Waist circumference is genetically correlated with incident Type 2 diabetes in Mexican-American families

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Abstract

Aims—We aimed to determine the genetic and environmental correlation between various anthropometric indexes and incident Type 2 diabetes with a focus on waist circumference.

Methods—We used the data on extended Mexican-American families (808 subjects, 7617.92 person-years follow-up) from the San Antonio Family Heart Study and estimated the genetic and environmental correlations of 16 anthropometric indexes with the genetic liability of incident Type 2 diabetes. We performed bivariate trait analyses using the SOLAR software package.

Results—All 16 anthropometric indexes were significantly heritable (range of heritabilities 0.24–0.99). Thirteen indexes were found to have significant environmental correlation with the liability of incident Type 2 diabetes. In contrast, only anthropometric indexes consisting of waist circumference (waist circumference, waist–hip ratio and waist–height ratio) were significantly genetically correlated (genetic correlation coefficients: 0.45, 0.55 and 0.44, respectively) with the liability of incident Type 2 diabetes. We did not observe such a correlation for BMI.

Conclusions—Waist circumference as a predictor of future Type 2 diabetes is supported by shared genetic influences.

Introduction

Recently, evidence to support the hypothesis that waist circumference is a predictor of future risk of Type 2 diabetes has grown substantially [1]. Large observational studies in populations of European and US descent have clearly demonstrated the usefulness of waist circumference as a simple and accurate predictor of future Type 2 diabetes [2,3]. Interestingly, both waist circumference and Type 2 diabetes have been identified as highly heritable traits [4]; therefore, these observations raise the possibility that waist circumference and Type 2 diabetes might share similar genetic influences. Such shared genetic features, if operational, might identify important pathophysiological and therapeutic targets for the prevention and control of Type 2 diabetes.

Previous studies have found that there is significant genetic correlation between waist circumference and risk of prevalent Type 2 diabetes [5,6]; however, since waist circumference has the potential to serve as a predictor of future Type 2 diabetes, it is of interest to investigate if a similar genetic correlation between waist circumference and risk of impending Type 2 diabetes is also evident. Given the importance of waist circumference in the pathophysiology of Type 2 diabetes, we hypothesized that there was a significant

genetic correlation between waist circumference and the liability of incident Type 2 diabetes. To test this hypothesis and to examine the specificity of this potential association, we determined the genetic and environmental correlations between several anthropometric measures and the risk of incident Type 2 diabetes in large extended Mexican-American families enrolled in the San Antonio Family Heart Study (SAFHS) [7].

Methods

The SAFHS is an ongoing study of 1431 Mexican-American individuals belonging to 42 large extended families from San Antonio, Texas, USA [7]. The SAFHS was designed to quantify the relative contributions of genetic and environmental factors to the risk of developing cardiovascular disease and metabolic syndrome. Study participants have been followed up for up to three visits. Informed consent was obtained from all participants before data and sample collection. The study was approved by the Institutional Review Board of the University of Texas Health Science Center at San Antonio. Details of phenotypic assessments for a number of traits related to metabolic syndrome have been described previously [7]. In the present study, we included 808 participants (from 42 families) who did not have Type 2 diabetes at enrolment (according to the diagnostic criteria recommended by the American Diabetes Association [8]) and for whom data on various metabolic, anthropometric and demographic variables were available at enrolment as well as at the two follow-up visits. During the follow-up visits, 100 participants were newly diagnosed with diabetes. These participants fulfilled at least one of the following criteria at the follow-up visits: fasting blood glucose 126 mg/dl, 2-h postprandial blood glucose 200 mg/dl or initiation of anti-diabetic treatment. Considering the follow-up of 7617.92 person-years, this translated to an estimated incidence rate of 13.1 Type 2 diabetes cases/1000 population/year. Using observed age-specific mortality rates within the study participants, life expectancy of 69.9 years and the statistical methods described by Magliano *et al*. [9] we estimated that in a hypothetical birth cohort of the study participants, the life-time prevalence of Type 2 diabetes would be 45.8%. This estimate compares well with the projected Type 2 diabetes lifetime prevalence of 50% in Latino-Americans [10], but is higher than the national average lifetime risk of Type 2 diabetes (25%) in the USA [11].

