

1 **Title:** Patients with inflammatory bowel disease have higher abdominal adiposity and
2 less skeletal mass than healthy controls.

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4 **Running title:** Abdominal body composition in IBD

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6 Teresa Barroso^{a*}, MSc, BSc Clinical Nutritionist teresa_nbarroso@hotmail.com

7 Fiona Conway^{a*} MBBS, PhD Consultant Colorectal Surgeon

8 Fiona.conway.2@glasgow.ac.uk

9 Sari Emel^b, MBBS Consultant Radiologist emel.sari@nhs.net

10 Donald McMillan^a, BSc, PhD Professor of Surgical Science

11 Donald.McMillan@glasgow.ac.uk

12 David Young^c, BSc, PhD Senior Lecturer in Mathematics and Statistics

13 david.young@strath.ac.uk

14 Hedvig Karteszi^b, MBBS Consultant Radiologist Hedvig.Karteszi@ggc.scot.nhs.uk

15 Daniel R Gaya^d, MBBS Consultant Gastroenterologist Daniel.gaya@nhs.net

16 Konstantinos Gerasimidis^a, BSc, MSc, PhD, Dietitian Senior Lecturer in Clinical

17 Nutrition Konstantinos.gerasimidis@glasgow.ac.uk

18

19 ^aSchool of Medicine, College of Medical, Veterinary and Life Sciences, University of

20 Glasgow, Glasgow Royal Infirmary, Glasgow, G31 2ER, UK

21 ^bDepartment of Radiology, Glasgow Royal Infirmary, Castle Street, Glasgow, G4 0SF,

22 UK

23 ^cDepartment of Mathematics and Statistics, University of Strathclyde, Glasgow, G1

24 1XH

25 ^dGastroenterology Unit, Glasgow Royal Infirmary, Castle Street, Glasgow, G4 0SF, UK

26

27

28 **Corresponding Author and reprints**

29 Dr Konstantinos Gerasimidis

30 Human Nutrition

31 School of Medicine

32 College of Medical, Veterinary and Life Sciences

33 University of Glasgow

34 New Lister Building

35 Glasgow Royal Infirmary

36 Glasgow

37 UK

38 G31 2ER

39 Tel: 0044 141 201 8689

40 Email: konstantinos.gerasimidis@glasgow.ac.uk

41

42 *contributed equally

43 **Main manuscript word count: 1,978**

44 **Abstract word count: 247**

45 **Author contribution:** TB, FC, SE carried out the CT scans analysis; DG, HK identified
46 the participants; TB collected data from patient records and produced the first draft; DY,
47 KG carried out statistical analysis; KG finalised the first draft; KG, DM, DG, HK
48 conceived and designed the study.

49 **Conflicts of interest disclosure:** The authors have no conflicts of interest associated
50 with this study to disclose

51 **Funding/financial disclosure:** No funding was available for this study

52

53 **What is already known about this subject?**

- 54 • Patients with inflammatory bowel disease often have altered body composition.
- 55 • The type and distribution of abdominal fat has been associated with complicated
- 56 disease and poor postoperative outcomes in patients with inflammatory bowel
- 57 disease.

58

59 **What are the new findings?**

- 60 • In patients with treatment refractory inflammatory bowel disease, abdominal body
- 61 composition is characterised by excessive fat deposition and skeletal muscle
- 62 deficits.
- 63 • Physiological relationships between skeletal muscle mass with subcutaneous and
- 64 visceral abdominal fat do not apply in inflammatory bowel disease or are reversed in
- 65 such patients.
- 66 • A larger body size is anticipated for the same anthropometry in patients with
- 67 inflammatory bowel disease than healthy controls.
- 68 • Pre-operative abdominal body composition is not predictive of post-operative
- 69 outcomes.

70

71 **Abstract**

72 **Background:** Abdominal fat type and distribution have been associated with
73 complicated Crohn's disease and adverse post-operative outcomes. There is a scarcity of
74 studies which have assessed the abdominal distribution of fat and lean stores in patients
75 with inflammatory bowel disease (IBD) and compared this with healthy controls.

76 **Objective:** This retrospective study aimed to compare the abdominal body composition
77 in IBD patients who failed medical treatment and who had Computed tomography (CT)
78 imaging prior to gastrointestinal surgery with healthy controls. Associations between
79 pre-operative abdominal body composition and post-operative outcomes within a year
80 of surgery were explored.

