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1 **Insulin clearance as the major player in the hyperinsulinaemia of black African men**  
2 **without diabetes**

3

4 **Short title: Insulin clearance, hepatic fat and insulin sensitivity in black and white men**

5

6 Meera Ladwa<sup>1</sup>, Oluwatoyosi Bello<sup>1</sup>, Olah Hakim<sup>1</sup>, Fariba Shojaee-Moradie<sup>2</sup>, Linda Boselli<sup>3</sup>,  
7 Geoff Charles-Edwards<sup>4</sup>, Marietta Stadler<sup>1</sup>, Janet L. Peacock<sup>5</sup>, A. Margot Umpleby<sup>2</sup>, Stephanie  
8 A. Amiel<sup>1</sup>, Riccardo C. Bonadonna<sup>6</sup>, Louise M. Goff<sup>1</sup>

9

10 <sup>1</sup>Department of Diabetes, School of Life Course Sciences, Faculty of Life Sciences &  
11 Medicine, King's College London, London, UK; <sup>2</sup>Faculty of Health and Medical Sciences,  
12 University of Surrey, Guildford, UK; <sup>3</sup>Division of Endocrinology and Metabolic Disease,  
13 University of Verona School of Medicine, Verona, Italy; <sup>4</sup>School of Biomedical Engineering  
14 & Imaging Sciences, King's College London, London, UK; <sup>5</sup>School of Population Health  
15 and Environmental Sciences, King's College London, London, UK; <sup>6</sup>Department of  
16 Medicine & Surgery, University of Parma and Azienda Ospedaliera Universitaria di Parma,  
17 Parma, Italy

18

19 **Corresponding author:** Dr Louise M. Goff, Department of Diabetes, School of Life Course  
20 Sciences, Faculty of Life Sciences & Medicine, King's College London, Franklin-Wilkins  
21 Building, Waterloo Campus, London, SE1 9NH, UK

22 Email - [louise.goff@kcl.ac.uk](mailto:louise.goff@kcl.ac.uk)

23 Phone - 0207 848 4273

24 Louise M. Goff ORCID ID: 0000-0001-9633-8759

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30 **ABSTRACT**

31

32 AIMS: Despite their low levels of ectopic fat accumulation, populations of African ancestry  
33 exhibit hyperinsulinaemia and increased metabolic risk. We aimed to investigate relationships  
34 between insulin clearance, insulin secretion, hepatic fat accumulation and insulin sensitivity in  
35 black African (BA) and white European (WE) men.

36 METHODS: 23 BA and 23 WE men with normal glucose tolerance, matched for age and body  
37 mass index, underwent a hyperglycaemic clamp to measure insulin secretion and clearance;  
38 hyperinsulinaemic-euglycaemic clamp with stable glucose isotope infusion to measure whole-  
39 body and hepatic-specific insulin sensitivity; and magnetic resonance imaging to quantify  
40 intrahepatic lipid (IHL).

41 RESULTS: BA men had higher glucose-stimulated peripheral insulin levels (48.1 (35.5, 65.2)  
42  $\times 10^3$  vs 29.9 (23.3, 38.4)  $\times 10^3$  pmol L<sup>-1</sup>  $\times$  min,  $p=0.017$ ) and lower endogenous insulin  
43 clearance (771.6 (227.8) vs 1381 (534.3) mL m<sup>-2</sup> BSA min<sup>-1</sup>,  $p<0.001$ ) compared with WE  
44 men. There were no ethnic differences in beta cell insulin secretion or beta cell responsiveness  
45 to glucose, even after adjustment for prevailing insulin sensitivity. In WE men, endogenous  
46 insulin clearance was correlated with whole-body insulin sensitivity ( $r=0.691$ ,  $p=0.001$ ) and  
47 inversely correlated with IHL ( $r= -0.674$ ,  $p=0.001$ ). These associations were not found in BA  
48 men.

49 CONCLUSIONS: While normally glucose tolerant BA men have similar insulin secretory  
50 responses to their WE counterparts, they have markedly lower insulin clearance, which does  
51 not appear to be explained by either insulin resistance or hepatic fat accumulation. Low insulin  
52 clearance may be the primary mechanism of hyperinsulinaemia in populations of African  
53 origin.

54 **KEY WORDS:** African, ethnicity, insulin clearance, insulin secretion, intrahepatic lipid

55

56 **ABBREVIATIONS**

57 BA: Black African

58 HFF: Hepatic Fat Fraction

59 EGP: Endogenous glucose production

60 FFM: Fat-free mass

61 iAUC: Incremental area under the curve

62 IHL: Intrahepatic lipid

63 ISR: Insulin secretion rate

64 MCRI: Metabolic clearance rate of insulin

65 NEFA: Non-esterified fatty acids

66 OGTT: Oral glucose tolerance test

67 WE: White European

## 68 INTRODUCTION

69

70 The multifaceted pathophysiology of type 2 diabetes (T2D) includes peripheral and hepatic  
71 insulin resistance, reduced insulin clearance and beta-cell dysfunction. Insulin secreted by the  
72 pancreatic beta cell is delivered directly via the portal vein to the liver, where the majority of  
73 endogenous insulin clearance occurs [1]. The predominant mechanism of hepatic insulin  
74 clearance involves insulin binding to its receptor on the hepatocyte surface, with endocytosis  
75 and internalisation of the insulin-receptor complex and subsequent degradation [2]. Therefore,  
76 hepatic insulin clearance is an integral part of insulin's action on the liver, with greater hepatic  
77 insulin sensitivity associated with greater clearance [3]. Intrahepatic lipid (IHL) plays a key  
78 role in glucose/insulin dysregulation; while the mechanisms are not fully understood, the  
79 accumulation of lipotoxic mediators has been found to inhibit insulin receptor activation [4].  
80 In this way, accumulation of IHL is believed to drive impairments in both insulin clearance  
81 and hepatic insulin sensitivity [5-8].

82

83 Populations of black African (BA) ethnicity suffer a disproportionately elevated risk of T2D  
84 [9, 10], yet they are relatively protected from ectopic fat deposition and exhibit lower IHL  
85 relative to other ethnicities (the so-called "African paradox") [11]. Distinctive features of  
86 insulin dynamics are well-documented in populations of African ethnicity [12], with an  
87 exaggerated insulin response to glucose in BA subjects demonstrated across a spectrum of  
88 glucose tolerance [13-17]. An important contributor to this phenomenon is the relatively low  
89 insulin clearance of BA populations, which has been consistently recognised [18-22].  
90 Reductions in insulin clearance appear to be a predictor of T2D in this ethnic group [23] and  
91 may be associated with increased markers of inflammation [24].

92 We have previously shown that fasting hepatic insulin resistance in BA men with early T2D  
93 appears to be independent of IHL [25] and that there are ethnic differences in the relationship  
94 between ectopic fat accumulation and insulin sensitivity [26]. This has led us to hypothesise  
95 that the role of IHL in insulin clearance may differ by ethnicity. To our knowledge, this is the  
96 first study to examine the impact of BA ethnicity on relationships between insulin clearance,  
97 insulin sensitivity and hepatic fat in adult men of normal glucose tolerance.

