



Ethnic differences in adiposity and diabetes risk – insights from genetic studies

H. Yaghootkar^{1,2,3} , B. Whitcher², J. D. Bell² & E. L. Thomas²

From the ¹Genetics of Complex Traits, University of Exeter Medical School, Royal Devon & Exeter Hospital, Exeter; ²School of Life Sciences, College of Liberal Arts and Science, University of Westminster, London, UK; and ³Division of Medical Sciences, Department of Health Sciences, Luleå University of Technology, Luleå, Sweden

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Type 2 diabetes is more common in non-Europeans and starts at a younger age and at lower BMI cut-offs. This review discusses the insights from genetic studies about pathophysiological mechanisms which determine risk of disease with a focus on the role of adiposity and body fat distribution in ethnic disparity in risk of type 2 diabetes. During the past decade, genome-wide association studies (GWAS)

have identified more than 400 genetic variants associated with the risk of type 2 diabetes. The Eurocentric nature of these genetic studies has made them less effective in identifying mechanisms that make non-Europeans more susceptible to higher risk of disease. One possible mechanism suggested by epidemiological studies is the role of ethnic difference in body fat distribution. Using genetic variants associated with an ability to store extra fat in a safe place, which is subcutaneous adipose tissue, we discuss how different ethnic groups could be genetically less susceptible to type 2 diabetes by developing a more favourable fat distribution.

Keywords: type 2 diabetes, obesity, ethnicity, genetics.

Introduction

Type 2 diabetes is a common disease worldwide, but its prevalence varies widely across different ethnic groups. The prevalence of diabetes in the USA, according to self-reported ethnicity and self-reported physician-diagnosed diabetes, ranges from 17.7% in white European individuals to 22.5% in Asians, 30.6% in Hispanics and Africans, and 45.2% in American Indians/Alaska Natives in adults ≥ 75 years of age [1]. This diversity is even evident in ethnic subgroups, where Indians have the highest risk of disease (38.8%) amongst Asians, and Mexicans have the highest prevalence (33.4%) amongst Hispanics [2]. In addition to ethnic disparity in prevalence, type 2 diabetes starts at a younger age and at lower BMI cut-offs in Africans and Asians than in white Europeans [3].

Although type 2 diabetes is typically diagnosed as high levels of blood glucose levels, it is a collection of metabolic derangements, some of which may

play a causal role in the ethnic differences in prevalence of type 2 diabetes, including body fat distribution, adipose tissue function and different levels of insulin secretion and insulin sensitivity (Fig. 1) which may be involved in the ethnic differences. The integration of extensive multidimensional data on glycaemic phenotypes, abdominal MRI scans of fat distribution and metabolic biomarkers in combination with dense and accurate genetic data has facilitated the understanding of diverse disease mechanisms.

Study of ethnic differences in type 2 diabetes risk could lead us to a better understanding of disease mechanisms and eventually have implications for clinical and public health efforts in targeting the prevention of the disease especially in the era of precision medicine. In this review, we will discuss the insights from genetic studies about pathophysiological mechanisms which determine risk of disease with a focus on the role of adiposity and body fat distribution in ethnic disparity in risk of type 2 diabetes.

