




## Conference on ‘Inter-individual differences in the nutrition response: from research to recommendations’

### Symposium 1: The effects of ethnicity on nutrient availability and disease

# Ethnic distinctions in the pathophysiology of type 2 diabetes: a focus on black African-Caribbean populations

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Type 2 diabetes (T2D) is a global public health priority, particularly for populations of black African-Caribbean ethnicity, who suffer disproportionately high rates of the disease. While the mechanisms underlying the development of T2D are well documented, there is growing evidence describing distinctions among black African-Caribbean populations. In the present paper, we review the evidence describing the impact of black African-Caribbean ethnicity on T2D pathophysiology. Ethnic differences were first recognised through evidence that metabolic syndrome diagnostic criteria fail to detect T2D risk in black populations due to less central obesity and dyslipidaemia. Subsequently more detailed investigations have recognised other mechanistic differences, particularly lower visceral and hepatic fat accumulation and a distinctly hyperinsulinaemic response to glucose stimulation. While epidemiological studies have reported exaggerated insulin resistance in black populations, more detailed and direct measures of insulin sensitivity have provided evidence that insulin sensitivity is not markedly different to other ethnic groups and does not explain the hyperinsulinaemia that is exhibited. These findings lead us to hypothesise that ectopic fat does not play a pivotal role in driving insulin resistance in black populations. Furthermore, we hypothesise that hyperinsulinaemia is driven by lower rates of hepatic insulin clearance rather than heightened insulin resistance and is a primary defect rather than occurring in compensation for insulin resistance. These hypotheses are being investigated in our ongoing South London Diabetes and Ethnicity Phenotyping study, which will enable a more detailed understanding of ethnic distinctions in the pathophysiology of T2D between men of black African and white European ethnicity.

#### Ethnicity: African: Type 2 diabetes: Insulin sensitivity: $\beta$ -cell function

#### Ethnic inequalities in type 2 diabetes in the UK

It is estimated that one in eleven adults worldwide is living with diabetes; this equates to 425 million people, a figure which is predicted to rise to 629 million by 2045<sup>(1)</sup>. The alarming rate at which diabetes is increasing makes it a global public health priority. In the UK, 3.7 million people have diagnosed diabetes, although the actual prevalence is thought to be nearer to 5 million when undiagnosed cases are considered<sup>(2)</sup>. Ethnic

inequalities in diabetes have been reported consistently in the scientific literature. The present paper will focus specifically on type 2 diabetes (T2D) as it is the burden of this disease that is most evident among ethnic minority groups.

In 2011, approximately 14% of the UK population identified as from a minority ethnic background; about half were of South Asian ancestry (originating mainly from India, Pakistan, Bangladesh and Sri Lanka), and approximately 25% were of black, African, Caribbean

**Abbreviations:** IHL, intrahepatic lipid; IPL, intrapancreatic lipid; SAT, subcutaneous adipose tissue; T2D, type 2 diabetes; VAT, visceral adipose tissue.

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or other black ancestry<sup>(3)</sup>. Among ethnic minority groups, the prevalence of T2D is estimated to be about three to five times higher than in people of white European ethnicity<sup>(4)</sup>. The London SABRE multi-ethnic cohort estimated that by age 80 years, 40–50 % of South Asian and black African-Caribbean men and women will have T2D, which is at least twice the proportion of their age-matched white European counterparts<sup>(5)</sup>. An earlier onset of T2D is also particularly noticeable. A recent analysis of UK primary care data showed the age of diagnosis to be 10–12 years younger, on average, in South Asians and black African-Caribbeans compared to white Europeans<sup>(6)</sup>. Moreover, a significantly greater proportion of people from ethnic minority backgrounds develop T2D before age 40 years compared to white Europeans: 30 % of South Asians and 23 % of black African-Caribbeans with T2D are under age 40 years compared to only 9 % of white Europeans (Fig. 1)<sup>(6)</sup>.