## 98 **METHODS**

### 99 **Study Design**

100 The data were collected as part of “Soul-Deep II”, a cross-sectional study of the development  
101 of type 2 diabetes in men resident in South London from two ethnic groups, white European  
102 (WE) and black (West) African (BA). Metabolic assessments were performed at the Clinical  
103 Research Facility, King’s College Hospital, London, UK, while MRI imaging took place at  
104 Guy’s Hospital, London, UK. The study was approved by the London Bridge National  
105 Research Ethics Committee (15/LO/1121). Recruitment of subjects and data collection took  
106 place between April 2016 and May 2018. Recruitment was carried out through advertising in  
107 the local press and via South London primary care practices. All subjects provided written  
108 informed consent prior to the study.

109

### 110 **Subjects**

111 Eligible subjects were male, aged 18-65 years, of either white European (WE) or black (West)  
112 African (BA) ethnicity. Ethnicity was self-declared and confirmed by grandparental  
113 birthplace. Eligible WE subjects had 4 WE grandparents with at least two of these from North  
114 West European countries as defined by the United Nations Statistics Division (UNSD) [27].  
115 Eligible BA subjects had 4 BA grandparents from West African countries as defined by UNSD.

116

117 Subjects were invited to a screening assessment at the Clinical Research Facility at King’s  
118 College Hospital, following a 10 hour fast, in order to undertake a screening questionnaire,  
119 anthropometric measurements and a 2 hour, 75g oral glucose tolerance test (OGTT). Eligible  
120 subjects were normal glucose tolerant according to World Health Organisation criteria [28].

121



122 Exclusion criteria were: a diagnosis of diabetes; treatment with oral hypoglycaemic agents,  
123 insulin, systemic steroids or beta blockers; any condition or medication considered by the  
124 investigators to have substantial impact on the study protocol or outcomes; serum creatinine of  
125  $>150 \mu\text{mol/l}$ ; serum alanine transaminase level  $>2.5$  fold above the upper limit of the reference  
126 range; sickle cell disease (trait permitted). Participants were instructed to refrain from 1)  
127 strenuous physical activity for 48-hours 2) alcohol consumption for 24-hours and 3) food and  
128 drink (other than water) for at least 10 hours prior to the study visits.

129  
130 **Hyperglycaemic clamp assessment of first- and second- phase insulin secretory function**  
131 **and insulin clearance**

132 Following an overnight fast, participants were admitted to the Clinical Research Facility and  
133 weighed in light clothing. A cannula was inserted into the antecubital fossa vein of the non-  
134 dominant arm for administration of the glucose infusion and a second cannula inserted  
135 retrogradely into the dorsum of the contralateral hand for blood sampling. The sampling hand  
136 was placed in a hand-warming unit at  $55 \text{ }^\circ\text{C}$  in order to achieve arterialised venous blood. A  
137 primed, variable rate intravenous infusion of 20% (wt/vol) dextrose was administered for 120  
138 minutes to achieve square-wave hyperglycaemia with a plasma glucose concentration of 6.9  
139 mmol/L above baseline, according to the protocol of DeFronzo et al [29]. Glucose, insulin,  
140 and C-peptide concentrations were measured at fasting (-20, -10, 0 minutes) and at 2, 4, 6, 8,  
141 10, 15, 20, 30, 40, 50, 60, 75, 90, 105, and 120 minutes.

142

143 **Hyperinsulinaemic-euglycaemic clamp assessment of insulin sensitivity**

144 The full methodology has been described [26]. In brief, a two-step hyperinsulinaemic–  
145 euglycaemic clamp with a stable glucose isotope infusion was used to assess whole-body and  
146 hepatic-specific insulin sensitivity. Participants were admitted to the Clinical Research Facility  
147 following an overnight fast and weighed in light clothing. During the basal phase, a primed

148 (2.0 mg/kg), continuous infusion ( $0.02 \text{ mg kg}^{-1} \text{ min}^{-1}$ ) of [6,6  $^2\text{H}_2$ ]-glucose (CK Gases,  
149 Cambridgeshire, UK) was initiated at -120 minutes. Blood samples were taken at -30, -20, -10  
150 and 0 minutes for basal assessments. The clamp began at 0 minutes with a primed continuous  
151 insulin infusion (Actrapid, Novo Nordisk, Bagsvaerd, Denmark) bound to albumin at a rate of  
152  $10 \text{ mU m}^{-2} \text{ BSA min}^{-1}$  for 2 hours (low dose insulin phase) for assessment of hepatic insulin  
153 sensitivity. For the final 2 hours, the insulin infusion rate was re-primed and increased to 40  
154  $\text{mU m}^{-2} \text{ BSA min}^{-1}$  (high dose insulin phase) for assessment of whole-body insulin sensitivity.  
155 Euglycaemia (5.0 mmol/l) was achieved using variable rate 20% (wt/vol) dextrose enriched  
156 with [6,6  $^2\text{H}_2$ ]-glucose (8 mg/g glucose) to maintain a constant tracer-to-tracee ratio. Blood  
157 was drawn at 30, 60, 90, 100, 110, 120, 150, 180, 210, 220, 230 and 240 minutes for the  
158 assessment of plasma glucose concentration, isotopic enrichment and insulin concentration.

159

#### 160 **Magnetic Resonance Imaging assessment of IHL**

161 The full imaging protocol has been reported [30]. In brief, a Dixon-based MRI sequence was  
162 used on a 1.5 Tesla Siemens scanner to obtain images from the neck to the knee (excluding  
163 arms). 384 contiguous, axial T1-weighted gradient-echo images with a slice thickness of 3mm  
164 were acquired, from which fat and water images were produced as part of the Dixon sequence.  
165 MRI data were analysed using the open source image analysis software HOROS V 1.1.7  
166 ([www.horosproject.org](http://www.horosproject.org); accessed 21/10/2017) by a single, blinded analyst (OH).

167 In each participant, two abdominal MRI images approximately 30mm apart were selected,  
168 representing the superior and inferior sections of the liver. In each pair of water and fat MRI  
169 images, 4 circular regions of interest (ROIs) in identical positions were placed within the liver  
170 tissue. The hepatic fat fraction (HFF) was quantified in each ROI by using the formula  $\% \text{HFF}$   
171  $= (F/(F+W)) * 100$  where F is the pixel signal intensity of the fat image and W is the pixel signal  
172 intensity of the water image. Intrahepatic lipid (IHL) was calculated as the mean of all 8 ROIs.

173 **Biochemical analyses**

174 Plasma glucose concentrations were determined at the bedside using an automated glucose  
175 analyser (Yellow Spring Instruments, 2300 STAT Glucose Analyzer, Ohio, USA). Plasma  
176 insulin concentrations were determined by immunoassay using chemiluminescent technology  
177 (ADVIA Centaur System, Siemens Healthcare Ltd. Camberly, UK). Plasma C-peptide  
178 concentrations were determined by radioimmunoassay (Millipore Ltd, Hertfordshire, UK).  
179 Plasma glucose isotope enrichments were measured by gas chromatography-mass  
180 spectrometry on an Agilent GCMS 5975C MSD (Agilent Technologies, Wokingham, UK).