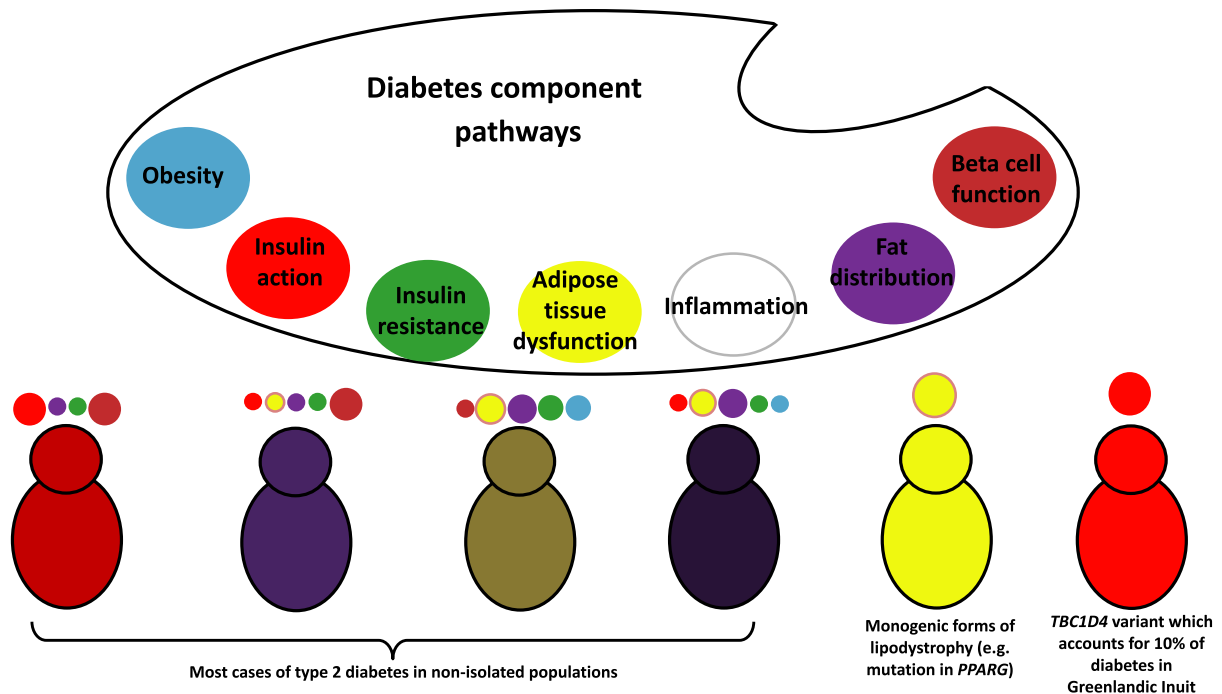


Fig. 1 The McCarthy 'palette' model of type 2 diabetes. In this model the colour of each individual is painted based on contribution of the 'base colours' representing the various pathophysiological processes underlying type 2 diabetes. Adapted from McCarthy [96].

Insights from genetic studies of type 2 diabetes

During the past decade, genome-wide association studies (GWAS) have dissected the genetic architecture of type 2 diabetes in a hypothesis-free way. In these studies, by comparing frequencies of alleles between cases and healthy controls, more than 400 genetic variants known as Single Nucleotide Polymorphisms (SNPs) have been implicated in the risk of type 2 diabetes [4]. These variants have unravelled diverse biological mechanisms and pathways involved in the pathogenicity of the disease. The majority of these variants modulate the risk through insulin secretion, either through direct effects on islet function (e.g. *KCNJ11*) or islet development (*HNF1A*, *WFS1*) or indirectly through impact on incretin signalling (*GLP1R*) [5]. In contrast, a handful of type 2 diabetes associated loci seem to primarily operate through insulin resistance (*PPARG*, *IRS1*), adipogenesis (*KLF14*, *PPARG*) and obesity (*FTO*) [5].

The discovery from GWAS of type 2 diabetes in populations of non-Europeans, including South Asians [6], East Asians [7,8], Hispanics/Latinos [9-

11], Africans [12-15] as well as some isolated populations [16,17], has been successful in identifying ancestry-specific signals that are rare or nonexistent in most populations but have large effects in their studied populations. These GWASs have helped identify novel risk loci, for example, the *KCNQ1* locus in the Japanese population [18], *ZRANB3* locus in Africans [19], *SLC16A11* in Mexicans [11], *ZFAND3* in East Asians [7] (Table 1).

Studies of relatively isolated populations have provided examples of common variants with large effects that are very rare in other populations. Examples include a *CREBRF* variant in Samoans [20], an *HNF1A* variant in Oji-Cree Indians [16] and *ITGA1* [21] and *TBC1D4* variants [17] in the Greenlandic Inuit (Table 1). The last example, *TBC1D4* variants, accounts for 10% of diabetes in Greenlandic Inuit where 14% of people carry at least one copy of the risk allele and those who have two copies, are at tenfold higher risk of type 2 diabetes.

The other unique opportunity provided by genetic studies of non-European populations is the

Table 1. Examples of genetic variants identified in GWAS of type 2 diabetes in populations of non-Europeans

SNP ID	Mapped gene	Function	Population	Effect on risk of type 2 diabetes in odds ratio
rs2283228	<i>KCNQ1</i>	Insulin secretion	Japanese	1.26
chr2:136064024	<i>ZRANB3</i>	β -cells production or maintenance	Africans	1.05
rs13342232	<i>SLC16A11</i>	hepatic lipid metabolism	Mexicans	1.29
rs9470794	<i>ZFAND3</i>	β -cells function	East Asians	1.16
rs373863828	<i>CREBRF</i>	Adipogenesis	Samoans	0.6
rs137853240	<i>HNF1A</i>	β -cells production or maintenance	Oji-Cree Indians	2
rs870992	<i>ITGA1</i>	β -cells function	Greenlandic Inuit	2.79
rs61736969	<i>TBC1D4</i>	Regulates the insulin-dependent uptake of glucose by skeletal muscle and fat tissues)	Greenlandic Inuit	10.3

identification of new drug targets. A genetic study of Mexicans identified a novel protective variant in *IGF2* associated with $\sim 20\%$ lower risk of type 2 diabetes [22]. The frequency of the protective allele is 17% in the Mexican population but the variant is rare in Europeans. Functional studies showed that the protective allele is associated with lower expression of *IGF2* in human liver and adipose tissue but has no effect on other tissues and no association with other traits [22]. These findings suggest that any compound which inhibits the expression of this gene in relevant tissues has potential as a new therapeutic drug for type 2 diabetes beyond Mexican population with no major adverse effects on health.

