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RESEARCH ARTICLE

Plasma complement system markers and their association with cardiometabolic risk factors: an ethnic comparison of White European and Black African men

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Abstract

Populations of Black African (BA) ancestry are disproportionately affected by cardiometabolic diseases, possibly due to dysregulation of the complement system. This study aimed to determine relationships between fasting complement markers and cardiometabolic risk in BA and White European (WE) men, and whether postprandial complement response differs by ethnicity. Eighty-eight BA and 97 WE men [age = 44.4 (42.0–47.6) yr, body mass index (BMI) = 29.2 ± 4.5 kg·m^{-2}] were assessed for fasting plasma complement markers and cardiometabolic risk factors. A second cohort (n = 20 men, 10 BA) [age = 31.0 ± 1.1 yr, BMI = 27.1 (26.0–28.6) kg·m^{-2}] men underwent a moderate-to-high-fat feeding protocol to measure postprandial plasma complement, serum insulin, plasma glucose, triacylglycerol (TAG), and nonesterified fatty acids. C4 and Factor D were lower, and iC3b was higher in BA compared with WE men. C3 and C4 were strongly associated with all adiposity markers in both ethnicities, but the WE cohort showed stronger associations between C3 and subcutaneous adipose tissue, C5 and WC, and iC3b and visceral adipose tissue compared with BA. C3 was associated with all cardiometabolic risk factors in both ethnicities. Associations between C5 and cholesterol, C4 and TAG, and terminal complement complex and (both total and LDL)-cholesterol were only observed in the WE cohort. There was a trend toward ethnic differences in postprandial Factor D (P = 0.097) and iC3b (P = 0.085). The weaker associations between the complement system markers with adiposity and lipid profiles in BA compared with WE men suggest ethnic differences in the determinants of complement production and activation, whereby adipose tissue may play a less important role in BA men.

NEW & NOTEWORTHY The present study found that markers of the complement system were less strongly associated with adiposity and lipid profiles in Black African men compared with White European men, suggesting ethnic differences in the determinants of complement production and activation. In Black African men, adipose tissue may play a less important role in complement production and activation and also in the link with traditional cardiometabolic risk factors.

complement system; ethnicity; lipid metabolism

INTRODUCTION

Populations of Black African (BA) ancestry experience greater cardiometabolic disease burden compared with White European (WE) populations, largely driven by higher rates of stroke and type 2 diabetes (T2D) (1, 2). BA populations present with a unique cardiometabolic risk profile; including higher levels of glycated hemoglobin (HbA1c) and insulin resistance (3–5), but paradoxically, lower waist circumference (WC), visceral adipose tissue (VAT) and a less atherogenic fasting lipid profile, comprising lower fasting triacylglycerol (TAG) and low-density lipoprotein (LDL)-cholesterol (6), compared with WE populations. Several theories attempt to explain the biological basis of the high cardiometabolic disease burden in BA (7), and one largely unexplored area is the potentially greater dysregulation of the complement system in BA compared with WE populations (7, 8).

The complement system, first identified as part of the innate immune system (9), comprises a complex network of over 50 plasma and membrane-bound proteins with wide-ranging biological roles in immune, inflammatory, and metabolic functions (10). Dysregulation of the complement system has been associated with T2D (11–13) and an increased risk of cardiovascular disease (14, 15). Although the liver

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accounts for the majority of complement protein production, adipose tissue also expresses a number of complement components and regulators (16, 17), suggesting that a greater degree of adiposity (i.e., obesity) may promote complement dysregulation. Indeed, both total and regional adiposity have been associated with elevated levels of C3 (13, 16, 18), C4 (16, 19), and C3a (20), which is a marker of C3 activation. Studies in mice suggest that excessive complement activation drives chronic low-grade inflammation, mediated by the production of C3a and C5a (anaphylatoxins) (21, 22). In humans, elevated plasma C3 and C4 concentrations have been associated with increased insulin resistance (12, 23), and increased plasma C3 has been associated with a more adverse lipoprotein phenotype (15, 24), including higher fasting and postprandial TAG concentrations (19, 25). These findings lend support to a role for complement dysregulation in promoting cardiometabolic risk. However, research to date has primarily been conducted in cohorts of WE ancestry, and there is a paucity of data relating complement to cardiometabolic risk factors in BA populations.

We have previously explored the relationship between fasting complement markers and glycemic risk profile [BMI, waist circumference, Homeostasis Model Assessment insulin resistance (HOMA-IR), and HbA1c] in WE and BA men (8). In the present study, we have expanded these analyses to investigate more detailed adiposity markers (subcutaneous and visceral adipose tissue) as well as fasting and postprandial lipids (triglycerides and LDL-, HDL-, and total-cholesterol) to more broadly look at cardiometabolic disease risk, particularly considering postprandial responses to a moderate-to-high-fat feeding protocol, which has previously been reported to activate the complement system (26, 27). Thus, the aim of the present study was *1*) to determine the relationship between fasting complement markers and cardiometabolic disease risk factors in WE and BA populations, and *2*) to determine whether the postprandial complement response differs by ethnicity and whether this finding may advance understanding regarding the greater risk of cardiometabolic disease in a BA population.

METHODS

Study Overview and Design

Our investigation consists of two analyses: *study 1* and *study 2*. In *study 1*, we assessed complement system markers and cardiometabolic risk factors in a cohort of WE and BA men. Data and sample collection were conducted between April 2013 and December 2019. The study was approved by the London Bridge National Research Ethics Committee (references: 15/LO/1121 and 12/LO/1859). In *study 2*, we assessed complement system markers in response to a moderate-to-high fat feeding protocol in overweight WE and BA men. Data and sample collection were conducted between December 2021 and January 2023. This study was approved by the King's College London research ethics committee (HR/DP-21/22-23409). All participants provided written informed consent.

Participants

Participants for *study 1* were recruited from the South London Diabetes and Ethnicity Phenotyping (SOUL-DEEP) study (28), which was designed to assess ethnic differences in the pathogenesis of type 2 diabetes (T2D) by recruiting people across a spectrum of glucose tolerance. Eligible participants were men of WE or BA ethnicity, aged 18–65 yr, with normal or impaired glucose tolerance or T2D diagnosis, and a body mass index (BMI) of 20–40 $kg \cdot m^{-2}$. Participants were excluded if they exhibited serum alanine transferase $>$ 150 $IU \cdot L^{-1}$ or serum creatinine $>$ 150 $\mu mol \cdot L^{-1}$, tested positive for anti-insulin, anti-GAD or anti-IA2 auto-antibodies, or had sickle cell disease.

Participants for *study 2* were recruited from advertisements placed in a local newspaper (London Metro), social media (Facebook and Instagram), local boroughs of London (Lambeth, Croydon, Southwark, and Lewisham), King's College London campuses and study volunteering pages, study recruitment websites (Gumtree and Call For Participants), and local community and church groups. Additional participants were recruited via word of mouth. Eligible participants were men of WE or BA ethnicity, aged 25–40 yr, at risk of cardiometabolic disease based on the presence of overweight/obesity (BMI $>$ 25 $kg \cdot m^{-2}$), and without impaired glucose tolerance or T2D (HbA1c $<$ 42 $mmol \cdot mol^{-1}$) or dyslipidemia (fasting TAG $<$ 3 $mmol \cdot L^{-1}$ and LDL-cholesterol $<$ 5 $mmol \cdot L^{-1}$).

Procedures

Study 1.