181

182 **Calculations**

183 Whole-body insulin sensitivity was quantified using the M value ( $\text{mg/kg FFM min}^{-1}$ ) measured  
184 during the final 30 min of the high-dose insulin phase of the clamp, calculated as total glucose  
185 disposal corrected for deviations in plasma glucose concentration [26]. Whole-body insulin  
186 sensitivity was also expressed as M/I, the M value corrected for the steady state insulin  
187 concentration during the last 30 minutes of the clamp ( $\text{mg kg}^{-1} \text{FFM min}^{-1}$ ) / ( $\text{pmol L}^{-1}$ ).

188

189 Steele's non-steady-state equations, modified for stable isotopes, were used to determine total  
190 glucose rate of appearance, Ra ( $\mu\text{mol kg}^{-1} \text{FFM min}^{-1}$ ) [31]. Endogenous glucose production  
191 (EGP) was calculated by subtracting exogenous glucose infusion rate from total glucose Ra.  
192 Hepatic insulin sensitivity was expressed as the percentage suppression of EGP from basal to  
193 the final 30 minutes of the clamp (% suppression of EGP).

194

195 The clearance rate of the exogenously administered insulin infusion during the  
196 hyperinsulinaemic-euglycaemic clamp (metabolic clearance rate of insulin, or MCRI) was

197 calculated as the insulin infusion rate divided by the insulin concentration during the steady  
198 state period in the final 30 minutes of the clamp ( $\text{mL m}^{-2} \text{BSA min}^{-1}$ ).

199

200 The incremental areas under the curve (iAUC) were calculated using the trapezoid rule for C-  
201 peptide, insulin and glucose. Classical indices of first- and second-phase insulin secretion  
202 during the hyperglycaemic clamp were determined by calculating the iAUC for C-peptide for  
203 0 to 10 minutes and 10 to 120 minutes respectively.

204

205 Parameters of beta cell function were obtained by modelling the glucose and C-peptide curves  
206 during the hyperglycaemic clamp using published methods [32, 33]. Model assessments were  
207 carried out using SAAM-II 1.2 software (SAAM Institute, Seattle, Washington). The main  
208 outputs of the model are: pre-hepatic endogenous insulin secretion (expressed as area under  
209 the curve of insulin secretion rate over 120 minutes,  $\text{AUC}_{\text{ISR}}$ ); beta cell glucose sensitivity of  
210 first-phase secretion ( $\sigma_1$ ), expressed as the amount of insulin secreted in response to a rate of  
211 increase in glucose of 1 mmol/L between time 0 and 1 minute of the study, in ( $\text{pmol m}^{-2}$   
212  $\text{BSA})/(\text{mmol L}^{-1} \text{min}^{-1})$ , beta cell glucose sensitivity of second-phase secretion ( $\sigma_2$ ), expressed  
213 as the steady-state insulin secretion rate in response to a step increase in glucose of 1 mmol/L  
214 above baseline, in ( $\text{pmol min}^{-1} \text{m}^2)/(\text{mmol L}^{-1})$ .

215

216 During the hyperglycaemic clamp, average (endogenous) insulin clearance was calculated  
217 according to the following formula [33]:

$$\text{Clearance}_{\text{Ins}} = \frac{\text{AUC}_{\text{ISR}}}{\text{AUC}_I + (I_{\text{Final}} - I_{\text{Basal}}) \cdot \text{MRT}_{\text{Ins}}}$$

218

219 where  $\text{AUC}_{\text{ISR}}$  is the area under the curve of insulin secretion rate,  $\text{AUC}_I$  is the area under the  
220 curve of insulin concentration,  $I_{\text{Final}}$  is insulin concentration at the end of the study,  $I_{\text{Basal}}$  is

221 insulin concentration at the beginning of the study, and  $MRT_{Ins}$  is the mean residence time of  
222 insulin, which was assumed to be 18 minutes as reported in Navalesi *et al* [34].

223

## 224 **Statistical analysis**

225 Log-transformation was used on skewed variables that showed a significant deviation from  
226 normality to achieve a normal distribution prior to the use of parametric tests. Data are  
227 expressed as means (SD) for non-transformed data and geometric mean (95% confidence  
228 intervals) for log-transformed data. Significance of differences in variables between the two  
229 ethnic groups were made using independent sample Student's *t* test. The strength of  
230 associations between variables of interest was assessed using Pearson's correlation. The ethnic  
231 differences in relationships between endogenous insulin clearance and whole-body insulin  
232 sensitivity, hepatic insulin sensitivity, intrahepatic lipid and MCRI, were examined by fitting  
233 a regression model between the pairs of variables with an interaction term for ethnicity. Prior  
234 to running the regression models, collinearity diagnostics were performed for the whole cohort  
235 for insulin clearance with ethnicity, hepatic fat (IHL), insulin sensitivity (M value) and insulin  
236 secretion (AUC\_ISR). The VIFs for these factors were used to exclude multicollinearity. An  
237 ANCOVA was used, with insulin secretion (AUC\_ISR), intrahepatic lipid (IHL), hepatic insulin  
238 sensitivity (% suppression of EGP) and whole-body insulin sensitivity (M value) as co-variates,  
239 to investigate ethnic differences in average endogenous insulin clearance. An ANCOVA was  
240 used with whole-body insulin sensitivity (M value) as a co-variate, to investigate ethnic  
241 differences in endogenous insulin secretion. Missing data were excluded pairwise for all  
242 analyses; in the case of the correlation analysis between IHL and insulin clearance, this led to  
243 skewing of the IHL data which was therefore log-transformed for this analysis. All analyses  
244 were conducted with SPSS version 25.0 and *p* values < 0.05 were considered statistically  
245 significant.

## 246 **RESULTS**

247

### 248 **Participant characteristics**

249 The characteristics of the 23 BA and 23 WE men are presented in Table 1. The two ethnic  
250 groups were well-matched for age, weight and BMI and showed no difference in HbA<sub>1c</sub>, blood  
251 pressure or fasting glucose (Table 1). The BA men had significantly lower fasting triglyceride  
252 levels (Table 1).

253

### 254 **Beta cell insulin secretory function**

255 There were no ethnic differences in fasting C-peptide or fasting insulin (Table 2). By design,  
256 there was no difference in “clamped” glucose during the hyperglycaemic clamp (BA= 12.1  
257 (0.65) vs WE = 12.0 (0.63) mmol/L,  $p= 0.635$ ).

258

259 Mean peripheral insulin levels were approximately 1.5-fold higher during both first and second  
260 phase of the hyperglycaemic clamp in BA compared with WE men (Figure 1a), while there  
261 were no ethnic differences in C-peptide response (Table 2, Figure 1b), endogenous beta cell  
262 insulin secretion (AUC<sub>ISR</sub>) (Table 2) or sensitivity of the beta cell to glucose during first or  
263 second phase insulin secretion,  $\sigma^1$  and  $\sigma^2$  (Table 2). This remained the case after measures of  
264 beta cell insulin secretion were adjusted for whole-body insulin sensitivity ( $p = 0.512$ ).

265

### 266 **Intrahepatic lipid and insulin sensitivity**

267 Data on IHL, whole body and hepatic insulin sensitivity, as previously reported by our group  
268 [26, 30] showed IHL was lower in BA men, while there were no ethnic differences in hepatic  
269 insulin sensitivity or whole-body insulin sensitivity by either M value or M/I (included in Table  
270 2 for reference).

