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African ancestry, lung function and the effect of genetics

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ABSTRACT African-Americans have smaller lung function compared with European-Americans. The aim of this study was to disentangle the contribution of genetics from other variables on lung function.

A cohort was followed from birth to 30 years of age in Brazil. Several variables were collected: genomic analysis based on DNA; forced expiratory volume in 1 s (FEV_1) and forced vital capacity (FVC) obtained by spirometry; height measured by anthropometrists; and thorax circumference evaluated by photonic scanner. Crude and adjusted linear regression models were calculated according to African ancestry.

The sample comprised 2869 participants out of 3701 members of the cohort. Males with higher African ancestry by DNA analysis had a smaller FEV_1 (−0.13 L, 95% CI −0.23–−0.03 L) and FVC (−0.21 L, 95% CI −0.32–−0.09 L) compared with those with less African ancestry, having accounted for height, sitting to standing height ratio and other confounders. Similar effects were seen in females.

After adjustment, ancestry remained significantly associated with lung function, but the large effect of adjustment for confounding among males (but not females) does not allow us to exclude the possibility that residual confounding may still account for these findings.

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Smaller lung function is related to African ancestry but adjustments for confounders reduced the effect sizes http://ow.ly/Iq0Ve

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Introduction

African-Americans have shown consistently smaller lung function compared with European-Americans [1–9]. In addition, forced expiratory volume in 1 s (FEV_1) and forced vital capacity (FVC) in African-Americans differed from those in Caucasians by the same percentage, signifying that, for the same age and height, lung dimensions differed proportionately [6]; it should be mentioned that the information about race and ethnicity in most of the literature has been self-reported. However, according to Kumar *et al.* [3], in the absence of genetic typing, predicted values in self-reported African-Americans may be biased by up to 200 mL. It should be emphasised that most of the literature does not define race at all [9].

Commonly reported ethnic and racial differences in pulmonary function have been attributed to differences in body build, such as chest size relative to height (approached by the Cormic index: sitting to standing height ratio). Lung function in general is proportional to body size as indicated by standing height. However, ethnic groups with smaller lung function also have historically lower socioeconomic status (determining bodily development in early life and leading to trends in body size and pulmonary function that continue into adulthood) and possibly other environmental factors [10–19], which are important determinants of lung growth and development.

A recent systematic review about race and/or ethnicity and lung function showed that researchers have failed to explore this association in a proper way, and an appeal was made to the scientific community to clarify this relationship [9]. Of the 226 eligible papers published between 1922 and 2008, in 83.6% of the articles it was reported that "other racial and ethnic groups" had a smaller lung volume compared with "white" groups, and 94% failed to examine socioeconomic status; in those papers that reported smaller lung function in "other racial and ethnic groups", 21.8 and 29.4% of explanations cited inherent factors and anthropometric differences, respectively, whereas 23.1% cited environmental and social factors [9].

The debate on this association has been ongoing for decades and in recent years it has been emphasised due to different interpretations of the available data [5, 7]. The present study addresses whether lung function varies according to the proportion of African genomic ancestry (based on DNA) and how this interacts with anthropometric measurements, socioeconomic status, smoking, comorbidities and birth weight.

Methods

In 1982, the maternity hospitals in Pelotas, a southern Brazilian city, were visited daily and all births were identified. Those live-borns whose family lived in the urban area of the city were examined and their mothers interviewed (n=5914). These subjects have been followed up several times [20–22].

The study protocol was approved by the Federal University of Pelotas Ethics Committee. In 2012–2013 (at 30 years of age), we invited all the cohort members to participate in a follow-up examination at the study clinic. Participants gave informed consent. Spirometry was undertaken in individuals who did not present any exclusion criteria (recent abdominal or thoracic surgery, pregnancy or possible pregnancy, cardiovascular diseases, retinal detachment or eye surgery, tuberculosis under treatment, or comprehension difficulties) using a portable, battery-operated, ultrasound transit time-based Easy-One spirometer (ndd Medical Technologies, Zurich, Switzerland). Spirometry was carried out following American Thoracic Society and European Respiratory Society recommended procedures [23], before and 15 min after inhalation of 200 μg salbutamol. The spirometric measures used in the current analysis were pre-bronchodilator FEV_1 and FVC.

