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1 **Ethnic differences in intrahepatic lipid and its association with hepatic insulin sensitivity**
2 **and insulin clearance between men of Black and White ethnicity with early type 2**
3 **diabetes**

4
5 **Short title: Ethnicity, hepatic fat and type 2 diabetes**
6

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31 **ABSTRACT**

32 Intrahepatic lipid (IHL) is linked with reduced hepatic insulin sensitivity and insulin clearance.
33 Despite their high risk for type 2 diabetes (T2D), there have been limited investigations of these
34 relationships in Black populations. We investigated these relationships in 18 White European
35 (WE) and 18 Black West African (BWA) men with T2D <5 years. They underwent magnetic
36 resonance imaging to quantify IHL, a hyperinsulinemic-euglycemic clamp with [6,6 ²H₂]
37 glucose infusion to assess hepatic insulin sensitivity and a hyperglycemic clamp to assess
38 insulin clearance. BWA men had lower IHL than WE men (3.7 (5.3) vs 6.6 (10.6) %, *p*=0.03).
39 IHL was inversely associated with basal hepatic insulin sensitivity in WE but not BWA men
40 (BWA: *r*=-0.01, *P*=0.96; WE: *r*=-0.72, *P*=0.006) with a significant interaction by ethnicity
41 (*P*_{interaction}=0.05), however, IHL was not associated with % suppression of endogenous glucose
42 production by insulin in either ethnicity. IHL showed a trend to an association with insulin
43 clearance in BWA only (BWA: *r*=-0.42, *P*=0.09; WE: *r*=-0.14, *P*=0.58). The lack of association
44 between IHL and hepatic insulin sensitivity in BWA men indicates IHL may play a lesser
45 detrimental role in T2D in BWA men.

46

47 **KEY WORDS:** Ethnicity, hepatic fat, insulin sensitivity, insulin clearance, African,
48 lipotoxicity

49 **ABBREVIATIONS**

50 ALT: Alanine aminotransferase

51 BSA: Body surface area

52 BWA: Black West African

53 HbA1C: Glycated hemoglobin

54 IHL: Intrahepatic lipids

55 MRI: Magnetic resonance imaging

56 SAT: Subcutaneous adipose tissue

57 VAT: Visceral adipose tissue

58 WE: White European

59 **INTRODUCTION**

60 Black populations are disproportionately affected by type 2 diabetes (T2D) with 2-3 times
61 greater prevalence compared to white populations¹ despite typically having lower intrahepatic
62 lipids (IHL) and visceral adipose tissue (VAT)^{1,2}. IHL is usually elevated in individuals with
63 T2D and is inversely associated with both hepatic insulin sensitivity and insulin clearance³.
64 Consistently, insulin clearance has been shown to be lower in Black populations compared to
65 White populations⁴. However, investigations of ethnic differences in hepatic insulin sensitivity
66 have shown inconsistent findings⁵⁻⁷. We have previously reported similar hepatic insulin
67 sensitivity but lower insulin clearance in Black West African (BWA) compared to White
68 European (WE) men^{8,9}. Despite the literature reporting ethnic differences in IHL, hepatic
69 insulin sensitivity, and insulin clearance between Black and White populations, these have not
70 previously been investigated in a single study to understand their relationships and how
71 ethnicity impacts on these in the development of T2D in Black populations. Therefore, our aim
72 was to investigate ethnic differences in IHL and its relationship with hepatic insulin sensitivity
73 and insulin clearance in BWA and WE men with early T2D.

74 **METHODS**

75 This investigation was conducted as part of the South London Diabetes and Ethnicity
76 Phenotyping study (Soul-Deep)¹⁰. Data on metabolic parameters for 92% of the present cohort
77 have been previously reported^{8,9}, the present analyses relate to the whole cohort in whom
78 relevant data were available. Participant recruitment and data collection took place April 2013
79 to January 2015. The study was approved by the London Bridge National Research Ethics
80 Committee (12/LO/1859); all participants provided written informed consent.

