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Cardiometabolic disease in Black African and Caribbean populations: an ethnic divergence in pathophysiology?

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In the UK, populations of Black African and Caribbean (BAC) ethnicity suffer higher rates of cardiometabolic disease than White Europeans (WE). Obesity, leading to increased visceral adipose tissue (VAT) and intrahepatic lipid (IHL), has long been associated with cardiometabolic risk, driving insulin resistance and defective fatty acid/lipoprotein metabolism. These defects are compounded by a state of chronic low-grade inflammation, driven by dysfunctional adipose tissue. Emerging evidence has highlighted associations between central complement system components and adipose tissue, fatty acid metabolism and inflammation; it may therefore sit at the intersection of various cardiometabolic disease risk factors. However, increasing evidence suggests an ethnic divergence in pathophysiology, whereby current theories fail to explain the high rates of cardiometabolic disease in BAC populations. Lower fasting and postprandial TAG has been reported in BAC, alongside lower VAT and IHL deposition, which are paradoxical to the high rates of cardiometabolic disease exhibited by this ethnic group. Furthermore, BAC have been shown to exhibit a more anti-inflammatory profile, with lower TNF-α and greater IL-10. In contrast, recent evidence has revealed greater complement activation in BAC compared to WE, suggesting its dysregulation may play a greater role in the high rates of cardiometabolic disease experienced by this population. This review outlines the current theories of how obesity is proposed to drive cardiometabolic disease, before discussing evidence for ethnic differences in disease pathophysiology between BAC and WE populations.

Cardiometabolic risk factors: Ethnicity: Lipid metabolism: Complement activation

The prevalence of cardiometabolic disease in Black African and Caribbean populations

In the UK, over 5 million people are estimated to be living with diabetes, and 90 % of these cases are type 2 diabetes[(1)]. Furthermore, atherosclerotic CVD remains the biggest killer in the UK, accounting for one in every four deaths each year[(2)]. Collectively, these conditions are known as cardiometabolic diseases, which share common risk factors and are largely preventable diseases. According to the 2021 consensus, over 2·4 million people of Black African and Caribbean (BAC) ethnicity reside

Abbreviations: ASP, acylation-stimulating protein; BAC, Black African and Caribbean; C3, complement component 3; IHL, intrahepatic lipid; IMCL, intramyocellular lipid; IPL, intrapancreatic lipid; LPL, lipoprotein lipase; SAT, subcutaneous adipose tissue; VAT, visceral adipose tissue; WE, White European.

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in England and Wales[3], and these populations experience a greater cardiometabolic disease burden[4–6].

This cardiometabolic disease burden is largely driven by very high rates of type 2 diabetes, which are up to three times higher in BAC compared to White European (WE) populations[4]. In addition, in BAC, the age of onset of type 2 diabetes is between 10 and 12 years earlier, resulting in 23 % of BAC with type 2 diabetes being younger than 40, compared to just 9 % of WE[7]. For CVD, BAC exhibit a specific risk profile. The SABRE (Southall and Brentford revisited) study revealed a high ischaemic stroke burden in BAC, which is 1·5–2·5 times more prevalent, compared to WE[5,6]. In contrast, BAC exhibit low rates of CHD which are up to 50 % lower in men and 20–30 % lower in women, compared to WE[5,6]. Whilst a complex interaction of lifestyle, socioeconomic and healthcare factors likely contribute to observed ethnic differences in cardiometabolic disease, differences in prevalence remain when controlling for these factors[8], suggesting an additional biological basis for the greater cardiometabolic risk in BAC populations. This review aims to address theories linking obesity, defective lipid metabolism, ectopic lipid accumulation, inflammation and the complement system to cardiometabolic disease, before discussing their relevance to BAC populations.

Current theories linking obesity to cardiometabolic disease

Obesity and body composition

Obesity is one of the strongest risk factors for cardiometabolic disease[9,10]. The increasing global prevalence of obesity has led to a concurrent increase in cardiometabolic disease morbidity and mortality[11]. Whilst obesity is clearly associated with cardiometabolic disease, it is a heterogenous condition, with some obese individuals preserving normal cardiometabolic function[12]. Body composition (or the distribution of adipose tissue) may explain this anomaly. Subcutaneous adipose tissue (SAT), located immediately below the skin, is considered the more 'metabolically safe' depot for excess fatty acid storage, whereas visceral adipose tissue (VAT) is located centrally and surrounds intra-abdominal organs[13]. The latter has been found to be strongly associated with the development of cardiometabolic disease, independently of BMI[14,15]. The mechanisms driving VAT accumulation, and its consequences on cardiometabolic disease pathophysiology remain an active area of research.

