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ARTICLE

Association of African genetic ancestry with fasting glucose and HbA_{1c} levels in non-diabetic individuals: the Boston Area Community Health (BACH) Prediabetes Study

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Abstract
Aims/hypothesis To test among diabetes-free urban community-dwelling adults the hypothesis that the proportion of African genetic ancestry is positively associated with glycaemia, after accounting for other continental ancestry proportions, BMI and socioeconomic status (SES).
Methods The Boston Area Community Health cohort is a multi-stage 1:1:1 stratified random sample of self-identified African-American, Hispanic and white adults from three Boston inner city areas. We measured 62 ancestry informative markers, fasting glucose (FG), HbA_{1c}, BMI and SES (income, education, occupation and insurance status) and analysed 1,387 eligible individuals (379 African-American, 411 Hispanic, 597 white) without clinical or biochemical evidence of diabetes. We used three-heritage multinomial linear regression models to test the association of FG or HbA_{1c} with genetic ancestry proportion adjusted for: (1) age and sex; (2) age, sex and BMI; and (3) age, sex, BMI and SES.
Results Mean age- and sex-adjusted FG levels were 5.73 and 5.54 mmol/l among those with 100% African or European ancestry, respectively. Using per cent European ancestry as the referent, each 1% increase in African ancestry proportion was associated with an age- and sex-adjusted FG increase of 0.0019 mmol/l (p=0.01). In the BMI- and SES-adjusted model the slope was 0.0019 (p=0.02). Analysis of HbA_{1c} gave similar results.
Conclusions/interpretation A greater proportion of African genetic ancestry is independently associated with higher FG levels in a non-diabetic community-based cohort, even accounting for other ancestry proportions, obesity and SES. The results suggest that differences between African-Americans and whites in type 2 diabetes risk may include genetically mediated differences in glucose homeostasis.

Keywords Fasting glucose · Genetic ancestry · Genetic association study · Genetic epidemiology · Genetics · HbA_{1c} · Health disparities · Prediabetes · Type 2 diabetes

Abbreviations
AIMs Ancestry informative markers
BACH Boston Area Community Health

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FG	Fasting glucose
SES	Socioeconomic status
SNP	Single nucleotide polymorphism

Introduction

African-Americans and US Hispanics appear to have higher prevalence, earlier onset and more rapidly progressive type 2 diabetes with higher levels of glycaemia (denoted by HbA_{1c}) at diagnosis and with more subsequent complications relative to US whites [1–6]. Race/ethnicity and related social and economic barriers to prevention weaken the translation to healthy lifestyles and effective healthcare necessary to reduce and ameliorate type 2 diabetes [4, 5, 7]. Although social and behavioural factors clearly increase diabetes disease risk [8], diabetes prevention efforts in the US aimed at social and behavioural factors remain incompletely effective, so further work incorporating racial/ethnic diabetes disparities upstream of diabetes development is needed to address the root causes [9, 10]. In particular, studies of regulation of glucose in the non-diabetic state can give clues to pre-type 2 diabetic risk [11].

Besides social and economic factors, there may be genetic differences across humans in glucose regulation and type 2 diabetes predisposition [12]. Transethnic studies show that genetic determinants of type 2 diabetes risk or glycaemic trait levels in whites also operate in African-Americans, albeit at varying allele frequencies; thus, absolute genetic differences between racial/ethnic groups in glycaemic trait levels or disease risk are generally small [13–18]. For instance, African-American type 2 diabetes admixture mapping is consistent with an independent effect of African ancestry proportion on type 2 diabetes risk but not on diabetes-related quantitative trait levels (such as fasting glucose [FG], insulin or HbA_{1c}) in non-diabetic individuals [12]. Under the assumption that identifying ancestral-specific variation will improve understanding of the phenotypic variation seen in type 2 diabetes and facilitate prevention efforts, we further investigated ancestry-based genetic influences on diabetes risk.

We tested the hypothesis that higher African genomic ancestry proportion is positively associated with glycaemia (FG [19] and HbA_{1c} levels) in a population-based random sample of non-diabetic participants. In diabetes-free individuals, lack of confounding by treatment or disease duration may help reveal relatively faint genetic influences on phenotype. This approach also limits the influence of race/ethnicity-based disparities to healthcare access and subsequent type and quality of healthcare on glycaemic regulation. We expected the African ancestry–glycaemia relationship to persist even after accounting for simultaneous European and Native American genomic ancestry proportions and after further accounting for BMI and socioeconomic status (SES). Ancestry measurement used ancestry informative markers (AIMs) to create a continuous measure of African ancestry that avoids the confounding that is produced when ancestry is measured by race, a socially constructed and influenced category of ancestral self-identity.