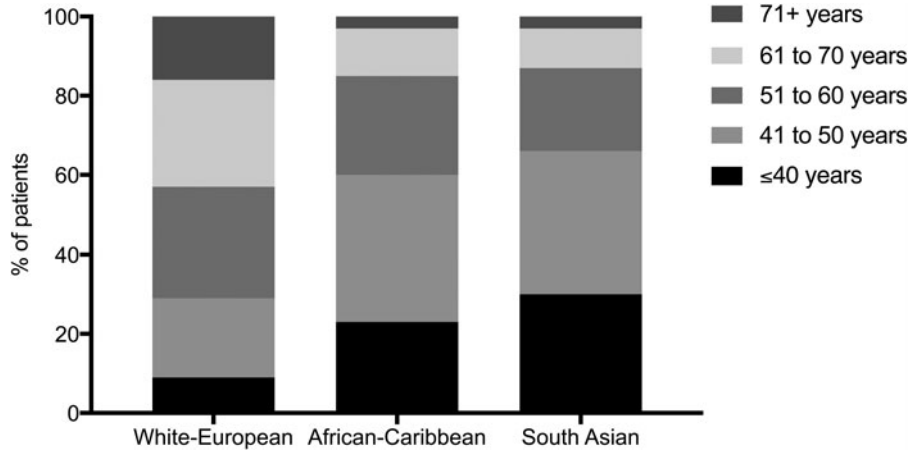
Following the recognition that 90 % of adults with T2D are overweight or obese, and T2D is five times more prevalent amongst adults with an obese BMI compared to those with a healthy weight<sup>(7)</sup>, obesity is now recognised to be one of the strongest contributors to the development of T2D. In the UK, about 60 % of adults are overweight or obese (BMI  $\geq 25$  kg/m<sup>2</sup>) and 25 % are obese (BMI  $\geq 30$  kg/m<sup>2</sup>)<sup>(8)</sup>. In some ethnic groups, obesity rates are high, for example, black African-Caribbean and Pakistani women, but in others (e.g. black African-Caribbean, Indian, Pakistani and Bangladeshi men), the rates are no different from white Europeans or the general population<sup>(4)</sup>. This pattern of obesity being more common among ethnic minority populations and particularly among ethnic minority females is replicated in America, in which African-American and Hispanic women suffer the highest rates of obesity<sup>(9–11)</sup>. The reasons for these ethnic and sex disparities are complex and not fully understood but are believed to involve both biological and environmental factors<sup>(12)</sup>. Recently several UK multi-ethnic cohort studies have identified a higher risk of T2D at lower levels of obesity among ethnic minority groups compared with white Europeans<sup>(6,13,14)</sup>. Modelling of UK Biobank data has demonstrated that the T2D risk associated with a BMI of 30 kg/m<sup>2</sup> in white Europeans is equivalent to a BMI of 22 kg/m<sup>2</sup> in South Asian groups and a BMI of 26 kg/m<sup>2</sup> in black African-Caribbean groups<sup>(13)</sup>. Data from The Health Improvement Network, a UK longitudinal general practice dataset, demonstrate that 38 % of South Asians and 29 % of black African-Caribbeans with T2D have a BMI below 30 kg/m<sup>2</sup> compared to only 26 % of white Europeans. Furthermore, both South Asians and black African-Caribbeans have a significantly higher probability of developing T2D in the normal and overweight BMI categories compared to white Europeans<sup>(6)</sup>. This evidence suggests that the commonly used clinical definitions for obesity, that are derived from populations of white European descent (BMI  $\geq 30$  kg/m<sup>2</sup>; waist circumference  $\geq 88$  cm in women and  $\geq 102$  cm in men), may not be appropriate for screening diabetes risk in non-white groups. Accordingly, the

WHO and International Diabetes Federation have proposed that overweight is defined as BMI  $>23$  kg/m<sup>2</sup>, and obesity  $>27.5$  kg/m<sup>2</sup>, in Asian adults, with waist circumference cut-offs of 80 cm for Asian women and 90 cm for Asian men<sup>(15,16)</sup>, although there is pressure for lower cut-offs to be introduced<sup>(17)</sup>. Currently there are no agreed specific cut-offs for men and women of black African-Caribbean ethnicity and European thresholds remain in use for these populations.