Fatty acid metabolism, inflammation and ectopic lipid deposition

Whilst fasting TAG is associated with both type 2 diabetes and atherosclerotic CVD[16,17], non-fasting TAG has been found to be a more powerful determinant of cardiometabolic risk[18,19]. During fasting conditions, endogenously produced TAG is predominantly transported in hepatically derived VLDL[20]. Postprandially, exogenous (meal-derived) TAG is transported in chylomicrons alongside VLDL–TAG[21]; the majority of TAG is transported to metabolically active tissues in these particles, which are collectively termed TAG-rich lipoproteins[22]. Upon arrival, TAG-rich lipoproteins are hydrolysed by lipoprotein lipase (LPL), liberating NEFA to be taken up by the tissue. However, a proportion of liberated NEFA escapes to the systemic circulation, termed NEFA spillover[23,24]. The hydrolysis of TAG-rich lipoproteins leads to the formation of smaller, TAG-poor remnants, which are removed from the circulation by the liver. Importantly, these remnants (particularly chylomicron remnants) may contain a substantial amount of TAG, providing an additional source of TAG for the liver[25]. An overview of TAG-rich lipoprotein metabolism is shown in Fig. 1. Adipose tissue lipolysis provides further NEFA to metabolically active tissues, and rates of intracellular lipolysis are highest whilst fasting[26]. In the transition to the postprandial period, where TAG concentrations are high, adipose tissue lipolysis is suppressed by insulin[27]. In lean/healthy individuals, SAT is responsible for sequestering the majority of fatty acids in the postprandial period. These are subsequently released during fasting, to provide an energy substrate for metabolically active tissues. However, in obesity a number of defects are evident[28].

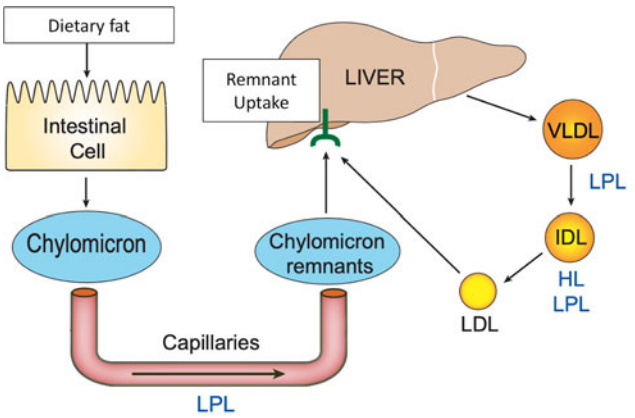

Fig. 1. Metabolism of TAG-rich lipoproteins during the postprandial period. Following the consumption of dietary fat, intestinal enterocytes package meal-derived fatty acids in chylomicrons as TAG. The secreted chylomicron–TAG is then hydrolysed by lipoprotein lipase (LPL) at peripheral tissues, liberating NEFA for uptake. This results in smaller, TAG-poor, chylomicron remnants, which are cleared by the liver along with the remaining TAG in these particles. The liver continues to secrete VLDL–TAG, which is also hydrolysed by LPL at peripheral tissues. This forms intermediate-density lipoprotein (IDL), which is also hydrolysed by LPL and by hepatic lipase (HL), forming TAG-poor low-density lipoproteins (LDL). IDL and LDL are removed from the circulation, predominantly by the liver. Adapted from Borén *et al.*[113].

During periods of overnutrition, SAT-adipocytes undergo hypertrophic expansion to accommodate excess fatty acids[29,30]. Increasing adipocyte size may promote hypoxia, apoptosis and endoplasmic reticulum stress, driving tissue damage and promoting macrophage infiltration[31–33]. Immune cell infiltration, together with large dysfunctional adipocytes, drive the secretion of

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pro-inflammatory cytokines including: TNF-α, IL-6 and IL-1β, and reduce the secretion of anti-inflammatory cytokines such as IL-10 and IL-5[34]. The transition of adipose tissue to a more pro-inflammatory phenotype is thought to be a major driver of chronic low-grade inflammation, which characterises obesity[34].

