included. The intra-class correlations suggested no genetic influence on the total ChEAT score of participants at the premenarche stage. For the premenarche participants, however, sources of variance suggested a very high heritability. Regarding the EDI sub-scales, only the trait "Ineffectiveness" exhibited a moderate heritability among premenarche subjects, while all the four eating sub-scales showed moderate heritability estimates in the premenarche stage group.

Conclusions. Our findings reveal that there are significant differences in genetic and environmental effects on eating attitudes and behaviors depending on being in a premenarche or premenarche stage. Therefore, clinicians should pay attention to female adolescents at high risk of developing ED, especially during the critical period of menarche.

Keywords: Eating Disorders, Menarche, Twins, Genetics

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Cambios en la influencia genética y ambiental en los trastornos de la alimentación entre niñas en estadio pre y post menarquia. Un estudio gemelar

Introducción. La incidencia y heredabilidad de los trastornos de la conducta alimentaria (TCA) se incrementa durante la pubertad. El objetivo de la presente investigación fue evaluar los cambios en las influencias genéticas ambientales sobre un amplio espectro de actitudes y conductas alimentarias anómalas durante la pubertad.

Metodología. participaron 160 parejas de gemelas adolescentes, que se categorizaron en dos grupos en función del estado de menarquia (pre y pos). Medidas de TCA: Las actitudes y conductas alimentarias anómalas fueron evaluadas mediante el ChEAT *(Children's Eating Attitudes Test)* y cuatro subescalas del EDI *(Eating Disorders Inventory);* Impulso a la delgadez, Insatisfacción corporal, Ineficacia y Perfeccionismo. Las correlaciones intrapareja en gemelas MZ (monozigotas) y DZ (dizigotas) se calcularon por separado en los grupos de premenarquia y posmenarquia para cada medida de TCA.

Resultados. Cuarenta y ocho gemelas premenarquia (30 MZ y 18 DZ) y 110 gemelas posmenarquia (66 MZ y 44 DZ). Las correlaciones sugirieron que no hay una influencia genética en la puntuación total del ChEAT en las niñas en estado

premenarquia, mientras que en las niñas posmenarquia el porcentaje de la varianza para las influencias genéticas es elevado. En relación a las subescalas del EDI, únicamente la variable "Ineficacia" mostró una moderada heredabilidad en las niñas en estadio premenarquia, mientras que las cuatro actitudes alimentarias mostraron una moderada heredabilidad en el grupo de niñas posmenarquia.

Conclusiones. Nuestro abordaje revela cambios significativos relacionados con la menarquia en las contribuciones de las influencias genéticas y ambientales sobre las conductas y actitudes alimentarias anómalas. Los clínicos deberían centrar su atención en las niñas adolescentes con alto riesgo de desarrollar TCA especialmente durante el periodo crítico de la menarquia.

Palabras clave: Trastornos de la Conducta Alimentaria, Menarquia, Gemelos, Genética

INTRODUCTION

Genetic and environmental basis of complex traits such as mental disorders can be examined by twin studies[1]. Heritability estimates refer to the percentage of individual differences in risk due to genetic differences among the subjects in a population at a given time[2]. Thus, if genetic conditions change or environmental circumstances are modified, heritability estimates will not remain the same[3]. On the contrary, a wide proportion of gene expression is influenced by the presence of other gene effects, environmental conditions, and prior levels of gene expression, including previous generations. Consequently, causal genetic influences are closely related to the presence of certain environmental conditions[4]. In this regard, twin studies have shown that the heritability of many behavioral traits, such as eating behaviors, may be more intense in permissive than in restrictive environments[2].

Regarding eating disorders (ED) and specific anomalous eating symptoms, they have been described by genetic twin studies as partially heritable[5-8]. As said, given that genetic influences are not static over time, it is of special interest to evaluate quantitative changes in ED etiological causes throughout different developmental periods. Recent studies have shown that heritability estimates for ED are higher during adolescence[9-11]. In fact, Klump et al. (2000) determined that the heritability of ED varied from 3-9% during childhood to 50% during adolescence, comparing twin samples at ages of 11 and 17 years old[9]. Furthermore, they stablished that rather than age, puberty should be considered to examine changes in the heritability of ED. In this line, they observed that this heritability is scarce in pre-puberty stages, measured by physical signs such as breast development or initiation of menses, while appears to be high at post-puberty stages[10]. In contrast, environmental influences among ED´s expression tend to decrease over time during the adolescence period[11]. However, it is still unclear what are the specific and characteristic factors related to changes in the heritability of ED (e.g., age versus puberty).