Ethnic-specific genetic predisposition to type 2 diabetes

An alternative explanation for ethnic differences in diabetes risk relates to genetic predisposition. A different degree of genetic predisposition has been shown previously to explain ethnic differences in the risk of some nondiabetic disease outcomes; for example, genetic studies have shown that variants in 8q24 [23] and variants in *MYH9* [24] contribute to excess disease risk of prostate cancer and kidney disease, respectively, in African Americans compared to European Americans. Is there any ethnic-specific genetic variation which could explain the excess risk of type 2 diabetes in that ethnic group?

Novel loci identified in ancestry-specific GWASs have been very successful in providing novel mechanistic insights and potential drug targets

for type 2 diabetes; however, they have not successfully explained ethnic disparities in type 2 diabetes risk. The majority of genetic variants associated with the risk of type 2 diabetes are common and have similar effect sizes and frequencies across ethnic groups [25–28]. Studies which looked at the role of genetic predisposition in ethnic-specific type 2 diabetes risk are based on comparisons of genetic risk scores between different ethnic groups. These genetic risk scores are defined as the number of risk alleles across multiple established type 2 diabetes variants. Studies have shown that African populations have the greatest genetic risk, Europeans an intermediate risk, whilst East Asians and American Indians have the lowest risk [29–32]. This pattern may partially explain some of the differences between Africans and Europeans but fails to explain the high prevalence of type 2 diabetes in American Indians [32].

The major limitation in the design of these studies is that they all have used genetic variants solely derived from GWASs of Europeans which have minimal ability to capture risk in individuals of non-European origin. Due to different linkage disequilibrium patterns across different populations, the correlation between established variants and true causal variants are different between Europeans and other populations. Furthermore, these studies have used a small number of established type 2 diabetes genetic markers that may not be the true causal variants. The true causal variants in these genetic regions may be more common in frequency and/or have larger effects

than the index signals in non-European populations. The other limiting factor is power. The established type 2 diabetes variants have very modest odds ratios (1.1–1.3 per copy of the risk allele). Therefore, their discovery required studies of more than tens of thousands of cases and controls to reach genome-wide significance in European populations. Available sample sizes in non-European studies have provided limited power to detect these modest effects. Finally, the increased prevalence of type 2 diabetes in non-European populations could be the result of environmental factors or genetic factors that remain largely unidentified.

The role of variation in adiposity in susceptibility to type 2 diabetes, evidence from observational studies

Epidemiological studies have highlighted the differences in anthropometry and body composition as one possible mechanism for ethnic differences in susceptibility to obesity-related metabolic disorders including type 2 diabetes [33,34]. This argument is based on a number of observational differences between ethnic groups which are presented here.

South Asians have been reported to have higher waist circumference, waist-to-hip ratio [35] and 5–7% higher total body fat at any given BMI [36] compared to white Europeans. This elevated central adiposity in South Asians has been linked to greater risk of developing type 2 diabetes, insulin resistance and cardiovascular disease at a lower BMI compared to white Europeans [37]. Lean mass and the lean-to-fat-mass ratio are also lower in South Asians compared to white Europeans and East Asians. The combination of low muscle mass and high truncal fat (estimated by high subscapular skinfold thickness) has been detected in South Asian newborns and is presumed to predispose to insulin resistance later in life [38].

East Asians have lower prevalence of obesity, although fat distribution appears to be less favourable. Data from Chinese, Japanese, Korean, Taiwanese and Filipino populations show that in both sexes, the per cent of abdominal adiposity is higher in East Asians compared to white Europeans. This pattern of fat distribution seems to arise early since prepubescent East Asian boys and girls have lower gynoid fat and fat in extremities compared to white children at pubertal age [39–41].

The prevalence of obesity and morbid obesity is particularly high in Africans, but they develop a favourable fat distribution in comparison to white Europeans in spite of the higher disease risk [42]. Individuals of West African descent have higher muscle mass and less central adiposity compared to white Europeans, yet have a higher risk of developing hypertension, stroke and type 2 diabetes [43,44]. The greater susceptibility to develop metabolic diseases in Africans therefore appears to be at odds with a favourable profile of less central fat mass and higher muscle mass. African Americans have a larger risk than whites at BMI of 22 kg m⁻² and an equivalent risk for both groups at BMI of 32 kg m⁻² [45]. Thus, the impact of BMI on diabetes risk seems to be different for African Americans and white Europeans.

