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ORIGINAL ARTICLE

Sex-specific muscle and metabolic biomarkers associated with gait speed and cognitive transitions in older adults: a 9-year follow-up

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Abstract Physical frailty and cognitive frailty share biological mechanisms, but sex-specific biomarkers associated with transitions in gait speed and cognition during ageing are poorly understood.Gait speed, cognition (3MSE), body composition (DXA) and serological biomarkers were assessed annually over 9 years in 216 males (72.7 + 8.07 years) and 384 females (71.1 ± 8.44 years). In females, maintaining normal gait speed was associated with lower percent body fat (IRR 0.793, $p = 0.001$, 95%CI 0.691–0.910) and lower lactate dehydrogenase (LDH) (IRR 0.623, p = 0.00, 95%CI 0.514–0.752), and in males, the association was with higher cholesterol (IRR 1.394, $p = 0.001$, 95%CI 1.154–1.684). Abnormal to normal gait speed transitions were associated with higher insulin in females (IRR 1.325, $p = 0.022$, 95%CI 1.041–1.685) and lower creatinine in males (IRR 0.520, $p = 0.01$, 95%CI 0.310–0.870). Normal to slow gait speed transitions in males were associated with IGF-1 (IRR 1.74, $p = 0.022$, 95%CI 1.08–2.79) and leptin in females (IRR 1.39, $p = 0.043$, 95%CI 1.01–1.91.) Maintaining normal cognition was associated with lower LDH in females (IRR 0.276, $p = 0.013$, 95%CI 0.099–0.765) and higher appendicular skeletal muscle mass in males (IRR 1.52, $p = 0.02$, 95%CI 1.076–2.135). Improved cognition was associated with higher leptin (IRR 7.5, $p = 0.03$, 95%CI 1.282–44.34) and lower triglyceride (IRR 0.299, $p = 0.017$, 95%CI 0.110–0.809) in males. Education was protective against cognitive decline in females (IRR 0.84, $p = 0.037$, 0.732–0.982). Sex-specific biomarkers of muscle (LDH, Creatinine, IGF-1, APSM) and metabolism (%fat, insulin,cholesterol, leptin, tryglycerides) were associated with gait speed and cognitive transitions. These data suggest that modifiable biomarkers of muscle and metabolism could be targeted for interventions.

Keywords Gait speed · Cognition · Biomarkers · Transitions · Sex-specific

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Background

Changes in physical frailty and cognitive frailty are seen throughout the lifespan with gait speed and cognition consistently reported as a progressive trajectory

of decline in older ages (Diehr et al. 2013). However, these changes can be transitory, masking a more complex trajectory of decline with periods of decline followed by recovery (Diehr et al. 2013; Qualls et al. 2017; Thielke et al. 2012). A person's ability to transition from a worsened health state back to an improved or "normal" state is influenced not only by age (Newman et al. 2016) but also by the overall state of health when the transition occurs (Newman et al. 2016) and can be sex-specific (Kojimaa et al. 2019; Kane and Sinclair 2019). Sometimes these transitions have been referred to as "tipping points" when the person cannot recover function and a cascade of events are set in place resulting in significant frailty that has low probability of recovery (Rikkert and Melis 2019). To identify those people whose function is in the early stages of transition and when intervention may be most effective, there is growing interest in identifying biomarkers associated with transitions in physical function and cognition.

The first step to understanding relationships between biomarkers, physical health transitions (gait speed) and cognitive health transitions (cognition) may be by exploring these relationships in longitudinal cohort study designs assessing who is able to maintain normal gait speed and cognitive function over time and those who transition from poorer gait and cognitive function back into an improved/normal state. These markers of "successful" ageing should also be compared to biomarkers associated with detrimental transitions, such as from a normal gait speed or cognition to an abnormal (lower) state of functioning. Biomarkers for physiological processes related to frailty have recently been proposed (Wang et al. 2019). These include structural and functional brain changes, endocrine dysregulation including changes in growth hormone, thyroid hormone, adrenocorticoids, estradiol and testosterone and metabolic processes including dysregulation of carbohydrate and energy metabolism (leptin, adiponectin), insulin signalling, vitamin D metabolism and changes in body composition. Chronic inflammatory markers such as IL-6, C-reactive protein, interleukin-1-receptor agonist, interleukin-18, and soluble TNF-α receptor 1 and metabolomics have also been proposed (Rodriguez-Manas et al. 2019; Pujos-Guillot et al. 2019). More general biomarkers were proposed by Kane and Sinclair (Kane and Sinclair 2019) including low albumin, markers of anaemia (haemoglobin, iron, ferritin), total cholesterol, LDL and low creatinine, and these investigators also stressed the importance of controlling for sex differences in identifying biomarkers.