81 **Participants**

82 Participants were recruited from primary care practices in London and deemed eligible to
83 participate if they were 1) 18-65 years old, 2) BMI of 25-40 kg/m², 3) self-reported WE or
84 BWA ethnicity, 4) diagnosis of T2D (less than 5 years), and 5) treated with lifestyle and/or
85 metformin only. Further details of eligibility criteria are published in the protocol¹⁰.
86 Participants attended all assessments after an overnight fast. If on metformin, participants were
87 instructed to cease taking it for 7-days prior to each visit. Physical activity was measured as
88 hours per day of moderate intensity activity using accelerometry watches worn for 4
89 consecutive days (MotionWatch 8.0, CamTech).

90 **Magnetic Resonance Imaging**

91 A Dixon-based MRI sequence was used on a 1.5 Tesla Siemens scanner to obtain images for
92 the quantification of IHL and VAT. Participants were scanned lying supine on a spine RF coil
93 with body phased array RF coils placed over the chest, abdomen and pelvis. While abdominal
94 images were acquired participants were instructed to complete three 17-second breath-holds.
95 From each participant, contiguous, axial T1-weighted gradient-echo images (repetition time:
96 6.77ms; echo times: 4.77ms (in-phase), 2.39ms (out-of-phase), flip angle: 10°) each with a
97 slice thickness of 3mm were acquired, from which water and fat images were produced. Images
98 were analyzed using HOROS v1.1.7 (www.horosproject.org; accessed 21/10/2017). IHL was

99 measured by selecting two abdominal MRI images representing the superior and inferior parts
100 of the liver. Four circular regions of interest (ROIs) in identical positions were placed within
101 the liver tissue of each pair of water and fat images (supplementary material, Figure 1). ROIs
102 were positioned to include the posterior, anterior, medial and lateral sections of the liver. ROI
103 areas ranged from 20 to 30cm², intending to cover as large an area of liver as possible while
104 avoiding blood vessels, bile ducts and artefacts. Using the formula: %IHL = (F/(F+W))*100,
105 where F is the pixel signal intensity of the fat image and W is the pixel signal intensity of the
106 water image, the hepatic fat fraction was calculated in each ROI and IHL was calculated as the
107 mean of all 8 ROIs. Total abdominal VAT and body SAT (neck to knee, excluding arms) was
108 determined using an automated MRI analysis technique (Klarismo Ltd., London, UK) as
109 previously described¹¹.

110 **Clamp assessments**

111 Whole-body insulin sensitivity (M-value) during the high dose insulin infusion (40 mU m⁻²
112 BSA min⁻¹), hepatic insulin sensitivity (% suppression of endogenous glucose production
113 (EGP) during the low dose insulin infusion (10 mU m⁻² BSA min⁻¹) and basal hepatic insulin
114 sensitivity index) were measured using a two-step hyperinsulinemic-euglycemic clamp with
115 the infusion of [6,6 ²H₂] glucose, according to previously described methodology⁹. The basal
116 hepatic insulin sensitivity index was calculated as the reciprocal of the product of basal EGP
117 rate (mmol/BSA min⁻¹) and fasting insulin concentration (pmol/l). To assess and model insulin
118 clearance, each participant underwent a hyperglycemic clamp, described in detail elsewhere⁸.

119 **Statistical analysis**

120 Ethnic differences were determined using independent samples t-test for normally distributed
121 variables or a Mann-Whitney test for variables that could not be log transformed to normal.
122 ANCOVA was used, with VAT, BMI and age as separate covariates, to investigate ethnic
123 differences in IHL and VAT. Correlations were assessed using Pearson's correlation; partial

124 correlation was used to investigate associations while adjusting for VAT, BMI and age.
125 Significance of an interaction by ethnicity was assessed using multiple regression with
126 ethnicity*logIHL used as an interaction term. Analyses were conducted with SPSS version
127 25.0; $P \leq 0.05$ were considered statistically significant.

