

Adiposity patterns in children and adolescents from Mozambique: a quantitative genetic study

Padrão de adiposidade em crianças e jovens de Moçambique: um estudo de genética quantitativa

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Abstract – The aim was to estimate the contribution of genetic factors in the skinfold (SF) patterning of children and adolescents from Mozambique. Six SF were measured, and seven phenotypes were derived: Σ 6SF, Σ SF from the trunk, Σ SF from the extremities, the Σ SF trunk/extremities ratio (TER), first, second and third principal components. Heritability (h²) and correlations (r) in sibships were calculated using the ASSOC and FCOR modules of the SAGE 5.3 Genetic Epidemiology software. The h² was high for TER (65%) and the third principal component (50%); moderate for Σ 6SF (48%), Σ SF from the extremities (45%), Σ SF from the trunk (42%), and the second and third principal components (39% and 33% respectively). Overall, r-values were moderate in same-gender sibships (0.21 to 0.44), and low in sibships of different gender (-0.02 to 0.18). In conclusion, genetic factors explain 33 to 65% of the total variance in different SF patterning phenotypes. Same-gender siblings showed greater familial aggregation in fat patterning than did opposite-gender siblings.

Key words: Adiposity; Genetics; Mozambique.

Resumo – O objetivo foi estimar a contribuição dos fatores genéticos no padrão de adiposidade subcutânea de crianças e jovens de Moçambique. Foram mensuradas seis dobras cutâneas (DC) e os sete fenótipos marcadores do padrão de adiposidade foram: Σ6DC, ΣDC tronco, ΣDC das extremidades, razão ΣDC tronco/extremidades (RTE), primeira, segunda e terceira componentes principais. A heritabilidade (h^2) e a correlação (r) nos pares de irmãos foi calculada nos módulos ASSOC e FCOR do software de Epidemiologia Genética SAGE 5.3. A h^2 foi elevada nos fenótipos RTE (65%) e terceira componente (50%); e moderada no Σ6DC (48%), ΣDC das extremidades (45%), ΣDC do tronco (42%), primeira e segunda componente (39% e 33%, respectivamente). No geral, os valores de r foram moderados nos irmãos do mesmo sexo (r entre 0,21 e 0,44) e baixos nos irmãos do sexo oposto (r entre -0,02 e 0,18). Conclui-se que os fatores genéticos são responsáveis por 33 a 65% da variabilidade dos diferentes fenótipos do padrão de adiposidade. Os irmãos do mesmo sexo apresentaram maior agregação familiar do que irmãos de sexo oposto.

Palavras-chave: Adiposidade; Genética; Moçambique.

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INTRODUCTION

The study of body composition in a clinical and epidemiological context has been made possible by methodological and instrumental advances and by progress in the establishment of strategies for mapping the distribution of subcutaneous and visceral fat¹. Broadly speaking, the adiposity pattern refers to the difference in skinfold (SF) thicknesses in various locations of the body, to these values corrected by lean mass or total body mass, or to the differences in the ratio of subcutaneous to visceral fat².

Increased central adiposity is associated with a greater predisposition to metabolic, endocrine and degenerative diseases, which are some of the leading causes of death in adults. The study of adiposity patterns is relevant to assessment of nutritional status and analysis of body composition³ and due to the dependence of these patterns on conditions of social inequality⁴.

Evidence suggests there is familial aggregation in adiposity patterns within nuclear families^{3,5-8}. However, values are discrepant, and the absence of consistency is related to the use of diverging quantitative definitions of adiposity pattern, different study designs, sample sizes, subject ages, number of families, and statistical methods used^{3,9-11}. Estimates of the heritability (h²) of adiposity patterns are highly variable, with values ranging from 12 to 76%^{5,12-15}. Although results are influenced to an unknown extent by environmental factors usually shared by several family members, as well as by interactions between different genotypes and environmental factors, the exclusive influence of additive genetic factors is evident³.

The studies cited above were all conducted in high-income countries, and, therefore, are not representative of the distinct characteristics of other populations³. There are no published studies from countries undergoing the sociodemographic and nutrition transition, as are African countries. The objective of this study was to estimate the contribution of genetic factors to the adiposity pattern of children and adolescents from the rural population of Calanga, Mozambique.