The New Mexico Ageing Process Study (NMAPS), which was a longitudinal study of "successful" ageing, provided data to explore many of these proposed biomarkers in association with transitions of gait speed and cognitive function. This analysis was a sequel investigation to our earlier work on the reversibility of gait speed and cognitive transitions into old age over 9 years of this 20-year cohort study (Qualls et al. 2017).

Methods

Participants

The NMAPS was a prospective cohort study of successful ageing that began in 1979 and is described elsewhere (Garry et al. 2007). To summarize, participants were 60 years of age or older, free of major medical conditions and living independently. Participants were seen annually and, for this analysis, had at least one consecutive annual assessment of cognitive status, gait speed, body composition and serological measures between 1993 and 2001. This analysis included 216 males (72.7 $\pm$ 8.07 years) and 384 females (71.1 $\pm$ 8.44 years). The NMAPS was originally approved by the University of New Mexico Health Sciences Internal Review Board and had approval for further data analyses.

Measurements

A description of the measurements has been previously reported (Garry et al. 2007). In brief, cognitive function was measured with the 100-point modified mini-mental state examination (3MSE). Low cognition was defined as a 3MSE score at or below the lower quartile (3MSE $\leq$ 84 in men and in women) of the annual measurement (Teng and Chui 1987). Gait speed was assessed over 25 ft (7.62 m) at usual pace (canes/walkers allowed). Slow gait speed was defined using sex-specific lower quartile cut scores of 0.80 m/s for males and 0.725 m/s for females (Newman et al. 2016). Body composition was assessed annually by dual energy x-ray absorptiometry (Lunar DPX, DXA Lunar Radiation Corp. Madison WI), and blood samples were collected to assess serological markers (Table 2). Biomarkers were chosen based on those collected as part of the NMAPS. The

rationale for included biomarkers was based on previously published literature.

Statistical analysis

Baseline demographics, biomarkers and body composition were created for each participant by taking the score for each individual participant in the year the participant was entered in the study. Total count scores were calculated for both gait speed and cognitive function by calculating each 1➔0 transition (abnormal to normal), 0➔0 transition (normal to normal) and 0➔1 (normal to abnormal). We began with analysis of one biomarker at a time before proceeding to a fully multivariable Poisson regression model considering all biomarkers simultaneously. Poisson regression analysis was performed for all variables, to explore their individual relationship with the total count score for different categories of transitions ("protective" gait 0➔0, gait 1➔0, and "harmful gait 0➔1 and similarly for cognition 0➔0, cognition 1➔0 and cognition 0➔1). Note that the 0➔0 transition is considered protective; and for example, this transition is the goal of a primary prevention of disease strategy. Analyses were stratified by sex and adjusted for age and APOE4 based on our previous analysis with this same cohort (Qualls et al. 2017). Analysis of cognitive transitions were also adjusted for education based on our previous analysis. All significant variables from the univariate analysis were included in a backward stepwise multivariate Poisson regression to create a final model for the different categories of transitions; these models were verified by (forward) stepwise Poisson regression. All multivariate analysis accounted for the total number of years people were entered in the study. Poisson regression coefficients were exponentiated in order to interpret the results. Exponentiation obtains the incident rate ratios (IRR) and their 95% CI. Each category of transition is a binary outcome allowing interpretation of an IRR to be analogous to the interpretation of an odds ratio. In all analyses, continuous predictors were divided 2 times their standard deviation so the that regression coefficients and corresponding IRRs for these continuous variables were comparable to the coefficients and IRRs for binary variables (coded as 0 or 1).

Results

Participant characteristics are shown in Table 1. During the 9-year follow-up, the number of gait speed transitions from abnormal to normal was 224 (males 93 and females 131) and 207 normal to abnormal transitions (males 83 and females 124), and the number of transitions maintaining normal gait speed was 1395 (males 508 and females 887). For cognitive transitions, the total number of transitions from abnormal to normal was 248 (males 88 and females 160) and 203 normal to abnormal transitions (males 71 and females 132), and the number of transitions for maintaining normal cognition was 1471 (males 518 and females 953).

Table 2 shows all biomarkers explored in the univariate analysis. The serological biomarker concentrations reported were within age normative ranges for laboratory assay values and did not have any "outlier" values that could have changed the results reported. Table 3 shows the univariate analysis results. Table 4 shows the