Hypertrophic SAT-adipocytes also exhibit higher basal rates of lipolysis and have a reduced capacity to store fatty acids[30,35,36]. In the spillover theory[28], these defects have been hypothesised to redistribute excess fatty acids, driving the accumulation of VAT and ectopic lipid (referring to lipid stored in non-adipose tissues, predominantly the liver, muscle and pancreas). Defective adipose tissue lipolysis, leading to elevated systemic NEFA, was traditionally proposed to be a major driver of this redistribution. However, obesity gives rise to only modest elevations in NEFA; in a systematic review, Karpe *et al*. reported just a 70 μmol/l difference in NEFA between obese and lean individuals (545 *v*. 472 μmol/l, respectively), which were unrelated to fat mass[37]. These findings suggest a down-regulation of lipolysis, per weight of adipose tissue, in obesity. Additionally, postprandial meal-derived NEFA spillover has been reported to be lower in obese compared to lean participants, suggesting meal-derived NEFA spillover may in fact be a signature of metabolic health[23]. These findings question the importance of adipose and meal-derived NEFA spillover in the accumulation of VAT and ectopic lipid. Obesity leads to more pronounced increases in fasting and postprandial plasma TAG[38–40], resulting from an overproduction and reduced clearance of VLDL–TAG and chylomicron–TAG[39,41,42]. Therefore, elevations in TAG and a reduction in SAT clearance of TAG may be a more important driver of VAT and ectopic lipid accumulation.

VAT has been proposed to accelerate ectopic lipid deposition, particularly intrahepatic lipid (IHL)[28]. VAT-adipocytes exhibit increased rates of lipolysis and a more pro-inflammatory profile compared to SAT[30]; VAT also drains directly to the liver via the portal circulation, exposing the liver to high concentrations of NEFA and inflammatory markers. Due to these characteristics, elevated VAT is hypothesised to drive IHL accumulation – the 'portal theory'[28]. Whilst VAT is significantly associated with IHL[43], the majority of NEFA exposed to the liver are of SAT origin[44]. In the postprandial period, hepatic uptake of meal-derived NEFA and remnant-TAG may also contribute to IHL deposition[45]. Therefore, it is likely that IHL accumulation results from a number of defective fatty acid metabolism pathways. The accumulation of IHL is proposed to be a primary defect in cardiometabolic disease pathophysiology, and has been shown to be a better marker of the metabolic defects associated with obesity than VAT[46]. IHL is associated with a host of metabolic derangements[47] and IHL is also positively associated with VLDL–TAG output[48], which is elevated in obesity[41]. In the twin-cycle hypothesis, elevations in IHL are proposed to drive VLDL–TAG output, leading to excess TAG delivery to the pancreas, thereby increasing intrapancreatic lipid (IPL) accumulation[49]. Increased VLDL–TAG may also contribute to fatty acid delivery to the muscle, increasing intramyocellular lipid (IMCL)[50].

It is apparent that obesity is associated with a plethora of fatty acid metabolism defects. These defects are believed to drive the accumulation of ectopic lipid (primarily IHL, IMCL and IPL), which may promote insulin resistance by lipotoxicity[51]. The manifestation of insulin resistance is tissue specific: in the liver it promotes endogenous glucose and VLDL–TAG production, and reduces hepatic insulin clearance[47]; in the pancreas, it drives β-cell dysfunction[52]; and in skeletal muscle, it promotes peripheral insulin resistance[53]. Such defects drive hyperglycaemia and ultimately the development of type 2 diabetes[54]. Furthermore, elevated plasma TAG is associated with the formation of a pro-atherogenic phenotype, whereby excess cholesterol ester transfer protein activity drives a reduction in HDL and elevations in small-dense LDL[55,56], the latter being an independent predictor of CVD[57]. These defects are compounded by a state of chronic low-grade inflammation which is typically observed in obesity, driven by elevated VAT and dysfunctional SAT[30,58].