Adiposity per se does not explain the excess risk for type 2 diabetes

Data from observational studies indicate that although different ethnic groups have different degrees of adiposity, these differences do not explain the excess risk. For example, nondiabetic African Americans and Hispanics have higher insulin resistance compared with nondiabetic white Europeans after adjusting for adiposity measures, suggesting that higher insulin resistance, independent of obesity, may be in part responsible for the higher prevalence of diabetes in these groups [46]. Other studies show African American nondiabetic children and adults exhibit hyperinsulinaemia due to a combination of higher insulin secretion and lower rates of insulin clearance [47–51] compared to other ethnicities [47,52–56] which is not explained by insulin resistance [47,53]. Hyperinsulinaemic feature in black African and whether it precedes insulin resistance or is merely a compensatory mechanism is reviewed in an accompanying paper by Goedecke and Olsson.

Evidence from Asian ethnic groups is different suggesting that an insulin secretory defect may play a more important role than insulin resistance in the pathogenesis of type 2 diabetes [57–59]. For example, impaired pancreatic β -cell function has been shown to be the driving force behind the high prevalence of diabetes in Asian Indians compared to white Europeans, Africans and Hispanics [60]. Studies of beta-cell function amongst individuals of Chinese, Malay and Asian-Indian ethnicity living in Singapore demonstrated early-phase insulin secretion trended highest amongst Chinese,

followed by Asian Indians and was the lowest amongst Malays. However, Chinese are the most insulin sensitive whilst Asian Indians are the least insulin sensitive [61].

BMI, body fat % and waist-to-hip ratio are poor predictors for adiposity, fat distribution and metabolic risk

Previous studies assessing the impact of ethnicity on body fat composition and risk of type 2 diabetes most often used indirect measurements of adiposity, including BMI, waist-to-hip ratio and/or measures of fat mass and lean mass derived from bioelectrical impedance. These measures are unable to differentiate between anatomically distinct fat depots. Accurate phenotyping of anthropometry and body fat distribution using medical imaging for precise mapping and quantification of body adiposity is therefore required to determine their potential contribution to ethnic differences in diabetes risk.

It is well established that BMI has numerous limitations; it cannot distinguish between fat and lean mass and is not indicative of body fatness. This may explain why ~ 50% of overweight and ~ 30% of obese individuals, based on BMI, are free from any obvious sign of metabolic and cardiovascular complications [62]. The problem with waist circumference or waist-to-hip ratio is that they cannot distinguish between visceral and abdominal subcutaneous fat depots. Figure 2 illustrates how two people with same BMI or waist circumference, same age and gender can have very different levels of subcutaneous, visceral and liver fat and therefore, different disease risk.

What MRI measures add to the evidence?

Not all fat depots are equally detrimental for health. A different anatomical location makes a substantial difference. Visceral fat and ectopic fat accumulation in or around the liver, pancreas and muscles are causally related to insulin resistance, impaired glucose homeostasis and type 2 diabetes. The divergent regulatory functions of visceral and subcutaneous fat depots may be the reason why some people are relatively protected against cardiometabolic diseases, especially type 2 diabetes.

There is limited data available regarding specific patterns of body fat distribution and liver fat content in different ethnic groups. In general,

observational data suggests that South Asians not only accumulate high amounts of adipose tissue, but also demonstrate a preferential central fat distribution with larger visceral depots in comparison to white European subjects matched for waist circumference [63,64] and also have higher levels of ectopic liver fat both postnatally [65] and in adulthood [66] compared with Europeans. CT and MRI studies show that visceral fat is higher in East Asians compared to Europeans [67-69] and they show the most deleterious abdominal fat distribution amongst white Europeans, Caribbean Africans, Hispanics and Southeast Asians, [70].

A number of studies have pointed out a potential role for deep abdominal subcutaneous fat in metabolic abnormalities [71]. However, most imaging studies of body adiposity do not differentiate between superficial and deep abdominal subcutaneous fat [72]. This is mainly due to the fact that it is not always feasible to distinguish between these depots in most volunteers. However, in the studies where this has been achieved, African women show larger superficial, and similar deep subcutaneous adipose tissue depots compared to white Europeans [73]. Comparing individuals of white European, Chinese, South Asian and Native American, fat in the deep compartment was higher in Native Americans and South Asians, and lower in Chinese [70,74].

Another potentially important ectopic fat depot is the intramuscular fat, which has been shown to be higher in African than in white Europeans and East Asian individuals [75]. There is evidence that Hispanic and African Americans have a tendency for higher lipid accumulation in skeletal muscle compared to white Europeans, independent of their overall body size, obesity or higher visceral and/or subcutaneous adipose tissue [76]. However, a recent study of healthy white European and black west African men reported similar levels of muscle fat in both groups [77].