Table 1 Participant characteristics

Variable	Male ($n = 216$)	Female ($n = 384$)
Age (years) *	**72.71 ± 8.07**	**71.10 ± 8.44**
Years of follow-up (%)	4.98 ± 2.70	5.04 ± 2.57
1–3 years	37.04%	31.77%
4–6 years	27.78%	35.68%
7–9 years	35.19%	32.56%
Education (%) *		
Less then 12 years	1.48	1.20
High school graduate	6.67	17.60
Some university	16.30	31.20
University degree	20.74	19.60
Some graduate degree study	16.30	8.80
Masters degree	23.70	13.60
Doctorate degree	9.63	2.40
Vocational/Technical training	5.19	5.60
Apolipoprotein E4 (%)	21.79	21.85
Gait speed (m/s) *	**0.85 ± 0.21**	**0.81 ± 0.21**
Modified mini-mental state exam (3MSE)	84.34 ± 6.14	84.65 ± 5.55
Waist circumference (cm) *	**97.32 ± 10.65**	**86.76 ± 10.63**
Body mass index (wt/h^2)	25.56 ± 3.54	24.94 ± 4.01
Health status (%)		
Excellent	30.73	28.71
Good	45.81	48.71
Fair	15.64	18.06
Poor	7.82	4.52

Mean ± St. deviation unless stated otherwise

Bold and * = significant sex difference $p < 0.05$

Table 2 Biomarkers for models

Serological biomarker variables	Males	Females
Oestrone (pg/mL)	–	42.67 ± 72.91
Glucose (mg/dL)	**93.75 ± 11.58***	**90.91 ± 13.53***
Hormone replacement therapy	–	0.27 ± 0.44
Insulin-like growth factor-1 (ng/ml)	**147.42 ± 52.04***	**122.94 ± 49.73***
IGF binding protein-3 (mcg/ml)	**3.13 ± 0.78***	**3.60 ± 0.80***
Insulin (mIU/L)	9.25 ± 7.29	8.10 ± 6.23
Leptin (ng/ml)	**7.76 ± 4.97***	**20.03 ± 14.38***
Soluble interleukin-2 receptor (U/ml)	684.18 ± 318.29	603.45 ± 729.79
Soluble interleukin-6 receptor (U/ml)	114.21 ± 73.06	122.90 ± 75.65
Testosterone (ng/dL)	**419.31 ± 151.46***	**13.83 ± 15.83***
Haematocrit (%)	**46.32 ± 3.99***	**43.48 ± 3.22***
Vitamin C (mg/dL)	**1.31 ± 0.36***	**1.42 ± 0.41***
Serum iron (mcg/dL)	**90.37 ± 28.83***	**85.28 ± 25.82***
Total iron binding capacity (μg/dL)	**285.66 ± 41.61***	**294.27 ± 40.69***
Vitamin B12 (ng/mL)	**478.37 ± 234.29***	**551.27 ± 316.72***
Ferritin (ng/mL)	**113.93 ± 113.24***	**90.96 ± 112.63***
Calcium (mg/dL)	**9.04 ± 0.36***	**9.16 ± 0.39***
Cholesterol (mg/dL)	**195.86 ± 34.91***	**217.52 ± 36.11***
Potassium (mEq/L)	4.28 ± 0.36	4.22 ± 0.51
Triglyceride (mg/dL)	**133.44 ± 78.66***	**150.94 ± 88.37***
Creatinine (mg/dL)	**1.20 ± 0.23***	**0.96 ± 0.16***
High-density lipoprotein cholesterol (mg/dL)	**51.30 ± 11.85***	**64.91 ± 14.64***
Haemoglobin (gm/dL)	**15.40 ± 1.34***	**14.24 ± 1.20***
Lactate dehydrogenase (units/L)	233.33 ± 128.03	248.20 ± 128.75
Low-density lipoprotein cholesterol (mg/dL)	108.24 ± 26.61	113.70 ± 32.16
Lymphocytes – absolute (K/MCL)	**1.54 ± 0.46***	**1.84 ± 0.86***
Mean corpuscular volume (fL/red cell)	**92.44 ± 4.35***	**91.21 ± 4.19***
Platelets (K/uL)	**221.39 ± 56.82***	**271.21 ± 124.25***
Red blood cell count (mcL)	4.87 ± 0.45	4.74 ± 2.65
Total protein levels (g/dL)	6.84 ± 0.46	6.84 ± 0.46
Uric acid (mg/dL)	**6.01 ± 1.24***	**4.86 ± 1.21***
White blood cell count (10^9/L)	5.90 ± 1.41	5.99 ± 1.64
Body composition biomarkers	**Males**	**Females**
Appendicular skeletal muscle mass (kg)	**23.56 ± 3.38***	**15.13 ± 2.05***
Bone mineral content lumbar spine (g)	**76.05 ± 16.89***	**50.63 ± 12.84***
Total bone mineral content (g)	**2942.66 ± 448.44***	**1995.88 ± 321.16***
Bone mineral content Ward's triangle (g)	**2.73 ± 0.70***	**1.79 ± 0.50***
Bone mineral density lumbar spine (SD)	**1.23 ± 0.22***	**1.02 ± 0.19***
Total bone mineral density (SD)	**1.18 ± 0.10***	**1.03 ± 0.10***
Bone mineral density (SD)	**0.87 ± 0.14***	**0.66 ± 0.11***
Bone mineral density Ward's triangle (SD)	**0.73 ± 0.15***	**0.63 ± 0.13***
Height (cm)	**174.19 ± 7.35***	**159.26 ± 6.61***
Weight (kg)	**77.45 ± 13.22***	**63.60 ± 11.40***
Total fat mass (kg)	**20.64 ± 7.81***	**24.20 ± 8.43***
Fat free mass (kg)	**53.38 ± 8.14***	**36.84 ± 4.50***
Lean mass (kg)	**54.01 ± 6.63***	**36.79 ± 3.92***
Total soft tissue (kg)	**74.65 ± 11.92***	**61.03 ± 10.55***