271

272 **Insulin clearance**

273

274 Average endogenous insulin clearance was almost 50% lower in BA compared with WE men  
275 during the hyperglycaemic clamp (Table 2). The ethnic difference remained significant after  
276 adjusting for whole-body insulin sensitivity (M value), endogenous insulin secretion ( $AUC_{ISR}$ ),  
277 intrahepatic lipid (IHL) and hepatic insulin sensitivity (% suppression of EGP) ( $p < 0.001$ ).  
278 Clearance of exogenous insulin as determined by MCRI was also lower in BA compared with  
279 WE men (Table 2).

280

281 **Relationships between endogenous insulin clearance and intrahepatic lipid, insulin**  
282 **sensitivity and insulin secretion**

283

284 In WE men, endogenous insulin clearance was correlated with whole-body (Figure 2a & 2b)  
285 and hepatic insulin sensitivity (Figure 2c) and with MCRI (Figure 2d), while it was inversely  
286 correlated with IHL (Figure 2e). These relationships were not found in the BA men (figure 2  
287 a-e).

288

289 In multiple regression analysis, an ethnicity interaction was found in the relationship between  
290 endogenous insulin clearance and whole-body insulin sensitivity (Figure 2a;  $p_{\text{interaction}} =$   
291  $0.022$ ). An ethnicity interaction was also found in the relationship between the measurements  
292 of endogenous insulin clearance and MCRI (Figure 2d;  $p_{\text{interaction}} = 0.021$ ). A trend was found  
293 for an ethnicity interaction between endogenous insulin clearance and hepatic insulin  
294 sensitivity (Figure 2c;  $p_{\text{interaction}}=0.057$ ). No ethnicity interaction was found between insulin  
295 clearance and IHL.

296

297 **DISCUSSION**

298 This study comprises a comprehensive investigation of insulin clearance and its relationships  
299 with hepatic fat and insulin sensitivity in white European and black African men with normal  
300 glucose tolerance. To our knowledge, it is the first to demonstrate that the markedly low insulin  
301 clearance of an African origin population may occur in the absence of insulin resistance. While  
302 the classical paradigm suggests that increased insulin resistance drives the excess diabetes risk  
303 in BA populations, these findings contribute to a newly emerging (and as yet, controversial)  
304 paradigm, which proposes that impairments in insulin clearance are the primary aetiological  
305 mechanism of glucose intolerance in this ethnic group [35, 36].

306

307 In this study, the response to intravenous glucose in the BA men was characterised by a  
308 pronounced hyperinsulinaemia compared with that of the WE men (Figure 1). While this is  
309 well-documented in the literature, it has previously been described as a compensatory response  
310 by the beta cell to increased insulin resistance and/or a consequence of “upregulated” beta cell  
311 function [14, 18, 37-39]. By contrast, in our study population we found that there were no  
312 ethnic differences in total beta cell insulin secretion, corroborating the findings of the Federal  
313 Women’s Study [22] and developing an evidence base which disputes the argument that people  
314 of African ancestry typically exhibit insulin hypersecretion.

315

316 We acknowledge that much of the literature, including the Federal Women’s study [22], report  
317 greater first phase beta cell responsivity in African-ancestry groups [38] whereas we found no  
318 ethnic differences in either first or second phase beta cell responsivity to glucose. Our results  
319 may differ as this is one of the few studies to comprise exclusively of adult men, rather than  
320 children/adolescents [18, 19, 37, 38, 40] or all-female cohorts [39, 41-45]. Two other adult  
321 non-diabetic all-male studies have examined ethnic differences in insulin responses [46, 47];



322 neither found increased insulin secretion in the African-ancestry subjects compared with white  
323 subjects, consistent with our findings. It is worth considering that the paucity of male  
324 participants in this area of the literature may have led to an overestimation of ethnic differences  
325 in insulin secretory response [48].

326

327 We found that the peripheral hyperinsulinaemia of our BA population was due to the ethnic  
328 difference in insulin clearance; furthermore, this difference persisted after adjustment for  
329 insulin sensitivity, hepatic fat content and insulin secretion rate. Whilst insulin clearance was  
330 associated with IHL and whole body and hepatic insulin sensitivity in WE men, these  
331 associations were absent in the BA men. Insulin clearance is a highly variable process which  
332 operates under the influence of multiple physiological factors. The predominant cellular  
333 mechanism is receptor-mediated uptake and therefore a correlation is typically seen between  
334 insulin sensitivity and insulin clearance [49, 50]. Our data in the WE men are in keeping with  
335 these expected relationships. In the BA men, where such relationships are not observed, we  
336 may postulate that such mechanisms operate differently between the ethnic groups, or with  
337 different dose-responses.

338

339 This leads us to propose that endogenous insulin clearance in BA may be determined by  
340 additional factors which are independent of insulin sensitivity, e.g. in the pathways involved in  
341 post-receptor insulin metabolism. This assertion is supported by recent evidence from a study  
342 investigating ethnic differences in the expression and activity of hepatic insulin-degrading  
343 enzyme (IDE) and carcinoembryonic antigen-related cell adhesion molecule 1 (CEACAM-1)  
344 between African-Americans and non-Hispanic White Americans, which reported lower IDE  
345 activity in African-Americans [51]. While reduced insulin clearance is widely regarded as an  
346 early response to insulin resistance [52, 53], it is also possible that changes in insulin clearance

347 are not only a compensatory mechanism but also a primary determinant of peripheral insulin  
348 levels [36, 54] in BA populations.

349

350 Low insulin clearance has been demonstrated in African American women [22], in pre-pubertal  
351 African-American children [18, 21, 55], in indigenous adult Ghanaians [56] and, with this  
352 study, in black West African men living in the UK. The finding of this distinctive physiological  
353 characteristic in diverse populations of African ancestry is suggestive of a genetic rather than  
354 environmentally mediated mechanism. The strong heritability of insulin clearance has been  
355 demonstrated in a Hispanic population [57] and this may also be the case in other ethnic groups.  
356 Molecular mechanisms that warrant further exploration include potential ethnic differences in  
357 inflammatory activity [24], the expression and activity of insulin-degrading enzyme [51], the  
358 liver-adiponectin pathway [58], or in liver CEACAM-1 expression/activity [2].

359

360 We note that clearance of exogenously administered insulin (as determined by the MCRI) is  
361 also lower in BA compared to WE, although the difference is not as marked as for endogenous  
362 insulin clearance. This may be expected, because while only endogenously secreted insulin  
363 undergoes first pass hepatic metabolism, exogenously administered insulin also undergoes both  
364 hepatic and extra-hepatic clearance (with around 60% of peripherally administered insulin  
365 thought to be cleared by the liver [59]).

366

367 Importantly, while MCRI is closely correlated with endogenous insulin clearance in WE, this  
368 is not the case in BA and ethnicity has a significant impact on the relationship between the two  
369 measures. We note that models have shown that while hepatic insulin clearance is lower in  
370 black ethnic groups compared with whites, extra-hepatic clearance is similar [20, 21] and that  
371 hepatic and extra-hepatic insulin clearance are differentially regulated [60]. As hepatic insulin

372 clearance contributes in greater proportion to endogenous compared with exogenous insulin  
373 clearance, this may explain why the MCRI does not reflect endogenous insulin clearance in the  
374 black African men. These finding have implications for the use of MCRI as a measure of  
375 insulin clearance in black ethnic groups.