It should be pointed out that in all the studies reporting ethnic differences in fat distribution, the classification of individuals into ethnic groups of white Europeans, Africans, and East and South Asian origin has been overly simplistic. Furthermore, there is evidence that differences in adiposity and fat distribution exist within ethnic subpopulations, for example, Kenyan and Chinese [78,79]. Another limitation which makes the current evidence less conclusive is that it is difficult to rule

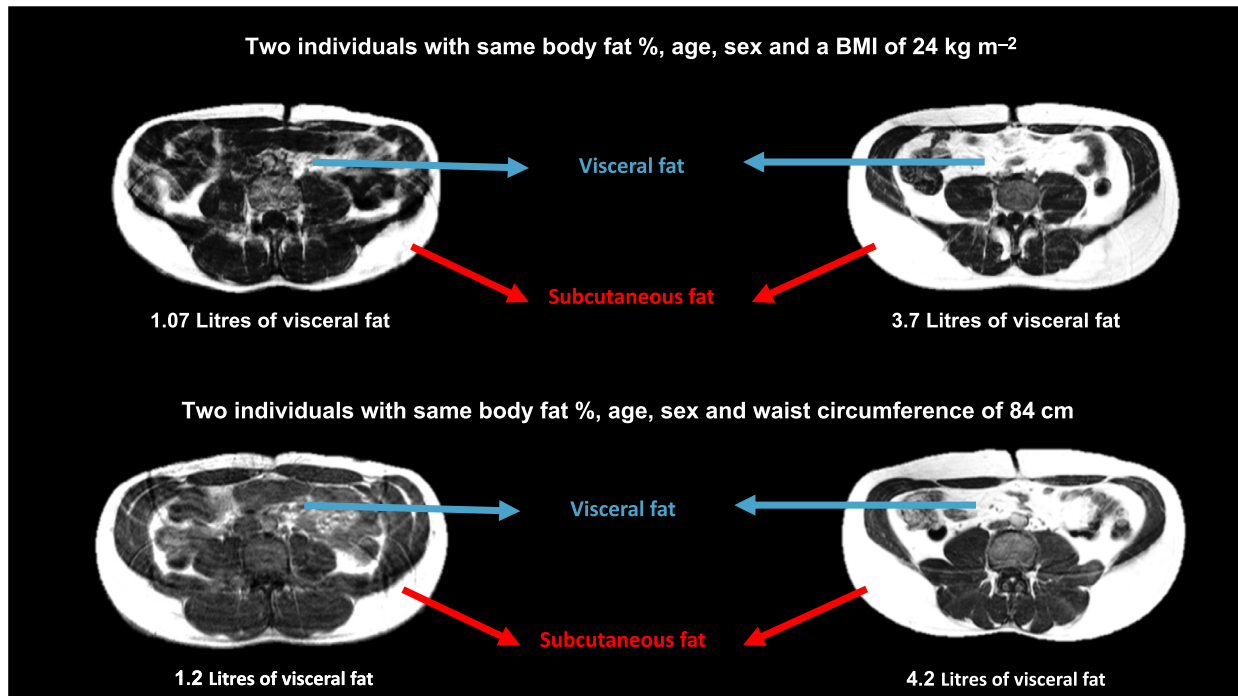


Fig. 2 Transverse slices of 4 participants from abdominal MRI measures. Intensity-corrected fat image using overlay colours illustrates how two people with same BMI or waist circumference, same age and gender can have very different levels of subcutaneous and visceral fat and therefore, different disease risk.

out the role of selection bias in all these studies. Participants may not be representative of their ethnic groups and may have other factors associated with less or more favourable metabolic profile.

To overcome these limitations, we analysed data from UK Biobank study [80] where we had access to adiposity measures including detailed phenotyping of fat depots from MRI scans in much larger sample size than previously reported. The availability of genetic data made it possible for us to identify ethnicity of participants who genetically clustered with white Europeans or Africans or South Asians. We did not observe any differences in visceral fat, liver fat or intramuscular fat, adjusted for age and BMI, between South Asians and white Europeans or Africans. The comparison of same phenotypes in another UK-based cohorts was consistent with results from UK Biobank (Alenaini *et al.*, unpublished). This observation could indicate that ethnic variations in susceptibility to cardiometabolic disease may not arise from differences in body fat distribution. These findings, like any observational studies, suffer from two

major limitations. Firstly, both cohorts we used might be subject to ‘healthy volunteer’ selection bias; and secondly, neither of the cohorts are fully representative of their original populations.

There is a genetic predisposition for adipose tissue expandability and fat storage capacity

Recent large-scale GWASs have provided evidence that a number of genetic variants implicate a paradoxically inverse relationship between adiposity and risk of cardiometabolic disease [81–86]. In the most recent study, we identified 14 genetic variants where the adiposity-increasing alleles were associated with a favourable metabolic profile and lower risk of type 2 diabetes, heart disease and hypertension (Table 2). These alleles were named as ‘favourable adiposity’ alleles as people carrying the greatest number have increased adiposity (higher body fat % and BMI), but paradoxically a reduced frequency of metabolic complications of obesity compared to noncarriers. For example, the 10% of subjects carrying the greatest number of favourable adiposity alleles had ~1.04% higher

body fat % and 0.4 kg m⁻² higher BMI but almost half risk of type 2 diabetes compared with the 10% of subjects carrying the fewest favourable adiposity alleles. Analysis of MRI based imaging data provided an important explanatory mechanism through fat distribution: the favourable adiposity alleles were associated with no differences in visceral fat, but higher subcutaneous and lower liver fat [81] (Fig. 3).