The complement system

The complement system was first identified as part of the innate immune system[59]; however, it is now recognised to be a complex network of over fifty plasma and membrane-bound proteins with wide ranging roles in immune, inflammatory and metabolic function[60]. As such, markers of the complement system and its activation have been associated with obesity, insulin resistance, type 2 diabetes and CVD[61–63]. Complement activation may result from three major pathways: the classical pathway; mannose-binding lectin pathway and/or the alternative pathway[64]. The latter is continuously active at low levels in order to prime complement for rapid activation and may also act as an amplification loop[65]. All three activation pathways converge on complement component 3 (C3), and its cleavage may ultimately activate the terminal cascade leading to membrane attack complex formation, which can directly lyse pathogens[65]. Complement activation is controlled by a number of positive and negative regulators[66]. Upon complement activation, a number of biologically active cleavage products are produced. These include opsonins which covalently bind to target cells (iC3b, C3b and C3d), and anaphylatoxins which are potent pro-inflammatory mediators (C3a and C5a)[65]. An overview of the complement system is presented in Fig. 2.

The majority of complement components are derived from the liver[61]. However, a number of alternative pathway components and regulators are expressed in adipose tissue, including C3, factor B, properdin, factor H and factor I. Furthermore, SAT is the primary site of factor D production[67,68]. Studies have reported elevations of alternative pathway proteins with obesity[69] and C3 is positively associated with VAT and SAT[61]. Adipocytes also express receptors for C3a and C5a (C3aR and C5aR, respectively) which are produced upon complement activation[70]. These findings suggest complement

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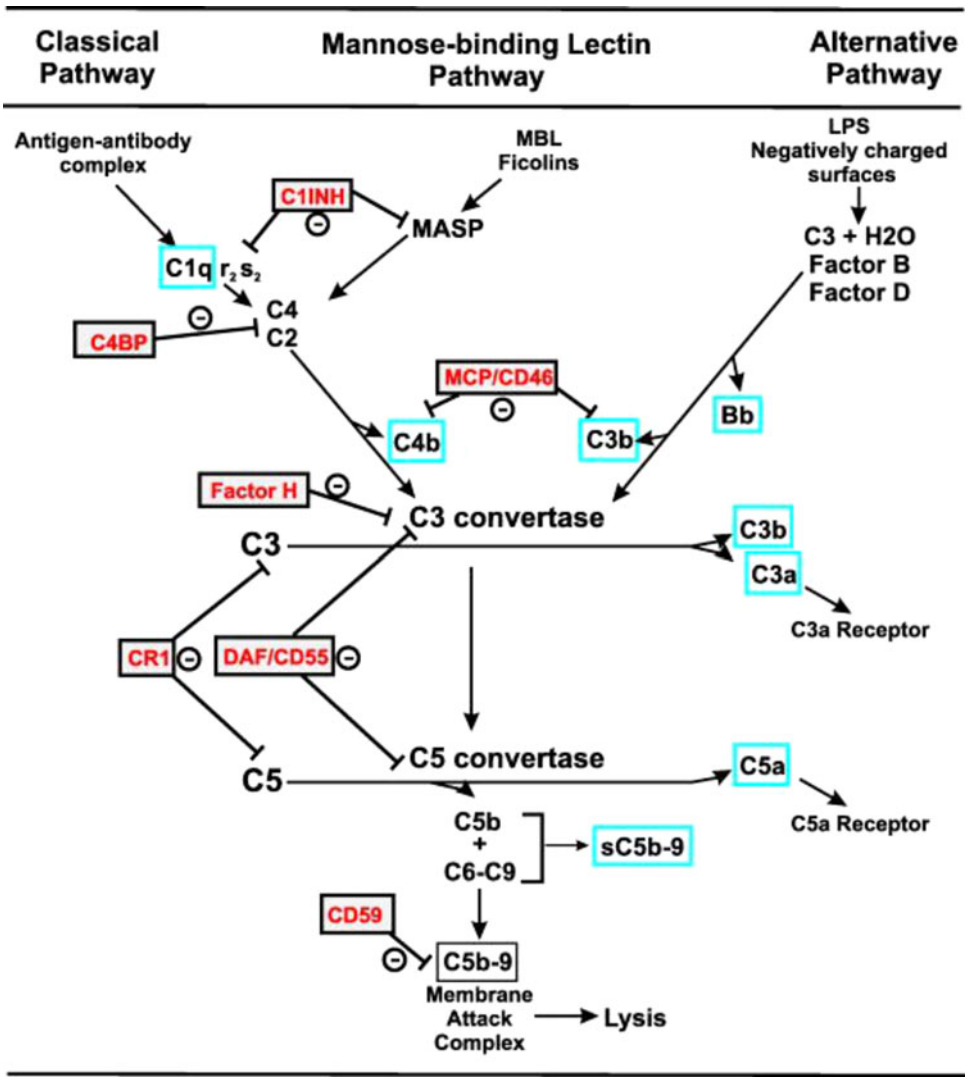