Our approach to genetic analyses was similar to that described elsewhere [12–15]. Since the outcome of interest was dichotomous, we used a liability threshold model for all genetic analyses. This approach assumed an individual to be a member of the disease class if the latent liability score was > 0. Liability was assumed to be multivariate normally distributed. The methods used to generate the unobserved distribution of the liability are described elsewhere [16], but include the characterization of a multivariate normal density that is dependent upon covariates such as age, sex and kinship coefficient structure, and on which a threshold is placed to reflect the prevalence of the dichotomous status of the trait. The correlation in liability of individuals i and j was modelled as $\rho_{ij}=2\phi_{ij}h^2+I_{ij}e^2$, where ρ is the correlation coefficient, ϕ is the kinship coefficient, h^2 is the heritability attributable to polygenic effects, I is an indicator variable for a random environmental component and e^2 is the complement of h^2. Genetic and environmental correlation coefficients (ρ_g and ρ_e, respectively) were determined by performing bivariate trait analyses with the SOLAR software package, using Type 2 diabetes liability and anthropometric index as the two traits [13]. All models were adjusted for age, sex, age^2, age × sex interaction and age^2 × sex interaction as covariates. Statistical significance for ρ_g and ρ_e was determined using a likelihood ratio chi-squared test by i) constraining the corresponding parameter to zero, ii) comparing the log-likelihood of the constrained and unconstrained models, and iii) testing the likelihood ratio chi-squared for one degree of freedom in a two-tailed test. Statistical significance was tested at a type I error rate of 0.05.

Results

Table 1 shows the clinical characteristics of the study participants. We excluded 623 subjects because of missing information during follow-up visits or the presence of Type 2 diabetes at enrolment. Of these, 212 (34%) had diabetes at enrolment and therefore were significantly different with regard to many characteristics when compared with the 808 subjects included for analyses in the study. When we compared the excluded subjects who did not have diabetes with the subjects included in this study we found that the included subjects had a larger proportion of women and were younger but their anthropometric and biochemical characteristics were similar (data not shown).

Most of the anthropometric indexes (with the exception of calf skinfold thicknesses) were significantly heritable (Table 2), as was the liability of incident Type 2 diabetes ($h^2r = 0.80$, $P = 5.9 \times 10^{-6}$). We studied the bivariate genetic and environmental correlation of 16 anthropometric indexes with incident Type 2 diabetes. Table 2 shows the results of these analyses. We observed that 13 anthropometric indexes (with the exception of height, lateral calf thickness and subscapular–triceps ratio) were significantly environmentally correlated with the liability of incident Type 2 diabetes. By contrast, only three anthropometric indexes showed significant genetic correlation with the liability of incident Type 2 diabetes. Although, waist circumference, waist–hip ratio and waist– height ratio showed a significant genetic as well as environmental correlation with the liability of incident Type 2 diabetes, the point estimate of genetic correlation was stronger as compared with that of environmental correlation ($\rho_g = 0.45$, 0.55 and 0.44, while $\rho_e = 0.23$, 0.32 and 0.36 for waist circumference, waist–hip ratio and waist–height ratio, respectively). This indicated a potential sharing of genetic background between the liability of incident Type 2 diabetes and the anthropometric indexes containing waist circumference as a component; however, if waist circumference was included as a covariate in the models for waist–hip ratio and waist– height ratio as the phenotypic traits, then the genetic correlation coefficients for these two traits were not significant ($\rho_g = 0.34$ and 0.14 and $P = 0.11$ and 0.29 for waist–hip ratio and waist–height ratio, respectively), indicating that the significant genetic correlations of waist– hip ratio and waist–height ratio with the liability of incident Type 2 diabetes were primarily attributable to the waist circumference component. Interestingly, BMI and weight were more environmentally than genetically correlated with the liability of incident Type 2 diabetes ($\rho_e = 0.48$ for both BMI and weight, while $\rho_g = 0.28$ and 0.23 for BMI and weight, respectively).

Discussion

In our high-risk, high-prevalence study sample of Mexican-Americans there were three important findings. First, the heritability of incident Type 2 diabetes was very high (0.80) and statistically significant. This estimate lies within the range of reported heritability estimates from other populations (0.64–0.73 in a Finnish [4] and 0.82 in a Chinese sample [17]). Such a high estimate of heritability for a prospectively measured trait can result from a complex interaction between the genetic distance and follow-up time [4]; however, since our sample included only one identical sib-pair, the estimated heritability of incident Type 2 diabetes in the present study is less likely to be influenced by the length–time bias. Nevertheless, the high heritability of incident Type 2 diabetes warrants an investigation into potentially shared genetic influences.