All participants attended an assessment visit at King's College Hospital (London, UK) that included a health questionnaire, anthropometric measurements [height, body weight, waist circumference, body fat percentage measured by bioelectrical impedance (Tanita, MC780)], blood pressure assessment, a fasting venous blood sample to assess full blood count, renal and liver function, HbA1c, plasma glucose, serum insulin, plasma lipid profile [triacylglycerol (TAG), low-density lipoprotein (LDL)-cholesterol and high-density lipoprotein (HDL)-cholesterol], sickle cell trait and autoantibodies. Blood samples were collected in ethylenediaminetetraacetic acid (EDTA) vacutainers (Beckton Dickinson, UK), immediately centrifuged at 3000 rpm for 15 min at 4°C, plasma separated and stored at −70°C until assay for the determination of complement markers [C3, C4, C5, Factor D, iC3b, and terminal complement complex (TCC)].

A subset of participants (WE: $n = 54$, BA: $n = 51$) attended the Clinical Imaging Department at Guy's Hospital (London, UK) for the determination of visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT) area, as described previously (29). Briefly, following an overnight fast, participants underwent a magnetic resonance imaging (MRI) scan on a 1.5 T Siemens Aera, scanning between the neck and the knee in the supine position. Gradient-echo images were acquired [repetition time: 6.77 ms; echo times: 4.77 ms (in-phase) and 2.39 ms (out-of-phase); flip angle: 10°; slice thickness: 3 mm], and water and fat images were produced as part of the Dixon sequence. MRI data were analyzed using HOROS V 1.1.7 (www.horosproject.org; accessed 21/10/2017) by a single analyst who was blinded to clinical data. Areas of VAT and SAT were determined from a single fat-only MRI image at the L4-5 anatomical position.

Study 2.

All participants attended an experimental study visit at the Metabolic Research Unit (King's College London, UK) to

undergo a moderate-to-high-fat feeding protocol to measure the postprandial response of plasma complement markers (C3, Factor D, Ba, iC3b, and TCC), serum insulin, plasma glucose, plasma TAG, and plasma nonesterified fatty acid (NEFA). Fasting concentrations of serum insulin and plasma glucose were consequently used in the Homeostasis Model Assessment 2 of insulin resistance (HOMA2-IR) to estimate insulin sensitivity (30). Participants were asked to avoid alcohol and strenuous exercise for the 48 h preceding their visit and were provided with a standardized meal on the evening before the meal test to be consumed before 10:00 PM (700 kcal: 45% carbohydrate, 33% fat, and 22% protein). Participants attended the research facility following an overnight fast (>10 h), and an antegrade cannula was inserted into an antecubital vein of the forearm. Moderate-to-high fat mixed meals were given at 0 and 300 min, containing 832 kcal, 52 g fat, and 70 g carbohydrate (*meal 1*; Supplemental Table S1) and 652 kcal, 33 g fat, and 70 g carbohydrate (*meal 2*; Supplemental Table S1), respectively. Blood samples were taken at −20, 0, 15, 30, 60, 90, 120, 180, 240, 300, 330, 360, 390, 420, and 480 min. Whole blood was dispensed into serum-separating (Becton Dickinson, UK), EDTA, and fluoride oxalate (Teklab Ltd., UK) tubes. The EDTA and fluoride oxalate tubes were centrifuged at 3000 rpm for 15 min at 4°C to obtain plasma. Serum tubes were left to stand at room temperature to clot for 15–20 min before centrifugation. The serum and plasma were then dispensed into aliquots and immediately frozen at −70°C until assay.

Laboratory Analyses

Plasma glucose concentrations were determined using an automated glucose analyzer (*study 1*; Yellow Spring Instruments, Ohio) or by automated enzymatic colorimetric assays (*study 2*; iLAB 650, Instrumentation Laboratories, Holliston). Serum insulin concentrations were determined by immunoassay utilizing chemiluminescent technology on an ADVIA Chemistry Analyzer (Siemens Healthcare Diagnostics, Camberley, UK).

Plasma lipids (TAG, LDL-, and HDL-cholesterol) and HbA1c were measured in the central clinical pathology laboratory at King's College London, UK (*study 1*) or Affinity Biomarker Laboratories, London, UK (*study 2*). In *study 2*, TAG and NEFA concentrations were determined by automated enzymatic colorimetric assays (iLAB 650, Instrumentation Laboratories, Holliston).

Plasma C3 and C4 were determined in the clinical chemistry laboratory (Addenbrookes Hospital, Cambridge, UK) with laser nephelometry (Beckman Coulter, Brea) (*study 1*). Plasma C3, C5, Factor D, Ba, iC3b, and TCC were determined at the Dementia Research Institute Cardiff, UK, using established in-house enzyme-linked immunosorbent assays (*study 2*), as previously decribed (8). Absorbance was measured at 492 nm, or 450 nm for Factor D, and sample analyses were repeated if the coefficient of variation between duplicate samples was >15%. Concentrations were determined in GraphPad Prism, as previously described (8).

Statistical Analysis

The dataset for *study 1* is from secondary outcomes of the SOUL-DEEP study (28). The primary outcome, upon which the sample size of the study was calculated, was insulin secretory function. Thus, the present manuscript reports exploratory analyses of the secondary outcomes of SOUL-DEEP, i.e., complement markers and cardiometabolic disease risk. Our sample size was predetermined, and there was no separate sample size calculation performed for these secondary outcomes of interest. For *study 2*, there were no existing data upon which to power the study; our study was intended to be exploratory/hypothesis generating, due to the novelty of the work. Our sample size was based on feasibility and intended to generate a dataset to inform future-powered investigations. Participant characteristics and fasting outcomes were analyzed using independent samples *t* tests; non-normally distributed data were log transformed or analyzed using Mann–Whitney *U* test where a normal distribution could not be obtained. Postprandial data were analyzed using repeated measures analysis of variance (ANOVA) with time and ethnicity as factors; pairwise analyses were conducted to examine ethnic differences at specific timepoints (Bonferroni adjusted statistics reported) where postprandial data were missing and timepoints were interpolated/extrapolated (<1% of outcome variables). The strength of relationships between fasting complement markers and cardiometabolic risk factors was estimated using Pearson's correlations. Ethnic differences in the strength of relationships were determined by fitting a linear regression model with an interaction term for ethnicity. Normally distributed data are presented as means ± SD (*study 1*), means ± SE (*study 2*), geometric mean (95% CI) for log transformed data; or median (IQR) for non-parametric data.

RESULTS

Study 1

Participant characteristics and fasting complement markers.

A total of 185 men (97 WE and 88 BA) participated in *study 1*. Clinical characteristics, adiposity measures, and fasting complement marker concentrations are presented in Table 1 and have been reported previously (8). The BA men were younger and exhibited lower waist circumference, fasting TAG, total- and LDL-cholesterol, and VAT, but higher HbA1c and systolic/diastolic blood pressure, compared with WE. There were no ethnic differences in body weight, BMI, fasting glucose, fasting insulin, HOMA2-IR, HDL-cholesterol, body fat percentage, fat mass, or SAT. BA men exhibited higher C4 and iC3b, but lower Factor D, compared with WE men. There were no ethnic differences in C3, C5, or TCC.

Associations between fasting complement and adiposity markers.