Effective fat storage in subcutaneous adipose tissue would separate potential detrimental lipids from ectopic fat storage or reduce lipotoxicity in cells or tissues lacking dedicated fat storage capacity. Amongst many possible mechanisms underlying this specific aetiology is the ability to generate new adipocytes. Adipocytes expand to store circulating free fatty acids postmeals in the form of triglycerides. This expansion occurs by the enlargement of pre-existing adipocytes (hypertrophy) or by generating new small adipocytes (hyperplasia), or both [87]. The expansion in the form of size or hypertrophy correlates with higher fasting insulin, insulin resistance and higher risk of type 2 diabetes [88,89]. Obese subjects with few large adipocytes are more glucose intolerant and hyperinsulinemic than those having the same degree of obesity but many small adipocytes [88,89].

Our initial results from more than 160 subcutaneous fat biopsies provide evidence that three favourable adiposity variants (in or near *PPARG*, *KLF14* and *FAM13A*) are linked with adipose tissue function [90]. These results indicate that adiposity-increasing alleles at these variants possibly protect from type 2 diabetes by increasing the pool of small adipocytes in the subcutaneous fat depots. For other favourable adiposity variants, it is not known which genes they are acting through; however, the nearest genes are enriched in mechanisms related to adipogenesis and adipocyte differentiation (*IRS1*, *DNAH10* and *CCDC92*), insulin signalling (*FAM13A*), adipose tissue maintenance (*TRIB1*), triglycerides lipase (*LYPLAL1*) and insulin sensitivity (*GRB14*), all mainly expressed in subcutaneous adipose tissue.

The pattern of association between favourable adiposity variants and adiposity, subcutaneous and ectopic fat and risk of type 2 diabetes is consistent with the 'adipose tissue expandability' hypothesis [91]. Type 2 diabetes occurs as a result of the inability of the adipose tissue to expand and accommodate excess fat following extra calories

independent of total adiposity [92]. In fact, genetics of favourable adiposity provides evidence that there is a genetic predisposition for adipose tissue expandability and the fat storage capacity may be in part genetically determined. If individuals are able to sufficiently expand their subcutaneous adipose tissue, they will be protected, to some extent, against the adverse effects of higher adiposity and have a normal metabolic profile despite considerable increase of their adipose tissue mass (Fig. 4).

Can genetics of favourable adiposity tell us about the ethnic difference in risk of type 2 diabetes?

Now the question is whether the genetic variants associated with favourable adiposity within Europeans have similar paradoxical association with adiposity and risk of diabetes in other ethnic groups. The unpublished results using genetic data from 10 700 South Asian individuals in the UK Biobank study indicates that favourable adiposity alleles have similar effect as seen in Europeans [93]. Comparison of the allele frequencies, however, has revealed that South Asians living in the UK have fewer of these protective alleles compared to white European participants in the UK Biobank study. This genetic difference could partly explain the differences in body fat distribution and its relationship with disease in South Asian. This ethnic group appears to carry a smaller number of alleles that are associated with the ability to store extra fat in a safe place which is subcutaneous adipose tissue.

There are very few observational studies investigated the cellular characteristics of adipose tissue across ethnicities but their results are consistent with our finding about the low frequency of favourable adiposity alleles in South Asians. Compared to white Europeans, South Asian men and women have been shown to have larger adipocytes [94]. The study of type 2 diabetes risk factors in obese Pima Indians indicated the best predictive factor for the onset of diabetes was adipocyte size independent of age, sex and body fat percentage, suggesting difficulty in differentiating new adipocytes plays an important role in disease mechanism [95].

Although these findings may partly explain the excess prevalence of type 2 diabetes in South Asians, it is very important to study the effect and frequencies of these genetic variants in other ethnic