Pubertal changes could be associated to the expression of ED through a range of different processes that could involve environmental and/or genetic factors. During the critical period of transition towards adulthood, adolescents suffer from numerous changes such as pubertal development and sexual maturity. They must face physical, hormonal, cognitive, and psychological changes that occur throughout puberty. These changes involve genetic, social, emotional and behavioral dimensions[12]. Heritability changes could be associated to other genetic changes that occur during this critical period (e.g., the ones related to endocrine changes such as the increase of gonadal hormones (estradiol) in girls[13-17]). On the other hand, one can postulate that during childhood, environmental factors are more restrictive for the expression of ED, while during adolescence genetic influences become more prominent due to a less strict environment.

Our goal was to clarify the extent to which the menarche period modifies the influence of genetic and environmental factors that determine a broad spectrum of disordered eating attitudes and behaviors. We did so by assessing four subscales of the Eating Disorder Inventory: Body dissatisfaction (BD), Drive for thinness (DT), Ineffectiveness, Perfectionism, and the Children's Eating Attitudes Test (ChEAT) in pre-menarche and post-menarche female twins.

METHODS

Sample

This study used data from the DITCA-CV program, carried out in our region (Valencia, Spain) every school year since 2001. This program aims at studying risk factors, early detection and preventing eating disorders *(Programa de Detección e Intervención en Trastornos de la Conducta Alimentaria de la Comunidad Valenciana)* in school children aged 13 to 17 years old. The survey was first approved by the Department of Public Health of the regional health administration. The participating schools obtained passive informed consent from parents. During these years, 571 schools, private and public, agreed to participate. From this adolescent community sample, 584 couples of twins were identified by matching on family name, date of birth, school and year of the survey[18]. Finally, 158 female twin pairs (96 monozygotic –MZ–, and 62 dizygotic –DZ) accepted to participate in the current investigation.

Zygosity determination

Zygosity determination was based on a twin physical similarity questionnaire, which has been described to predict zygosity with an accuracy of 98%[19]. School teachers answered this questionnaire. Teachers' determination of zygosity has previously been validated by our group (see[20]).

Menarche determination

Age at menarche was derived from parents' answers obtained by a telephonic interview. Parents reported data related to the month and year of menarche for both twins. Thus, we categorized twins in two groups according to this data: "pre-menarche" or "post-menarche" stage.

ED measures

Disordered eating attitudes and behaviors were assessed using the validated Spanish version of the Children's Eating Attitudes Test (ChEAT)[21]. Crombach Coefficient alpha for the ChEAT total score showed a high reliability (α=0.86).

In addition, four of the eight subscales of the Eating Disorder Inventory[22] were applied. The EDI is a self-reporting instrument that has been adapted to the Spanish population[23], and assesses anorexia and bulimia symptoms. The four applied subscales were: (i) Drive for thinness (DT) (α=0.81; concern with dieting, preoccupation with weight, and fear of weight gain); (ii) Body dissatisfaction (BD) (α=0.70; not being satisfied with one's physical appearance); (iii) Ineffectiveness (zα=0.60; feeling of inadequacy, insecurity, worthlessness and having no control over their lives); and (iv) Perfectionism (α=0.60; not being satisfied with anything less than perfect).

Body Mass Index (BMI)

Measurements of weight and height were collected by the physical education teacher during their classes. For this purpose, students had to wear light clothing and no shoes. With these data BMI was calculated as weight (kg)/height^2 (m^2).

Data analysis

SPSS v.16 software program was used to carry out the statistical analysis. Intra-class correlations in MZ and DZ twins were calculated separately in the pre-menarche and post-menarche groups for each ED subscale.

The analysis of similarity between MZ and DZ twins was introduced by Siemens[1,24], who established the basic principles for the twin pathology: a heritable illness among identical twins (MZ) will be more concordant than among non-identical twins (DZ), and in non-siblings the illness concordance will be even lower. Twin studies assess the influence of factors on an observed trait or phenotype comparing the resemblance of MZ twins with the resemblance of DZ twins for that phenotype (covariation)[24,25]; they test, among others, the influence of age, cohort and sex differences in gene expression[1].