376

377 The strengths of this study include the well-matched ethnic groups and the use of rigorous,  
378 gold-standard methods of metabolic analysis. Unlike some previous ethnic comparison studies  
379 [48], the subject groups were tightly characterised; of single sex with metabolic status  
380 confirmed by OGTT.

381

382 In terms of limitations, the study is cross-sectional and is only able to recognise the presence  
383 or absence of associations, between hepatic fat, insulin sensitivity and insulin clearance. Only  
384 longitudinal measures would be able to determine the true dynamics of these mechanisms and  
385 determine causality. The measure of average endogenous insulin clearance does not enable  
386 differentiation between hepatic and extra-hepatic insulin clearance, although it has been shown  
387 that approximately 80% of endogenous insulin is cleared by the liver [1]. Furthermore, the  
388 influence of gut-modulated insulin secretion and clearance was not assessed. There is evidence  
389 that the incretin hormones reduce post-prandial insulin clearance [61-63] and ethnic differences  
390 in incretin hormones have been recognised [33, 64, 65], albeit the data are inconsistent.  
391 However, it is not clear whether incretins contribute to ethnic differences in insulin clearance,  
392 which would be an important line of enquiry for future investigations. We also acknowledge  
393 that the failure to find an association between IHL and insulin clearance in the BA men does  
394 not mean that an association does not exist. Our sample size is comparable with other studies  
395 in the literature, but we may not be powered to reliably detect such associations. While the  
396 narrow range in IHL among our black participants also may have hindered our ability to detect

397 a linear correlation between IHL and insulin clearance, the range in IHL that we observed is  
398 reflective of IHL in black populations, as reported in a large epidemiological study [66] . In  
399 data we have previously reported from an obese diabetic population [25], we did find a trend  
400 to an inverse relationship between insulin clearance and intrahepatic lipid in the BA  
401 participants, suggesting that there may be a threshold mechanism at play and that IHL may not  
402 have a significant role in the determination of insulin clearance until higher levels of  
403 accumulation have occurred.

404

405 The study comprises male subjects only and therefore may not be generalisable to women;  
406 however, as the majority of the work in this area has been carried out in African ancestry  
407 females [48], this cohort offers a valuable addition to the field.

408

409 In conclusion, this study demonstrates low insulin clearance in black African men despite lower  
410 hepatic fat and similar whole-body and hepatic insulin sensitivity to their white European  
411 counterparts. It is increasingly recognised that type 2 diabetes is a heterogenous disease, where  
412 different aetiological components may have an impact on progression rates and choice of  
413 therapeutic strategy [67]. Ethnic disparities in treatment response have already been  
414 recognised [68] and may be explained, at least in part, by inherent physiological variations. In  
415 healthy black African men, the lack of association of endogenous insulin clearance with either  
416 intrahepatic lipid or insulin sensitivity supports the hypothesis that low insulin clearance is a  
417 primary phenomenon in this ethnic group. Such a phenomenon warrants further exploration,  
418 as it may offer novel therapeutic targets for the treatment and prevention of diabetes. Both the  
419 determinants of low insulin clearance and its role in the high risk of metabolic dysfunction in  
420 African ethnic populations remain to be elucidated.

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## **Statement of Data Availability**

Data are available from the authors (LMG) on request.

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## **Contribution statement**

L.M.G. formulated the research question and designed the study, supervised data collection and interpretation. S.A.A. formulated the research question and designed the study. J.L.P. formulated the research question, designed the study, and provided statistical advice. A.M.U. formulated the research question and designed the study. RCB supervised modelling analysis and contributed to the interpretation. O.B. supervised data collection, performed the metabolic assessments and undertook data analysis. FSM supervised data collection and undertook data analysis. MS performed metabolic assessments and contributed to the interpretation. M.L. supervised data collection, performed the metabolic assessments, undertook data analysis and interpretation and drafted the manuscript. O.H. undertook MRI data analysis. G.C.E. coordinated MRI data acquisition. LB undertook modelling analysis. All authors contributed to the intellectual content and reviewed the final version of the submitted manuscript.

LMG is the guarantor of this work, had full access to all the data and takes full responsibility for the integrity of the data and the accuracy of data analysis

## **Conflict of interest statement**

SAA has served on advisory boards for NovoNordisk, Medtronic and Roche. The other authors declare no conflict of interest.

## Legends

**Table 1:** Clinical characteristics of study participants.

**Table 2:** Metabolic parameters of insulin secretion and insulin clearance

### Figure 1

**a:** Plasma insulin response by ethnic group during the hyperglycaemic clamp.

**b:** Plasma C-peptide response by ethnic group during the hyperglycaemic clamp.

### Figure 2

**a:** Associations between endogenous insulin clearance and whole-body insulin sensitivity (M value).

**b:** Associations between endogenous insulin clearance and whole-body insulin sensitivity (M/I).

**c:** Associations between endogenous insulin clearance and hepatic insulin sensitivity (% suppression EGP)

**d:** Associations between average endogenous insulin clearance and MCRI

**e.** Associations between endogenous insulin clearance and intrahepatic lipid (IHL)

422 **Table 1: Clinical characteristics of study participants.**  
 423

	<i>BA (n=23)</i>	<i>WE (n=23)</i>	<i>p value</i>
<i>Age (years)</i>	30.7 (12.0)	35.9 (13.9)	0.18
<i>Weight (kg)</i>	84.1 (14.6)	86.5 (16.5)	0.60
<i>BMI (kg m<sup>-2</sup>)</i>	26.7 (3.6)	26.5 (4.6)	0.86
<i>Waist circumference (cm)</i>	87.5 (9.3)	93.8 (14.6)	0.09
<i>Fasting glucose (mmol L<sup>-1</sup>)</i>	5.25 (0.4)	5.20 (0.4)	0.51
<i>HbA<sub>1c</sub> IFCC (mmol/mol)</i>	37.0 (5.3)	35.9 (2.9)	0.37
<i>HbA<sub>1c</sub> DCCT (%)</i>	5.54 (0.48)	5.44 (0.24)	0.38
<i>Systolic blood pressure (mmHg)</i>	123.1 (12.3)	121.9 (9.1)	0.70
<i>Diastolic blood pressure (mmHg)</i>	70.7 (11.5)	71.1 (8.2)	0.88
<i>LDL-cholesterol (mmol L<sup>-1</sup>)</i>	2.66 (0.87)	2.99 (0.82)	0.19
<i>HDL-cholesterol (mmol L<sup>-1</sup>)</i>	1.30 (0.42)	1.27 (0.31)	0.75
<i>Total cholesterol (mmol L<sup>-1</sup>)</i>	4.27 (1.06)	4.76 (1.05)	0.13
<i>Triglycerides (mmol L<sup>-1</sup>)</i>	0.68 (0.25)	1.10 (0.56)	0.003

424 Data presented as mean (SD). Differences between the two ethnic groups determined using independent sample  
 425 Student's *t* test. Fasting glucose values taken at screening visit. Abbreviations: BA black African; DCCT  
 426 Diabetes Control and Complications Trial; HbA<sub>1c</sub> glycated haemoglobin; HDL high density lipoprotein; IFCC  
 427 International Federation of Clinical Chemistry; LDL low density lipoprotein; WE white European.  
 428