METHODS

Study location

Mozambique is located on the Eastern coast of Africa (Figure 1). It covers an area of 799 390 km², mostly consisting of a low plateau. The Calanga region belongs to the district of Manhiça, located 75 km north of Maputo, with an area of 2373 km². It is bordered by the district of Magude to the North, the district of Bilene to the Northeast, the Indian Ocean to the West, the district of Marracuene to the South and the district of Moamba to the Southeast.

The population of Mozambique has been estimated at \approx 20 million. Calanga has 9451 inhabitants, of which 3361 are children and adolescents between the ages of 6 and 20¹⁶. Family agriculture is the main livelihood. Families typically live in quite isolated rural areas and are of a low socio-

economic level. Housing conditions are precarious; there is no running water, electricity, or medical care; and the educational system is deficient. The sole routes of access are unpaved dirt roads, which become impassable during some of the year¹⁷.



Figure 1: Geographic location of Mozambique

Participants

According to National Education System data, the locality of Calanga-Manhiça, Maputo Province, had 12 primary and secondary schools at the time of the study. Of these, six were selected randomly for sampling. At selected schools, the objectives of the study were explained to principals, who then helped publicize the project among students and their families.

Families were invited and children were enrolled in the study only if they showed interest in doing so. Only children and adolescents who were duly enrolled in the selected schools and who had a brother or sister enrolled at another school in town were added to the sample. Those with symptoms of malaria or chronic malnutrition were excluded from the sample, as were sibships in which one sibling was over the age of 18.

The study sample comprised 330 participants (52.7% males), belonging to 132 families of two to seven children in the 7-to-17 age range. Participants accounted for approximately 10% of the population of Calanga in the 6-to-20 age range. Mean age was 11.6±3.1 years in boys and 10.7±2.6 years in girls. Subjects were participants of the first stage of the "Estudo da Variabilidade Biológica em Moçambique" project, which had as its main objective to provide information on biological variability in the population of Mozambique, its significance and scope in the context of public health and socioeconomic and educational policies¹⁷.

Anthropometric parameters

Anthropometric measurements were obtained by an experienced examiner, using a calibrated GPM^* -brand skinfold caliper with a range of 0-45

millimeters. Triceps, subscapular, supra-iliac, abdominal, thigh, and calf skinfold thicknesses were measured 18.

Adiposity pattern

Two sets of markers were used to determine the adiposity pattern. The first set was based on the four indicators proposed by Perusse et al.¹²: 1) Σ SF6 = triceps + subscapular + supra-iliac + abdominal + thigh + calf; 2) sum of trunk skinfolds, or Σ TSF = subscapular + supra-iliac + abdominal; 3) sum of extremity skinfolds, or Σ ESF = triceps + thigh + calf; and 4) trunk to extremity skinfolds ratio (TER) = Σ TSF/ Σ ESF.

The second set followed the suggestion of Hattori et al.¹⁹: extract the most relevant principal components of the covariance matrix of the six SFs (with eigenvalues \geq 1).

Ethical aspects

The objectives of the study were explained to parents, school principals, post chiefs and local administration officials, and community leaders. When literate, those responsible for education read and signed an informed consent form that provided a detailed description of the study objectives and procedures. For illiterate subjects, the informed consent form was read aloud and consent was requested in the form of a right thumbprint in lieu of a signature. The study was approved by the national health and education authorities of Mozambique and by the National Committee of Bioethics for Health (*Comitê Nacional de Bioética para a Saúde*).

Statistical procedures

Statistical analysis was carried out in several stages. The first stage consisted of exploratory analysis with the objective of detecting potential errors in data entry, outliers, assessing the normality of data distributions (Kolmogorov-Smirnov test) and calculating mean values for each set in each sibship. The second stage consisted of verification of the data structure for each sibship with the PEDSTATS software package and exploratory analysis of the indicators of adiposity pattern in the two proposed models. The third stage consisted of stepwise multiple linear regression, with the intent of removing the effect of covariates of the study phenotypes. The tested covariates were age, sex, age2, age*sex and age2*sex. The standardized residuals of the best regression model for each phenotype were considered for later calculation of h² estimates and correlations between sibships (intraclass correlation for same-sex siblings and interclass correlation for opposite-sex siblings) in SPSS 15.0. Finally, correlations between sibships and h2 estimates were calculated in the S.A.G.E. 5.3 genetic epidemiology software, using modules FCOR and ASSOC respectively. The significance level was set at 5%. Further details on the theoretical model used for h2 estimation are available elsewhere in the literature^{3,20-22}.