The associations between fasting complement markers and adiposity measures are presented for each ethnicity in Table 2. C3 concentration was positively associated with all measures of adiposity (BMI, waist circumference, VAT and SAT) in both ethnic groups, although the association with SAT was weaker in BA men. C4 concentration was positively associated with waist circumference, SAT and VAT in both ethnic groups, but the association with BMI was observed only in the WE men. For both C5 and iC3b concentrations,

Table 1. *Clinical characteristics, total and regional adiposity, and fasting complement markers of WE and BA men in Study 1 and Study 2*

	Study 1			Study 2		
	WE (n = 97)	BA (n = 88)	P^1	WE (n = 10)	BA (n = 10)	P^2
Clinical characteristics						
Age, yr	48.1 (44.7–51.7)	41.3 (38.3–44.5)	**0.018**	33.3 ± 1.7	28.8 ± 1.2	**0.045**
Weight, kg	91.9 (88.2–95.7)	88.2 (85.0–91.5)	0.316	89.7 ± 3.9	89.3 ± 3.2	0.946
BMI, kg·m^{-2}	29.3 ± 5.2	29.1 ± 4.0	0.793	26.8 (25.8–31.0)	27.5 (26.0–28.6)	0.999
Waist circumference, cm	104 ± 15	97 ± 12	**0.003**	94 ± 3	91 ± 3	0.506
Systolic blood pressure, mmHg	126 ± 12	130 ± 13	**0.042**	129 ± 3	124 ± 3	0.299
Diastolic blood pressure, mmHg	76 ± 10	79 ± 11	**0.037**	77 ± 3	72 ± 3	0.167
HbA1c, mmol·mol^{-1}	40 (39–42)	42 (40–43)	**0.017**	32 ± 1	34 ± 2	0.487
Fasting glucose, mmol·L^{-1}	5.7 (5.5–5.9)	5.6 (5.4–5.8)	0.403	5.7 ± 0.2	5.8 ± 0.2	0.671
Fasting insulin, pmol·L^{-1}[a]	69 (58–82)	63 (56–70)	0.362	39.5 (29.2–53.5)	49.3 (41.2–59.0)	0.172
HOMA2-IR[a]	1.5 (1.3–1.8)	1.3 (1.1–1.5)	0.238	0.8 (0.6–1.0)	1.0 (0.8–1.1)	0.180
Fasting TAG, mmol·L^{-1}	1.3 (1.2–1.4)	0.9 (0.8–1.0)	**<0.001**	0.9 (0.8–1.1)	0.7 (0.5–0.8)	**0.017**
Fasting NEFA, mmol·L^{-1}				0.3 ± 0.1	0.6 ± 0.1	0.252
Total cholesterol, mmol·L^{-1}	4.8 ± 0.9	4.3 ± 0.9	**<0.001**	5.1 ± 0.3	4.4 ± 0.6	**0.049**
HDL-cholesterol, mmol·L^{-1}	1.2 (1.1–1.3)	1.2 (1.1–1.3)	0.572	1.3 (1.2–1.5)	1.4 (1.2–1.7)	0.429
LDL-cholesterol, mmol·L^{-1}	2.9 ± 0.8	2.6 ± 0.7	**0.011**	3.5 ± 0.2	2.6 ± 0.2	**0.010**
Total and regional adiposity						
Body fat, %[b]	22.2 ± 6.8	21.8 ± 6.6	0.814	22.2 ± 2.7	21.1 ± 2.0	0.738
Fat mass, kg[b]	20.8 ± 9.9	20.3 ± 9.6	0.839	18.4 (12.8–26.6)	17.7 (13.2–23.9)	0.770
VAT, cm^{2c}#	121 (98–148)	77 (63–94)	**0.009**			
SAT, cm^{2c}#	239 (209–275)	236 (205–272)	0.885			
Fasting complement markers						
C3, μg·mL^{-1}	1120 ± 200	1160 ± 190	0.268	2000 ± 120	1140 ± 110	0.754
C4, μg·mL^{-1}	229.0 ± 57.0	257.0 ± 74.0	**0.005**			
C5[d], μg·mL^{-1}	85.3 (79.3–91.8)	82.3 (77.6–87.4)	0.473			
Factor D[d], μg·mL^{-1}	2.0 ± 1.1	1.6 ± 0.9	**0.031**	2.3 (1.8–3.6)	1.4 (1.1–2.2)	0.062
iC3b[d], μg·mL^{-1}	2.2 (1.8–2.7)	4.5 (3.6–5.7)	**<0.001**	2.7 ± 0.2	3.9 ± 0.8	0.127
TCC[d], μg·mL^{-1}	12.3 (11.1–13.6)	14.0 (12.6–15.5)	0.109	12.5 ± 1.6	13.3 ± 2.1	0.774
BA, μg·mL^{-1}				1.6 ± 0.2	1.8 ± 0.3	0.499

Study 1: Data were analyzed using independent samples t test and are presented as means ± SD or geometric mean (95% CI) for log transformed data. P values in bold represent statistical significance of $P < 0.05$. [a]WE: n = 54, BA: n = 51; [b]WE: n = 35, BA: n = 32; [c]WE: n = 54, BA: n = 51; [d]WE: n = 81, BA: n = 85. BA, Black African ancestry; BMI, body mass index; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; HOMA2-IR, homeostatic model assessment 2-insulin resistance; LDL, low-density lipoprotein; SAT, subcutaneous adipose tissue; TAG, triacylglycerol; TCC, terminal complement complex; VAT, visceral adipose tissue; WE, White European ancestry. *Study 2*: Data analyzed using independent samples t test and are presented as means ± SE, geometric mean (95% CI) for log transformed data, or median (IQR) for data analyzed with Mann–Whitney U test (marked by #). [a]WE: n = 9, BA: n = 10; [b]WE: n = 80, BA: n = 85. BA, Black African ancestry; BMI, body mass index; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; HOMA2-IR, homeostasis model assessment 2-insulin resistance; LDL, low-density lipoprotein; NEFA, nonesterified fatty acid; TAG, triacylglycerol; TCC, terminal complement complex; WE, White European ancestry.

associations with adiposity were observed in only the WE men, whereas associations between TCC and adiposity measures were observed only in the BA men. Factor D was not associated with any measure of adiposity in either ethnic group.

Associations between fasting complement and metabolic risk factors.

There were ethnic differences in the associations between complement markers and metabolic risk factors (Table 3). In both ethnic groups, C3 concentration was positively associated with HbA1c, HOMA-IR, and TAG, and inversely associated with HDL-cholesterol. C3 concentration was positively associated with total cholesterol concentration in WE, but not BA men. Conversely, there was a trend for a positive association between C3 and LDL-cholesterol in BA (P = 0.093), but not WE men. C4 concentration was positively associated with HbA1c in both ethnic groups, but the associations with HOMA2-IR and TAG were observed only in WE. C5 concentration was positively associated with HbA1c in both ethnic groups, but the association with HOMA2-IR was present only in the WE men. There were no associations between C5 and TAG or HDL-cholesterol in either ethnic group. In both ethnic groups, Factor D was inversely associated with HbA1c, but there were no associations with HOMA2-IR, fasting TAG, total-cholesterol, or LDL-cholesterol, and the association with HDL-cholesterol was present only in WE. For iC3b concentration, positive associations were observed with total- and LDL-cholesterol in WE men. In both ethnic groups, TCC was inversely associated with HbA1c, whereas the associations with total- and LDL-cholesterol were found only in WE men, and the association with TAG was found only in BA men.

Study 2

Participant characteristics and fasting complement markers.

