

Background

- The kinin-kallikrein system has been implicated in muscle performance
- The kinin bradykinin is a peptide that promotes glucose uptake and blood flow in muscle through bradykinin receptor 2 (BDKRB2) [1]
- Bradykinin levels can be lowered by angiotensin converting enzyme (ACE), also implicated in muscle performance, by breaking it down into inactive peptides
- Thus the BDKRB2 may impact on muscle performance directly through bradykinin, which is partly regulated by ACE activity
- BDKRB2 variants include rs1799722 and rs5810761, where the T and -9 alleles respectively have associated with increased transcriptional rates and were overrepresented in endurance athletes [1,2]
- However, these variants have rarely been studied among older people or those with sarcopenia.

Methods

- The LACE study was a randomised controlled trial comparing outcomes in short physical performance battery (SPPB) among those treated with the ACE-inhibitor Perindopril and/or leucine against placebo.
- Eligibility included 70 years of age and above with low gait speed and low handgrip strength
- Participants' blood samples had DNA extracted and were genotyped for rs179972 using TaqMan and rs5810761 by amplification through Hotstar Taq (and visualised through 4% agarose gel electrophoresis)
- The differences in genotypes for each variant against physical performance measures (e.g. six-minute walk distance [6MWD]) was calculated using t-tests or Mann-Whitney tests where appropriate. Genotypes were also tested for Hardy-Weinberg equilibrium (HWE) using Chi-squared test.
- Ethics approval was obtained through the East of Scotland Ethics Committee (ref 14/ES/1099)

Results

Table 1: baseline characteristics

Characteristic	Male (n=64)	Female (n=72)
age, years	76.5 (IQR 74-84)	77.5 (IQR 74-82)
weight (kg)	81.6 (± 13.3)	63.1 (± 11.0)
height (m)	1.71 (± 6.32)	1.57 (± 6.30)
BMI (kg/m ²)	27.7 (± 3.9)	26.2 (± 3.9)
SARC-F score	4.0 (IQR 3-4)	4.0 (IQR 3-5)
SPPB score	8.0 (± 2.2)	7.0 (± 2.5)
Grip strength (kg)	23.4 (IQR 20-25.8)	13.3 (IQR 10.5-16.7)
6MWD (m)	297 (IQR 240.5-400)	339 (IQR 250 – 364)

Data are presented as mean SD for normally distributed data and as median (IQR) for data that did not fit a normal distribution :

6MWD; 6 minute walk distance, SARC-F; SPPB; short physical performance battery

The baseline characteristics of the participants are shown in table 1. The distribution of the genotypes for both variants are shown in table 2. There was no statistically significant difference between the observed distribution compared to the population for Rs1799722 (p=0.248 by Chi squared test) or Rs5810761 (p=0.269 by Chi squared test)

Table 2: distribution of genotypes for each variant

Rs1799722				
	Minor TT	Major CC	Heterozygous CT	P value
Observed	17	48	71	0.248
Expected	0.18	0.33	0.49	
Rs5810761				
	-9-9	+9+9	Heterozygous -9+9	P value
Observed	31	43	60	0.269
Expected	0.26	0.26	0.48	

Rs1799722

- Table 3 shows the results of muscle performance for Rs1799722.
- The TT genotype had greater 6MWD compared to CC/CT group (p=0.007) and also greater leg muscle mass (p=0.005) among men (see figure 1) but not women.

Table 3

Rs1799722	Females			Males		
	TT	CT/CC	P value	TT	CT/CC	P value
6MWD, m	277	300	0.490	400	312	0.007
Grip, kg	14.2	13.0	0.420	24.9	23.2	0.209
SPPB	7.5	7	0.691	9	7	0.069
Gait time, sec	5.0	5.6	0.900	4.5	5.1	0.153
Leg muscle, kg	9.7	10.7	0.128	17.6	15.3	0.005
Arm fat, kg	2.94	3.14	0.707	2.98	2.59	0.280
Leg fat, kg	8.45	9.39	0.851	7.22	6.47	0.182

Rs5810761

- Table 4 shows the results of muscle performance Rs5810761
- Arm fat was significantly lower in the -9-9 genotype than +9-9/+9+9 (p=0.005) among men (figure 2).