Methods

Boston Area Community Health cohort The Boston Area Community Health (BACH) survey is a population-based observational study that uses a multi-stage stratified random sample to recruit adults in three racial/ethnic groups from the city of Boston [20, 21]. The third follow-up recruitment wave of this ongoing study was conducted from 2010 to 2012 and yielded a sample of 3,155 adults aged 37–88 (1,184 men and 1,971 women). During morning home interviews, trained research staff measured BMI, administered surveys that included several different indicators of SES, and collected fasting blood samples for FG and DNA for genotyping. The sampling design allowed for multiple people to be interviewed per household: 565 individuals (17.9%) were in the same household as at least one other interviewee, but there was no information with respect to relatedness. All participants provided written informed consent and the study was approved by the New England Research Institutes' Institutional Review Board.

Measurements/instruments The home visit included anthropometric measurements (i.e. height, weight and waist circumference) and an interview, conducted in English or Spanish, to obtain information about diabetes status, comorbidities, lifestyle and SES. The individual SES indicators or 'social factors' considered were: household income, educational attainment, occupation and health insurance status, measured at baseline. Household income, originally grouped into 12 ordinal categories, was collapsed into the following three categories: <US$20,000, US$20,000–49,999 and ≥US$50,000. Educational attainment was categorised as less than high school, high school graduate or equivalent, some college, and college or advanced degree (the latter were combined due to smaller numbers). Current or former occupation was categorised according to the 2000 US census into four groups: (1) managerial, professional, sales and office occupations; (2) service occupations; (3) manual labour, which included construction, maintenance, farming, production and transportation occupations; and (4) never worked. Health insurance status was categorised as public, private or other health insurance. Physical activity was measured using the Physical Activity Scale for the Elderly, categorised into low, moderate or high. Diet was assessed using the results of the Block Food Frequency Questionnaire classified into a seven point healthy

eating score composed of sodium, vegetables, fruits, meats/beans, grains, fibre and saturated fat, largely based upon US Department of Agriculture and American Heart Association guidelines for healthy eating. A trained phlebotomist conducted the morning fasting blood draw during the home visit, including FG measured with a HemoCue 201 point-of-care analyser (HemoCue, Brea, CA, USA). HbA_{1c} was measured using a Tina-Quant HbA_{1c} generation 2 assay with an analytic measurement range of 3.4–18% HbA_{1c} (Quest Diagnostics, Madison, NJ, USA).

AIMs Specific single nucleotide polymorphisms (SNPs) that have widely divergent allele frequencies in ancestral populations, commonly termed AIMs, are highly informative for continental geographic ancestry. Small sets of these randomly distributed AIMs can be used to derive an accurate estimate of genetic ancestry, expressed as a proportion of each individual's genome. For this study we analysed a panel of 62 AIMs, including 33 autosomal SNPs with allele frequencies differing by ~82% in Native Americans vs European Americans, allowing estimation of Native American ancestry in Hispanics, and 30 SNPs discriminating West Africans from European Americans, such that with 62 uncorrelated SNPs combined we could discriminate for each individual their West African, European and Native American ancestry proportion (electronic supplementary material [ESM] Table 1) [22, 23]. Eleven Native North and South American populations were used to define Native American AIMs [22].

High-quality genotyping was conducted at the Broad Institute (Cambridge, MA, USA) using the Sequenom iPLEX platform (Sequenom, San Diego, CA, USA). The average call rate was 97.4%; 1.6% of samples failed quality control with call rates <90% and two SNPs failed with call rates <90%. Ancestry proportions were calculated using ADMIXTURE, (www.genetics.ucla.edu/software/admixture/; accessed 1 November 2012) with k=3, and data were plotted using STRUCTURE (http://pritchardlab.stanford.edu/structure.html; accessed 1 November 2012) and R (version 2.15.3, accessed 21 May 2013; www.r-project.org).