A total of 20 men (10 WE and 10 BA) participated in *study 2*. Participant characteristics and fasting complement marker concentrations are presented in Table 1. The BA men were younger than WE men, and they exhibited lower fasting TAG, total-, and LDL-cholesterol. There were no ethnic differences in body weight, BMI, waist circumference, fat mass, systolic or diastolic blood pressure, HbA1c, fasting plasma glucose, fasting serum insulin, HOMA2-IR, fasting plasma NEFA, or HDL-cholesterol. In addition, there were no ethnic differences

Table 2. *Associations between fasting complement markers and adiposity in WE and BA men*

	WE (n = 97)		BA (n = 88)		Interaction
	r	*P*	*r*	*P*	*P*
C3 (WE: n = 97, BA: n = 88)					
BMI	0.625	<0.001	0.571	<0.001	0.698
Waist circumference	0.660	<0.001	0.585	<0.001	0.878
VAT#[a]	0.688	<0.001	0.531	<0.001	0.279
SAT#[a]	0.675	<0.001	0.421	0.002	**0.047**
C4 (WE: n = 97, BA: n = 88)					
BMI	0.303	<0.001	0.195	0.068	0.896
Waist circumference	0.382	<0.001	0.234	0.029	0.904
VAT#[a]	0.423	0.002	0.310	0.032	0.956
SAT#[a]	0.399	0.005	0.315	0.029	0.942
C5# (WE: n = 81, BA: n = 85)					
BMI	0.210	0.060	−0.006	0.955	0.176
Waist circumference	0.285	0.010	0.009	0.935	0.073
VAT#[a]	0.274	0.062	0.098	0.513	0.324
SAT#[a]	0.303	0.038	0.019	0.900	0.112
Factor D (WE: n = 81, BA: n = 85)					
BMI	0.075	0.506	0.011	0.917	
Waist circumference	0.126	0.270	0.013	0.909	
VAT#[a]	0.040	0.787	0.022	0.885	
SAT#[a]	0.019	0.897	0.185	0.214	
iC3b# (WE: n = 81, BA: n = 85)					
BMI	0.138	0.219	−0.028	0.800	
Waist circumference	0.197	0.081	−0.068	0.537	0.112
VAT#[a]	0.354	0.015	−0.109	0.468	**0.026**
SAT#[a]	0.214	0.148	−0.102	0.496	
TCC# (WE: n = 81, BA: n = 85)					
BMI	−0.089	0.435	−0.057	0.607	
Waist circumference	−0.064	0.577	−0.205	0.061	0.269
VAT#[a]	−0.098	0.517	−0.346	0.017	0.156
SAT#[a]	−0.050	0.741	−0.232	0.117	

Correlation coefficients determined using Pearson's correlations and differences in the strengths of associations assessed by fitting a linear regression with an ethnicity interaction term. *P* values in bold represent statistical significance of $P < 0.05$. #Non-normally distributed data were log transformed before analysis. [a]WE: n = 54, BA: n = 51. BA, Black African ancestry; BMI, body mass index; SAT, subcutaneous adipose tissue; TCC, terminal complement complex; VAT, visceral adipose tissue; WE, White European.

in fasting C3, Ba, iC3b, or TCC concentrations, but there was a trend for lower Factor D in BA compared with WE.

Postprandial hormones and metabolites.

The postprandial plasma glucose, serum insulin, plasma TAG, and NEFA responses of the BA and WE men are shown in Supplemental Fig. S1. There was a trend toward a main effect of ethnicity on plasma TAG response ($P = 0.071$), whereby the BA men exhibited a lower plasma TAG response to the meal at −20, −10, 15, 30, 60, and 360 min (Supplemental Fig. S1*C*). There was no main effect of ethnicity on postprandial plasma glucose, serum insulin, or plasma NEFA response. However, NEFA response differed between ethnicities over time, with BA exhibiting lower NEFA concentrations after the *meal 2* (time × ethnicity interaction; $P = 0.056$) (Supplemental Fig. S1*D*).

Postprandial complement markers.

The postprandial plasma C3, Factor D, Ba, iC3b, and TCC response of the BA and WE men are shown in Fig. 1. There was a trend toward lower Factor D in BA compared with the WE men (ethnicity main effect; $P = 0.097$), which trends toward a difference over time (time × ethnicity; $P = 0.073$). In this regard, Factor D was lower at −20, 15, and 390 min in BA than WE (Fig. 1*B*). There was also a trend toward higher iC3b in BA compared with WE (ethnicity main effect; $P = 0.085$), with BA exhibiting higher iC3b concentrations at 120 and 240 min (Fig. 1*D*). There were no ethnic differences in postprandial C3, Ba, or TCC response.

DISCUSSION

This study is the first, to our knowledge, to examine ethnic differences in markers of the complement system, and the

Table 3. *Associations between fasting complement markers and metabolic risk factors in WE and BA men*

	WE (n = 97)		BA (n = 88)		Interaction
	r	*P*	*r*	*P*	*(P)*
C3 (WE: n = 97, BA: n = 88)					
HbA1c#	0.350	<0.001	0.516	<0.001	0.073
HOMA2-IR#[a]	0.630	<0.001	0.561	<0.001	0.233
Fasting TAG#	0.570	<0.001	0.380	<0.001	0.215
Total cholesterol	0.218	0.035	0.156	0.147	0.790
HDL-cholesterol#	−0.344	<0.001	−0.244	0.036	0.615
LDL-cholesterol	0.148	0.155	0.180	0.093	0.805
C4 (WE: n = 97, BA: n = 88)					
HbA1c#	0.240	0.018	0.462	<0.001	0.248
HOMA2-IR#[a]	0.339	0.011	0.200	0.156	0.163
Fasting TAG#	0.397	<0.001	0.075	0.485	**0.008**
Total cholesterol	0.177	0.088	0.165	0.125	0.745
HDL-cholesterol#	−0.153	0.140	0.073	0.501	
LDL-cholesterol	0.098	0.346	0.131	0.224	
C5# (WE: n = 81, BA: n = 85)					
HbA1c#	0.372	<0.001	0.219	0.044	0.507
HOMA2-IR#[a]	0.351	0.010	0.125	0.383	0.253
Fasting TAG#	0.143	0.202	−0.002	0.985	
Total cholesterol	−0.330	0.003	−0.036	0.742	0.098
HDL-cholesterol#	−0.160	0.155	0.077	0.486	
LDL-cholesterol	0.195	0.081	0.139	0.204	0.090
Factor D (WE: n = 81, BA: n = 85)					
HbA1c#	−0.220	0.048	−0.240	0.027	0.550
HOMA2-IR#[a]	0.041	0.771	0.112	0.436	
Fasting TAG#	0.051	0.654	−0.094	0.391	
Total cholesterol	0.097	0.391	0.064	0.563	
HDL-cholesterol#	−0.221	0.047	−0.048	0.662	0.461
LDL-cholesterol	0.062	0.538	0.230	0.034	0.934
iC3b# (WE: n = 81, BA: n = 85)					
HbA1c#	−0.173	0.124	-0.108	0.326	
HOMA2-IR#[a]	0.130	0.352	0.149	0.297	
Fasting TAG#	0.141	0.210	0.174	0.112	
Total cholesterol	0.238	0.033	0.156	0.155	0.535
HDL-cholesterol#	0.005	0.964	−0.076	0.490	
LDL-cholesterol	0.251	0.024	0.156	0.153	0.405
TCC# (WE: n = 81, BA: n = 85)					
HbA1c#	−0.395	<0.001	−0.396	<0.001	0.783
HOMA2-IR#[a]	−0.244	0.081	−0.245	0.084	0.757
Fasting TAG#	−0.041	0.720	−0.240	0.027	0.228
Total cholesterol	0.388	<0.001	0.070	0.527	**0.029**
HDL-cholesterol#	−0.037	0.746	0.183	0.093	0.160
LDL-cholesterol	0.476	<0.001	0.115	0.293	**0.006**

Correlation coefficients determined using Pearson's correlations. *P* values in bold represent statistical significance of $P < 0.05$. #Non-normally distributed data were log transformed before analysis. [a]WE: n = 54, BA: n = 51. BA, Black African ancestry; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; HOMA2-IR, homeostatic model assessment 2-insulin resistance; LDL, low-density lipoprotein; TCC, terminal complement complex; WE, White European ancestry.