The development of diabetes often manifests itself, clinically, as the metabolic syndrome. First described in the 1980s, the metabolic syndrome is a clustering of metabolic abnormalities, namely abdominal obesity, hypertension, dyslipidaemia (low HDL-cholesterol and high TAG concentrations) and hyperglycaemia, which are associated with insulin resistance and commonly precede the onset of T2D<sup>(18)</sup>. In 2006, the International Diabetes Federation published a consensus worldwide definition to aid detection of metabolic syndrome<sup>(16)</sup>. Using these criteria, it is estimated that about 22 % of adults have the metabolic syndrome and will go on to develop T2D<sup>(19)</sup>. Studies that have investigated the prevalence of metabolic syndrome among high-risk ethnic groups have identified that the diagnostic criteria fail to detect T2D risk in populations of black African ancestry<sup>(20–23)</sup>. Looking in more detail, several interesting differences from other ethnic groups have been described, and a distinct metabolic phenotype is emerging. Consistently, black African-Caribbean populations have been reported to exhibit pronounced insulin resistance<sup>(24–27)</sup> and higher rates of hypertension compared to other ethnic groups<sup>(28,29)</sup> but in the absence of abdominal obesity<sup>(25,30–32)</sup> and the characteristic dyslipidaemia of the metabolic syndrome<sup>(26,30,33)</sup>. Raised fasting TAG and low HDL-cholesterol concentrations are the principal lipid abnormalities associated with insulin resistance and T2D and are included in the diagnostic criteria for the metabolic syndrome. Often the TAG:HDL ratio is used as a lipid metric to detect T2D risk but there is extensive evidence to show that it fails to detect risk in populations of black African-Caribbean ethnicity<sup>(20–23)</sup>. These findings from large epidemiological studies have provided evidence to suggest there are ethnic distinctions in the pathophysiology of T2D among black African-Caribbean ethnic groups, which have been investigated in detail in recent years.

### Pathophysiology of type 2 diabetes

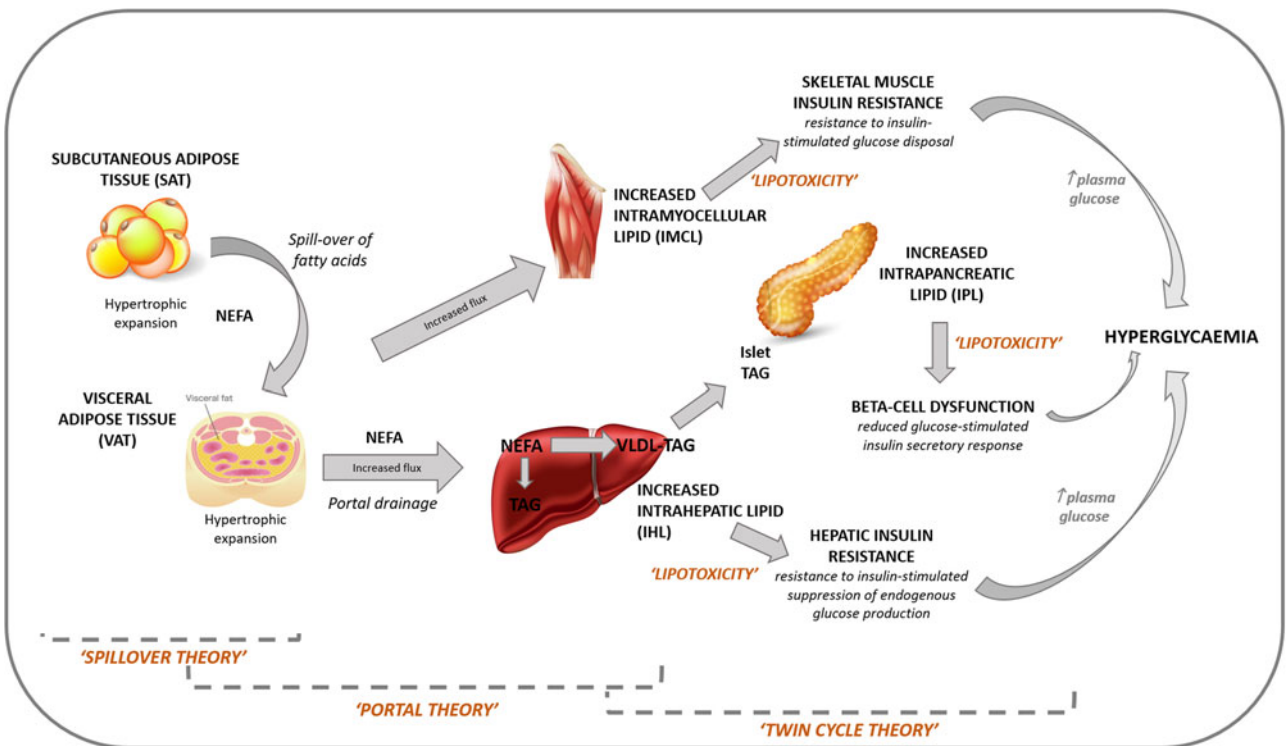
The main processes underlying the development of T2D are well described and emphasise the role of obesity, visceral and ectopic fat accumulation, insulin resistance and insulin secretory failure<sup>(34)</sup>. Originally insulin resistance was proposed as the primary abnormality<sup>(18)</sup> but earlier defects within adipose tissue are now believed to trigger a cascade of metabolic abnormalities, involving the liver, skeletal muscle and pancreas<sup>(35)</sup>. Three separate, but not mutually exclusive, theories explain how dysfunctional adipose tissue, and its inability to buffer excess fat, is proposed to be a primary defect underlying the