Second, in spite of the high heritabilities of most of the anthropometric indexes, only the ones that included waist circumference showed a significant genetic correlation with the liability of incident Type 2 diabetes. There was no significant genetic correlation between BMI and the liability of incident Type 2 diabetes, despite both traits having a high

heritability. Our findings are consistent with those of Lehtovirta *et al.* [4] and Mathias *et al.* [5] and support the notion that waist circumference might be a more valuable and specific anthropometric index than BMI for Type 2 diabetes. It is notable that these studies have used different methods and designs, but have arrived at concurring inferences. For example, the study by Lehtovirta *et al.* [4] used monozygotic and dizygotic twins with a very long duration of follow-up, while both the study by Mathias *et al.* [5] and the present study used complex pedigrees. Moreover, our study included a prospective component to estimate the liability of incident Type 2 diabetes which the Mathias *et al.* [5] study did not use.

Third, of the anthropometric indexes studied here, waist circumference provides the maximum promise for unraveling the genetic underpinnings of Type 2 diabetes. Several genetic association studies and meta-analyses have already shown promising potential associations of the variations of melanocortin-4 receptor (*MC4R*), and the fat-mass and obesity-associated (*FTO*) genes with the risk of Type 2 diabetes as well as with waist circumference [18–21]. It is also of interest that at least one family-based study [22] provides additional indirect evidence of the potential role of an *FTO* variant (rs17817449) by demonstrating a common link between waist circumference and insulin resistance. One of the other notable candidate genes that is becoming a focus of interest is the lysophospholipase-1-like (*LYPLAL1*) gene [18, 23, 24]. Furthermore, there is some evidence that the methionine sulphoxide reductase A (*MSRA*) gene variants are a partial explanation for the genetic link between waist circumference and Type 2 diabetes [24, 25]. In general, however, evidence for genetic variants as potential leads in family-based settings is currently lacking. It is notable that family-based genome-wide association studies may offer more informative insights into the potential associations of rare or private genetic variants with Type 2 diabetes. Together, there exists a compelling need to pursue the putative genetic connection between waist circumference and Type 2 diabetes. Our results indicate that additional genome-wide association studies, especially in the family settings, are required.

Two limitations of the present study need to be considered before generalizing these results. First, the statistical pleiotropy demonstrated in our study does not automatically imply biological pleiotropy; therefore, our finding that waist circumference and Type 2 diabetes share a common genetic background needs to be replicated in future studies. Second, Lee *et al.* [26] argue that the genetic correlation coefficients estimated using complex pedigrees can be confounded by shared environmental influences. To that end the genetic correlations estimated in this study also need to be replicated using genome-wide polymorphisms as discussed above. Nevertheless, to our knowledge, this is the first study in Mexican-American families that has estimated the degree of genetic correlation between anthropometric indexes and the liability to develop incident Type 2 diabetes. Our results call for a renewed scrutiny of the genetic basis of associations between waist circumference and Type 2 diabetes.

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What's new?

- The study uses prospectively collected data from a large set of Mexican-American individuals.

- Statistical analyses involved bivariate trait analyses for partitioning genetic and environmental components of correlations.

- Waist circumference was the most significantly genetically correlated anthropometric index with liability to develop incident Type 2 diabetes.

- Waist circumference was found to be the most suitable anthropometric index for predicting future risk of Type 2 diabetes based on shared genetic influences.