128 **RESULTS**

129 **Participant characteristics**

130 The 18 BWA and 18 WE men were well-matched for age and BMI, Table 1. The BWA men
131 had significantly lower IHL and total VAT mass, Table 1 (Figure 2, supplementary data). After
132 adjustment for BMI, the ethnic differences in VAT remained significant ($P=0.008$) but not for
133 IHL ($P=0.18$). After adjustment for VAT, there were no ethnic differences in IHL (WE: 6.07
134 (SE 1.16) vs BWA: 5.56 (SE 1.16) %, $P=0.70$). Non-alcoholic fatty liver disease, defined as
135 liver fat above 5% determined by Dixon-MRI¹², was present in 33% of BWA men compared
136 to 67% of WE men ($P=0.047$).

137 **Metabolic characteristics**

138 There were no ethnic differences in whole-body insulin sensitivity (M-value) or hepatic insulin
139 sensitivity, expressed as % suppression of EGP during the low dose insulin infusion, Table 1;
140 consistent with earlier findings we reported from a smaller sample from this cohort⁹. However,
141 there was a trend towards higher basal hepatic insulin sensitivity index in the BWA men, Table
142 1. Insulin clearance was not different between the BWA and WE men (Table 1), again
143 consistent with our earlier report⁸.

144 **Relationships between IHL and insulin sensitivity**

145 Relationships between IHL and the measures of insulin sensitivity are presented in Figure 1
146 (A, B and C). The inverse associations between IHL and both whole-body insulin sensitivity
147 (M-value) and basal hepatic insulin sensitivity reached statistical significance in only the WE
148 men. In multiple regression analysis a significant ethnicity interaction was found in the
149 relationship between IHL and basal hepatic insulin sensitivity ($P_{\text{interaction}}=0.05$); no other
150 significant ethnicity interactions were found. There were no changes in the associations after
151 adjustment for VAT, BMI or age except for the relationship between IHL and M-value which
152 reduced in significance in WE men after adjustment for BMI ($P=0.13$) (supplementary data).

153 **Relationships between IHL and insulin clearance**

154 Relationships between IHL and insulin clearance, are presented in Figure 1 (D). IHL was
155 inversely associated with insulin clearance, which neared significance, in BWA but not WE
156 men; partial correlation adjusting for VAT reduced the significance of this relationship (BWA:
157 $r=-0.41$, $P=0.11$; WE: $r=-0.29$, $P=0.27$); no significant ethnicity interaction was found
158 ($P_{\text{interaction}}=0.40$).

159 CONCLUSIONS

160 In this study of White European and Black West African men with early T2D, we investigated
161 ethnic differences in hepatic fat and its relationship with hepatic insulin sensitivity and insulin
162 clearance. Consistent with published data¹³, BWA men had lower IHL and VAT. We found
163 additional ethnic differences in relationships between IHL and hepatic insulin sensitivity and
164 insulin clearance whereby in WE men, IHL was inversely related to basal hepatic insulin
165 sensitivity and whole-body insulin sensitivity, which was not the case in BWA men. In BWA
166 men we found a trend towards an inverse relationship between IHL and insulin clearance which
167 was not found in the WE men. Our findings suggest that IHL is implicated in the metabolic
168 derangements of the liver in T2D differently according to ethnicity. To our knowledge, this is
169 the first study to investigate relationships between IHL and insulin clearance in a Black
170 population; the trend towards an inverse relationship in BWA but not WE men suggests that
171 the reduction of insulin clearance may be modulated differently depending on ethnicity.

172 Despite relationships between IHL and whole-body insulin resistance being commonly
173 reported, the mechanisms that link the two are less understood. Current investigations show an
174 excess of liver fat leads to accumulation of lipid intermediates causing hepatic mitochondrial
175 dysfunction, inflammation and increased VLDL-TAG production which may result in hepatic
176 and systemic insulin resistance¹⁴. Our finding of IHL being inversely associated with basal
177 hepatic insulin sensitivity and whole-body insulin sensitivity which reached significance in
178 WE but not BWA men may indicate the above detrimental effects of lipid intermediates
179 occurring to a greater extent in WE men.