RESULTS

Table 1 shows descriptive measures of the six SFs used for calculation of adiposity pattern phenotypes. SF thicknesses were higher among sisters than in brothers.

Table 1. Skinfold thicknesses (mean \pm SD) used for calculation of adiposity pattern phenotypes. Calanga, Mozambique (2006).

Skinfold	Brothers (n=174)		Sisters (n=156)		
	Mean ± SD	Range	Mean ± SD	Range	
Triceps (mm)	6.0±1.4	3.5 – 11.2	7.5±2.1	3.8 – 15.0	
Subscapular (mm)	5.4±0.9	3.3 – 8.4	6.4±1.5	3.6 – 12.5	
Supra-iliac (mm)	5.8±1.8	3.0 – 11.8	7.6±3.0	3.1 – 19.2	
Abdominal (mm)	5.6±1.6	2.9 – 11.2	6.9±2.6	2.9 – 16.7	
Thigh (mm)	8.0±2.2	3.1 – 16.0	11.8±4.1	5.3 – 27.7	
Calf (mm)	7.6±1.8	4.1 – 14.3	9.2±2.3	4.8 – 16.9	

mm: millimeters of fatty tissue

Girls exhibited higher values in the three first adiposity pattern phenotypes (Table 2). The last three phenotypes refer to the mean scores of each principal component. Principal component analysis yielded three components that explain 80% of total variance. The first component represents adiposity of the lower trunk relative to the lower extremity (calf) (eigenvalue=2.07; explained variance=34%). The second refers to the adiposity of the upper trunk relative to the lower extremity (thigh) (eigenvalue=1.67; explained variance=28%). The third component was a single indicator, triceps SF thickness (eigenvalue=1.06; explained variance=18%).

Table 2. Mean values (\pm SD) for the various adiposity pattern phenotypes. Calanga, Mozambique (2006).

Adiposity pattern phenotypes	Brother	s (n=174)	Sisters (n=156)		
Adiposity pattern pricriotypes	Range	Mean ± SD	Range	Mean ± SD	
ΣSF6 (mm)	38.5±7.4	21.5 – 63.2	49.3±13.6	29.8 – 100.8	
ΣESF (mm)	21.8±4.4	14.5 – 37.3	27.2±5.8	17.1 – 39.9	
ΣTSF (mm)	16.8±3.7	10.1 – 27.1	20.8±6.5	11.8 – 45.1	
TER	0.8±0.1	0.5 – 1.2	0.7±0.1	0.5 – 1.1	
1st component	0.1±1.0	-2.5 – 2.7	-0.1±1.0	-3.1 – 2.6	
2nd component	0.4±0.9	-2.2 – 2.6	-0.4±1.0	-2.8 – 2.4	
3rd component	0.1±1.0	-2.2 – 3.0	-0.1±0.9	-2.5 – 2.4	

Σ: sum; SF: skinfolds; TER: trunk to extremity skinfolds ratio

Estimated heritability (h^2) was moderate for Σ SF6 (46%), Σ ESF (44%), Σ TSF (39%), and the first component (38%) and second component (33%), and high for TER (64%) and the third component (49%) (Table 3).

Table 4 shows correlation coefficients (r) for each of the seven adiposity pattern phenotypes. Coefficients were moderate (0.28 – 0.44) for brothers, with the exception of Σ TSF (r=0.11) and Σ SF6 (r=0.18). A similar pattern was found among sisters, with coefficients ranging from 0.21 to 0.34 (except for

the second component, r=0.05). Lower values were detected in opposite-sex sibships, except for Σ SF6 (r=0.25) and Σ ESF (r=0.21).

Table 3. Estimated heritability (±standard error) of adiposity pattern phenotypes. Calanga, Mozambique (2006).