Participant eligibility From the third (January 2010 to March 2012) BACH survey cohort (n=3,155), we excluded all individuals with missing FG, HbA_{1c} or AIMs data, those with diagnosed diabetes (including drug- and diet-treated diabetes), and, for analyses of FG, individuals with no FG data or with FG levels > 6.94 mmol/l; for analyses of HbA_{1c}, individuals with $HbA_{1c} \geq 6.5\%$ (47.5 mmol/mol) were excluded. Our final analysis cohort included 1,387 individuals (379 African-American, 411 Hispanic and 597 white). The proportion of missing data for other measures was: 19.5% for household income, 0.7% for education, 0.7% for occupation and 0.3% for BMI. To reduce bias produced by missing data [24–26], multiple imputation was implemented for exposure covariates (except for AIMs) using the Multivariate Imputation by Chained Equations (MICE) [27] algorithm in R. Fifteen multiple imputation datasets were created. Imputations were conducted separately for each racial/ethnic group by sex combination to preserve interaction effects.

Statistical methods Statistical analyses of the association of AIMs with glycaemia were performed using SUDAAN 11 (Research Triangle Institute, Research Triangle Park, NC, USA). To account for the survey design, individuals' clinical characteristics were weighted inversely to their probability of selection at baseline, adjusted for non-response bias at follow-up, and post-stratified to the Boston census population in 2010 [28, 29]. Ancestry proportions, FG and HbA_{1c} levels were neither weighted nor imputed. Three-ancestry multinomial linear regression models were used to estimate y-intercepts (the FG or HbA_{1c} level for an individual with 100% ancestry of the referent group) and regression coefficients for a 1% difference in African, Native American or European ancestry, using one of the ancestry groups as the referent and the other two as dependent variables in the models. Our primary hypothesis was that the FG slope is steeper comparing African with European ancestry, i.e. an increasing per cent African ancestry is positively associated with higher FG levels in non-diabetic individuals. We set $p<0.05$ as the significance level for the primary hypothesis. We tested the HbA_{1c} slope to confirm the FG hypothesis. Second level models tested the hypotheses that obesity or social factors weaken glycaemia–ancestry relationships. We specified three sequential models: Model 1: FG (or HbA_{1c})=age+sex+$ancestry_1$+$ancestry_2$; Model 2: FG=age+sex+$ancestry_1$+$ancestry_2$+BMI; and Model 3: FG=age+sex+$ancestry_1$+$ancestry_2$+BMI+income+education+occupation+insurance. Physical activity and dietary behaviour could also influence ancestry–glycaemia associations, although these likely mediate the effects of BMI and social factors; nonetheless, we fitted a fourth model that added physical activity and diet score to Model 3. Finally, to evaluate the potential contribution of insulin resistance to the observed associations, we fitted Models 1–4 using fasting insulin among non-diabetic people as the dependent variable.

Results

Participants Table 1 shows that among 1,387 non-diabetic BACH participants, there were more white than African-American individuals; Hispanic individuals were younger, poorer, less well educated and had lower employment compared with African-American or white individuals; and African-Americans had higher BMI compared with the other groups.