**Table 2: Metabolic parameters of insulin secretion and insulin clearance**

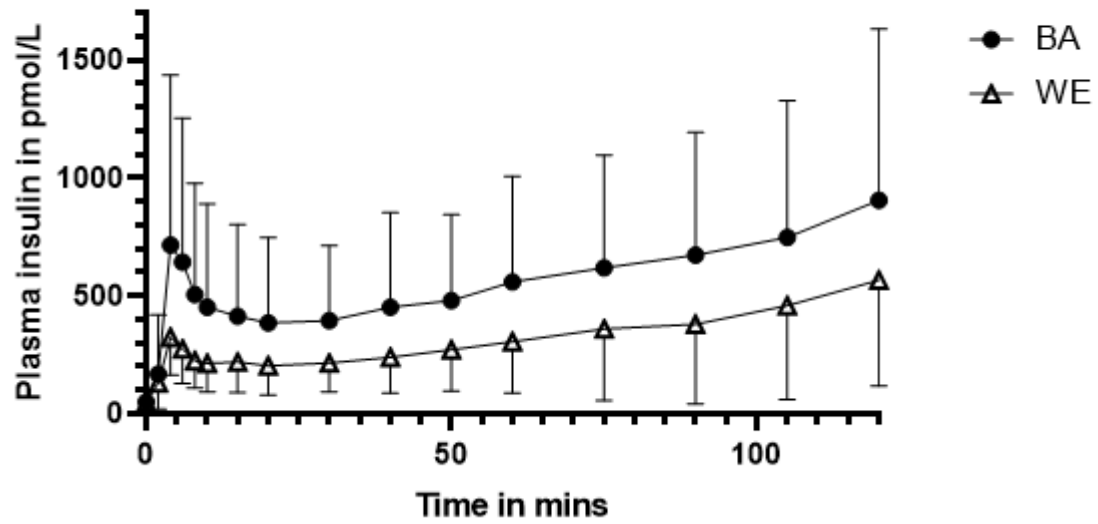
	BA (n=23)	WE (n=23)	Mean difference or ratio of geometric mean (95% CI)	p value
<b>Fasting plasma glucose</b> (mmol L <sup>-1</sup> )	5.26 (0.35)	5.19 (0.32)	-0.07 (-0.28, 0.13)	0.460
<b>Fasting plasma C-peptide</b> (nmol L <sup>-1</sup> ) <sup>†</sup>	0.54 (0.47, 0.62)	0.61 (0.50, 0.76)	1.14 (0.89, 1.47)	0.281
<b>Fasting plasma insulin</b> (pmol L <sup>-1</sup> ) <sup>†</sup>	46.2 (38.6, 55.3)	39.4 (30.2, 51.6)	0.85 (0.62, 1.17)	0.314
<b>iAUC<sub>c-pep</sub> 0-10 mins</b> <sup>†</sup> (nmol L <sup>-1</sup> x min)	8.45 (6.17, 11.6)	6.88 (5.83, 8.3)	0.81 (0.58, 1.15)	0.240
<b>iAUC<sub>c-pep</sub> 10-120 mins</b> (nmol L <sup>-1</sup> x min)	242.1 (109.9)	213.2 (60.4)	-28.9 (-82.0, 24.3)	0.277
<b>iAUC<sub>ins</sub> 0-10 mins</b> <sup>†</sup> (pmol L <sup>-1</sup> x min)	2.46 (1.85, 3.28) x10 <sup>3</sup>	1.75 (1.5, 2.1) x10 <sup>3</sup>	0.71 (0.51, 0.98)	0.040
<b>iAUC<sub>ins</sub> 10-120 mins</b> <sup>†</sup> (pmol L <sup>-1</sup> x min)	48.1 (35.5, 65.2) x10 <sup>3</sup>	29.9 (23.3, 38.4) x10 <sup>3</sup>	0.62 (0.42, 0.91)	0.017
<b>AUC<sub>ISR</sub> over 120 mins</b> (pmol m <sup>-2</sup> BSA x min)	58.9 (24.0) x10 <sup>3</sup>	54.4 (16.9) x10 <sup>3</sup>	-4.50 (-17.1, 8.14)	0.477
<b>σ<sup>1</sup></b> <sup>†</sup> (pmol m <sup>-2</sup> BSA)/ (mmol L <sup>-1</sup> min <sup>-1</sup> )	692.9 (505.9, 948.9)	550.5 (464.9, 651.8)	0.80 (0.56, 1.13)	0.190
<b>σ<sup>2</sup></b> (pmol min <sup>-1</sup> m <sup>2</sup> BSA)/ (mmol L <sup>-1</sup> )	49.8 (20.1)	47.1 (18.8)	-2.67 (-14.4, 9.07)	0.649
<b>Average (endogenous) insulin clearance</b> (mL m <sup>-2</sup> BSA min <sup>-1</sup> )	771.6 (227.8)	1381 (534.3)	609.5 (349.5, 869.6)	<0.001
<b>MCRI</b> (mL m <sup>-2</sup> BSA min <sup>-1</sup> )	482.8 (70.6)	530.7 (78.7)	47.9 (1.6, 94.3)	0.043
<b>Basal EGP</b> (μmol kg <sup>-1</sup> FFM min <sup>-1</sup> )	4.69 (2.39)	4.04 (2.29)	-0.65 (-2.13, 0.83)	0.377
<b>% suppression EGP</b> <sup>‡</sup>	65.7 (16.1)	69.8 (17.7)	4.15 (-6.5, 14.8)	0.437
<b>% IHL</b> <sup>§</sup>	3.78 (1.13)	6.08 (5.04)	2.29 (0.06, 4.52)	0.044
<b>M value</b> <sup>‡</sup> mg kg <sup>-1</sup> FFM min <sup>-1</sup>	9.65 (2.32)	9.51 (3.86)	-0.14 (-2.08, 1.81)	0.89
<b>M/I</b> <sup>‡</sup> (mg kg <sup>-1</sup> FFM min <sup>-1</sup> )/ (pmol L <sup>-1</sup> )	0.0171 (0.0059)	0.0189 (0.0094)	0.00184 (-0.0030, 0.0066)	0.44

Data presented as mean (SD) or geometric mean (95% CI) for log transformed data (†). Differences between the two ethnic groups were determined using independent samples t-tests. Fasting plasma glucose levels from hyperglycaemic clamp visit. ‡ Previously reported data [26] § Previously reported data [30]