Fig. 2. Complement system. Complement may be activated through three activation pathways: the classical pathway; mannose-binding lectin pathway; and the alternative pathway. All three pathways converge on complement component 3 (C3), and its cleavage may result in terminal pathway activation and the formation of the membrane attack complex (C5b-9n). Complement activation also leads to the production of opsonins and anaphylatoxins (C3a and C5a). Adapted from Regal *et al.*[64]. C1inh, C1 inhibitor; C4BP, C4 binding protein; CD, complement decay accelerating factor; LPS, lipopolysaccharide; MASP, mannose binding lectin associated serine proteases; MBL, mannose binding lectin; MCP, membrane cofactor protein; sC5b-9, inactive membrane attack complex.

activation may increasingly act locally, at the adipose tissue, in obesity. This may promote a pro-inflammatory environment and exert deleterious consequences on adipose tissue biology[70].

Beyond the inflammatory influence of complement, its involvement in macronutrient metabolism has been recognised. During the postprandial period, transient elevations in C3 have been reported and are correlated with postprandial TAG concentration[71,72]; there is also evidence of increased complement activation, particularly of the alternative pathway[60,73]. Fujita *et al.* found a dose–response relationship between chylomicrons and alternative pathway activation *in vitro*[74], suggesting the consumption of dietary fat may stimulate complement by this pathway. In the alternative pathway, the interaction of factors B and D with C3 generates C3a which is rapidly cleaved to produce C3-acylation-stimulating protein (ASP). ASP promotes TAG synthesis and glucose transport, whilst reducing lipolysis in healthy adipocytes[75,76]. Obesity is associated with elevated fasting ASP[77], which is positively correlated with postprandial TAG concentration[78]. These findings suggest that dysregulation of ASP production and signalling (termed ASP resistance) may promote reduced adipose tissue TAG clearance[67]. Furthermore, Xin *et al.* reported an association between complement

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components and an adverse lipoprotein profile, with significant associations between C3 and a greater number and particle size of VLDL, greater number and smaller particle size of intermediate-density lipoprotein and LDL, and fewer and smaller HDL particles; the authors suggest that binding of C3 to lipoproteins may negatively influence their metabolism[79]. These findings suggest an emerging role of complement activation in the development of adipose dysfunction, inflammation and the promotion of a pro-atherogenic lipoprotein phenotype, all of which are central defects in the pathophysiology of cardiometabolic disease.

Evidence for ethnic differences in cardiometabolic disease pathophysiology in Black African and Caribbean populations

Obesity and body composition

Considering the high rates of cardiometabolic disease in BAC and the strong association between obesity and disease risk, high rates of obesity may also be expected in BAC populations. In a recent UK survey, BAC children, adolescents and adults indeed suffered a high prevalence of obesity[4]. However, earlier work has highlighted pronounced sex differences in obesity within BAC populations, with an alarmingly high prevalence in women, but rates of obesity in men which are similar to that of WE[80,81]. This pattern is also evident in the USA[80]. Interestingly, in both sexes, data modelled from the UK Biobank revealed that BAC with a BMI of 26 kg/m^2 experience an equivalent risk of type 2 diabetes as WE with a BMI of 30 kg/m^2[82]. This may suggest BAC populations are more sensitive to the effects of excess adiposity. However, weaker associations between BMI and cardiometabolic risk factors have also been reported in BAC[83], suggesting factors outside of adiposity may be more important in the development of cardiometabolic disease in this population. This hypothesis is supported by a higher probability of BAC being diagnosed with type 2 diabetes in the normal and overweight BMI categories[7].

VAT is associated with cardiometabolic risk independently of BMI[14,15]. Ethnic differences in body composition are well studied and have revealed significantly lower VAT alongside similar or greater SAT in BAC populations, regardless of sex[84–87]. This gives rise to a more beneficial VAT:SAT ratio, which suggests BAC populations preferentially store excess fatty acids in SAT. In line with these observations, BAC women have been found to exhibit a lower increase in VAT per unit of waist circumference, raising concerns regarding the use of waist circumference to predict VAT in BAC populations[88]. The consequence of this is that whilst VAT is associated with most cardiometabolic risk factors in WE, in BAC, these associations are weaker or non-existent[89]. If BAC have a more favourable VAT:SAT ratio, why are there such high rate of cardiometabolic disease in these populations? What is the relevance of VAT in disease pathophysiology in BAC?