180 There was no relationship between IHL and suppression of EGP in either ethnic group. This
181 could indicate a decreased effect of IHL on hepatic insulin sensitivity in the insulin stimulated
182 state compared to the basal state in WE men. To our knowledge only one other study has
183 investigated the relationship between IHL and hepatic insulin sensitivity using the

184 hyperinsulinemic-euglycemic clamp with infusion of isotopically labelled glucose⁶; they found
185 that IHL was associated with hepatic insulin sensitivity in obese Black South African women
186 but not in obese White South African women, which contradicts our findings. There are several
187 potential explanations for this, such as glycemic state; our study included participants with
188 T2D whereas the South African women were normal glucose tolerant. The disparities may also
189 be due to gender differences as there is consistent evidence demonstrating that the phenotype
190 of T2D differs by gender within populations of African descent¹⁵.

191 The presence of NAFLD was comparable to that reported in other large multi-ethnic cohorts¹⁶
192 and was significantly lower in the BWA men. One of the main theories that explains how IHL
193 accumulates is the “portal theory”, which states that excess VAT releases free fatty acids
194 directly into the portal vein, subsequently depositing as IHL¹⁷. Our study may support the portal
195 theory as after adjustment for VAT, IHL no longer differed by ethnicity, suggesting that the
196 lower IHL in BWA men may be driven by lower VAT. Indeed, ethnic differences in the
197 mechanisms of SAT expansion may explain the differences we found in VAT as others have
198 suggested¹⁸; however, we did not directly measure adipogenesis in our study which may be an
199 implication for further research.

200 The strengths of this study include the use of the rigorous hyperinsulinemic-euglycemic clamp
201 method combined with the infusion of [6,6 ²H₂] glucose to determine both whole-body and
202 hepatic insulin sensitivity. However, our study is not without its limitations. Our sample size
203 is relatively small; in these secondary analyses we may not have sufficient power to reliably
204 detect ethnic differences. Our measurement of insulin clearance does not differentiate hepatic
205 from extrahepatic insulin clearance, rather it is a measure of whole-body insulin clearance.
206 However, it has been shown that approximately 80% of endogenous insulin is degraded in the
207 liver³. Our WE men had greater statin use which may have resulted in lower hepatic fat
208 accumulation and reduced the ethnic discrepancies due to the lipid lowering effects of statins.

209 Another limitation is studying only men with T2D, however previous studies have mostly
210 focused on women, due to the greater prevalence of T2D in Black women compared to men.
211 Our study redresses this.

212 In conclusion, our study demonstrates ethnic differences in the relationships between IHL and
213 metabolic parameters of the liver. The lack of inverse association between IHL and basal
214 hepatic insulin sensitivity in the BWA men, found in the WE men, suggests that fasting hepatic
215 insulin resistance occurs independently of IHL in BWA men. However, the reduction of insulin
216 clearance may be influenced by IHL more so in Black men with T2D compared to White men.

217 **Author contributions**

218 L.M.G. formulated the research question and designed the study, supervised data collection
219 and interpretation, and performed the minimal modelling analysis. S.A.A. formulated the
220 research question and designed the study, supervised data collection and interpretation. J.L.P.
221 formulated the research question, designed the study, and provided statistical advice. A.M.U.
222 formulated the research question and designed the study. K.G.M.M.A. supervised data
223 collection and interpretation. C.M. coordinated the study and data acquisition, and performed
224 the metabolic assessments. T.B. undertook data acquisition and analysis. G.C.E. coordinated
225 MRI data acquisition. B.W. and H.S. undertook MRI data analysis. F.S. and N.J. undertook
226 data acquisition. R.B. and L.B. performed the modelling analysis. O.H. undertook data
227 analysis, statistical analysis and drafted the manuscript. All authors contributed to the
228 intellectual content and reviewed the final version of the submitted manuscript.

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247 Louise Goff is the guarantor of this work, had full access to all the data, and takes full
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252 **Duality of interests:** The authors declare that there is no duality associated with this
253 manuscript.

