

Supplemental information

Online resource for the following manuscript:

Title: Sex differences in the contribution of different physiological systems to physical function in older adults

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Appendix 1

Echocardiography extended methods

Cardiac function was measured by transthoracic echocardiographic imaging (EPIQ 7, Phillips) fitted with a matrix array transducer (X5-1 xMATRIX, Philips) and conducted according to the American Society of Echocardiography's (ASE) guidelines.⁽¹⁾ The examination was performed by one of two experienced sonographers. Participants were in the left lateral decubitus position, ECG leads were placed to ensure a clear QRS complex throughout image acquisition. Data analysis was performed off-line (QLAB 3.3.2, Philips). Further details of the methods for echocardiography are provided in previously published work. (2, 3)

Left ventricular (LV) dimensions and wall thickness were measured from the parasternal long axis window. LV end systolic (ESV) and diastolic (EDV) volumes were calculated using the Teichholz formula (4) and stroke volume was calculated as EDV minus ESV. LV mass was estimated according to ASE recommendations.⁽¹⁾ Myocardial volume was estimated from the LV mass estimation (see above) divided by the density of myocardial tissue (1.04 g/ml). Myocardial contraction fraction (MCF) was calculated as the ratio of stroke volume to myocardial volume.⁽⁵⁾ Ejection fraction (EF) and cardiac output (CO) were estimated from ESV, EDV and resting heart rate (CO only). Cardiac index (CI) was calculated as CO/body surface area (BSA). Total peripheral resistance (TPR) was estimated from a clinical brachial blood pressure measurement of mean arterial pressure (MAP) and CO measured by echocardiography.

The mitral inflow pattern was imaged using spectral pulsed wave Doppler with sample volume placed at the tips of the mitral valve inside the LV. Peak early diastolic velocity (E) was measured from traces. Wall motion was measured using Tissue Doppler imaging (TDI) at the level of the mitral valve in the 4 chamber window, an average of lateral and medial peak longitudinal systolic (s') and early relaxation (e') velocities were calculated. An index of LV filling pressure was calculated as E/e' .

Pulse wave velocity (PWV) & intima-media thickness (IMT) extended methods

Carotid to femoral Pulse Wave Velocity (PWV), a measure of arterial stiffness, was measured using a commercially available cuff-based device (Vicorder, Skidmore Medical, UK). Intima-Media thickness was measured using carotid artery ultrasound imaging (Vivid I, GE, Boston) equipped with a linear-array transducer (12L-RS, GE, Boston). Settings were adjusted to obtain optimum image quality ensuring that the carotid bifurcation and the intima and media at both the near and far wall were visible over a length of at least 10 mm in the common carotid artery. A cine loop of at least 5 cycles at 3 angles (lateral, posterior and anterior) on each side was captured. Measurements were made offline

using validated software (AMS II). The region of interest was defined as 1 cm proximal to the bifurcation.

Near-infrared Spectroscopy extended methods

Skeletal muscle microvascular function and oxidative capacity were assessed using near infrared spectroscopy (NIRS) measurements of changes in oxygenated and deoxygenated haemoglobin and tissue saturation index (TSI%) during exercise and arterial occlusions. The NIRS device (Portamon, Artinis Medical Systems, the Netherlands) was positioned on the lateral head of the gastrocnemius where the calf girth was greatest. The difference between TSI% at rest and at the end of exercise was calculated. Greater absolute reductions in this value for a given workload during exercise are thought to represent haemodynamic insufficiency.(6) Immediately post-exercise, a rapid inflation cuff (Hokanson, SC10D/E20; PMS Instruments, Maidenhead, UK) placed on the thigh proximal to the location of NIRS measurement was inflated transiently to induce complete arterial occlusions (5–8 s intervals) throughout a 3 min recovery period to determine the kinetics of muscle recovery, represented by a time constant.(7) The time constant has shown good reproducibility and agreement with the established ³¹P-MRS method of measuring skeletal muscle oxidative capacity.(8, 9) All analysis of NIRS data was conducted off-line using custom written programs in MATLAB R2014a (MathWorks, Natick, MA, USA).