Table 2. Genetic variants associated with favourable adiposity

SNP ID	Chromosome	Position	Nearest gene	Function of the nearest gene	Is there an association between the SNP and the nearest gene expression in adipose tissue?
rs11118306	1	219627486	<i>LYPLAL1</i>	Triglyceride lipase	
rs13389219	2	165528876	<i>GRB14</i>	Adipogenesis, lipid metabolism, and insulin signalling	Yes
rs2943653	2	227047771	<i>IRS1</i>	Adipogenesis, lipid metabolism, and insulin signalling	Yes
rs1801282	3	12393125	<i>PPARG</i>	Master transcriptional regulator of adipocyte differentiation	Yes
rs2276936	4	89726283	<i>FAM13A</i>	Adipose development and insulin sensitivity	Yes
rs40271	5	55796319	<i>ANKRD55</i>		
rs632057	6	139834012	<i>CITED2</i>		Yes
rs998584	6	43757896	<i>VEGFA</i>		
rs972283	7	130466854	<i>KLF14</i>	Master regulator of gene expression in adipose tissue	
rs2980888	8	126507308	<i>TRIB1</i>	Adipose tissue maintenance	
rs7133378	12	124409502	<i>DNAH10</i>	Adipogenesis/adipocyte differentiation	Yes
rs11045172	12	20470221	<i>AEBP2</i>		
rs7258937	19	33938800	<i>PEPD</i>	Adipogenesis, lipid metabolism, and insulin signalling	Yes
rs2267373	22	38600542	<i>MAFF</i>		Yes

groups. The discovery of favourable adiposity variants was originally made in populations of European descent and therefore may not adequately capture genetic variation in individuals of non-European descent. Furthermore, the allelic architecture of favourable adiposity may differ for African, native American and Asians versus Europeans.

Type 2 diabetes, a disease with a heterogeneous spectrum of metabolic disturbance

Insulin resistance and insulin secretory failure are two well-established characteristics of type 2

diabetes. Insulin resistance may initially be compensated by increased insulin secretion, and progression to type 2 diabetes is thought to occur when beta-cells are unable to compensate to a sufficient degree. However, type 2 diabetes is a multisystem disease which involves abnormalities in the pancreas, fat, muscle, liver and, probably, the brain. Despite the huge enthusiasm and extensive effort to identify distinct subtypes for type 2 diabetes, there is an increasing body of evidence from GWAS studies supporting the concept that considerable variation exists in the phenotype of individuals with type 2 diabetes not only across ethnic groups but also within each ethnic group.

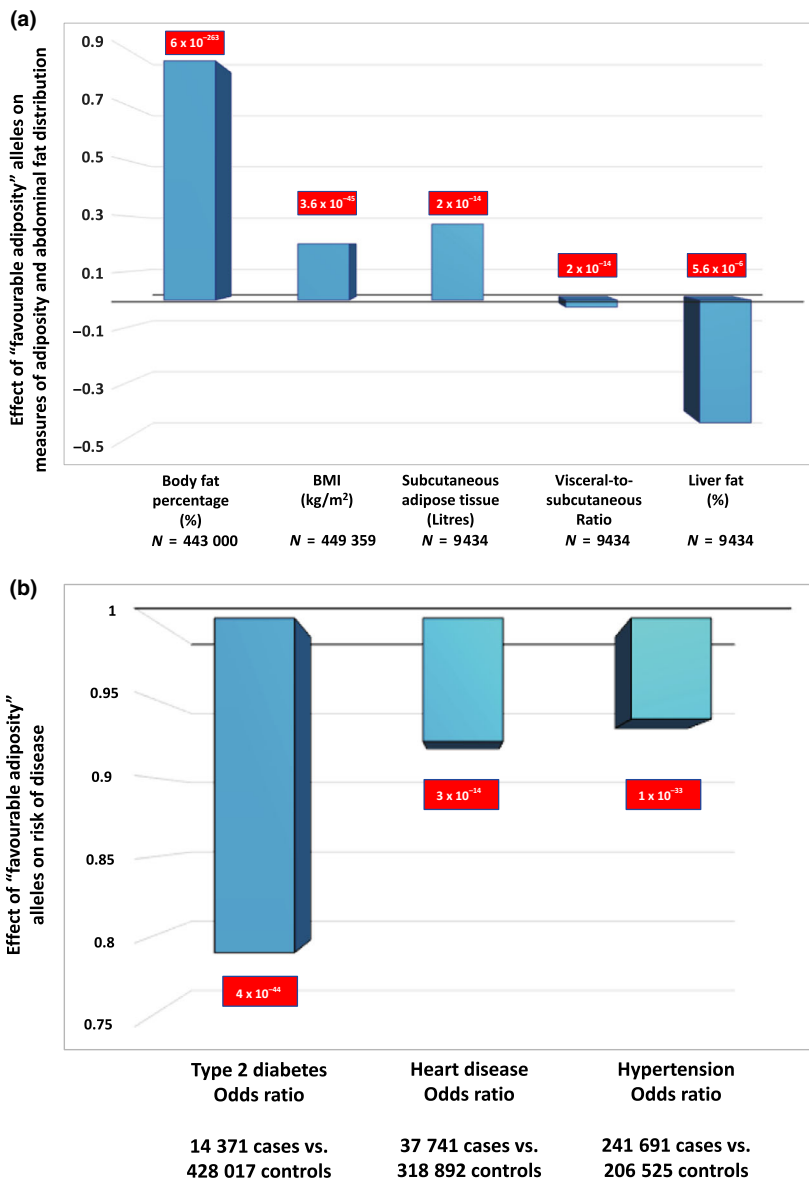


Fig. 3 The effect of 'favourable adiposity' genetic score on (a) measures of adiposity, MRI abdominal fat distribution and (b) cardiometabolic disease risk. Data from Ji *et al.* (81). Effects are per carrying 5 additional adiposity-increasing alleles. Red box shows *p*-value for the association.

