

Medication use, n (%)	FH-	FH+	Type 2 diabetes
Metformin	-	-	10 (83) <sup>§,¶</sup>
Sulphonylureas	-	-	1 (8)
GLP-1 RA	-	-	3 (25)
DPP-4 inhibitors	-	-	5 (42) <sup>§,¶</sup>
Insulin	-	-	-
ACEi/ARB	-	-	2 (17)
Calcium channel blockers	-	1 (6)	-
Statins	-	-	7 (58) <sup>§,¶</sup>
Other	6 (33)	6 (38)	6 (50)

**ESM Table 1:** Medication use.

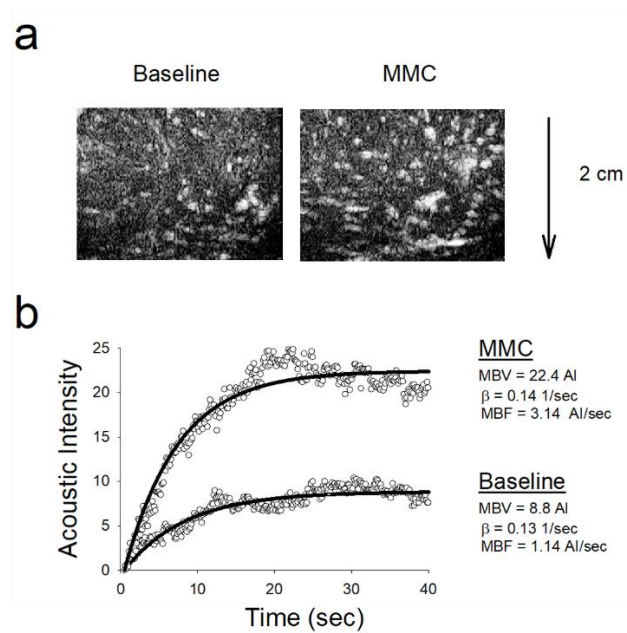
Data are expressed as number (percent). <sup>§</sup> $p < 0.05$  vs FH-, <sup>¶</sup> $p < 0.05$  vs FH+.

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; DPP-4, dipeptidyl peptidase 4; GLP-1 RA, glucagon-like peptide-1 receptor agonist.

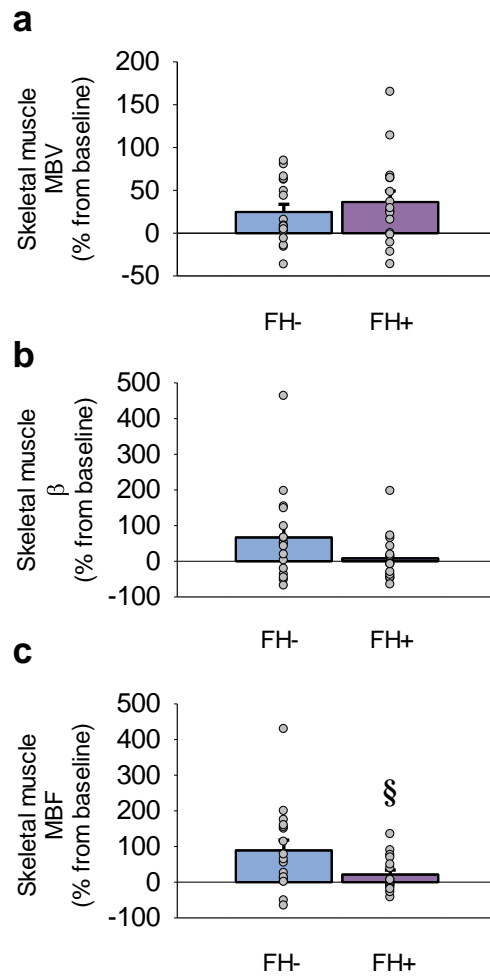
	<b>FH-</b> <b>(n=10)</b>	<b>FH+</b> <b>(n=8)</b>
Age (y)	45 ± 5	40 ± 3
Height (cm)	179 ± 2	177 ± 2
Weight (kg)	80.9 ± 2.7	80.2 ± 2.9
BMI (kg/m <sup>2</sup> )	25.1 ± 0.5	25.7 ± 0.9
Total body fat (%)	21.5 ± 1.8	25.6 ± 1.6
Glucose AUC (mmol/l x 120 min)	646 ± 21	681 ± 18
Insulin AUC (pmol/l x 120 min)	20,022 ± 2,215	25,934 ± 3,779
HOMA-IR	0.9 ± 0.1	1.2 ± 0.2
Metabolic Flexibility ( $\Delta$ RER x 60 min)	2.2 ± 0.3	-0.5 ± 0.5 <sup>§</sup>
MBF (AI/sec)		
0 min	1.3 ± 0.3	1.4 ± 0.2
60 min	2.0 ± 0.4*	1.7 ± 0.3
Brachial artery flow (ml/min)		
0 min	51.8 ± 4.6	70.1 ± 7.7
60 min	86.1 ± 15.4*	81.9 ± 16.4
Forearm vascular resistance (mmHg min ml <sup>-1</sup> )		
0 min	2.1 ± 0.2	1.6 ± 0.2
60 min	1.4 ± 0.2*	1.6 ± 0.3

**ESM Table 2:** Exploratory analysis of FH- and FH+ males with similar age, height, weight, BMI and % body fat. Unpaired t-test or two way repeated measures ANOVA were used where appropriate.

Data are expressed as mean ± SEM. \* $p < 0.05$  vs 0 min, <sup>§</sup> $p < 0.05$  vs FH-. AUC, area under the time curve; BMI, body mass index; HOMA-IR, Homeostatic model assessment of insulin-resistance; MBF, microvascular blood flow.



**ESM Figure 1:** Example of (a) ultrasound images and (b) representative background subtracted curve fits before (baseline) and after (60 min) a mixed meal challenge (MMC) in a healthy FH- participant. The white in the image represent opacification of the contrast agent contained within the vasculature. The participant had greater tissue opacification after the MMC. The curve fit of the images show a higher microvascular blood volume (MBV), rate of microvascular re-filling ( $\beta$ ) and microvascular blood flow (MBF) after the MMC.



**ESM Figure 2:** Skeletal muscle microvascular responses (% change from baseline) 60 min following the MMC in FH- (blue) and FH+ (purple). **(a)** Forearm muscle microvascular blood volume (MBV), **(b)**  $\beta$  and **(c)** microvascular blood flow (MBF). Unpaired t-test or Mann-Whitney Rank Sum test (if data were not normally distributed) were used where appropriate. Data expressed as means  $\pm$  SEM with individual data points. <sup>§</sup> $p < 0.05$  vs FH-.