81 **Participants/setting:** Abdominal body composition was performed in 22, pre-surgical
82 patients with medically refractory IBD (18 with Crohn's disease) and 22 healthy
83 controls, using routinely acquired CT. Total fat, subcutaneous fat, visceral fat, and
84 skeletal muscle cross-sectional area were measured.

85 **Results:** An independent disease effect was also observed explaining a fat deposition
86 excess of 38 cm² and a skeletal muscle deficit of 15 cm² in IBD. Abdominal skeletal
87 muscle correlated with visceral fat, for the control ($\rho=0.51$, $p=0.015$), but not for the
88 IBD group ($\rho=-0.13$, $p=0.553$). A positive correlation observed between subcutaneous
89 fat with skeletal muscle in the controls ($\rho=0.47$, $p=0.026$), was reversed in the IBD
90 group ($\rho=-0.43$, $p=0.045$). Pre-operative abdominal body composition was not
91 predictive of post-operative outcomes.

92 **Conclusions:** A higher degree of abdominal adiposity, less skeletal mass and a larger
93 body size is anticipated for the same anthropometry in IBD patients. Pre-operative
94 abdominal body composition is not associated with surgical outcomes.

95

96

97 **Keywords:** Inflammatory bowel disease, computed tomography, body composition

98

99 **Introduction**

100 Alterations in the body composition of patients with IBD have been previously
101 described from studies using bioelectrical impedance analysis and dual x-ray
102 absorptiometry [1]. However, as conventional body composition constants, such as
103 hydration level of lean mass, have been developed in health, but differ in IBD [2],
104 methods (e.g. DXA, impedance, double labelled water) which consider these constants
105 in the calculation of body composition might produce erroneous results.

106 There are limited studies which have explored the segmental distribution of fat
107 and lean stores in people with IBD using more sophisticated techniques. This is of
108 particular importance as abdominal fat type and distribution has associated with
109 aggressive disease [3] and infectious complications following bowel resection in
110 Crohn's disease [4]. In a recent retrospective study, abdominal myopenia was associated
111 with primary nonresponse to biologics [5].

112 Computed tomography (CT) and magnetic resonance imaging are routinely
113 undertaken in clinical practice in IBD patients. A CT scan obtained at the third lumbar
114 vertebrae offers the possibility to measure directly body compartments such as
115 abdominal skeletal muscle mass, subcutaneous and visceral adipose tissue [6,7].

116 The primary aim of this study was to assess the abdominal body composition
117 characteristics in a group of IBD patients who have failed medical treatment and have
118 had a CT scan prior to gastrointestinal surgery. A secondary aim was to explore
119 associations between pre-operative abdominal body composition and post-operative
120 outcomes, within a year of IBD surgery.

121

122 **Subjects and methods**

123 *Participants*

124 The electronic pathology database from the NHS of Greater Glasgow & Clyde was
125 searched for all IBD patients who had undergone a gastrointestinal surgery for
126 medically refractory IBD between the periods 2012 to 2013. The medical records were
127 then searched to identify patients who underwent a pre-operative CT scan of abdomen
128 and 22 (18 with Crohn's disease and four with ulcerative colitis) were identified with
129 anthropometry measurements available (Table 1). Disease characteristics, disease
130 phenotype, prescribed medication and information on post-operative complications and
131 incidence of clinical relapse within 12 months of operation were collected from the
132 medical notes of the IBD participants (Table 1). Data on the postoperative
133 complications were collected via review of the original surgical notes and notes of any
134 surgical readmissions over the ensuing 12 months. The IBD patients had raised median
135 concentration of CRP and low median serum albumin, indicating active systemic
136 inflammatory response (Table 1). Two (9%) IBD patients had a BMI below 18.5 kg/m²
137 (underweight) and two (9%) were obese (BMI>30 kg/m²).

138 A cohort of 22, patients who had CT studies due to acute abdominal pain and in
139 whom no chronic or inflammatory pathology was found, was used as a control group.
140 This group was selected from the same pathology database as the IBD group. None in
141 the control group was underweight and 8 (36%) were obese (Table 1).

142 As this is a retrospective analysis of existing clinical data, no ethical committee
143 review was required according to National Research Ethics Service guidance [8].