Skin colour was self-reported by the subjects and categorised into white, brown (or mixed), black or as "other" (52 subjects reported yellow skin colour and 45 reported as indigenous).

Standing height was assessed to the nearest 0.1 cm using a full-length wall-mounted stadiometer (SECA 240; Birmingham, UK) [24]; all anthropometric measurements were carried out twice and the mean value was used. Thorax circumference was measured by photonic scanner (TC^2 3D Body Scanner; Textile Clothing and Technology Corporation, Cary, NC, USA).

The genomic ancestry analysis was based on DNA samples of 3736 cohort members who had been evaluated at 22–23 years of age. The Illumina Omni 2.5M array (Illumina, Inc., San Diego, CA, USA) was used for genotyping, and the Admixture analyses [25] were based on 370 539 single nucleotide polymorphisms (SNPs) shared by samples from the HapMap Project (http://hapmap.ncbi.nlm.nih.gov), the Human Genome Diversity Project (HGDP) (www.hagsc.org/hgdp) and the Pelotas cohort. As external panels, we used the following HapMap samples: 266 Africans, 262 Europeans (Americans from European ancestry and Italian), 77 admixed Mexican-Americans and 83 African-Americans; and 93 native Americans from the HGDP. For each subject the proportion of European, African-American and native American ancestry was estimated. By using parental populations from different public sources, we believe we included the relevant contributors to Latin-American populations: Yoruba from Western Africa (one of the main

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ethnic groups that contributed to the African diaspora from this region), Luyha from Kenya (East Africa), two European populations and four native American populations.

The following variables were considered as possible confounders in the multivariate analyses: standing height and sitting/standing height ratio, chest circumference, family income and maternal schooling at birth (as number of completed years), maternal smoking during pregnancy (number of cigarettes smoked per day), birth weight in grams (using paediatric scales with a precision of 10 g), household asset index in childhood (obtained through factor analysis and based on the ownership of household goods), pneumonia-related hospitalisation in the first 2 years and wheezing (defined according to the International Study of Asthma and Allergies (ISAAC) questionnaire [26]). Socioeconomic status was evaluated again during the 2012–2013 follow-up visit on the basis of number of years of achieved schooling and the possession of 17 different household assets [27]. A household asset index based on the possession of household assets was estimated using factor analysis. Prevalence of smoking and wheezing (in the past 12 months) were also collected during the 2012–2013 follow-up visit.

Statistical analyses

Descriptive analysis was performed according to the African ancestry percentiles in our cohort (0–40, 40–80, and 80–100%), which corresponded to the following categories for proportion of African ancestry: 0–5.2, 5.3–25.8, and 25.9–87.9. Analyses were based on a conceptual framework of the determinants of the association between African ancestry and pulmonary function. Crude and adjusted linear regression models for FEV_1 and FVC according to self-reported skin colour and African ancestry were carried out.

The regression models were adjusted by adding new variables to African ancestry (model 1): standing height (model 2); sitting/standing height ratio and chest circumference (model 3); current asset index, current achieved schooling, current smoking, wheezing (in 2012), family income and maternal schooling at birth, birth weight, gestational age, asset index in 1984, maternal smoking during pregnancy, and history of wheezing and pneumonia from birth to 1984 (model 4).

Analyses were stratified by sex and statistical significance was *a priori* defined as $p<0.05$. All analyses were performed using R 3.0.2 (The R Project for Statistical Computing; www.r-project.org).

Results

In the 2012–2013 follow-up (participants aged 30 years old), 3701 subjects were interviewed, which added to the 366 subjects who were known to have died represents a 68.8% follow-up rate. The present analysis took into account only those individuals who had information on ancestry (from follow-up at 22–23 years of age) and on lung function (obtained at the 2012–2013 visit) (n=2869).

Table 1 shows the percentage of subjects with spirometric and ancestry data and the total number of individuals evaluated at 2012–2013 follow-up visit. More than 75% of individuals evaluated in the last follow-up visit were included in the present analysis. For those with the highest family income at birth and those born to mothers who had ⩾12 years of schooling the percentage participating in the last follow-up visit was lower compared with those individuals with less favourable socioeconomic variables.