Mean ± St. deviation unless stated otherwise. Bold and * = significant sex difference $p < 0.05$

Table 3 Univariate Poisson regression analysis

Gait speed					**Cognitive status**				
1➔0					1➔0				
Variable	**Coefficient**	**Std. error**	***p* value**	**95% CI**	**Variable**	**Coefficient**	**Std. error**	***p* value**	**95%CI**
Female					*Female*				
Leptin	0.358	0.162	*0.027*	0.040–0.676	–				
Lymphocytes	0.461	0.165	*0.005*	0.137–0.785					
Insulin	0.281	0.122	*0.022*	0.041–0.521					
Male					*Male*				
Creatinine	− 0.654	0.263	*0.013*	− 1.169–0.138	Leptin	0.939	0.457	*0.04*	0.044–1.834
					Triglyceride	− 0.667	0.325	*0.04*	− 1.303–0.031
0➔0					0➔0				
Female					*Female*				
Leptin	− 0.173	0.073	*0.018*	− 0.317–0.029	HRT	0.210	0.092	*0.023*	0.028–0.389
Cholesterol	0.184	0.070	*0.008*	0.048–0.321	LDH	−0.423	0.108	*0.000*	−0.635 - 0.211
Weight	− 0.174	0.087	*0.044*	− 0.344–0.005					
% Body fat	− 0.189	0.069	*0.006*	− 0.325–0.053					
HDL	0.169	0.080	*0.034*	0.013–0.325					
LDH	− 0.399	0.095	*0.000*	− 0.585–0.212					
Soft tissue	− 0.199	0.085	*0.019*	− 0.366–0.033					
Creatinine	0.250	0.104	*0.017*	0.062–0.455					
Male					*Male*				
Cholesterol	0.313	0.095	*0.001*	0.128–0.499	APSM	0.416	0.175	*0.028*	0.041–0.721
BMCWRD	− 0.220	0.110	*0.046*	− 0.436–0.003	LBM	0.381	0.174	*0.017*	0.074–0.759
					LDH	− 0.288	0.142	*0.043*	− 0.566–0.010
0➔1					0➔1				
Female					*Female*				
Leptin	0.456	0.225	*0.043*	0.014–0.898	Triglyceride	− 0.848	0.379	*0.025*	− 1.591–0.105
Male					*Male*				
IGF1	0.566	0.226	*0.012*	0.123–1.009	–				
Creatinine	− 0.550	0.270	*0.042*	− 1.080–0.021					
Lymphocytes	− 0.572	0.291	*0.049*	− 1.141–0.002					

Gait univariate analysis are adjusted for age and APOE4. Cognitive univariate analysis are adjusted for age, APOE4 and education. *APOE4* apolipoprotein E4, *HDL* high-density lipoprotein cholesterol, *LDH* lactate dehydrogenase, *BMCWRD* bone mineral content Ward's triangle, *HRT* hormone replacement therapy, *APSM* appendicular skeletal muscle mass, *LBM* lean body mass

results of the multivariate analysis and presents the significant biomarkers associated with beneficial and harmful transitions in gait speed and cognitive function.

For maintaining a normal gait speed in females, the primary biomarkers associated were a lower percent body fat (IRR 0.793, $p = 0.001$, 95%CI 0.691–0.910) and lower lactate dehydrogenase (LDH) (IRR 0.623, $p < 0.001$, 95%CI 0.514–0.752). Maintaining gait speed in males was associated with higher cholesterol (IRR 1.394, $p = 0.001$, 95%CI 1.154–1.684). The number of transitions from a low gait speed into a normal gait speed was associated with higher insulin (IRR 1.325, $p = 0.022$, 95%CI 1.041–1.685) in females and lower creatinine (IRR 0.520, $p = 0.01$, 95%CI 0.310–0.870) in males. Maintaining normal cognitive function in females was associated with lower lactate dehydrogenase (IRR 0.276, $p = 0.013$, 95%CI 0.099–0.765) and for males with higher appendicular skeletal muscle mass (APSM) (IRR 1.52, $p = 0.02$, 95%CI 1.076–2.135). Improving cognitive state was associated with higher leptin (IRR 7.5, $p = 0.03$, 95%CI 1.282–44.34) and lower triglyceride (IRR 0.299, $p = 0.017$, 95%CI 0.110–