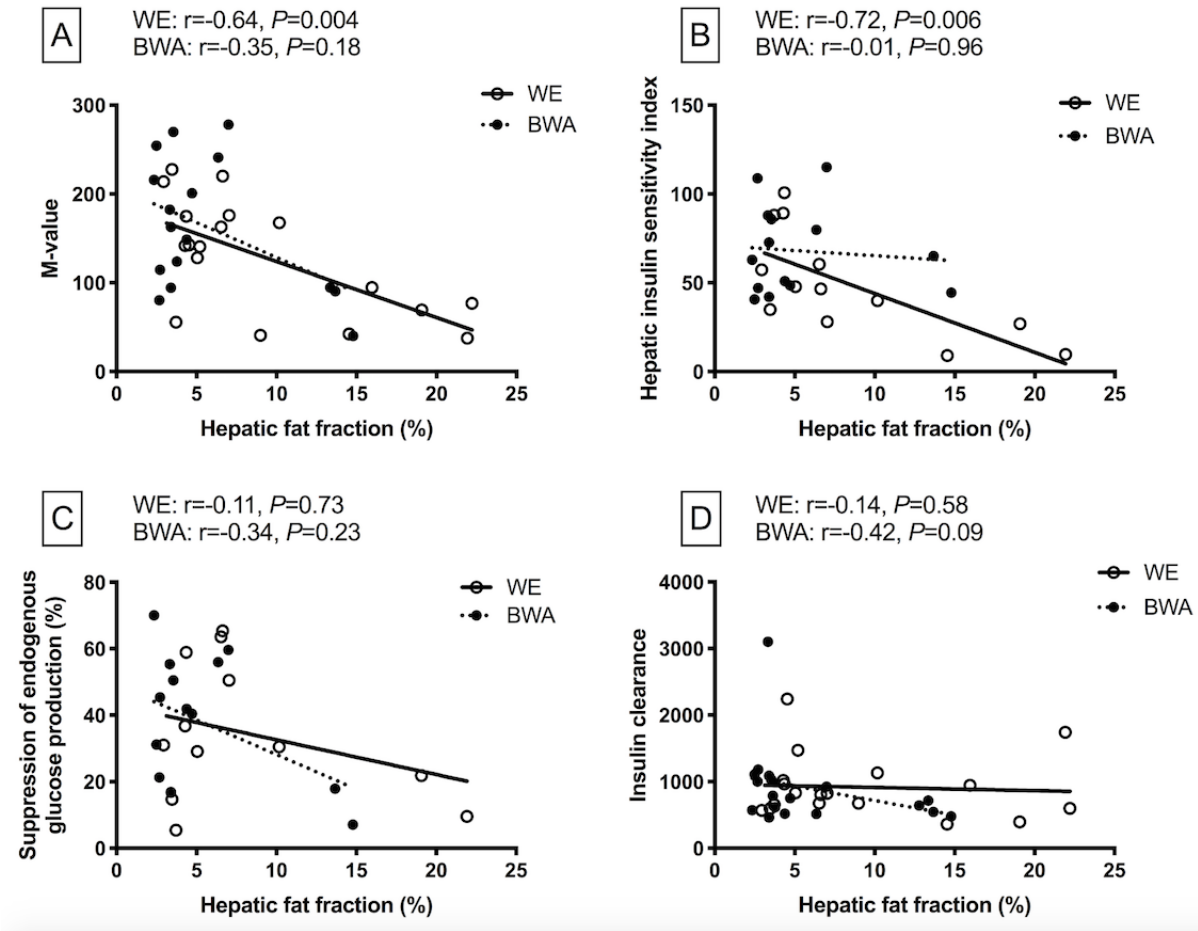
254 **Table 1: Clinical and metabolic characteristics of Black West African and White**
 255 **European men**