That is to say, correlation coefficients constitute a way to summarize the resemblance between a twin pair (rMZ: correlation coefficient between MZ, and rDZ: correlation coefficient between DZ). The effect of additive genetic factors can be deduced when rMZ>rDZ. As we know, MZ twins share 100% of their genes while DZ twins share 50% of theirs on average. Hence, heritability (h^2) of the phenotype can be estimated from twice the difference between MZ and DZ correlations [h^2=2x(rMZ-rDZ)] . Finally, the proportion of the variance that is due to a shared environment is the difference between the total twin correlation and the part that is explained by heritability; rMZ – h^2 in MZ or rDZ – $h^2/2$ in DZ twins[1].

Classic twin studies postulate that total variation can be decomposed in various latent etiological factors: genetic factors (A), common environmental factors (C), and unique environmental factors (E). Additive genetic factors are the cumulative effects of many genes, each of which has a small to moderate effect. Thus, if the expression of a trait or phenotype is completely due to genetic factors, then the MZ correlation will be 1 and DZ correlation will be 0.5. Common (or shared) environmental factors constitute those influences to which both members of a twin pair are exposed regardless of zygosity, and so promote twins' similarity[26]. So, they affect siblings similarly and contribute equally to MZ and DZ correlations. Hypothetically, if a trait or phenotype is totally regulated by shared environmental influences, then rMZ and rDZ would be both equal to 1[27]. Finally, unique environmental factors represent those influences that only one of the two twins experience. Hence, E factors make members different from rather than similar to each other[28]. If the trait expression was completely under the influence of E factors, then rMZ and rDZ would both be 0[27]. Because measurement errors also contribute to make twins different, they are commonly included in E.

To summarize[27]:

- When rMZ=rDZ=0 sources of variance only are related to E (E Model)
- When rMZ=rDZ>0 sources of variance only are related to C and E (CE Model)

- When rMZ=2 x rDZ sources of variance only are related to A and E (AE Model)
- When rMZ>rDZ, rMZ<2 x rDZ sources of variance are related to A, C and E (ACE Model).

Generally, the values for the intra-class correlations (rMZ and rDZ) do not follow the extreme examples previously mentioned, and show a pattern of A, C, and E influences[27]. Genes and environment mutually affect each other to influence risk[26], and so heritability estimates are not static over time. The genetic influence among the trait varies depending on environmental circumstances or the individuals' vital cycle moment[2,26].

RESULTS

The sample was composed of 158 female twin; 48 pre-menarche twins (30 MZ twins and 18 DZ twins) and 110 post-menarche twins (66 MZ and 44 DZ twins). Table 1 presents the results for descriptive statistics according to menarche and zigosity. The mean age at the time of the study was 14.2±1.06 years. No statistical differences were found due to sex or zigosity. Age of menarche was 11.85±1.47 years for MZ females and 12.07±1.9 years for DZ post-menarche females, with no-significant differences between MZ and DZ twins in the age of menarche (p=0.51).

In addition, BMI showed non-significant differences between MZ and DZ twins in the pre-menarche group (p=0.93) and the post-menarche group (p=0.23). As we can observe, the BMI intra-class correlations suggested a higher heritability among pre-menarche subjects, compared to subjects at the post-menarche stage. Moreover, the presence of common environmental influences among BMI in post-menarche subjects can also be inquired.

Children's Eating Attitudes Test (ChEAT)

The cross-twin, within-trait correlations for disordered eating attitudes and behaviors are presented in Table 2. The intra-class correlations suggested no genetic influence among the total ChEAT score for individuals at the pre-menarche stage, whereas for the post-menarche individuals, sources of variance show a very high heritability.

Eating Disorder Inventory (EDI)

Table 2 show results of the intra-class correlations for the four subscales of the EDI. The "Drive for Thinness", "Body dissatisfaction" and "Perfectionism" subscales did not present a genetic influence on pre-menarche subjects. Only the trait "Ineffectiveness" exhibited a moderate heritability at this developmental status.

In contrast, these four subscales showed moderate heritability estimates at the post-menarche stage group.