Table 4 Multivariate Poisson regression analysis

Gait speed					**Cognitive status**				
1➔0					1➔0				
Variable	**IRR**	**Std. error**	***p* value**	**95% CI**	**Variable**	**IRR**	**Std. error**	***p* value**	**95%CI**
Female					*Female*				
Age	1.048	0.012	0.000	1.024–1.072	Age	1.002	0.019	0.910	0.966–1.040
APOE4	0.908	0.198	0.659	0.592–1.394	APOE4	0.876	0.246	0.638	0.506–1.519
Insulin	1.325	0.163	*0.022*	1.041–1.685	Education	0.932	0.059	0.263	0.824–1.054
Male					*Male*				
Age	1.056	0.018	0.001	1.021–1.091	Age	1.010	0.034	0.781	0.944–1.079
APOE4	1.331	0.333	0.253	0.815–2.175	APOE4	1.136	0.405	0.720	0.565–2.284
Creatinine	0.520	0.137	*0.013*	0.310–0.870	Education	0.951	0.087	0.583	0.794–1.138
					Leptin	7.539	6.814	*0.025*	1.282–44.34
					Triglyceride	0.299	0.152	*0.017*	0.110–0.809
0➔0					0➔0				
Female					*Female*				
Age	0.948	0.005	0.000	0.938–0.958	Age	0.985	0.012	0.196	0.961–1.008
APOE4	0.972	0.079	0.732	0.829–1.141	APOE4	1.144	0.145	0.288	0.893–1.466
% Body fat	0.793	0.056	*0.001*	0.691–0.910	Education	1.059	0.028	0.032	1.005–1.116
LDH	0.623	0.060	*0.000*	0.514–0.752	LDH	0.276	0.144	*0.013*	0.099–0.765
Male					*Male*				
Age	0.961	0.007	0.000	0.948–0.974	Age	0.985	0.010	0.148	0.966–1.005
APOE4	0.870	0.098	0.217	0.697–1.085	APOE4	0.844	0.110	0.193	0.653–1.089
Cholesterol	1.394	0.135	*0.001*	1.154–1.684	Education	1.021	0.032	0.512	0.960–1.086
					APSM	1.516	0.265	*0.017*	1.076–2.135
0➔1					0➔1				
Female					*Female*				
Age	1.041	0.014	0.003	1.014–1.069	Age	1.020	0.021	0.335	0.979–1.063
APOE4	1.102	0.255	0.673	0.699–1.737	APOE4	0.999	0.295	1.000	0.560–1.784
Leptin	1.389	0.226	*0.043*	1.010–1.911	Education	0.856	0.856	0.037	0.740–0.990
Male					*Male*				
Age	1.066	0.023	0.003	1.022–1.111	Age	1.070	0.037	0.054	0.999–1.146
APOE4	1.140	0.353	0.671	0.621–2.093	APOE4	1.936	0.711	0.072	0.942–3.977
IGF-1	1.737	0.419	*0.022*	1.082–2.787	Education	1.053	0.104	0.600	0.867–1.280

Age and APOE4 were used to adjust in the final gait speed multivariate model. Age, APOE4 and education are used to adjust in the final cognitive status multivariate model. *APOE4* apolipoprotein E4, *LDH* lactate dehydrogenase, *APSM* appendicular skeletal muscle mass

0.809) in males, and no biomarkers were statistically significant for females.

Harmful gait speed transitions (0–1) in males was associated with IGF-1 (IRR 1.74, $p = 0.022$, 95%CI 1.08–2.79) and leptin in females (IRR 1.39, $p = 0.043$, 95%CI 1.01–1.91). None of the biomarkers considered were associated with harmful cognitive transitions (0➔1).

Discussion

We explored the possible relationships between biomarkers with gait speed and cognitive transitions and investigated these relationships in people who are able to maintain gait speed and cognitive function over time, those who transitioned from a worsened state back to an improved/normal state and with those

who transitioned from a normal state to abnormal state (harmful transition).

Associations of biomarkers with trajectories of health status change have been previously reported. Trajectories can be described by (linear or nonlinear) trends over longer times, but transitions can be described by probabilities of transitions in health status over shorter timeframes (e.g. 1 year) but are assessed over longer periods of time. Thus, investigations using trajectories or transitions apply different analyses. Associations of biomarkers with trajectories has been reported on 13 different health variables that declined in a trajectory path with advancing age, but all the health variables investigated in this study declined at significantly different rates (Diehr et al. 2013). Newman and colleagues also reported that trajectories of functional decline accelerate late in life (Newman et al. 2016). However, transitions, that is, changes from normal status to abnormal, abnormal status back to normal or maintaining normal function over time, rather than measuring trajectories, have not been investigated, and understanding these transitions and possible biomarkers associated with transition may provide opportunities for early intervention.