	BWA (n=18)	WE (n=18)	P
Age (years)†	54.9 (9.3)	58.5 (6.3)	0.67
Weight (kg)	92.3 ± 12.3	99.8 ± 16.7	0.14
BMI (kg/m ²)	29.8 ± 3.5	31.5 ± 4.1	0.18
Waist circumference (cm)	104.9 ± 10.2	111.9 ± 13.0	0.08
SAT (neck to knee) (kg)‡	12.6 (10.5-15.2)	14.6 (12.2-17.6)	0.24
VAT, total (kg) ^a	3.99 ± 1.54	6.09 ± 2.46	0.006
IHL (%)†	3.7 (5.3)	6.6 (10.6)	0.03
Diabetes duration (years)†	3.0 (2.2)	3.0 (1.3)	0.42
Statin use§	10/18	16/18	0.026
Fasting glucose (mmol/l)	6.63 ± 0.67	6.88 ± 1.38	0.50
HbA1c (%)	6.67 ± 0.68	6.64 ± 0.70	0.90
ALT‡ (IU/l)	26.7 (21.8-32.5)	31.2 (25.7-37.7)	0.24
Systolic BP (mm Hg)	136.7 ± 13.8	130.9 ± 14.2	0.22
Diastolic BP (mm Hg)†	89.0 (8.7)	83.0 (12.5)	0.06
Total cholesterol (mmol/l)	4.11 ± 0.73	4.27 ± 0.70	0.50
LDL-cholesterol (mmol/l)	2.32 ± 0.56	2.28 ± 0.66	0.85
HDL-cholesterol (mmol/l)	1.18 ± 0.38	1.19 ± 0.25	0.92
Triglyceride (mmol/l)†	1.05 (0.70)	1.60 (1.25)	0.03
Moderate activity time (hours/day) ^c	2.1 ± 0.66	1.9 ± 0.90	0.74
Metabolic characteristics			
M value (mg/m ² BSA min ⁻¹) ^d	162.0 ± 75.0	128.5 ± 63.7	0.17
Hepatic basal insulin sensitivity index ((mmol/m ² BSA min pmol l) ⁻¹) ^e	68.0 ± 24.6	49.1 ± 29.4	0.09
Suppression of endogenous glucose production (%) ^e	37.9 ± 19.5	34.7 ± 20.7	0.70
Average insulin clearance (mL/m ² BSA min ⁻¹)†	732.8 (505.7)	814.6 (450.2)	0.61

256 Data presented as mean ± SD or geometric mean (95% CI) for log transformed data (‡) or median (interquartile
 257 range) for non-parametric data (†) or number of participants for ordinal data (§). P values determined using
 258 independent samples t-tests for normally distributed data, Mann-Whitney test for non-parametric data or chi-

259 squared test for ordinal data. N for ^aWE=17, BWA=17; ^bWE=17, BWA=16; ^cWE=10, BWA=7; ^dWE=18,
260 BWA=16; ^eWE=12, BWA=14.

261 Abbreviations: ALT, alanine aminotransferase; BP, blood pressure; BWA, Black West African; HbA1c, glycated
262 hemoglobin; HDL, high density lipoprotein; IHL, intrahepatic lipid; LDL, low density lipoprotein; SAT,
263 subcutaneous adipose tissue; VAT, visceral adipose tissue; WE, White European.



264

265 **Figure 1:** Relationships between hepatic fat fraction and (A) hepatic insulin sensitivity index
 266 (basal) ($\text{mmol/m}^2 \text{BSA min pmol l}^{-1}$), (B) suppression of hepatic glucose production (%), (C)
 267 whole-body insulin sensitivity (M-value) ($\text{mg/m}^2 \text{BSA min}^{-1}$), and (D) insulin clearance (mL/m^2
 268 BSA min^{-1}) in WE and BWA men. Relationships between hepatic insulin clearance and (E)
 269 suppression of endogenous glucose production, and (F) hepatic insulin sensitivity index (basal)
 270 in WE and BWA men. Black circles with dotted line = BWA men, white circles with solid line
 271 = WE men.