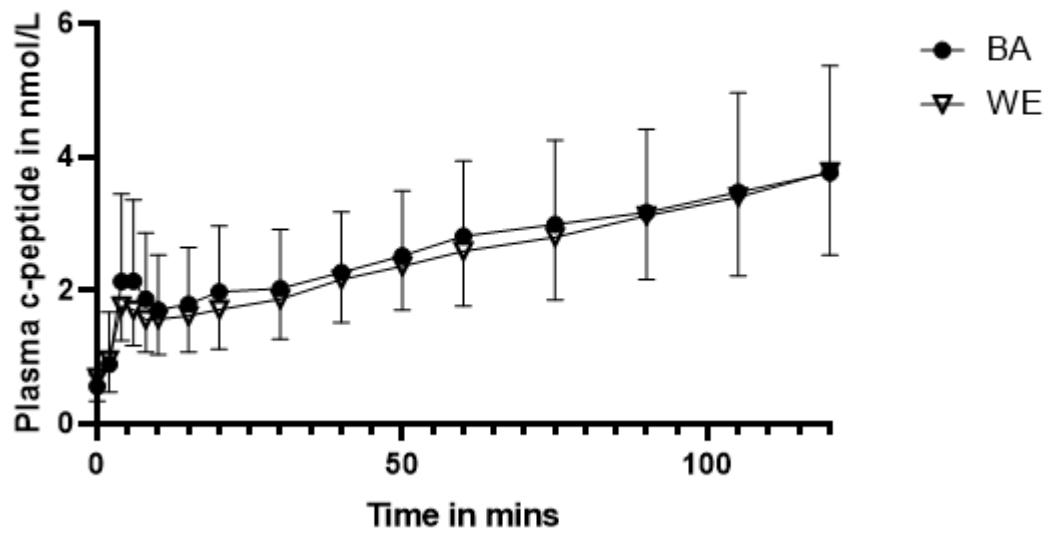
Abbreviations: BA, black African; BSA: Body surface area; EGP, Endogenous glucose production; FFM, Fat free mass. IHL, Intrahepatic lipid; WE, white European; iAUC, incremental area under the curve; AUC(ISR), area under the curve of insulin secretion rate over 120 minutes; MCRI, metabolic clearance rate of insulin.



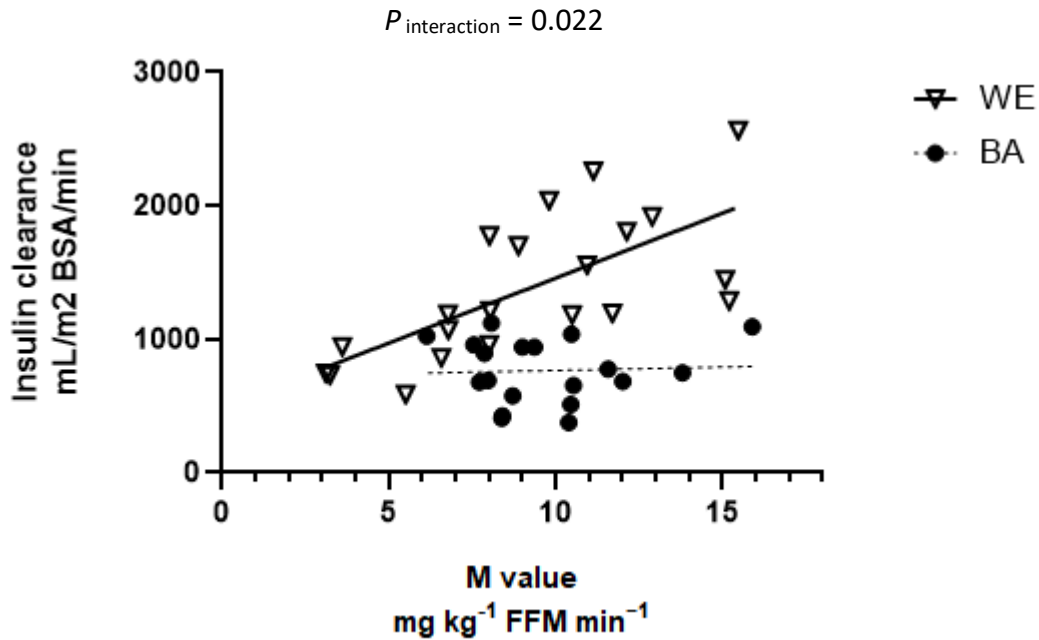
**Figure 1a:** Plasma insulin response by ethnic group during the hyperglycaemic clamp. BA = black African, WE = white European. Data shown are mean and SD.



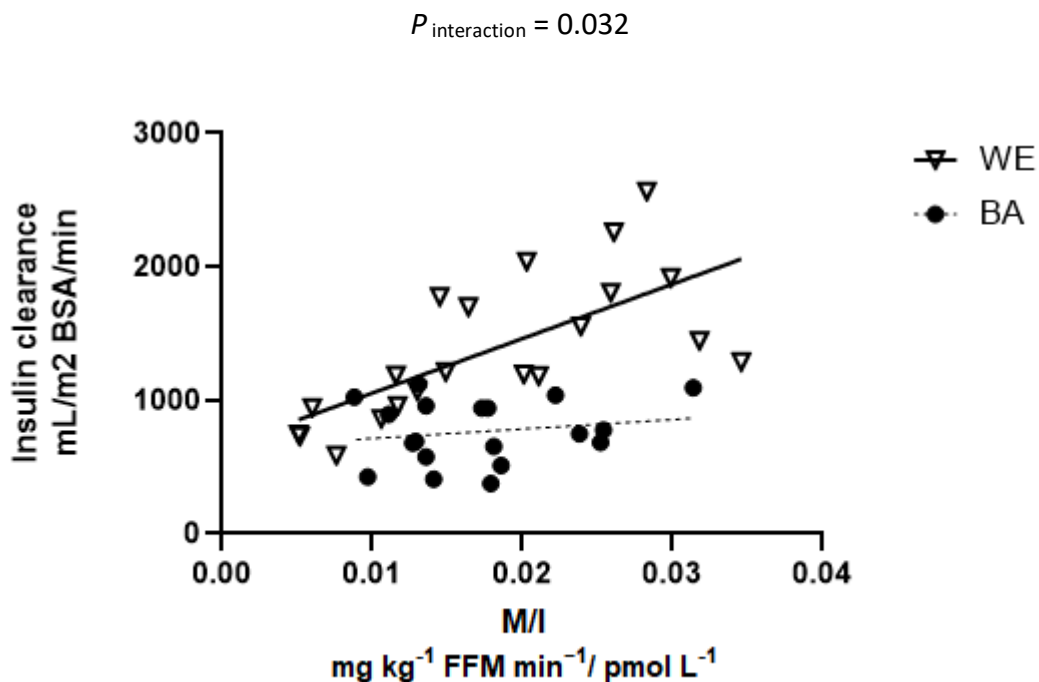
**Figure 1b:** Plasma C-peptide response by ethnic group during the hyperglycaemic clamp. BA = black African, WE = white European. Data shown are mean and SD.



**Figure 2a:** Associations between average insulin clearance and whole-body insulin sensitivity (M value) in white European (WE) and black African (BA) men. Data presented using the Pearson correlation coefficient: BA:  $r=0.051$ ,  $p=0.837$ ; WE:  $r=0.691$ ,  $p=0.001$ . Interaction by ethnicity was assessed using linear multiple regression. FFM, fat free mass.