Table 2 shows that those who had more than one quarter African ancestry had lower birth weight, as well as income and maternal schooling at birth. By the same token, socioeconomic indicators at 30 years were unfavourable for those with higher proportion of African ancestry. Current anthropometric variables were inversely associated with African ancestry, except mean chest circumference (table 2).

Table 3 shows the crude and adjusted association between African ancestry with FEV_1 and FVC stratified by sex. We opted for using the denominator of 927 for males and 943 for females due to missing information for some covariables. For males, those with more than 25.9% African ancestry had a smaller FEV_1 (crude analysis $\beta=-0.31$ L, 95% CI -0.43 – -0.20 L; and full adjusted β (model 4)$=-0.13$ L; 95% CI -0.23 – -0.03 L) and FVC (crude analysis $\beta=-0.46$ L; 95% CI -0.59 – -0.32 L; and fully adjusted β (model 4)$=-0.21$ L; 95% CI -0.32 – -0.09 L) compared with those with <5% African ancestry. For females, the results were similar, but the strength of the association was lower compared with males.

The linear regression coefficients (height and sitting/standing height ratio in cm) and the adjusted-R^2 values according to African ancestry are shown in table 4. African ancestry explains less of the variability for height than for the sitting/standing height ratio, especially in males; the R^2 for the crude model was 2% for height and around 6% for the sitting/standing height ratio.

Discussion

Our results show smaller lung function volumes among those subjects with increased African ancestry after adjustment for anthropometrics and several other variables. We have shown that the sitting to

TABLE 1 Proportion of eligible individuals among the entire 2012 follow-up[#] according to study variables

	Follow-up at 30 years of age n	Follow-up at 30 years of age with spirometry and ancestry data	
		n	%
Subjects	3467	2869	
Sex			
Males	1733	1416	81.7
Females	1734	1453	83.8
Family income at birth (US dollars)[¶]			
⩽50	680	564	82.9
51–100	1713	1443	84.2
101–300	676	554	82.0
301–500	206	158	76.7
>500	176	134	76.1
Maternal schooling at birth years[¶]			
0–4	1122	949	84.6
5–8	1487	1244	83.7
9–11	379	311	82.1
⩾12	474	360	75.9
Asset index in quintiles (1984) [¶,+]			
First (poorest)	635	534	84.1
Second	654	547	83.6
Third	1094	912	83.4
Fourth	299	249	83.3
Fifth (wealthiest)	489	397	81.2
Maternal smoking during pregnancy cigarettes			
Have not smoked	2256	1854	82.2
1–14 cigarettes per day	920	767	83.4
⩾15 cigarettes per day	291	248	85.2
Wheezing from birth until 1984[¶]			
No	2619	2187	83.5
Yes	558	457	81.9
Pneumonia from birth until 1984[¶]			
No	2648	2200	83.1
Yes	527	443	84.1
Asset index in quintiles in 2012[¶,+]			
First (poorest)	751	642	85.5
Second	685	561	81.9
Third	861	724	84.1
Fourth	307	268	87.3
Fifth (wealthiest)	643	505	78.5
Years of achieved schooling in 2012[¶]			
0–4	206	178	86.4
5–8	679	561	82.6
9–11	1038	876	84.4
⩾12	1509	1231	81.6
Smoking in 2012[¶]			
Never-smoker	2009	1658	82.5
Ex-smoker	611	510	83.5
Smoker	814	680	83.5
Wheezing in 2012[¶]			
No	2400	2169	90.4
Yes	763	686	89.9
Height quartiles[¶]			
First (shortest)	868	732	84.3
Second	871	743	85.3
Third	859	688	80.1
Fourth (tallest)	858	698	81.4

[#]: 234 individuals out of the total of 3701 followed-up were not eligible for spirometry; [¶]: variables with at least one missing observation, the maximum number of missing values was 296 (complete sample), which was observed in asset index in the 1984 follow-up; [+]: calculated for the complete follow-up.