Ectopic lipid

According to the theory of ectopic lipid deposition, lower VAT in BAC populations would be expected to drive lower ectopic lipid deposition. To investigate this hypothesis, we conducted a systematic review and meta-analysis to compare IHL, IMCL and IPL deposition in BAC compared to other ethnic populations[90]. We found strong evidence for lower IHL in BAC compared to WE, Hispanics and south Asian populations, which was supported by meta-analyses; these differences held regardless of sex, age, BMI and glycaemic status[90]. These findings are in line with observations in adolescents[91,92] and the observation of markedly lower rates of non-alcoholic fatty liver disease in BAC compared to other ethnic groups[93]. The mechanism(s) driving lower IHL accumulation in BAC are not well understood. In line with the portal theory[28], lower VAT in BAC appears to translate to lower IHL. However, whilst VAT is significantly associated with IHL in WE, neither VAT nor SAT is associated with IHL in BAC[43,86]. This suggests that fatty acid pathways other than adipose tissue lipolysis make a larger contribution to IHL deposition in BAC. The accumulation of IHL and the promotion of hepatic insulin resistance are postulated to be primary defects in the development of cardiometabolic disease[46], therefore lower IHL in BAC populations is paradoxical to their high rates of disease. Interestingly, both BAC and WE women exhibit significant negative associations between IHL and hepatic insulin sensitivity[94,95], but no such associations have been reported in BAC men[96,97]. These contrasting findings suggest BAC women may be more sensitive to the lipotoxic effects of IHL accumulation, whereas factors other than IHL promote cardiometabolic disease in BAC men. However, this requires further investigation.

Less research has been conducted into ethnic differences of IMCL. The majority of studies report no ethnic differences between BAC and WE (six out of eight studies identified in our systematic review)[90]. However, few studies account for ethnic differences in muscle fibre type, of which BAC are characterised by more type 2 and less type 1 fibres[98]; a less oxidative phenotype may influence their propensity to IMCL deposition and future studies should account for this variable. In BAC, studies have failed to find an association between IMCL and peripheral insulin sensitivity regardless of sex[99,100], which suggests factors other than IMCL are promoting peripheral insulin resistance in this population. Whilst IMCL has been found to be associated with peripheral insulin resistance in WE[53], lipid metabolites such as diacylglycerol and ceramides are thought to be more important in the promotion of insulin resistance that total IMCL[101]. Therefore, future studies should focus on ethnic differences in lipid metabolites, and their role in peripheral insulin resistance in BAC.

Whilst few studies have investigated ethnic differences in IPL, those that have done so predominantly report lower IPL in BAC than WE[90]. In the twin-cycle hypothesis, it is postulated that elevations in IHL drive IPL deposition via increased VLDL–TAG output[49].

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Therefore, it may be hypothesised that lower IHL is driving lower IPL in BAC[86]. However, more studies are needed to clarify ethnic differences in the mechanisms of IPL accumulation and its influence on markers of β-cell function in BAC populations.

Fatty acid metabolism

Ectopic lipid deposition is proposed to be a consequence of deleterious fatty acid metabolism, driven by aberrant adipose tissue function[28,49]. Therefore, exploring the pathways leading to lower IHL and IPL in BAC populations is of interest. BAC populations have a more beneficial fasting lipid profile, with lower TAG and LDL, alongside higher HDL[102,103]. BAC populations are also reported to exhibit lower small-dense LDL compared to WE[104]. Whilst this profile is in line with the lower CHD rates experienced by this population, it remains paradoxical to their high risk of type 2 diabetes and ischaemic stroke[4,5]. Interestingly, in the USA, there is evidence for BAC populations losing their cardioprotective fasting lipid profile and levels of HDL do not appear to differ to those in WE[105]; these findings may represent progressive acculturation to a western nutritional and lifestyle environment.