Table 1 Descriptive statistics and twin correlations by menarche classification

	Pre-menarche twins (N=48)		Post-menarche twins (N=110)	
	MZ (N=30)	DZ (N=18)	MZ (N=66)	DZ (N= 44)
Age Mean (SD)	13.54 (±0.65)		14.48 (±1.06)	
Age of menarche Mean (SD)	-	-	11.85 (1.47)	12.07 (1.9)
BMI				
Mean (SD)	18.28 (2.52)	18.21 (2.5)	20.32 (3.75)	18.21 (2.58)
rMZ, rDZ	0.93	0.11	0.98	0.72
p	< 0.001	0.77	0.001	0.002
Model	AE		ACE	

DZ: Dizigotics, MZ: Monozigotics, r: Pearson correlation coefficients between members of the twin pair, A: additve genetic influence, C: shared environmental influence, E: unique environmental influence, h2: heritability, BMI: Body Mas Index, SD: Standard deviation.
When rMZ=rDZ=0 sources of variance implied to E (E Model)
When rMZ=rDZ>0 sources of variance implied to C and E (CE Model)
When rMZ=2 x rDZ sources of variance implied to A and E (AE Model)
When rMZ>rDZ, rMZ<2 x rDZ sources of variance implied to A, C and E (ACE Model)

Tabla 2 Twin correlations and heritability by menarche in eating attitudes and behavior

r p	PRE-MENARCHE			POST-MENARCHE		
	rMZ	rDZ	Model h2	rMZ	rDZ	Modelo h2
Total ChEAT	0.162	0.537	CE	0.52	0.02	**AE**
	0.56	0.14	h^2=0	0.002*	0.91	$h^2 \approx 1$
Drive for thinness	0.56	0.70	CE	0.61	0.10	**AE**
	0.030*	0.030*	h^2=0	<0.001*	0.65	**h^2=1**
Body dissatisfaction	0.37	0.32	CE		0.46	ACE
	0.16	0.40	h^2=0	0.71 <0.001*	0.030*	h^2=0.5
Ineffectiveness	0.34	0.16	AE		0.39	ACE
	0.21	0.68	h^2=0.36	0.71 <0.001*	0.08	h^2=0.65
Perfectionism	0.29	0.36	CE	0.36	0.22	ACE
	0.30	0.34	h^2=0	0.040*	0.33	h^2=0.28

ChEAT: Children's Eating Attitudes Test, DZ: Dizigotics, MZ: Monozigotics, r: Pearson correlation coefficients between members of the twin pair, A: additive genetic influence, C: shared environmental influence, E: unique environmental influence, h2: heritability.
When rMZ=rDZ=0 sources of variance implied to E (E Model)
When rMZ=rDZ>0 sources of variance implied to C and E (CE Model)
When rMZ=2 x rDZ sources of variance implied to A and E (AE Model)
When rMZ>rDZ, rMZ<2 x rDZ sources of variance implied to A, C and E (ACE Model)

DISCUSSION

Individuals on the pre-menarche stage showed no genetic influence among the measured variables, with only one exception; "Ineffectiveness". The intra-class correlations analyses suggested that the expression of these variables is due to environmental influences: unique environmental influences to which one member of a twin pair is exposed but not the other, and common environmental influences which are shared by both members of the twin pair. However, "Ineffectiveness" showed a low genetic influence.

On the contrary, the analyses at the post-menarche stage subjects showed that the expression of these variables is in part due to the cumulative impact of many individual genes that act additively, and to unique environmental influences.