**Fig. 1.** Age distribution of people with type 2 diabetes in White-European, African-Caribbean and South Asian ethnic groups in the UK. Reproduced from Paul SK *et al.*<sup>(6)</sup>.

development of T2D (Fig. 2). The spillover theory proposes that it is a limited capacity of subcutaneous adipocytes to store fatty acids which results in an overflow of fatty acids to the visceral compartment and expansion of this depot<sup>(36)</sup>. The portal theory proposes that hypertrophic dysfunctional visceral adipocytes are highly lipolytic and have a greater flux of fatty acids than

subcutaneous adipocytes, which are released into the portal circulation and become deposited in the liver, leading to ectopic fat accumulation in the liver and hepatic insulin resistance<sup>(37)</sup>. The twin-cycle hypothesis proposes that increased hepatic fat accumulation leads to increased export of VLDL-TAG from the liver, which then deposits in other organs and tissues, particularly



**Fig. 2.** Role of adipose tissue dysfunction and ectopic fat accumulation in the pathogenesis of type 2 diabetes. The spillover theory proposes that it is a limited capacity of subcutaneous adipocytes to store fatty acids which results in an overflow of fatty acids to the visceral compartment and expansion of this depot. The portal theory proposes that hypertrophic dysfunctional visceral adipocytes are highly lipolytic and have a greater flux of fatty acids, which are released into the portal circulation and become deposited in the liver, leading to ectopic fat accumulation in the liver and hepatic insulin resistance. The twin-cycle hypothesis proposes that increased hepatic fat accumulation leads to increased export of VLDL-TAG from the liver, which then deposits in other organs and tissues, particularly the pancreatic  $\beta$ -cells, leading to the  $\beta$ -cell failure that underlies the development of type 2 diabetes.



the pancreatic  $\beta$ -cells, leading to the  $\beta$ -cell failure that underlies the development of frank T2D<sup>(38)</sup>. It is the accumulation of TAG within these ectopic depots that is believed to play an integral role in the development of T2D by causing metabolic disturbances within the organs/tissues in which it resides, termed lipotoxicity. Ectopic depots of importance include intrahepatic lipid (IHL), intramyocellular lipid and intrapancreatic lipid (IPL). In response to hepatic and peripheral insulin resistance, compensatory hypersecretion of insulin ensues to maintain normoglycaemia. Eventually ' $\beta$ -cell exhaustion' or 'burn-out' occurs whereby the  $\beta$ -cells are unable to secrete sufficient insulin and a hyperglycaemic state develops<sup>(35)</sup>. Heterogeneity in the relationship between insulin sensitivity and insulin secretion has been recognised whereby glucose tolerance can be maintained, even in the presence of severe insulin resistance, if the insulin secretory capacity of the  $\beta$ -cells is able to balance the degree of insulin resistance. Conversely, an individual can become hyperglycaemic with a relatively low level of insulin resistance if they possess a relatively low  $\beta$ -cell secretory capacity<sup>(39)</sup>.