In the current study, biomarkers associated with maintaining gait speed in females were lower percentage body fat and LDH, and an increase in percentage body fat and increase in LDH were associated with a worse ability to maintain normal gait speed. Previous research has reported that high percentage body fat is associated with poorer physical performance in older adults (Stefano et al. 2015) and a high LDH may reflect tissue damage and injuries (Cardoso et al. 2018) and skeletal muscle damage (Paschalis et al. 2007). Interestingly, beneficial gait speed transitions in females in our study were associated with higher insulin concentrations and a better ability to improve one's gait speed. The mean insulin concentrations of these female participants were within normal values albeit at the higher end of the normal range. While this finding may seem paradoxical, insulin sensitivity is essential for normal physiological functioning in mammals, and higher insulin concentrations has been speculated to extend longevity, suggesting an adaptive rather than a maladaptive role (Barzilai and Ferrucci 2012).

Our analysis showed that higher cholesterol was associated with better ability to maintain normal gait speed. Note that the mean cholesterol in our sample was in the normal range, and a higher cholesterol, therefore, was not reflecting abnormal cholesterol levels, but levels that are at the higher end of the normal range for this assay. A Swedish longitudinal study, also with 9-years follow up, reported that several cardiovascular risk factors, especially when they coexisted, appeared to increase the risk of walking speed limitation in older adults, particularly those younger than 78 years of age (Heiland et al. 2017). The NMAPS cohort mean age was younger than 78 years ($\sim 72 \pm 8.4$ years) and had all the common cardiovascular risks factors measured, which were included in the univariate analysis, but only cholesterol and insulin remained significant. The analysis of the Swedish cohort was stratified by age (young/old and old/old) but not by sex, as we did in the current analysis make comparisons with this study more problematic, particularly with the recent emphasis on sex-specific differences when investigating biomarkers and frailty (Kojimaa et al. 2019; Kane and Sinclair 2019).

In the current study, the ability to improve from a slower gait speed to a normal gait speed was associated with higher creatinine in males. Higher creatinine levels in older adults have been associated with a history of diabetes or heart attack and in those reporting the use of cimetidine and diuretic medications (Salive et al. 1995). It may therefore be expected that higher creatinine could be associated with a decrease in the amount of beneficial gait speed transitions. In the recent review by Kane and Sinclair (Kane and Sinclair 2019), low creatinine was a biomarker for frailty, although these authors stressed that much of the evidence to date on biomarkers for frailty are from cross-sectional studies and the studies did not controlled for sex. Thus, in the current study, higher creatinine could be a marker of an ability to transition from slow to normal gait speed in males that warrants further investigation.

"Harmful" gait speed transition (transition from normal to slower gait) had fewer metabolic and muscle biomarkers (IGF-1 in males and leptin in females). Recent evidence has suggested that IGF-1 may be related to both functional and cognitive performance; however, the direction and strength of these associations have been mixed as well as being reported as sex-specific. Wennberg and colleagues (Wennberg et al. 2018) reported IGF measures were not associated with cognitive or functional performance for men, but for women, higher levels of IGF-1 was associated with better attention, visuospatial and global cognitive domain performance, independent of gait speed. Our findings are more similar to that reported by Doi and colleagues (Doi et al. 2015 2016) where lower levels of IGF-1 were associated with

both slow gait speed (Doi et al. 2015) and incident disability (Doi et al. 2016). However, other studies have found the opposite (Meng et al. 2015) or no association (Perice et al. 2016). Therefore, whether a relationship exists between IGF-1 concentrations and gait speed in males or females remains an enigma.

Higher leptin has been associated with higher body fat, and higher body fat has been associated with greater risk of frailty and functional deficits (Harris 2014; Jequier 2002; García-Esquinas et al. 2015). We reported that higher leptin was associated with greater likelihood of a harmful transition from normal gait speed to slower gait speed in females only. This agrees with two investigations by Lana and colleagues (Lana et al. 2016, 2017) who reported higher leptin levels in the large cohort study Seniors-ENRICA and reported associations with muscle weakness (using the Fried frailty phenotype criteria) and self-reported impaired mobility and agility, lower extremity function and overall physical performance, which was independent of total body fat.

Maintaining cognitive status in females was associated with lower LDH levels. High LDH serum concentrations have been reported to decrease the stability of cognitive status as higher levels of LDH reflect tissue damage and cellular injuries (Cardoso et al. 2018). In our males participants, maintaining cognitive status was associated with a higher APSM, which agrees with the AGES-Reykjavik study with 5169 participants (mean age 76 years, 42.9% men) where only males with a 1 standard deviation increase in thigh muscle had an associated significant decrease in the likelihood of developing dementia (Spauwen et al. 2017).