144 *Assessment of body composition*

145 Abdominal body composition was performed using CT images at the third lumbar
146 vertebrae level. The images were analysed by two raters independently, as described
147 previously [7]. In brief, the two raters defined the margins of the cross-sectional area
148 (cm²) of each abdominal body composition compartment using the freeware program
149 NIH ImageJ (version 1.48). Total fat (excluding intramuscular fat), subcutaneous fat,
150 visceral fat, visceral-to-subcutaneous fat ratio and skeletal muscle cross-sectional area
151 [3] were identified using the Hounsfield unit (HU) thresholds (adipose tissue: -190 to -
152 30; muscle: -29 to +150) [7]. An example is presented in Figure 1.

153 *Statistical analysis*

154 Differences in body composition compartments between the two groups were assessed
155 with forward stepwise multivariate regression analysis. Univariate regression analysis
156 was performed separately for each of the body composition compartments using *a*
157 *priori* selected predictors (height, BMI, age and gender). Participant's condition (i.e.
158 control or IBD) was a fixed term. Predictors with a p-value<0.1 were entered one-by-
159 one in the multivariate model, starting with the one which was the most significant in
160 univariate analysis. A final model was produced which included only significant
161 predictors and the participant's condition (i.e. control or IBD); thus the independent
162 effect of IBD on body composition could be explored controlling at the same time for
163 the effect of other confounders such as age, height, gender and BMI. Correlations
164 among composition characteristics were explored with Spearman rho correlation.
165 Associations between body composition with short-term post-operative complications
166 and a clinical relapse event within 12 months of IBD surgery were explored with
167 logistic regression analysis.

168 **Results**

169 *Predictors of abdominal body composition characteristics and the effect of IBD*

170 In multivariate analysis, BMI was the strongest positive predictor of visceral and
171 subcutaneous fat and so was height for skeletal mass (Table 2). Each unit of BMI
172 increase was associated with 9.4 of visceral and 10.7 cm² increase of subcutaneous fat
173 respectively. No such effect was found for skeletal muscle. Age was positively
174 associated with visceral and subcutaneous fat (Table 2) and gender with skeletal muscle
175 (Table 2). Females had on average 45 cm² less muscle than males (Table 2).

176 An independent effect of the participant's condition (i.e. IBD or control) was
177 observed for subcutaneous fat and skeletal muscle but not for visceral fat (Table 2).
178 After accounting for the effect of other confounders, an excess of 38 cm² for
179 subcutaneous fat and a deficit of 15 cm² for skeletal muscle mass was observed in IBD
180 people compared with controls (Table 2). There were no significant correlations
181 between the abdominal body composition characteristics of the IBD patients with
182 measurements of plasma CRP or serum albumin (all $p > 0.05$).

183

184 *Relationships among abdominal body composition characteristics*

185 Relationships between abdominal body composition characteristics are displayed in
186 Figure 2. Visceral fat was positively correlated with subcutaneous fat for both groups
187 (IBD: $\rho = 0.62$, $p = 0.002$) vs Controls: $\rho = 0.61$, $p = 0.002$). Abdominal skeletal muscle
188 was positively associated with visceral fat for the control group only (IBD: $\rho = -0.13$,
189 $p = 0.553$) vs Controls: $\rho = 0.51$, $p = 0.015$). While a positive correlation was observed

190 between subcutaneous fat with skeletal muscle in the controls ($\rho=0.47$, $p=0.026$), this
191 relationship was reversed in IBD patients ($\rho=-0.43$, $p=0.045$) (Figure 2).

192

193 *Pre-operative abdominal body composition characteristics and risk of post-operative*
194 *complications and subsequent clinical relapse*

195 Eight participants (38%) presented a post-operative complications with the majority of
196 them being wound infections ($n=5$), followed by anastomosis leak ($n=2$) and pelvic
197 abscess (Table 1). Four patients relapsed within 12 months of operation. None of the
198 abdominal body composition characteristics was predictive of an increased risk of post-
199 operative complications or a subsequent clinical relapse within 12 months of surgery
200 (Table 3).

201 **Discussion**

202 Patients with medically refractory IBD were characterised by deficits in abdominal
203 skeletal muscle mass and an accrual of subcutaneous fat. No alterations were observed
204 with regard to visceral fat. Together, these abdominal body composition characteristics
205 are suggestive of features of nutritional cachexia similar to those seen in other
206 inflammatory conditions, like cancer [9] and can be attributed to undernutrition, the
207 effect of pro-inflammatory cytokines and steroid treatment [10].