### Ethnic distinctions in type 2 diabetes pathophysiology: a focus on black African-Caribbean populations

#### *Insulin resistance*

The role of insulin resistance in the development of T2D in black African-Caribbean populations has been investigated in many studies. Large cohort studies have consistently reported exaggerated insulin resistance among black African-Caribbean populations<sup>(26,30)</sup>. The first of these was the insulin resistance atherosclerosis study<sup>(24,25)</sup>, which was conducted in America in the 1990s. A limitation of these epidemiological studies is their use of indirect methods for assessing insulin sensitivity, such as the homeostatic model assessment<sup>(40)</sup> and the intravenous glucose tolerance test, which provide just an estimate of insulin sensitivity, and only measure at a whole-body level. The euglycaemic-hyperinsulinaemic clamp is considered the gold standard method for assessing insulin sensitivity<sup>(41)</sup>, which, when used with the addition of stable isotopes, enables specific measurement of hepatic and skeletal muscle insulin sensitivity, thus providing greater insight as to where the defects in insulin action are occurring. There have been several studies investigating *in vivo* tissue-specific insulin resistance using the euglycaemic-hyperinsulinaemic clamp method with isotopes in black and white communities. These studies have primarily focused on women and high-risk adolescents, e.g. those with morbid obesity or prediabetes. In adolescents, peripheral insulin sensitivity has been shown to be lower<sup>(42-44)</sup> or no different<sup>(45-47)</sup> in black compared to white populations with no clear reasoning as to why they are different. In terms of hepatic insulin sensitivity, black populations show no difference<sup>(42-45,48-51)</sup> or greater sensitivity<sup>(46)</sup> compared to white adolescents. The greater hepatic insulin sensitivity in black adolescents is acknowledged as a surprise to the authors who believe it may be explained by lower

visceral adipose tissue (VAT). Studies in women assessing peripheral insulin sensitivity show either no ethnic differences<sup>(52)</sup> or reduced sensitivity<sup>(53)</sup> in black compared to white populations. The differences here are likely due to the choice of female adiposity status (obese *v.* lean participants, respectively). Studies in women, which have assessed hepatic insulin sensitivity, show no difference<sup>(53,54)</sup>, greater<sup>(52)</sup> or lower<sup>(55)</sup> sensitivity in black compared to white populations. The inconsistencies here are likely due to methodological differences, where hepatic insulin resistance has been measured either at basal or during a hyperinsulinaemic state, or the obesity status of the participant populations. The very limited mixed sex studies have revealed no ethnic differences in peripheral<sup>(56,57)</sup> or hepatic<sup>(56)</sup> insulin sensitivity in black compared to white populations. Within black populations, women have been shown to display lower insulin sensitivity in comparison to men<sup>(58,59)</sup>. They also present with a different body composition which suggests a sex-specific pathophysiology may be present. Overall these inconsistent findings could imply that the methods to assess insulin sensitivity are affected by ethnicity or that insulin resistance is not the sole driver for the increased T2D risk in black populations.

#### *Insulin secretory function*

Unlike the assessment of insulin sensitivity, there is no widely accepted gold standard methodology for the determination of insulin secretory function; therefore, the exploration of ethnic differences in this area has been complicated by the wide variety of techniques used. The most common techniques measure the insulin response to stimulation of the  $\beta$ -cell by glucose, either intravenously (as in the case of the hyperglycaemic clamp or intravenous tolerance test) or orally (as in the case of the oral glucose tolerance test or the mixed meal tolerance test). Surrogate indices are also used, which may be derived from fasting glucose and insulin, such as homeostasis model assessments of  $\beta$ -cell function<sup>(40)</sup>, or from the oral glucose tolerance test or mixed meal tolerance test, such as the insulinogenic index. Each method has its strengths and limitations, for example, oral glucose and mixed meal tests are highly physiological while intravenous techniques allow specific assessment of the  $\beta$ -cell by excluding the modulating effect of the incretin hormones<sup>(60,61)</sup>. Most of the studies in the literature have employed the intravenous glucose tolerance test in their measurement of insulin secretion. A recent review of these studies concluded that black African-Caribbeans exhibit a higher insulin response to glucose compared to white Europeans<sup>(62)</sup>. This has been demonstrated in studies in black populations both in African countries<sup>(63,64)</sup> and across the globe<sup>(24,33,65)</sup>. Furthermore, this higher insulinaemic response can be demonstrated from early childhood<sup>(66-68)</sup>.