Previous research has shown that genetic factors' influence varies in different symptoms of ED[8,29,30]. As it generally happens with phenotypes, Anorexia Nervosa (AN) and Bulimia Nervosa (BN) have shown to be partially heritable[7,31,32]. Evaluating endophenotypes, such as the variables measured in our study, gives more feedback about the nature of the etiologic causes of the illness. For instance, the investigation carried out by Mazzeo et al. on a sample of adult female twins, evaluated the heritability of BN and its symptoms. Their results indicated that BN showed a heritability estimate of 62%, while symptoms such as compensatory behaviors (vomiting and taking laxatives, diuretics or diet pills) had heritability estimates ranging from 0.43 to 0.53[33]. Moreover, the study conducted by Mitchell et al. examined the heritability of binge eating disorder (BED) as well as different BED symptoms in a sample of twin female adults. Their findings evidenced that the liability to BED was moderately heritable (h^2=45%), while among its symptoms studied separately, such as "loss of control during binges" and "distress due to bingeing", genetic effects accounted for 29–43% of the variance and "compensatory behaviors" demonstrated a greater environmental influence[34]. Finally, in a study of AN in an adult twin female sample, examined by means of the EAT (Eating Attitudes Test), a heritability estimate of 41% was observed, while heritability estimates for AN symptoms, measured by means of the EDI were 52% and 44% for Body dissatisfaction and Drive for thinness respectively[29]. As in previous studies, our investigation suggested that ED, measured by means of the ChEAT score, show a high genetic component for women at the post-menarche stage. On the contrary, examining symptoms separately throughout the

EDI subscales, our study offered qualitative differences in the sources of variance in additive genetic influences (A) and in common environmental influences (C). Thus, Drive for thinness appeared to have a very high genetic influence, whereas Perfectionism and Body dissatisfaction revealed a moderate heritability estimate.

As mentioned, it has been noticed that the incidence and heritability of ED significantly increase during puberty[35,36]. The results of our study are reasonably consistent with data from previous surveys that have shown that menarche is related to increases in heritability estimates for ED and their symptoms[5,11,37-39] However, it must be pointed out that most studies have been conducted with adult population samples while, as it is known, ED are worldwide prevalent among adolescent girls[35]. For this reason, studies based on adolescent samples, as our work, provide the best approximation to the etiological causes of these disorders. Furthermore, early menarche, before 10 years of age, has been associated with a risk increment in developing a diverse range of psychological outcomes, including depression, eating disorders, substance abuse disorders, risky sexual behavior and unwanted pregnancies during adolescence[40-42]. Thus, the early onset of menarche in our sample (11.94±1.69) may be related to a high risk of ED through increments in genetic influences.

There are numerous mechanisms that could be involved in changes in genetic and environmental influences. Firstly, the progression of puberty in girls is associated with body weight and fat gains[41]. It has been consistently established that genetic influences on variations in BMI are high during adolescence and range from 47% to 90%[43-46]. Moreover, body weight and body fat gains cause a psychological impact related to ED symptoms[35]. Gains in body fat are against the cultural expectations of thinness. This may cause body dissatisfaction and negative mood that leads to high-risk of ED[36]. Secondly, endocrine changes such as the increase of gonadal hormones (estradiol) in women, are linked to rises in ED symptoms during puberty[13-17]. These associations may be due to high estrogen levels that may activate the ED genetic influence in girls during puberty[15,39]. On the contrary, other studies have not been able to conclude that these hormonal changes that occur during puberty, and are related to the menarche, are associated with genetic variations among symptoms of disordered eating[47]. This controversy could be due to different methodological approaches between studies. As Culbert et al. noticed, some studies focus on age differences and some on puberty signs, while others consider menarche as a physical characteristic to establish when to evaluate changes in genetic and environmental influences in ED[17,48,49]. Moreover, there is no agreement either in whether to study changes among the heritability of eating disorders' phenotypes (AN and BN) or eating disorders' endophenotypes, such as eating disorders' concerns (i.e. body dissatisfaction or drive for thinness) and eating disorders' behaviors (i.e. dieting or exercise).

The limitations of the present study should be recognized. Firstly, twins may not be representative of general population and, therefore, results may not be generalizable to non-twin samples. Secondly, our sample was relatively small for a twin study. This could have potentially reduced our possibility to discern common environmental (C) effects. Thirdly, the cross-sectional design of our work cannot conclude a causal relationship between menarche and changes in the heritability of ED. Finally, there is a potential source of bias in our group classification according to menarche, rather than pubertal development. That is to say, adolescents with advanced pubertal development, but not yet experienced menarche, were included in the pre-menarche group.

Our approach reveals significant changes related to menarche in contributions of genetic and environmental effects among eating attitudes and behaviors. Clinicians should pay special attention to adolescent girls at high risk of developing an ED especially during the critical period of menarche.

Future research will need to characterize the nature of the relationship between menarche and pubertal development and disordered eating by means of longitudinal twin studies.

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