Despite the established ethnic differences in fasting lipid profiles, little is understood about postprandial fatty acid handling in BAC. In the few studies investigating ethnic differences in postprandial fatty acid dynamics, lower total postprandial TAG has been reported in BAC compared to WE women[106–108], and a single study revealed lower total postprandial TAG in young BAC compared to WE men[109]. Findings of lower postprandial TAG concentrations in BAC are in line with lower ectopic lipid deposition and a more beneficial fasting lipid profile in this population[90,102,103], yet remain paradoxical to the their high rates of cardiometabolic disease[4,5]. In studies investigating ethnic differences in the incremental TAG response to feeding (adjusting for baseline TAG which is consistently lower in BAC populations) conflicting findings have been produced. Lower[108], as well as equivalent[108,110], postprandial TAG increments have been reported in BAC compared to WE women, whereas both lower[109] and higher[111] increments have been reported in BAC men. We have utilised stable isotope techniques to conduct in depth investigations of postprandial fatty acid trafficking between overweight and obese, but otherwise healthy, BAC and WE men. Stable isotope techniques are considered the gold standard for lipid and lipoprotein research, enabling the differentiation between endogenous and meal-derived fatty acids[112,113]. In response to consecutive moderate-high fat meals, with the first of these meals containing a U–^{13}C palmitate stable isotope tracer to label meal-derived fatty acids, we observed a trend for a greater plasma TAG tracer:tracee ratio in BAC compared to WE men[114], suggesting that meal-derived fatty acids (transported predominantly in chylomicrons) make a greater relative contribution to total postprandial TAG concentrations in BAC. Whether there are ethnic differences in chylomicron–TAG metabolism requires further research, however lower fasting VLDL–TAG has been reported in BAC men and women[115–117]. Considering the association between IHL and VLDL–TAG in WE[48], these findings are in line with lower IHL typically observed in this population[90]. Therefore, the greater tracer:tracee ratio in BAC men may be explained by lower VLDL–TAG rather than elevated chylomicron–TAG, however this has yet to be directly compared in the postprandial period.

Postprandial TAG concentration is determined by both the production and clearance of TAG-rich lipoproteins. VLDL–TAG and chylomicron–TAG compete for LPL affinity, however it appears large TAG-rich chylomicrons are preferentially hydrolysed[118]. If BAC populations exhibit lower VLDL–TAG during the postprandial period, this would imply less competition for LPL affinity and may allow for more efficient chylomicron–TAG clearance. Furthermore, BAC populations have been found to exhibit greater post-heparin LPL activity[108,109,119] and higher LPL expression in SAT[108]. Taken together, these findings suggest BAC populations may have a greater capacity for TAG clearance, which is in line with their more beneficial VAT:SAT ratio[84–87]. In our own work, we reported a lower concentration of meal-derived U–^{13}C palmitate in TAG at a density of Svedberg floatation rate (Sf) 20–400 (which approximates VLDL–TAG)[120]. Whilst meal-derived TAG is predominantly transported in chylomicrons, during the late postprandial period, meal-derived TAG may enter the hepatic VLDL–TAG pool via uptake of meal-derived NEFA spillover and chylomicron–remnant-TAG[45]. In BAC, the lower meal-derived U–^{13}C palmitate in TAG within Sf 20–400 TAG suggests that meal-derived fatty acids are being cleared by adipose tissue, preventing hepatic uptake and incorporation into VLDL–TAG. However, this may also be influenced by ethnic differences in hepatic partitioning of meal-derived fatty acids, favouring storage and/or oxidation, rather than VLDL–TAG export[45]. Further studies that combine stable isotope and arteriovenous difference techniques are required to elucidate ethnic differences in adipose tissue TAG clearance in BAC populations.

Inflammation and complement

Obesity is associated with a state of chronic low-grade inflammation; however obese BAC populations exhibit a specific inflammatory profile. Adiponectin is consistently reported to be lower in BAC compared to WE[121,122]. Described as an insulin sensitiser, adiponectin is significantly associated with insulin sensitivity in WE; however an association between adiponectin and insulin sensitivity is not found in BAC men[123], which questions its metabolic function in this population. BAC also exhibit lower TNF-α[121,122,124], alongside higher or similar IL-10[121,124], suggesting a relatively more anti-inflammatory profile compared to WE. Similarly, associations between pro-inflammatory cytokines (TNF-α and IL-6) and insulin sensitivity appear to be weaker in BAC compared to WE[123,124]. Ethnic differences in the associations between inflammatory

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markers and adiposity have also been reported. Adiponectin is significantly associated with SAT in WE but not BAC, and IL-6 is associated with VAT and SAT in WE but not BAC[121]. Taken together, this implies a specific inflammatory profile in BAC, with lower adiponectin and TNF-α and greater IL-6. There also appear to be differences in the associations between adipose tissue depots and insulin sensitivity, suggesting differences in obesity-induced chronic low-grade inflammation and its role in cardiometabolic disease.