Table 1 Study cohort characteristics overall and by self-reported race/ethnicity

Characteristic	All *N*=1,387	Self-reported race/ethnicity			
		African-American *n*=379	Hispanic *n*=411	White *n*=597	*p* value
Age, years					
34–44	281 (30.38)	71 (32.31)	99 (45.61)	111 (26.60)	< 0.001
45–54	421 (28.31)	136 (34.86)	147 (30.47)	138 (25.35)	
55–64	372 (18.25)	86 (15.78)	118 (16.73)	168 (19.50)	
65–74	209 (12.28)	65 (12.06)	34 (4.62)	110 (13.89)	
75–87	104 (10.79)	21 (4.99)	13 (2.57)	70 (14.67)	
Sex (% male)	519 (44.95)	135 (39.98)	143 (45.86)	241 (46.69)	0.262
Income, US$					
<20,000	455 (22.53)	141 (33.44)	205 (39.51)	109 (14.92)	< 0.001
20,000–49,999	405 (25.65)	129 (34.80)	146 (36.61)	129 (19.92)	
≥50,000	527 (51.83)	109 (31.77)	59 (23.89)	358 (65.16)	
Education					
Less than high school	174 (6.48)	41 (8.43)	117 (22.24)	16 (2.57)	< 0.001
High school or equivalent	397 (23.12)	144 (38.53)	156 (37.46)	96 (14.29)	
Some college	290 291 (20.65)	106 (32.59)	76 (18.11)	109 (16.54)	
College or more	526 (49.75)	88 (20.45)	62 (22.18)	376 (66.59)	
Occupation					
Professional, managerial, sales and office	794 (67.97)	213 (59.32)	119 (40.42)	463 (76.81)	< 0.001
Service	333 (17.03)	93 (22.86)	171 (32.06)	68 (11.78)	
Manual labour	187 (11.76)	63 (16.27)	71 (17.61)	52 (8.84)	
Never worked	74 (3.24)	10 (1.55)	50 (9.91)	14 (2.57)	
Private insurance	807 (70.27)	199 (55.57)	157 (47.80)	451 (80.44)	< 0.001
Public insurance	676 (40.67)	206 (51.37)	238 (49.29)	232 (34.81)	< 0.001
BMI, kg/m^2					
Normal (<25)	337 (26.30)	72 (16.24)	71 (18.00)	194 (31.85)	< 0.001
Overweight (25–29)	515 (39.23)	132 (34.47)	162 (44.20)	221 (40.09)	
Obese (≥30)	535 (34.46)	175 (49.29)	178 (37.80)	182 (28.06)	
Systolic blood pressure, mmHg	128 (0.74)	133 (1.49)	127 (0.99)	127 (0.97)	< 0.001
Diastolic blood pressure, mmHg	80 (0.43)	84 (0.84)	80 (0.75)	78 (0.56)	< 0.001
LDL-cholesterol, mmol/l	2.89 (0.31)	3.01 (0.06)	2.99 (0.06)	2.82.0 (0.04)	< 0.001
Fasting glucose, mmol/l	5.63 (0.03)	5.72 (0.04)	5.67 (0.05)	5.59 (0.04)	< 0.001
HbA_{1c}, %	5.53 (0.01)	5.68 (0.03)	5.57 (0.02)	5.47 (0.02)	< 0.001
HbA_{1c}, mmol/mol	36.9 (0.14)	38.6 (0.32)	37.4 (0.23)	36.3 (0.17)	< 0.001
African ancestry, %	28.3 (1.41)	78.2 (1.12)	30.0 (1.97)	8.63 (0.54)	< 0.001
Native American ancestry, %	7.58 (0.45)	5.95 (0.48)	25.3 (2.15)	4.68 (0.33)	< 0.001
European ancestry, %	64.2 (1.50)	15.9 (1.06)	44.8 (2.05)	86.7 (0.65)	< 0.001

All categorical variables are *n* (%); all continuous variables are mean (SE) unless specified otherwise

Values may not all sum up to 1,387 owing to rounding

Figure 1 and Table 2 show the distribution of AIMs by self-reported race. The clustering of the blue or red dots in the corners of the triangle plot illustrates that for those self-reporting white (blue) or African-American (red) race most of the genomes were of European (93%) or African (87%) ancestry, respectively. Self-reported Hispanic participants (green dots) generally were admixed Native American (42%) or European (33%). Of 1,387 participants, 136, 40 and 1 had >99.99% European, African or Native American genetic ancestry, respectively, contributing to regression models predicting glycaemia.

AIMs and glycaemia Also depicted in Fig. 1 and Table 2, individuals with 100% African genetic ancestry were predicted to have 0.19 mmol/l higher FG and 0.27% higher HbA_{1c} (%) levels than those with 100% European ancestry. For