In the current analysis, improving cognitive status in males was associated with leptin and triglyceride. This aligns with previous literature, which concluded that older individuals with higher serum leptin appeared protected against cognitive decline (Holden et al. 2009) and lower levels of leptin may be involved in cognitive deficits (Farr et al. 2006). An increase in triglyceride has been associated with a decrease in the ability to improve cognitive status. This is also in line with what is previously shown in both human and animal studies that obesity is associated with cognitive impairment and the administration of triglycerides to mice decreases the learning and memory and impairs long-term potential (Farr et al. 2008; Morley and Banks 2010). Cardiometabolic abnormalities are independently associated with a high risk of dementia and cardiometabolic syndromes (described as three or more cardiometabolic risk factors: inflammation, central obesity, raised triglycerides, low high-density lipoprotein [HDL] cholesterol, hypertension, and hyperglycaemia or diabetes) (Kontari and Smith 2019). However, our data did not identify any clusters of metabolic risk factors associated with cognition, but rather individual biomarkers that appeared to be sex-specific.

A strength of this study is the long-term longitudinal data collection, which other investigators have raised as necessary to move biomarker research forward. The cohort was also relatively healthy (successfully ageing) and was followed up annually. A limitation of the study would be some current biomarkers of interest reported in other studies were either not collected or had incomplete data, which did not allow those to be included in the analysis. The NMAPS participant was also primarily Caucasians from higher socio-economic status, thus limiting generalizations to other groups.

In conclusion, of all biomarkers investigated, sex-specific biomarkers of muscle (LDH, creatinine) and metabolism (%fat, insulin and cholesterol) were associated with "protective" changes in gait speed over 9 years of observation. Moreover, metabolic biomarkers (APSM, leptin and triglycerides) were associated with cognitive change in males, but not in females. Only education was protective against harmful cognitive transitions in females. Muscle and metabolic biomarkers were also associated with positive or sustained cognitive function (APSM, leptin and triglycerides) in males only. It is also possible that transitions in biomarkers may poorly correlate with transitions in health status, thus supporting independence in stochastic modelling across systems as previously reported (Sanders et al. 2014). However, our longitudinal data that controlled for sex and age suggests that there may be sex-specific modifiable biomarkers that could be targeted for interventions. These findings need to be replicated in other longitudinal cohorts in order to take the next step of targeted intervention studies to assess causal inferences.

References

Barzilai N, Ferrucci L (2012) Insulin resistance and aging: a cause or a protective response? J Gerontol A Biol Sci Med Sci 67: 1329–1331

Cardoso AL, Fernandes A, Aguilar-Pimentel JA, de Angelis MH, Guedes JR, Brito MA, Ortolano S, Pani G, Athanasopoulou S, Gonos ES, Schosserer M, Grillari J, Peterson P, Tuna BG, Dogan S, Meyer A, van Os R, Trendelenburg AU (2018)

Towards frailty biomarkers: candidates from genes and pathways regulated in aging and age-related diseases. Ageing Res Rev 47:214–277

Diehr PH, Thielke SM, Newman AB, Hirsch C, Tracy R (2013) Decline in health for older adults: five-year change in 13 key measures of standardized health. J Gerontol A Biol Sci Med Sci 68:1059–1067

Doi T, Shimada H, Makizako H, Tsutsumimoto K, Hotta R, Nakakubo S et al (2015) Association of insulin-like growth factor-1 with mild cognitive impairment and slow gait speed. Neurobiol Aging:942–947

Doi T, Shimada H, Makizako H, Tsutsumimoto K, Hotta R, Nakakubo S et al (2016) Insulin-like growth factor-1 related to disability among older adults. J Gerontol A Biol Sci Med Sci:797–802

Farr SA, Banks WA, Morley JE (2006) Effects of leptin on memory processing. Peptides. 27:1420–1425

Farr SA, Yamada KA, Butterfield DA, Abdul HM, Xu L, Miller NE et al (2008) Obesity and hypertriglyceridemia produce cognitive impairment. Endocrinology. 149:2628–2636

García-Esquinas E, José García-García F, León-Muñoz LM, Carnicero JA, Guallar-Castillón P, Gonzalez-Colaço HM et al (2015) Obesity, fat distribution, and risk of frailty in two population-based cohorts of older adults in Spain

Garry PJ, Wayne SJ, Vellas B (2007) The New Mexico aging process study (1979-2003) a longitudinal study of nutrition, health and aging. J Nutr Health Aging 11:125–130

Harris RB (2014) Direct and indirect effects of leptin on adipocyte metabolism

Heiland EG et al (2017) Cardiovascular risk burden and future risk of walking speed limitation in older adult. J Am Geriatr Soc: 2418–2424

Holden KF, Lindquist K, Tylavsky FA, ., Rosano C, Harris TB, Yaffe K. Serum leptin level and cognition in the elderly: findings from the health ABC study. Neurobiol Aging 2009;30:1483–1489