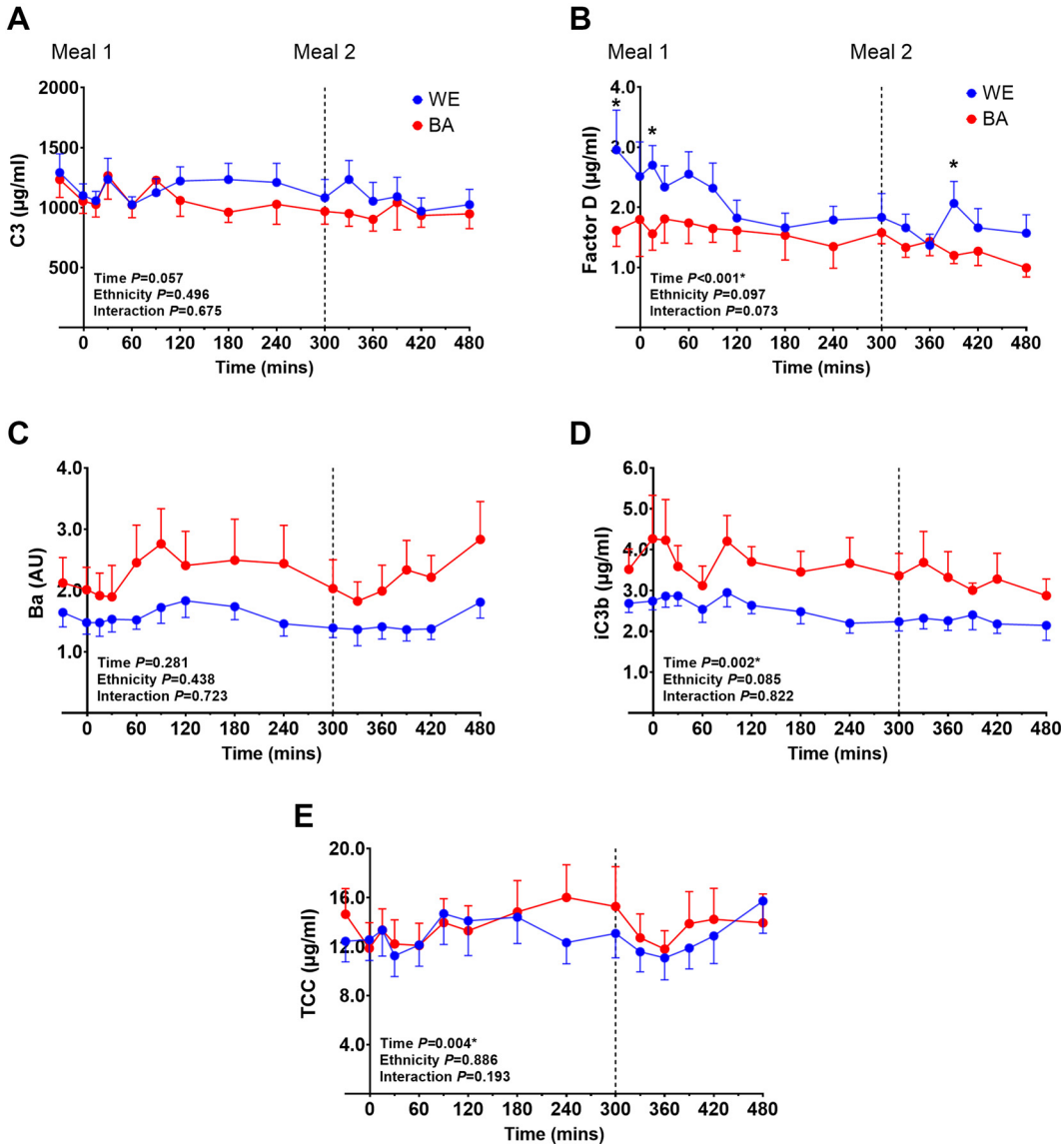

Figure 1. Postprandial concentrations of complement markers in WE and BA men (*study 2*). Postprandial C3 (*A*), Factor D (*B*), Ba (*C*), iC3b (*D*), and TCC (*E*) concentrations in WE and BA men following consecutive moderate-to-high fat mixed meal ingestion. *Meal 1* and *meal 2* contained approximately 52 g and 33 g fat, respectively, as well as 70 g carbohydrate. Factor D and TCC – WE: $n = 9$, BA: $n = 10$; C3 – WE: $n = 9$, BA: $n = 10$; Ba and iC3b – WE: $n = 10$, BA: $n = 9$. Data are means ± SE and were compared using repeated measures ANOVA with pairwise analyses; $*P < 0.05$ for effect of ethnicity. ANOVA, analysis of variance; AU, arbitrary units; BA, Black African ancestry; TCC, terminal complement complex; WE, White European ancestry.

relative associations with cardiometabolic risk factors, under fasting conditions and postprandially in response to a moderate-to-high-fat feeding protocol between WE and BA men. Our primary findings include the stronger association between C3 and SAT, C5 and WC, and iC3b and VAT in the WE compared with the BA cohort (*study 1*). Similarly, the WE cohort exhibited stronger associations between complement parameters and lipid proteins, including the C5 and TCC associations with LDL- and total-cholesterol, and C4 with TAG that were not present in the BA population. Moreover, C3 and C4 were more strongly associated with HbA1c in the BA than WE men, despite similar or weaker associations with HOMA2-IR, suggesting an important role of complement dysregulation in hyperglycemia in BA, independent of insulin sensitivity. Finally, there was a trend toward ethnic differences in the postprandial complement response, with the BA men exhibiting lower Factor D and higher iC3b compared with the WE men (*study 2*).

Adipose tissue expresses a number of complement components and regulators (17), and thus obesity has been hypothesized to drive the overproduction of complement proteins (10, 17). In our WE cohort, the central complement components C3, C4, and C5 were positively associated with BMI, WC, VAT, and SAT. These findings are consistent with previous studies that reported positive associations between C3 and BMI/adipose tissue mass (16) and higher C4 in obese compared with lean participants (31). However, in the BA men, the relationship between C3 and SAT was weaker compared with WE, and C5 was not associated with any of the adiposity markers. Similarly, iC3b, a marker of classical, lectin, and alternative pathway activation, was positively associated with VAT in the WE

men. However, no association existed with TCC, a marker of terminal pathway activation, and adiposity markers, which aligns with previous work that reported greater early complement activation with obesity, without greater terminal pathway activation (32). Conversely, although the BA men exhibited greater fasting and postprandial iC3b than WE men, there was no association between this complement marker and adiposity. Interestingly, there was an inverse association between TCC and VAT in BA, and hence, the mechanism for this relationship warrants further investigation. Collectively, these findings suggest that factors other than obesity/adipose tissue account for the greater complement activation pathway flux in BA men.