Very little is known about the complement system in BAC populations, despite its emerging role in cardiometabolic disease[61–63]. The potential for ethnic differences in complement were first considered in response to COVID-19, in which BAC populations suffered one of the highest mortality rates of all ethnic groups[125]. Following the identification of complement dysregulation in severe COVID-19[126], it was hypothesised that BAC may exhibit greater complement dysregulation, predisposing this population to severe COVID-19, but also to high rates of cardiometabolic disease. In the first ethnic comparison of fasting circulating complement markers, Goff *et al.*[127] investigated ethnic differences between BAC and WE men. Age-adjusted C3, a central complement component, as well as C4 of the classical pathway were higher in BAC[127]. C3 and C4 are the most abundant complement proteins, and elevated concentrations may suggest a greater capacity for complement activation. BAC also exhibited significantly greater iC3b, indicating greater upstream activation of C3. Additionally, there were significant ethnic differences in markers of the alternative pathway, with BAC exhibiting lower factor D and higher properdin compared to WE[127]. Factor D is enzyme primarily secreted by adipose tissue that activates the alternative pathway by cleaving factor B; properdin is also expressed in adipose tissue and stabilises the C3 convertase complex[67,68]. Considering BAC have a lower body fat percentage for any given BMI[128], ethnic differences in factor D may be attributed to lower fat mass in BAC. However, greater concentrations of properdin in this population may suggest a greater propensity for C3 cleavage (by C3 convertase), driving greater downstream complement activation. These findings suggest greater complement dysregulation in BAC, which are in line with reports of a higher prevalence of genetic variants associated with regulators promoting complement activation in BAC[129].

Considering the positive association between complement markers and insulin resistance/type 2 diabetes[63], it may be that complement dysregulation is an important contributor to the high rates of type 2 diabetes observed in BAC populations. In support of this, we revealed an association between HbA1c and C3 independent of adiposity in BAC, but not WE[130]. Understanding ethnic differences in the role of complement in adipose tissue function, lipid metabolism and inflammation in BAC populations is an important avenue of research, particularly in the postprandial period. Complement dysregulation is also associated with an adverse lipoprotein profile and atherosclerotic CVD[62,79]. Interestingly, despite exhibiting greater complement dysregulation, BAC participants are recognised to have a more beneficial fasting lipid profile[102–104]. Therefore, there may be ethnic differences in the role of complement in CVD in BAC populations. Exploration of the mechanisms driving complement dysregulation in BAC and their role in cardiometabolic disease requires further investigation.

Conclusion

In WE populations, obesity is hypothesised to promote cardiometabolic disease by driving defective fatty acid metabolism, VAT and ectopic lipid accumulation, as well as promoting a state of chronic low-grade inflammation. However, despite their high rates of cardiometabolic disease, BAC populations are characterised by paradoxically lower fasting and postprandial TAG, lower VAT, IHL and IPL, and a more anti-inflammatory profile. According to current theories, this phenotype would be associated with cardiometabolic protection, resulting in less lipotoxicity-mediated insulin resistance and a more cardioprotective lipid profile. Indeed, lower fasting and postprandial TAG are in line with the lower IHL and IPL observed in this population and may explain their low rates of CHD; however, these findings remain highly paradoxical to the high rates of type 2 diabetes and ischaemic stroke. This may suggest factors other than postprandial fatty acid metabolism and ectopic lipid deposition account for the high risk of cardiometabolic disease in BAC, but further mechanistic studies clarifying ethnic differences in fatty acid metabolism and its role in ectopic lipid deposition are warranted. Complement is an emerging risk factor for cardiometabolic disease and early studies show greater complement dysregulation in BAC compared to WE, which was independently associated with HbA1c. Understanding of the ethnic differences in cardiometabolic disease risk factors and pathophysiology is critical to implementing strategies to tackle the high rates of cardiometabolic disease in this population.

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Conflict of Interest

None.

Authorship

R M. R. drafted the manuscript, M. B W. and L M. G. supervised the work and revised and approved the final manuscript.

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