Table 1

Characteristics of the study participants

Characteristic	Included subjects, *N*=808	Excluded subjects, *N*=623	*P*[*]
Demographics			
Mean (SD) age, years	34.9 (13.9)	45.1 (18.5)	<0.001
Women, *n* (%)	513 (63.5)	336 (53.9)	0.001
Diabetes at enrolment, *n* (%)	-	212 (34.0)	<0.001
Anthropometric indexes			
Mean (SD) skinfold thickness, mm			
Biceps	12.9 (6.6)	12.9 (6.9)	0.997
Forearm	12.0 (4.4)	11.2 (4.3)	0.003
Triceps	20.7 (8.3)	19.6 (8.6)	0.035
Subscapular	27.2 (9.7)	27.7 (9.8)	0.407
Abdominal	41.2 (13.5)	42.7 (14.8)	0.073
Suprailiac	29.1 (12.5)	30.4 (13.6)	0.099
Medial calf	18.6 (7.6)	16.7 (7.6)	<0.001
Lateral calf	12.7 (5.1)	11.3 (4.8)	<0.001
Mean (SD) circumferences, cm			
Waist	92.3 (16.3)	97.9 (16.3)	<0.001
Hip	104.7 (13.1)	105.2 (13.3)	0.483
Mean (SD) ratios			
BMI, kg/m^2	29.0 (6.4)	29.5 (6.3)	0.114
Waist–hip ratio	0.88 (0.09)	0.93 (0.09)	<0.001
Waist–height ratio	0.57 (0.10)	0.61 (0.12)	<0.001
Subscapular–triceps ratio	1.41 (0.51)	1.55 (0.58)	<0.001
Others, mean (SD)			
Weight, kg	76.0 (18.4)	77.0 (17.4)	0.292
Height, m	1.62 (0.88)	1.61 (0.95)	0.164
Mean (SD) blood pressure, mmHg			
Systolic	116.6 (16.2)	125.6 (20.6)	<0.001
Diastolic	69.9 (9.9)	71.6 (10.8)	0.003
Mean (SD) biochemical indexes			
Fasting glucose, mmol/L	4.85 (0.59)	6.55 (3.48)	<0.001
Fasting insulin, μU/mL	14.1 (15.4)	18.5 (23.4)	<0.001
Total serum cholesterol, mg/dl	186.5 (38.1)	193.3 (41.2)	0.002
Serum triglycerides, mg/dl	138.5 (128.3)	166.2 (126.6)	<0.001
HDL cholesterol, mg/dl	50.8 (12.8)	49.3 (13.0)	0.036
LDL cholesterol, mg/dl	109.7 (31.8)	112.3 (35.2)	0.157

[*] Student's *t*-test for continuous variables (all values were first inverse-normalized in SOLAR) and chi-squared test for categorical variables.

Table 2

Genetic (ρ_g) and environmental (ρ_e) correlations between liability of incident Type 2 diabetes and anthropometric indexes[*]

Anthropometric index	Heritability		Genetic correlation		Environmental correlation	
	h^2r	P	ρ_g (SE)	P	ρ_e (SE)	P
Skinfold Thickness						
Biceps	0.51	8.6×10^{-14}	0.20 (0.16)	0.2126	0.47 (0.10)	3.11×10^{-6}
Forearm	0.49	1.1×10^{-13}	0.08 (0.16)	0.6086	0.38 (0.12)	0.0014
Triceps	0.53	7.7×10^{-15}	0.07 (0.14)	0.6117	0.40 (0.13)	0.0023
Subscapular	0.51	2.4×10^{-13}	0.31 (0.17)	0.0631	0.25 (0.07)	0.0001
Abdominal	0.48	3.1×10^{-10}	0.28 (0.18)	0.1205	0.34 (0.09)	8.58×10^{-5}
Suprailiac	0.53	1.0×10^{-11}	0.30 (0.17)	0.0787	0.38 (0.08)	3.04×10^{-6}
Medial Calf	0.46	3.0×10^{-12}	−0.14 (0.17)	0.4081	0.73 (0.19)	9.13×10^{-5}
Lateral Calf	0.44	4.5×10^{-10}	−0.13 (0.17)	0.4523	0.32 (0.28)	0.2598
Circumferences						
Waist	0.62	1.2×10^{-15}	0.45 (0.16)	0.0058	0.23 (0.04)	2.05×10^{-7}
Hip	0.68	2.0×10^{-19}	0.20 (0.15)	0.1849	0.46 (0.11)	1.37×10^{-5}
Ratios						
BMI	0.59	2.7×10^{-16}	0.28 (0.15)	0.0638	0.48 (0.09)	3.23×10^{-7}
Waist–hip ratio	0.24	2.2×10^{-4}	0.55 (0.18)	0.0025	0.32 (0.06)	4.28×10^{-7}
Waist–height ratio	0.59	2.1×10^{-16}	0.44 (0.14)	0.0021	0.36 (0.06)	1.19×10^{-8}
Subscapular–triceps ratio	0.44	1.6×10^{-11}	0.25 (0.15)	0.1013	−0.26 (1.20)	0.8290
Others						
Weight	0.63	5.6×10^{-19}	0.23 (0.14)	0.1038	0.48 (0.10)	4.77×10^{-6}
Height	0.99	9.3×10^{-38}	0.06[†]	1.0000	−0.28 (1.05)	0.7896

[*] All analyses were adjusted for age, sex, age^2, $age \times sex$ interaction and $age^2 \times sex$ interaction.

[†] SE could not be estimated.