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TABLE 2 Sample descriptions stratified according to proportion of African ancestry

	African ancestry %			p-value
	0.0–5.2	5.3–25.8	25.9–87.9	
Subjects n	1148	1147	574	
Family income at birth				
0–3 minimum salaries	60.2	72.5	86.5	<0.001
Maternal schooling at birth#				
0–4 complete years	26.2	32.4	48.5	<0.001
Gestational age weeks#	39.4±1.8	39.4±1.7	39.2±1.8	0.101
Birth weight kg	3.26±0.51	3.24±0.51	3.14±0.54	<0.001
Asset index (1984)#				
1st quintile (poorest)	23.8	36.6	48.8	<0.001
Maternal smoking during pregnancy				
Have not smoked	70.8	60.9	59.6	<0.001
Wheezing (from birth until 1984)#				
Yes	15.6	17.1	21.1	0.025
Pneumonia (from birth until 1984)#				
Yes	13.4	18.4	20.3	<0.001
Asset index (in 2012)#				
1st quintile (poorest)	34.2	46.9	60.7	<0.001
Achieved schooling in years (in 2012)#				
0–4	4.2	6.8	9.1	<0.001
Smoking (in 2012)#				
Smoker	20.5	26.2	26.0	0.015
Wheezing (in 2012)#				
Yes	21.0	26.3	25.5	0.008
Height cm#	168.9±9.2	167±9.2	166.7±8.9	<0.001
Chest circumference cm#	103.6±11.3	103.2±11.5	103.5±11.4	0.783

Data are presented as % or mean±SD, unless otherwise stated. #: variables with at least one missing observation. The maximum number of missing values was 569, observed in gestational age.

standing height ratio is related to African ancestry having taken into account socioeconomic confounders, whereas overall height is not affected by African ancestry *per se* (table 4). This confirms the work of others showing that height, sitting/standing height ratio and thoracic circumference are linked to the association between African ancestry and lung function [2, 6, 7, 13, 28, 29]. We did not include sitting height on its own in our analysis due to its colinearity with other variables.

Having taken into account height and the sitting to standing height ratio African ancestry was still associated with significantly lower FEV_1 (−150 mL in men and −200 mL in women) and FVC (−240 and −190 mL, respectively). After then accounting for all the additional confounders in table 2 these estimates were only changed by 10–30 mL. We accept that residual confounding may still be an issue and that 18% of the variance in height in our subjects was related to our measured confounders. However, the effect of African ancestry, height and sitting to standing height ratio on determining FEV_1 and FVC are much larger than that of the confounders we have measured.

Socioeconomic status may affect health in a variety of ways [30], including adverse environmental exposures, and it is unlikely that specific indicators, or even a combination of indicators, can take into account all of its impact. In addition, socioeconomic status has impacts throughout life, even before birth, and current status may differ from that present at key stages of growth and development. In fact, separating genetic African ancestry from socioeconomic status may be unfeasible for some time as both have been deeply linked for centuries and it will require a considerable population of individuals with high African ancestry living their whole life in adequate socioeconomic status. A key strength of our study was the availability of socioeconomic status at more than one time point.

Although several researchers have carried out genomic ancestry analysis it should be mentioned that this method has some limitations; in the present study inferred ancestry was performed through a larger set of SNPs from different datasets and not only from Pelotas. We believe we have adjusted for a variety of indicators of ancestral history that contribute to current Latin-American populations, and therefore have partially reduced the problem of studying an unusually varied population.

TABLE 3 Linear regression coefficients (in litres) for FEV_1 and FVC according to African ancestry