Complement dysregulation is suggested to drive metabolic dysfunction (10, 17). In the WE cohort, we observed a positive association between the complement components C3 and C4 and the metabolic markers HbA1c, HOMA-IR, fasting TAG, and total-cholesterol. These findings are consistent with previous reports of positive associations between complement markers and HbA1c and insulin resistance (10, 17), fasting and postprandial TAG (25, 33), a more adverse lipid profile (15, 24), and incidence of the metabolic syndrome (34). Interestingly, in the BA men, C3 and C4 were more strongly associated with HbA1c than in the WE men, despite similar (C3) or weaker (C4) associations with HOMA2-IR. These findings indicate that complement dysregulation may be a more important determinant of hyperglycemia in BA, independent of insulin sensitivity. However, the accuracy of HOMA2-IR in a BA population has been questioned (35), and thus more precise measures of insulin sensitivity would be required to confirm this hypothesis. Also noteworthy was the observation that the relationships between complement components and lipid markers were weaker or nonsignificant in BA compared with WE, which is consistent with previous data demonstrating that glycemic markers such as HbA1c and HOMA-IR do not have strong associations with lipid markers in BA, compared with WE. Despite significantly lower postprandial TAG in BA, there were no ethnic differences in postprandial C3. Interestingly, BA populations are characterized by higher HbA1c (4), lower total- and LDL-cholesterol (6), and lower fasting and postprandial TAG (6, 36, 37) compared with WE, manifesting as higher rates of T2D and lower rates of coronary heart disease (38, 39). However, it is unknown whether the dysregulation in complement causes higher HbA1c, with a lesser influence on fasting lipid profile, or whether a higher HbA1c is driving complement dysregulation (40), independent of an effect on lipid profile in the BA population.

The moderate-to-high-fat meal challenge decreased Factor D and increased TCC and iC3b in both ethnicities. We observed a trend toward lower postprandial Factor D and higher postprandial iC3b in the BA compared with WE men. These trends, however, appear to be largely driven by fasting concentrations of Factor D and iC3b, as Factor D was higher and iC3b lower in WE men at baseline, resulting in higher and lower postprandial concentrations, respectively. Adjusting for baseline removes the trends toward an interaction, and it is likely that the high-fat meal challenge was not sufficient to stimulate a robust postprandial complement response, therefore, further research is required to determine whether ethnic differences occur in the postprandial period after a sufficiently stimulatory meal challenge. We also observed a trend toward a postprandial increase in C3 in both the ethnic groups ($P = 0.057$). Previous data have shown that C3 is increased in response to a high-fat meal in both healthy individuals and those with cardiometabolic disease (26, 41). Although speculative, it is likely that a more substantial postprandial increase in C3 would have been observed in the present study if we had used a high-fat meal alone, as the presence of carbohydrate has previously been shown to prevent the postprandial increase in C3 (42). Although adipose tissue is an important contributor, the liver is responsible for the bulk of complement production, which may be stimulated by proinflammatory cytokines (43). However, despite the similar or higher fasting complement concentrations reported in this study, BA typically present with a more anti-inflammatory profile than WE (44, 45). Thus, further research is required to understand the role hepatic and adipose tissue play in (fasting and postprandial) complement production in a BA population.

This study has several strengths. Our ethnic groups were well matched for BMI and body fat. In addition, VAT and SAT were determined using gold standard MRI methodology, although a single L4-5 image was used in the analysis, this technique correlates strongly with VAT and SAT determined by multislice methods (46). This study also has limitations worth noting. Due to incomplete datasets, correlational analyses between complement markers and HOMA2-IR, VAT, and SAT, as well as ethnic comparisons of postprandial complement concentrations, were limited to population subsets. We also did not adjust for confounders within our analysis, and, as the BA population was younger, with lower waist circumference and higher blood pressure and HbA1c, these factors may have confounded the results. Therefore, the observed associations may be secondary to other factors, and further research is required to unravel these contributions. Due to the exploratory nature of the present analysis, there was no power calculation underpinning the study, and therefore it increases the likelihood of type 2 error. It would also be helpful to measure inflammatory markers, such as CRP and TNF-α, to further elucidate the link between the postprandial inflammatory response and complement activation. Furthermore, our data are limited to groups of WE and BA men; future work is required to identify ethnic differences between WE and BA women. Finally, the cross-sectional nature of this analysis limits the mechanistic implications of the findings—further longitudinal studies are required to elucidate the importance of the complement system in cardiometabolic disease pathophysiology in this population.

In conclusion, markers of the complement system were less strongly associated with adiposity and lipid profiles but more strongly associated with HbA1c in BA compared with WE men. These findings suggest ethnic differences in the determinants of complement production and activation, whereby adipose tissue plays a less important role in BA and also the link with traditional cardiometabolic risk factors. Another possibility is that the greater complement dysregulation in BA could promote higher HbA1c, aligning with the higher risk of T2D in BA than WE, but further work is required to confirm the direction of this relationship.

DATA AVAILABILITY

The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request.

SUPPLEMENTAL MATERIAL

Supplemental Table S1 and Supplemental Fig. S1: https://doi.org/10.25392/leicester.data.28473869.v1.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

R.M.R., M.B.W., and L.M.G. conceived and designed research; R.M.R. and W.M.Z. performed experiments; R.M.R. analyzed data; R.M.R., B.P.M., S.L., S.O., M.B.W., and L.M.G. interpreted results of experiments; R.M.R. and G.W. prepared figures; R.M.R. and G.W. drafted manuscript; R.M.R., W.M.Z., B.P.M., G.W., S.L., S.O., O.C.W., M.B.W., and L.M.G. edited and revised manuscript; R.M.R., W.M.Z., B.P.M., G.W., S.L., S.O., O.C.W., M.B.W., and L.M.G. approved final version of manuscript.