Adiposity pattern phenotypes	Components of variance				
Adiposity pattern phenotypes	Polygenic	Residual	Total variance	h²	р
ΣSF6 (mm)	0.46±0.14	0.49±0.12	0.95±0.08	0.48±0.14	<0.001
ΣESF (mm)	0.44±0.15	0.55±0.13	0.98±0.08	0.45±0.14	0.001
ΣTSF (mm)	0.39±0.14	0.55±0.12	0.93±0.08	0.42±0.14	0.001
TER	0.64±0.16	0.35±0.12	0.99±0.08	0.65±0.13	< 0.001
1st component	0.38±0.14	0.61±0.13	0.99±0.08	0.39±0.13	0.002
2nd component	0.33±0.14	0.66±0.13	0.99±0.08	0.33±0.14	0.007
3rd component	0.49±0.15	0.49±0.12	0.99±0.08	0.50±0.13	<0.001

Σ: sum; SF: skinfolds; TER: trunk to extremity skinfolds ratio

Table 4. Correlation coefficients (±standard error) for adiposity pattern phenotypes according to the sex makeup of sibships. Calanga, Mozambique (2006).

Adiposity pattern phenotypes	Brothers (77 sibships)	Sisters (71 sibships)	Opposite-sex sibships (145 sibships)
	r ± SE	r ± SE	r ± SE
ΣSF6 (mm)	0.18±0.12	0.24±0.13	0.25±0.09
ΣESF (mm)	0.28±0.12	0.21±0.16	0.21±0.09
ΣTSF (mm)	0.11±0.11	0.26±0.13	0.17±0.09
TER	0.44±0.11	0.34±0.16	0.12±0.10
1st component	0.34±0.12	0.31±0.13	-0.02±0.10
2nd component	0.30±0.12	0.05±0.12	0.15±0.09
3rd component	0.39±0.11	0.28±0.13	0.18±0.09

Σ: sum; SF: skinfolds; TER: trunk to extremity skinfolds ratio

DISCUSSION

Aggregation studies seek to ascertain the presence of the genetic and cultural factors of a set of phenotypes within a nuclear family³. One of the statistics most often used to identify this aggregation is heritability (h^2), a measure that expresses how much of typical total phenotype variance is explained by shared genetic factors. Despite their recognized importance, the biological aspects of adiposity patterns related to genetic factors have been the object of few studies, particularly in siblings^{5,12-14}. In this study, estimated h^2 was significant, ranging from 33 to 65%, thus indicating the importance of genetic factors to adiposity in sibships.

Most family-based studies assess SFs individually, their sums, and TER⁶⁻⁸. In the present study, the h^2 values of Σ TSF, Σ ESF, Σ SF6 and TER were 42%, 45%, 48% and 65% respectively. These findings are similar to those reported elsewhere. The evidence highlights the importance of genetic factors in the variability of distinct subcutaneous fat distribution patterns^{5,12-14,23}. Linkage studies have identified regions in several chromosomes that are believed to contain genes responsible for the variation in cutaneous adiposity, as well as case-control association studies with

candidate genes, which can identify the significance of estimates with greater rigor and precision²⁴.

We were unable to identify any genetic epidemiology studies conducted on samples of populations from countries undergoing the sociodemographic and nutrition transition, particularly countries in Sub-Saharan Africa³. This research gap reveals a lack of knowledge on the influence of genetic factors on adiposity patterns in populations within the vast nation of Mozambique. Heritability estimates (h²) in the present study are relevant due to environmental pressures of a nutritional nature, lack of primary health care, and presence of infectious diseases, all of which characterize the Calanga region. This circumstance could constitute an obstacle to the genetic potential of the studied phenotypes. The fact that this did not occur may suggest an association with the common environment shared by the family and/or with factors of a socio-cultural nature. For instance, in communities that depend on subsistence agriculture, the hierarchy whereby (nutrient-poor) food is distributed usually holds that all siblings will receive equal portions.

Even so, the findings of this study are consistent with those reported in high-income countries. Fermino et al. ¹⁵ assessed 107 nuclear families in Portugal and found h² estimates ranging from 35 to 43% for a variety of adiposity phenotypes. Perusse et al. ¹² assessed 483 U.S. members of 99 nuclear families and found moderate-to-high h² estimates of 31%, 34%, 36%, and 50% for total fat, peripheral fat, central fat, and TER respectively. Katzmarzyk et al. ¹⁴ assessed 102 Canadian nuclear families and reported variability in TER, the first component and Σ SF, with h² estimates of 30%, 48% and 54% respectively. A similar pattern was reported by Butte et al. ^{6,7} in 319 Spanish families (h² of central adiposity, 31%), by Rice et al. ¹³ in U.S. residents, and by Hunt et al. ⁵ in Canadians, with h² estimates for total body fat ranging between entre 34% and 54%.