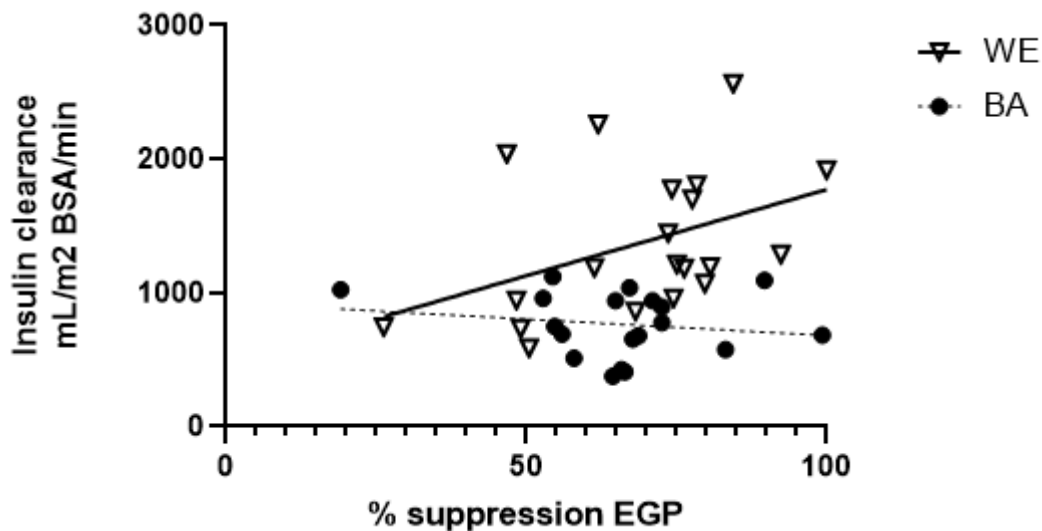


**Figure 2b:** Associations between average insulin clearance and whole-body insulin sensitivity (M/I) in white European (WE) and black African (BA) men. Data presented using the Pearson correlation coefficient: BA:  $r=0.179$ ,  $p=0.464$ ; WE:  $r=0.697$ ,  $p<0.001$ . Interaction by ethnicity was assessed using linear multiple regression.



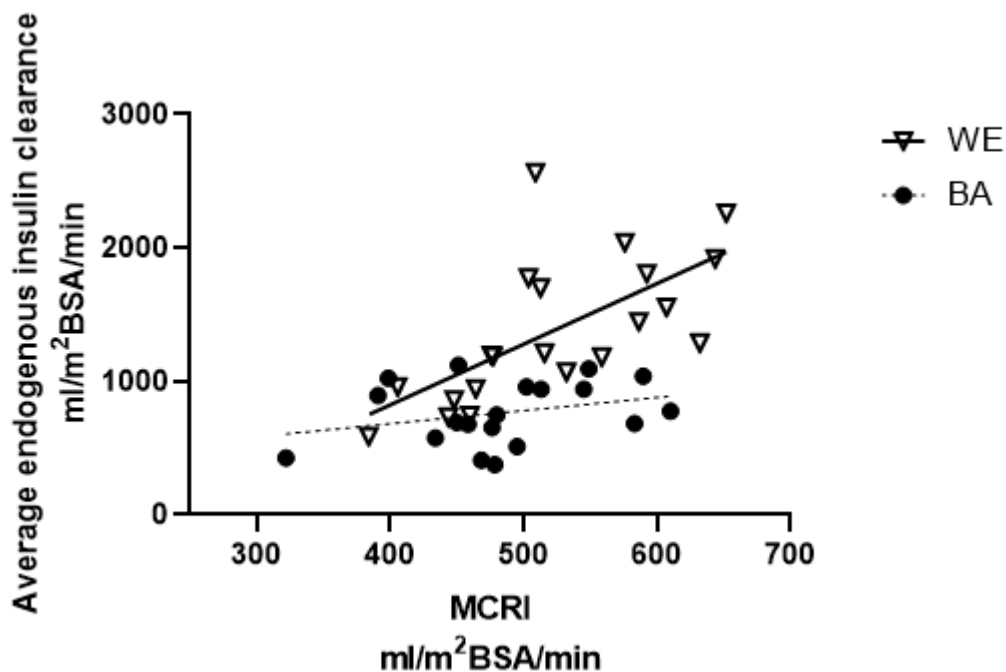
**Figure 2c:** Associations between average insulin clearance and hepatic insulin sensitivity (% suppression EGP) in white European (WE) and black African (BA) men. Data presented using the Pearson correlation coefficient: BA:  $r = -0.169$ ,  $p = 0.488$ ; WE:  $r = 0.417$ ,  $p = 0.068$ . Interaction by ethnicity was assessed using linear multiple regression.

$$P_{\text{interaction}} = 0.057$$

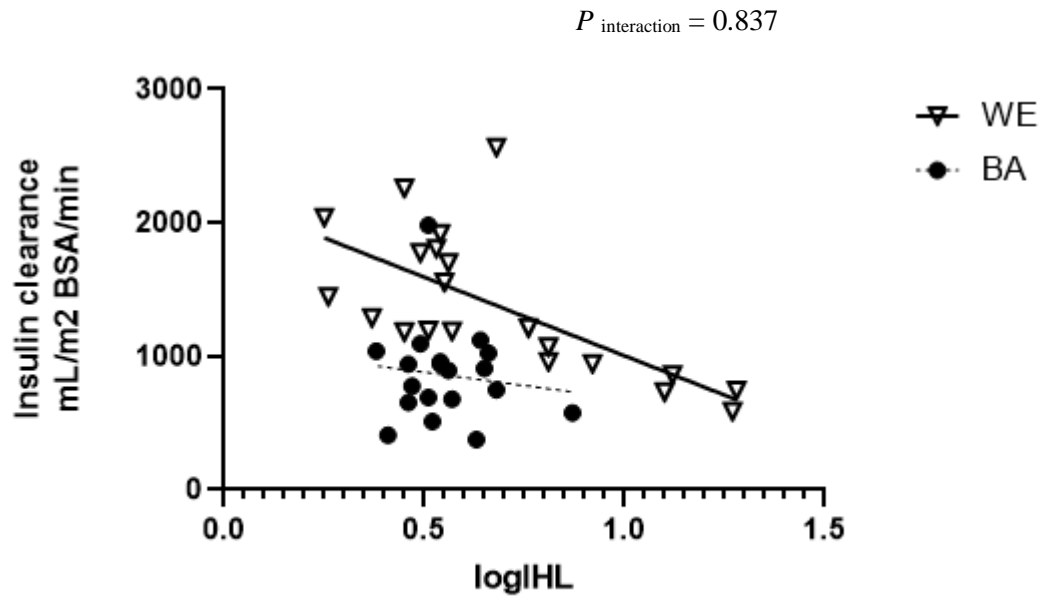


**Figure 2d:** Associations between average endogenous insulin clearance (measured during hyperglycaemic clamp) and metabolic clearance rate of (exogenous) insulin (MCRI, measured during hyperinsulinaemic-euglycaemic clamp) in white European (WE) and black African (BA) men. Data presented using the Pearson correlation coefficient:  $r = 0.298$ ,  $p = 0.215$ ; WE:  $r = 0.661$ ,  $p = 0.001$ . Interaction by ethnicity was assessed using linear multiple regression.

$$P_{\text{interaction}} = 0.021$$



**Figure 2e:** Associations between average insulin clearance and intrahepatic lipid (IHL) in white European (WE) and black African (BA) men. Data presented using the Pearson correlation coefficient: BA:  $r = -0.134$ ,  $p = 0.584$ ; WE:  $r = -0.674$ ,  $p = 0.001$ . Interaction by ethnicity was assessed using linear multiple regression.



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