	Models[#]			
	1	2	3	4
	β (95% CI)	β (95% CI)	β (95% CI)	β (95% CI)
FEV_1				
Males[¶]	Adj-R^2=3.3, p<0.001	Adj-R^2=31.4, p<0.001	Adj-R^2=32.1, p=0.007	Adj-R^2=34.6, p=0.030
African ancestry %				
0.0–5.2	Reference	Reference	Reference	Reference
5.3–25.8	−0.17 (−0.26–−0.08)	−0.08 (−0.15–0.00)	−0.07 (−0.15–0.00)	−0.06 (−0.14–0.01)
25.9–87.9	−0.31 (−0.43–−0.20)	−0.20 (−0.30–−0.10)	−0.15 (−0.25–−0.05)	−0.13 (−0.23–−0.03)
Females[+]	Adj-R^2=4.6, p<0.001	Adj-R^2=33.1, p<0.001	Adj-R^2=33.9, p<0.001	Adj-R^2=36.1, p<0.001
African ancestry %				
0.0–5.2	Reference	Reference	Reference	Reference
5.3–25.8	−0.10 (−0.16–−0.04)	−0.04 (−0.09–0.01)	−0.03 (−0.08–0.02)	−0.02 (−0.08–0.03)
25.9–87.9	−0.26 (−0.34–−0.19)	−0.24 (−0.31–−0.18)	−0.20 (−0.27–−0.14)	−0.19 (−0.26–−0.12)
FVC				
Males[¶]	Adj-R^2=4.5, p<0.001	Adj-R^2=37.8, p<0.001	Adj-R^2=39.1, p<0.001	Adj-R^2=40.7, p=0.002
African ancestry %				
0.0–5.2	Reference	Reference	Reference	Reference
5.3–25.8	−0.22 (−0.32–−0.11)	−0.09 (−0.18–−0.01)	−0.09 (−0.17–0.00)	−0.09 (−0.17–0.00)
25.9–87.9	−0.46 (−0.59–−0.32)	−0.30 (−0.41–−0.19)	−0.24 (−0.35–−0.12)	−0.21 (−0.32–−0.09)
Females[+]	Adj-R^2=3.2, p<0.001	Adj-R^2=35.8, p<0.001	Adj-R^2=36.9, p<0.001	Adj-R^2=38.3, p<0.001
African ancestry %				
0.0–5.2	Reference	Reference	Reference	Reference
5.3–25.8	−0.09 (−0.16–−0.02)	−0.02 (−0.08–0.04)	−0.01 (−0.07–0.05)	−0.02 (−0.08–0.04)
25.9–87.9	−0.26 (−0.35–−0.17)	−0.23 (−0.31–−0.16)	−0.19 (−0.27–−0.11)	−0.20 (−0.27–−0.12)

Note: for African ancestry categories, the statistical software creates dummy variables coded as 0 (reference) and 1 (category of African ancestry evaluated). FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity. [#]: model 1: African ancestry (crude model); model 2: model 1 plus height (cm); model 3: model 2 plus sitting height/height ratio and chest circumference (cm); model 4: model 3 plus current asset index (quintiles), current achieved schooling (categorised), current smoking, wheezing (in 2012), family income at birth (minimum salaries), maternal education at birth (complete years), birth weight (g), gestational age (weeks), asset index in quintiles (1984), maternal smoking during pregnancy (number of cigarettes), wheezing (from birth until 1984), and pneumonia (from birth until 1984). [¶] : n=927. [+]: n=943.

The additional analysis carried out to identify whether height was more determined by genetics or by the environment shows that the inclusion of African ancestry resulted in minor increases in the R^2 and adjusted-R^2 values for both sexes. There was no convincing evidence supporting that the genetic differences among ethnic groups in our sample played an important role in explaining the differences in height.

The complex relationship between lung function and race and/or ethnicity [5, 7] has been addressed in several studies; a key issue in this discussion is to disentangle the contribution of "genetics" and "other variables" which is very difficult or impossible to achieve at present time. To the best of our knowledge this is the first study in a middle-income country assessing the independent role of genomic ancestry on lung function and several anthropometric measures, indicators of socioeconomic status at birth and later in life, morbidities, smoking, and birth weight in a longitudinal cohort.

Brazil is a huge country and it is common to use three skin colour categories to assess race: white, brown or "mixed", and black [31]. In the city of Pelotas, site of the present study, 80% of the population classify themselves as white [32]; however, the population is highly admixed [33, 34]. It has been shown that those subjects who self-reported their skin colour as black had lower lung function parameters compared with those who self-reported white skin colour (table S1). Previous data from the genome-wide study in Brazil showed that self-reported skin colour has a good correlation with genomic ancestry (data not shown).

Categorising subjects into racial/ethnical groups is done on the assumption that race/ethnicity is a proxy for genetic relatedness, but this can misrepresent genetic variation and leads to confounding [8]. Yaeger *et al.* [35], comparing genetic ancestry and self-described race, found that self-reported race generally agreed well with the inferred genetic population cluster, but did not reveal the extent of admixture; other researchers have found a good correlation between self-defined race with inferred genetic clusters [36, 37]. However, the opposite has also been found: a poor correlation between self-reported race and genetic typing [38], with practical consequences such as lung function underestimation using predictive equations based on self-reported race alone [3].