Based on data from clinical, biochemical, immunological, anthropometric and, more importantly, genetic measures, it seems more probable that individuals develop type 2 diabetes due to a combination of defects in multiple pathways albeit to a different degree. This concept was introduced by McCarthy as the palette model of diabetes [96]. In this model, different 'base colours' represent

pathophysiological pathways which in combination, but with different degrees of contribution, transport individuals in a journey from health to diabetes (Fig. 1). These pathways include beta-cell development, size, and function, islet autoimmunity, incretin activity, obesity, fat distribution, adipose tissue dysfunction, insulin resistance and many other mechanisms that are still unknown

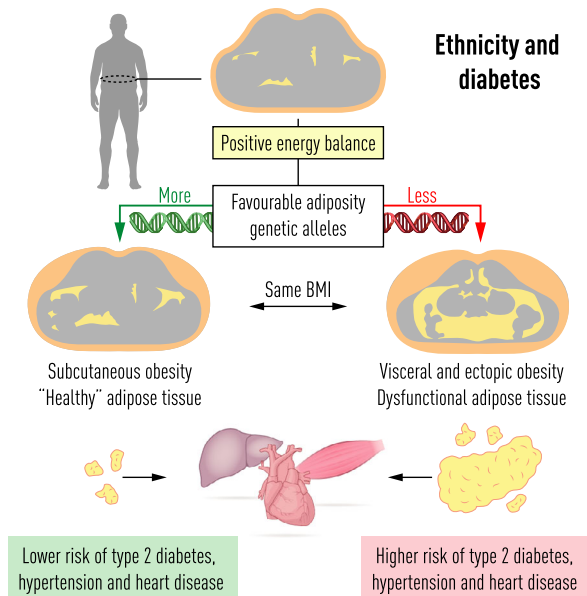


Fig. 4 Genetic variants associated with ‘favourable adiposity’ are associated with the ability to store the extra fat in a safe depot. Individuals carrying the greatest number of ‘favourable adiposity’ alleles are able to sufficiently expand their subcutaneous adipose tissue to protect important organs from ectopic fat. They will be protected, to some extent, against the adverse effects of higher adiposity and have a normal metabolic profile despite considerable increase of their adipose tissue mass.

[96]. As shown in Fig. 1, the palette model illustrates a colour for each individual based on contribution of each ‘base colour’ (pathophysiological pathway).

With inconclusive evidence from studies which try to unravel the mystery of ethnic difference in risk of type 2 diabetes, it seems reasonable to consider the palette model in study design and also interpretation of results. With the exception of isolated populations, where common genetic variants impair a distinct pathway and explain a large proportion of disease risk, in majority of populations, type 2 diabetes is indeed a complex polygenic disease, where multiple common low-impact risk variants contribute to the disease mechanism.

To understand the impact and role of each pathway in different populations, it makes more sense to design a multiomic approach by measuring (i) genetic variants associated with each pathway (e.g. beta-cell function, obesity, lipodystrophy and

disrupted liver lipid metabolism) and (ii) intermediate phenotypes as captured by transcriptome, proteome or metabolome. If the degree of pathogenesis differs based on ethnicity, one would expect to see enrichment of different ‘base colours’ in different ethnic groups.

Summary

Our current knowledge on genetic architecture of type 2 diabetes is Eurocentric where more than 55% of samples are from white European ethnicity whereas majority of people with type 2 diabetes are of non-European ethnicity. The comparatively limited number of non-European GWASs have been very successful in providing insights about the disease mechanisms and drug targets but they have not been effective in identifying mechanisms that make non-European more susceptible to higher risk of disease. It is expected that completion of large-scale GWASs and whole genome/exome sequencing in non-Europeans provide more resolution about the disease mechanism in these populations. Since type 2 diabetes is driven by not only genetic variation but also by variation in different environmental exposures, any ethnic-specific contribution of genetic background to individual predisposition needs to be merged with information on internal (e.g. microbiome) as well as the external (e.g. lifestyle) environment.

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Conflict of interest statement

No conflict of interest was declared.

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Correspondence: Hanieh Yaghootkar, Genetics of Complex Traits, University of Exeter Medical School, Royal Devon & Exeter Hospital, Exeter EX2 5DW, UK.
(e-mail: h.yaghootkar@exeter.ac.uk). ■