208 The relationship between skeletal muscle and the two adipose tissue
209 compartments, seen in controls, was absent or reversed in IBD. The exact mechanism of
210 this association is unknown but it is likely to be multifactorial and to involve diminished
211 physical activity in patients with active IBD, the effect of inflammatory cytokines on
212 muscle mass[11] and protein metabolism[12], the excessive use of steroids or a primary
213 role of visceral fat in the initiation of colonic inflammation [13,14]. A previous study
214 showed that normalisation of BMI at 2 years follow-up was not been associated with an
215 increment in fat free mass CD [15] and collectively this evidence suggests that BMI
216 change might not be good proxy for body alterations in IBD.

217 The clinical significance of these results should also be evaluated in the context
218 of their ability to predict clinical outcomes. Previous research suggested an association
219 between the visceral-to-subcutaneous fat ratio with post-operative complications [4] and
220 disease severity [3] but this was not replicated in this small retrospective study of
221 patients with medically refractory disease, prior to gastrointestinal surgery. Patients
222 with IBD are at a higher risk of adverse cardiovascular events [16] than the general
223 population and based on the current findings, a higher degree of abdominal adiposity for
224 a given BMI than healthy individuals should be expected. Thus clinical attention should

225 be given to the avoidance of overnutrition, particularly now that the epidemic of obesity
226 is becoming common in IBD [17]. It might be that the focus on the dietetic support of
227 IBD patients should be extended from the management of undernutrition to the
228 prevention and correction of obesity and interventions with physical activity and
229 exercise to improve muscle mass.

230 The strength of this study is the inclusion of an essentially healthy control group
231 for first time [3,4], as well as the direct and independent assessment of each of the
232 abdominal compartments. This is a major advantage compared to previous studies in
233 IBD where measurement error in one body compartment might have propagated to the
234 estimation of the others [1]. The main limitations are the small sample size, the
235 heterogeneous patient population in terms of disease characteristics and the
236 retrospective design of the study. Use of concomitant treatment following surgery may
237 have also influenced the risk of post-operative complications and subsequent clinical
238 relapse. Also, our control group was younger and had higher BMI than our IBD
239 patients, which may have confounded the results of this study. However, instead of
240 stratifying our analysis by these confounders, which would have compromised further
241 statistical power and increase bias due to multiple testing, we chose to apply
242 multivariate regression modelling to control for their effect. A lack of a biological
243 association between adipose tissue with gender was not observed, but not unexpectedly,
244 as our analysis was performed in a cross-section of the abdomen, and expressed in units
245 of area, rather than as a percentage of the total area.

246 **Conclusions**

247 Abdominal body composition characteristics in this study highlight the incidence of
248 sarcopenia in medically refractory IBD patients. The significance of these findings in
249 terms of clinical disease course and long-term outcomes of IBD should be explored in
250 future prospective studies, particularly now that radiation-free MRI assessment is
251 becoming more accessible and affordable. This study has clear implications for the
252 nutritional assessment and management of people with IBD.

253 **Figure Legends**

254

255 **Figure 1:** Abdominal body composition analysis using NIH ImageJ

256

257 *Panels: (a) The original CT image (b) the scale is set at a known distance (10 cm) from*
258 *the original image, (c) definition of the total body fat area, applying the thresholds (-*
259 *190 to -30 HU) (d) definition of skeletal muscle area, after cropping the abdominal*
260 *contents and L3 vertebrae and applying the thresholds (-29 to + 150 HU).*

261

262 **Figure 2:** Correlations among abdominal body characteristics in people with IBD and
263 controls (blue circles: controls, brown squares: IBD)

264

265 *Panels: (a) Subcutaneous fat vs skeletal muscle: IBD: (rho: -0.43, p=0.045) vs*
266 *Controls: (rho: 0.47, p=0.026); (b) Visceral fat vs skeletal muscle: (rho: -0.13,*
267 *p=0.553) vs Controls (rho: 0.51, p=0.015); (c) Subcutaneous fat vs visceral fat; IBD:*
268 *(rho: 0.61, p=0.002) vs Controls: (rho: 0.62, p=0.002)*

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325 **Table 1:** Participants characteristics