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TABLE 4 Linear regression coefficients and adjusted-R^2 values for height and sitting/standing height ratio according to African ancestry

	Height cm		Sitting/Standing height ratio cm	
	Crude	**Adjusted#**	**Crude**	**Adjusted#**
Males				
Adjusted-R^2_{model} %	2.0	18.4	5.8	8.0
Adjusted-$R^2_{ancestry}$ %¶	2.0	0.2	5.8	5.0
	Regression coefficients cm			
	β (95% CI)	**β (95% CI)**	**β (95% CI)**	**β (95% CI)**
African ancestry %	p<0.001	p=0.147	p<0.001	p<0.001
0.0–5.2	Reference	Reference	Reference	Reference
5.3–25.8	−1.94 (−2.92 – −0.96)	−0.91 (−1.83–0.02)	0.0004 (−0.0014–0.0022)	0.0003 (−0.0016–0.0021)
25.9–87.9	−2.40 (−3.66 – −1.13)	−0.73 (−1.94–0.48)	−0.0083 (−0.0106 – −0.0059)	−0.0081 (−0.0105 – −0.0056)
	Height (cm)		**Sitting/Standing height ratio (cm)**	
	Crude	**Adjusted***	**Crude**	**Adjusted***
Females				
Adjusted-R^2_{model} %	1.1	11.7	8.5	10.8
Adjusted-$R^2_{ancestry}$ %¶	1.1	0.8	8.5	8.5
	Regression coefficients cm			
	β (95% CI)	**β (95% CI)**	**β (95% CI)**	**β (95% CI)**
African ancestry %	p=0.002	p=0.022	p<0.001	p<0.001
0.0–5.2	Reference	Reference	Reference	Reference
5.3–25.8	−1.50 (−2.34 – −0.67)	−0.82 (−1.64–0.01)	−0.0014 (−0.0031–0.0003)	−0.0016 (−0.0034–0.0002)
25.9–87.9	−0.50 (−1.54–0.54)	0.50 (−0.55–1.55)	−0.0102 (−0.0123 – −0.0080)	−0.0107 (−0.0130 – −0.0084)

Note: for African ancestry categories, the statistical software creates dummy variables coded as 0 (reference) and 1 (category of African ancestry evaluated). The p-values refer to the test with three degrees of freedom (heterogeneity test). #: adjusted for African ancestry, family income at birth (minimum salaries), maternal education at birth (complete years), birth weight (g), gestational age (weeks), asset index in quintiles (1984), maternal smoking during pregnancy (number of cigarettes), asthma (from birth until 1984), pneumonia (from birth until 1984), current asset index (quintiles), current achieved schooling (categorised), current smoking, and wheezing (in 2012). ¶: calculated by subtracting the adjusted-R^2 from the adjusted model without African ancestry as a covariate from the adjusted-R^2 value of the full model (*i.e.*, containing African ancestry).

Study strengths and limitations

Although the analysed sample was smaller than that seen at the 2012–2013 follow-up, information was available for more than 75% of the original eligible subjects. We should acknowledge the limitation of the chest circumference measurement by the photonic scanner, since this equipment measures the thorax circumference for men and women in the same way. Among women we should consider that differences in breast size and position could introduce some error in this measurement. We hope the stratification by sex in the multivariate analysis has minimised this problem.

Some strengths of this study should be mentioned: 1) the high quality of the spirometric tests; 2) the possibility of taking into account so many variables and measures due to the longitudinal design of this study and that these were measured prospectively; and 3) the very large number of markers used in genomic ancestry analysis.

The socioeconomic indicators we adjusted for in the present analysis are highly correlated, but the main objective of including them into the models was to take into account possible confounders of the association between African ancestry and lung function.

Conclusion

In summary, those individuals with high percentage of "African ancestry" presented lower lung function as compared to those with less "African ancestry", but this was largely explained by differences in anthropometric variables (mainly height).

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