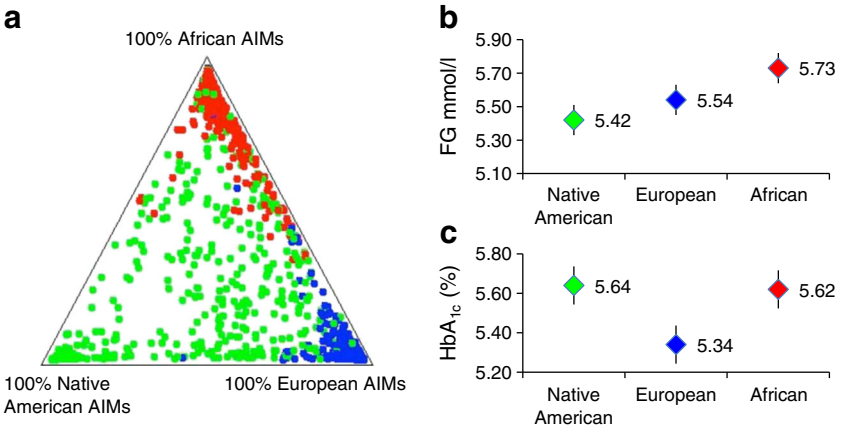

Fig. 1 The triangle (**a**) shows the distribution of AIMs by self-reported race. Clustering of the blue or red dots in the corners of the triangle plot for those self-reporting white (blue) or African-American (red) race show that most of their genomes were of European (93%; Table 2) or African (87%) ancestry. Self-reported Hispanic participants (green dots) were generally admixed Native American (42%) and European (33%). Individuals predicted to have 100% African genetic ancestry had 0.19 mmol/l higher FG (**b**) and 0.27% higher HbA_{1c} levels (**c**) than those with 100% European ancestry. To convert values for HbA_{1c} in % into mmol/mol, subtract 2.15 and multiply by 10.929

individuals in the triangle plot increasingly far from the 100% African corner, each 1% increase in European ancestry was associated with a decrease of −0.0019 mmol/l in FG (p=0.01), and for Native American ancestry, −0.0031 mmol/l, simultaneously accounting for changes in each other's ancestry proportion. Likewise, for HbA_{1c}, each 1% increase in European ancestry was associated with a decrease of −0.003% HbA_{1c} (p<0.001), and for Native American ancestry, an increase of 0.0002% HbA_{1c}, simultaneously accounting for changes in each ancestry proportion.

AIMs, glycaemia, obesity and indicators of SES Table 3 shows that statistical adjustment for BMI and indicators of SES did not materially change the ancestry–glycaemia association. In Model 3, after simultaneous adjustment for Native American ancestry, age, sex, BMI, income, education, occupation and health insurance status, each 1% increase in European ancestry was associated with an FG decrease of −0.0019 mmol/l (p=0.02); likewise, for HbA_{1c} in adjusted models, each 1% increase in European ancestry was associated with a decrease of −0.002% HbA_{1c} (p<0.001). Further accounting for physical activity and dietary behaviour slightly diminished the ancestry–FG association (−0.0017, p=0.08 per 1% increase in European ancestry; ESM Table 2) but did not materially influence the ancestry–HbA_{1c} association (−0.0020, p<0.001 per 1% increase in European ancestry; ESM Table 3). Although greater insulin resistance in African-Americans could alternatively explain the association of African ancestry with glycaemia, the association of African ancestry proportion and fasting insulin was weakened by

Table 2 Proportion of membership for 1,387 non-diabetic individuals in each of k=3 clusters

Self-reported race/ethnicity	Inferred AIMs clusters[a]			*n*	%
	Native American	European	African		
African-American, %	4	10	87	379	27
Hispanic, %	42	33	25	411	30
White, %	3	93	4	597	43
Predicted FG (mmol/l) for 100% AIMs	5.42	5.54	5.73		
Difference vs European	−0.12		0.19		
Change in FG (mmol/l) per 1% change in AIMs proportion vs 100% African ancestry	−0.0031	−0.0019			
p value that change in FG not=0	0.05	0.01			
Predicted HbA_{1c} (%) for 100% AIMs	5.64	5.34	5.62		
Difference vs European	0.30		0.27		
Change in HbA_{1c} (%) per 1% change in AIMs proportion vs 100% African ancestry	0.0002	−0.0027			
p value that change in HbA_{1c} not=0	0.8	< 0.001			

To convert values for HbA_{1c} in % into mmol/mol, subtract 2.15 and multiply by 10.929

[a] AIMs clusters inferred from ADMIXTURE analysis

Table 3 Association of ancestry with glycaemia, adjusted for obesity and social factors, in 1,387 non-diabetic individuals