However, Rice et al.²³ evaluated 412 members of 105 Canadian nuclear families and found an estimated heritability of only 16% for total body fat. Perusse et al.¹² suggest that TER is susceptible to greater genetic influence than the amount of subcutaneous fat, and have identified a candidate gene (ADRAZ: 10p24-q26) that is believed to regulate these values²⁵.

Descriptions of subcutaneous adiposity patterns based on principal components analysis is relatively varied in countries such as the U.S. and Canada. There is a consensus that three or more components^{14,26}, described as those employed in the present study, should be used. Conversely, few studies have addressed aspects of the genetic dependence of adiposity patterns. From sibships of Calanga, Mozambique, we extracted three principal components, which yielded h² estimates of 39%, 33%, and 50% respectively. The highest value was found for the third component, which consisted of a single marker (triceps SF thickness). Likewise, other studies have stressed that a significant percentage of variation in each component is due to genetic factors shared by family members. Li et al. ²⁶ assessed 1237 Canadian members of 308 nuclear families and found that the additive

effect of genes explained 34%, 40%, and 48% of variation in the first, second, and third components respectively. Katzmarzyk et al. 14 reported h² estimates of 48% for the first component. There is no evidence to suggest that this set of components is associated with any single gene with a greater effect, their association with candidate genes notwithstanding, as well as QTLs (quantitative trait loci) with reduced magnitude of effect²⁴. Even though the influence of genetic factors on the principal components of adiposity patterns are unequivocal, some authors suggest that genetic and environmental factors interact to affect the variability observed in adiposity patterns⁵. Hunt et al. 5 highlight the importance of environmental factors shared by nuclear families (such as dietary habits and physical activity) to observed variability in adiposity patterns.

Another potential method for interpretation of h² estimates is to analyze the pattern of familial aggregation on the basis of the correlation coefficients detected in sibships³. The correlation pattern found for adiposity phenotypes suggests the presence of familial aggregation, which reinforces the hypothesis that a genetic component governs the variability detected in our sample of sibships from the rural population of Calanga, Mozambique. Fermino et al.15, in an assessment of siblings in the same range as that of our sample, found positive correlations ranging between 0.01 and 0.65 for several markers of adiposity. Bouchard²⁷ reported values of 0.32 to 0.42. Despite correction for several covariates, the correlation observed between sisters may have been related to differences in maturity, as the sample included pre- and postpubertal subjects alike. The lowest correlations were detected within opposite-sex sibships. This suggests that sexual dimorphism plays a role in the differential expression of adiposity patterns, probably due to changes in morphology and growth (subcutaneous fat distribution and development of adipose tissue^{28,29}) during youth. In puberty, changes in the adiposity pattern lead to greater fat buildup in girls. Nevertheless, boys tend to develop fat buildup in an android pattern, whereas girls tend to follow a gynoid pattern of adiposity.

It is important to note that findings of sibship studies are influenced by a shared effect. Proof that environmental factors play an important role in the variation of measures in these phenotypes is of the utmost importance to primary care and nutritional interventions, as they add obvious repercussions to work in these areas.

Although this was the only genetic epidemiology study conducted in a low-income country, some limitations should be taken into account when interpreting its results. The small sample size and cross-sectional design did not enable emphasis on the complex interaction between genotype and environmental conditions. On the other hand, sibship analyses provide an adequate understanding of the components that underlie observed variation in distinct phenotypes of subcutaneous adiposity patterns. Further cross-sectional, longitudinal, and case-control studies should be conducted in sibship samples or nuclear families with the objective of clarifying the contribution of genetic factors to markers of body fat distribution.

Likewise, further studies focusing on the interaction between genotypes and environmental factors in distinct nutritional scenarios (malnutrition/obesity) and physical activity levels are warranted.

CONCLUSION

Genetic factors explain 33 to 65% of variability in the distinct phenotypes of subcutaneous adiposity. Same-sex siblings exhibited greater familial aggregation than opposite-sex siblings.

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