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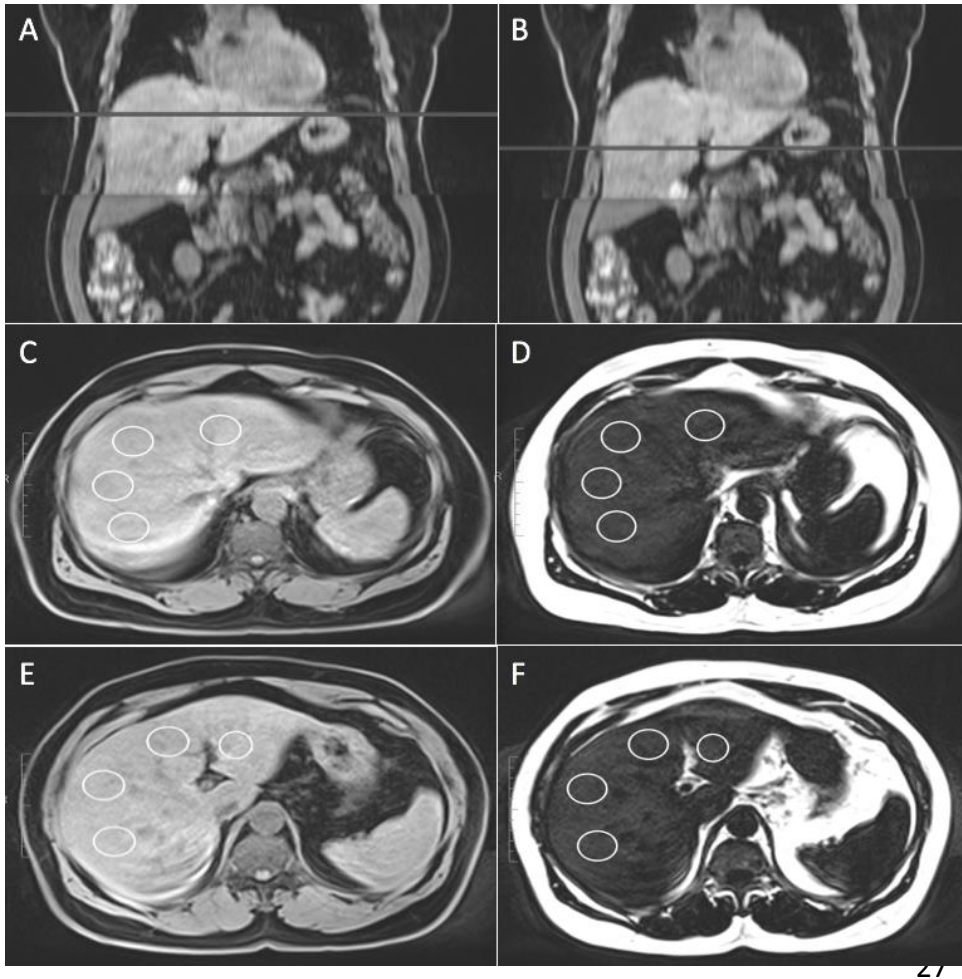
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Supplementary data:

Table 1: Pearson’s correlation and partial correlation coefficients showing relationships between hepatic fat fraction and measures of insulin sensitivity and insulin clearance in white European and black West African men