References for extended methods

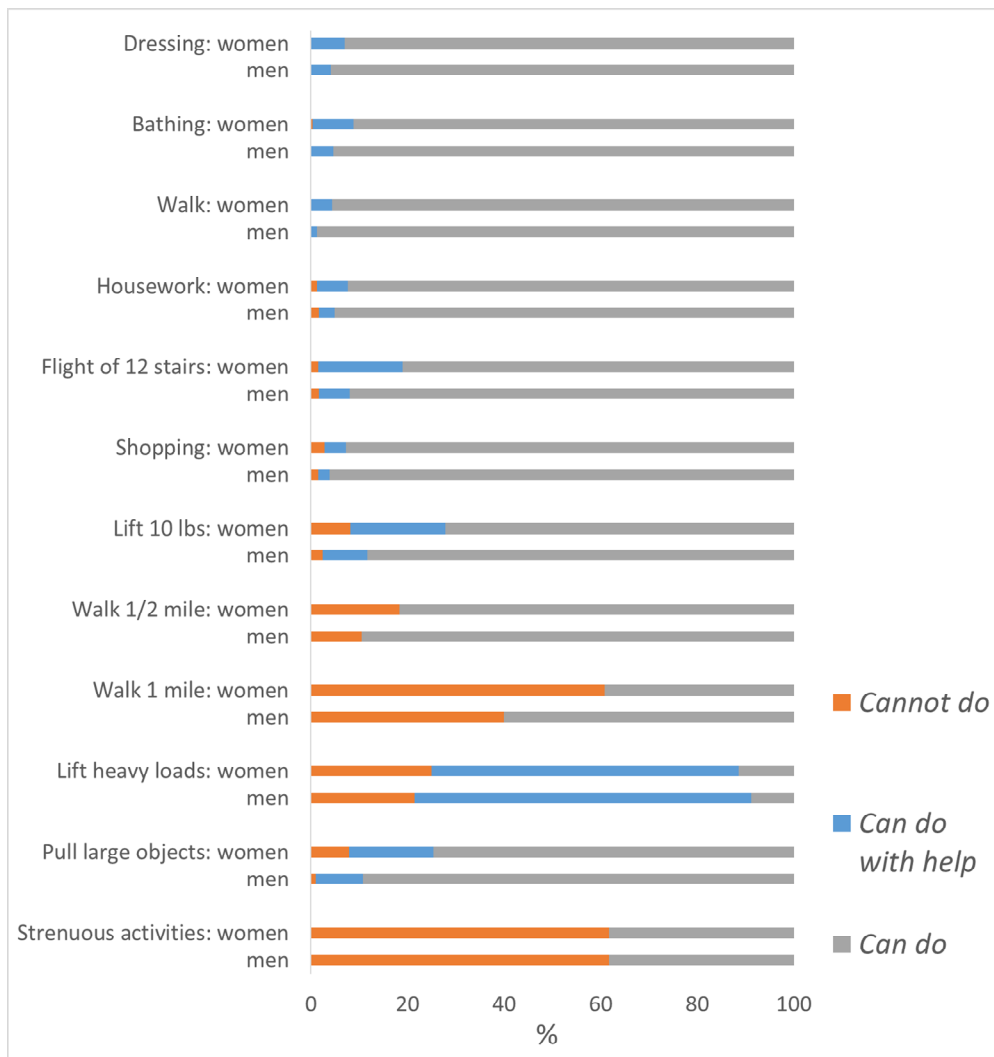
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Appendix 2

Characteristic	Mean±SD, median (IQR) or n(%)				
	<i>n</i>	Women	<i>n</i>	Men	<i>p</i>
Age (years)	228	70±7	303	75±6	<0.001
Weight (kg)	228	71.7±13.5	303	79.0±12.1	<0.001
Height (cm)	228	158.8±6.4	303	170.8±6.9	<0.001
BMI (kg/m ²)	228	28.4±4.8	303	27.1±3.6	<0.001
WHR	228	0.90±0.07	302	1.0±0.07	<0.001
Ethnicity (E/SA/AFC) <i>n</i> (%)	228	95/60/73 (42/26/32)	303	165/99/39 (55/33/13)	<0.001
Years of education	209	12.5±3.5	284	12.4±3.7	0.640
Current smoke, <i>n</i> (%)	227	8(4%)	299	8(3%)	0.575
Diabetes, <i>n</i> (%)	228	50(22%)	303	67(22%)	0.960
CVD, <i>n</i> (%)	222	11(5%)	300	50(17%)	<0.001
PFS*	228	20(18,21)	303	21(19,22)	<0.001
MCF	184	44±10	233	42±10	0.090
EF (%)	184	68±8	233	66±10	0.007
TDI s ¹ (m/s)	221	7.3±1.1	292	8.0±1.6	<0.001
CI (L/m ²)	183	2.1±0.50	233	2.2±0.53	0.294
E (cm/s)	214	69±15	285	67±17	0.142
E/e'*	210	9.0(7.6,11.0)	278	8.4(7.2,10.1)	0.013
PWV (m/s)	209	10.7±2.1	278	11.5±3.4	<0.001
TPR (mmHg/L)	183	28.7±8.6	233	25.8±7.4	<0.001
IMT (mm)	226	0.85±0.22	302	0.92±0.19	0.003
ΔTSI% exercise	180	-1.7±4.1	261	-3.2±4.6	<0.001
ACR elevated (≥3), <i>n</i> (%)	228	14(6%)	303	33(11%)	0.056
eGFR (ml/min/1.73m ²)	225	81.9±15.6	301	75.3±14.4	<0.001
WMH vol. (ml)*	179	2.32(1.23,5.63)	260	2.98(1.49,8.92)	0.015
FVC (L)	191	2.48±0.68	260	3.43±0.84	<0.001
FEV1 (L)	193	1.90±0.51	265	2.55±0.65	<0.001
FEV1:FVC ratio	191	0.77±0.12	260	0.75±0.09	0.023
Est. $\dot{V}O_2$ max (ml/min/kg)	198	21.8±3.2	276	22.2±2.9	0.133
OUES (ml/min/(logL/min))	203	1.40±0.34	271	1.79±0.42	<0.001
Grip strength (kPa/kg-weight)	228	0.83±0.22	303	1.04±0.26	<0.001
Muscle oxidative capacity (s)*	37	45(32,68)	107	43(29,61)	0.355

Appendix 3



The distribution of answers to questions related to each of the 12-items necessary to calculate physical function score stratified by sex. Grey bars indicate the percentage of participants who reported they can do the activity, blue bars indicate those who can do the activity with assistance and orange bars indicate those who cannot do the activity.

Appendix 4

Sensitivity model, sub-group (*n*: men=228; women=303)