Table 4

rs5810761	Females			Males		
	-9-9	+9-9/+9+9	P value	-9-9	+9-9/+9+9	P value
6MWD, m	308	290	0.483	321	340	0.574
Grip, kg	12.4	13.4	0.930	23.6	22.8	0.655
SPPB	8	7	0.107	7	8	0.519
Gait time, sec	5.0	5.8	0.052	5.0	5.1	0.928
Leg muscle, kg	11.1	10.6	0.915	15.6	15.7	0.684
Arm fat, kg	3.15	2.97	0.618	2.39	2.72	0.005
Leg fat, kg	9.53	9.11	0.531	6.40	6.94	0.304

Figure 1

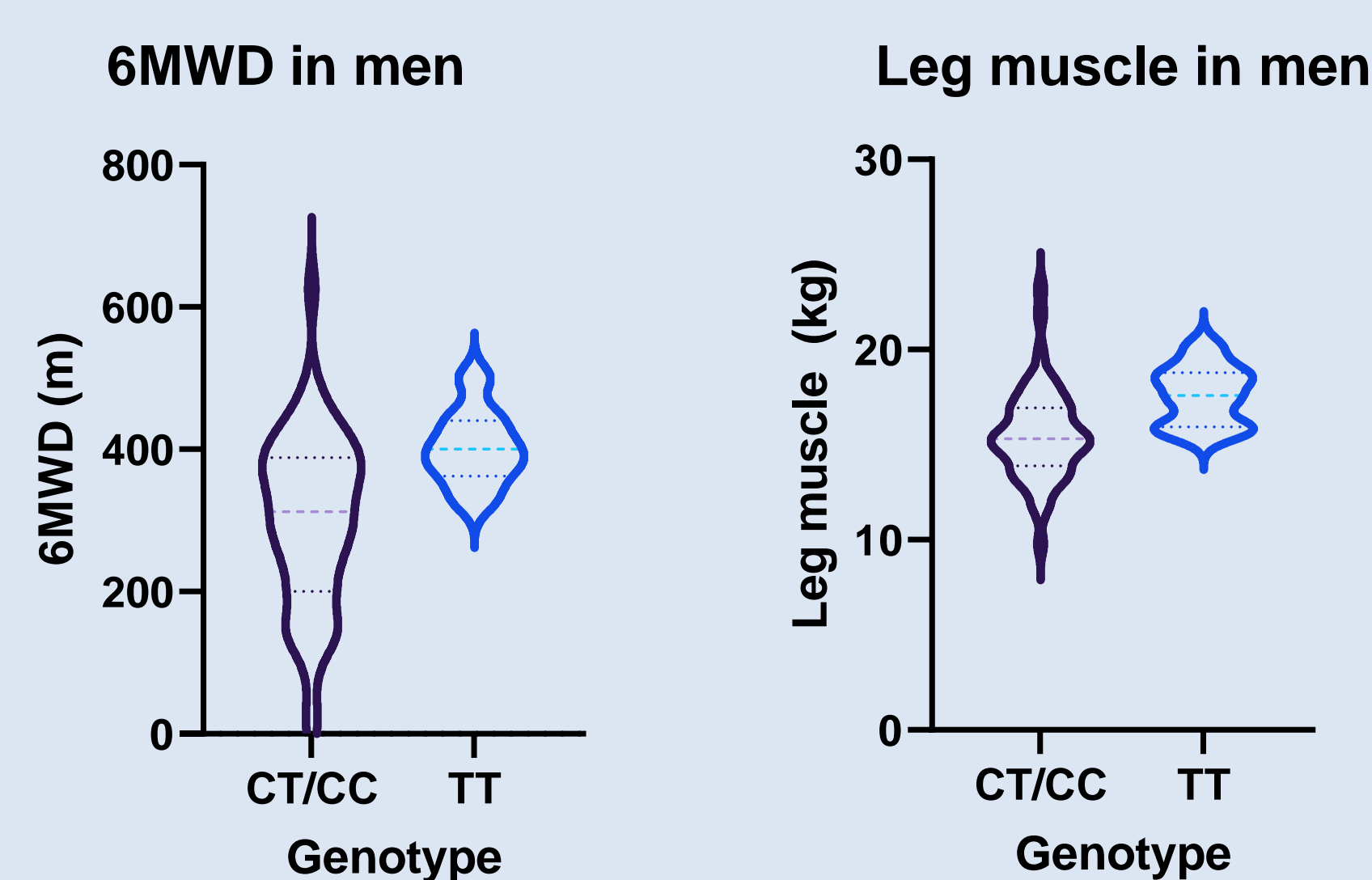
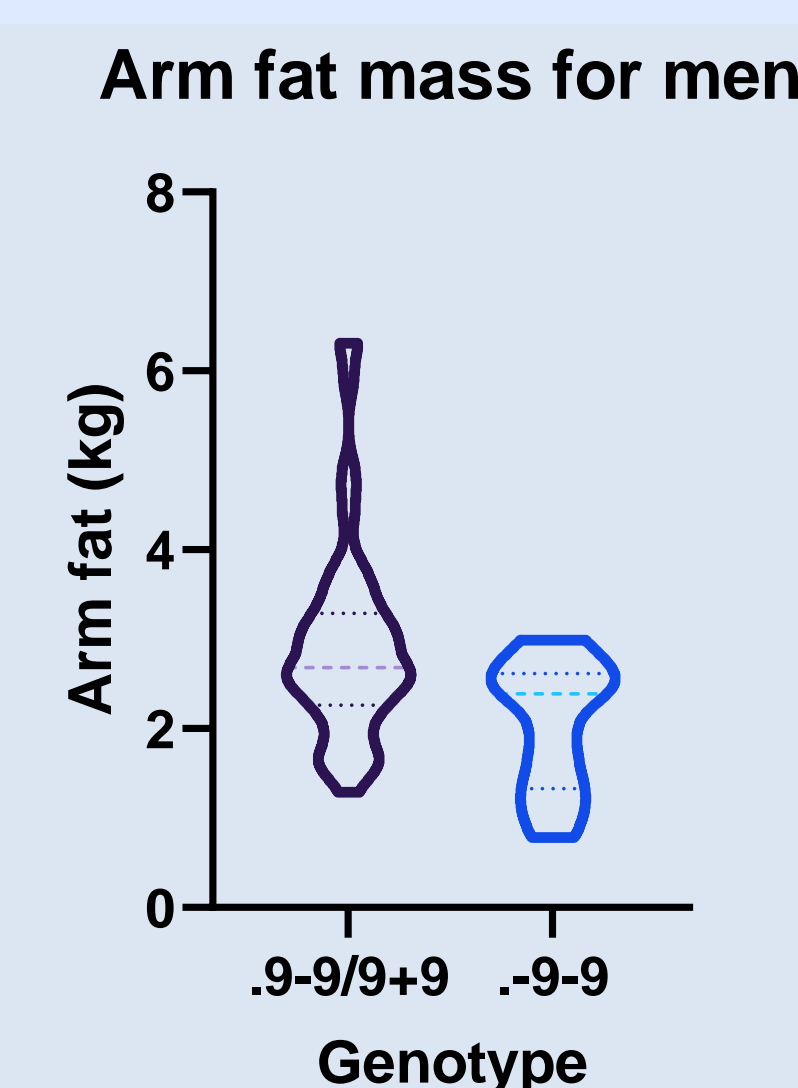