Jequier E (2002) Leptin signaling, adiposity, and energy balance

Kane AE, Sinclair DA (2019) Frailty biomarkers in humans and rodents: current approaches and future advances. Mech Ageing Dev:117–128

Kojimaa G, Taniguchi Y, Iliffe S, Jivraj S, Walters K (2019) Transitions between frailty states among comminuty-dwelling older people: a systematic review and meta-analysis. Ageing Res Rev:81–88

Kontari P, Smith KJ (2019) Risk of dementia associated with cardiometabolic abnormalities and depressive symptoms: a longitudinal cohort study using the English longitudinal study of ageing. Int J Geriatr Psychiatry 34:289–298

Lana A, Struijk E, Guallar-Castillón P, Martín-Moreno JM, Rodríguez Artalejo F, Lopez-Garcia E (2016) Leptin concentration and risk of impaired physical function in older adults: the Seniors-ENRICA cohort. Age Ageing 45(6):819–826

Lana A, Valdés-Bécares A, Buño A, Rodríguez-Artalejo F, Lopez-Garcia E (2017) Serum leptin concentration is associated with incident frailty in older adults. Aging Dis 8(2):240–249

Meng Y, Wu H, Yang Y, Du H, Xia Y, Guo X et al (2015) Relationship of anabolic and catabolic biomarkers with muscle strength and physical performance in older adults: a population-based cross-sectional study

Morley JE, Banks WA (2010) Lipids and cognition. J Alzheimers Dis 20:737–747

Newman AB, Sanders JL, Kizer JR, Boudreau RM, Odden MC, Al Hazzouri AZ et al (2016) Trajectories of function and biomarkers with age: the CHS all stars study. Int J Epidemiol: 1135–1145

Paschalis V, Giakas G, Baltzopoulos V, Jamurtas AZ, Theoharis V, Kotzamanidis C, Koutedakis Y (2007) The effects of muscle damage following eccentric exercise on gait biomechanics. Gait Posture 25:236–242

Perice L, Barzilai N, Verghese J, Weiss EF, Holtzer R, Cohen P et al (2016) Lower circulating insulin-like growth factor-I is associated with better cognition in females with exceptional longevity without compromise to muscle mass and function

Pujos-Guillot E, Pétéra M, Jacquemin J, Centeno D, Lyan B, Montoliu I et al (2019) Identification of Pre-frailty Sub-Phenotypes in Elderly Using Metabolomics. Front Physiol

Qualls C, Waters DL, Vellas B, Villareal DT, Garry PJ, Gallini A et al (2017) Reversible states of physical and/or cognitive dysfunction: a 9-year longitudinal study. J Nutr Health Aging 21:271–275

Rikkert MGMO, Melis RJF (2019) Rerouting geriatric medicine by complementing static frailty measures with dynamic resilience indicators of recovery potential. Front Physiol 723

Rodriguez-Manas L, Araujo De Carvalho I, Bhasin S, Bischoff-Ferrari HA, Cesari M, Evans WJ et al (2019) ICFSR Task Force Perspective on Biomarkers For Sarcopenia and Frailty. J Frailty Aging

Salive ME, Jones CA, Guralnik JM, Agodoa LY, Pahor M, Wallace RB (1995) Serum creatinine levels in older adults: relationship with health status and medications. Age Ageing 24:142–150

Sanders JLDV, Arnold AM, Kaplan RC, Cappola AR, Kizer JR, Boudreau RM, Cushman M, Newman AB (2014) Do changes in circulating biomarkers track with each other and with functional changes in older adults? J Gerontol Ser A 69A:174–181

Spauwen PJJ et al (2017) Associations of fat and muscle tissue with cognitive status in older adults: the AGES-Reykjavik Study. Age Ageing 46:250

Stefano FD, Zambon S, Giacometti L (2015) al. e. Obesity, muscular strength, muscle composition and physical performance in an elderly population. J Nutr Health Aging 19:785

Teng EL, Chui HC (1987) The modified mini-mental state (MMS) examination. J Clin Psychiatry 48:314–318

Thielke SM, Whitson H, Diehr P, O'Hare A, Kearney PM, Chaudhry SI et al (2012) Persistence and remission of musculoskeletal pain in community-dwelling older adults: results from the cardiovascular health study. J Am Geriatr Soc: 1393–1400

Wang J, Maxwell CA, Yu F (2019) Biological processes and biomarkers related to frailty in older adults: a state-of-the-science literature review. Biol Res Nurs:80–106

Wennberg AMV et al (2018) The association between peripheral total IGF-1, IGFBP-3, and their molar ratio levels and functional and cognitive outcomes in the Mayo Clinic study of aging Neurobiol aging. Neurobiol Aging:68–74

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