	IBD (n=22)	Healthy Controls (n=22)	p-value
<i>*Disease location, n</i>			
<i>L1</i>	6		
<i>L2</i>	8		
<i>L3</i>	4		
<i>E1</i>	1		
<i>E2</i>	1		
<i>E3</i>	2		
<i>*Disease behaviour, n</i>			
<i>B1</i>	6		
<i>B2 + B2p</i>	10		
<i>B3 + B3p</i>	6		
Treatment, n			
<i>Aminosalicylates</i>	13		
<i>Steroids</i>	16		
<i>Thiopurines</i>	7		
<i>Biologics</i>	7		
Type of surgery, n			
<i>CD; colectomy</i>	6		
<i>CD; right hemicolectomy</i>	9		
<i>CD; left hemicolectomy</i>	2		
<i>CD; limited small bowel</i>	1		
<i>UC; subtotal colectomy</i>	4		
Sex, males:females, n	12:10	12:10	1.000
^a Age, years	47.5 (33:63)	39.5 (30.8:45.5)	0.045

^a BMI, kg/m ²	23.6 (20.2:26.8)	27.3 (22.8:34.0)	0.037
^a Height, m ²	166.0 (156:175)	171 (165:180)	0.078
^a Albumin, g/L	25 (23.0:30.5)		
^a Haemoglobin, g/L	104.5 (98.5:121.2)		
^a C-reactive protein, mg/L	66 (20:142)		
Post-operative complications	8		
<i>Wound infection</i>	5		
<i>Anastomotic leak</i>	2		
<i>Pelvic abscess</i>	1		
Number relapsed at 12 months	4		

326 ^aMedian (inter-quartile range); CD: Crohn's disease; UC: Ulcerative colitis; * disease
327 phenotype based on the Montreal classification.

328

329

330 **Table 2:** Multivariate regression analysis of predictors of CT based abdominal body composition characteristics

	Visceral fat (cm ²)	Subcutaneous fat (cm ²)	Skeletal muscle (cm ²)	Visc-to-subc ratio	Total fat (cm ²)
	<i>β coefficient; p-value</i>				
Gender, males	NS	NS	30; p<0.001	0.3; 18%; p=0.004	NS
Age, years	1.6; p=0.004	1,1; p=0.038	NS	NS	2.7; p=0.001
BMI, kg/m ²	9.4; p<0.001	10.7; p<0.001	NS	NS	20.1; p<0.001
Height, cm ²	NS	NS	153; p<0.001	NS	NS
Condition, IBD ^a	NS	38; p=0.035	-14.7; p=0.012	NS	62.7; p=0.019
R ² of final model ^b	64%	65%	79%	18%	77%

331 NS: non-significant; ^a participant condition (IBD or controls) was a fixed term in both univariate and multivariate regression analysis; visc-to-332 subc fat ratio: ratio between visceral and subcutaneous fat area; ^b R² coefficient of determination

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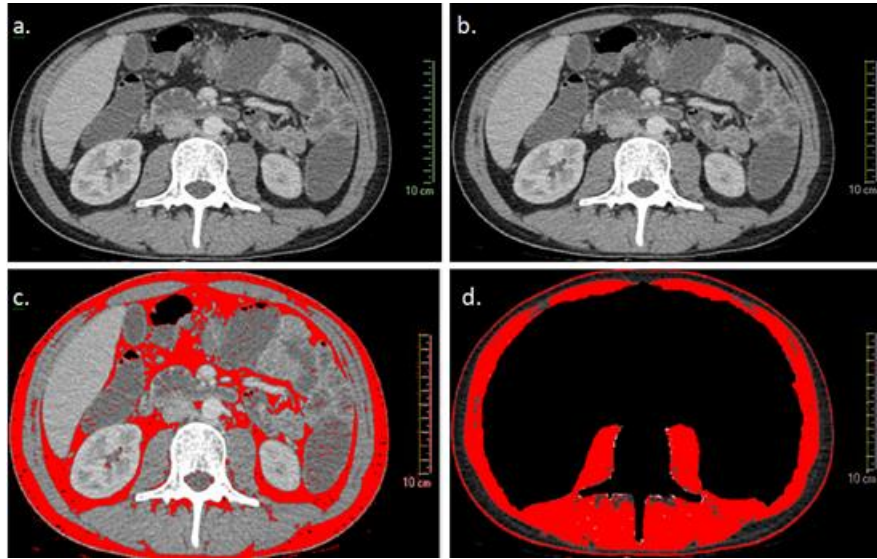
336 **Table 3:** Pre-operative abdominal body composition characteristics and risk of post-
 337 operative complications and subsequent clinical relapse at 12 months follow up