In a widely accepted paradigm of T2D, increased insulin secretion represents a compensation for insulin resistance in order to maintain normoglycaemia. Therefore, it is important to note that when studies make an adjustment for the prevailing insulin sensitivity of black

populations (e.g. through the calculation of a disposition index<sup>(69)</sup>), their insulin response to glucose remains greater than that of white Europeans, suggesting that the phenomenon is not simply a compensatory response to increased insulin resistance<sup>(44,45,70,71)</sup>. It has therefore been speculated that  $\beta$ -cell function may be upregulated in black populations, contributing to their increased risk of T2D by predisposing to early  $\beta$ -cell exhaustion<sup>(45)</sup>.

#### *Hepatic insulin clearance*

Circulating concentrations of insulin are determined by a balance between the rate of insulin secretion from the pancreatic  $\beta$ -cells and insulin degradation, which occurs predominantly in the liver. Upon its secretion from pancreatic  $\beta$ -cells, insulin reaches the liver through the portal circulation. Approximately 80 % of endogenous insulin is cleared by the liver during the first portal passage prior to reaching the systemic circulation. While the liver is the primary site of insulin clearance, the kidneys and skeletal muscle are also involved in its degradation<sup>(72)</sup>. To quantify and differentiate the processes of insulin secretory function and hepatic insulin clearance, it is necessary to measure both c-peptide and insulin. C-peptide is co-secreted with insulin in equimolar concentrations but undergoes negligible metabolism in the liver; therefore, the measurement of circulating c-peptide provides a true assessment of the rate of insulin secretion<sup>(73)</sup>. Looking at all the studies of  $\beta$ -cell function, it is important to note that only a small minority include the measurement of c-peptide and are therefore able to differentiate between insulin secretory function and hepatic insulin clearance. There is increasing evidence that the hyperinsulinaemic response to glucose in black subjects is due to ethnic differences in rates of insulin clearance as well as  $\beta$ -cell insulin secretion. These studies have consistently observed lower rates of insulin clearance in black subjects compared to white<sup>(44,68,74)</sup>. Furthermore, recent advances in modelling techniques have demonstrated that this is due to differences in hepatic rather than extra-hepatic insulin clearance<sup>(75)</sup> and that reduced hepatic insulin clearance in black subjects can also be demonstrated from early childhood<sup>(76)</sup>.

#### *Visceral and ectopic fat deposition*

The observation that abdominal/visceral fat is a more sensitive predictor of insulin sensitivity than BMI has led to considerable interest in visceral fat in black populations. These studies have recognised that, despite being at high risk of T2D, black populations exhibit significantly less visceral fat than other ethnic groups<sup>(77)</sup>, a phenomenon that has been coined the African paradox. In a large pooled analysis of black women, Sumner *et al.* demonstrated a lesser increase in visceral fat per unit increase in waist circumference in black compared to white women<sup>(78)</sup>, raising a question regarding the role and importance of visceral fat in the development of T2D in black populations<sup>(79)</sup>.

Ectopic fat, defined as the deposition of TAG within cells of non-adipose tissue, is proposed to be central to the development of T2D by causing metabolic

disturbances in the organs/tissues in which it resides<sup>(80)</sup>. Ectopic fat accumulation typically occurs during increasing adiposity due to reduced expandability of adipocytes within subcutaneous adipose tissue (SAT), which leads to a spillover of NEFA into other organs<sup>(81)</sup>. However, individuals who have lipodystrophies, where genetic factors result in an inability to adequately store fat in SAT depots, also have high ectopic fat accumulation and develop insulin resistance at severely low BMI levels<sup>(82)</sup>. Therefore, an increase in ectopic fat is also considered to be a marker of a metabolic state of overwhelmed dysfunctional SAT caused by its limited expandability. This state is characterised by several features of SAT including hypertrophic adipocyte expansion, increased infiltration of macrophages, reduced insulin sensitivity and increased release of inflammatory cytokines, which are an indicator of chronic low-grade inflammation of SAT<sup>(83)</sup>. The degree of expandability of SAT, which determines the point at which it dysfunctions, is mostly influenced by intrinsic factors, such as sex, as women have a greater capacity to store SAT leading to lower ectopic fat storage and a lower risk of T2D<sup>(84)</sup>. Recent research in South Asians has indicated that ethnicity may also influence the genetic factors that determine SAT expandability and ectopic fat storage<sup>(85)</sup>.