Characteristic	FG				HbA_{1c}			
	Model 2		Model 3		Model 2		Model 3	
	Estimate[a]	*p* value[b]	Estimate	*p* value	Estimate	*p* value	Estimate	*p* value
Intercept, mmol/l or % HbA_{1c}	5.62		5.82		5.49		5.47	
European ancestry	−0.0014	0.05	−0.0019	0.02	−0.0024	< 0.001	−0.0021	<0.001
Native American ancestry	−0.0029	0.06	−0.0035	0.02	0.0004	0.57	0.0001	0.90
Age, years								
34–44	Ref.		Ref.		Ref.		Ref.	
45–54	0.356	0.78	0.162	0.89	0.073	0.005	0.068	0.009
55–64	1.736	0.16	1.387	0.25	0.147	< 0.001	0.142	< 0.001
65–74	2.416	0.11	1.926	0.2	0.252	< 0.001	0.242	< 0.001
75–87	0.787	0.69	0.529	0.76	0.318	< 0.001	0.291	< 0.001
Male sex	0.435	0.66	0.232	0.81	−0.016	0.48	−0.022	0.31
BMI, kg/m^2								
<25	Ref.		Ref.		Ref.		Ref.	
25–30	0.304	0.78	0.244	0.82	0.101	< 0.001	0.096	< 0.001
≥30	3.284	0.003	3.421	0.002	0.186	< 0.001	0.180	< 0.001
Income, US$								
<20,000			−0.010	1.00			0.008	0.84
20,000–49,999			0.374	0.77			0.054	0.09
≥50,000			Ref.				Ref.	
Education								
Less than high school			−2.362	0.14			0.065	0.22
High school or equivalent			−3.965	0.006			0.009	0.76
Some college			−2.751	0.07			−0.002	0.95
College or more			Ref.				Ref.	
Occupation								
Professional			Ref.				Ref.	
Service			0.662	0.63			−0.016	0.61
Manual labour			2.349	0.19			0.056	0.18
Never worked			5.266	0.005			−0.046	0.27
Private insurance vs public/other			−2.357	0.09			−0.015	0.65

To convert values for HbA_{1c} in % into mmol/mol, subtract 2.15 and multiply by 10.929

[a] Changes in FG (mmol/l) or HbA_{1c} (%) per 1% change in AIMs proportion from 100% African ancestry

[b] *p* value that change in FG or HbA_{1c} not = 0

Ref., reference group

adjustment for BMI (ESM Table 4), suggesting that any potential differences in insulin resistance between groups was controlled by adjustment for BMI.

Discussion

Despite increased type 2 diabetes risk in African-Americans, few genetic studies have specifically examined the association of African ancestry with hyperglycaemia and diabetes risk. It has not been clear to what extent African genomic background influences ambient glycaemia itself, behind the strong, correlated concurrent, confounding factors of obesity and SES. In a case–control analysis in Mexico City and Colombia, European ancestry proportion was associated with lower diabetes risk, and adjustment for SES substantively weakened the association [8]. Recently Cheng et al reported a large-scale admixture mapping study involving 7,021 African-Americans (2,373 with type 2 diabetes and 4,648 without), in which greater degrees of African genomic background increased the risk of type 2 diabetes, independently of adjustment for

BMI and SES [12]. In individuals not receiving treatment for diabetes, African genomic background was also associated with levels of HbA_{1c} but not FG; the HbA_{1c} association was weakened with adjustment for BMI and SES. In the BACH Prediabetes Study we tested the hypothesis that increasing African genomic ancestry proportion is positively associated with glycaemia, taking into account comprehensive physical and social phenotyping. To test the genomic ancestry–glycaemia hypothesis we analysed only non-diabetic individuals, where weak glycaemic regulatory genetic signals may be clearer to detect due to reduced misclassification by glycaemic level associated with both untreated and treated diabetes [30, 31]. We showed that, in comparing those with 100% African vs European ancestry, African ancestry was associated with 0.19 mmol/l higher FG and 0.27% higher HbA_{1c} levels compared with European ancestry. We showed that the African ancestry–glycaemia relationship persisted when accounting for simultaneous European and Native American genomic ancestry proportions, BMI, indicators of SES, age and sex. In models with these factors, as well as physical activity and dietary behaviour, the African–European FG gradient diminished from −0.0019 to −0.0017 mmol/l per 1% increase in per cent European ancestry, but the same gradient for HbA_{1c} was not altered. One interpretation would be that the ancestry–FG association is slightly confounded by energy balance behaviours, after accounting for obesity and social factors. Alternatively, as physical activity and dietary behaviour are in large part the mechanisms through which BMI and social factors act, models including physical activity, diet, obesity and social factors may be over-fitted for 'environmental' exposures, producing over-adjusted results for genetic effects. We think the data show a clear African–European-ancestry–glycaemia gradient, even after accounting for obesity, social factors and the mediating factors of physical activity and dietary behaviour. The results provide support for previous observations that African-American genetic ancestry is associated with higher ambient glycaemia and greater type 2 diabetes risk when compared with European ancestry [4, 5, 12].