Figure 2



Discussion

- In this study both variants remained in Hardy Weinberg equilibrium however the sample size was small.
- We did not find any significant difference in baseline grip strength or SPPB between the different genotypes.
- We found the TT genotype was associated with longer 6MWD and higher muscle mass in men
- The -9-9 genotype may be associated with lower regional fat mass in men
- These differences were not seen in women
- These differences are consistent with previous studies suggesting greater performance in endurance athletes with these genotypes
- These findings need replicating in larger studies

References

- [1] Williams AG, Dhamrait SS, Wootton PTE, Day SH, Hawe E, Payne JR, et al. Bradykinin receptor gene variant and human physical performance. J Appl Physiol. 2004 Mar;96(3):938-42.
- [2] Tsianos GI, Evangelou E, Boot A, Carola Zillikens M, van Meurs JBJ, Uitterlinden AG, et al. Associations of polymorphisms of eight muscle- or metabolism-related genes with performance in Mount Olympus marathon runners. J Appl Physiol. 2010 Mar;108(3):567-74
- [3] Saunders CJ, de Milander L, Hew-Butler T, Xenophontos SL, Cariolou MA, Anastassiades LC, et al. Dipsogenic genes associated with weight changes during Ironman Triathlons. Hum Mol Genet. 2006 Oct 15;15(20):2980-7.

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