Ectopic fat has been studied in ethnic minority groups to understand the impact of ethnicity on ectopic fat deposition and its role in the development of T2D. South Asian populations exhibit greater levels of VAT and IHL at similar levels of whole-body adiposity compared to white populations<sup>(86,87)</sup>. This has commonly been used to explain the greater risk of T2D in South Asians since they have a reduced capacity to store excess energy in SAT leading to increased ectopic fat deposition<sup>(88)</sup>. However, the same cannot be said for black populations who, despite being at greater risk of T2D, have lower levels of ectopic fat compared to their white counterparts<sup>(79,89)</sup>. This phenomenon has previously been coined the African ectopic fat paradox<sup>(90)</sup>.

The advancement of imaging technologies, such as computerised tomography and MRI, has allowed the direct quantification of regional fat deposition. Thereafter, several studies have reported ethnic differences in regional fat deposition between black and white populations. From as early as the 1990s, several studies have reported lower levels of VAT in black populations compared to white populations which has become a well-accepted phenomenon<sup>(79,89)</sup>. Furthermore, with increasing whole-body adiposity, VAT has been shown to increase to a lesser extent in blacks compared to whites, indicating a greater capacity to store excess energy in the more favourable SAT depot in blacks<sup>(91)</sup>.

While the pathogenic potential of VAT is well accepted in T2D risk, several reports have shown that the accumulation of IHL is more detrimental and plays a greater role in the development of T2D<sup>(92–94)</sup>. Similarly to VAT, IHL has also been reported to be consistently lower in black compared to white populations<sup>(95,96)</sup>. Furthermore, several large cohort studies have shown that the prevalence of non-alcoholic fatty liver disease is considerably lower in black populations



and, in some studies, the prevalence is half that of white populations<sup>(97,98)</sup>. Lower levels of IHL, along with more favourable lipid profiles and reduced metabolic disturbances of the liver, have led researchers to question the understanding of the role of metabolic disturbances of the liver in the development of T2D in black populations<sup>(54,99)</sup>.

Unlike VAT and IHL, there has been less investigation of IPL and intramyocellular lipid in black populations, which may be due to limitations in the techniques used to determine these depots, or the lack of clarity regarding their role in the development of T2D. Current investigations show that while intramyocellular lipid does not appear to differ between black and white populations, it is inversely associated with insulin sensitivity in white populations but not black populations, which may indicate a lesser role for intramyocellular lipid in insulin resistance in black individuals<sup>(100,101)</sup>. Investigations of IPL in black populations provide inconclusive findings; while IPL appears lower in black populations compared to whites<sup>(102,103)</sup>, some reports find it to be inversely associated with  $\beta$ -cell insulin secretory function in blacks<sup>(102)</sup>, while others report no such association<sup>(103)</sup>. In a study investigating the role of IHL and IPL in blacks, Toledo-corrall *et al.* showed IPL predicted prediabetes status in blacks while IHL did not, indicating IPL may be more detrimental than IHL in black populations<sup>(104)</sup>.

#### *The South London Diabetes and Ethnicity Phenotyping study*

The South London Diabetes and Ethnicity Phenotyping (SouL-DeEP) study is being conducted to provide a detailed comparison of the principal pathophysiological processes involved in the development of T2D between men of black west African and white European ethnicity, to test the hypothesis that T2D is driven by relatively early failure of  $\beta$ -cell insulin secretory function in black west African men. Highly sophisticated techniques are being used: hyperglycaemic clamp and meal tolerance test methods enable the assessment of  $\beta$ -cell function, hepatic insulin clearance and incretin secretion; the euglycaemic-hyperinsulinaemic clamp with stable isotope infusions enables the assessment of insulin sensitivity at a whole-body level as well as distinguishing hepatic, skeletal muscle, and adipose tissue insulin sensitivity; and MRI and spectroscopy methods are being used to assess visceral fat and ectopic fat deposition in the skeletal muscle, liver and pancreas. Our study focuses on men as there is consistent evidence for sex differences in T2D pathophysiology in populations of black African ancestry<sup>(105,106)</sup>. While the development of T2D in black women has been reasonably well studied<sup>(52,64,107)</sup>, there is a relative lack of studies conducted in men, despite high rates of T2D, which we aim to address through our work.