It is not yet known what specific genomic regions on the African genome confer risk for hyperglycaemia. Admixture mapping has not identified strong specific signals for type 2 diabetes risk [12, 32]. Recent biracial genome-wide association studies and meta-analyses of association datasets have shown for the most part there are more similarities than differences in African-American vs white genetic determinants of glycaemia [14–17, 32–36]. One could hypothesise that the African genome has concentrated a set of genetic variations that at one time conferred selective advantage for energy storage and survival but that are now deleterious and predispose to metabolic disease [37]. Or, overall West African genomic risk as measured here is likely not 'African' but rather concentrating subcontinental, clade-specific mutations, given the complex underlying clade architecture characterising the global African genome [38]. Our observation that both FG and HbA_{1c} are higher in African ancestry argues against ancestral differences in erythrocyte biology (which may influence HbA_{1c} measurement) having a major effect on the glycaemic/HbA_{1c} racial differences that have been observed [39, 40]. Ongoing large-scale transethnic genomic analyses of glycaemia and erythrocyte biology will fill knowledge gaps in these areas.

Strengths of our analysis include use of a community-based random sample and early morning measurement of fasting individuals, giving a more accurate racial/ethnic prevalence of hyperglycaemia than one obtained by socially confounded reliance on individuals to visit a medical centre research facility. We focused on individuals prior to diabetes onset, an approach that reduces 'downstream' sources of racial/ethnic disparities that can arise from differential access to and quality of care. We used direct assessment of exposures (especially obesity) and outcomes with reliable exclusion of medical and biochemical diabetes from the analysis. SES was assessed with four separately modelled domains, allowing the full variability of income, education, occupation and insurance to be individually controlled. Thus, using a few dozen carefully selected AIMs we were able to show a robust positive association of per cent African vs per cent European genetic ancestry and glycaemia.

Our study has limitations to consider. We did not see a marked difference in glycaemia and Native American ancestry (primarily self-reported Hispanic individuals), comparing African with European ancestry. Given extensive admixture in the Hispanic group, where individuals are genetically somewhat similar to either African or European individuals, we would not expect to see strong between-group differences. There were more self-reported white individuals than African-American individuals in the sample. One might think that this could be due to preferential screening-out of diabetes among African-Americans in the sample; but, if this were true, one would expect to see lower and not higher glycaemic levels in African-Americans. Our data are cross-sectional, but genetic variation, as an exposure, can always be considered to have pre-dated most other exposures and all outcomes. Further, the cross-sectional approach characteristic of current glycaemic genetic discovery has uniformly identified variants that predict future type 2 diabetes [41]. The size of the difference between individuals with 100% African genomes and those with 100% European ancestry genomes (individuals in both groups arguably common) was ~0.2 mmol/l or 0.27% HbA_{1c}, both potentially clinically meaningful, potentially deleterious separations in glycaemic level. However, genetically mediated higher ambient glycaemic levels are not always associated with actual type 2 diabetes risk [42, 43]; but, to the extent that FG levels predict future type 2 diabetes, genetic variation may be one contributor to racially/ethnically noted differences in diabetes phenotypes.

In conclusion, a greater degree of African genetic ancestry proportion was independently associated with higher FG levels in a non-diabetic community-based cohort, even accounting for other ancestry proportions, obesity and indicators of SES. The results suggest that differences between African-Americans and whites in type 2 diabetes risk may include genetic or biologically mediated differences in glucose homeostasis.

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Contribution statement JBM and JBMc made substantial contributions to the conception and design of the study, the acquisition, analysis and interpretation of data, and drafted the article and revised it critically for important intellectual content. RWG, LL, JCF and LM made substantial contributions to the conception of the study and interpretation of data, and critically revised the article for important intellectual content. RP and BP made substantial contributions to the study design, the acquisition, analysis and interpretation of data, drafting the article and revising it critically for important intellectual content. All authors gave final approval of the version to be published. JBM is responsible for the integrity of the work as a whole.

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