REFERENCES

1. **Raleigh VS**, **Holmes J.** The health of people from ethnic minority groups in England. 2021: King's Fund (Online). https://www.kingsfund.org.uk/insight-and-analysis/long-reads/health-people-ethnic-minority-groups-england [2025 Mar 7].
2. **Sproston K**, **Mindell J.** *Health Survey for England 2004: The Health of Minority Ethnic Groups*. Scotland, UK: NHS Health and Social Care Information Centre, 2005.
3. **Selvin E**, **Brancati FL.** A conundrum addressed: the prognostic value of HbA1c. *Nat Rev Endocrinol* 7: 1, 2011. doi:10.1038/nrendo.2010.126-c1.
4. **Kirk JK**, **D'Agostino RB Jr**, **Bell RA**, **Passmore LV**, **Bonds DE**, **Karter AJ**, **Narayan KM.** Disparities in HbA1c levels between African-American and non-Hispanic white adults with diabetes: a meta-analysis. *Diabetes care* 29: 2130–2136, 2006. doi:10.2337/dc05-1973.
5. **Haffner SM**, **D'Agostino R**, **Saad MF**, **Rewers M**, **Mykkänen L**, **Selby J**, **Howard G**, **Savage PJ**, **Hamman RF**, **Wagenknecht LE.** Increased insulin resistance and insulin secretion in nondiabetic African-Americans and Hispanics compared with non-Hispanic whites: the Insulin Resistance Atherosclerosis Study. *Diabetes* 45: 742–748, 1996. doi:10.2337/diabetes.45.6.742.
6. **Zoratti R.** A review on ethnic differences in plasma triglycerides and high-density-lipoprotein cholesterol: is the lipid pattern the key factor for the low coronary heart disease rate in people of African origin? *Eur J Epidemiol* 14: 9–21, 1998. doi:10.1023/a:1007492202045.
7. **Reed RM**, **Whyte MB**, **Goff LM.** Cardiometabolic disease in Black African and Caribbean populations: an ethnic divergence in pathophysiology? *Proc Nutr Soc* 1–11, 2023. doi:10.1017/S0029665123004895.
8. **Goff LM**, **Davies K**, **Zelek WM**, **Kodosaki E**, **Hakim O**, **Lockhart S**, **O'Rahilly S**, **Morgan BP.** Ethnic differences in complement system biomarkers and their association with metabolic health in men of Black African and White European ethnicity. *Clin Exp Immunol* 212: 52–60, 2023. doi:10.1093/cei/uxad011.
9. **Sim R**, **Schwaeble W**, **Fujita T.** Complement research in the 18th–21st centuries: progress comes with new technology. *Immunobiology* 221: 1037–1045, 2016. doi:10.1016/j.imbio.2016.06.011.
10. **Shim K**, **Begum R**, **Yang C**, **Wang H.** Complement activation in obesity, insulin resistance, and type 2 diabetes mellitus. *World J Diabetes* 11: 1–12, 2020. doi:10.4239/wjd.v11.i1.1.
11. **Engström G**, **Hedblad B**, **Eriksson KF**, **Janzon L**, **Lindgärde F.** Complement C3 is a risk factor for the development of diabetes: a population-based cohort study. *Diabetes* 54: 570–575, 2005. doi:10.2337/diabetes.54.2.570.
12. **Wlazlo N**, **van Greevenbroek MM**, **Ferreira I**, **Feskens EJM**, **van der Kallen CJ**, **Schalkwijk CG**, **Bravenboer B**, **Stehouwer CD.** Complement factor 3 is associated with insulin resistance and with incident type 2 diabetes over a 7-year follow-up period: the CODAM Study. *Diabetes Care* 37: 1900–1909, 2014. doi:10.2337/dc13-2804.
13. **Jiang J**, **Wang H**, **Liu K**, **He S**, **Li Z**, **Yuan Y**, **Yu K**, **Long P**, **Wang J**, **Diao T**, **Zhang X**, **He M**, **Guo H**, **Wu T.** Association of complement C3 with incident type 2 diabetes and the mediating role of BMI: a 10-Year Follow-Up Study. *J Clin Endocrinol Metab* 108: 736–744, 2023. doi:10.1210/clinem/dgac586.
14. **Onat A**, **Hergenç G**, **Can G**, **Kaya Z**, **Yüksel H.** Serum complement C3: a determinant of cardiometabolic risk, additive to the metabolic syndrome, in middle-aged population. *Metabolism* 59: 628–634, 2010. doi:10.1016/j.metabol.2009.09.006.
15. **Onat A**, **Uzunlar B**, **Hergenç G**, **Yazici M**, **Sari I**, **Uyarel H**, **Can G**, **Sansoy V.** Cross-sectional study of complement C3 as a coronary risk factor among men and women. *Clin Sci (Lond)* 108: 129–135, 2005. doi:10.1042/CS20040198.
16. **Gabrielsson BG**, **Johansson JM**, **Lönn M**, **Jernås M**, **Olbers T**, **Peltonen M**, **Larsson I**, **Lönn L**, **Sjöström L**, **Carlsson B**, **Carlsson LM.** High expression of complement components in omental adipose tissue in obese men. *Obes Res* 11: 699–708, 2003. doi:10.1038/oby.2003.100.
17. **Hertle E**, **Stehouwer CD**, **van Greevenbroek MM.** The complement system in human cardiometabolic disease. *Mol Immunol* 61: 135–148, 2014. doi:10.1016/j.molimm.2014.06.031.
18. **Xin Y**, **Hertle E**, **van der Kallen CJH**, **Schalkwijk CG**, **Stehouwer CDA**, **van Greevenbroek MMJ.** Longitudinal associations of the alternative and terminal pathways of complement activation with adiposity: the CODAM study. *Obes Res Clin Pract* 12: 286–292, 2018. doi:10.1016/j.orcp.2017.11.002.
19. **Nilsson B**, **Hamad OA**, **Ahlström H**, **Kullberg J**, **Johansson L**, **Lindhagen L**, **Haenni A**, **Ekdahl KN**, **Lind L.** C3 and C4 are strongly related to adipose tissue variables and cardiovascular risk factors. *Eur J Clin Invest* 44: 587–596, 2014. doi:10.1111/eci.12275.
20. **Wlazlo N**, **van Greevenbroek MM**, **Ferreira I**, **Jansen EH**, **Feskens EJ**, **van der Kallen CJ**, **Schalkwijk CG**, **Bravenboer B**, **Stehouwer CD.** Activated complement factor 3 is associated with liver fat and liver enzymes: the CODAM study. *Eur J Clin Invest* 43: 679–688, 2013. doi:10.1111/eci.12093.
21. **Mamane Y**, **Chung Chan C**, **Lavallee G**, **Morin N**, **Xu LJ**, **Huang J**, **Gordon R**, **Thomas W**, **Lamb J**, **Schadt EE**, **Kennedy BP**, **Mancini JA.** The C3a anaphylatoxin receptor is a key mediator of insulin resistance and functions by modulating adipose tissue macrophage infiltration and activation. *Diabetes* 58: 2006–2017, 2009. doi:10.2337/db09-0323.
22. **Phieler J**, **Chung KJ**, **Chatzigeorgiou A**, **Klotzsche-von Ameln A**, **Garcia-Martin R**, **Sprott D**, **Moisidou M**, **Tzanavari T**, **Ludwig B**, **Baraban E**, **Ehrhart-Bornstein M**, **Bornstein SR**, **Mziaut H**, **Solimena M**, **Karalis KP**, **Economopoulou M**, **Lambris JD**, **Chavakis T.** The complement anaphylatoxin C5a receptor contributes to obese adipose tissue inflammation and insulin resistance. *J Immunol* 191: 4367–4374, 2013. doi:10.4049/jimmunol.1300038.
23. **Bratti LOS**, **do Carmo ÍAR**, **Vilela TF**, **Wopereis S**, **de Moraes ACR**, **Borba BGM**, **Souza LC**, **Filippin-Monteiro FB.** Complement component 3 (C3) as a biomarker for insulin resistance after bariatric surgery. *Clin Biochem* 50: 529–532, 2017. doi:10.1016/j.clinbiochem.2017.02.006.
24. **Xin Y**, **Hertle E**, **van der Kallen CJH**, **Vogelzangs N**, **Arts ICW**, **Schalkwijk CG**, **Stehouwer CDA**, **van Greevenbroek MMJ.** C3 and alternative pathway components are associated with an adverse lipoprotein subclass profile: the CODAM study. *J Clin Lipidol* 15: 311–319, 2021. doi:10.1016/j.jacl.2021.01.011.
25. **van Oostrom AJ**, **Alipour A**, **Plokker TW**, **Sniderman AD**, **Cabezas MC.** The metabolic syndrome in relation to complement component 3

and postprandial lipemia in patients from an outpatient lipid clinic and healthy volunteers. *Atherosclerosis* 190: 167–173, 2007. doi:10.1016/j.atherosclerosis.2006.01.009.