In our study of men with T2D, we have demonstrated greater insulin secretory deficits in black west African men compared with white Europeans<sup>(108)</sup>. Moreover, we have recognised that black west African men exhibit a comparable circulating insulin concentration to that

of white Europeans through a greater reduction in hepatic insulin clearance, which acts to preserve circulating insulin concentrations<sup>(108)</sup>. Importantly, we have recognised that these ethnic differences in  $\beta$ -cell function and hepatic insulin clearance are not in response to differences in insulin sensitivity, as our clamp methods demonstrate comparable whole body, hepatic and peripheral insulin sensitivity<sup>(109,110)</sup>.

Our imaging methods have enabled us to quantify visceral, liver and pancreatic fat and to investigate the associations between these measures and the metabolic processes. The black west African men have been found to have significantly lower visceral, hepatic and pancreatic fat compared to the white European men<sup>(111–114)</sup>, yet they exhibit comparable insulin resistance<sup>(110)</sup> and greater  $\beta$ -cell failure<sup>(108)</sup>. We have investigated whether there are ethnic differences in the associations between the fat depots and the metabolic variables and have found that whilst visceral fat associates with insulin resistance in both ethnic groups<sup>(109,110)</sup>, hepatic fat associates with hepatic insulin resistance in only the white European men<sup>(113)</sup> but associates with hepatic insulin clearance in only the black west African men<sup>(113)</sup>. Pancreatic fat has been found to associate with  $\beta$ -cell function but only in the white European men<sup>(114)</sup>. These findings, taken together, show clear evidence of ethnic distinctions in the pathophysiology of T2D.

Our findings challenge the relevance of existing theories that put ectopic fat at the centre of the pathophysiology of T2D (Fig. 2), to populations of black African-Caribbean ethnicity. We have shown lower visceral and hepatic fat in black west African men, yet comparable insulin sensitivity; furthermore, the association between hepatic fat and insulin resistance that was seen in white European men was not evident in black west African men. Pancreatic fat is believed to be a principal driver of  $\beta$ -cell failure, according to the twin cycle hypothesis<sup>(38)</sup>, yet  $\beta$ -cell function was associated with pancreatic fat only in our white European men. These findings lead us to hypothesise that insulin resistance and  $\beta$ -cell failure develop independently of ectopic fat accumulation in black west African populations, and that ectopic fat is not the primary defect underlying the development of T2D. We are currently extending our work to investigate these mechanisms in men who are normally glucose tolerant and in men with impaired glucose tolerance to provide a greater understanding of how they are implicated in the progression to T2D. Data from our normal glucose-tolerant participants show that black men exhibit a pronounced hyperinsulinaemia compared to white men, and that this is driven by significantly lower hepatic insulin clearance rates rather than upregulated insulin secretion<sup>(115)</sup>. This leads us to hypothesise that hyperinsulinaemia is a primary defect in black west African men that occurs as a result of lower rates of hepatic insulin clearance, rather than in response to relative reductions in insulin sensitivity. We await further data on ectopic fat deposition and tissue-specific insulin sensitivity in our cohort of healthy men and in the men with impaired glucose tolerance, which will enable us

to shed further light on our hypothesis and a much greater understanding of ethnic distinctions in the pathophysiology of T2D.

### Conclusions

Populations of black African-Caribbean ethnicity are disproportionately affected by T2D. While the mainstream understanding of T2D pathophysiology focuses on the role of visceral and ectopic fat accumulation leading to insulin resistance and insulin secretory failure, there is compelling evidence for distinct processes in black populations. In populations of black African-Caribbean ethnicity, there is less central obesity and absence of the dyslipidaemia associated with insulin resistance. Furthermore, the metabolic syndrome criteria have little clinical utility for recognising T2D risk in black populations. More detailed investigations, showing lower VAT and hepatic fat deposition in black populations, provide evidence to suggest that ectopic fat plays a less central role in the development of insulin resistance in black populations. Hyperinsulinaemia is present, even in a healthy, normal glucose-tolerant state, driven by lower rates of hepatic insulin clearance rather than upregulated insulin secretion, and may be a primary defect in black populations. A greater understanding of these processes and the mechanisms underlying the development of T2D in black populations may lead to much needed improvements in prevention and treatment strategies.

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### Conflict of Interest

None.

### Authorship

L. M. G. was lead author and took overall responsibility for the preparation of the manuscript; M. L. contributed

to the writing of the insulin secretion and clearance sections; O. H. contributed to the writing of the ectopic fat section; O. B. contributed to the writing of the insulin resistance section.

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