	Post-operative complications	p-value	Relapse within 12 months	p-value
	<i>Odd ratio, 95 CI</i>		<i>Odd ratio, 95% CI</i>	
Visceral fat	1.00 (0.99 : 1.01)	0.433	1.00 (0.99 : 1.02)	0.386
Subcutaneous fat	1.00 (0.99 : 1.01)	0.557	1.00 (0.99 : 1.02)	0.401
Skeletal muscle	1.00 (0.98 : 1.02)	0.949	0.99 (0.96 : 1.03)	0.785
Visc-to-subc ratio	0.69 (0.06 : 8.6)	0.773	1.12 (0.06 : 21.7)	0.942
Total fat	1.00 (1.00 : 1.01)	0.472	1.00 (1.00 : 1.01)	0.372

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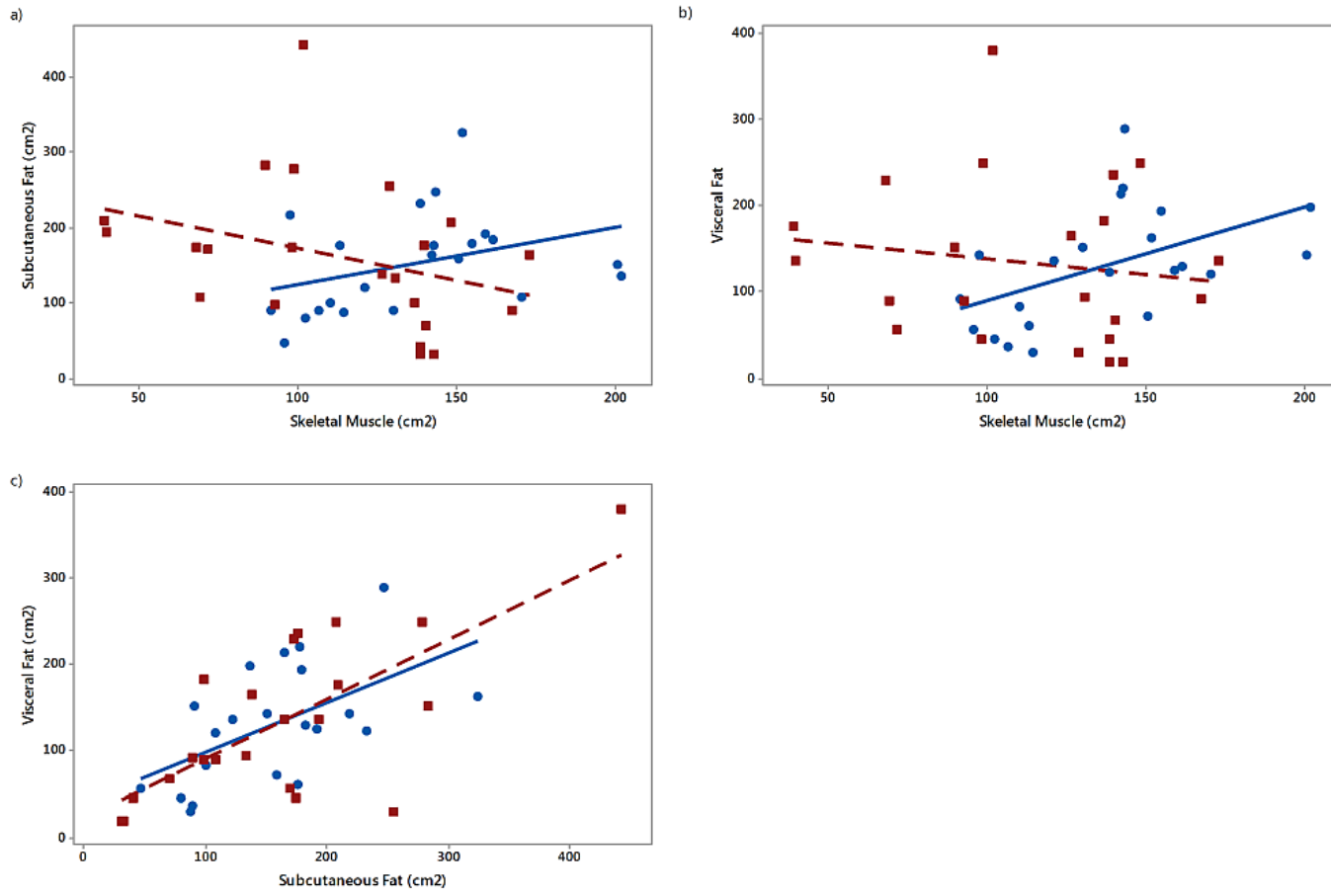
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341 Figure 1
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344 Figure 2



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