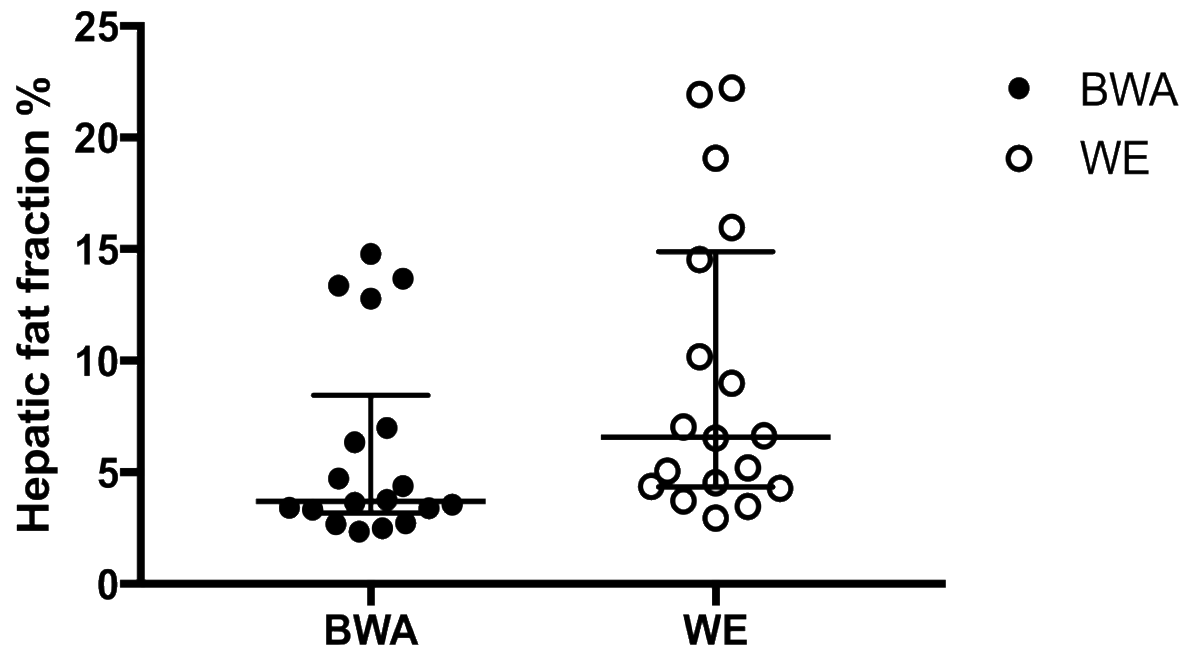
	WE		BWA	
	<i>r</i>	<i>p</i>	<i>r</i>	<i>p</i>
M-Value	-0.64	0.004	-0.35	0.18
Adjusted for age	-0.07	0.003	-0.39	0.15
Adjusted for BMI	-0.38	0.13	-0.05	0.85
Adjusted for VAT	-0.56	0.02	-0.06	0.85
Hepatic insulin sensitivity index	-0.72	0.006	-0.01	0.96
Adjusted for age	-0.70	0.01	-0.12	0.96
Adjusted for BMI	-0.60	0.04	-0.16	0.60
Adjusted for VAT	-0.73	0.01	0.35	0.26
% Suppression of endogenous glucose production	-0.11	0.73	-0.34	0.23
Adjusted for age	-0.12	0.72	-0.51	0.07
Adjusted for BMI	-0.04	0.91	-0.21	0.50
Adjusted for VAT	-0.03	0.93	-0.02	0.95
Insulin clearance	-0.14	0.58	-0.42	0.09
Adjusted for age	-0.15	0.57	-0.44	0.07
Adjusted for BMI	0.14	0.59	-0.27	0.29
Adjusted for VAT	-0.29	0.27	-0.41	0.11

Abbreviations: BMI, body mass index; BWA, black West African; VAT, visceral adipose tissue; WE, white European



28 **Figure 1:** Quantification of intrahepatic lipids by selection of two axial MRI images with
29 regions of interest positioned on the right and left lobes of the liver as well as the posterior,
30 anterior, medial and lateral sections.

31 Panel A shows a coronal MRI image with the horizontal line depicting the position of axial
32 images C and D. Panel B shows a coronal MRI image with the horizontal line depicting the
33 position of axial images E and F. Panel C shows 4 circular regions of interest on an axial
34 abdominal MRI water image on the superior section of the liver. Panel D shows the axial
35 abdominal MRI fat image that corresponds to image C with 4 identical regions of interest.
36 Panel E shows 4 circular regions of interest on an axial abdominal MRI water image on the
37 inferior section of the liver. Panel F shows the axial abdominal MRI fat image that corresponds
38 to image E with 4 identical regions of interest.



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41 **Figure 2:** Boxplot of hepatic fat fraction in White European (WE) and Black West African
42 men (BWA) with early type 2 diabetes matched for both age and BMI

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