26. **Halkes CJ**, **van Dijk H**, **de Jaegere PP**, **Plokker HW**, **van Der Helm Y**, **Erkelens DW**, **Castro Cabezas M.** Postprandial increase of complement component 3 in normolipidemic patients with coronary artery disease: effects of expanded-dose simvastatin. *Arterioscler Thromb Vasc Biol* 21: 1526–1530, 2001. doi:10.1161/hq0901.095276.
27. **Halkes CJ**, **van Dijk H**, **Verseyden C**, **de Jaegere PP**, **Plokker HW**, **Meijssen S**, **Erkelens DW**, **Cabezas MC.** Gender differences in postprandial ketone bodies in normolipidemic subjects and in untreated patients with familial combined hyperlipidemia. *Arterioscler Thromb Vasc Biol* 23: 1875–1880, 2003. doi:10.1161/01.ATV.0000092326.00725.ED.
28. **Goff L.** *Soul-Deep II: The South London Diabetes and Ethnicity Phenotyping Study*. London, UK: King's College London, 2013.
29. **Hakim O**, **Bello O**, **Ladwa M**, **Christodoulou D**, **Bulut E**, **Shuaib H**, **Peacock JL**, **Umpleby AM**, **Charles-Edwards G**, **Amiel SA**, **Goff LM.** Ethnic differences in hepatic, pancreatic, muscular and visceral fat deposition in healthy men of white European and black west African ethnicity. *Diabetes Res Clin Pract* 156: 107866, 2019. doi:10.1016/j.diabres.2019.107866.
30. **Caumo A**, **Perseghin G**, **Brunani A**, **Luzi L.** New insights on the simultaneous assessment of insulin sensitivity and beta-cell function with the HOMA2 method. *Diabetes care* 29: 2733–2734, 2006. doi:10.2337/dc06-0070.
31. **Nestvold TK**, **Nielsen EW**, **Ludviksen JK**, **Fure H**, **Landsem A**, **Lappegård KT.** Lifestyle changes followed by bariatric surgery lower inflammatory markers and the cardiovascular risk factors C3 and C4. *Metab Syndr Relat Disord* 13: 29–35, 2015. doi:10.1089/met.2014.0099.
32. **Kaye S**, **Lokki AI**, **Hanttu A**, **Nissilä E**, **Heinonen S**, **Hakkarainen A**, **Lundbom J**, **Lundbom N**, **Saarinen L**, **Tynninen O**, **Muniandy M**, **Rissanen A**, **Kaprio J**, **Meri S**, **Pietiläinen KH.** Upregulation of early and downregulation of terminal pathway complement genes in subcutaneous adipose tissue and adipocytes in acquired obesity. *Front Immunol* 8: 545, 2017. doi:10.3389/fimmu.2017.00545.
33. **Lewis RD**, **Narayanaswamy AK**, **Farewell D**, **Rees DA.** Complement activation in polycystic ovary syndrome occurs in the postprandial and fasted state and is influenced by obesity and insulin sensitivity. *Clin Endocrinol (Oxf)* 94: 74–84, 2021. doi:10.1111/cen.14322.
34. **Xin Y**, **Hertle E**, **van der Kallen CJH**, **Schalkwijk CG**, **Stehouwer CDA**, **van Greevenbroek MMJ.** Complement C3 and C4, but not their regulators or activated products, are associated with incident metabolic syndrome: the CODAM study. *Endocrine* 62: 617–627, 2018. doi:10.1007/s12020-018-1712-3.
35. **Pisprasert V**, **Ingram KH**, **Lopez-Davila MF**, **Munoz AJ**, **Garvey WT.** Limitations in the use of indices using glucose and insulin levels to predict insulin sensitivity: impact of race and gender and superiority of the indices derived from oral glucose tolerance test in African Americans. *Diabetes Care* 36: 845–853, 2013. doi:10.2337/dc12-0840.
36. **Friday KE**, **Srinivasan SR**, **Elkasabany A**, **Dong C**, **Wattigney WA**, **Dalferes E Jr**, **Berenson GS.** Black-white differences in postprandial triglyceride response and postheparin lipoprotein lipase and hepatic triglyceride lipase among young men. *Metabolism* 48: 749–754, 1999. doi:10.1016/s0026-0495(99)90175-0.
37. **Punyadeera C**, **Crowther NJ**, **van der Merwe MT**, **Toman M**, **Immelman AR**, **Schlaphoff GP**, **Gray IP.** Metabolic response to a mixed meal in obese and lean women from two South African populations. *Obes Res* 10: 1207–1216, 2002. doi:10.1038/oby.2002.165.
38. **Tillin T**, **Hughes AD**, **Godsland IF**, **Whincup P**, **Forouhi NG**, **Welsh P**, **Sattar N**, **McKeigue PM**, **Chaturvedi N.** Insulin resistance and truncal obesity as important determinants of the greater incidence of diabetes in Indian Asians and African Caribbeans compared with Europeans: the Southall And Brent REvisited (SABRE) cohort. *Diabetes Care* 36: 383–393, 2013. doi:10.2337/dc12-0544.
39. **Chaturvedi N.** Ethnic differences in cardiovascular disease. *Heart* 89: 681–686, 2003. doi:10.1136/heart.89.6.681.
40. **Ghosh P**, **Sahoo R**, **Vaidya A**, **Chorev M**, **Halperin JA.** Role of complement and complement regulatory proteins in the complications of diabetes. *Endocr Rev* 36: 272–288, 2015. doi:10.1210/er.2014-1099.
41. **Meijssen S**, **van Dijk H**, **Verseyden C**, **Erkelens DW**, **Cabezas MC.** Delayed and exaggerated postprandial complement component 3 response in familial combined hyperlipidemia. *Arterioscler Thromb Vasc Biol* 22: 811–816, 2002. doi:10.1161/01.atv.0000014079.98335.72.
42. **van Oostrom AJ**, **van Dijk H**, **Verseyden C**, **Sniderman AD**, **Cianflone K**, **Rabelink TJ**, **Castro Cabezas M.** Addition of glucose to an oral fat load reduces postprandial free fatty acids and prevents the postprandial increase in complement component 3. *Am J Clin Nutr* 79: 510–515, 2004. doi:10.1093/ajcn/79.3.510.
43. **Gao B**, **Jeong WI**, **Tian Z.** Liver: an organ with predominant innate immunity. *Hepatology* 47: 729–736, 2008. doi:10.1002/hep.22034.
44. **Hakim O**, **Bello O**, **Ladwa M**, **Peacock JL**, **Umpleby AM**, **Charles-Edwards G**, **Amiel SA**, **Goff LM.** The link between obesity and inflammatory markers in the development of type 2 diabetes in men of Black African and White European Ethnicity. *Nutrients* 12: 3796, 2020. doi:10.3390/nu12123796.
45. **Beasley LE**, **Koster A**, **Newman AB**, **Javaid MK**, **Ferrucci L**, **Kritchevsky SB**, **Kuller LH**, **Pahor M**, **Schaap LA**, **Visser M**, **Rubin SM**, **Goodpaster BH**, **Harris TB**; **Health ABC study.** Inflammation and race and gender differences in computerized tomography-measured adipose depots. *Obesity (Silver Spring)* 17: 1062–1069, 2009. doi:10.1038/oby.2008.627.
46. **Demerath EW**, **Shen W**, **Lee M**, **Choh AC**, **Czerwinski SA**, **Siervogel RM**, **Towne B.** Approximation of total visceral adipose tissue with a single magnetic resonance image. *Am J Clin Nutr* 85: 362–368, 2007. doi:10.1093/ajcn/85.2.362.